FRIEDRICH-ALEXANDER
UNIVERSITÄT
ERLANGEN-NÜRNBERG

FACULTY OF MEDICINE

Research Report 2013

Faculty of Medicine

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Research Report 2013

Faculty of Medicine

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Medical Research in Erlangen

It is with great pleasure that the Faculty of Medicine of the Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU) presents the research report for the years 2011 – 2012. Following an established tradition, this report gives an overview of the research areas and projects carried out by the various preclinical and clinical theoretical institutes and by the chairs established at the departments and divisions of the FAU and the Universitätsklinikum Erlangen (UK Erlangen). It is meant to be read by anyone interested from inside and/or outside the university area. It is intended to serve as a base for the intensification of both, internal and interdisciplinary communication, and to encourage suggestions for future cooperative projects.

The Faculty of Medicine of the FAU has established four focal areas of research, all of which were given a high rating by the German Science Council in 2006:
1. Immunology and infection research
2. Renal and vascular research
3. Neurosciences, including pain and ophthalmology research
4. Tumor research.

These research focuses are interconnected through three interdisciplinary fields: Molecular Medicine, Medical Technology, and Clinical Studies. Translational Research, i.e. an active effort to transpose findings from basic research into clinical studies involving patients, is the overarching purpose of all research activity at the Faculty of Medicine. Thus, the objective of medical research is seen not solely as being that of discovering new facts and expanding medical knowledge for its own sake; it is also seen as being that of striving for effectiveness in the pursuit of better therapeutic outcomes for our patients.

The current fields of research are to be pursued in the future consistently. However, new questions that emerge at interdisciplinary interfaces will be advanced, so that they can develop into potential research focuses. Such focal research areas are characterized by interdisciplinary networks supported by third-party funding provided in the framework of collaborative research centers, research training groups, DFG research groups, as well as network projects funded by the BMBF and the EU. A new clinical research group funded by the DFG could be established at the Department of Medicine 1 – Gastroenterology, Lung Diseases, and Endocrinology on "Molecular pathogenesis and optimized therapy of chronic inflammatory bowel disease". A more detailed account of these networks and research groups is given in the second part of this report.

Moreover, our Faculty of Medicine plays an important role in the scientific research focuses of the FAU "Molecular Life Sciences and Medicine", "Medical Technology", as well as "Optics and Optical Technologies". There is a close cooperation between the Faculty of Medicine and the relevant science and engineering faculties in the various research networks.

The third-party funding has been rising continuously for the last few years. In 2011, the Faculty of Medicine attracted almost 40 million Euro of third-party funding which ranks Erlangen among the "Top Ten" of all German medical faculties regarding third-party funding. In the fields of microbiology, virology, and immunology, Erlangen even holds the leading position nationwide.

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

In the course of the report period 2011 - 2012, diverse activities were carried out, aiming at moving forward with the process of enhancing the reputation of our Faculty of Medicine as an international top player in the fields of research and education. The research focus of our Faculty of Medicine is reflected by the existence of the Interdisciplinary Center for Clinical Research (IZKF), the Franz Penzoldt Center (FPZ), as well as the Center for Clinical Studies (CCS). The latter is responsible, among others, for coordinating the legal aspects of bench-to-bedside research projects.

The multitude of outstanding research initiatives requires increased lab space. This is met by different construction projects which shall meet the need for more research areas. With the Translational Research Center (TRC) – topping-out ceremony on March 2012 –, the UK Erlangen will provide an innovative interdisciplinary infrastructure for clinical research, so far unprecedented by another German university. The TRC will join all areas with a need to translate research into diagnostic and therapeutic process in an exemplary manner. Thus, our Faculty of Medicine will be able to counteract the many times emphasized lack of advancement in clinical research and to create new research focuses on the basis of a planned strategy.

A further improvement of research conditions resulted from the DFG's introduction of a lump sum to cover indirect costs incurred by projects. Part of this sum is passed on by the FAU or the UK Erlangen to institutes or departments to use at their own discretion for research-related purposes. With the introduction of a project lump sum by the BMBF in 2011, this research support for the institutes and departments could be increased considerably. However, the distribution of research fundings as well as the execution of joint research funding programs is difficult due to a financial separation within the Faculty of Medicine administration (UK Erlangen's budget versus non-clinical institutes' budget). A working group on the structures of our Faculty of Medicine is endeavoring to develop tools to overcome this organizational separation by integrating the structures. The measures are supported by the Bavarian State Ministry within an agreement on objectives.

In July 2012, the "Center of Excellence for Medical Technology", funded by BMBF under the roof of the Medical Valley EMN at the Leading Edge Cluster competition, was granted a prolongation of its funding until

2015 in this highly competitive environment thanks to convincing results and future-oriented visions gained in the first funding period. The aim of the Center of Excellence for Medical Technology is to develop technologies which increase life expectancy, improve quality of life, and reduce costs in the public health sector. The Imaging Science Institute (ISI), founded as a joint venture between Siemens Healthcare and the Institute of Radiology of the FAU in 2005, plays an important role for the development and implementation of innovative imaging methods within the Medical Valley EMN. The close cooperation between chairs of the medical, technical, and natural sciences faculties of the FAU, Siemens Healthcare, the Fraunhofer IIS, and more than 50 companies in the field of medical technology from the metropolitan area complement the outstanding research conditions in Erlangen. Additionally, the Central Institute of Medical Engineering (ZiMT) further supports the interdisciplinary cooperation in the field of medical engineering.

New developments in teaching

It was already in 2006 that the Science Council underscored the trans-regional activities carried out by our Faculty of Medicine to promote further development of teaching. Therefore, our report also lists information on teaching for each facility at the Faculty of Medicine.

The completion of the newly built medical lecture halls meets not only the need of the Faculty of Medicine for more lecture halls and classrooms, but also offers excellent venues for congresses, meetings, and other public events during term breaks. The generous foyer is an attractive location for receptions and poster presentations, too.

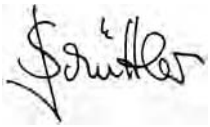
The Faculty of Medicine of the FAU currently has five degree programs: Human Medicine, Dentistry, Molecular Medicine (Bachelor of Science and Master of Science), Speech Therapy (Bachelor of Science), and Medical Process Management (Master of Science). These degree programs will be presented in more details in the second part of the research report. Since 2007, the students at the Faculty of Medicine have regularly ranked among the best out of 36 medical faculties in the first phase of degree examinations and have also been in the top group in terms of grades received on state examinations relating to clinical training. Our Faculty of Medicine has consistently undertaken efforts to seize on and apply new ideas in teaching in order to maintain these rankings. A changeover to the bachelor's and master's degree system is not planned in Erlangen for the degree programs Human Medicine and Dentistry, given that this is not expected to produce any time advantages in the training of students and, as such, would not enable graduates to find a medical occupation any earlier. In a memorandum, our Faculty of Medicine stated its opposition to the general implementation of the "Bologna Process" for the medical education. However, bachelor's and master's degree structures have been firmly established in specialized fields, such as Medical Process Management, Molecular Medicine, and Speech Therapy.

In summer term 2007, a skills lab, PERLE (Practice, Experience, and Learning), was created with money taken from tuition fees. PERLE helps students to improve their skills and prepare for practical examinations. The students are supported by medical specialists and trained student tutors. Funds from this source are also used to finance research projects in teaching. Networked courses continue to be created in interdisciplinary subjects, all courses are systematically evaluated, and the professionalization of student management in the practical year (11th and 12th term) continues to be pursued.

On behalf of the Faculty of Medicine administration I would like to thank all those members of our staff who helped produce this report. Particular thanks go to U. Niederweis, Prof. Dr. K. Schiebel, and Dr. S.A. Thomas for their active involvement in formulating the text. The report can be downloaded from the website of the Dean's office of the Faculty of Medicine as well as from the homepage of the UK Erlangen.

We hope our readers enjoy the information we have provided on the wide range of research carried out at our Faculty of Medicine. The scientists involved will be happy to answer questions on their projects in oral or written form.

Erlangen, July 2013



Prof. Dr. med. Dr. h.c. Jürgen Schüttler
Dean

Abbrevations

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

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

Structure of the Department

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

Research

Innervation of the gastrointestinal tract

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

Nervous system, inflammation, and pain

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

Cell biology of the NF2 tumor suppressor protein

Project manager: PD Dr. M. Kressel
The neurofibromatosis type 2 (NF2) protein merlin is a classical tumor suppressor protein. Disturbed function or loss of function, e.g. through inherited NF2 gene mutation, typically results in neurinomas of the VIIIth cranial nerve. Data from Drosophila suggest the NF2 protein as one of the regulatory components of the so-called hippo pathway which turned out to be a universal cellular regulator of limb and organ size. Cell biology studies in order to elucidate the function of the NF2 protein were continued. We focused on subcellular localization of merlin, since one isoform turned out to be a nucleo-cytoplasmic shuttle protein. This extended the classical view of merlin from a purely plasma membrane associated protein towards a nuclear regulator of proliferation. The mechanisms determining cytoplasmic and nuclear localization, respectively, are being studied with a set of molecular biological and morphological methods in order to define protein domains relevant for the respective localization. As a first result, transport of merlin into the nucleus was found to be coupled to specific membranes of the endolysosomal system whose origin is the focus of ongoing research.

Teaching

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

Selected Publications

Jabari S, da Silveira AB, de Oliveira EC, Neto SG, Quint K, Neuhuber W, Brehmer A (2011) Partial, selective survival of nitrergic neurons in chagasic megacolon. Histochem Cell Biol, 135: 47-57

Kustermann A, Neuhuber W, Brehmer A (2011) Calretinin and Somatostatin Immunoreactivities Label Different Human Submucosal Neuron Populations Anat Rec, 294: 858-869

Hempfling C, Neuhuber WL, Wörl J (2012) Serotonin-immunoreactive neurons and mast cells in the mouse esophagus suggest involvement of serotonin in both motility control and neuroimmune interactions. Neurogastroenterol Motil, 24: e67-78

Horling L, Neuhuber WL, Raab M (2012) Pitfalls using tyramide signal amplification (TSA) in the mouse gastrointestinal tract: endogenous streptavidin-binding sites lead to false positive staining. J Neurosci Methods, 204: 124-32

Jabari S, da Silveira AB, de Oliveira EC, Neto SG, Quint K, Neuhuber W, Brehmer A (2012) Selective survival of calretinin- and vasoactive-intestinal-peptide-containing nerve elements in human chagasic submucosa and mucosa. Cell Tissue Res, 349: 473-81

Jabari S, da Silveira AB, de Oliveira EC, Quint K, Neuhuber W, Brehmer A (2012) Preponderance of inhibitory versus excitatory intramuscular nerve fibres in human chagasic megacolon. Int J Colorectal Dis, 27: 1181-9

International Cooperations

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

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

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

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

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

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

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

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

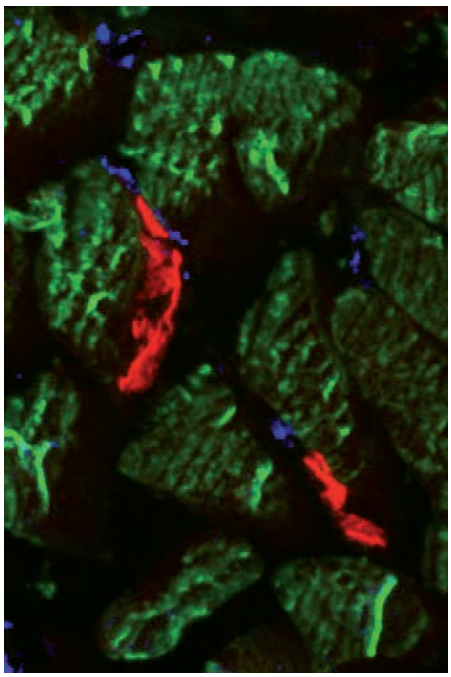
Meetings and International Training Courses

23.-25.02.2011: 8th International Course on Diagnostics and Surgery of Salivary Gland Diseases in Consideration of New Techniques (gemeinsam mit HNO-Klinik Erlangen), Erlangen

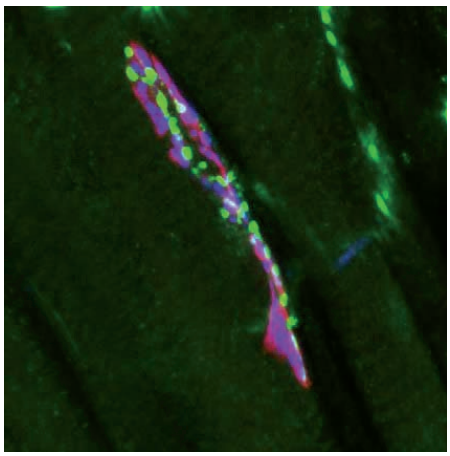
17.-20.05.2011: 10th International Erlangen Course in Facial Plastic Surgery (gemeinsam mit HNO-Klinik Erlangen), Erlangen

05.-06.10.2012: Aufbau- und Masterkurs der Gesellschaft für Fußchirurgie, Erlangen

08.12.2012: Fortgeschrittenenkurs im Rahmen des 28. Nürnberger Arthroskopiekurses und Gelenksymposiums (gemeinsam mit Klinik für Unfall- und Orthopädische Chirurgie des Klinikums Nürnberg), Erlangen



Striated muscle fibers in the mouse esophagus immunolabeled for fast myosin (green). Motor endplates (red) receive enteric VIP positive axons (blue).



Motor endplate in the mouse esophagus labeled with α-bungarotoxin (red) receiving vagal cholinergic (blue) and enteric serotoninergic (green) innervations.

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Research Focus
- Pathophysiology of the Meibomian gland dysfunction (MGD)
- Neurodegenerative changes in the retina of the DBA/2J mouse
- Characterization and detection of surfactant proteins
- Project test anxiety
- Investigations in glaucoma pathogenesis

Structure of the Department

The Institute of Anatomy consists of the Chair of Anatomy I and the Chair of Anatomy II. Since the inauguration of Prof. Dr. F. Paulsen in 2010 as new director, the Department has been in a continuous restructuring and renovation which is expected to be completed in late 2014. In the past two years, most of the office space was renovated, newly furnished, and equipped. The renewal of some of the laboratory space has already begun. Currently, 25 staff members are employed at the Institute. In the period from 2011 to 2012, seven employees were funded by grants. Eight PhD students, two graduate students, and a Bachelorand of molecular medicine were involved in scientific work. The functional anatomy of the body, including embryology, the entire microscopic anatomy, and parts of neuroanatomy were represented in teaching. In addition, members of the Chair of Anatomy II participated in the lessons of the macroscopic anatomy given by the Chair of Anatomy I. There were collaborations with other projects, particularly with regard to the SFB initiative "hoarseness" and several long-time international collaborations. Since 2011, the W2 professorship of the Chair has been held by Prof. Dr. L. Bräuer who works on surface-active proteins (mainly surfactant proteins) and supports the research interests of the Department. In 2012, Prof. Dr. F. Paulsen was offered a chair for Anatomy at the Medical University of Vienna which he has declined by now.

Research

Pathophysiology of the Meibomian gland dysfunction (MGD)

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

Meibomian gland dysfunction (MGD), a term used to describe a diffuse abnormality of the meibomian glands which are specialized sebaceous glands in the eye lids, is considered to be the most common cause of dry eye syndrome (DES), a disease with an estimated prevalence of 12 million people alone in Germany. It is currently thought that MGD is caused primarily by terminal duct obstruction due to hyperkeratinization of the ductal epithelium and an increased viscosity of meibum. However, the molecular mechanisms that underlie this process are unclear. Many proteins being essential for epidermal differentiation and keratinization constitute the 'epidermal differentiation complex' (EDC). They function beside epidermal differentiation and keratinization also in innate immune defense belonging to the group of antimicrobial peptides (AMP). The hypotheses are: Chronic inflammatory conditions at the ocular surface induce upregulation of AMPs which are correlated to genes of the EDC that function in epidermal differentiation and keratinization. Thus, induction of EDC associated AMPs triggers hyperkeratinization of Meibomian glands and increases viscosity of meibum. The goal of the study is to get deeper insights into the pathophysiology of MGD by performing in vivo experiments in an established mouse model of dry eye and in vitro experiments using cultivated human Meibomian gland epithelial cells in three-dimensional culture to determine factors that could serve as possible targets for therapeutic intervention in MGD.

Neurodegenerative changes in the retina of the DBA/2J mouse

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

In close cooperation with the Department of Ophthalmology (Prof. Dr. J. Kremers; Experimental Ophthalmology) and the Chair of Animal Physiology at the Department of Biology (Prof. Dr. J.H. Brandstätter), morphological and molecular studies on the structure and changes in the retina of the DBA/2J mouse model were performed. Previous electrophysiological investigations of the stimulation responses of retinal neurons showed functional changes which suggest the involvement of photoreceptor cells within the degenerative process of the retina in these animals. In our studies, we found both, a reduction in the thickness of the outer plexiform layer of the retina which is the area of first synaptic connections for the transmission of visual signals as well as age-dependent and progressive degenerative changes in the structural morphology of the rod ribbon synapses itself. This synaptic phenotype was described for the first time and contributes significantly to the further understanding of the pathogenesis of degenerative changes within the retina of this animal model.

Characterization and detection of surfactant proteins

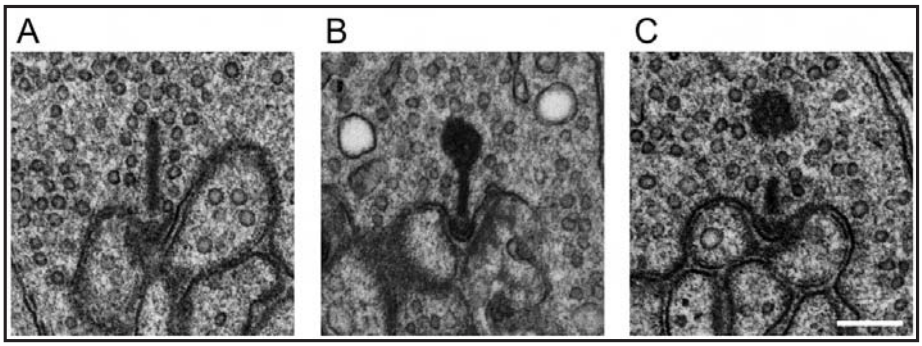
Project managers: M. Schicht, Prof. Dr. L. Bräuer, Prof. Dr. F. Paulsen

Besides the evolving investigation and characterization of the known surfactant proteins in different tissues and organs, two new yet unknown proteins could be detected for the first time by means of genome analysis. Both proteins, named SP-G and SP-H, may represent a new class of surfactant proteins. Using bioinformatics and genome analyses, RT-PCR experiments as well as immunological investigations (Western-Blot, immunohistochemistry), the two unknown proteins could be detected and characterized for the first time at RNA/DNA- and protein level within a variety of human tissues (e.g. tissues of the ocular system, kidney, liver, and lung). In addition, we were able to show that different strains of Staphylococcus aureus and Pseudomonas aeruginosa express and secrete proteins that react with commercially available antibodies against human surfactant proteins. The results may reflect the existence of a new group of bacterial surfactant proteins currently lacking in the relevant sequence and structure databases.

Project test anxiety

Project managers: Dr. O.Y. Tektas, PD Dr. M. Scholz, Prof. Dr. F. Paulsen

Test anxiety (TA) is an underestimated and widespread problem among students. It can result in poor course achievements, psychiatric and somatic disorders as well as in addictive disorders. The Chair of Anatomy II offers a pilot project which addresses affected students and is supported by several collaborators. The program comprises a series of lectures with guest lecturers as well as different tutorials which are conducted by specialized psychologists. At the



Rod photoreceptor synaptic ribbons disintegrate in aging DBA/2J mice. Synaptic ribbon profiles were classified as rod-shaped (A), club-shaped (B), and spherical-shaped (C). Scale bar: 0.2 mm.

same time, research approaches are performed about this topic within the project. A huge census revealed important findings about the prevalence of test anxiety, its impacts to study specific performances, and its correlations to drug and alcohol consumption behavior. Currently, long term effects of different therapies and supervision procedures are investigated.

Investigations in glaucoma pathogenesis

Project managers: Dr. O.Y. Tektas, Prof. Dr. M. Eichhorn, Prof. Dr. E. Lütjen-Drecoll

Glaucoma comprises a number of different eye diseases and is defined as a progressive damage of the optic nerve. One of the main risk factors for the disease is an elevated intraocular pressure. The exact pathogenesis of the disease is not known yet. In collaboration with several workgroups (Münster/Germany, London/GB, Wisconsin and New York City/USA), changes of the aqueous humor pathways and the optic nerve are investigated at the Chair of Anatomy II. Besides molecular and morphological investigations of donor tissues from patients suffering from different types of glaucoma (pigment dispersion syndrome, uveitis induced glaucoma, primary open angle glaucoma), the workgroup performs research using different animal models. In collaboration with the group of Dr. J. Danias (New York City), changes of the trabecular meshwork of sheep eyes with drug treatment are investigated. In a further cooperation with the group of Dr. D. Overby (London), it could recently be demonstrated that changes in the trabecular meshwork of mice eyes with drug treatment could induce intraocular pressure elevation.

Teaching

The Chair of Anatomy II has performed the lectures on the functional aspects of human anatomy with accompanying demonstration courses and the general and specific histology (including embryology) in combination with the courses of microscopic anatomy and associated seminars. In the seminar on functional and clinical anatomy of the musculoskeletal system, the students were increasingly teached on wet specimens that have been created continuously since 2010. The microscopic anatomy is conceptually transformed into a model of the future that makes use of the virtual histology. In this context, in collaboration with the Institute of Anatomy at the University of Regensburg (Chair of Histology, Prof. Dr. R. Witzgall) and in close cooperation with the Fraunhofer Institute for Integrated Circuits and the Virtual University of Bavaria, a first online course "General anatomy with clinical implications" can be booked at the virtual University of Bavaria which is free for all students at Bavarian universities. In addition, most of the histological specimens used in the courses in Erlangen and Regensburg can be viewed online with high resolution. All courses are attended by students of medicine, dentistry, and molecular medicine. In addition, students of the study course Medical Process Management were teached in anatomy. Prof. Dr. M. Eichhorn and Prof. Dr. F. Paulsen are included in teaching courses of MAOT and SAOT graduate schools and organize lectures and demonstration courses for interested students of the study course medical engineering.

Selected Publications

Garreis F, Gottschalt M, Schlorf T, Gläser R, Harder J, Worlitzsch D, Paulsen FP (2011) Expression and regulation of antimicrobial peptide psoriasin (S100A7) at the ocular surface and in the lacrimal apparatus. Invest Ophthalmol Vis Sci, 52: 4914-22

Bräuer L, Schicht M, Stengl C, Heinemann F, Götz W, Scholz M, Paulsen F (2012) Detection of surfactant proteins A, B, C, and D in human gingiva and saliva. Biomed Tech (Berl), 57: 59-64

Fuchs M, Scholz M, Sendelbeck A, Atorf J, Schlegel C, Enz R, Brandstätter JH (2012) Rod photoreceptor ribbon synapses in DBA/2J mice show progressive age-related structural changes. PLoS ONE, 7: e44645

Hampel U, Klonisch T, Sel S, Schulze U, Garreis F, Paulsen FP (2012) Relaxin 2 is functional at the ocular surface and promotes corneal wound healing. Invest Ophthalmol Vis Sci, 53: 7780-90

Tektaş OY, Paulsen F. (2012) Medizinstudium: Gegen die Prüfungsangst. Deutsches Ärzteblatt, 109: 29-30

Rausch F, Schicht M, Paulsen F, Ngueya I, Bräuer L, Brandt W (2012) "SP-G", a putative new surfactant protein--tissue localization and 3D structure. PLoS ONE, 7: e47789

International Cooperations

E. Cuerda, University, Madrid: Spain

M. Wilcox, University, Sydney: Australia

Y. Diebold, University, Valladolid: Spain

M. Berry, University, Bristol: UK

P. Kaufman, University, Madison: USA

D. Overby, University, London: UK

J. Danias, University, New York City: USA

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Research Focus

- Receptors and receptor associated diseases of the nervous system
- In vivo functions of glycine transporters
- Molecular heterogeneities and posttranslational modifications of proteins
- Structure and function of synaptic signaling complexes in the central nervous system

Structure of the Department

The Institute of Biochemistry comprises the Chair of Biochemistry and Molecular Medicine and the Chair of Biochemistry and Pathobiochemistry. In addition, the Professorship of Bioinformatics is integrated in the Institute. The Institute of Biochemistry constitutes the interdisciplinary Emil-Fischer-Center together with the Institute of Experimental and Clinical Pharmacology and Toxicology of the Faculty of Medicine and the Institute of Pharmaceutical Chemistry of the Science Faculty.
The Chair has a total of 30 employees (half of them funded by grants), including eight scientists, seven postgraduate students, and eight technicians.

Research

Receptors and receptor associated diseases of the nervous system

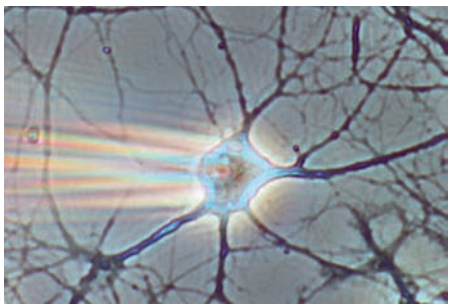
Project managers: Prof. Dr. C.-M. Becker, Dr. C.J. Kluck, Prof. Dr. C. Villmann, Dr. V. Eulenburg, Dr. N. Vogel
Glycine is the most important inhibitory neurotransmitter in the human spinal cord and brain stem. Upon binding of glycine to postsynaptic glycine receptors (GlyR), a member of the Cys-Loop receptor superfamily, an intrinsic chloride channel opens which is responsible for inhibition of the postsynaptic cell. Mutations within the human GlyR-genes are associated with neuromotor-disorders, such as hyperekplexia (startle disease, stiff baby syndrome), leading to enhanced startle reactions and episodic muscle stiffness. The GlyR is a pentameric ion channel comprising 2 α- and 3 β-subunits. Every subunit encloses a large extracellular ligand binding domain followed by four transmembrane domains connected by loops. The focus of our research is the investigation of the pathomechanisms of GlyR channelopathies. Human hyperekplexia is inherited either dominantly or recessively with incomplete penetrance. A newly characterized dominant mutation in the extracellular domain alters - due to its position in the ligandbinding domain - the binding of glycine, whereas most known recessive mutations in the ligandbinding domain lead to reduced surface expression. This can be attributed to endoplasmatic retention and accelerated proteasomal degradation of the glycin receptor. This altered biogenesis of glycine receptor variants leads eventually to impaired surface localization of the receptor.
Murine models carrying mutations within the GlyR display a similar phenotype as compared to humans (spastic, spasmodic, and oscillator). Here, our group has shown previously that the mutant mouse line spastic that is characterized by a strong reduction in glycine receptor expression carries an insertion of a retrotransposon called LINE element in the glycine receptor gene Glrb. Since the insertion is not within the coding region for the glycine receptor β subunit, we investigated an alternative mechanism that explains the reduction in expression. We could show that the insertion of the LINE alters the splicing of the Glrb mRNA and that this alteration is dependent on the genomic context.
In another project, sera from patients suffering from the non-heridiatry form of stiff-person-syndrome were analyzed for presence of anti-GlyR autoantibodies. The recognized epitopes are identified and mapped within the amino acid sequence of the receptor. In addition, in vitro experiments to elucidate the pathomechanism were performed.
In summary, by analysis of newly described mutations leading to amino acid changes in the glycine receptor α1 subunit, we could enhance our knowledge about critical loops and their roles in protein folding and assembly into functional pentamers. Furthermore, the dominant mutation points to the sensitivity of the ligand binding pocket for spatial changes in ligand binding. Also a complex altered splicing behavior as shown for the murine Glrb in the mouse model spastic can cause disease. Sera from patients suffering from a late onset form of hyperekplexia contain anitbodies against the glycine receptor.

In vivo functions of glycine transporters

Project manager: Dr. V. Eulenburg
Neurotransmission with high temporal and spatial resolution requires the rapid termination of synaptic transmission. At glycinergic synapses, this is achieved by rapid uptake of the presynaptically released glycine into the nerve terminal and the surrounding glial cells by high affinity transporters named GlyT1 and GlyT2. By complex genetical, biochemical, and behavioral approaches, we have shown that neuronal and glial expressed Glyt1 have different functions depending of the cell type expressing the transporter. We could show that inactivation of GlyT1 in glial cells results in severe hyotonic movement disorders, whereas the loss of neuronal GlyT1 results in disturbances in higher brain functions, like learning and memory. Interestingly, the precise functions of the respective GlyTs appear to change during development. Directly after birth the extracellular glycine concentration is exclusively controlled by GlyT1. At later developmental stages, however, GlyT2 contributes to the regulation of the extracellular transmitter concentration, too. These changes in function are accompanied by alterations in the expression levels of the respective transporters. In conclusion, our research has contributed to a better understanding of how glial and neuronal expressed transporters influence synaptic transmission.

Molecular heterogeneities and post-translational modifications of proteins

Project manager: Dr. W. Xiang
The identification of pathological molecular alterations is crucial for the development of improved diagnostic and therapeutic approaches of neurodegenerative diseases and many other neurological disorders. We develop mass spectrometry-based methods to determine molecular heterogeneities, focusing on pathology relevant genetic polymorphisms and mutations as well as alterations of lipid profiles. We also characterize posttranslational modifications (PTMs) of proteins using MALDI-TOF MS as well as LC-ESI-MS/MS: After separation of complex protein mixtures, peptide mass fingerprint data are compared to database entries. We gain further information about the site of modification by using LC-ESI-MS/MS.



Patch-clamp technique on hippocampal neurons

Oxidative stress is an important pathological modifier in the pathogenesis of many neurodegenerative disorders. Oxidative stress is characterized by elevated levels of free radicals which can induce increased PTMs of amino acid residues. To understand the molecular and cellular effects of oxidative stress regarding PTMs, we investigate oxidative stress-induced PTMs of α-Synuclein, the crucial protein in the pathogenesis of Parkinson's disease. Our studies show that oxidative PTMs can significantly alter the structural and functional characteristics of α-Synuclein. More importantly, several oxidative PTMs accelerate the accumulation of α-Synclein species which lead eventually to neuronal cell death.

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

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

The electric excitability of the central nervous system is regulated by a coordinated interplay of neurotransmitter receptors and ion channels with enzymes and scaffold proteins that assemble into macromolecular signal complexes at synapses. Malfunction may cause diseases, including epilepsy und autism. Thus, synaptic proteins represent interesting targets for therapeutic intervention.

To investigate molecular mechanisms of synaptic signal transduction, we analyze structure, expression, and function of synaptically localized macromolecular signal complexes that are associated with metabotropic glutamate receptors (mGluRs) and GABAc receptors (GABAcR). As mGluR binding partners, we identified the proteinphosphatase PP1, members of the SUMOylation cascade and band 4.1 proteins. Furthermore, we observed that GABAcR interact with PNUTS and ZIP proteins. We compared the expression of interacting proteins in the retina, mapped binding regions, and analyzed their 3D-structure. Based on these studies, we demonstrated expression of multimeric signal complexes, consisting of GABAcR, PNUTS/PP1, and ZIP3/PKC, or of mGluRs, PP1, and SUMO proteins. These protein complexes regulate intracellular signal cascades and subcellular targeting of neurotransmitter receptors.

The Fragile X Syndrome is an autism spectrum disorder which is caused by the loss of a single protein, the Fragile X Mental Retardation Protein FMRP. FMRP regulates excitation driven protein synthesis depending on mGluR signaling. For this purpose, FMRP may associate with approximately 4% of all mRNAs in the mammalian brain and thereby governs their transport and translation. We analyze the relevance of two novel proteins in this matter.

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 practicals of students of pharmacy. For students of molecular medicine, the Chair organizes the module of neuroscience.

Selected Publications

Dütting E, Schröder-Kress N, Sticht H, Enz R (2011) SUMO E3 ligases are expressed in the retina and regulate SUMOylation of the metabotropic glutamate receptor 8b. Biochem J, 435: 365-71

Urbanczyk A, Jünemann A, Enz R (2011) PKCβ-interacting protein ZIP3 is generated by intronic polyadenylation, and is expressed in the brain and retina of the rat. Biochem J, 433: 43-50

Becker K, Braune M, Benderska N, Buratti E, Baralle F, Villmann C, Stamm S, Eulenburg V, Becker CM (2012) A retroelement modifies pre-mRNA splicing: the murine Glrb(spa) allele is a splicing signal polymorphism amplified by long interspersed nuclear element insertion. J Biol Chem, 287: 31185-94

Guo D, Xiang W, Seebahn A, Becker CM, Strauss O (2012) Modulation of TTX-sensitive voltage-dependent Na^+ channels by β-bungarotoxin in rat cerebellar neurons. BMC Neurosci, 13: 36

Lall D, Armbruster A, Ruffert K, Betz H, Eulenburg V (2012) Transport activities and expression patterns of glycine transporters 1 and 2 in the developing murine brain stem and spinal cord. Biochem Biophys Res Commun, 423: 661-6

Unterer B, Becker CM, Villmann C (2012) The importance of TM3-4 loop subdomains for functional reconstitution of glycine receptors by independent domains. J Biol Chem, 287: 39205-15

International Cooperations

S. Lummis, Department of Biochemistry, University of Cambridge, Cambridge: UK

A. Vincent, Wetherall Institute, University of Oxford, Oxford: UK

E. Buratti und F. Baralle, International Center of Genetic Engineering and Biotechnology, University Triest, Triest: Italy

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

Research Equipment

Bruker Daltonik, Esquire 6000 ESI-IT MS

Bruker Daltonik, Autoflex 1 MALDI-TOF MS

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Research Focus

- Transcription factors as regulators of neural development
- SoxC Proteins
- SoxD Proteins
- SoxE Proteins
- Signal transduction processes at the forming neuromuscular synapse
- GCM proteins as switches in organ development
- β-thymosins, substrates of transglutaminases during blood coagulation, angiogenesis, wound healing, and apoptosis

Structure of the Department

The Chair of Biochemistry and Pathobiochemistry, the Chair of Biochemistry and Molecular Medicine, and the Professorship of Bioinformatics constitute the Institute of Biochemistry. They are furthermore part of the Emil-Fischer-Center which in addition harbors the Institute of Experimental and Clinical Pharmacology and Toxicology (Faculty of Medicine), the Chair of Medicinal Chemistry, and the Chair of Food Chemistry (both Faculty of Natural Sciences). The Chair of Biochemistry and Pathobiochemistry employs 36 scientists and technicians of whom 22 are funded by grant money.

Several groups study transcription and post-transcriptional processes as well as β-thymosins with regard to molecular mechanisms and physiological roles in development, disease, and regeneration of the nervous system and other organ systems. The technological spectrum is broad and ranges from biochemical and molecular methods to the generation and characterization of transgenic mice.

Research

Transcription factors as regulators of neural development

Several groups are interested in the characterization of transcriptional regulators that participate during development of the mammalian nervous system in determination and differentiation of neural stem cells to glia and neurons. Work is mainly focused on transcription factors 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.

SoxC Proteins

Project manager: PD Dr. E. Sock

All SoxC proteins occur according to our own data 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 of the strong expression of all three SoxC proteins in the developing nervous system, neural defects become visible only upon combined deletion of more than one SoxC protein. Nervous system defects are predominantly caused by changes in proliferation and apoptosis. Overexpression studies in the mouse have, however, also pointed to an influence of SoxC proteins on neural maturation.

SoxD Proteins

Project manager: Prof. Dr. C. Stolt

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

SoxE Proteins

Project manager: Prof. Dr. M. Wegner

Transgenic mouse models have shown that the three closely related group E Sox proteins, Sox8, Sox9, and Sox10, have numerous functions during nervous system development. Sox9 and Sox10 are essential for survival and pluripotency of neural crest stem cells, the source for most cells of the peripheral nervous system. Sox9 and Sox10 furthermore determine which derivatives develop from neural crest stem cells. In Sox10-deficient mice, glial cells are missing from the peripheral nervous system. The enteric nervous system is completely absent.

In the central nervous system, Sox9 and Sox10 regulate several steps in gliogenesis. Sox9 is responsible for the specification of neural stem cells into oligodendrocytes, whereas Sox10 guides terminal differentiation and myelination in oligodendrocytes as a direct activator of myelin genes. During the period between specification and terminal differentiation, oligodendrocyte development is jointly regulated by Sox9 and Sox10. Functional support comes from the related Sox8 which is co-expressed at lower levels. Their mode of action includes recruitment of the basal transcription machinery in a mediator-dependent manner as well as interactions with chromatin-remodeling complexes.

Functions of group E Sox proteins were not only obvious in transgenic mouse models, but are equally reflected in human disease. Heterozygous haploinsufficient Sox10 mutations lead to Waardenburg-Hirschsprung disease, whereas dominant-negative heterozygous mutations present as a combination of Waardenburg-Hirschsprung disease, peripheral neuropathy, and central leukodystrophy.

Signal transduction processes at the forming neuromuscular synapse

Project manager: Prof. Dr. S. Hashemolhosseini

Muscle-specific MuSK and Lrp4 act as the main switches for synaptogenesis at the postsynaptic apparatus of the neuromuscular junction. Own work identified, among more than ten candidates, Erbin and CK2 as binding partners of MuSK. Protein kinase CK2 furthermore bound MuSK via its β subunit, phosphorylates MuSK and thereby regulates the stability of acetylcholine (AChR) clusters. Muscle-specific CK2β-deficient mice are myasthenic. To identify the cause for the destabilization of AChR aggregates in CK2β-deficient muscles, their phenotype is compared with the one of CK2α/CK2α′-deficient muscles. Behavioral tests and electrophysiological studies are performed and changes of transcriptome and phosphopro-

teome are determined in muscle cells deficient for CK2 subunits. For the first time, the molecular function of CK2 subunits at the postsynapse can be determined and the contribution of CK2-dependent signal transduction to human myasthenia and myopathy can be understood.

GCM proteins as switches in organ development

Project manager: Prof. Dr. S. Hashemolhosseini
Mammals contain GCMa and GCMb as members of the GCM family of transcription factors. GCMa is selectively expressed in placenta, kidney, and thymus, whereas GCMb occurs exclusively in the parathyroid gland. All GCM proteins regulate differentiation as transcriptional switches. Altered GCMa expression has been associated with pre-eclampsia and intra-uterine growth retardation, GCMb malfunctions with hypoparathyroidism and tumors of thyroid and parathyroid glands. Current work focuses on the role of GCMa in kidney and thymus of the adult organism, particularly under pathological conditions.

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

Project manager: Prof. Dr. E. Hannappel
Thymosins were originally isolated from thymus, but do not represent thymic hormones. Thymosin β-4 is now regarded as the main intracellular G-actin sequestering peptide in most mammalian cells. Domains of thymosin β-4 were identified which are important for the interaction with G- and F-actin. Apart from this intracellular function of thymosin β-4, this peptide seems to be a player in wound healing and inflammation. β-thymosins are substrates of transglutaminases. Glutaminyl residues of β-thymosins can be cross-linked to amino groups of other molecules. Surprisingly, these derivatives are still able to sequester G-actin. Blood platelets contain a high concentration of thymosin β-4. During aggregation of blood platelets, thymosin β-4 is cross-linked by factor XIIIa to the fibrin clot. This research thus also provides insight into how small, soluble peptides can be fixed to extracellular structures by transglutaminases to promote further physiological effects.
β-Thymosins can be labeled by fluorescent derivatives of cadaverine. The fluorescent β-thymosins are comparable to the natural β-thymosins with respect to their G-actin sequestering ability. Therefore, these fluorescent peptides are novel tools to study the interaction of β-thymosins with other proteins as well as their intracellular distribution in living cells. Surprisingly, thymosin β-4 is actively transported and enriched in the nucleus. The signal sequence responsible for the translocation into the nucleus resides in the N-terminal part of the peptide. Because of the size (5000 da), thymosin β-4 was expected to freely diffuse through the nuclear pore complex into the nucleus. However, when thymosin β-4 is added to permeabilized cells, it is evenly distributed within cytoplasm, but excluded from the nucleus. Present studies aim at the mechanisms for the asymmetric distribution of thymosin β-4 in cells and its impact on apoptosis and cancerogenesis.

Teaching

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

Selected Publications

Küspert M, Hammer A, Bösl MR, Wegner M (2011) Olig2 regulates Sox10 expression in oligodendrocyte precursors through an evolutionary conserved distal enhancer. Nucleic Acids Res, 39: 1280-93

Küspert M, Weider M, Müller J, Hermans-Borgmeyer I, Meijer D, Wegner M (2012) Desert hedgehog links transcription factor Sox10 to perineurial development. J Neurosci, 32: 5472-80

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Weider M, Küspert M, Bischof M, Vogl MR, Hornig J, Loy K, Kosian T, Müller J, Hillgärtner S, Tamm ER, Metzger D, Wegner M (2012) Chromatin-remodeling factor Brg1 is required for Schwann cell differentiation and myelination. Dev Cell, 23: 193-201

Wegner M (2013) Mighty bugs: leprosy bacteria turn schwann cells into stem cells. Cell, 152: 15-6

International Cooperations

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

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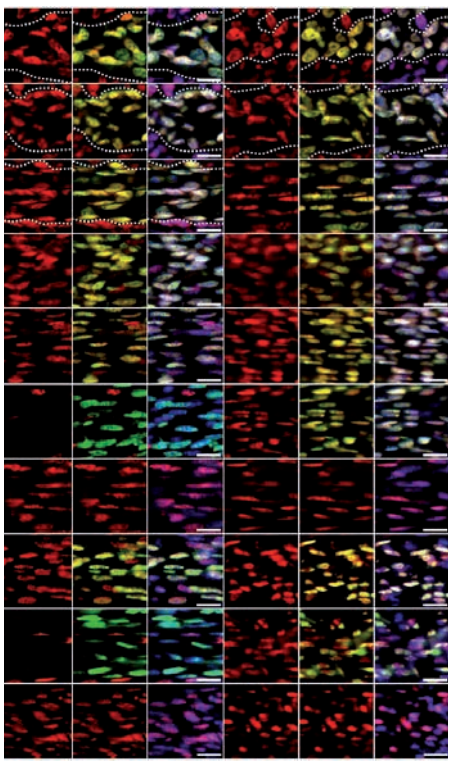
Dr. R. Hill, MRC Human Genetics Unit, Edinburgh Western General Hospital, Edinburgh: Scotland



Shown is an immunohistochemical staining of peripheral nerves at different developmental timepoints (getting older from top to bottom). Nerve boundaries are marked by white stippled lines. Nearly all cell nuclei (blue) in the nerves are positive for Sox10 (green). The presence of different proteins (red) was analyzed in diverse mouse lines.

Institute of Biochemistry - Emil-Fischer-Center

Professorship of Bioinformatics

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Research Focus

- Bioinformatics of biomolecular interactions
- Host-pathogen interactions: Computational analysis of linear interaction motifs and globular protein interfaces in effector proteins
- Design of novel Alzheimer drugs via computer simulations of protein aggregation
- Application of methods from information theory in protein-protein docking analysis
- Molecular mechanisms of drug resistance of HIV-1 protease

Structure of the Department

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

Research

Bioinformatics of biomolecular interactions

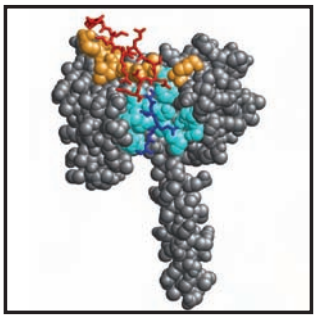
Protein-protein interactions play a crucial role for the transduction of information in biological signaling pathways. The identification of the underlying principles of molecular recognition is important for the understanding of regulatory mechanisms and for the prediction of novel, physiologically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

Host-pathogen interactions: Computational analysis of linear interaction motifs and globular protein interfaces in effector proteins

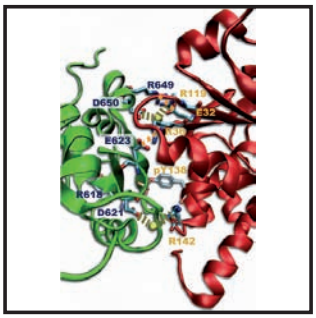
Specific interactions with host proteins are pivotal for a successful infection by a pathogen. This project focuses on the prediction and structural characterization of host-pathogen protein interactions using computational tools. The recognition processes either occur between short sequence motifs that bind complementary adapter modules or between pairs of globular protein domains. These types of interactions do not only differ from a structural point of view, but also with respect to the computational tools required for their prediction and analysis.
One particular problem for the prediction of functional interaction motifs is the short length of the respective sequence patterns resulting in a large number of false-positive hits which prove to be non-functional in subsequent experiments. Therefore, we aim at improving the specificity of the predictions by assessing the importance of motif-specific flanking sequence regions. In order to further increase the reliability of the predictions, modeling of sequence motifs in complex with the respective adapter domains is performed, thus allowing for judging the likelihood of an interaction based on a three-dimensional structure.
For the analysis of host-pathogen interactions formed between globular proteins 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.

Design of novel Alzheimer drugs via computer simulations of protein aggregation

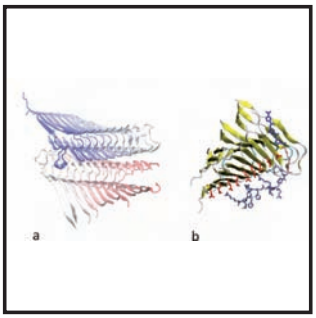
Protein conformational diseases are unique since a change in the three-dimensional structure of a protein leads to a biological loss and/or gain of function. Most often, a stable change in conformation involves a structural conversion from primarily α-helical conformation with good solubility to an insoluble β-sheet conformation. Cells have evolved mechanisms to clear these insoluble deposits; however, once clearance pathways are overloaded, these proteins are deposited in the form of insoluble intracellular inclusions or extracellular plaques. Protein deposits or aggregates are also hallmark of many neurodegenerative diseases. The most prevalent neurodegenerative disease is Alzheimer's disease which is characterized by extracellular protein deposition of the peptide fragment aβ from the amyloid precursor protein (APP), and intracellular tau-containing filaments, called neurofibrillary tangles.
The 3D structure of the Alzheimer's amyloid-β (1-42) deposits revealed the overall topology of the fibrils, but gives only limited information about the role of individual residues for fibril formation. The latter type of information, however, is important for the development of novel drugs that are capable of preventing aggregation or of solubilizing aggregates by targeting those residues that represent the "hot spots" of binding affinity in the fibrillar structure. We address this point by molecular dynamics simulations of fibrillar aβ42 oligomers and thermodynamic analyses of the aggregation interfaces. In addition, we investigate the effect of different solvent environments on the conformational stability of such aβ42 oligomers.
Another aspect of the project focuses on the molecular modeling of Abeta in complex with different ligands. These ligands which are experimentally characterized by our collaboration partners were shown to block aβ aggregation by binding to small aβ oligomers. Computational tools were employed to identify the



Model of the Tio protein from Herpesvirus ateles (stick presentation) in complex with human TRAF3 (space-filled presentation).



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



Molecular dynamics simulations of fibrillar Amyloid-β-oligomers. a) double stack of 2x12 aβ-molecules (colored in shades of blue and red) after 50 ns of simulation. B) Hybrid compound JM169 bound to a nonameric aβ-oligomer.

Structure of HIV-protease bound to the inhibitor Amprenavir (shown as sticks)

binding site of these known ligands and also for the design of novel, more affine ligands.

Application of methods from information theory in protein-protein docking analysis

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

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

Molecular mechanisms of drug resistance of HIV-1 protease

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

Teaching

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

Selected Publications

Hochdörffer K, März-Berberich J, Nagel-Steger L, Epple M, Meyer-Zaika W, Horn AH, Sticht H, Sinha S, Bitan G, Schrader T (2011) Rational design of β-sheet ligands against Aβ42-induced toxicity. J Am Chem Soc, 133: 4348-58

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Othersen OG, Stefani AG, Huber JB, Sticht H (2012) Application of information theory to feature selection in protein docking. J Mol Model (Online), 18: 1285-97

Rücker P, Wieninger SA, Ullmann GM, Sticht H (2012) pH-dependent molecular dynamics of vesicular stomatitis virus glycoprotein G. Proteins, 80: 2601-13

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Research Focus
- Renal epithelial ion channels
- Cardiac ion channels

Structure of the Department

The Institute of Cellular and Molecular Physiology (Chair of Physiology (Vegetative Physiology)) is housed in a teaching and research building located centrally in Erlangen. In addition to modern research laboratories, the building offers a lecture hall with a capacity for 200 students as well as seminar rooms for small group teaching and practical classes. The Institute makes a substantial contribution to the physiology teaching of preclinical medical and dental students and is also involved in the molecular medicine course. The renal physiology research group in the Institute is headed by the head of the Institute, Prof. Dr. C. Korbmacher, the additional cardiac physiology research group is headed by an associate professor, Prof. Dr. T. Volk.

The research focus of the Institute is the study of renal and cardiac ion channels. This research area is of pathophysiological relevance since an inappropriate regulation of renal and cardiac ion channels may cause arterial hypertension or cardiac arrhythmias, respectively.

The analysis of ion channels involves studies at the level of the cell membrane, but also includes aspects of cellular physiology, such as protein trafficking, endocytosis/exocytosis, protein-protein interactions between transport and regulatory proteins as well as interactions with elements of the cytoskeleton. The experimental investigation of these complex topics requires a range of sophisticated electrophysiological, cellular, molecular, and biological methods. In addition to cellular model systems (cell culture, heterologous expression systems), transgenic and knock-out mice are used to study the function and regulation of ion transport processes in native tissues and in the whole animal. This integrated approach provides fascinating opportunities to gain novel insights into physiological and pathophysiological mechanisms and may lead to a better understanding of disease processes.

Research

Renal epithelial ion channels

Project manager: Prof. Dr. C. Korbmacher

In the kidney and other epithelial tissues, ion channels are involved in the highly selective and regulated control of ion fluxes across apical and basolateral membranes of epithelial cells. These ion channels are important for intracellular ion homeostasis and transepithelial electrolyte transport. The delicate regulation of these ion channels is pivotal for the maintenance of a healthy 'milieu interieur' as evidenced by severe disease states that result from abnormal ion channel function. Indeed, the study of molecular mechanisms involved in epithelial ion channel regulation is likely to be relevant to understand a range of diseases (e.g. cystic fibrosis, kidney stones, high arterial blood pressure, and salt wasting syndromes).

Acute and chronic diseases of the kidney are often associated with high blood pressure. Moreover, the kidney is thought to play a critical role in the pathogenesis of essential hypertension, a condition affecting about 50% of the population over the age of 50. There is emerging evidence that subtle damage to the kidney may compromise renal salt excretion causing salt retention which may lead to arterial hypertension. In particular, sodium transport processes in the distal nephron and collecting duct appear to be important for the long term control of blood pressure. Therefore, it is important to understand the molecular mechanisms involved in the regulation of these transport processes.

In this context, the group investigates the complex mechanisms involved in the regulation of the epithelial sodium channel (ENaC). Ion flux through ENaC is the rate limiting step for sodium absorption in the aldosterone sensitive distal nephron. The appropriate regulation of ENaC activity is critical for the maintenance of body sodium balance and hence for the long term control of arterial blood pressure. This is evidenced by 'gain of function' mutations of ENaC which cause a hereditary form of severe salt-sensitive arterial hypertension (Liddle's syndrome).

The molecular mechanisms involved in ENaC regulation are still incompletely understood and involve a complex network of regulatory proteins, kinases, and proteases. Proteolytic activation of ENaC may be pathophysiologically relevant in the context of inflammatory kidney disease and may contribute to sodium retention in nephrotic syndrome. The group uses a combination of electrophysiological and molecular biological techniques to characterize the functional interaction of ENaC with regulatory proteins and to identify channel regions that are relevant for ENaC regulation by kinases and proteases. Moreover, it investigates the role of lipid microdomains ('lipid rafts') in the plasma membrane for ENaC function and its association with regulatory proteins.

A better understanding of the molecular mechanisms involved in ENaC regulation will hopefully provide novel insights into the physiology and pathophysiology of arterial hypertension. This ultimately may lead to new diagnostic and therapeutic concepts.

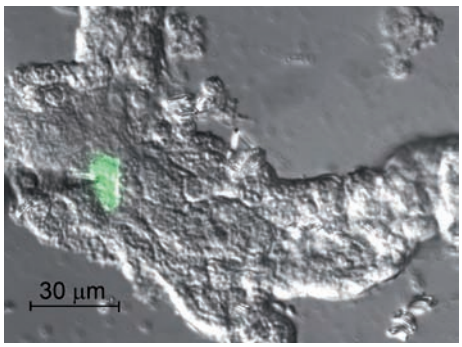
Cardiac ion channels

Project manager: Prof. Dr. T. Volk

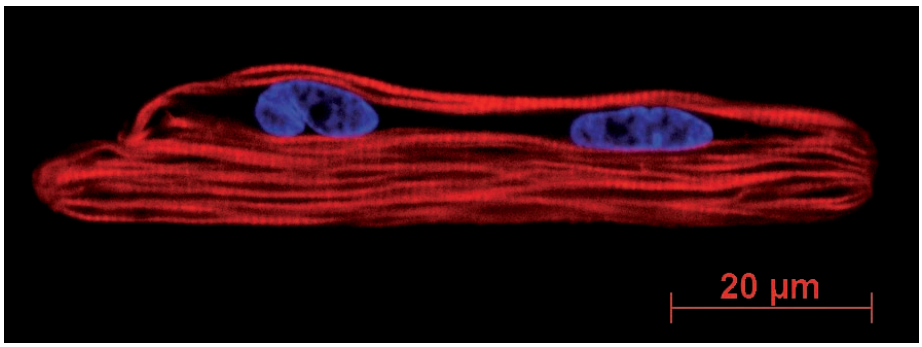
The key interest of this group is to identify cellular and molecular mechanisms that regulate the function and expression of cardiac ion channels and thereby lead to differences in action potential duration (APD) and contractility in the heart.

It is well established that regional differences in APD in different areas of the heart are of great importance for a normal course of repolarization. Within the left ventricular free wall, for example, APD is much longer in endocardial than in epicardial myocytes with the consequence that endocardial myocytes repolarize last, although they become depolarized first. Hence, the wave of excitation travels from endocardial to epicardial regions, while the wave of repolarization travels in the opposite direction.

Under pathological conditions, such as cardiac hypertrophy or failure, this well-organized sequence of events is altered which is thought to contribute to the increased risk of cardiac arrhythmia and sudden cardiac death of patients with cardiac hypertrophy or failure. An increasing body of evidence supports the observation that cardiac hypertrophy or failure leads to an increase in APD primarily in epicardial regions, whereas midmyocardial or endocardial regions are less affected.



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



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

In order to understand the mechanisms underlying this region-specific effect of cardiac hypertrophy, this group investigates the consequences of cardiac hypertrophy in animal models. Using the patch-clamp technique on isolated myocytes from different regions of the left ventricular free wall of rats with ascending aortic stenosis, a decrease in the transient outward potassium current (I_{to}) was identified as the primary cause underlying the increase in APD in epicardial regions. The specific importance of I_{to} for an altered organization of repolarization in cardiac hypertrophy is underlined by the observation that other ionic currents, such as the L-type Ca^{2+} current, are largely unaffected by hypertrophy.

Apart from affecting the regional organization of repolarization, alterations in the magnitude of Ito indirectly influence the intracellular Ca^{2+} homeostasis of ventricular myocytes. A reduction of I_{to} leads to an increase in transmembrane Ca^{2+} influx, a phenomenon which can also be observed as a result of a reduction of Ito in cardiac hypertrophy, thereby suggesting a mechanism by which cellular contractility is increased.

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

Teaching

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

Selected Publications

Stewart AP, Haerteis S, Diakov A, Korbmacher C, Edwardson JM (2011) Atomic force microscopy reveals the architecture of the epithelial sodium channel (ENaC). J Biol Chem, 286: 31944-52

Wagner M, Moritz A, Volk T (2011) Interaction of gonadal steroids and the glucocorticoid corticosterone in the regulation of the L-type Ca^{2+} current in rat left ventricular cardiomyocytes. Acta Physiol (Oxf), 202: 629-40

Foltz WU, Wagner M, Rudakova E, Volk T (2012) N-acetylcysteine prevents electrical remodeling and attenuates cellular hypertrophy in epicardial myocytes of rats with ascending aortic stenosis. Basic Res Cardiol, 107: 290

Haerteis S, Krappitz M, Diakov A, Krappitz A, Rauh R, Korbmacher C (2012) Plasmin and chymotrypsin have distinct preferences for channel activating cleavage sites in the γ subunit of the human epithelial sodium channel. J Gen Physiol, 140: 375-89

Krueger B, Schlötzer-Schrehardt U, Haerteis S, Zenkel M, Chankiewitz VE, Amann KU, Kruse FE, Korbmacher C (2012) Four subunits (αβγδ) of the epithelial sodium channel (ENaC) are expressed in the human eye in various locations. Invest Ophthalmol Vis Sci, 53: 596-604

Nesterov V, Dahlmann A, Krueger B, Bertog M, Loffing J, Korbmacher C (2012) Aldosterone-dependent and -independent regulation of the epithelial sodium channel (ENaC) in mouse distal nephron. Am J Physiol Renal Physiol, 303: F1289-99

International Cooperations

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

Prof. L.G. Dobbs, MD, University of California (UCSF), San Francisco: USA

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

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

Prof. J. Teulon, Université Pierre et Marie Curie, Paris: France

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

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

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

Prof. J.-J. Cassiman & Prof. H. Cuppens, Katholieke Universiteit Leuven, Leuven: Belgium

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Research Focus

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

Structure of the Department

The Institute comprises one chair and two professorships of physiology with their work groups and two further groups led by an academic director and a professor emeritus. In addition, the Institute houses collaborating work groups from the Departments of Medicine I and IV, Anesthesiology, and Neurology of the UK Erlangen. In the context of long-standing scientific collaborations, the Institute regularly welcomes guest scientists from the USA, Japan, Czech Republic, Hungary, and Romania who often stay for extended research periods.
A total of 80 persons works at the Institute, 20 of them are funded by grants. The research is conducted by 17 PhD/MD scientists, 35 doctoral students, and 19 technical assistants.
The Institute has successfully integrated new work groups who study synapses and ion channels of central nervous system neurons using electrophysiological and cell biological methods, thereby bringing new biophysical and molecular biological expertise to the Institute. Many common interests and technical synergies arise from the established groups who focus on pain physiology and predominantly work on primary and secondary sensory neurons. The overall research spectrum ranges from cellular and molecular biological topics and the microphysiology of neuronal networks to behavioral physiology and human studies, with the latter including microneurography, functional imaging, and psychophysics in healthy volunteers and chronic pain patients.

Research

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

Project manager: Prof. Dr. C. Alzheimer
Our research focuses on the electric behavior of CNS neurons under normal and pathological conditions. Using high resolution neurophysiologic techniques, we investigate function and regulation of ion channels and synapses. Our aim is to understand fundamental neural processes which are essential for cognitive and motor functions as well as for affective behavior and whose dysfunctions might give rise to neuropsychiatric disorders. In particular, we are studying the following topics:
1) Role of activin, a member of the Transforming Growth Factor β family, as a "master molecule" tuning glutamatergic and GABAergic neurotransmission, and its impact on cognition, emotions, and neuroprotection;
2) Interaction between BACE1, a crucial enzyme in the amyloid cascade of Alzheimer's disease, and properties and expression of Na^+ and K^+ channels;
3) Role of microtubule-associated tau protein in synaptic function;
4) Neurophysiologic mechanisms of deep brain stimulation in Parkinson's disease.

Transduction, integration, plasticity in primary nociceptive neurons

Project manager: Prof. Dr. P.W. Reeh
The research focuses on primary nociceptive neurons, their electrophysiological and neurochemical responses to noxious and pruritogenic stimuli and chemical mediators. Isolated preparations and cultured dorsal root ganglion cells as well as transfected cell lines are used to study action potential discharge, ionic currents, calcium transients, and release of the neuropeptides substance P and calcitonin gene-related peptide. Aim is to elucidate nociceptive transduction and integration of stimuli as well as possible pharmacological interventions. Specific topics are sensitization by tissue acidosis, inflammatory mediators, and gasotransmitters as well as their intracellular signal transduction. Transgenic mouse strains lacking different metabotropic and ionotropic receptors or thermally activated ion channels (e.g. TRPV1) are studied. Voltage-controlled ion channels (Na_V, HCN) came in focus, because only few subtypes decide on excitability, i.e. on generation, frequency, and propagation of action potentials to the central nervous system. Neuroimmunology is a rapidly growing field that, for example, studies the interaction of substance P with the immune system which may essentially contribute to chronic inflammatory, including autoimmune diseases.

Trigeminal nociception and headache generation

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

Properties of peripheral human C-fibers

Project manager: PD Dr. B. Namer
Morphological and electrical properties of peripheral unmyelinated neurons (C-fibers) are studied directly in healthy subjects and patients with painful and painless neuropathies. The focus lies on nociceptors and mechanisms which contribute to genesis of pain, in particular spontaneous neuropathic pain. The methods to examine C-fibers in awake humans include

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

Functional imaging of brain activity by fMRI

Project manager: Prof. Dr. C. Forster

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

Teaching

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

The Institute participates with lectures, seminars, and practical courses in the bachelor and master program "molecular medicine".

In addition, interdisciplinary lectures are given to students of natural and technical sciences, to pharmacists, and to students of psychology who select medicine as a subsidiary subject or a main focus. For them, not only neurophysiology, but all topics of physiology are covered.

Selected Publications

Sydow A, Van der Jeugd A, Zheng F, Ahmed T, Balschun D, Petrova O, Drexler D, Zhou L, Rune G, Mandelkow E, D'Hooge R, Alzheimer C, Mandelkow EM (2011) Tau-induced defects in synaptic plasticity, learning, and memory are reversible in transgenic mice after switching off the toxic Tau mutant. J Neurosci, 31: 2511-25

Zheng F, Lammert K, Nixdorf-Bergweiler BE, Steigerwald F, Volkmann J, Alzheimer C (2011) Axonal failure during high frequency stimulation of rat subthalamic nucleus. J Physiol, 589: 2781-93

Bierhaus A, Fleming T, Stoyanov S, Leffler A, Babes A, Neacsu C, Sauer SK, Eberhardt M, Schnölzer M, Lasitschka F, Lasischka F, Neuhuber WL, Kichko TI, Konrade I, Elvert R, Mier W, Pirags V, Lukic IK, Morcos M, Dehmer T, Rabbani N, Thornalley PJ, Edelstein D, Nau C, Forbes J, Humpert PM, Schwaninger M, Ziegler D, Stern DM, Cooper ME, Haberkorn U, Brownlee M, Reeh PW, Nawroth PP (2012) Methylglyoxal modification of Nav1.8 facilitates nociceptive neuron firing and causes hyperalgesia in diabetic neuropathy. Nat Med, 18: 926-33

De Col R, Messlinger K, Carr RW (2012) Repetitive activity slows axonal conduction velocity and concomitantly increases mechanical activation threshold in single axons of the rat cranial dura. J Physiol, 590: 725-36

Kankel J, Obreja O, Kleggetveit IP, Schmidt R, Jørum E, Schmelz M, Namer B (2012) Differential effects of low dose lidocaine on C-fiber classes in humans. J Pain, 13: 1232-41

Vetter I, Touska F, Hess A, Hinsbey R, Sattler S, Lampert A, Sergejeva M, Sharov A, Collins LS, Eberhardt M, Engel M, Cabot PJ, Wood JN, Vlachová V, Reeh PW, Lewis RJ, Zimmermann K (2012) Ciguatoxins activate specific cold pain pathways to elicit burning pain from cooling. EMBO J, 31: 3795-808

International Cooperations

Dr. I. Vetter, Institute of Molecular Bioscience, St. Lucia: Australia

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

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

Prof. Dr. P. McNaughton, University of Cambridge, Cambridge: UK

Prof. Dr. K. Mizumura, College of Life and Health Sciences, Chubu University Kasugai, Kasugai: Japan

Prof. Dr. E. Jørum, Department of Clinical Neurophysiology, University of Oslo, Oslo: Norway

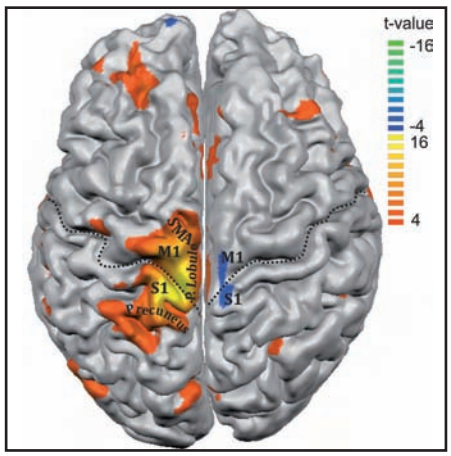
Prof. Dr. A. Babes, University of Bucharest, Bucharest: Romania

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

Prof. Dr. V. Vlachova, Department of Cellular Neurophysiology, Academy of Sciences, Prague: Czech Republic

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

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



Cortical activation pattern induced by delayed onset muscle soreness (DOMS). Dotted line: central sulcus, M1/S1 primary motor/sensory cortex, SMA supplementary motor area, P. Lobule somatosensory association cortex. Red-yellow: higher changes in BOLD-signal during DOMS-related painful contraction; blue-green clusters: higher changes in BOLD-signal during non-painful contraction of the left quadriceps group. Strongest and widespread DOMS pain-related activation was located in the primary motor and sensory cortex in areas somatotopically related to the thigh (from: Zimmermann K et al (2012). PLoS ONE 7 (10):e47230)

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

Chair of Occupational and Social Medicine

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Research Focus

- Work related health research
- Population related health studies
- Dermatoxicology
- Molecular markers of exposure to hazardous substances
- Psychomental occupational medicine
- Quality assurance of biomonitoring methods
- Quality assurance of health promoting actions

Structure of the Department

The Institute and Outpatient Clinic of Occupational, Social, and Environmental Medicine belongs to the clinical theoretical institutes of the FAU.
The Institute has 45 employees (21 of them are financed by third-party funds). Research is carried out by twelve PhD scientist, five PhD students, and eleven technical assistants.
Different work groups develop molecular markers of exposure to hazardous substances as well as procedures to quantify skin penetration of hazardous substances. They also standardize diagnostical premedical findings. Furthermore, the Institute examines work-related exposure of employees and the exposure of the general population within the framework of population studies.
The department of the medical officers for the FAU is located at the Institute. Its doctors carry out the preventive medical checkups of all the university's employees and students. They also advice the heads of FAU and UK Erlangen in terms of occupational health protection and offer measures for health promotion.
The Institute directs the work groups „Biological limit values" and „Analysis in biological materials" of the Commission of the Investigation of Health Hazards of Chemical Compounds in the Work Area of the DFG and houses the scientific offices of these work groups.
Next to this, the Institute is in charge of the German External Quality Assessment Scheme (G-EQUAS) which has been carried out since 1982 on behalf of the German Association for Occupational and Environmental Medicine (DGAUM).
The laboratories of the Institute serve as reference laboratories for G-EQUAS and other quality assessment schemes worldwide.

Research

Work related health research
Manifest diseases, resulting from chronic exposure at work, often cause substantial social-medical problems. Therefore, the Institute carries out field studies at the work place which aim at detecting physiological and pathophysiological changes long before manifest diseases appear. Questions always arise when new technologies or working materials are introduced. For example new welding techniques used in the aluminum processing industry or the replacement of classical solvents by alternative solvents are named here. Furthermore allergically mediated diseases at the workplace are still a problem although hygienic conditions have been clearly improved. Therefore, an important focus for the Institute is on the assessment of exposure and on the effect of toxic, mutagenous, and sensitizing working materials. Many qualified field studies determine cutaneous absorption by carefully considering the data of ambient monitoring (air pollution and dermal exposure) and biomonitoring with regard to the workplace conditions. These studies are often carried by the Gesetzliche Unfallversicherungsträger (German Social Insurance) or the German Ministry of Labor and Social Affairs.

Population related health studies
Environmental medicine relates to occupational medical questions by critically proving exposure and its possible effects. The Institute in particular has to offer fast and adequate help if the public is postulated with high exposure to chemical agents, like PCB in schools, phthalates in pharmaceuticals/toys, or aromatic amines in clothes. These studies are often carried by the local authorities, the Bavarian State Ministry of the Environment and Public Health and the German Federal Environment Agency.

Dermatoxicology
At the Institute different research projects deal with procedures to determine dermal penetration of chemicals and standardize preclinial skin damages.
All the scientific projects focussing on skin penetration examine influence factors of dermal penetration by using in vitro models (static diffusion chamber, microdialysis on freshly excidized human skin) and in vivo models (microdialysis of volunteers). These projects are supported by the DFG and the German employer's liability insurance association. Furthermore one work group of the Institute deals with the evaluation of skin penetration for the establishment of occupational medical threshold values for the Commission of Investigation of Health Hazards of Chemical Compounds in the Work Area of the DFG. The ad hoc group "skin absorption" has developed a systematic approach for labeling hazardous substances which is highly recognized on an international level. This work group also labels chemical substances with a skin designation in Germany.
Additionally, procedures to early diagnose preclinical skin damages and irritations, like the Erlanger Skin-Score, are developed and validated.

Molecular markers of exposure to hazardous substances
This research area develops and validates procedures for the quantitative assessment of molecular markers of individual exposure to hazardous substances (exposure monitoring), for the disposition for hazardous substances in the metabolism (susceptibility monitoring), and the effects of hazardous substances (biological effect monitoring). A special focus is 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 single biomarkers is examined in studies which give information about the specificy, sensitivity, and toxicokinetic behavior of the different parameters.
An important pre-requisite for sensitive and specific biomonitoring is the use of very sensitive and molecular-structural distinguishing analyzing techniques. The Institute therefore possesses excellent technical equipment which is modernized on a regular basis. Gas chroma-

tographic techniques as well as high performance liquid chromatographic systems which are particularly connected to one-dimensional and multiple-dimensional mass spectrometry (GC-MS/MS and LC-MS/MS) and to modern analytical techniques for the determination of metals in body fluids (GF-AAS und ICP/MS) belong to the equipment.

Psychomental occupational medicine

This work group deals with evidence-based examinations of interventions after psychic traumatization caused by extreme situations at work. This concerns not only combat mission forces and disaster relief forces, but also employees of the police, bank, retail, healthcare, and public transport sector. Important and necessary components of preventive concepts are the immediate and fast acute care of those affected in order to cope with psychic traumatization and to prevent manifest diseases.
A recent research project of the Institute investigates how far these concepts are scientifically evident by examining the psycho-social acute care of employees from the public transport sector after accidents, suicides, and attacks.

Quality assurance of biomonitoring methods

On behalf of the German Association for Occupational and Environmental Medicine, the Institute currently organizes the most comprehensive external quality assessment scheme worldwide for the evaluation of occupational and environmental biomarkers. The 50th round robin test of G-EQUAS was finished within the report period. At the moment G-EQUAS comprises 151 analysis parameters; 150 to 200 laboratories worldwide (2/3 international) take part in G-EQUAS every six months.

Quality assurance of health promoting actions

Within the framework of company health management, companies often offer and implement measures which support the health resources and wellbeing of the employees. The Institute develops concepts to examine the effectivity and sustainability of health promotion in companies and uses them in practice. The evaluation concepts are developed and implemented for individual companies or networks like "Erlanger model of workplace health promotion" or "Medical Valley" (program for the region of Nürnberg-Fürth). 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 in general.

Teaching

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

Selected Publications

Eckert E, Schmid K, Schaller B, Hiddemann-Koca K, Drexler H, Göen T (2011) Mercapturic acids as metabolites of alkylating substances in urine samples of German inhabitants. Int J Hyg Environ Health, 214: 196-204

Göen T, Dobler L, Koschorreck J, Müller J, Wiesmüller GA, Drexler H, Kolossa-Gehring M (2011) Trends of the internal phthalate exposure of young adults in Germany--follow-up of a retrospective human biomonitoring study. Int J Hyg Environ Health, 215: 36-45

Weistenhöfer W, Baumeister T, Drexler H, Kütting B (2011) How to quantify skin impairment in primary and secondary prevention? HEROS: a proposal of a hand eczema score for occupational screenings. Br J Dermatol, 164: 807-13

Göen T, Schaller KH, Drexler H (2012) External quality assessment of human biomonitoring in the range of environmental exposure levels. Int J Hyg Environ Health, 215: 229-32

Korinth G, Schaller KH, Bader M, Bartsch R, Göen T, Rossbach B, Drexler H (2012) Comparison of experimentally determined and mathematically predicted percutaneous penetration rates of chemicals. Arch Toxicol, 86: 423-30

Korinth G, Wellner T, Schaller KH, Drexler H (2012) Potential of the octanol-water partition coefficient (logP) to predict the dermal penetration behaviour of amphiphilic compounds in aqueous solutions. Toxicol Lett, 215: 49-53

International Cooperations

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

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

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

P. J. Parsons, PhD, Department of Health (DOH), State of New York, Albany: USA

Research Equipment

Sciex API 2000, LC-MS/MS-System

Agilent, GC-MS/MS System 7000

Agilent, ICP-MS System 7500 cx

Psycho-social acute care of an employee from the public transport sector (© VBG)

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Research Focus
- Mechanisms of cardiac pacemaking
- Ventricular hypertrophy
- HCN channels and pain
- Pharmacological imaging and image analysis

Structure of the Department

The Chair of Pharmacology and Toxicology, the Chair of Clinical Pharmacology and Clinical Toxicology, and the Doerenkamp-Chair for Innovations in Animal and Consumer Protection together form the Institute of Experimental and Clinical Pharmacology and Toxicology.
The position of executive director of the Institute rotates between the Chair of Pharmacology and Toxicology (Prof. Dr. A. Ludwig) and the Chair of Clinical Pharmacology and Clinical Toxicology (Prof. Dr. M.F. Fromm) on a two-year basis.
The Chair has a staff of 27 employees. Research work is carried out by six PhD graduates, five postgraduate students, and five research technicians.
Main research areas are the function of various ion channels and exchangers (HCN channels, calcium channels, Na/Ca-exchanger) in the heart focusing on the generation of the cardiac rhythm and mechanisms of hypertrophy and failure. In addition, the role of HCN channels in the nervous system, in particular for the generation of pain, is studied. Another research field is small animal imaging, focusing mainly, but not exclusively, on pain processing mechanisms.
These areas are explored by combining methods from molecular biology, mouse genetics, whole-animal studies, electrophysiology, and functional MRI. Research is supported by the DFG and BMBF. Together with the Chair of Clinical Pharmacology and Clincal Toxicology, a drug information service is provided for clinicians of the UK Erlangen as well as for physicians in private practice.

Research

Mechanisms of cardiac pacemaking

Project managers: PD Dr. J. Stieber, Dr. S. Herrmann, Prof. Dr. A. Ludwig
The complex mechanisms of rhythmogenesis in the sinoatrial node are examined by using various knock-in and knock-out mouse models. Principally two different mechanisms of cardiac pacemaking are currently discussed including ion channel-dependent processes as well as cytoplasmic Ca-dependent mechanisms. Both hypotheses are studied by using conditional mouse mutants. A sinoatrial deletion of the cardiac sodium-calcium exchanger NCX1 was generated. Resulting animals display a significantly reduced heart rate and cardiac failure. Ca transients and other parameters are currently analyzed in sinoatrial cells of these mutants.
In addition the role of I_f for generation of the spontaneous cardiac rhythm was analyzed further. We could show that beneath HCN4, HCN1 is strongly expressed in the sinoatrial node (low levels of HCN2 were also found). Therefore an inducible HCN triple-mutant (HCN1/2/4-KO) was generated. These mutants display a complete lack of I_f in sinoatrial node cells. Remarkably, the lack of I_f is incompatible with life since animals die several weeks after induction and develop a deep bradycardia. In addition, a strong chronotropic incompetence is observed. Action potentials recorded from isolated sinoatrial node cells display similar changes. These results demonstrate the pivotal role of I_f for cardiac pacemaking.

Ventricular hypertrophy

Project managers: Dr. S. Herrmann, Prof. Dr. A. Ludwig
Cardiac hypertrophy is accompanied by reprogramming of gene expression where the altered expression of ion channels increases the risk of life-threatening arrhythmias. The role of the depolarizing current I_f was analyzed which has been recently suggested to contribute to arrhythmogenesis in the hypertrophied ventricle. Mice with induced ventricular hypertrophy showed an increased number of I_f positive ventricular myocytes and a strongly enhanced I_f. HCN2 and HCN4 were the predominantly expressed subunits in healthy and hypertrophied hearts. Unexpectedly, only HCN1 was significantly upregulated in response to hypertrophy. Nevertheless, the combined deletion of HCN2 and HCN4 disrupted ventricular I_f completely. The lack of I_f in hypertrophic double-knockouts resulted in a strong attenuation of pro-arrhythmogenic parameters since action potential prolongation was significantly decreased and lengthening of the QT interval was reduced. We suggest that the strongly increased HCN channel activity in hypertrophied myocytes prolongs the repolarization of the ventricular action potential and thereby increases the arrhythmogenic potential.

HCN channels and pain

Project managers: Dr. S. Herrmann, Prof. Dr. A. Ludwig
The processing of painful stimuli in the dorsal root ganglion involves among several ion channels probably also HCN channels. We found that HCN2 constitutes the predominant HCN isoform in nociceptive neurons and characterized nociceptive-selective HCN2-knockout animals. Conditional deletion of HCN2 was accomplished by using the Cre/loxP-system (figure 1). Basal pain responsiveness of the mutants was normal, whereas hypersensitivity in inflammatory and neuropathic pain models was severely reduced. This finding could be reproduced in wildtype animals by application of an unspecific HCN blocker, however, the substance had no effect in mutants. Single-fiber recordings from isolated inflamed skin-nerve preparations were performed in collaboration with Prof. Dr. P.W. Reeh, Institute of Physiology and Pathophysiology of the FAU. These experiments demonstrated a significantly reduced discharge activity in mutants as compared to wildtype. In addition, the HCN-mediated mechanical sensibilization involves not only peripheral, but also spinal terminals of DRG neurons. Functional MRI analyses (work group PD Dr. A. Hess) showed that mutant animals indeed generated less nociceptive input to various supraspinal pain processing areas. Our results demonstrated that HCN2 channels are critically involved in peripheral as well as central pain sensitization. Hence, this ion channel constitutes a novel target in the therapy of neuropathic and inflammatory pain conditions.

Pharmacological imaging and image analysis

Project manager: PD Dr. A. Hess

In the last two years the group focused its research on the unique superiority of functional Magnetic Resonance Imaging (fMRI) for translational research from mice to patients. Utilizing different transgenic mice models, we were able to reveal in cooperation with Prof. Dr. P.W. Reeh (Institute of Physiology and Pathophysiology) that ciguatoxin induces cold allodynia in wild-type mice which is absent in TRPA-1 deficient mice. Ciguatoxins are activator toxins of sodium channels and cause the most common form of ichthyosarcotxism in man. In cooperation with the group of Prof. Dr. A. Ludwig, we could demonstrate by fMRI in a neuropathic pain model that HCN2 deficient mice show significantly reduced mechanical hyperalgesia. The translational aspect of fMRI was strongly demonstrated in cooperation with Prof. Dr. G. Schett (Department of Medicine 3). Investigating the hTNF overexpressing mice as a model of rheumatoid arthritis, we could show that infliximab, an TNF antibody, provokes a very rapid pain relieve within 24h after the first application. This fast and unexpected effect could be repeated in fMRI investigations of RA-patients after infliximab treatment. Solely fMRI, but no established clinical measure was able to objectify the fast and significant reduction of pain rating in patients. Recently, applying advanced graph-theoretical analyses, we were able to show that certolizumab, another TNF antibody, also was able to significantly reduce activity within the pain-matrix of patients. In this study, we were also able to differentiate anti-TNF responders and non-responders. This differentiation might open new ways to tailor pharmacological treatments to individualized therapeutic applications. In our project within the Emerging Field Inititative of the FAU Neurotrition (cooperation with Prof. Dr. M. Pischetsrieder), we discovered the "craving" potential of potato-chips for rats. MEMRI MRI in rats fed with potato chips revealed significant enhanced activity in brain areas devoted to addiction, but also locomotor activity and a deactivation of sleep relevant areas in the brain stem. Finally, we supported small animal imaging for a large variety of projects within the Faculty of Medicine.

Teaching

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

In addition, 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, terminology as well as seminars and laboratory internships.

Selected Publications

Herrmann S, Layh B, Ludwig A (2011) Novel insights into the distribution of cardiac HCN channels: an expression study in the mouse heart. J Mol Cell Cardiol, 51: 997-1006

Christel CJ, Cardona N, Mesirca P, Herrmann S, Hofmann F, Striessnig J, Ludwig A, Mangoni ME, Lee A (2012) Distinct localization and modulation of Cav1.2 and Cav1.3 L-type Ca2+ channels in mouse sinoatrial node. J Physiol, 590: 6327-42

Froese A, Breher SS, Waldeyer C, Schindler RF, Nikolaev VO, Rinné S, Wischmeyer E, Schlueter J, Becher J, Simrick S, Vauti F, Kuhtz J, Meister P, Kreissl S, Torlopp A, Liebig SK, Laakmann S, Müller TD, Neumann J, Stieber J, Ludwig A, Maier SK, Decher N, Arnold HH, Kirchhof P, Fabritz L, Brand T (2012) Popeye domain containing proteins are essential for stress-mediated modulation of cardiac pacemaking in mice. J Clin Invest, 122: 1119-30

Hofmann F, Fabritz L, Stieber J, Schmitt J, Kirchhof P, Ludwig A, Herrmann S (2012) Ventricular HCN channels decrease the repolarization reserve in the hypertrophic heart. Cardiovasc Res, 95: 317-26

Vetter I, Touska F, Hess A, Hinsbey R, Sattler S, Lampert A, Sergejeva M, Sharov A, Collins LS, Eberhardt M, Engel M, Cabot PJ, Wood JN, Vlachová V, Reeh PW, Lewis RJ, Zimmermann K (2012) Ciguatoxins activate specific cold pain pathways to elicit burning pain from cooling. EMBO J, 31: 3795-808

International Cooperations

Dr. M. Mangoni, Institut de Génomique Fonctionnelle, Université de Montpellier I et II, Montpellier: France

Prof. A. Tinker, The London School of Medicine & Dentistry, London: UK

Prof. M. Boyett, PhD, School of Medicine, University of Manchester, Manchester: UK

Prof. Dr. T. Brand, Faculty of Medicine - Cardiovascular Sciences, Imperial College London, London: UK

Dr. H. Wakimoto, Department of Genetics, Harvard Medical School, Boston: USA

Prof. C.T. Kuo, MD, Department of Cell Biology, Pediatrics and Neurobiology, Duke University Medical Center, Durham: USA

Research Equipment

Bruker, 4,7 Tesla small animal-MRT

Zeiss, confocal Laserscanning-Microscop LSM 5

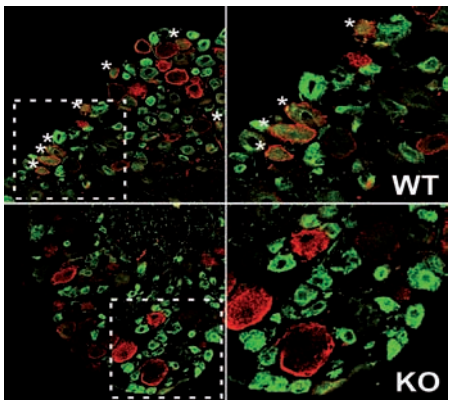

Figure 1: NospHCN2-knockout mice lack HCN2 selectively in nociceptive DRG neurons (upper panels). Asterisks mark HCN2-positive nociceptive neurons in the wildtype (lower panels). Boxed areas are enlarged to the right.

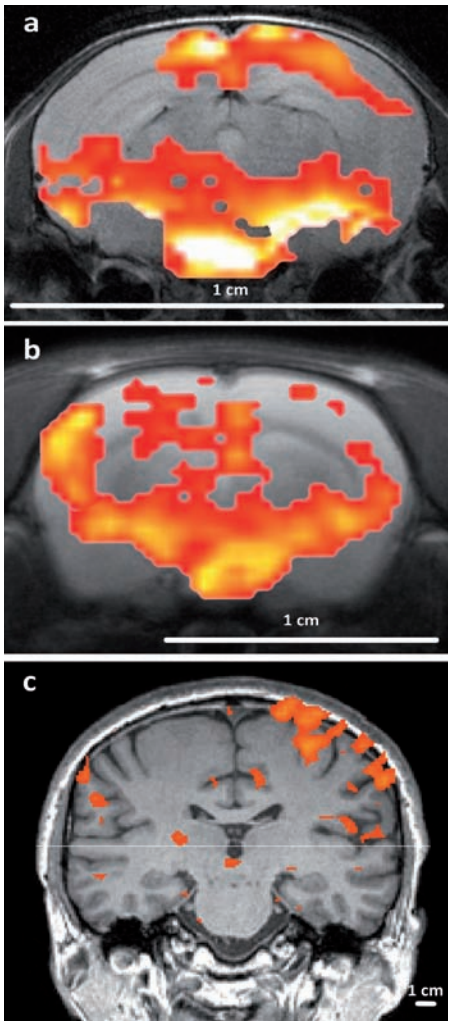

Figure 2: Depicted are cerebral activation patterns after mild painful thermal stimulation for mouse (a), rat (b), and after a slight mechanical compression of the hand for human (c). Please note the dramatic change in proportions. The white bars in all three images indicate 1 cm.

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
- Characterization and interactions of the drug uptake transporter OATP1B3
- Personalized drug therapy
- Molecular and clinical characterization of therapeutic targets in the L-arginine-NO-nitrate pathway
- Analysis of drugs and endogenous substances
- Safety in drug therapy

Structure of the Department

The Chair of Clinical Pharmacology and Clinical Toxicology constitutes together with the Chair of Pharmacology and Toxicology and the Doerenkamp-Chair for Innovations in Animal and Consumer Protection the Institute of Experimental and Clinical Pharmacology and Toxicology. The position of the executive director of the Institute rotates between the Chair of Pharmacology and Toxicology (Prof. Dr. A. Ludwig) and the Chair of Clinical Pharmacology and Clinical Toxicology (Prof. Dr. M.F. Fromm) on a two-year basis.
31 persons are working at the Chair with 14 of them being funded by extramural sources. Research is conducted by eight scientists, three of them being specialists in clinical pharmacology, ten MD or PhD students, and eight technicians. 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 Chair has excellent opportunities for drug analytics and a clinical trial unit. In addition, a drug information service is available for the physicians of the UK Erlangen and for external physicians.
The following topics, funded e.g. by the DFG, the German Cancer Aid, the German Federal Ministry of Health (BMG), and the BMBF, are in the focus of our studies: Uptake and efflux transporters for drugs, genetic determinants of drug effects (pharmacogenomics), drug uptake in tumors, cardiovascular pharmacology and risk factors, alterations of the L-arginine-NO-metabolism, and safety in drug therapy.

Research

Molecular characterization of drug transporters

Project managers: Prof. Dr. J. König, Dr. F. Müller, Prof. Dr. M.F. Fromm
Transport proteins located in distinct membrane domains are important for the uptake, distribution, and excretion of drugs and drug metabolites. Therefore, the molecular characterization of drug transporters is in the focus of our research.
Analyzing transporter-mediated drug-drug interactions, we could demonstrate that oral antidiabetic drugs or non-steroidal anti-inflammatory drugs not only inhibit transporter-mediated statin uptake, but at low concentrations also stimulate statin transport which is a new and only partially investigated mechanism of transporter-mediated drug-drug interactions.
For the investigation of transcellular transport processes and for the analysis of transporter-metabolism interplay, several multiple-transfected cell lines were established recombinantly overexpressing transport proteins or transporters together with metabolizing enzymes. Using such a double-transfected cellular model, we could clarify the molecular mechanism of the renal secretion of the antimalarial drug chloroquine.
In cooperation with Dr. A. Birkenfeld (Charité, Berlin) we characterized the human sodium-coupled citrate transporter NaCT which is now under further investigations regarding its possible role for drug therapy.

Characterization and interactions of the drug uptake transporter OATP1B3

Project manager: PD Dr. H. Gläser
The clinical relevance of hepatically expressed OATP uptake transporters for drug action and elimination is already well understood. However, the understanding of certain molecular structures, such as specific amino acids for the transport function of these transporters, was still limited. With the performed studies which are funded by the DFG, we could show that the positive charge of certain lysine residues of OATP1B3 is important for its transport function. Using molecular modeling, we found that the difference in substrate spectrum within the OATP-family is influenced by the pore size of the different OATP members. Furthermore, we showed that flavonoids which are constituents of food and herbal drugs are able to inhibit the cellular uptake of drugs mediated by hepatically expressed drug uptake transporters. This is a further mechanism for food-drug-interactions.

Personalized drug therapy

Project managers: PD Dr. O. Zolk, Prof. Dr. M.F. Fromm
Marked differences in treatment effects between individual patients are frequently observed, leading to treatment failure or enhanced toxicity. Unlike standard therapy ('one-size-fits-all'), personalized therapy aims at identifying clinically relevant subpopulations of patients for a targeted treatment. Genetic, molecular, or cellular markers are the basis for the selection of patients suitable for a specific therapy. The central topic of our research is the identification of (genetic) markers which allow prediction of ‚responder' and ‚non-responder' to a pharmacotherapy. A collaborative project with the Heart Center Bad Krozingen revealed an association of genetic markers (polymorphisms in the drug metabolizing enzyme CYP2C19) with the antiplatelet effect of clopidogrel, a frequently prescribed drug for patients with coronary artery disease. The currently most important field of applications for personalized drug therapy, however, is cancer treatment. The basic question of another collaborative research project (together with the Department of Otorhinolaryngology, Head and Neck Surgery, UK Erlangen) was whether the expression of transport proteins in tumor tissue correlates with the efficiency of anticancer drugs and thus survival of patients with head-neck squamous cancer.

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

Project manager: Prof. Dr. R. Maas
A major focus of the group is the experimental and clinical characterization of new cardiovascular risk factors as potential targets for thera-

peutic intervention. Presently we study the regulation of the L-arginine-NO-nitrate pathway by endogenously formed compounds, such as ADMA and SDMA and the metabolic fate and transport of these compounds. For in vitro and in vivo investigations, new isotope and mass spectrometry-based methods are developed. Collaborating with the Department of Medicine 4 in an intramural IZKF-project, we currently investigate alternative pathways for the metabolism of methylarginines. In a DFG-funded collaboration project with the local Institute and Outpatient Clinic of Occupational, Social, and Environmental Medicine and the Framingham Heart Study in the USA, we currently examine the human nitrate metabolism.

Analysis of drugs and endogenous substances

Project manager: Dr. M. Mieth

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

Safety in drug therapy

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

An important research focus is safety in drug therapy. Here we are partners in a project funded by the BMG to implement and evaluate measures to improve therapeutic safety in an emergency ward. Prerequisite for this was the creation of an infrastructure that permits identification and recording of adverse drug events. This infrastructure is now available for other projects as well. We investigated new approaches to improve drug therapy safety that are based on the evaluation of the local risk profile and the application of the "Paretro principle". In addition, we developed an improved classification system for adverse drug events. As a partner in the BMBF funded cluster "Medical Valley Europäische Metropolregion Nürnberg" therapeutic systems project, we currently work on new software and chemoinformatic databases to improve drug safety in psychiatry. In addition, problems of safety of drug therapy in elderly patients are in the focus of collaborative projects (see figure).

Teaching

The Chair coordinates the interdisciplinary lecture series and seminar Clinical Pharmacology/Pharmacotherapy for medical students applying problem-based learning. In addition, we teach students of dental medicine, molecular medicine, pharmacy, and medical process management in clinical pharmacology by lectures, seminars, and practical exercises. Students of pharmacy and medicine are welcome to work with us during their final year.

Selected Publications

Birkenfeld AL, Lee HY, Guebre-Egziabher F, Alves TC, Jurczak MJ, Jornayvaz FR, Zhang D, Hsiao JJ, Martin-Montalvo A, Fischer-Rosinsky A, Spranger J, Pfeiffer AF, Jordan J, Fromm MF, König J, Lieske S, Carmean CM, Frederick DW, Weismann D, Knauf F, Irusta PM, De Cabo R, Helfand SL, Samuel VT, Shulman GI (2011) Deletion of the mammalian INDY homolog mimics aspects of dietary restriction and protects against adiposity and insulin resistance in mice. Cell Metab, 14: 184-95

König J, Glaeser H, Keiser M, Mandery K, Klotz U, Fromm MF (2011) Role of organic anion-transporting polypeptides for cellular mesalazine (5-aminosalicylic acid) uptake. Drug Metab Dispos, 39: 1097-102

Mandery K, Sticht H, Bujok K, Schmidt I, Fahrmayr C, Balk B, Fromm MF, Glaeser H (2011) Functional and structural relevance of conserved positively charged lysine residues in organic anion transporting polypeptide 1B3. Mol Pharmacol, 80: 400-6

Strobel J, Mieth M, Endreß B, Auge D, König J, Fromm MF, Maas R (2012) Interaction of the cardiovascular risk marker asymmetric dimethylarginine (ADMA) with the human cationic amino acid transporter 1 (CAT1). J Mol Cell Cardiol, 53: 392-400

Fromm MF, Maas R, Tümena T, Gaßmann KG (2013) Potentially inappropriate medications in a large cohort of patients in geriatric units: association with clinical and functional characteristics. Eur J Clin Pharmacol, 69: 975-84

Zolk O, Schnepf R, Muschler M, Fromm MF, Wendler O, Traxdorf M, Iro H, Zenk J (2013) Transporter gene expression in human head and neck squamous cell carcinoma and associated epigenetic regulatory mechanisms. Am J Pathol, 182: 234-43

International Cooperations

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

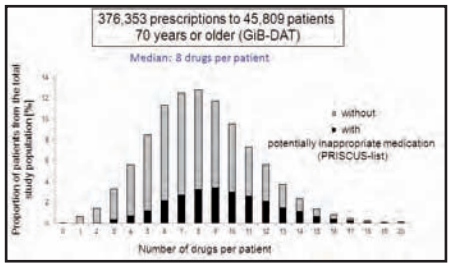
Prof. R. Vasan, Framingham Heart Study, Framingham: USA

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

Research Equipment

Applied Biosystems, API 4000 MS/MS System Package

Zeiss, confocal laserscanning-Microskope LSM 5 Pascal



Analysis of the medication at discharge in 45,809 patients from geriatric units in Bavaria. The figure also shows the proportion of patients receiving at least one drug classified as potentially inappropriate for elderly according to the PRISCUS list (cooperation with Prof. Dr. K.-G. Gaßmann, Geriatrie-Zentrum Erlangen, and GiB-DAT).

Institute of Experimental and Clinical Pharmacology and Toxicology

Doerenkamp-Chair for Innovations in Animal and Consumer Protection

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Research Focus

- Non-invasive functional imaging (Animal Protection)
- Analgesics (Consumer Protection)

Structure of the Department

The endowed Doerenkamp-Chair is one of three full professorships implemented at the Institute of Experimental and Clinical Pharmacology and Toxicology.
The funding of the Doerenkamp-Chair will be ending on June 30, 2013. Funds, donated by the person the chair is named after, are used to finance the chair holder, one administrative/academic management person, and up to three academic co-workers. In addition, there is a close collaboration of this Chair with researchers of the other two chairs. Together with these senior scientists, grants finance currently two post-doctoral and two doctoral collaborators.
The research goals of the endowed Doerenkamp-Chair are pursued in close collaboration with Prof. Dr. B. Hinz (formerly senior scientist at the Institute, presently chairman of the Department of Toxicology and Pharmacology at the University of Rostock) and PD Dr. A. Hess (member of the Chair of Pharmacology and Toxicology at the Institute). In collaboration with these senior co-workers, the following results were achieved.

Research

Non-invasive functional imaging (Animal Protection)

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

Analgesics (Consumer Protection)

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

Teaching

The engagement of Prof. Dr. Dr. h.c. K. Brune as speaker at international conferences and his membership in several administrative bodies and advisory structures has led to many additional invitations to comment on current problems of drug therapy in man. In addition, Prof. Dr. Dr. h.c. K. Brune is engaged in the production of many national and international guidelines, textbooks, etc. A sample of publications related to these activities can be found on the homepage of the Institute. Prof. Dr. Dr. h.c. K. Brune is a member of the Executive Committee of IUPHAR (International Union of Basic and Clinical Pharmacology).

Selected Publications

Neely GG, Hess A, Costigan M, Keene AC, Goulas S, Langeslag M, Griffin RS, Belfer I, Dai F, Smith SB, Diatchenko L, Gupta V, Xia CP, Amann S, Kreitz S, Heindl-Erdmann C, Wolz S, Ly CV, Arora S, Sarangi R, Dan D, Novatchkova M, Rosenzweig M, Gibson DG, Truong D, Schramek D, Zoranovic T, Cronin SJ, Angjeli B, Brune K, Dietzl G, Maixner W, Meixner A, Thomas W, Pospisilik JA, Alenius M, Kress M, Subramaniam S, Garrity PA, Bellen HJ, Woolf CJ, Penninger JM (2010) A genome-wide Drosophila screen for heat nociception identifies α2δ3 as an evolutionarily conserved pain gene. Cell, 143: 628-38

Hess A, Axmann R, Rech J, Finzel S, Heindl C, Kreitz S, Sergeeva M, Saake M, Garcia M, Kollias G, Straub RH, Sporns O, Doerfler A, Brune K, Schett G (2011) Blockade of TNF-α rapidly inhibits pain responses in the central nervous system. Proc Natl Acad Sci U S A, 108: 3731-6

Ruff CT, Morrow DA, Jarolim P, Ren F, Contant CF, Kaur A, Curtis SP, Laine L, Cannon CP, Brune K (2011) Evaluation of NT-proBNP and high sensitivity C-reactive protein for predicting cardiovascular risk in patients with arthritis taking longterm nonsteroidal antiinflammatory drugs. J Rheumatol, 38: 1071-8

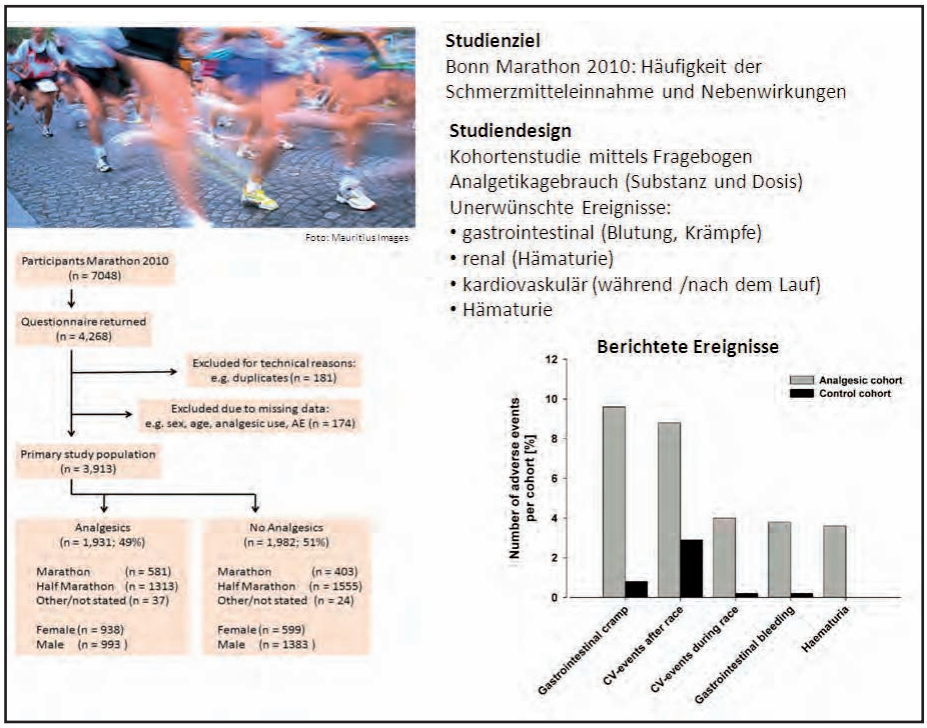
Hinz B, Brune K (2012) Paracetamol and cyclooxygenase inhibition: is there a cause for concern? Ann Rheum Dis, 71: 20-5

Renner B, Walter G, Strauss J, Fromm MF, Zacher J, Brune K (2012) Preoperative administration of etoricoxib in patients undergoing hip replacement causes inhibition of inflammatory mediators and pain relief. Eur J Pain, 16: 838-48

Küster M, Renner B, Oppel P, Niederweis U, Brune K (2013) Consumption of analgesics before a marathon and the incidence of cardiovascular, gastrointestinal and renal problems: a cohort study. BMJ Open, 3:e002090

Research Equipment

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



Analgesics do not improve the performance during a marathon, but increase the risk of organ damage.

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Chair of Forensic Medicine

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Research Focus

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

Structure of the Department

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

Research

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

Project manager: PD Dr. T. Lederer

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

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

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

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

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

Project manager: Prof. Dr. S. Seidl

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

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

Project manager: Dr. K. Müller

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

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

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

Teaching

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

Selected Publications

Grobosch T, Schwarze B, Stoecklein D, Binscheck T (2012) Fatal poisoning with Taxus baccata: quantification of paclitaxel (taxol A), 10-deacetyltaxol, baccatin III, 10-deacetylbaccatin III, cephalomannine (taxol B), and 3,5-dimethoxyphenol in body fluids by liquid chromatography-tandem mass spectrometry. J Anal Toxicol, 36: 36-43

Schietke RE, Hackenbeck T, Tran M, Günther R, Klanke B, Warnecke CL, Knaup KX, Shukla D, Rosenberger C, Koesters R, Bachmann S, Betz P, Schley G, Schödel J, Willam C, Winkler T, Amann K, Eckardt KU, Maxwell P, Wiesener MS (2012) Renal Tubular HIF-2α Expression Requires VHL Inactivation and Causes Fibrosis and Cysts. PLoS ONE, 7: e31034

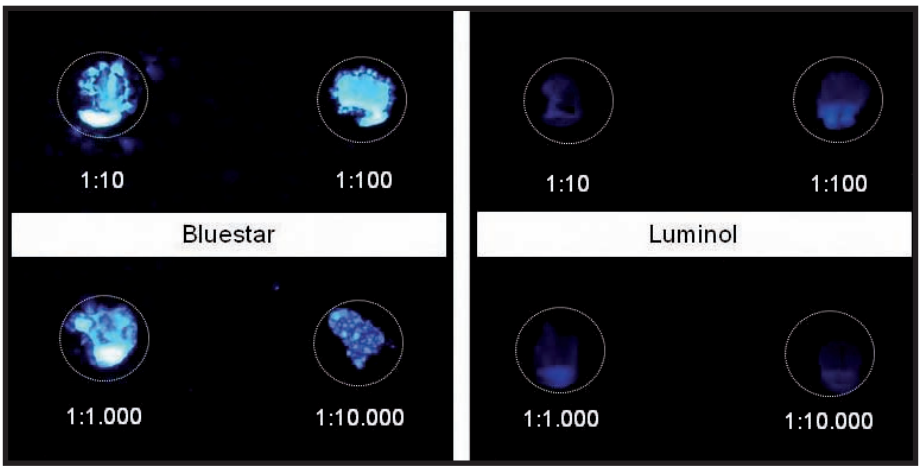
Wiest I, Alexiou C, Kuhn C, Schulze S, Kunze S, Mayr D, Betz P, Jeschke U, Dian D (2012) Expression of different carbohydrate tumour markers and galectins 1 and 3 in normal squamous and malignant epithelia of the upper aaerodigestive tract. Anticancer Res, 32: 2023-9

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

Research Equipment

Applied Biosystems, DNA-Sequenzer

Waters, UPLC/MS-MS



Luminescence signals of different blood-dilutions on carpet using the reagents "Bluestar" (left) and "Luminol" (right)

Institute of Medical Informatics, Biometry, and Epidemiology

Chair of Medical Biometry and Epidemiology

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

Structure of the Department

The Institute comprises the Chair of Medical Informatics (Prof. Dr. H.U. Prokosch) and the Chair of Medical Biometry and Epidemiology. Staff of the chair of Medical Biometry and Epidemiology includes 14 scientists (seven post-docs, seven doctoral students) and two further employees. Of all staff positions, six are financed by external funds.
Different working groups address biostatistical methods and epidemiological research. Moreover, the Chair cooperates with various clinical researchers. A computing cluster with 36 nodes is available as infrastructure for computer-intensive biostatistical simulation studies.

Research

Computational Biostatistics

Project managers: PD Dr. M. Schmid, Prof. Dr. O. Gefeller
The statistical analysis of high-dimensional data containing large numbers of features has become increasingly important in biomedical practice. Consequently, statistical methods for analyzing data with complex dependency patterns and for separating informative features from non-informative ones are needed. Boosting is a promising statistical method to address these issues. The project focuses on improving and developing boosting methodology for data structures that cannot yet be analyzed with the help of classical boosting techniques. For example, a new boosting algorithm for modeling ordinal outcomes was developed. The suggested algorithm can e.g. be used to predict cancer stages (measured on an ordinal scale) using small sets of marker genes that are automatically selected by the boosting algorithm. Classical boosting methods were further extended to generalized additive models for location, scale, and shape (GAMLSS). GAMLSS are a popular statistical approach for simultaneously modeling multiple parameters of a response distribution in regression models. Current fitting procedures for GAMLSS are infeasible for high-dimensional data setups and require heuristic (or potentially biased) feature selection methods. The new algorithm allows for simultaneous estimation of predictor effects and feature selection in GAMLSS. In the course of the project, boosting methods were further analyzed with regard to their general performance as optimization method for AUC-based performance criteria in classification and survival analysis.

Dermatoepidemiology

Project managers: Prof. Dr. A. Pfahlberg, Prof. Dr. W. Uter
In clinical contact allergy research, a close cooperation with the German contact dermatitis group (DKG) e.V. and the multi-centric project information network of department 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 "ESSCA" has been collecting and analyzing such data on a European level since 2002, with the data center at the Chair.
The epidemiology of malignant melanoma and acquired melanocytic nevi is a further research interest: Acquired melanocytic nevi, surrogate or potential precursor of malignant melanoma, are addressed by the current MONA-study which includes standardized assessment of student cohorts. In 2011, a repeat-survey ("Erlking 2011") with parents of children at kindergarten age was performed, addressing knowledge, attitude, and behavior regarding skin cancer risk factors and sun protection.

Cooperative epidemiological and clinical studies

This area of activity comprises diverse research topics addressed in cooperation with different departments and institutes. Usually, biometrical aspects of study design and statistical analysis have been performed by our institute in these cooperative projects. The most important projects in the reporting period include:
- A cross-sectional study in the field of occupational medicine addressing the association between exposure to CS_2 in the viscose industry and a number of neurological and cardiovascular endpoints;
- A study coordinated by the Institute of Biomedicine of Aging regarding risk factors of frailty and sarcopenia;
- A multi-centric European studying on "Accelerated Partial Breast Irradiation", a controlled clinical trial on the multimodal therapy of rectal cancer (CAO/ARO/AIO-04), and a controlled clinical trial on radiochemotherapy in patients with locally advanced head/neck tumors stage III and IVA-B (PACCIS), all chaired by the Department of Radiation Oncology of the UK Erlangen;
- The multi-centric "German Chronic Kidney Disease Study (GCKD)", funded by the BMBF and the "Kuratorium für Heimdialyse";
- The implementation of the "German Weight Maintenance" registry and biostatistical support of a multi-center study on the therapy of eating disorders (INTERBED), chaired by the Department of Psychiatry and Psychotherapy of the UK Erlangen;
- The multicenter POLYPROBE Study examines the expression of 61 marker genes in patients with carcinoma of the colon, using PCR. The association with UICC stages, survival, and response to (radio-) chemotherapy will be analyzed.

Teaching

In the context of curricular teaching, the Chair contributes to the "Querschnittsbereich I" (medical informatics, biometry, and epidemiology) for medical students (lecture and seminars in small groups, one contact hour each). Moreover, this introduction to biometry and epidemiology (lecture and seminars in small groups, one contact hour each) is part of the bachelor phase of the course on "molecular

medicine" together with a seminar on the practice of data analysis (two contact hours) which teaches basic programming knowledge in the statistical programme "R". Regarding the new master course "Medical Process Management", the Chair is responsible for a part of module 2.2 "health care management II", namely "public health and evidence-based medicine" (seminar, three contact hours). For students of medicine and dental medicine, a seminar on "design and data analysis in clinical and experimental studies" is being offered twice each term. This seminar can be used by the students to discuss any statistical issues they encounter when working at their medical thesis. As compulsory elective seminar in the master part of the course "Life Science Engineering" of the technical faculty, the Chair offers a module in epidemiology. Moreover, biometry and epidemiology are part of an introductory seminar for students of information science specializing in medical informatics.

Selected Publications

Schmid M, Hielscher T, Augustin T, Gefeller O (2011) A robust alternative to the schemper-henderson estimator of prediction error. Biometrics, 67: 524-35

Li J, Uter W, Pfahlberg A, Gefeller O (2012) A comparison of patterns of sun protection during beach holidays and everyday outdoor activities in a population sample of young German children. Br J Dermatol, 166: 803-10

Mayr A, Gefeller O, Prokosch HU, Pirkl A, Fröhlich A, de Zwaan M (2012) Web-based data collection yielded an additional response bias--but had no direct effect on outcome scales. J Clin Epidemiol, 65: 970-7

Schmid M, Potapov S (2012) A comparison of estimators to evaluate the discriminatory power of time-to-event models. Stat Med, 31: 2588-609

Uter W, Aberer W, Armario-Hita JC, Fernandez-Vozmediano JM, Ayala F, Balato A, Bauer A, Ballmer-Weber B, Beliauskiene A, Fortina AB, Bircher A, Brasch J, Chowdhury MM, Coenraads PJ, Schuttelaar ML, Cooper S, Czarnecka-Operacz M, Zmudzinska M, Elsner P, English JS, Frosch PJ, Fuchs T, García-Gavín J, Fernández-Redondo V, Gawkrodger DJ, Giménez-Arnau A, Green CM, Horne HL, Johansen JD, Jolanki R, Pesonen M, King CM, Krêcisz B, Chomiczewska D, Kiec-Swierczynska M, Larese F, Mahler V, Ormerod AD, Peserico A, Rantanen T, Rustemeyer T, Sánchez-Pérez J, Sansom JE, Silvestre JF, Simon D, Spiewak R, Statham BN, Stone N, Wilkinson M, Schnuch A (2012) Current patch test results with the European baseline series and extensions to it from the 'European Surveillance System on Contact Allergy' network, 2007-2008. Contact Dermatitis, 67: 9-19

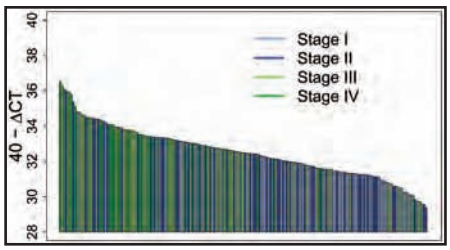
Uter W, Gefeller O, Geier J, Schnuch A (2012) Methylchloroisothiazolinone/methylisothiazolinone contact sensitization: diverging trends in subgroups of IVDK patients in a period of 19 years. Contact Dermatitis, 67: 125-9

International Cooperations

Prof. J. Duus Johansen, National Allergy Research Center, Gentofte Hospital, University of Copenhagen, Copenhagen: Denmark

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

Prof. A.-M. Giménez-Arnau, Hospital del Mar, IMAS, Autonomous University of Barcelona, Barcelona: Spain



Distribution of 4 UICC stages in patients with colorectal carcinoma in different grades of expression of the gene COL10A1, ordered by size (POLYPROBE-Study)

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Research Focus
- Architecture of 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 Department

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

Research

Architecture of health information systems

For many years, the major issue concerning the design, implementation, and management of Hospital Information Systems (HIS) has been the optimization of communication processes and the integration of heterogeneous departmental systems into a comprehensive HIS. Today, the integration efforts go beyond the borders of one institution with the goal to establish health telematics networks. Within the hospital, requirements have also changed. The focus has moved from simple order entry/results review and medical documentation towards intelligent support for clinical pathways and workflows with integrated electronic decision support functions.
Within the OPAL Health project, a wireless sensor network for logistics has been designed and developed. Furthermore, the applicability of this technology for mobile device management and transfusion safety was evaluated.
Shared decision making and patient guidance services are the main topics in the EU-project eHealthMonitor. Innovative information and knowledge management technologies synergize to bring the most adequate information to physicians, patients, and their relatives.
In addition to such grant funded projects, the Chair of Medical Informatics also pursues and supports several pilot projects embedded in the SOARIAN® hospital information system environment and within various health telematics projects.

Medical ontologies and medical knowledge processing

The use of knowledge processing systems in medicine is aimed at optimizing the quality of medical care by prospective measures (decision support and decision monitoring).
In this context, our research projects concentrate on knowledge modeling and the implementation of standardized knowledge modules for example to support drug therapy and drug prescription or within intensive care units (ICU).
The BMBF project "systematic optimization of the medication process in hospitals to promote medication safety" uses decision-support functions for early alerting of potentially hazardous situations and measures the effect of the electronic interventions on the increase of medication safety.
In the BMBF project "personalized pharmacotherapy in psychiatry", a chemo-informatics-based approach is used, considering the chemical structure and physicochemical properties of the drugs. Based on this, a data-and model-driven software module for individualized, optimized pharmacotherapy for psychiatric outpatient and inpatient care is designed and developed as a prototype.
Another project implemented knowledge-based support functions within the patient data management system (PDMS) of an intensive care unit to allow for example for monitoring of dangerously low blood glucose levels with direct feedback as text messages on the DECT-phone, for the calculation and trending of scores, and for quality assurance measures supporting the DRG-based billing in complex ICU patients.

Evaluation of health information systems

When introducing new information technologies, it is essential to evaluate their effect on user satisfaction, work processes, and process costs to avoid adverse effects of these technologies on medical care. Successful use of IT in medicine may be hindered by negative user attitudes, user-unfriendly interfaces, and insufficient usability in general.
We have initiated before/after evaluation studies in the context of the introduction of a new patient data management system in ICU of UK Erlangen. Further studies have used Thinking Aloud and Cognitive Walkthrough methods and a small mobile usability laboratory to evaluate the usability of different order entry systems with the formative goal to develop better user interfaces for such systems. Finally, we have participated in a study financed by the Barmer Health Insurance to evaluate the usage of a personal electronic health record.
The project Prospective Health Technology Assessment (ProHTA), part of the cluster of excellence initiative, uses simulation tools to forecast the potential impact of future technologies and their potential return on invest even before development is even started.

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, appro-

priate and flexible visualization methods are required. A further important new challenge for medical informatics might be the possible increase of the efficiency of clinical and translational research by reusing such data for research projects. Current technologies support data extraction and data consolidation, but rarely semantic integration between diverse databases, navigation in huge databases, or appropriate visualization of their content.
In cooperation with Harvard University Medical Center, the i2b2 (informatics for integrating biology and the bedside) platform has been integrated with the UK Erlangen Clinical Data Warehouse and enhanced by semantic integration between databases und timeline-based visualization methods. It serves as a research integration platform for several projects at UK Erlangen, but also within national collaborations. The project "cloud4health" aims at automatically unlocking the information contained in free text, discharge summaries, and surgical reports for further analysis. A combined approach of textual analysis and data warehouse technologies is used and can be deployed as a cloud-based service.

IT-infrastructure applications for medical research

Today, medical research is often pursued within networked multi center structures which require efficient and safe IT-infrastructures. The Chair of Medical Informatics has designed and established such web-based electronic data capture systems for many medical multicenter research projects, such as the Epidermolysis Bullosa Research Network, the Polyprobe Study, the German Weight Control Registry, and the nation-wide Registry for Chronic Kidney Diseases, GCKD. Current activities further comprise IT infrastructures to support biobanking and single source reuse of patient data for clinical research. The Chair of Medical Informatics is member and active in many projects and working groups of the TMF (German technology and methods platform for networked medical research) and has promoted the foundation of the new GMDS working group "Use of electronic patient records for clinical research".
Within the project „EHR-based patient recruitment for clinical trials", we have analyzed recruitment processes and currently available HIS components to support these processes within five German university hospitals. This led to the design of a generic architecture for EHR-integrated IT components supporting patient recruitment and to the successful evaluation of this concept.
Within the EFPIA-funded Innovative Medicine Initiative, we are partner in the EHR4CR-project developing adaptable, reusable, and scalable solutions for reusing data from electronic health record systems for clinical research. The solutions are validated for different scenarios (e.g. patient identification and recruitment, clinical trial execution, adverse event reporting), across different therapeutic areas, and across several European countries.

Translational cancer research

A special research focus for the reuse of clinical data in the research context is the efficient IT support in the context of cancer care and translational cancer research. Here, we have designed and established a comprehensive single source framework of IT components supporting tissue banking, multicenter cancer trials, cancer registration, and routine cancer care documentation.
While interfacing the new cancer registry database of UK Erlangen's Comprehensive Cancer Center with our EHR-system, we designed a reference model for cancer documentation comprising a set of elementary documentation packages, related processes within patient care, quality assurance and research, respective information systems as well as interfaces to be established.
One of our publications from this project was awarded the Rolf Hansen prize for the best article on electronic medical records at the medical informatics Europe conference 2012 in Pisa.

Teaching

The Endowed Chair of Medical Informatics is teaching medical students in the cross-sectional subject medical informatics, biometry, and epidemiology. It further offers medical informatics courses for computer science students of the technical faculty and has a considerable teaching part in the Master course Medical Process Management of the Faculty of Medicine as well as the Bachelor and Master program Medical Devices Technology of the Technical Faculty.
In this context, the Chair of Medical Informatics has mentored 22 master and diploma theses as well as nine bachelor theses and one term paper in the years 2011/2012.

Selected Publications

Eckardt KU, Bärthlein B, Baid-Agrawal S, Beck A, Busch M, Eitner F, Ekici AB, Floege J, Gefeller O, Haller H, Hilge R, Hilgers KF, Kielstein JT, Krane V, Köttgen A, Kronenberg F, Oefner P, Prokosch HU, Reis A, Schmid M, Schaeffner E, Schultheiss UT, Seuchter SA, Sitter T, Sommerer C, Walz G, Wanner C, Wolf G, Zeier M, Titze S (2012) The German Chronic Kidney Disease (GCKD) study: design and methods. Nephrol Dial Transplant, 27: 1454-60

Mayr A, Gefeller O, Prokosch HU, Pirkl A, Fröhlich A, de Zwaan M (2012) Web-based data collection yielded an additional response bias--but had no direct effect on outcome scales. J Clin Epidemiol, 65: 970-7

Prokosch HU, Mate S, Christoph J, Beck A, Köpcke F, Stephan S, Beckmann MW, Rau T, Hartmann A, Wullich B, Breil B, Eckardt KU, Titze S, Habermann JK, Ingenerf J, Hackmann M, Ries M, Bürkle T, Ganslandt T (2012) Designing and implementing a biobanking IT framework for multiple research scenarios. Stud Health Technol Inform, 180: 559-63

Ries M, Golcher H, Prokosch HU, Beckmann MW, Bürkle T (2012) An EMR based cancer diary - Utilisation and initial usability evaluation of a new cancer data visualization tool. Stud Health Technol Inform, 180: 656-60

Strobel J, Jörns H, Weisbach V, Ganslandt T, Zimmermann R, Eckstein R (2012) Audit on the usage of plasma derived/recombinant coagulation factor concentrates at a German university hospital. Vox Sang, 103: 122-9

International Cooperations

Prof. Dr. K.-P. Adlassnig, Section for Medical Expert and Knowledge-Based Systems, Medical University of Vienna, Vienna: Austria

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

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

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

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Research Focus
- Multimodal Imaging in Pre-clinical Research
- PET/MR Hybrid Imaging
- 3D Imaging and Image Processing for Musculoskeletal Applications

Structure of the Department

In addition to the chair and full professorship of Medical Physics, the Institute of Medical Physics (IMP) comprises the professorship of Magnetic Resonance Imaging (held by Prof. Dr. H.H. Quick since 10/2009). The Institute employs a total of 60 persons, whereof 42 are financed by third-party funds. The researchers, 30 of them doctoral students, are working on a wide range of topics in the area of medical physics. The projects focus on different issues of the following research areas:
- Computed tomography
- Dosimetry and Radiation Protection
- Magnetic Resonance Tomography
- Medical Imaging
- Medical Image Processing
- Preclinical Imaging
- Osteoporosis Research.

An important basis for the research at the Institute is fundraising: Public grants by the European Union, BMBF, DFG, Bavarian Research Foundation and cooperations with industrial partners reach an amount of about one and a half million Euros per year.

The focus of the 35 ongoing research projects and cooperations is the development and the application of imaging procedures in medical diagnosis and image-guided therapy. Besides the achievements in the field of computed tomography (CT) where the institute has gained a world-wide leading position, the research focuses on magnetic resonance imaging (MRI), PET/MR imaging, and medical imaging processing. Selected research projects are described briefly in the following.

Research

Multimodal Imaging in Pre-clinical Research

From 10/2006 to 09/2012, the DFG supported the Research Unit 661: "Multimodal Imaging in Pre-clinical Research" (Speaker: Prof. Dr. Dr. h.c. W.A. Kalender). At the Institute of Medical Physics, the projected CT developments, in particular for micro-CT, focussed on optimization of image quality at minimal dose, the implementation of dual-energy methods, and the development of tools for dynamic micro-CT. More detailed information on this project can be found in the section describing special research areas or major research projects funded by the DFG within this research report.

PET/MR Hybrid Imaging

Project manager: Prof. Dr. H.H. Quick

In April 2010, the world's first installation of a diagnostic system for simultaneous PET/MR whole-body hybrid imaging has been installed at the IMP. The hybrid system (Biograph mMR, Siemens AG, Erlangen) consists of a 3.0 Tesla high-field magnetic resonance (MR) system in which a MR compatible positron emission tomography (PET) detector has been fully integrated. This allows for simultaneous acquisition of MR data with excellent soft tissue contrast and high spatial resolution as well as of PET data providing high sensitivity in detecting tumor cells that have been labeled with a specific radiotracer.

This new technology is being investigated at the IMP in close research collaboration with the industrial partner Siemens AG and with the Department of Nuclear Medicine, the Institute of Radiology, and the Department of Neuroradiology from the UK Erlangen.

The systematic technical testing (figure 1) of the system performed at the IMP was followed by first clinical evaluation and validation of 100 oncologic patients. Since July 2011, the hybrid system has been CE certified and has reached medical product status. Currently (03/2013), about 40 of such hybrid systems are installed worldwide. The MR imaging research group at the IMP - a team formed of doctoral, diploma, and master students - performs state-of-the-art research to further improve the technology and to assess and to validate further clinical applications of PET/MR hybrid imaging. Also clinical studies are scientifically supported. The spectrum of research projects encompasses development of new methods for MR-based attenuation and motion correction, development and technical integration of PET-transparent radiofrequency coils for integrated PET/MR hybrid imaging, facilitation of the clinical workflow for maximization of diagnostic information while reducing PET/MR data acquisition time, as well as strategies for improving the quantification of PET data, to name just a few. In cooperation with the laboratory for pattern recognition, new methods for MR-based attenuation correction are developed and evaluated.

3D Imaging and Image Processing for Musculoskeletal Applications

Project manager: Prof. Dr. K. Engelke

The focus of the image processing activities is the development of the 3D segmentation and analysis toolkit MIAF (medical image analysis framework) which is now widely used in the field of osteoporosis with the aim of improving fracture prediction and monitoring treatment effects of anti osteoporosis medication. In the framework of the BMBF funded project 'Biomechanically founded individualized osteoporosis Assessment and treatment' (BMBF, BioAsset 01EC1005D), a 3D segmentation and analysis module was developed for the complete thoracolumbar spine that includes an analysis of the disk volume and the 3D shape of the vertebrae. Further areas of applications targeted recently and partly supported by the BMBF funded project 'A Network on Clinics and Pathophysiology of Osteophytes and Ankylosis' (BMBF, Ankyloss 01EC1002D) are rheumatoid arthritis and osteoarthritis. The onset of rheumatoid arthritis is characterized by the development of bone erosions. As an example, figure 2 shows an advanced erosion within the metacarpophalangeal joints in a patient with rheumatoid arthritis along with the outer bone surface.

MIAF also provides sophisticated CT-CT and CT-MRI registration functionalities which were recently used to characterize bone marrow lesions of the knee in patients with osteoarthritis. The quantification of BMD and bone structure in addition to the measurement of

cartilage properties may improve the diagnosis of osteoarthritis, another important musculoskeletal disease affecting in particular large parts of the elderly population. The next step is the incorporation of muscle properties, such as the amount of intramuscular fat that deteriorates muscle function which eventually contributes to the decrease of bone strength. This work will be conducted within the research collaboration 'Research Consortium Muscle Wasting (Sarcopenia) and Osteoporosis - Consequences of impaired tissue regeneration in the elderly (FORMOsA)' that recently has received funding from the Bavarian Research Foundation. Industrial partners of the IMP within Formosa are Miha Body Tech GmbH (Augsburg), Siemens Healthcare (Erlangen), and Physiomed Elektromedizin AG (Schnaittach/Laipersdorf). The aim of FORMOsA is the development of diagnostic criteria for sarcopenia and their standardization in order to better assess the effect of potential interventions in combination with an experimental preclinical and clinical program to explore intervention strategies.

Teaching

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

Selected Publications

Braun H, Ziegler S, Paulus DH, Quick HH (2012) Hybrid PET/MRI imaging with continuous table motion. Med Phys, 39: 2735-45

Engelke K (2012) Assessment of bone quality and strength with new technologies. Curr Opin Endocrinol Diabetes Obes, 19: 474-82

Engelke K, Stampa B, Timm W, Dardzinski B, de Papp AE, Genant HK, Fuerst T (2012) Short-term in vivo precision of BMD and parameters of trabecular architecture at the distal forearm and tibia. Osteoporos Int, 23: 2151-8

Paulus DH, Braun H, Aklan B, Quick HH (2012) Simultaneous PET/MR imaging: MR-based attenuation correction of local radiofrequency surface coils. Med Phys, 39: 4306-15

Zerfass P, Lowitz T, Museyko O, Bousson V, Laouisset L, Kalender WA, Laredo JD, Engelke K (2012) An integrated segmentation and analysis approach for QCT of the knee to determine subchondral bone mineral density and texture. IEEE Trans Biomed Eng, 59: 2449-58

Quick HH, von Gall C, Zeilinger M, Wiesmüller M, Braun H, Ziegler S, Kuwert T, Uder M, Dörfler A, Kalender WA, Lell M (2013) Integrated Whole-Body PET/MR Hybrid Imaging: Clinical Experience. Invest Radiol, 48: 280-9

International Cooperations

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

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

Prof. CA Mistretta, Department of Medical Physics, University of Wisconsin, Madison: USA

Research Equipment

Siemens, Biograph mMR

Siemens, C-Bogen-CT-Scanner Axiom Artis zeego

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

Siemens, Somatom Dual-Source CT Scanner Flash

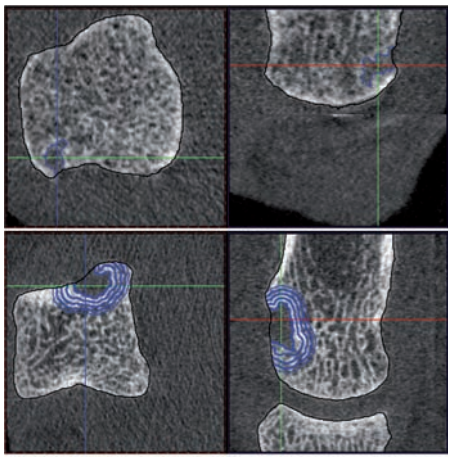

Figure 2: Examples of segmented erosions. In the last case, the periosteal surface had to be reconstructed manually due to the large cortical break. Apart from that, the segmentation in these examples worked fully automatically. Also, in the last image, concentric VOIs (Volume of Interest) for BMD (Bone Mineral Density) calculations are shown.

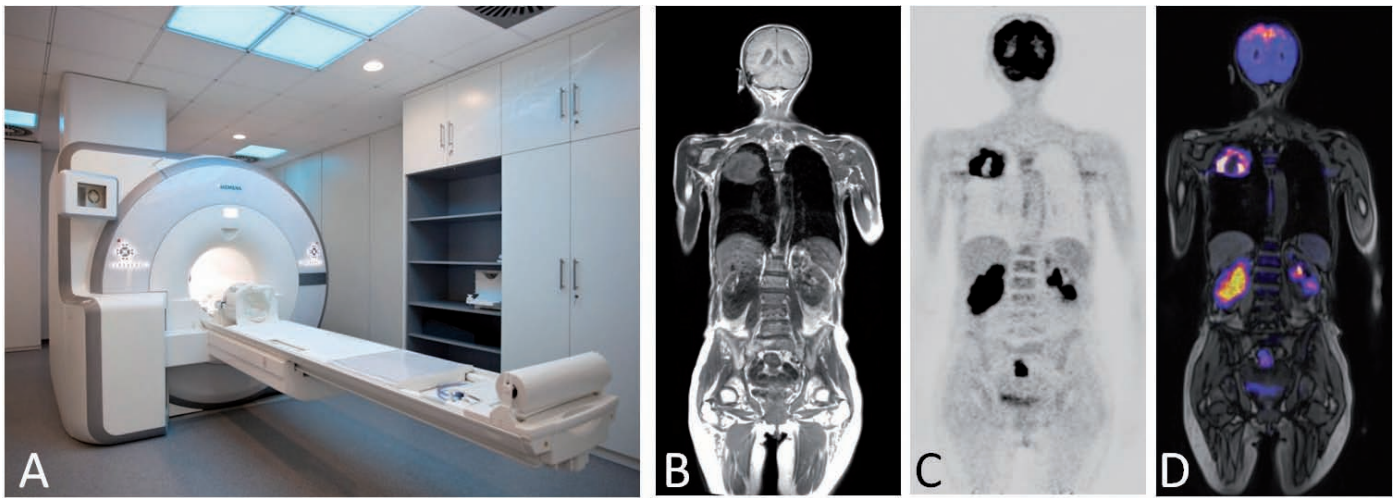

Figure 1: (A) Integrated PET/MR Hybrid System (Biograph mMR, Siemens AG) at IMP. (B) MR data of a patient with bronchial carcinoma and additional metastasis. (C) PET data of the same patient that were acquired simultaneously with MR data. (D) Exact fusion of MR and PET data in a PET/MR hybrid imaging data set. MR data provides highly detailed image resolution and excellent soft tissue contrast while PET data shows accumulation of radiotracer in the tumor with high sensitivity.

Institute of the History of Medicine and Medical Ethics

Chair of the History of Medicine

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Research Focus

- Galen - Compendium and Catalogue of Galenic Writings
- Receptions of Ancient Psychopathology
- Leprosy and Vagrancy in Southern German Free Imperial Cities
- Early 18th Century Medical Practice: Physician Johann Christoph Götz (1688 - 1733) from Nürnberg
- Ernst Wilhelm Baader (1892 - 1962), Occupational Medicine and Nazism
- Medical Crime and the Social Practice of Terror - SS-Physicians in Concentration Camps, 1934 - 1945
- History of the Bavarian Society for Gynecology and Obstetrics in the 20th Century (in cooperation with the Department of Obstetrics and Gynecology)
- The Establishment of Medical Applications of X-Ray-Technology: Radiation Poisoning, Radiation Protection, and Radiotherapy in Early 20th Century

Structure of the Department

The Chair of the History of Medicine and the Professorship for Medical Ethics (see separate report) constitute the Institute of the History of Medicine and Medical Ethics. It includes the Forum "Medizin und Menschenrechte" ("Forum on Medicine and Human Rights"), founded in 2006, and the Coordinating Office of the Clinical Ethics Committee. Furthermore, the Institute harbors the Erlangen Medical Collection. In total, the staff of the Institute consists of 14 members, twelve are academic personnel including seven part-time positions. Chair and Professorship cooperate in joint research projects on history and contemporary history of medical ethics (e.g. medicine in NS-Germany, history of the Faculty of Medicine Erlangen, medical ethics in Germany after 1945).

Research

Galen - Compendium and Catalogue of Galenic Writings

Project manager: Prof. Dr. K.-H. Leven

The Greek physician Galenus of Pergamum (129 - approx. 210 AD) figures as the most influencal medical author of the Roman imperial period. A very prolific writer, the extent of his œuvre surpasses what remains of any other ancient author; his work decidedly influenced not only his successors in late antiquity, but was of fundamental importance for all premodern medicine. "Galenism" profoundly shaped medieval science across cultural and religious boundaries (Byzantium, Islamic medicine, the Latin West), it was constitutional to Renaissance medicine in the 16th century, and remained influential well into modern times. 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 named.

On the one hand the project is devoted to a compendium of Galenic Medicine. On the other hand an annotated catalogue of all remaining Galenic writings (approximately 400) is devised to provide a much needed reference work for scholars in the field.

Receptions of Ancient Psychopathology

Project manager: Dr. N. Metzger

The look back to ancient medicine and its most illustrious protagonists has been seminal to physicians, their learning and identity for centuries. They have drawn onto ancient texts for orientation, legitimation, and distancing, thus using the ancient for their own purposes. Madness is intertwined like no other medical concept with its cultural background, therefore reception of ancient psychopathology is deeply affected by new medical outlooks, epistemological developments, and cultural surroundings and can be used to line out the changing faces of medicine in history.

This project focuses on reception in Byzantine late antiquity, early modern times, and the 19th century. In all three epochs, fundamental social and epistemological changes left their mark on how physicians read their ancient counterparts. Case studies include the medical encyclopedia of Paulos Nikaios (approximately 7th/9th AD), the early modern receptions of ancient illnesses contributed by physicians to the contemporaneous witchcraft debate (lycanthropy, incubus), and early trauma concepts in 19th century medicine.

Leprosy and Vagrancy in Southern German Free Imperial Cities

Project managers: PD Dr. F. Dross, Dr. A. Kinzelbach

Extensive research has been done on medieval leprosaria; nevertheless, their contextualization with (municipal) health care is still deficient. This project focuses on a social group which is especially hard to pinpoint - vagrant lepers whose traces in archive material tied to a certain place are particularly elusive. Extensive archival research concentrates on Free Imperial Cities (Reichsstädte) in Swabia and Franconia with the intention of establishing basic facts urgently needed for further resarch. Furthermore, this research is able to shed light on the very beginnings of health care policies in medieval urban communities.

Early 18th Century Medical Practice: Physician Johann Christoph Götz (1688 - 1733) from Nürnberg

Project manager: Prof. Dr. M.M. Ruisinger

This project is part of the DFG funded research cluster on 17th to 19th century medical practices ("Ärztliche Praxis im 17.-19. Jahrhundert", spokesperson Prof. Dr. Dr. M. Stolberg, Würzburg). It is dedicated to quantitative and qualitative analysis of the early 18th century medical records by the hand of J.C. Götz which have fortunately been preserved in the Trew Collection of the local university library Erlangen. His patients, their ailments and social status, furthermore his arrangements and contemporaneous medical knowledge can be brought to surface. Selected case stories especially rich in detail are closely scrutinized.

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

Project managers: Prof. Dr. K.-H. Leven, P. Rauh

Funded by Stifterverband für die Deutsche Wissenschaft and Deutsche Gesellschaft für Arbeitsmedizin und Umweltmedizin e.V.

Directed to optimize physical performance and work output, occupational medicine played a leading role in NS health, labor, and social pol-

icy. This project evaluates the contribution of E.W. Baader, one of the dominating figures in the field during the times of Weimar Republic, NS, and early Bundesrepublik, in relation to its respective cultural and ideological background. Research focuses on Baader's scientific contribution, his leeway of choices especially in the NS era, his relationships with exiled Jewish colleagues, his reestablishment during the early days of the Bundesrepublik, and, channeling all the questions mentioned, the complex issue of Vergangenheitsbewältigung. Drawing on so far unused archive material, the formation of German occupational medicine during Baader's lifetime is to be reassessed.
The concluding volume will be published in early 2013.

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

Project managers: Prof. Dr. K.-H. Leven, P. Rauh
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.

History of the Bavarian Society for Gynecology and Obstetrics in the 20th Century (in cooperation with the Department of Obstetrics and Gynecology)

Project managers: PD Dr. F. Dross, PD Dr. W. Frobenius
The Bavarian Society for Gynecology and Obstetrics ("Bayerische Gesellschaft für Geburtshilfe und Frauenheilkunde" [BGGF]) was established in 1912. On the occasion of its centenary, this project is dedicated to the history of the society focusing on its professional policy in 20th century Western Germany. The role of the society and its members in Nazi Germany will be highlighted as well as its dealing with this matter afterwards.

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

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

Teaching

Medical Terminology (first term students in human medicine/dentistry); Querschnittsbereich Q 2 "History, Theory, and Ethics of Medicine" (seventh term medicine) and "History of Science and Ethics" (degree program in molecular medicine), Querschnittsbereich Q 7 "Medicine and Aging" in the section concerned with old age in past and present.
Medical Terminology introduces students to the specific technical language employed in anatomy and clinical medicine. At the same time it aims at placing medicine in its social and historical context.
History, Theory, and Ethics of Medicine includes lectures dedicated to the basic principles of the medical humanities while the specific skills are imparted in seminars. Teaching methods include text interpretation, discussion of case histories, role play, multimedia presentations, and excursions.
Elective seminars offer further insight into historical and ethical subjects to students with special interest in the medical humanities (Wahlpflichtfach), such as "Death and Dying in Cultural Perspective", Chair of History of Medicine in collaboration with the Chair of Anatomy I, furthermore "Introduction to methods and objectives of medical historiography". Seminars on selected topics close to current research interests are offered each term, in certain cases in conjunction with the Master Program "Mittelalter- und Renaissance-Studien" and/or colleagues in the Philosophical Faculty.
In addition, courses in ethics and interpersonal skills are provided as part of the Introduction to Clinical Medicine. Courses range from "Skills in Ethical Communication" over "Breaking Bad News" and "Speaking about Death and Dying" to "Intercultural Communication", some of those featuring simulated patients to practice difficult communicative situations.
The lecture series "Über den Tellerrand" caters current research topics to a wider audience. Invited external medical historians give insight into their work in the monthly "Medizinhistorische Vortragsreihe".

Selected Publications

Dross F, Kinzelbach A (2011). „nit mehr alls sein burger, sonder alls ein Frembder." Fremdheit und Aussatz in frühneuzeitlichen Reichsstädten. Medizinhist J, 46: 1-23

Rauh P (2011) Victory for the „most enduring" hearts: The treatment of physically exhausted soldiers in the German Army (1914-1918). Neuere Med Wiss Quellen Stud, 26: 160-82

K.-H. Leven: Apolls Sonne über dem Abendland. Medizin zwischen Orient und Okzident. In: Sitzungsberichte der Physikalisch-Medizinischen Sozietät zu Erlangen. Neue Folge, Bd. 11, Heft 4. Erlangen, Jena 2011, S. 1-22.

K.-H. Leven, P. Rauh: E. W. Baader (1892-1962) und die Arbeitsmedizin im Nationalsozialismus. Arbeitsmedizin, Sozialmedizin, Umweltmedizin 47 (2012), S. 72-75.

R. Wittern-Sterzel: Frauenärztinnen in der ersten Hälfte des 20. Jahrhunderts. In: C. Anthuber, M. W. Beckmann, J. Dietl, F. Dross, W. Frobenius (Hrsg.) Herausforderungen. 100 Jahre Bayerische Gesellschaft für Geburtshilfe und Frauenheilkunde, Stuttgart: Thieme 2012, S. 47-59.

N. Metzger: Wolfsmenschen und nächtliche Heimsuchungen. Zur kulturhistorischen Verortung vormoderner Konzepte von Lykanthropie und Ephialtes, Remscheid: Gardez Verlag 2011.

Meetings and International Training Courses

26.-28.09.2011: Medizin und Technologie: XIII. Medizinhistorische Gemeinschaftstagung, Posen, Polen

Lecture series for a wider audience on current research of the Institute of the History of Medicine and Medical Ethics

Institute of the History of Medicine and Medical Ethics

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Research Focus

- Clinical Ethics and Ethics Counseling
- Project Title: Medical Ethics and Human Rights: Reassessing 50 Years of the Declaration of Helsinki (1964 - 2014)
- Medicine and Human Rights
- Philosophy of Medicine and Enhancement

Structure of the Department

The Professorship for Medical Ethics together with the Chair of the History of Medicine constitute the Institute of the History of Medicine and Medical Ethics. It includes the Forum Medicine and Human Rights ("Forum Medizin und Menschenrechte"), founded in 2006, and the Coordinating Office of the Clinical Ethics Committee. Furthermore, the Institute harbors the Erlangen Medical Collection. In total, 16 employees work at the Institute, of which 14 are academic personnel with eight in part-time positions. Chair and Professorship cooperate in joint research projects on history and contemporary history of medical ethics (e.g. medicine in NS-Germany, history of the Faculty of Medicine Erlangen, medical ethics in Germany after 1945).

25 doctoral theses are being supervised at the Professorship for Medical Ethics and ten academic book series are being edited.

The main areas of research are clinical ethics and ethics counseling, medicine and human rights, and the philosophy of medicine and enhancement.

The field of clinical ethics deals with foundational ethical questions concerning the adequate supply of patients, motivation of the acts of physicians during the daily routine, and conflict situations in hospital and other medical facilities. Central questions deal with issues at the beginning of life (prenatal diagnosis, pregnancy challenges, neonatology etc.) during a crisis (oncology, genetic advice, psychiatry, transplantation) and at the end of life (advance directives, euthanasia, terminal care). Some important means of clinical ethics are the analysis of arguments of applied medical ethics and bioethics, advice via ethics committees, and empirical research.

The field "Medicine and Human Rights" deals with several aspects of the relationships between human rights, medicine, and the biological sciences ("Dual obligations" of physicians, health care for migrants and „Sans Papiers", female genital mutilation, torture and medicine etc.). This topic is unique at a Faculty of Medicine in Germany. It is grounded institutionally in the "Forum Medicine and Human Rights".

The field "Philosophy of Medicine and Enhancement" covers theoretical questions concerning the concept "disease" and medical ethical issues with respect to the increase of the life span and the enhancement of cognitive and emotional capacities.

Research

Clinical Ethics and Ethics Counseling

Project managers: Prof. Dr. A. Frewer, PD Dr. L. Bergemann, Dr. F. Bruns, L. Fröhlich-Güzelsoy, Dr. K. Krása

A main field of expertise of the Professorship for Medical Ethics is research concerning clinical ethics counseling whereby a close cooperation with the Clinical Ethics Committee is given. Theoretical groundwork and documentation of ethics counseling and the evaluation of ethical counseling belong to this field of inquiry. Files of patient's advocates are being dealt with in the project "Clinical Ethics from the Patient's Perspective".

A further field of research are end of life conflicts, e.g. projects on ethical counseling, 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.

Project Title: Medical Ethics and Human Rights: Reassessing 50 Years of the Declaration of Helsinki (1964 - 2014)

The Declaration of Helsinki is one of the most important landmarks in human subject research which is aimed at protecting human participants in experimental science. By the beginning of the 1960s, even more frequent revelations about unethical research on disadvantaged and vulnerable populations and the widely publicised Thalidomide tragedy had prompted calls for greater state regulation. In June 1964, after years of debate, the WMA adopted the Declaration during its General Assembly in Helsinki, Finland. Efforts to safeguard human subjects in non-therapeutic experiments have intensified ever since the first Helsinki Declaration and are now codified in many national and international laws and regulations. The implementation of Institutional Review Boards (Research Ethics Committees) was a key element in that development. The current process of revising the Declaration of Helsinki is meant to coincide with the 50th anniversary of this important document which is why it receives global attention (Funding: Fondation Brocher, Wellcome Trust, Thyssen Stiftung).

Medicine and Human Rights

Project managers: Prof. Dr. A. Frewer, Dr. S.L. Sorgner, H. Furtmayr, M. Mylius, Dr. S. Kolb, Dr. J. Graf, Dr. K. Krása, W. Bornschlegl

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

Philosophy of Medicine and Enhancement

Project managers: Prof. Dr. A. Frewer, Dr. S.L. Sorgner

The field of enquiry "Philosophy of Medicine and Enhancement" deals with questions concerning the notion "disease" and human aging, moral evaluations of various aspects of hu-

man enhancement, preimplantation diagnosis, and deep brain stimulation. In this context, two academic book series are being edited: "Ars moriendi nova" and "Beyond Humanism: Trans- and Posthumanism".
Genetic enhancement discusses the moral relevance of promoting genes; neuroenhancement deals with ethical questions on the improvement of capacities of the brain in particular by means of psychoactive and neuroactive substances, but also via deep brain stimulation or brain-computer interfaces.

Teaching

The Institute of the History of Medicine and Medical Ethics is responsible for teaching the following courses according to medical curriculum: Medical Terminology (1st term students in human medicine/dentistry); Querschnittsbereich (cross-sectional area) Q 2 "History, Theory, and Ethics of Medicine" (7th term medicine) and "History of Science and Ethics" (degree program in molecular medicine). Furthermore, it contributes to cross-sectional area Q 7 "Medicine and Aging" in the section concerned with old age in past and present.
Medical Terminology introduces students to the specific technical language employed in anatomy and clinical medicine; this includes basic understanding of Latin grammar and vocabulary necessary for anatomical terms, furthermore Greek for clinical usage. At the same time it aims at placing medicine in its social and historical context.
History, Theory, and Ethics of Medicine includes lectures dedicated to the basic principles of the medical humanities while the specific skills are imparted in seminars. In these seminars, small groups of students are made familiar with current questions, methods, and approaches in the field. They aim at sharpening the student's eye for social, ethical, and institutional problems. Teaching methods include text interpretation, discussion of case histories, role play, multimedia presentations, and excursions.
In addition, courses in ethics and interpersonal skills are procured as part of the "Introduction to Clinical Medicine". Courses range from "Skills in Ethical Communication" over "Breaking Bad News" and "Speaking about Death and Dying", "Intercultural Communication" to "Medical Acting on Borders", some of those featuring simulated patients to practice difficult communitative situations.
In cooperation with the Philosophical Faculty, courses on medical ethics and bioethics are being offered.
Furthermore, a lecture course on "Medicine, Ethics, and Human Rights" and an interdisciplinary series of presentations on questions concerning the history and ethics of medicine entitled "Jenseits des Tellerrands" ("Beyond one's own Nose") are being offered.

Selected Publications

Frewer, A./Bruns, F./May, A. (Hrsg.) (2012) Ethikberatung in der Medizin. Heidelberg u.a.

Schäfer, D./Müller-Busch, C./Frewer, A. (Hrsg.) (2012) Perspektiven zum Sterben. Ars moriendi nova, Band 2. Stuttgart.

Frewer, A./Bruns, F./Rascher, W. (Hrsg.) (2012) Medizin, Moral und Gefühl. Emotionen im ethischen Diskurs. JEK 5. Würzburg.

Frewer, A./Bruns, F./Rascher, W. (Hrsg.) (2011) Gesundheit, Empathie und Ökonomie. Kostbare Werte in der Medizin. JEK 4. Würzburg.

Bruns, F./Frewer, A. (2011) Ethics Consultation and Empathy. Finding the Balance in Clinical Settings. In: HEC Forum (2011) DOI 10.1007/s10730-011-9164-7.

Frewer, A. (2011) Strangers in the Hospital? In: Historia Hospitalium 27 (2011), S. 105-114.

International Cooperations

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

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

Meetings and International Training Courses

25.05.2011: Aktuelle Stunde zur Medizinethik. Vorgeburtliche Diagnostik, Behinderung und Gesellschaft. Forum in Zusammenarbeit mit dem Klinischen Ethikkomitee, Erlangen

29.06.2011: Workshop des Klinischen Ethikkomitees und der Professur für Ethik in der Medizin: Ethikberatung in der Medizin. Grundlagen - Modelle - Praxis, Erlangen

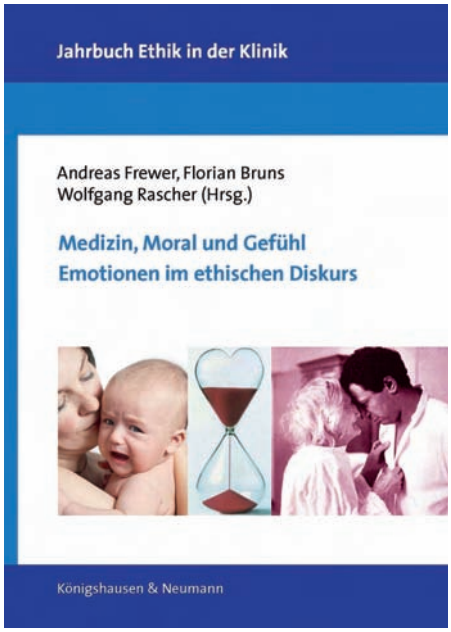
21.-23.10.2011: Transforming Human Nature in Science, Technology, and the Arts. Internationale Konferenz unter Beteiligung der Professur für Ethik in der Medizin, Dublin, Ireland

05.11.2011: 10. Ethiktag des Klinischen Ethikkomitees und der Professur für Ethik in der Medizin: Emotion und Ethik in der Medizin, Erlangen

23.05.2012: Workshop des Klinischen Ethikkomitees und der Professur für Ethik in der Medizin: Fehler in der Medizin - wie gehen wir damit um? Erlangen

27.10.2012: 11. Ethiktag des Klinischen Ethikkomitees: Risiko - Patient - Medizin. Fehler als Herausforderungen in der Gesundheitsversorgung, Erlangen

BMBF Project 'Clinical Ethics': Professorship for Medical Ethics edits new basic book.



Emotions in Medicine and Ethics - an important field of expertise: Yearbook of the Professorship for Medical Ethics documents scientific discourse.

Nikolaus-Fiebiger-Center of Molecular Medicine

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Research Focus

- The immune system, salt, and hypertension-induced target organ damage
- Cardiovascular and non-cardiovascular functions of the (pro)renin receptor
- The role of fibulin-4 in the mechanostability of the muskuloskeletal connective tissue
- Molecular mechanisms of endochondral ossification and skeletal development

Structure of the Department

The Chair of Experimental Medicine I is located at the NFZ and is, together with the Chair of Experimental Medicine II, responsible for the organization and administration of the Center. In 2011 - 2012, about seven scientists and technical staff were involved in research and teaching at the Chair of Experimental Medicine I, three of them supported by grants. Prof. Dr. D.N. Müller hold the Chair from April 2011 until October 2012. Since then, Prof. Dr. J. Behrens has been acting as temporary chairman. Prof. Dr. K. von der Mark (retired) continued to lead a research group financed by grants and participated in teaching molecular medicine. In a translational approach, the Müller lab focuses on the vessels, hearts, kidneys with the recent work extending these concepts to analyze how epigenetic factors, such as high salt, influence immune cells, and target organ damage.

Research

The immune system, salt, and hypertension-induced target organ damage

Project manager: Prof. Dr. D.N. Müller

The research of this working group is aimed at better understanding the role of innate and adaptive immunity in hypertension-induced organ damage. T cells, macrophages, and dendritic cells all harbor the AT1 receptor. We also observed that regulatory T cells modulate Ang II-induced cardiac damage to a point of therapeutic utility. Since our data suggested an interaction of the renin-angiotensin system, immune system, and target organ damage (see EM-figure), we are investigating the role of angiotensin II in autoimmunity.

In collaboration with Prof. Dr. R. Linker (Department of Neurology), we investigated whether blockade of the RAS improves non-cardiovascular autoimmunity. Our results suggest that by blocking the aspartyl protease renin, ACE, and the AT1 receptor, autoimmune encephalitis in rodents can be effectively inhibited.

We are now extending our immunological studies to the investigation of inflammatory activation in the interstitium by hyperosmolarity through sodium. This line of investigation was initiated with Prof. Dr. J. Titze (NFZ), with whom we have an intensive collaboration. With dietary sodium excess, sodium accumulates in the skin and activates the osmotic stress gene tonicity-responsive enhancer binding protein (TonEBP/NFAT5) in macrophages. TonEBP activity in macrophages results in secretion of VEGF-C promoting the clearance of hypertonic fluid from the interstitium. This circuit is critically dependent on macrophages and their ability to ward off hypertension in case of excess sodium supply. We have initiated a program to determine how hypertonicity induced by deranged sodium chloride storage affects the differentiation of T cells and macrophages.

Cardiovascular and non-cardiovascular functions of the (pro)renin receptor

The (pro)renin receptor (PRR) is a relatively newly discovered member of the renin-angiotensin system (RAS). Initially, PRR was believed to directly contribute to cardiovascular disease by activating the RAS and several signaling cascades. However, recent publications have shown that PRR plays an essential and non-RAS related role in the activation of Wnt signal transduction and cellular development. In light of this, our understanding of the role of the PRR in physiology and pathology has changed dramatically and we are now focused on determining these non-RAS functions of PRR.

We have initiated several PRR tissue-specific conditional knockout models. Generation of podocyte-specific PRR knockout mice (cKO) resulted in the death of the animals ~2-3 weeks after birth. Within 14 days, these cKO animals developed nephrotic syndrome and albuminuria, due to podocyte foot process fusion (compare figure) and cytoskeletal changes.

Our in vivo and in vitro findings indicated a functional block in autophagosome-lysosome fusion and overload of the proteasome protein degradation machinery. These results suggest that the PRR is essential for podocyte function and survival by maintaining autophagy and protein turnover machinery. We are now investigating the effect of PRR deletion in other cell types, namely T cells, pancreatic b-cells and renin-producing cells.

The role of fibulin-4 in the mechanostability of the muskuloskeletal connective tissue

Project manager: Dr. T. Sasaki

Fibulin-4 is a 50 kDa extracellular matrix protein which is essential - together with elastin and fibrillin - for assembly and function of elastic fibers of the cardiovascular, musculoskeletal, and lung elastic tissues. Patients with a recessive missense mutation in fibulin-4 display not only defects in elastogenesis, but also multiple bone fractures at birth; two patients showed arachnodactyly. Deficiency in fibulin-4 in mice is perinatally lethal due to cardiovascular and lung abnormalities and leads to joint contractures during fetal development. The goal of this DFG-funded project is to clarify the role of fibulin-4 in skeletal development. To this aim, the skeletal phenotype of fibulin-4 deficient mouse embryos is analyzed using morphological, immunohistochemical, and in situ hybridization techniques. Potential impairment of cell differentiation, alterations of matrix assembly, and dysregulation of TGF-β/BMP signaling are assessed in vitro, using primary cells isolated from wild type and fibulin-4 deficient mice. Particular attention is paid to identify further fibulin-4 binding proteins in order to elucidate the mechanisms by which the absence of fibulin-4 leads to abnormalities in mice and human. Furthermore, pathological consequences of missense mutations found in human patients will be analyzed using mutagenized, recombinantly produced fibilin-4 mutants in vitro. The proposed studies will provide novel insights into the role of fibulin-4 in skeletal system as well as in the development and homeostasis of cardiovascular tissue.

Molecular mechanisms of endochondral ossification and skeletal development

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

Cartilage cells (chondrocytes) have two rather adverse properties and functions in the fetal and the adult skeleton: A transient role during skeletal development and a permanent in adult cartilages of the joint, trachea, and in elastic cartilages of nose and ear. During development of the vertebral skeleton, chondrocytes shape the cartilage model of the subsequent bony skeleton. They grow and differentiate rapidly and will be replaced by bone cells in a complex process called

"endochondral ossification". For reproducible skeletal growth, a precise spatially and temporally coordinated control of endochondral ossification is an absolute requirement. Similar processes also occur during fracture callus healing and development of osteophytes in osteoarthritic joints. Therefore, elucidation of factors and mechanisms involved in endochondral ossification is essential not only for our understanding of the regulation of normal skeletal growth and skeletal dysplasias, but also for the development of new tools in the diagnosis and therapy of joint degeneration, fracture healing, and cartilage and bone repair. The analysis of these factors by means of in vitro techniques, cell and organ culture systems, and transgenic mouse models is currently the major focus of a DFG-funded research project.

The development of a collagen 10-specific targeting vector for recombination into BACs (bacterial artificial chromosomes) allowed the specific expression of transgenes, such as lacZ reporter genes, cre-recombinase as well as the transcription factor Sox9 in the hypertrophic zone of the murine growth plate. Overexpression of Sox9 significantly blocked resorption of hypertrophic cartilage, capillary invasion, and bone marrow formation in the developing long bones, resulting in impaired skeletal growth and reduced bone length. This demonstrated for the first time a novel role of Sox9 as angiogenic inhibitor of cartilage vascularization. The generation of Col10-specific Cre-deleter mice opened the possibilities for specific deletion of floxed genes in the hypertrophic zone of the growth plate. Mating the Col10-Cre mice with conditional β-catenin mice (Prof. Dr. R. Kemler, Freiburg) with floxed catenin alleles resulted in transgenic mice lacking trabecular bone in the subchondral zone of the diaphysis (compare figure). This deficiency was due to enhanced RANKL activity stimulating osteoclast differentiation in β-catenin deficient cartilage (compare figure). Several cooperations were started with laboratories in Vienna (Prof. Dr. C. Hartmann), Boston (Prof. Dr. B. Lanske), Houston (Prof. B. de Crombrugghe, MD) and Freiburg (Prof. Dr. B. Zabel) for specific gene inactivation studies of the hypertrophic zone using the Col10-Cre deleter mouse.

Teaching

The Chairs of Experimental Medicine I and II organize lectures, seminars, and experimental classes in cell, molecular, and developmental biology at basic and advanced levels for students of molecular medicine, human medicine, and biology. Special lectures, including tumor biology and oncology, molecular mechanism of cell differentiation, and development, cell-cell and cell-extracellular matrix interactions are given.

Selected Publications

Gelse K, Klinger P, Koch M, Surmann-Schmitt C, von der Mark K, Swoboda B, Hennig FF, Gusinde J (2011) Thrombospondin-1 prevents excessive ossification in cartilage repair tissue induced by osteogenic protein-1. Tissue Eng Part A, 17: 2101-12

Klinger P, Surmann-Schmitt C, Brem M, Swoboda B, Distler J, Carl HD, von der Mark K, Hennig FF, Gelse K (2011) Chondromodulin 1 stabilizes the chondrocyte phenotype and inhibits endochondral ossification of porcine cartilage repair tissue. Arthritis Rheum, 63: 2721-31

Riediger F, Quack I, Qadri F, Hartleben B, Park JK, Potthoff SA, Sohn D, Sihn G, Rousselle A, Fokuhl V, Maschke U, Purfürst B, Schneider W, Rump LC, Luft FC, Dechend R, Bader M, Huber TB, Nguyen G, Muller DN (2011) Prorenin receptor is essential for podocyte autophagy and survival. J Am Soc Nephrol, 22: 2193-202

Eitzinger N, Surmann-Schmitt C, Bösl M, Schett G, Engelke K, Hess A, von der Mark K, Stock M (2012) Ucma is not necessary for normal development of the mouse skeleton. Bone, 50: 670-80

Markó L, Kvakan H, Park JK, Qadri F, Spallek B, Binger KJ, Bowman EP, Kleinewietfeld M, Fokuhl V, Dechend R, Müller DN (2012) Interferon-γ signaling inhibition ameliorates angiotensin II-induced cardiac damage. Hypertension, 60: 1430-6

Park J, Bauer S, Pittrof A, Killian MS, Schmuki P, von der Mark K (2012) Synergistic control of mesenchymal stem cell differentiation by nanoscale surface geometry and immobilized growth factors on TiO2 nanotubes. Small, 8: 98-107

International Cooperations

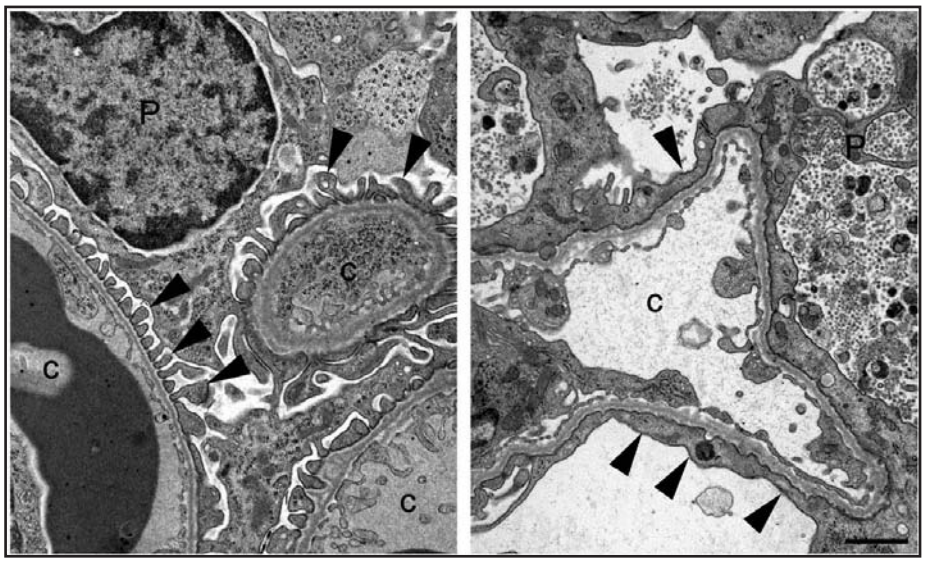
Prof. Dr. C. Hartmann, Institute of Molecular Pathology, IMP, Institute of Molecular Pathology, IMP, Vienna: Austria

Dr. G. Nguyen, College de France, Paris: France

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

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

Dr. M. Kleinewietfeld, Yale Medical School, New Haven: USA



EM shows normal epithelial cells and foot processes in control animals (left). cKO mice (right) developed foot process fusion (c=capillary, p=podocyte).

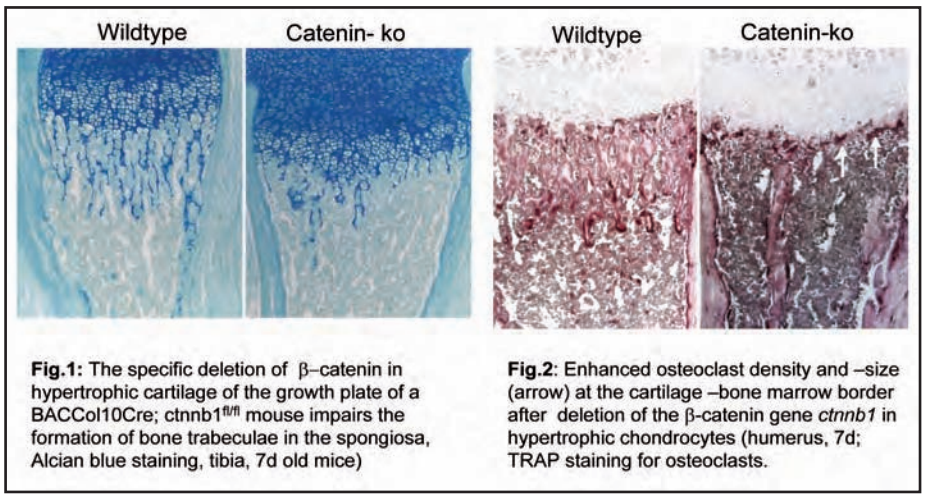


Fig.1: The specific deletion of β–catenin in hypertrophic cartilage of the growth plate of a BACCol10Cre; ctnnb1$^{fl/fl}$ mouse impairs the formation of bone trabeculae in the spongiosa, Alcian blue staining, tibia, 7d old mice)

Fig.2: Enhanced osteoclast density and –size (arrow) at the cartilage –bone marrow border after deletion of the β-catenin gene *ctnnb1* in hypertrophic chondrocytes (humerus, 7d; TRAP staining for osteoclasts.

Nikolaus-Fiebiger-Center of Molecular Medicine

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Research Focus

- Molecular oncology of Wnt signaling
- Amer proteins
- Role of conductin during the cell cycle
- Tumor suppressor APC
- Functional genomics of renal cell carcinoma

Structure of the Department

The Chair of Experimental Medicine II is situated at the NFZ. There are 16 staff members, nine of them scientists financed by third-party funds. During the reported period there were six PostDocs, six PhD students, three technicians, and one secretary. Our main goal is to investigate the molecular mechanisms of tumor development and progression by cell and molecular biological methods to find new ways for diagnosis, prognosis, and therapy.

Research

Molecular oncology of Wnt signaling

The Wnt signaling pathway regulates various processes during embryonic development and can lead to cancer. Wnts are secreted glycoproteins which induce the accumulation of β-catenin in cytoplasm and nucleus by binding to frizzled and LRP receptors. β-Catenin interacts with TCF transcription factors and activates target genes. The destruction of β-catenin is induced by phosphorylation in a multi-protein complex which consists of the scaffold component conductin, the serine/threonine kinase GSK3β and the tumor suppressor APC (Adenomatous Polyposis Coli). The Wnt signal inhibits phosphorylation of β-catenin and thereby leads to its stabilization. In colorectal tumors, mutations of APC or conductin or mutations of the serine/threonine phosphorylation sites of β-catenin lead to stabilization of β-catenin and trigger constitutive signaling to the nucleus. Such β-catenin mutations are also found in a multitude of other tumor types suggesting that aberrant activation of Wnt signaling is a key mechanism of oncogenic transformation. During the report period, we have characterized novel APC binding partners identified by our groups, the Amer proteins, as regulators of Wnt signaling and the cytoskeleton. We also found that the negative Wnt regulator Conductin/Axin2 is regulated during the cell cycle leading to differential activity of the Wnt pathway at different cell cycle phases. Finally, we showed that truncated APC tumor suppressor protein serves an essential function in colorecla cancer by regulating Wnt pathway activity.

Amer proteins

Project managers: Dr. K. Tanneberger, Dr. A. Pfister, K. Brauburger

The Amer protein family consists of three members, Amer1, Amer2, and Amer3. These proteins are characterized by their ability to interact with APC, and Amer1 and Amer2 were shown to be able to recruit APC to the plasma membrane. Hence the name Amer for "APC membrane recruitment" was chosen. Amer3 lacks membrane association and interacts with APC at the microtubule cytoskeleton and in the cytoplasm. Amer1 is identical to the tumor suppressor WTX and can inhibit Wnt/β-catenin signaling which requires membrane binding of Amer1. Moreover, we found that Amer1 acts as a positive regulator of Wnt signaling by binding to the LRP 6 receptor and thereby promoting its phosphorylation (figure). We have furthermore characterized the related Amer2 protein. Amer2 interacts with APC, like Amer1, thus reducing Wnt signal transduction. In addition, Amer2 binds to the microtubule-associated EB1 protein and can lead to microtubule stabilization. Thus, Amer proteins act as regulators of Wnt signaling, but are also involved in other pathways and molecular mechanisms suggesting a complex picture of Amer function for which the in vivo consequences are not yet clear.

Role of conductin during the cell cycle

Project managers: Dr. M. Hadjihannas, M. Brückner

We found that conductin levels are regulated during the cell cycle with lowest levels present during the G1/S phase and highest during G2/M. Following exit from mitosis, conductin expression levels decline in parallel with those of mitotic regulators, such as cyclin B1. In line, Wnt/β-catenin target genes are low at G2/M and high at G1/S, and β-catenin phosphorylation oscillates during the cell cycle in a conductin-dependent manner. Conductin is degraded by the anaphase-promoting complex/cyclosome cofactor CDC20. Knockdown of CDC20 blocks Wnt signaling through conductin. CDC20-resistant conductin inhibits Wnt signaling and attenuates colony formation of colorectal cancer cells. We propose that CDC20-mediated degradation of conductin regulates Wnt/β-catenin signaling for maximal activity during G1/S.

Tumor suppressor APC

Project managers: Dr. V. Chandra, Dr. J. Schneikert

The tumor suppressor APC is truncated in most colon cancers, but is not completely lost. It is not clear why colon cancer cells retain the truncated APC fragment. We found that the transcriptional repressor C-terminal binding protein (CtBP) promotes the oligomerization of truncated APC through binding to the 15 amino acid repeats of truncated APC. CtBP can bind to either first, third, or fourth 15 amino acid repeats, but not to the second. CtBP-mediated oligomerization requires both, dimerization domains of truncated APC as well as CtBP dimerization. This suggests that the sensitivity of truncated APC to oligomerization by CtBP constitutes an essential facet of tumor development.

RNA interference was used to down-regulate truncated APC in several colorectal cancer cell lines expressing truncated APCs of different lengths, thereby performing an analysis covering most of the mutation cluster region. The consequences on proliferation in vitro, tumor formation in vivo, and the level and transcriptional activity of β-catenin were investigated. Down-regulation of truncated APC results in an inhibition of tumor cell population expansion in vitro in six cell lines out of six and inhibition of tumor outgrowth in vivo as analyzed in one of these cell lines, HT29. Down-regulation of truncated APC is accompanied by an up-regulation of the transcriptional activity of β-catenin and in most cases β-catenin levels, indicating that truncated APC can still modulate Wnt sign-

aling through controlling the level of β-catenin. Thus, truncated APC is an essential component of colorectal cancer cells, required for cell proliferation, possibly by adjusting β-catenin signaling to the "just right" level.

Functional genomics of renal cell carcinoma

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

We have established gene expression patterns of renal cell carcinomas in order to identify genes relevant for the tumor biology and clinical course of this disease. We found that Activin B, a member of the TGFβ family, is highly overexpressed in kidney tumors as compared to normal kidneys and that its expression is regulated by the VHL/HIF system. In the report period, we found that Activin B regulates Rho/Rac signaling, thus altering cell morphology and the invasiveness of renal cancer cells.

Teaching

Training in cell biology for students of Molecular Medicine in cooperation with the Chair of Experimental Medicine I.

Selected Publications

Schneikert J, Brauburger K, Behrens J (2011) APC mutations in colorectal tumours from FAP patients are selected for CtBP-mediated oligomerization of truncated APC. Hum Mol Genet, 20: 3554-64

Tanneberger K, Pfister AS, Brauburger K, Schneikert J, Hadjihannas MV, Kriz V, Schulte G, Bryja V, Behrens J (2011) Amer1/WTX couples Wnt-induced formation of PtdIns(4,5)P(2) to LRP6 phosphorylation. EMBO J, 30: 1433-43

Tanneberger K, Pfister AS, Kriz V, Bryja V, Schambony A, Behrens J (2011) Structural and Functional Characterization of the Wnt Inhibitor APC Membrane Recruitment 1 (Amer1). J Biol Chem, 286: 19204-14

Hadjihannas MV, Bernkopf DB, Brückner M, Behrens J (2012) Cell cycle control of Wnt/β-catenin signalling by conductin/axin2 through CDC20. EMBO Rep, 13: 347-54

Pfister AS, Hadjihannas MV, Roehrig W, Schambony A, Behrens J (2012) Amer2 protein interacts with EB1 protein and adenomatous polyposis coli (APC) and controls microtubule stability and cell migration. J Biol Chem, 287: 35333-40

Pfister AS, Tanneberger K, Schambony A, Behrens J (2012) Amer2 protein is a novel negative regulator of Wnt/β-catenin signaling involved in neuroectodermal patterning. J Biol Chem, 287: 1734-41

International Cooperations

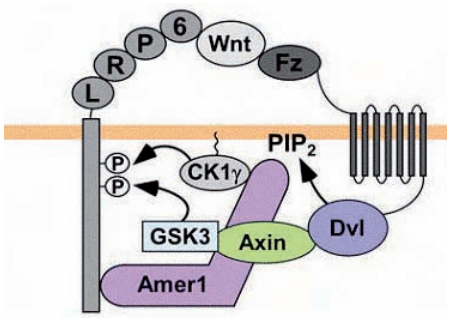
Dr. V. Bryja, Institute of Experimental Biology, University of Brno, Brno: Czech Republic

Prof. Dr. O. Ritvos, Biomedicum Helsinki, University of Helsinki, Helsinki: Finland

Research Equipment

Dako Cytomation, MoFlo - cell sorter

Applied Biosystems, Genetic Analyzer ABI 3130



Regulation of LRP6 Phosphorylation by Amer1. Amer1 is recruited to the plasma membrane after Wnt-stimulated synthesis of Phosphatidylinositol(4,5)bisphosphate (PIP2) by PI4KII and PIP5KI and associates with LRP6. As a consequence, associated protein kinases GSK3 und CK1γ are recruited to the vicinity of LRP6 and phosphorylate its cytoplasmic domain. Phosphorylated LRP6 inhibits β-Catenin degradation, thereby initiating the Wnt/β-catenin signaling cascade.

Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH

Chair of Orthopedics and Orthopedic Surgery

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

Structure of the Department

14 medical doctors work in the Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH. The research is accomplished by two postdoctorate medical doctors, 20 graduate students, and one study nurse.
In the endoprosthesis working group, apart from the standardized clinical and radiological long-term investigations for quality control after navigated and non-navigated total hip and knee surgery, periprosthetic bone density measurements are accomplished by means of computer tomography (CT)-assisted osteodensitometrie and radiostereometric analysis (RSA) for the evaluation of the migration pattern of the prostheses. The influence of navigation, the prosthesis design, and the prosthesis coating on the longevity of the implant is investigated by these procedures.
The research group for neuromuscular disorders is engaged in a study and evaluation of conservative and operative treatment in children and adult patients with neuromuscular disorders (anterior horn cell diseases, spinal muscular atrophies, post polio syndrome, muscular dystrophies).
The common aim of research in care for patients with cerebral palsy is the evaluation of results of botulinum toxin therapy and optimizing of orthopedic treatment strategies to improve the quality of life of these patients.
The clinical focuses of our Department are: Total hip-, knee-, and shoulderarthroplasty, spine surgery, pediatric orthopedics, foot surgery, tumorsurgery, arthroscopic operations.

Research

Computer assisted surgery of the hip joint

Project managers: Prof. Dr. R. Forst, PD Dr. L. Müller
The aim of this study is to develop a navigation system for total hip arthroplasty and to use it for the surgery process as well as to test the accuracy of the system with integrated modules. The system works with three-dimensional CT-data. The received data are used for the virtual positioning of the implant preoperatively. Intraoperatively, the navigation system compares the virtual data with the surgical view to achieve an exact position of the implant. The preoperative CT is then compared with a new postoperative CT to evaluate the accuracy of the implantation. Postoperatively, osteointegration of the implant is analyzed using CT-osteodensitometry. Thus for all steps (planning, surgery, and evaluation) of computer assisted surgery, highly precise measurements are conducted which allow an exact comparison of the received data. 50 patients will be analyzed.

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

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

Radiostereometric analysis for quality control in total hip arthroplasty

Project managers: Prof. Dr. R. Forst, Dr. S. Sesselmann
Recent studies lead to the conclusion that a measurement of migration within the first two years forms a basis for predicting the long-term outcome of the acetabular and femoral component when considered separately. The quality control is achieved with thorough documentation and precise analysis of fixation.
Measurements on conventional radiographs can have an accuracy of 1-5mm and 1°- 6° depending on the technique employed, the anatomic region investigated, and the number of examiners. RSA has proven to be an accurate and safe method to objectify skeletal kinematics. RSA is based on radiographic examinations of calibration cages and object markers implanted in the skeleton. Accurate measurement of radiographs and computer-assisted calculation can provide a three-dimensional motion analysis. RSA can be performed with an accuracy of 10-250 μm and 0.03°-0.6°. Altogether, 200 patients have been supervised with RSA after total hip replacement in Erlangen since 1998. The following examinations are carried out with these clients in different studies: Measuring of migration of polyethylene cups after bone grafting and reinforcement of acetabular ring with hook for severe acetabular dysplasia, measuring of initial stability of acetabular components with alumina and polyethylene liner in a comparison essay, measuring of migration of cemented femoral components into dependence of various cementing techniques in a comparison essay, and measuring of migration of uncemented femoral components after early load transfer.

Neuromuscular disorders

Project managers: PD Dr. J. Forst, Dr. A. Fujak, Prof. Dr. R. Forst
The research group for neuromuscular disorders is engaged in an evaluation of orthopedic symptoms, conservative and operative treatment in children and adult patients with neuromuscular disorders. The aim of research is the optimization of orthopedic treatment, improvement of the medical care and quality of life of these patients. The studies are particularly focused on anterior horn cell diseases, spinal muscular atrophies, post polio syndrome, and muscular dystrophies.
Although knowledge of the gene defect and the coded protein - the dystrophin - is given, there is no causal therapy of Duchenne mus-

cular 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 prospective study in collective of more 500 patients with genetically confirmed diagnosis of DMD. Positive effect of this treatment could be proven, and a stage-oriented therapy concept could be developed.
In close cooperation with the Department of Anesthesiology, 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.

Teaching

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

Selected Publications

Fujak A, Kopschina C, Forst R, Mueller LA, Forst JX (2011) Use of orthoses and orthopaedic technical devices in proximal spinal muscular atrophy. Results of survey in 194 SMA patients. Disabil Rehabil Assist Technol, 6: 305-11

Kress AM, Schmidt R, Vogel T, Nowak TE, Forst R, Mueller LA (2011) Quantitative computed tomography-assisted osteodensitometry of the pelvis after press-fit cup fixation: a prospective ten-year follow-up. J Bone Joint Surg Am, 93: 1152-7

Müller LA, Wenger N, Schramm M, Hohmann D, Forst R, Carl HD (2011) 17-year follow-up of the rough-blasted threaded Weill cup in uncemented total hip arthroplasty. Arch Orthop Trauma Surg, 131: 557-61

Fujak A, Raab W, Schuh A, Kreß A, Forst R, Forst J (2012) Operative treatment of scoliosis in proximal spinal muscular atrophy: results of 41 patients. Arch Orthop Trauma Surg, 132: 1697-706

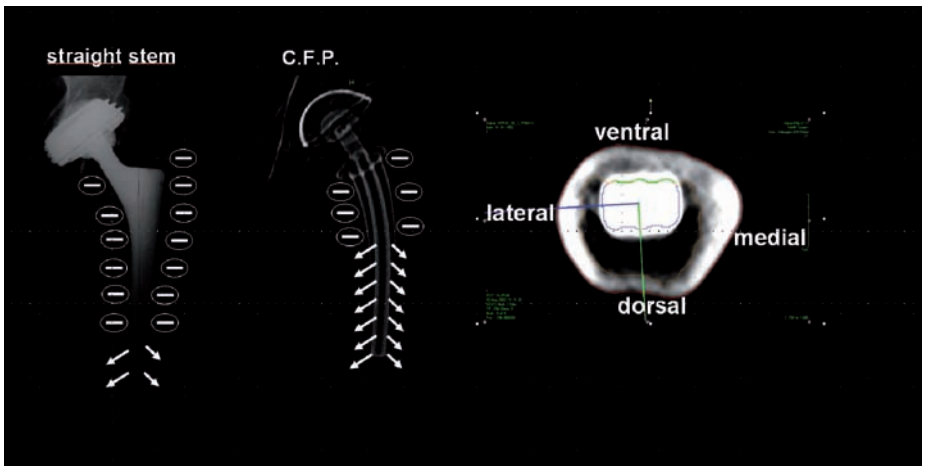
Fujak A, Müller K, Legal W, Legal H, Forst R, Forst J (2012) [Long-term results of Imhäuser osteotomy for chronic slipped femoral head epiphysiolysis]. Orthopade, 41: 452-8

Kress AM, Schmidt R, Nowak TE, Nowak M, Haeberle L, Forst R, Mueller LA (2012) Stress-related femoral cortical and cancellous bone density loss after collum femoris preserving uncemented total hip arthroplasty: a prospective 7-year follow-up with quantitative computed tomography. Arch Orthop Trauma Surg, 132: 1111-9

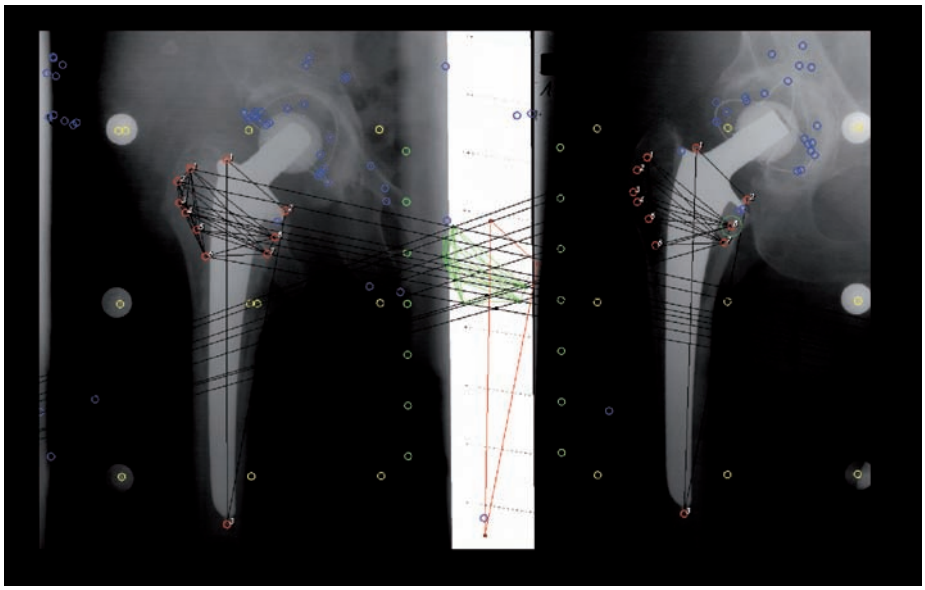
International Cooperations

Institute Duchenne de Boulogne, Poitiers: France

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



CT-osteodensitometry: Distribution of forces after femoral neck-conserving versus standard hip endoprothesis.



RSA after hip joint replacement surgery is based on the radiologic research of marked carcass sections and enables a 3D-analysis of micro-movement with an accuracy of 1-250 µm and 0.03°- 0.6°.

Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH

Division of Orthopedic Rheumatology

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Research Focus

- Arthroscopic synovectomy
- Dynamic pedobarography
- Endoprostheses for degenerative and inflammatory joint diseases
- Cellular and molecular basis of cartilage degeneration and regeneration - Mechanisms for the stabilization of the chondrocyte phenotype

Structure of the Department

The Division of Orthopedic Rheumatology is an independent institution of the FAU which is associated with the Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH.
Clinical activities focus on the treatment of patients with degenerative and inflammatory joint diseases. The head of the Division is also speaker of the Erlangen Arthritis Center which is an interdisciplinary association of physicians treating these patients.
Clinical research activities concentrate on the evaluation of surgical treatments. Of interest are preventive procedures, like synovectomies. Comparing joint replacements in patients with degenerative and inflammatory joint diseases will help to identify different preoperative findings, different intraoperative challenges as well as long term patients´ satisfaction.
Another focus of basic research are the mechanisms of induction and progression of osteoarthritis. Projects are funded by the DFG. A better understanding of osteoarthritis will help to develop new therapeutic approaches, like tissue engineering.
The scientific projects are performed by three medical doctors which are also involved in patient care and one technician. Three scientists are funded by the DFG.

Research

Arthroscopic synovectomy

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

Dynamic pedobarography

Project managers: PD Dr. H.-D. Carl, Dr. J. Pauser
Dynamic pedobarography is a computer-based method to assess forces from the ground-sole interface with sensor-loaded insoles. The parameter "peak plantar pressure" has been in the focus of several studies, as it has been described as a risk factor for plantar ulcers and metatarsal fractures. The Division of Orthopedic Rheumatology currently conducts the following studies:
- Foot loading with partial weight bearing following total hip and knee replacement;
- Foot loadings in elite male soccer players;
- Evaluation of several orthotic devices that intend to reduce foot loading;
- Foot loading in relation to knee joint mobility.

Endoprostheses for degenerative and inflammatory joint diseases

Project managers: Dr. A. Jendrissek, Prof. Dr. B. Swoboda
Clinical studies are conducted on the clinical outcome of large joint arthroplasty, especially in patients with degenerative and inflammatory joint diseases. For this purpose, different preoperative findings, surgical requirements, postoperative outcome, and patient satisfaction are examined. First and foremost, the long-term treatment results are observed in the different patient groups. The main focus of this work is knee replacement.

Cellular and molecular basis of cartilage degeneration and regeneration - Mechanisms for the stabilization of the chondrocyte phenotype

Project manager: PD Dr. K. Gelse
This project focuses on the mechanisms that induce chondrogenesis and stabilize the phenotype of articular chondrocytes. In a project funded by the DFG, it could be demonstrated that Chondromodulin-I (Chm-I) and Thrombospondin-1 (TSP-1) exert a stabilizing effect on the chondrocyte phenotype and inhibit the terminal differentiation. Both factors exerted a strong anti-angiogenic effect in vitro and could prevent inadvertent excessive endochondral ossification in cartilage defects in an animal cartilage repair model. Gene expression studies indicated that the observed effects depend on an inhibitory effect on the cell cycle, since the cell cycle inhibitor p21cip/waf was identified as one of the main upregulated target genes. Furthermore, the inhibition of the expression of GADD45β seemed to prevent terminal chondrocyte differentiation.
Further gene expression analyses (cDNA arrays) demonstrated that a number of inhibitory factors, such as the BMP-inhibitor Grem-1 or the Wnt-inhibitors FRZB1 or WISP3, are significantly higher expressed in permanent articular cartilage as compared to the transient type of cartilage (e.g. osteophyte cartilage). These observations imply that the generation of hyaline repair cartilage does not solely rely on chondrogenic growth factors, but also on inhibitory-acting factors which may particularly be of immanent importance to prevent terminal chondrocyte differentiation and inadvertent ossification of repair cartilage tissue. Thus, in future therapeutic settings, it would be useful to load bioactive matrices with a cocktail of specific stimulatory and inhibitory factors for the generation of hyaline repair cartilage and for the inhibition of excessive ossification.

Teaching

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

Selected Publications

Goetz M, Klug S, Gelse K, Swoboda B, Carl HD (2011) Combined arthroscopic and radiation synovectomy of the knee joint in rheumatoid arthritis: 14-year follow-up. Arthroscopy, 27: 52-9

Gusinde J, Pauser J, Swoboda B, Gelse K, Carl HD (2011) Foot loading characteristics of different graduations of partial weight bearing. Int J Rehabil Res, 34: 261-4

Klinger P, Surmann-Schmitt C, Brem M, Swoboda B, Distler J, Carl HD, von der Mark K, Hennig FF, Gelse K (2011) Chondromodulin 1 stabilizes the chondrocyte phenotype and inhibits endochondral ossification of porcine cartilage repair tissue. Arthritis Rheum, 63: 2721-31

Pauser J, Jendrissek A, Swoboda B, Gelse K, Carl HD (2011) Inaccuracy of a physical strain trainer for the monitoring of partial weight bearing. Arch Phys Med Rehabil, 92: 1847-51

Carl HD, Swoboda B (2012) Presurgical and postsurgical orthotic management of the rheumatoid foot. Z Rheumatol, 71: 680-4

Gelse K, Ekici AB, Cipa F, Swoboda B, Carl HD, Olk A, Hennig FF, Klinger P (2012) Molecular differentiation between osteophytic and articular cartilage - clues for a transient and permanent chondrocyte phenotype. Osteoarthritis Cartilage, 20: 162-71

International Cooperations

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

Meetings and International Training Courses

21.05.2011: "Schulter-Nacken-Schmerz - Häufige Symptome in der täglichen Praxis", Internistische Schwerpunktpraxis, Erlangen

23.06.2012: "Was Sie schon immer über "Rheuma" wissen wollten", Schindlerhof, Nürnberg

Institute for Biomedicine of Aging

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Research Focus

- Clinical nutrition in the elderly
- Impact of long term high fat diets on the development of sarcopenia
- Sarcopenia
- Intensive care medicine
- Emergency medicine

Structure of the Department

The Institute for Biomedicine of Aging (IBA) is part of the Chair of Internal Medicine - Geriatrics at the FAU under the direction of Prof. Dr. C.C. Sieber. Research is clinically-epidemiologically and experimentally oriented and focused on nutrition and metabolism in the elderly, age-related decline of muscle mass and function (sarcopenia) and frailty. The clinical nutrition research is performed within the Theo and Friedl Schöller Foundation Professorship for Clinical Nutrition in the Elderly, hold by Prof. Dr. D. Volkert. Experimental research is headed by Prof. Dr. C. Bollheimer with a translational approach. Main focus there is aging with obesity and the accompanying loss of muscle mass and function, so-called sarcopenic obesity. The Institute is characterized by a high degree of interdisciplinary research with staff having a nutritonal, nursing, sports science, biology, and biochemistry background. It forms part of the Interdisciplinary Center of Aging Research (ICA; compare own report) of the FAU.

Research

Clinical nutrition in the elderly

Project manager: Prof. Dr. D. Volkert

Within the scope of the Theo and Friedl Schöller Foundation Professorship for Clinical Nutrition in the Elderly, one research project focused on the nutritional and health situation of home-cared older adults in Germany. This cross-sectional multicenter study was funded by the German Federal Ministry of Food, Agriculture, and Consumer Protection and performed on behalf of the German Nutrition Society (DGE). In Germany, the majority (70%) of about 2.5 million persons in need of care is living in private households and is being cared for by relatives and professional service providers. Nevertheless, only little is known about the nutritional situation of this specific population group. Aim of this study was a detailed evaluation of the nutritional situation of German home care receivers considering nutritional status, food, and nutrient intake as well as structural, social, and health factors. Recommendations to improve the situation and to reduce the burden on the caregivers should be derived. In a total of 353 home cared adults aged 65 years or older, nutritional problems were frequently observed. They were, however, less pronounced than in institutionalized elderly. The awareness of nutrition as one important contributor for health and functionality should be increased in the home care setting by expanding information and counseling, by integration of the topic "nutrition" in training and specialized courses for nurses and doctors, and by routine screening for malnutrition in the older population.

In another project, nutritional situation of community-dwelling older patients was evaluated in cooperation with general practitioners. Based on a standardized screening, kind and prevalence of nutritional problems and resulting need for advice and intervention were examined in outpatients aged 75 years or older in the family doctors practices. In patients with malnutrition or at risk of malnutrition, adequate nutrition was mainly compromised or jeopardized by health problems, pain, xerostomia, and chewing problems. Due to lacking cooperation of family doctors, the results cannot be regarded as representative and should be substantiated by future studies.

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

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

Sarcopenia denotes the exceeding decline of muscle mass, strength, and performance with age which could be induced by a lot of different pathological conditions. For example, obesity has been supposed to be one major risk factor and has led to the concept of sarcopenic obesity. The dietary animal model of aging high fat rat enables us to study molecular mechanisms by which obesity might be linked with sarcopenia. Employing Magnetic Resonance Imaging und Magnetic Resonance spectroscopy techniques, we further monitor the morphology of the muscle and muscular features with functional impact (such as fat and iron content) as well as the whole body fat distribution. During the whole lifetime of the rats, blood samples were collected and at 24 month of age, the animals were sacrificed and the organs were stored frozen. In the last years several devices were renewed and bought from third party funding and university grants (real time quantitative PCR with TaqManTM; ChemiDoc MP Imaging System from BioRad). Furthermore a method was established for analysis of fatty acid profiles in blood and muscle samples using the gas chromatography-mass spectrometry instrument in our laboratory. Aim of this study is the establishment of new metabolic biomarkers for sarcopenia induced by a high fat diet. Based on this preparatory work, the samples will be analyzed for pathologic abnormalities induced by the dietary intervention using multiple biochemical and histological approaches. We are especially interested in the pathways of AMP-activated protein kinase and the Peroxisome proliferator-activated receptor γ coactivator 1-α which are essential regulators of the metabolism and functionality of the muscle cells. This project is part of the Bavarian Research Association Sarcopenia and Osteoporosis - consequences of reduced regeneration at old age (FORMOsA).

Sarcopenia

Project manager: Dr. M. Drey

The Institute for Biomedicine of Aging was involved in an international, multicentric, randomized, controlled trial for sarcopenia, sponsored by third-party funds. Aim of the study was to investigate the improvement of physical performance in community dwelling older adults by a nutritional supplement. Recruitment ended in August 2012. Results are expected on an international level at the end of 2013.

Besides the mentioned nutritional intervention in sarcopenic patients, the Institute has focused on neurodegenerative aspects in the onset of sarcopenia. For that reason, an electromyographical technique, called the Motor

Unit Number Index (MUNIX), coming from Neurology for monitoring the loss of motoneurons in patients suffering from Amyotrophic Lateralsclerosis (ALS), was used in sarcopenic patients. In sarcopenia, the age associated loss of motoneurons should lead to a degeneration of its muscle fibers, ending in muscle loss. In the cohort of sarcopenic patients from the aforementioned study, it could be shown that the mean MUNIX of the hypothenar muscle was between the mean MUNIX of ALS patients and the mean MUNIX of healthy controls. 25% of the sarcopenic patients had pathological MUNIX values suggesting that this subgroup suffers from sarcopenia caused by loss of motoneurons. In an EU-Cooperation Project FP7 (support code: 01QE1107B), the hypothesis was tested whether older adults with pathological MUNIX values suffer from muscle loss compared to healthy controls. Additionally, the concentration of C-terminal-Agrin Fragment (CAF) was measured to investigate the relationship to the degeneration of the neuromuscular junction as a cause of muscle loss. The study will be finished in 2013.

Intensive care medicine

Project managers: PD Dr. H.J. Heppner, Dr. K. Singler, Dr. P. Bahrmann

The research group is engaged in life-threatening diseases in old adults and their intensive care treatment. The main research is diagnosis and therapy of severe infections, primarily in lower respiratory tract in this patient group. The researchers light the physiological specific characteristics within infections as well as the difficulties in finding diagnosis and initiating treatment. Infections and sepsis in the elderly are the main focus of their scientific work. PD Dr. H.J. Heppner is speaker of the Geriatric section of the German Sepsis Society.

Emergency medicine

Project managers: PD Dr. H.J. Heppner, Dr. K. Singler, Dr. P. Bahrmann

Furthermore improvement of diagnosis and treatment of geriatic patients in the emergency department is another topic the research group is dealing with in tight collaboration with the emergency department of the Nuremberg Hospital. The target is to ensure appropriate treatment and supply according to the demographic shift. Implementation of structured clinical pathways, teaching of the medical staff, strengthening of geriatric know-how, and conduction of prospective trials to improve quality in treatment is the main focus of the scientific work in this area.

Teaching

"Instant Aging" is a simulation model of aging. It was integrated in the practical geriatric training of the Internal Medicine (Q 7). "Instant Aging" provides tools for medical students to bodily experience different age- and illness-related limitations of activity. The compulsory elective subject "Clinical Nutrition" focuses on nutritional issues of hospital patients.

Selected Publications

Bollheimer LC, Buettner R, Pongratz G, Brunner-Ploss R, Hechtl C, Banas M, Singler K, Hamer OW, Stroszczynski C, Sieber CC, Fellner C (2012) Sarcopenia in the aging high-fat fed rat: a pilot study for modeling sarcopenic obesity in rodents. Biogerontology, 13: 609-20

Drey M, Zech A, Freiberger E, Bertsch T, Uter W, Sieber CC, Pfeifer K, Bauer JM (2012) Effects of Strength Training versus Power Training on Physical Performance in Prefrail Community-Dwelling Older Adults. Gerontology, 58: 197-204

Heppner HJ, Singler K, Kwetkat A, Popp S, Esslinger AS, Bahrmann P, Kaiser M, Bertsch T, Sieber CC, Christ M (2012) Do clinical guidelines improve management of sepsis in critically ill elderly patients? A before-and-after study of the implementation of a sepsis protocol. Wien Klin Wochenschr, 124: 692-8

Wirth R, Voss C, Smoliner C, Sieber CC, Bauer JM, Volkert D (2012) Complications and mortality after percutaneous endoscopic gastrostomy in geriatrics: a prospective multicenter observational trial. J Am Med Dir Assoc, 13: 228-33

Bollwein J, Diekmann R, Kaiser MJ, Bauer JM, Uter W, Sieber CC, Volkert D (2013) Dietary quality is related to frailty in community-dwelling older adults. J Gerontol A Biol Sci Med Sci, 68: 483-9

Bollwein J, Volkert D, Diekmann R, Kaiser MJ, Uter W, Vidal K, Sieber CC, Bauer JM (2013) Nutritional Status According to the Mini Nutritional Assessment (MNA®) and Frailty in Community Dwelling Older Persons: A Close Relationship. J Nutr Health Aging, 17: 351-6

International Cooperations

European Academy for Medicine of Ageing (EAMA), Sion: Switzerland

Department of Anesthesiology

Chair of Anesthesiology

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Research Focus
- Clinical and experimental pharmacology of anesthesia
- Research projects furthering the curriculum and the medical education
- Medical technology of diagnostic and therapeutic procedures
- Pain research: Determinants and modulators of perioperative and palliative pain

Structure of the Department

The Department of Anesthesiology maintains 50 anesthesia units, 37 of which are run continuously, to provide anesthesia service to 15 surgical departments or independent divisions and several diagnostic and interventional departments of the UK Erlangen. The Department of Anesthesiology also includes an outpatient's anesthesia division with a unit for lung function diagnostics and a pain clinic. The Department of Anesthesiology is responsible for the management of the interdisciplinary surgical intensive care unit with 36 beds and, together with the Department of Neurology, holds the Center for Interdisciplinary Pain Therapy. Additionally, the Department of Anesthesiology is responsible for the management of the ambulance service for the city of Erlangen, the county of Erlangen-Höchstadt, and the Herzogenaurach location. The Department also engages in the field of air rescue with the air ambulance of the region (Christopher 27) as well as ambulance aircrafts for repatriation of patients.
The Chair of Anesthesiology of the FAU (Prof. Dr. Dr. h.c. J. Schüttler) as well as the extra Ordinariates for Experimental Anesthesiology (Prof. Dr. Dr. H. Schwilden) and Anesthesiology/Pain Research (Prof. Dr. C. Nau) are located at the Department of Anesthesiology. An autonomous unit with an Extraordinariate for Molecular Pneumology (Prof. Dr. S. Finotto) is affiliated to the Chair of Anesthesiology. An endowed chair for palliative medicine (Prof. Dr. C. Ostgathe) has been established since 2010. The Department of Anesthesiology employs 112 medical doctors and nine scientific members with responsibilities in research and teaching.

Research

Clinical and experimental pharmacology of anesthesia

This research focus considered a quantitative mathematical modeling of the pharmacokinetics and pharmacodynamics of anesthetic substances and neuromuscular blocking agents. Aims of this undertaking were: Model identification, computer simulation of the dynamics in time of anesthetic interventions to improve scientific study design and for educational purposes, and model based dosing strategies for therapeutic optimization.
Pharmacokinetic and pharmacodynamic modeling were performed for hydromorphon and sufentanil. In conjunction with the Department of Anesthesiology, University Turku, Finland, the pharmacokinetics of the α2-agonist dexmedetomidine during long term sedation in intensive care patients were investigated. Special focus was given on the influence of individual variability and covariates.
The investigation of the clinical pharmacology of neuromuscular blocking agents focused on the anesthetic management with respect to the interaction of i.v. anesthetics with muscle relaxants, especially for orthopedic surgery caused by the disease progression of muscle atrophy type Duchenne.

Research projects furthering the curriculum and the medical education

The Department of Anesthesiology (KfA) implemented several projects with the aim to gain further scientific insight as well as to improve the quality of the curriculum, the medical education, and training.
The KfA made an important contribution for the compilation of the new sample-curriculum for the specialization in anesthesiology on behalf of the German Medical Association and also gave important impetus for the specializations in intensive care, emergency, and pain medicine. Therefore these curricula could be brought into the line of modern concepts of educational sciences, indicated by a strong orientation on competencies and modularisation.
In order to broaden the range of teaching, the KfA set up and improved several innovative teaching projects, like the elective subject "perioperative medicine" and an internship in the emergency rescue service. We have been very successful at launching courses for emergency care in the fields of pediatric anesthesia and over several weeks an interprofessional one-day-course for all staff of the KfA on crisis management. In the latter course, a scientific focus was set on blockings in the communication over a hierarchy.
Another focus in the research on medical education is the study within a virtual environment. With the help of two initial fundings by ELAN, the KfA together with the chair for educational psychology continued a research project studying the learning process in a situational simulated environment with the focus on the determining factors of each type.
In cooperation with the Department of Oral and Cranio-Maxillofacial Surgery, we started a research project in order to improve the emergency competencies of dentists on basis of a blended-learning-concept, initiated by an elaborate needs assessment.

Medical technology of diagnostic and therapeutic procedures

Within the scope of the National Leading Edge Cluster Medical Valley EMN for Medical Technology, our research is focused on the development of new technologies for continuous and variable application of fluid drugs through miniaturized infusion pumps for a personalized, patient-individual, and effect-controlled drug treatment. New methods for a more precise measurement of opioid concentration in blood plasma have been developed, and the accuracy of existent dosing algorithms has been investigated. On the basis of the gathered experiences, the next step will be the implementation of new dosing strategies including the patient response to the target effect and the monitoring of analgesic adverse effects by respiratory and cardio-vascular parameters.
In the Medical Technology Test and Demonstration Center (METEAN), we investigated new methods for continuous and non-invasive acquisition of biosignals of the respiratory and cardiovascular system for therapy-relevant pa-

rameters for hemodynamic monitoring in cooperation with the Fraunhofer Institute for Integrated Circuits and the Max-Schaldach Chair for Medical Technology. An important goal of this research concentrated on the development of techniques for continuous, non-invasive, long-term acquisition of the central arterial blood pressure under daily standard conditions. A further research goal concentrated on the mathematical modeling of the arterial pulse wave.

Pain research: Determinants and modulators of perioperative and palliative pain

An interdisciplinary clinical research unit (KFO 130, compare own report) focused on postoperative pain that persists beyond the expected healing period. It was funded by the DFG until the end of 2012. The interdisciplinary and translational team focused on mechanisms in the peripheral and central nervous system that contribute to postoperative pain sensitization, on the influence of anesthetic and analgesic substances as well as on the questions in which cortical and subcortical regions postoperative pain sensitization is represented, which genetic factors determine increased postoperative pain and the risk for the development of persistent pain, and which psychological traits predict postoperative pain. The team employed basic, disease-, and patient-related methods of pain research.

Other preclinical projects investigated the role of TRP-channels in hereditary pain diseases, the role of the nociceptive-specific ion channels Nav1.7 and Nav1.8 in diabetic neuropathy, and the interaction of Nav1.7 with local anesthetics.

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

Teaching

The Department of Anesthesiology organizes the three cross-sectional areas Q8, Q12, Q14. Professional lecturers and instructors of the Department of Anesthesiology organize the cross-sectional area Q8 Emergency Medicine and are firmly committed to apply new concepts of teaching, such as the use of teaching simulators installed in the simulation and training center of the Department of Anesthesiology. Cross-sectional area Q12 Rehabilitation is organized as an interdisciplinary lecture series in the first lecture week of each term. The area Q14 Pain Medicine was first introduced in 2012 and has besides anesthesiology contributions from neurology and psychiatry. The curricular class "Klinische Anästhesiologie" teaches the scientific foundation of anesthesia for surgical interventions. Additionally, the Department offers six elective classes and some non-curricular classes in the fields of anesthesiology, intensive care medicine, emergency medicine, pain therapy, and palliative medicine as lectures, internships, seminars, and exercises.

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

Selected Publications

Leffler A, Lattrell A, Kronewald S, Niedermirtl F, Nau C (2011) Activation of TRPA1 by membrane permeable local anesthetics. Mol Pain, 7: 62

Tschaikowsky K, Hedwig-Geissing M, Braun GG, Radespiel-Troeger M (2011) Predictive value of procalcitonin, interleukin-6, and C-reactive protein for survival in postoperative patients with severe sepsis. J Crit Care, 26: 54-64

Bierhaus A, Fleming T, Stoyanov S, Leffler A, Babes A, Neacsu C, Sauer SK, Eberhardt M, Schnölzer M, Lasitschka F, Lasischka F, Neuhuber WL, Kichko TI, Konrade I, Elvert R, Mier W, Pirags V, Lukic IK, Morcos M, Dehmer T, Rabbani N, Thornalley PJ, Edelstein D, Nau C, Forbes J, Humpert PM, Schwaninger M, Ziegler D, Stern DM, Cooper ME, Haberkorn U, Brownlee M, Reeh PW, Nawroth PP (2012) Methylglyoxal modification of Nav1.8 facilitates nociceptive neuron firing and causes hyperalgesia in diabetic neuropathy. Nat Med, 18: 926-33

Iirola T, Ihmsen H, Laitio R, Kentala E, Aantaa R, Kurvinen JP, Scheinin M, Schwilden H, Schüttler J, Olkkola KT (2012) Population pharmacokinetics of dexmedetomidine during long-term sedation in intensive care patients. Br J Anaesth, 108: 460-8

Muenster T, Mueller C, Forst J, Huber H, Schmitt HJ (2012) Anaesthetic management in patients with Duchenne muscular dystrophy undergoing orthopaedic surgery: a review of 232 cases. Eur J Anaesthesiol, 29: 489-94

Fechner J, Ihmsen H, Schüttler J, Jeleazcov C (2013) The impact of intra-operative sufentanil dosing on post-operative pain, hyperalgesia and morphine consumption after cardiac surgery. Eur J Pain, 17: 562-70

International Cooperations

Prof. Y. Tian, Department of Anesthesiology Tongji Medical College, Huazong University for Science and Technology, Wuhan: China

Prof. B. Yu, Department of Anesthesiology Rui Jin Hospital, Shanghai Jiao Tong University, Shanghai: China

Prof. K.T. Olkkola, Department of Anaesthesiology, Intensive Care, Emergency Care, and Pain Medicine, University of Turku, Turku: Finland

Prof. S.G. Waxman, Center for Neuroscience and Regeneration Research, Yale School of Medicine, New Haven: USA

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

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Research Focus
- Immunopathogenesis of lung tumor and allergic asthma

Structure of the Department

The Division of Molecular Pneumology consists of eleven employees, currently supported by the Division, a grant from the SFB 643 (Role of NFAT family members in lung tumor), the DFG (Immuno-regulatory role of IL-28/Interferon λ in allergic asthma), the GK (Role of BATF in allergic asthma), and the European grant (Post-infectious reprogramming and its association with persistence and chronicity of respiratory allergic diseases, PreDicta). Research is conducted by ten scientists (besides Chairman one postdoctoral fellow, five PhD students, and four technicians). The team investigates the immunological responses present in experimental lung tumor and allergic asthma. This comprises analysis of the lung tumor infiltrating lymphocytes and lung lymphocytes present in allergic asthma. In collaboration with the Division of Thoracic Surgery, directed by Prof. Dr. H. Sirbu, the Institute of Pathology (Prof. Dr. A. Hartmann and Prof. Dr. R. Rieker), and Prof. Dr. L. Bräuer/Dr. M. Schicht of the Chair of Anatomy II at the FAU, our Division analyzes changes in immunological parameters at the protein and mRNA level in tissue after lung resection, obtained from patients with lung tumor. The aim of this study is to identify important genes involved in the pathogenesis of lung cancer to set up new experimental molecular therapeutical strategies to cure lung cancer. In addition, we recently received support from a European Grant, investigating the immunological response in asthmatic and non-asthmatic children after rhinovirus infection (PreDicta). For this study, we collaborate with several groups in Europe and with the Department of Pediatrics and Adolescent Medicine in Erlangen (Prof. Dr. T. Zimmermann's division of allergy and pulmonary diseases). A variety of molecular and cellular methods is applied for the investigation of isolated and purified lung immuno-competent cells. We are indebted to the numerous collaborations with different scientific departments worldwide which are providing us with updated material to advance our understanding and improvement of the therapy against these two world spreading lung diseases.

Research

Immunopathogenesis of lung tumor and allergic asthma

During the last five years our laboratory identified a number of genes which play a protective or pathogenetic role in the immuno-regulation of lung cancer development. Some examples for those genes are described below: EBV-induced gene 3 (EBI-3) encodes for a soluble type I receptor homologous to the p40 subunit of IL-12 that is expressed by APCs following activation. In a recent study we demonstrated that targeting EBI-3 leads to a T-bet-mediated CD8+ anti-tumor T cell response in a murine model of lung melanoma. T-bet (T-box-expressed in T cells) is a transcription factor expressed by T cells which controls Interferon γ production. T regulatory cells are also known as T suppressor cells because they inhibit the immuno-response and as such are increased in tumor. It is therefore the aim of our research to set up therapeutical tools to inhibit the T regulatory cells which are present in the lung bearing tumor. It has been recognized that the most important transcription factor of the T regulatory cells is Forkhead box P 3 (FoxP-3). We have recently described reduction of Nuclear Factor of Activated T cells -2 (NFATc2) mRNA expression in the lungs of patients with bronchial adenocarcinoma. Engagement of GITR with an agonistic antibody, known to suppress T regulatory cells and expand effector T cells, in NFATc2 (-/-) mice induced IFN-γ in the airways which reversed the suppression by T(reg) cells, and co-stimulated effector and memory T cells, resulting in abrogation of carcinoma progression delineating new possible strategies to turn on an immunoresponses in lung cancer. We recently described that targeted deletion of T-bet (T-box expressed in T cells), the main transcription factor inducing IFN-γ, resulted in enhanced lung tumor load and metastasis far beyond that seen in the wild type littermates in the same model. We are thus currently investigating disregulation of anti-tumor immune response present in T-bet deficient mice to better understand this disease. Moreover, we recently found increased IL-17A in the absence of T-bet and are investigating the role of IL-17A in lung adenocarcinoma both, in experimental setting as well as in translational studies in humans. Along with IL-17A, we are investigating the role of IL-6 and TGF-β, two Th17 inducing cytokines in lung adenocarcinoma. Allergic asthma is a disease characterized by imbalance of the CD4+ T helper cell subsets Th2/Th1 cytokines and transcription factors with a pathological expansion of the Th2 cells associated with a defect in T regulatory cells. We first identified GATA-3 as the main transcription factor of Th2 cells involved in the pathogenesis of allergic asthma and blocked it locally by intranasal delivery of an antisense molecule achieving inhibition of inflammation, airway hyperresponsiveness in treated mice comparable to steroid treatment. We then discovered that targeted deletion of T-bet in experimental asthma resulted in an asthmatic phenotype. Local blockade of IL-13 in T-bet deficient mice resulted in amelioration of the asthmatic phenotype in the absence of T-bet. Moreover, blockade of the α chain of the IL-6R resulted in local expansion of positive CD4+CD25+FoxP3+ Tregs with increased immunosuppressive functions. Thus, we found that local inhibition of IL-6 signaling emerges as a novel molecular approach for the treatment of allergic asthma. We are currently investigating the role of IL-6 in T-bet deficiency induced asthma. In addition, Tyrosine kinase 2 (Tyk2) is an ubiquitously expressed member of the mammalian Janus kinase (JAK) family of non-receptor protein tyrosine kinases which consists of three additional kinases (JAK1-3). We recently discovered that Tyk-2 signaling is involved in IL-17A production and are analyzing the molecular mechanism involved in this disregulation.

Teaching

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

Selected Publications

Koltsida O, Hausding M, Stavropoulos A, Koch S, Tzelepis G, Ubel C, Kotenko SV, Sideras P, Lehr HA, Tepe M, Klucher KM, Doyle SE, Neurath MF, Finotto S, Andreakos E (2011) IL-28A (IFN-λ2) modulates lung DC function to promote Th1 immune skewing and suppress allergic airway disease. EMBO Mol Med, 3: 348-61

Neurath MF, Finotto S (2011) IL-6 signaling in autoimmunity, chronic inflammation and inflammation-associated cancer. Cytokine Growth Factor Rev, 22: 83-9

Reppert S, Boross I, Koslowski M, Türeci Ö, Koch S, Lehr HA, Finotto S (2011) A role for T-bet-mediated tumour immune surveillance in anti-IL-17A treatment of lung cancer. Nat Commun, 2: 600

Andreev K, Graser A, Maier A, Mousset S, Finotto S (2012) Therapeutical measures to control airway tolerance in asthma and lung cancer. Front Immunol, 3: 216

Karwot R, Übel C, Bopp T, Schmitt E, Finotto S (2012) Increased immunosuppressive function of CD4(+)CD25(+) Foxp3(+)GITR+ T regulatory cells from NFATc2((-/-)) mice controls allergen-induced experimental asthma. Immunobiology, 217: 905-11

Neurath MF, Finotto S (2012) The emerging role of T cell cytokines in non-small cell lung cancer. Cytokine Growth Factor Rev, 23: 315-22

International Cooperations

Prof. N.G. Papadopoulos, Allergy and Clinical Immunology Unit, 2nd Pediatric Clinic, National and Kapodistrian University of Athens (NKUA), Athens: Greece

Prof. M.L. Kowalski, Department of Immunology, Rheumatology and Allergy, Faculty of Medicine, Medical University, Central University Hospital, Medical University of Lodz, Lodz: Poland

Dr. C. Bachert, Upper Airway Research Laboratory (UGENT), University of Ghent, Ghent: Belgium

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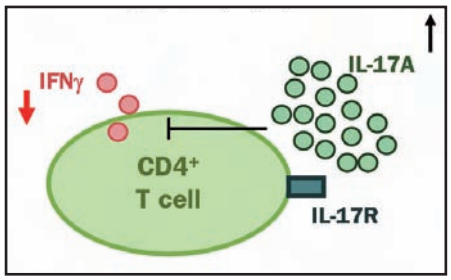
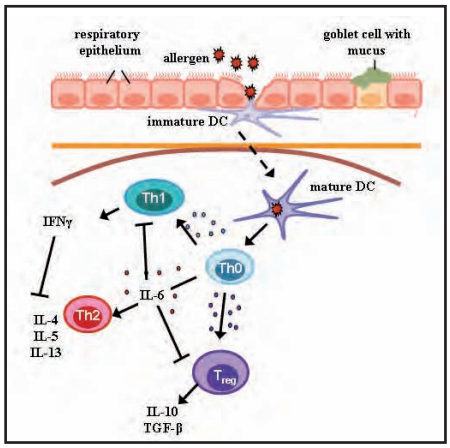
Dr. C. I. Ho, MD, Department of Rheumatology, Harvard University, Brigham and Women's Hospital, Boston, Massachusetts: USA

L.H. Glimcher, MD., Weill Cornell Medical College, New York: USA



Lung Tumour infiltrating Lymphocytes (TIL)
In lung adenocarcinoma, we found that lung tumor infiltrating lymphocytes release much IL-17A, a cytokine which inhibits according to our findings interferon γ (IFN-γ), an anti-tumor cytokine. IL-17R= IL-17A receptor



T cell differentiation in allergic asthma
After allergen challenge, dendritic cells mature and release proinflammatory mediators, such as IL-6 which directs Th0 differentiation into Th2 cells which in turn releases IL-4, IL-5, and IL-13, and are increased in allergic asthma. IL-6 inhibits T regulatory cells and Th1 cells, both known to have a protective role in asthma.

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Division of Palliative Medicine

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Research Focus

- Outcome Criteria and Quality Indicators in Palliative and Hospice Care in Germany
- Quality Management in Palliative Care in Germany
- Desire for Hastened Death in Patients Receiving Palliative Care
- Health Care Research

Structure of the Department

The Division of Palliative Medicine provides care to patients suffering from advanced or terminal disease and aims at improving quality of life for patients and their relatives. The holistic view of care requires flexible and individual concepts of different professionals.
Since July 2011, the palliative care consultation team (physicians, nurses, psychosocial worker) has adviced other hospital units of the UK Erlangen on inquiry. Advice can be given for palliation of symptoms, palliative care, psychosocial support, counseling in modification of therapy objective, medical information, and clarification of further patient care.
Research is besides clinical practice and teaching one of the main cornerstones of this academic palliative care institution. Our research aims at the development, evaluation, and improvement of palliative and hospice care services and structures and at specific treatment approaches for seriously ill and dying patients. Although research in this vulnerable population of patients is limited by patient characteristics, research projects taking these limitations into account are ethical and justifiable.

Research

Outcome Criteria and Quality Indicators in Palliative and Hospice Care in Germany

Currently, the discussion about appropriate quality indicators in palliative medicine is controversial and still open. Whilst quality indicators for symptom control are widely established (e.g. symptom check lists), there is a lack of generally accepted indicators for psychosocial and spiritual support. Therefore, the task force `research´ of the German Association of Palliative medicine (DGP) initiated a research program for the identification of outcome criteria as quality indicators in palliative medicine.
The research program is divided in several phases:
The first phase is relating to the record of material dimensions and ongoing used measuring devices. A discourse analysis for the definition of palliative medicine and a focus group discussion on outcome indicators were performed and published. Furthermore, a systematic analysis of literature towards ongoing measuring devices was conducted. The corresponding original publication deals with the question how quality in palliative care can be determined.
The second project phase is meant to describe meta-concepts and to develop a framework for the evaluation of central outcome indicators.
In the third project phase, potential quality indicators will be identified and evaluated.
In a subproject of OPCARE9 "European collaboration to optimise research and clinical care for cancer patients in the last days of life", quality indicators were tested upon feasibility for use in the dying phase (2012). Overall, 34 indicators relating to the dying phase could be identified and seven of them were evaluated useable for clinical practice. The development of valid and reasonable indicators is of special interest for the dying phase.

Quality Management in Palliative Care in Germany

Project managers: Prof. Dr. C. Ostgathe, Dr. S. Stiel
The discussion about suitable quality indicators in palliative care and nationwide quality management is a current research topic in Germany. Since 1996, a working group has developed a standardized basic documentation tool (Hospice and Palliative Care Evaluation (HOPE)) for palliative care patients in Germany.
This documentation system is recommended by the DGP for quality management of palliative care services. It assesses a data set with personal data of patients, their social situation, the stage of their disease, the individual symptom burden, current medication, and all measures and activities carried out to support the patient as well as satisfaction with treatment. Core data from HOPE is transferred to the National Hospice and Palliative Care Register and used for a nationwide benchmarking of institutions.
We succeeded in publishing further investigations on this research topic in 2012: The validation of the symptom- and problem checklist of HOPE investigated - according to the self-assessment instrument Minimal Documentation System (MIDOS²) - the extended multidimensional symptom and problem checklist (HOPE-SP-CL) from the core documentation HOPE. Another publication on the use of antibiotics in palliative medicine reflects barriers and strategies for decision-making, indication, treatment withdrawal and withholding of antibiotics. Fears concerning life-shortenings effects or prolongation of the dying phase are discussed. Special research attempts were focused on the non-cancer patients in specialized palliative care in Germany.
More research attempts concentrated on the analysis of subjective definitions of symptoms and problems from team members in palliative care.

Desire for Hastened Death in Patients Receiving Palliative Care

Project managers: Dr. S. Stiel, Prof. Dr. C. Ostgathe
A multicenter study funded by the DFG investigated three highly relevant topics using mixed methodology. Two work packages will be introduced here.
a) The desire for hastened death (DhD) in terminally ill patients is an important end-of-life issue. Although this wish is expressed only by few patients receiving palliative care, it may cause a challenging dilemma. In order to investigate the motivations and expectations of patients asking for hastened death, we conducted a qualitative study using Grounded Theory (GT).
b) To be able to study DhD in patients receiving palliative care, research tools reflecting the thoughts of patients are needed. The German version of the assessment tool „Schedule of Attitudes towards Hastened Death" (SAHD) was validated. We investigated whether the

SAHD-D is appropriate to assess (1) DhD in patients with little burden, (2) the characteristics and intensity of DhD, and (3) the desire in follow-up sessions.
The validation of the SAHD-D illustrates good discriminant validity, demonstrating that depression, anxiety, physical state, and DhD are separate constructs. The unidimensionality of the SAHD could not be reproduced. The criterion validity is insufficient. The field notes suggest that DhD has to be differentiated into actual and non-actual DhD.

Health care research

Project managers: Prof. Dr. C. Ostgathe, Dr. C. Klein
There are several approaches in health care research that aim at implementing recommendations of the World Health Organisation (WHO) into palliative care practice. The feasibility and benefit of integration of palliative care early within patients' disease trajectories as recommended by the WHO was investigated.
Although a better utilization and understanding of palliative care could be demonstrated with the "early integration" approach, the adoption of the WHO recommendation was not enough to integrate palliative care into routine cancer care early in the course of the illness. Therefore, the development of disease specific guidelines is advocated.
A central project of the Division (funded by ELAN) is the attempt that aims at generating an image of the clinical practice of palliative sedation (PS) in Germany which may enable the development of a national guideline based on the framework for PS of the EAPC. Therefore, all palliative care institutions listed in official address registers were asked by questionnaire about their clinical practice of PS.

Teaching

Our goal in teaching palliative care is to relate medical knowledge in specific aspects of palliative medicine (symptom control, communication skills, weighing possible therapeutic goals and treatment regimens in advanced disease, ethical decisions). We also try to create a setting for our students to support reflecting their bearing and values pertaining advanced diseases, dying, and death. In our way to teach palliative medicine, we try to reflect our goals in teaching. Almost exclusively we teach small groups of students and our tutors come from all sections of the multidisciplinary team.
Our teaching scope encompasses:
- Mandatory classes in palliative care;
- Voluntary course (symptom control, measures in dying patients, hospice work in Germany, ethical questions, nursing in palliative care, psychology in palliative care);
- Voluntary course (treatment of two virtual patients in a setting of case-based learning);
- Voluntary classes (talks on different aspects of palliative care);
- Voluntary participation in rounds and team meetings;
- Talks on contemporary aspects of palliative care medicine (students, health professionals, and open to the public);
- Colloquium on scientific approaches in medicine.

Mandatory and voluntary teaching by our Division is continually evaluated both, in regard to formative as well as academic aspects.
In addition to classes held exclusively by our Division, we take part in classes held by other medical faculties (e.g. anesthesiology, medical sociology, medical psychology, anatomy) and other specialties (medical process management, psychogerontology) at the FAU.

Selected Publications

Ostgathe C, Alt-Epping B, Golla H, Gaertner J, Lindena G, Radbruch L, Voltz R, the Hospice and Palliative Care Evaluation (HOPE) Working Group (2011) Non-cancer patients in specialized palliative care in Germany: What are the problems? Palliat Med, 25: 148-152

Voltz R, Galushko M, Walisko J, Karbach U, Ernstmann N, Pfaff H, Nauck F, Radbruch L, Ostgathe C (2011) Issues of "life" and "death" for patients receiving palliative care - comments when confronted with a research tool. Support Care Cancer, 19: 771-7

Raijmakers N, Galushko M, Domeisen F, Beccaro M, Lundh Hagelin C, Lindqvist O, Popa-Velea O, Romotzky V, Schuler S, Ellershaw J, Ostgathe C; OPCARE9 (2012) Quality indicators for care of cancer patients in their last days of life: literature update and experts' evaluation. J Palliat Med, 15: 308-16

Stiel S, Pollok A, Elsner F, Lindena G, Ostgathe C, Nauck F, Radbruch L (2012) Validation of the Symptom and Problem Checklist of the German Hospice and Palliative Care Evaluation (HOPE). J Pain Symptom Manage, 43: 593-605

Stiel S, Krumm N, Pestinger M, Lindena G, Nauck F, Ostgathe C, Radbruch L, Elsner F (2012) Antibiotics in palliative medicine-results from a prospective epidemiological investigation from the HOPE survey. Support Care Cancer, 20: 325-33

Stiel S, Pastrana T, Balzer C, Elsner F, Ostgathe C, Radbruch L (2012) Outcome assessment instruments in palliative and hospice care - a review of the literature. Support Care Cancer, 20: 2879-93

International Cooperations

OPCARE9: an EU 7th Framework Collaboration & Support Action grant to optimise research for the care of cancer patients in the last days of life: Europe

Meetings and International Training Courses

12.02.2011: 11. Erlanger Schmerz- und Palliativtag, UK Erlangen, Erlangen

10.-11.02.2012: 12. Erlanger Schmerz- und Palliativtage, UK Erlangen, Erlangen

16.-20.07.2012: Ausrichtung einer Präsenzwoche für den Studiengang Master in Palliative Care der Dresden International University (DIU), UK Erlangen, Erlangen

Silence room

Department of Cardiac Surgery

Chair of Cardiac Surgery

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Research Focus

- Chronic rejection of allografts
- Therapy of end-stage heart failure: Heart transplantation or support with a left or right ventricular assist device
- Neuropeptide release of the heart
- Hospital-economics and management
- The arterialization of cardiac veins as an alternative myocardial revascularization strategy in an experimental long term model in pigs
- Tissue engineering of cardiovascular implants

Structure of the Department

20 medical doctors work in the Department of Cardiac Surgery. The research is accomplished by all medical doctors, seven graduate students, and two technical assistants.

Research

Chronic rejection of allografts

Today transplant arteriosclerosis represents the major obstacle for indefinite graft survival and has become the leading cause of death in cardiac transplant recipients who survive beyond the third year after transplantation. Pharmacological agents that effectively prevent acute graft rejection have proven inadequate for averting late graft loss caused by transplant arteriosclerosis. Transplant arteriosclerosis is the main reason for late graft failure and develops in all other vascularized organ transplants, such as liver and kidney. In order to develop effective therapeutical strategies and translate them into clinical success, a detailed understanding of the mechanisms responsible for the development of transplant arteriosclerosis is essential. We have recently established and characterized the abdominal aortic allograft model as a suitable tool to study the development of transplant arteriosclerosis. Ongoing projects involve the role and importance of chemokines and chemokine-receptors, in particular CCR7 and CXCR5, in the development of transplant arteriosclerosis. CCR7, the major homing receptor for trafficking of T and B cells, plays a crucial role in leukocyte homing. Experiments using CCR7-/- mice as recipients of aortic allografts showed increased amounts of transplant arteriosclerosis during the absence of this receptor and suggest an interesting role of this receptor in this disease. Recent findings implicate an important role of human cytomegalovirus infection (HCMV) for the development of inflammatory-proliferative vascular lesions in transplanted vascularised allografts. Therefore, the major aim of this project is to develop a human peripheral blood lymphocyte (hu-PBL)/severe combined immunodeficiency (SCID) mouse xenograft-model to investigate the immunological and pathological mechanisms of HCMV in the modulation and progression of transplant arteriosclerosis.

Therapy of end-stage heart failure: Heart transplantation or support with a left or right ventricular assist device

Orthotopic cardiac transplantation is the therapy of choice for cardiac insufficient patients. Due to an increasing shortage of donor organs, a considerable number of patients dies. If necessary, these patients can be bridged with an implantable ventricular assist device until a suitable donor organ is available. In some cases heart disease has already progressed to such an extent that the patients need to be stabilized with a left ventricular assist device or - in case of additional right heart failure - with a biventricular assist device.

Neuropeptide release of the heart

Project manager: PD Dr. T. Strecker
Calcitonin-Gene Related Peptide (CGRP) is a neuropeptide consisting of 37 amino acids and its biological action results in a strong vasodilatation. CGRP is mainly produced by the sensoric A-δ- and C-fibres. Recent data suggested that it may play an important role in myocardial ischemia. Neural fibres with a high CGRP content are found in both atria, the pericardium and within the adventitia of coronary arteries. Changes in CGRP production correlate with increased activity within cardiac afferent fibres. It was shown in vitro that elevated CGRP concentrations were able to increase the coronary blood flow and reduce the coronary resistance and the mean arterial blood pressure. Furthermore, CGRP was demonstrated to be cardio-protective and reduce the infarct size of myocardial infraction.
The aim of our project (cooperation with Prof. Dr. K. Messlinger, Institute of Physiology and Pathophysiology) is to develop an experimental mouse model in order to investigate the effects and kinetics of CGRP production in greater detail. In addition, analyses of human CGRP production are planned by using tissue from the right ventricle or ascending aortic tissue.

Hospital-economics and management

Project managers: PD Dr. R. Feyrer, U. Kunzmann
This group is a collaboration between the Department of Cardiac Surgery and the competent office of Healthcare Resource Groups (DRGs). One of the main tasks of this group since the introduction of the DRGs has been to face the changes in hospital reimbursement from retrospective payment to a prospective flat rate payment. Other current projects involve the development of the so called 'clinical pathways' in order to improve cost unit calculations and enable us to create computer-simulated scenarios of complex problems of hospital cost management. In cooperation with the Department of Anesthesiology, we perform a study analyzing the costs involving intensive care patients, and together with the German Heart Center in Berlin, we are trying to set up a database regarding long-term costs of patients on cardiac assist devices.

The arterialization of cardiac veins as an alternative myocardial revascularization strategy in an experimental long term model in pigs

In ischemic hearts, venous retroperfusion is a potential myocardial revascularization strategy. The goal underlying retrograde coronary sinus (CS) perfusion is perfusion of the ischemic myocardium proximal to the occlusion or stenosis. The lack of suitable target vessels remains a challenge for aortocoronary bypass grafting in end stage coronary heart disease. This study aimed at investigating the arterialization of cardiac veins as an alternative myocardial revascularization strategy in an experimental long term model in pigs.
In a pig model of myocardial ischemia, selective retrograde perfusion of a coronary vein (aorta to coronary vein bypass, retrobypass) was performed. A ligation of the ramus interventricu-

laris paraconalis (equivalent to the left anterior descending artery (LAD) in humans) was performed in 20 German landrace pigs (Sus scrofa domestica). Retroperfusion (RP) of the concomitant vein of the LAD was performed in four pigs (RP+), but not in the other four (RP-), and the vena cordis magna (VCM) was ligated (L+) in four pigs in each of these groups, but left open (L-) in the remaining animals.
Hemodynamic performance (e.g. cardiac output) was significantly better in RP+L+ (4.1 L/min) pigs that underwent selective retroperfusion with proximal ligation of vena cordis magna as compared to all other animals (RP+L-, 2.5 L/min), (RP-L+, 2.2 L/min), (RP-L-, 1.9 L/min). Long term survival was significantly better in RP+L+ pigs (112 +16 d) than in all other groups. Histological follow-up studies showed significantly smaller area of necrosis in all animals of the RB+L+ group.
Venous retroperfusion is an effective technique to achieve long term survival after acute LAD occlusion in a pig model. In this setting, proximal ligation of V. cordis magna is mandatory.

Tissue engineering of cardiovascular implants

The background for these studies is the development of an ingrowth matrix within the tissue engineering of cardiovascular grafts. The purpose of these investigations is to show whether it is possible to influence the mobility of endothelial cells, smooth muscle cells, and fibroblasts within a fully synthetic matrix by incorporating bioactive peptides. The purpose is to define a matrix which provides optimal mobility for those cells needed for a functional cardiovascular implant. Such a matrix could be integrated into a cardiovascular prosthesis in order to facilitate and direct the ingrowth of the patient's own tissue. A single cell migration model was used to compare the influence of different cell interactive peptides on the mobility of vascular cell lines as microvascular endothelial cells (MVEC) and aortic vascular smooth muscle cells (SMC). In previous studies it could already be shown that selectively MVEC, but not SMC accelerate on a PEG matrix covered with RGD (fibronectin) and YIGSR (laminin) in comparison to a matrix covered only with RGD. These experiments were extended to the peptide sequences SIKVAV, RYVVLPR (both laminin), and DGEA (collagen) also known from the literature as being vascular cell interactive. For sufficient cellular adhesion, RGD was added to the matrix again. At an average migration speed of 21.1 µm/h for MVEC and 26.9 µm/h for SMC on RGD-PEG hydrogels, both cell lines showed a reduced cell speed on RGD plus RYVVLPR and RGD plus DGEA (MVEC: -22% on RYVVLPR+RGD, -21% on DGEA+RGD; SMC: -27% on RYVVLPR+RGD, - 22% on DGEA+RGD). For the combination of SIKVAV and RGD, only MVEC showed a small, but not significant increase in mobility whereas SMC did not show any difference.

Teaching

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

Selected Publications

Harig F, Schmidt J, Hoyer E, Eckl S, Adamek E, Ertel D, Nooh E, Amann K, Weyand M, Ensminger SM (2011) Long-term evaluation of a selective retrograde coronary venous perfusion model in pigs (Sus scrofa domestica). Comp Med, 61: 150-7

Heim C, Eckl S, Abele-Ohl S, Ramsperger-Gleixner M, Mahmoudian S, Stamminger T, Weyand M, Ensminger SM (2011) Murine Cytomegalovirus Infection Is Associated with Increased Number of T- and Dendritic Cells in Murine Aortic Allografts J Heart Lung Transplant, 30 S: S138-S138

Ramsperger-Gleixner M, Spriewald BM, Tandler R, Kondruweit M, Amann K, Weyand M, Ensminger SM (2011) Increased transcript levels of TNF-α, TGF-β, and granzyme B in endomyocardial biopsies correlate with allograft rejection. Exp Clin Transplant, 9: 387-92

Strecker T, Munch F, Weyand M (2012) One hundred ten days of extracorporeal membrane oxygenation in a young women with postpartum cerebral venous thrombosis and acute respiratory distress syndrome. Heart Surg Forum, 15(4): 180-E181

Abele-Ohl S, Leis M, Wollin M, Mahmoudian S, Hoffmann J, Müller R, Heim C, Spriewald BM, Weyand M, Stamminger T, Ensminger SM (2012) Human cytomegalovirus infection leads to elevated levels of transplant arteriosclerosis in a humanized mouse aortic xenograft model. Am J Transplant, 12: 1720-9

Abele-Ohl S, Heim C, Eckl S, Weyand M, Stamminger T, Ensminger SM (2012) Procurement regimens to reduce ischemia reperfusion injury of vascular grafts. Eur Surg Res, 49: 80-7

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Research Focus

- Aortic arch surgery
- Biomaterial bank for congenital heart disease
- Development of new surgical procedures and treatment of strategies for the univentricular heart
- Myocardial protection - comparative study of variant cardioplegic solutions
- Reconstruction of the right ventricular outflow tract
- Role of thymic tissue in immune cell differentiation
- Migration of plasticizers into patients blood

Structure of the Department

Four doctors cover the medical service in the newly established Division of Pediatric Cardiac Surgery. Patient care is provided in close cooperation with the Division of Pediatric Cardiology. In May 2009, the "expert network for patients with congenital heart disease in northern Bavaria" was founded by both divisions in cooperation with all pediatric cardiologists in the north Bavarian region. Using a new telemedicine platform, optimal patient care after surgical or interventional procedures is much easier to achieve. Currently, eight medical students are involved in scientific projects.

Research

Aortic arch surgery

Surgery of the aortic arch has been a research focus of the Division of Pediatric Cardiac Surgery for a long time and several organ protective perfusion methods have been introduced by the research group into clinical practice. Based on our own research results, pediatric aortic arch surgery is currently performed in hypothermic low-flow perfusion, avoiding deep hypothermic circulatory arrest. Our research in this topic was awarded with the highest scientific award of the German Society for Thoracic and Vascular Surgery. Other parts of the research project received the "Congenital Heart Surgery Award" from the EACTS (European Association for Cardio-Thoracic Surgery). Current animal experiments are validating the practicability of hypothermic low-flow perfusion in combination with a beating-heart technique. The experimental setup is funded by the ELAN-Fond of the Faculty of Medicine.

Biomaterial bank for congenital heart disease

In cooperation with the Division of Pediatric Cardiology (Dr. O. Toka), a database and storage option for tissue samples was established in September 2008. Tissue samples routinely removed and resected during surgery are systematically collected for examination in cooperation with the Institute of Pathology and preserved for further studies afterwards. Erlangen has the largest tissue sample database for children with congenital heart disease. Dr. O. Toka has been awarded for this project by the "German Foundation for Cardiac Research".

Development of new surgical procedures and treatment of strategies for the univentricular heart

One of the most hazardous defects in congenital heart disease is the hypoplastic left heart syndrome. Staged treatment requires three operations, each of them carrying a substantial risk of mortality. The aim of our Division is to lower the operative risk to the level of standard neonatal operations. The first surgical step (Norwood I) carries a mortality risk of about 30% in Europe. In conjunction with the Division of Pediatric Cardiology, we have established processes to lower the risk of mortality below 15% for hypoplasts. In parallel, we have developed a novel surgical technique for the first step in the treatment of patients with hypoplastic left heart syndrome in December 2010 which was approved by the ethics committee.

Myocardial protection - comparative study of variant cardioplegic solutions

One project investigates myocardial protection during routine operations. Variant cardioplegic solutions are being investigated concerning cardioprotective qualities. Surgical standard for newborns and children is the use of cold christalloid cardioplegic solutions. In the field of adult cardiac surgery, blood cardioplegia has been established for a long time especially for critically ill patients. The myocardial study group aims at optimal cardioprotection for children with congenital heart disease through use of a modified blood cardioplegia. Therefore extensive blood and hemodynamic analyses are being collected and documented in a detailed patient register.

Reconstruction of the right ventricular outflow tract

A large number of congenital heart defects require surgical reconstruction of the right ventricular outflow tract with or without placement of a pulmonary valve. Biological valved conduits are often used although they have to be replaced over time. Major problems are the lack of growth and valvar degeneration. Implantation of decellularized valves is widely propagated as being the ultimate solution to this dilemma. In collaboration with the Department of Medicine 2 - Cardiology and Angiology (Prof. Dr. C. Garlichs, PD Dr. Y. Cicha), explanted decellurized tissue valves were systematically examined. It could be shown that pathological mechanisms responsible for degeneration of decellularized valves are similar to those of other valved conduits (xenografts, homografts).
However, tissue engineering will hopefully result in the production of implantable, non-antigenic and growing bioimplants in the near future. Thus, further research in this field makes a lot of sense.

Role of thymic tissue in immune cell differentiation

In cooperation with the Department of Dermatology (Prof. Dr. D. Dudziak) and the Department of Medicine 5 - Hematology and Oncology (Prof. Dr. E. Ullrich), a project about differentiation of immunocompetent cells of children with congenital heart defects was started. 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 about the natural maturation of the immune system. The project is funded by the ELAN-Fond of the Faculty of Medicine.

Migration of plasticizers into patients blood

Current studies focus on migration of phthalate plasticizers (DEHP) from the cardiopulmonary bypass circuit into the patients blood. These plasticizers are toxic, especially in children.
In cooperation with the Institute and Outpatient Clinic of Occupational, Social, and Environmental Medicine (Prof. Dr. T. Göen), the Division of Pediatric Cardiac Surgery investigates leaching of alternative plasticizers and investigates alternative materials which do not contain plasticizers. The topic is of paramount importance. In the past years phthalate contaminants were repeatedly found in plastic toys, baby bottles, and soothers. It has been proven that phthalate plasticizers are endocrinal disruptors and provoke change in the development of reproductive organs and fertility which is of particular interest in children.

Teaching

Main lecture, internship, and clinical traineeship are being held throughout the year.
Special operative techniques, anatomic considerations, and pathogenesis of congential heart disease are being taught in separate student tutorials in small groups.
Teaching is supported by modern technical equipment. All operative steps could be followed on additional screens in the operating theatre.

Selected Publications

Cicha I, Rüffer A, Cesnjevar R, Glöckler M, Agaimy A, Daniel WG, Garlichs CD, Dittrich S (2011) Early obstruction of decellularized xenogenic valves in pediatric patients: involvement of inflammatory and fibroproliferative processes. Cardiovasc Pathol, 20: 222-31

Dragu A, Birkholz T, Kleinmann JA, Schnürer S, Münch F, Cesnjevar R, Schmidt J, Taeger C, Kneser U, Horch RE (2011) Extracorporeal perfusion of free muscle flaps in a porcine model using a miniaturized perfusion system. Arch Orthop Trauma Surg, 131: 849-55

Ruffer A, Cicha I, Dittrich S, Cesnjevar RA (2011) Re: Early failure of xenogenous de-cellularised pulmonary valve conduits: a word of caution! Reply. Eur J Cardiothorac Surg, 39: 284-284

Rüffer A, Arndt F, Potapov S, Mir TS, Weil J, Cesnjevar RA (2011) Early Stage 2 Palliation Is Crucial in Patients With a Right-Ventricle-to-Pulmonary-Artery Conduit. Ann Thorac Surg, 91: 816-22

Rüffer A, Wittmann J, Potapov S, Purbojo A, Glöckler M, Koch AM, Dittrich S, Cesnjevar RA (2012) Mid-term experience with the Hancock porcine-valved Dacron conduit for right ventricular outflow tract reconstruction. Eur J Cardiothorac Surg, 42: 988-95

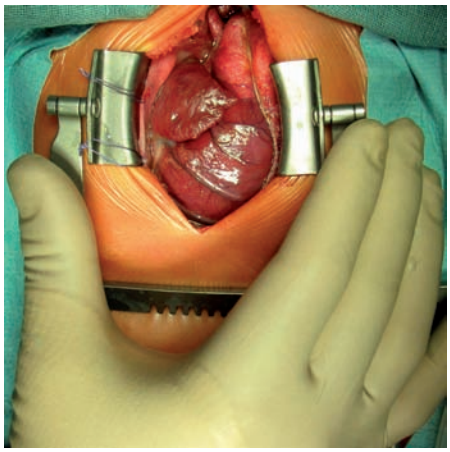
Rüffer A, Webinger J, Glöckler M, Purbojo A, Dittrich S, Cesnjevar RA, Carbon R (2012) Pericardial cyst or teratoma? Change of strategy during mediastinal tumor surgery. Thorac Cardiovasc Surg, 60: 488-90

International Cooperations

Prof. Dr. M.R. de Leval, Cardiothoracic Unit, Great Ormond Street Hospital, London: UK

Prof. Dr. A. Philips, Cincinnati Children´s, Cincinnati: USA

Prof. Dr. J. Cheatham, Nation Wide Children´s Hospital, Columbus: USA



Heart with hypoplastic left heart syndrome in comparison to the surgeon's hand

View in the operating theater

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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 dendritic cell subpopulations and antigen presentation
- Generation, composition, and function of extracellular vesicles (EV)
- Characterization of the toponome of tissue and cells by multi-epitope-ligand-cartography (MELC)
- Identification of biomarkers in malignant melanoma
- Regulatory T cells for cell-based therapy in inflammatory bowel disease
- Identification and modulation of allergenic structures

Structure of the Department

More than 200 people are employed at the Chair of Skin and Venereal Diseases, among them 39 medical doctors and 26 scientists. In the different working groups clinically-relevant questions are addressed in the areas of dendritic cell (DC) biology, DC-based vaccine development, oncology with a focus on malignant melanoma, and allergy. The Department of Dermatology focuses on the development and clinical validation of innovative cellular therapies with an emphasis on ex-vivo generated DC-based vaccines. For this, a modern GMP-facility is available. The projects at the Department are all third-party funded, e.g. by the SFB 643 "Strategies of cellular immune intervention" (see own report).

Research

Cellular Immune Intervention

Project managers: PD Dr. B. Schuler-Thurner, Prof. Dr. E. Kämpgen, Dr. S. Groß, Prof. Dr. G. Schuler

The production and clinical testing of innovative cellular therapies is the task of the Experimental Immunotherapy Unit which is organized into the GMP laboratory and a clinical trial unit. Close interaction with the Dermatooncology and the FACS and Immunomonitoring Core Unit is essential. Metastasized melanoma patients have been vaccinated with autologous ex vivo generated tumor-peptide loaded DCs, and more recently with DCs electroporated with mRNAs coding for defined tumor antigens (Mage-A3, MelanA, and survivin). This strategy not only allows a broader immune response, but alleviates the restriction to certain HLA haploytpes inherent to the use of peptides. This RNA-DC approach is now optimized for vaccination against mutated antigens of a given tumor. A randomized multicenter phase III trial using DCs transfected with autologous tumor-RNA (DCaT-RNA) starts in 2013 in uveal melanoma patients whose tumor cells have lost one chromosome 3 indicating an unfavorable prognosis. Based on respective clinical work (see below), we plan the adoptive transfer of T cells reprogrammed by RNA electroporation as well as the adoptive transfer of autologous regulatory T cells.

RNA electroporation to improve DC vaccines and to generate antigen-specific T cells

Project managers: PD Dr. N. Schaft, Dr. J. Dörrie
The RNA-group focuses its research on two distinct topics:
1) the optimization of vaccination against melanoma by modulation of mRNA-transfected DCs and
2) the generation of tumor specific T cells by transfer of T cell- and chimeric antigen specific receptors (TCR, CAR).
1) In vitro, our group found MelanA-specific CD8+ T cells to be exhausted after re-stimulation with the DC vaccine. The transfection of mRNAs coding for CD40L, CD70, and constitutively active TLR4 led to an improvement of the DC immunogenicity. In addition, in in vitro culture experiments it could be shown that CD4+ T cells, CD8+ T cells, and DCs must concomitantly interact to allow repetitive CTL stimulation.
2) Chimeric HIV, CMV, or Ewing's sarcoma specific TCR/CAR were transfected into T cells, thus leading to an improved recognition of HIV-, CMV-infected, or tumor cells. Furthermore, a protocol for the expansion of T cells under GMP conditions was developed which will allow for the clinical application of CAR-transfected T cells.

Functional role of dendritic cell subpopulations and antigen presentation

Project manager: Prof. Dr. D. Dudziak
The Emmy-Noether and BayGene research group 'Dendritic Cell Biology' focuses on the characterization of murine and human DC subsets. DCs as most important antigen presenting cells direct immune responses and tolerance. By antigen-coupled antibodies murine DC can be loaded with antigens in vivo. Depending on the DC subpopulation the group found that T cell responses could be directed and were either CD4+ T-helper responses when CD11c+CD8– DC presented the antigen or prominent cytotoxic T cell responses, when CD11c+CD8+ DC were targeted. Recently, in close collaboration with Prof. Dr. M. Karlsson (Karolinska-Institute), it could be shown that the Autoimmune regulator gene (AIRE) is expressed on peripheral CD-11c+CD8- DC in murine spleens and not only in thymic stroma. These results suggest that AIRE expression in CD11c+CD8- DC might be necessary for the maintenance of peripheral tolerance. At the moment the group focuses on the translation of the concept of antigen targeting from the murine into the human system. In close collaboration with various clinical institutions (Erlangen, Bamberg), DC subpopulations and other antigen presenting cells from human tissues are characterized and human antigen targeting antibodies are generated.

Generation, composition, and function of extracellular vesicles (EV)

Project manager: PD Dr. A. Baur
This group investigates the molecular mechanisms leading to the generation of EV, but is also interested in their composition and function in the microenvironment of malignant melanoma and in HIV-infected cells. It could be demonstrated that EV play an important role in the differentiation of monocytes into DC. Interestingly, in HIV and cancer patients a higher proportion of EV could be detected. In melanoma as well as HIV-infected cells, EV secretion is initiated by an integrin-dependent mechanism in which the signaling proteins Paxilin, Pak1, and Pak2 play crucial roles. Interestingly, several of the identified micro-RNAs in those EV point to a single signaling pathway, known to play an important role in the pathogenesis of cancer.

Characterization of the toponome of tissue and cells by multi-epitope-ligand-cartography (MELC)

Project manager: Dr. A. J. Pommer

The Toponome group deals with the characterization of cell cultures and tissues by means of the innovative MELC technology which permits to stain 100 antigens on one and the same tissue section. This method was used to identify a large panel of murine leukocyte subpopulations in a whole frozen section of a peripheral lymph node (see figure) as well as non-inflamed versus inflamed tissues of brain and spinal cord in an experimental autoimmune encephalomyelitis model. Furthermore, the Toponome group tries to extend the MELC-technology to formalin-fixed paraffin-embedded (FFPE) tissue sections. The MELC-technology has great potential in different key research areas and can be used in cooperation with other groups to answer questions in basic research, applied medicine, and diagnostic.

Identification of biomarkers in malignant melanoma

Project manager: Prof. Dr. L. Heinzerling

The Biomarker research group focuses on predictive and therapeutic biomarkers in melanoma to optimize selection of therapeutic options. With a semi-automated mRNA extraction from formalin fixed paraffin-embedded (FFPE) sections of primary melanomas and melanoma metastases, a set of 20 indicator genes, previously identified by array analyses, was evaluated. The comparison of responders and non-responders for different immunotherapy options (DC-vaccination, anti-CTLA-4 antibody ipilimumab) resulted in differential gene expression signatures. Furthermore, a large biobank of melanoma patients (including tumor mutations) is established (in collaboration with the Institute of Pathology).

Regulatory T cells for cell-based therapy in inflammatory bowel disease

Project managers: Dr. C. Bosch-Voskens, Prof. Dr. G. Schuler

The focus of this project funded by KFO 257 (see own report) is on regulatory T cells (Treg). They play a key role in the maintenance of peripheral tolerance by suppression of proliferating effector T cells. In inflammatory bowel disease, it is postulated that insufficient numbers of Treg cells expand to attenuate local proliferation of effector T cells in the gut. A protocol has been established for the optimized in vitro expansion of Treg cells of colitis ulcerosa patients. Such cells will be intravenously administered in an upcoming clinical trial to mitigate disease activity (collaboration Prof. Dr. M.F. Neurath, Department of Medicine 1).

Identification and modulation of allergenic structures

Project manager: Prof. Dr. V. Mahler

This group focuses on the elucidation of relevant allergenic structures in plants and plant-derived food and their modification with the aim to obtain hypoallergenic crops as proof of principle [in collaboration with the Division of Biochemistry, FAU (Prof. Dr. U. Sonnewald); Paul-Ehrlich-Institute, Langen (Prof. Dr. S. Vieths); Institute of Phytopathology, Giessen (Prof. Dr. K.H. Kogel)]. After the identification of allergic target-structures and the use of RNAi-constructs, relevant allergens could be silenced in planta resulting in a reduced allergen content in tomato fruits and carrot roots.

Teaching

The Chair of Dermatological and Venereal Diseases teaches students of human medicine, dental medicine, molecular medicine, and Biology in molecular and cellular immunology in combination with translational applications (GMP-laboratory). The educational program is organized in seminars, practical training courses in the clinic and the laboratories, lectures as well as bachelor, master, and medical theses. The clinic is responsible for the organization of dermatological advanced training courses for physicians.

Selected Publications

Biburger M, Aschermann S, Schwab I, Lux A, Albert H, Danzer H, Woigk M, Dudziak D, Nimmerjahn F (2011) Monocyte subsets responsible for immunoglobulin G-dependent effector functions in vivo. Immunity, 35: 932-44

Hofmann C, Höfflin S, Hückelhoven A, Bergmann S, Harrer E, Schuler G, Dörrie J, Schaft N, Harrer T (2011) Human T cells expressing two additional receptors (TETARs) specific for HIV-1 recognize both epitopes. Blood, 118: 5174-7

Paulus KE, Schmid B, Zajic D, Schäfer A, Mahler V, Sonnewald U (2012) Hypoallergenic profilin - a new way to identify allergenic determinants. FEBS J, 279: 2727-36

Eckhardt J, Ostalecki C, Kuczera K, Schuler G, Pommer AJ, Lechmann M (2013) Murine whole-organ immune cell populations revealed by multi-epitope-ligand cartography. J Histochem Cytochem, 61: 125-33

Lee JH, Wittki S, Bräu T, Dreyer FS, Krätzel K, Dindorf J, Johnston IC, Gross S, Kremmer E, Zeidler R, Schlötzer-Schrehardt U, Lichtenheld M, Saksela K, Harrer T, Schuler G, Federico M, Baur AS (2013) HIV Nef, paxillin, and Pak1/2 regulate activation and secretion of TACE/ADAM10 proteases. Mol Cell, 49: 668-79

Lindmark E, Chen Y, Georgoudaki AM, Dudziak D, Lindh E, Adams WC, Loré K, Winqvist O, Chambers BJ, Karlsson MC (2013) AIRE expressing marginal zone dendritic cells balances adaptive immunity and T-follicular helper cell recruitment. J Autoimmun, 42: 62-70

International Cooperations

Prof. P.G. Coulie, de Duve Institute, Université catholique de Louvain, Brussels: Belgium

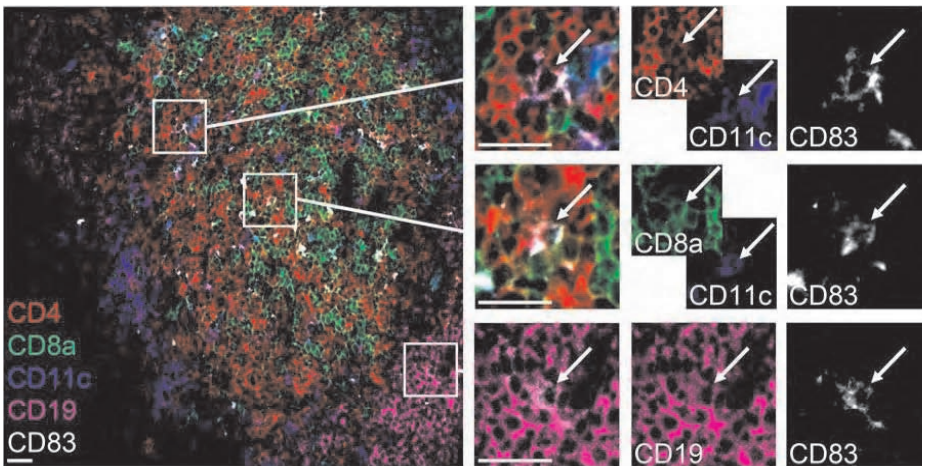
Prof. M.C. Nussenzweig, Rockefeller University, Rockefeller University, Laboratory of Molecular Immunology, New York: USA

Prof. J.V. Ravetch, Rockefeller University, Rockefeller University, Laboratory of Molecular Genetics and Immunology, New York: USA

Meetings and International Training Courses

24.-25.03.2011: 6th International Symposium on the Clinical Use of Cellular Products, Erlangen

23.11.2011: DCs, T cells and beyond, Erlangen



Department of Dermatology

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Research Focus

- Immune-modulation in autoimmunity and transplantation by soluble CD83
- Transcriptional in vivo targeting of dendritic cells (DC) using the human CD83 promoter
- Intracellular signal transduction of CD83 in DC
- Interaction DC cells und viruses

Structure of the Department

In the Division of Immune Modulation, headed by Prof. Dr. A. Steinkasserer, more than 20 researchers are working. Five research groups concentrate on basic immunological questions, whereby the translation of basic results into clinically applicable therapeutic strategies is a major goal. Especially autoimmune disorders and the transplantation studies are in the focus of our research activities. The interaction between viruses and dendritic cells (DC) represents the second major research area of the Division. The identification and characterization of specific viral immune escape strategies will be exploited to develop new antiviral strategies. This research work is mainly supported by research grants funded by the DFG, SFB, GK, and scientific foundations.

Research

Immune-modulation in autoimmunity and transplantation by soluble CD83

Project manager: Dr. E. Zinser

The project group focuses on the immuno-suppressive properties of soluble CD83 (sCD83). Using a recombinantly expressed sCD83 molecule, it was possible to inhibit the paralyses associated with EAE, an animal model for the early, inflammatory phase of Multiple Sclerosis in a prophylactic as well as in a therapeutic setting. Furthermore, 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 (Tregs) and that indoleamine 2,3-dioxygenase (IDO) plays a major role. Interestingly, a naturally occurring sCD83 molecule has been identified in the serum of tumor patients, whereby high concentrations of sCD83 correlated with a reduced treatment free survival in CLL patients, indicating its relevance also in tumor patients. In the long run, sCD83 will be developed as a new therapeutic option also for humans.

Transcriptional in vivo targeting of dendritic cells (DC) using the human CD83 promoter

Project manager: Dr. I. Knippertz

The major aim of the research group is the functional characterization of the human DC-specific CD83 promoter. The membrane-bound CD83 molecule is a 45 kDa glycoprotein expressed on the surface of mature DC and is to date one of the best known markers for human mature DC. Since CD83 is not expressed on immature DCs, its regulatory DNA region, the CD83 promoter, is of high interest in the context of a DC-mediated vaccination strategy for the modulation of mature DC by the targeted in vivo gene expression of different therapeutic transgenes. For this purpose, different immune-modulatory and therapeutic transgenes will be expressed in vivo (directly in patients) under the control of the cell type- and stadium specific CD83 promoter. Initially, the characterization of the human CD83 promoter was accomplished by a ChIP-chipTM Microarray analysis, by which, in addition to the minimal promoter, a short enhancer sequence was identified. Further, bio-informatical analysis identified an additional promoter region which was shown to build a ternary promoter-complex together with the minimal promoter and the enhancer. Moreover, we have demonstrated that this ternary promoter-complex is not only highly inducible, but it is also cell type- and maturation specific. Finally, we have identified the transcription factors involved in this process.

Intracellular signal transduction of CD83 in DC

Project managers: Dr. M. Stein, K. Blume

The main research focus of the project concentrates on structural- and signal transduction pathway analyses of the membrane bound CD83 molecule. Specific binding domains/-partners have been identified using a yeats two hybrid screen. Site directed mutagenesis-, transfection-, immune-precipitation-, and co-immunofluorescence-studies have been used to further characterize the protein-protein interaction, the N-linked glycosylation, and the activation of mCD83 on a molecular level. To identify possible binding motifs in silico, a bioinformatic modeling study has been performed. The elucidation of the mCD83 signaling pathway in mature human DC will open new and specific therapeutic targets.

Interaction of DC und viruses

Project manager: Dr. M. Kummer

The project group "DC and viruses" analyzes the interaction between DC and viruses. Particular attention has been given to HSV-1 and HCMV infections. In this respect, the group was able to identify several new immune-escape mechanisms. For instance, the infection of DC with HSV-1 leads to a complete degradation of CD83 which correlates with a reduced immuno-stimulatory capacity of these infected DC. This degradation is mediated by the viral immediate early protein ICP0 and the cellular proteasome. The exact mechanism of this degradation is subject of current research. Interestingly, infection of mature DC with HCMV induced the shedding of a soluble CD83 molecule from the cell surface which has immune-suppressive activities. Moreover, it could be shown that the infection of mature DC with HSV-1 leads to an inhibition of STAT1 signaling, presumably via loss of the IFNγ-receptor 1. Furthermore, the group is also interested in the replication of HSV-1 in mature DC. In contrast to earlier reports, recently the replication of HSV-1 in mature DC could be reported. Although this replication is very inefficient, it could very well be of biological importance in vivo, since progeny virus could be passed on to primary keratinocytes. During this cell-to-cell mediated infection, the viral glycoprotein gE plays a major role.

An additional project deals with the HSV-1 mediated modulation of DC migration. It could be shown that HSV-1 interferes with the chemokine mediated DC-migration which is an absolutely essential step in order to induce potent antiviral immune responses.

Teaching

The co-worker 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, master, and PhD theses. In addition, the Collaborative Research Centre/SFB 643 (strategies of cellular immune intervention; compare own report) is coordinated together with the Department of Dermatology.

Selected Publications

Goldwich A, Prechtel AT, Mühl-Zürbes P, Pangratz NM, Stössel H, Romani N, Steinkasserer A, Kummer M (2011) Herpes simplex virus type I (HSV-1) replicates in mature dendritic cells but can only be transferred in a cell-cell contact-dependent manner. J Leukoc Biol, 89: 973-9

Knippertz I, Stein MF, Dörrie J, Schaft N, Müller I, Deinzer A, Steinkasserer A, Nettelbeck DM (2011) Mild hyperthermia enhances human monocyte-derived dendritic cell functions and offers potential for applications in vaccination strategies. Int J Hyperthermia, 27: 591-603

Seifarth C, Littmann L, Resheq Y, Rössner S, Goldwich A, Pangratz N, Kerek F, Steinkasserer A, Zinser E (2011) MCS-18, a novel natural plant product prevents autoimmune diabetes. Immunol Lett, 139: 58-67

Theodoridis AA, Eich C, Figdor CG, Steinkasserer A (2011) Infection of dendritic cells with herpes simplex virus type 1 induces rapid degradation of CYTIP, thereby modulating adhesion and migration. Blood, 118: 107-15

Schierer S, Hesse A, Knippertz I, Kaempgen E, Baur AS, Schuler G, Steinkasserer A, Nettelbeck DM (2012) Human dendritic cells efficiently phagocytose adenoviral oncolysate but require additional stimulation to mature. Int J Cancer, 130: 1682-94

Zinser E, Rössner S, Littmann L, Pangratz N, Schuler G, Steinkasserer A (2012) The IL-2 diphtheria toxin fusion protein denileukin diftitox modulates the onset of diabetes in female nonobese diabetic animals in a time-dependent manner and breaks tolerance in male nonobese diabetic animals. J Immunol, 189: 1173-81

International Cooperations

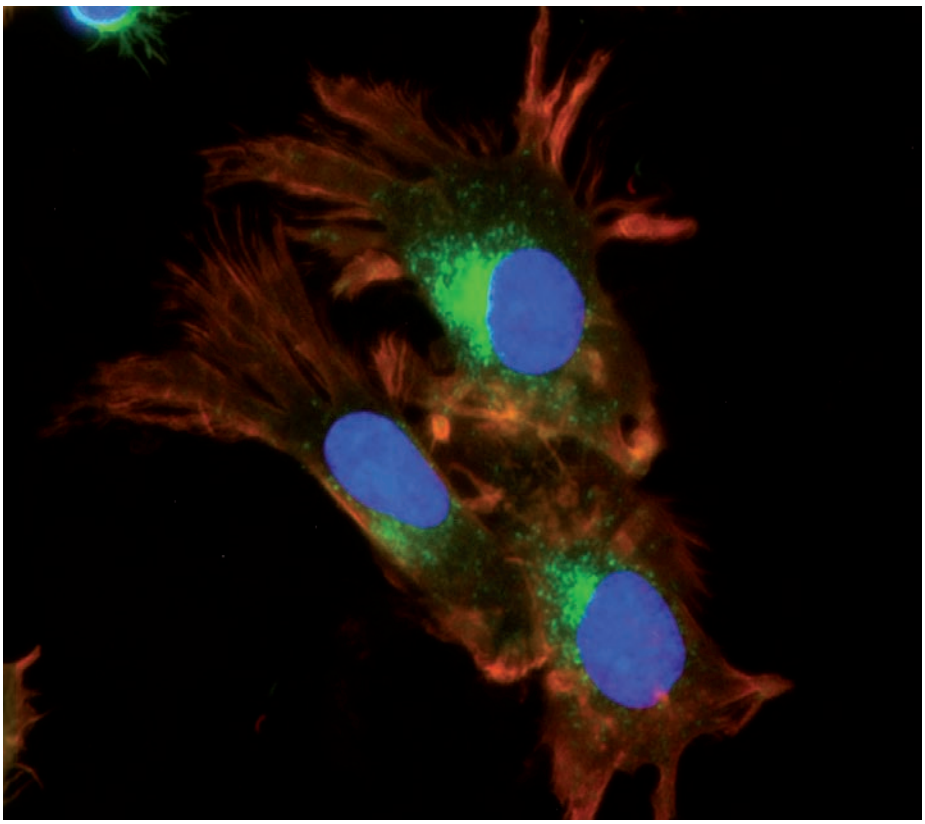
Prof. Dr. H. Wang, Lawson Health Research Institute, University of Western Ontario, London: Canada

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

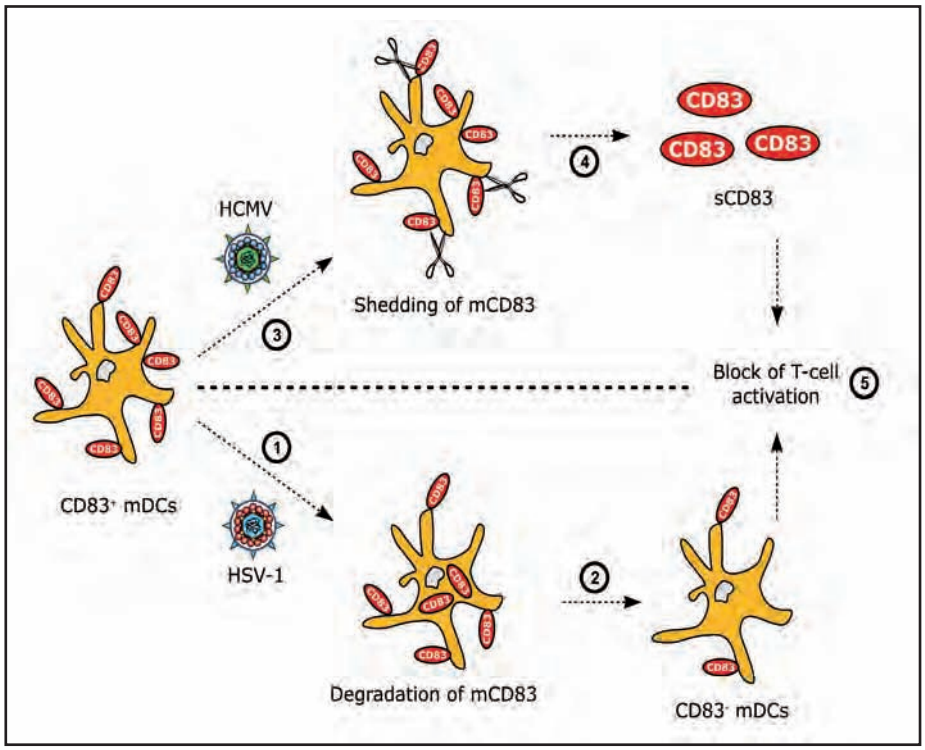
Prof. Dr. R.D. Everett, MRC-Center for Virus Research, University of Glasgow, Glasgow: UK

Prof. Dr. N. Romani, Department of Dermatology, Medical University Innsbruck, Innsbruck: Austria

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



Immune-fluorescence staining of mature dendritic cells



HSV-1 and HCMV specifically target CD83 to evade immune responses

Department of Medicine 1 – Gastroenterology, Lung Diseases, and Endocrinology

Chair of Internal Medicine I

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Research Focus

- Intestinal diseases
- Endocrinology
- Experimental hepatology
- Immunomodulatory strategies for the treatment of chronic inflammatory diseases
- Division of clinical and experimental pulmonology
- Molecular endoscopy
- Molecular gastroenterology
- Patient-oriented research in IBD
- Ultrasound
- Cytokines and transcription factors in IBD

Structure of the Department

The Department of Medicine 1 covers research in the fields of gastroenterology, hepatology, endocrinology, pneumology, intensive care medicine, infectious diseases as well as endoscopy and ultrasound. Several research groups cover these fields in clinical and basic research.
In the past two years, the research division of the Department of Medicine 1 has continuously expanded. This has become possible due to the successful raising of financial means from public bodies, including the DFG and the European Community.
A special highlight was last year's establishment of a Clinical Research Unit on the topic of inflammatory bowel disease (KFO 257, CEDER, compare own report).
The laboratories of the Department of Medicine 1 are located at the Kussmaulcampus for Medical Research. In these laboratories, ten research groups with overall 80 staff members investigate the cause of different diseases and develop new therapeutical strategies.

Research

Intestinal diseases

Project managers: Dr. C. Neufert, Dr. M. Waldner
We are interested in the molecular mechanisms driving intestinal inflammation and colitis-associated tumorigenesis. Current topics are cytokine research in colitis and investigations into growth factors that are differentially regulated between different tumor entities in the large intestine. Moreover, our studies have a closer look at the molecular crosstalk between stromal cells, such as cancer-associated fibroblasts and intestinal epithelial cells. The research performed by our group may help to improve future therapeutic options for various intestinal diseases.

Endocrinology

Project manager: Prof. Dr. C. Schöfl
The Calcium-Sensing-Receptor (CaSR) is pivotal for calcium homeostasis. Mutations of the CaSR cause hyper- and hypocalcemic disorders. Our group characterizes inactivating and activating CaSR mutations and tests how the detrimental effects of these mutations can be corrected pharmacologically.
Treatment of patients suffering from hypocalcemia due to activating mutations of the CaSR is unsatisfactory and often has side effects. Recent results from our group indicate that novel calcilytics currently in clinical testing may offer a superior treatment option for patients suffering from Autosomal Dominant Hypocalcemia and Bartter-Syndrome Type V.

Experimental hepatology

Project manager: Dr. S. Wirtz
In this research focus, we are particularly interested in the role of the novel pro- and anti-inflammatory cytokines IL-28, IL-33, and IL-27 in the context of acute and chronic liver diseases. We have observed that the expression of these factors is upregulated early during hepatocellular stress and inflammatory liver diseases. Preclinical studies showed that they significantly contribute to gradual accumulation of extracellular matrix components and hepatic tissue remodeling. In the long run, we want to identify in these translational research projects new molecular mechanisms of liver pathophysiology and identify potential prognostic markers or therapeutic targets in liver disease.

Immunomodulatory strategies for the treatment of chronic inflammatory diseases

Project manager: Dr. I. Atreya
Our research group is interested in immunomodulatory strategies for the treatment of chronic inflammatory diseases. Innovative therapeutic approaches are evaluated preclinically in order to define their immunomodulatory capacity and to potentially pave the way for clinical trials.
New as well as clinically established immunosuppressive compounds are monitored in order to describe their interaction with specific intracellular signaling cascades and their resulting impact on pro-inflammatory immune cell function. Through a more detailed understanding of the underlying mechanism of action, we intend to optimize immunosuppressive strategies or even to identify new therapeutic target structures.

Division of clinical and experimental pulmonology

Project managers: Dr. F. Fuchs, Prof. Dr. K. Hildner
Our clinical research attempts to evaluate new imaging methods during bronchoscopy. Our data highlight in vivo confocal laser-endomicroscopy as a real time and safe method to visualize malignant lesions. Furthermore, we perform feasibility and surplus studies of chromo-bronchoscopy in vivo.
Our preclinical studies try to shed light on the immunopathogenesis of lung cancer both, in murine model systems and in patients. We are establishing clinically relevant mouse tumor models and started to bank human lung tissue for further molecular analysis.

Molecular endoscopy

Project manager: Prof. Dr. H. Neumann
Molecular endoscopy offers the unique potential to significantly impact on current diagnostic and therapeutic approaches based on in vivo minimally invasive visualization of disease-specific morphologic or functional tissue alterations. In this context, recent data indicate the potential of molecular endoscopy for in vivo molecular imaging of therapeutic targets of gastrointestinal cancers.
Main emphasis of this research project is the identification and investigation of highly specific markers to recognize lesions at risk and to predict response to targeted treatment.

Molecular gastroenterology

Project manager: Prof. Dr. C. Becker

The research group focuses on the immunological and molecular mechanisms that lead to the development of infection, chronic inflammation, and cancer within the gut. In the past two years, this group has developed a new concept for the pathogenesis of chronic inflammatory bowel disease (IBD). The researchers could show that the molecule caspase-8 plays an important role for regulating cell survival and cell death in the gut. If caspase-8 levels or the function of the protein is insufficient in epithelial cells, these cells become highly susceptible to necroptosis, a new mode of programmed cell death. Particularly affected are Paneth cells, specialized epithelial cells which produce substances to control or even kill bacteria. As a consequence, bacteria can penetrate the intestinal wall and trigger inflammatory reactions such as those in patients with chronic IBD. On the basis of these research results, new treatment methods allowing the targeted manipulation of such cellular processes will be developed in order to better treat patients with chronic IBD.

Patient-oriented research in IBD

Project manager: Prof. Dr. R. Atreya

Aim of our research group is the characterization on the immunpathogenesis of IBD and especially the molecular mechanism of action of immunosuppressive therapies. Another aim is the establishment of therapy-specific predictors of response. These predictors are derived from cytokine mediated signaling pathways and transcription factors. The use of endoscopic molecular imaging for the individual prediction of therapeutic response in IBD represents another field of our research group.

Ultrasound

Project manager: Prof. Dr. D. Strobel

Research includes contrast enhanced ultrasound (CEUS), elastography, acoustic radiation force imaging (ARFI), and interventional ultrasound.

- CEUS for the detection of liver metastasis in colorectal cancer (multicenter trial German Society for Ultrasound in Medicine)
- CEUS for the characterization of hepatic tumors and monitoring of antiangiogenetic therapy
- CEUS in IBD
- CEUS quantification
- ARFI of chronic hepatic diseases and tumors
- ARFI of extrahepatic disorders (pancreas, gastrointestinal tract)
- Sonographically guided abdominal interventions (multicenter trial German Society for Ultrasound in Medicine).

Cytokines and transcription factors in IBD

Project manager: Dr. B. Weigmann

Crohn's disease and ulcerative colitis are classic defined entities of IBD which have a characteristic profile of cytokines. Crohn's disease is characterized by Th1 cytokines as well as IL-23 and IL-17 producing cells, whereas in patients suffering from ulcerative colitis a more Th2-mediated cytokine profile is observed. In former studies, a key regulatory role of the Th1 associated transcription factor t-bet, regulating IFN-γ, could be found. Actually, the function of Th2-associated transcription factors, like c-maf, GATA-3 and NFAT, is in the focus of our research. Likewise, influence of these transcription factors in the pathogenesis of colorectal carcinoma is currently being analyzed.

Teaching

The Department of Medicine 1 contributes to curricular teaching for medical students from second to final year. The necessary skills are taught in practical courses (introduction to clinical medicine, physical examination course, internal medicine) and with models and simulators. Several lectures deal with general internal medicine and the different foci of the clinic.

Selected Publications

Atreya R, Zimmer M, Bartsch B, Waldner MJ, Atreya I, Neumann H, Hildner K, Hoffman A, Kiesslich R, Rink AD, Rau TT, Rose-John S, Kessler H, Schmidt J, Neurath MF (2011) Antibodies against tumor necrosis factor (TNF) induce T-cell apoptosis in patients with inflammatory bowel diseases via TNF receptor 2 and intestinal CD14+ macrophages. Gastroenterology, 141: 2026-38

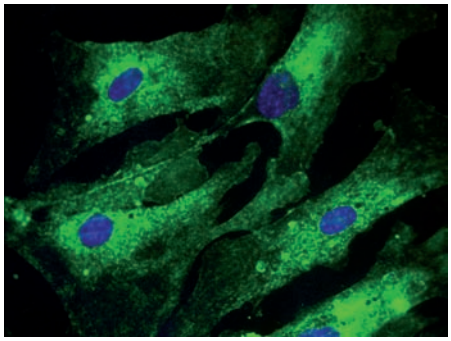
Günther C, Martini E, Wittkopf N, Amann K, Weigmann B, Neumann H, Waldner MJ, Hedrick SM, Tenzer S, Neurath MF, Becker C (2011) Caspase-8 regulates TNF-α-induced epithelial necroptosis and terminal ileitis. Nature, 477: 335-9

Neumann H, Vieth M, Neurath MF, Fuchs FS (2011) In vivo diagnosis of small-cell lung cancer by endocytoscopy. J Clin Oncol, 29: e131-2

Wirtz S, Billmeier U, McHedlidze T, Blumberg RS, Neurath MF (2011) Interleukin-35 mediates mucosal immune responses that protect against T-cell-dependent colitis. Gastroenterology, 141: 1875-86

Dornhoff H, Becker C, Wirtz S, Strand D, Tenzer S, Rosfa S, Neufert C, Mudter J, Markl J, Siebler J, Neurath MF (2012) A variant of Smurf2 protects mice against colitis-associated colon cancer by inducing transforming growth factor β signaling. Gastroenterology, 142: 1183-1194.e4

Wang J, Sun Q, Morita Y, Jiang H, Gross A, Lechel A, Hildner K, Guachalla LM, Gompf A, Hartmann D, Schambach A, Wuestefeld T, Dauch D, Schrezenmeier H, Hofmann WK, Nakauchi H, Ju Z, Kestler HA, Zender L, Rudolph KL (2012) A differentiation checkpoint limits hematopoietic stem cell self-renewal in response to DNA damage. Cell, 148: 1001-14



Hepatic Stellate Cells

In 2010, the Department of Medicine 1 moved into the laboratories of the new research building at the Hartmannstraße.

Department of Medicine 2 – Cardiology and Angiology

Chair of Internal Medicine II

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Research Focus
- Electrophysiology
- Interventional cardiology
- Echocardiography
- Cardiac magnetic resonance tomography
- Cardiac computed tomography
- Molecular and experimental cardiology

Structure of the Department

The Department of Medicine 2 focuses on cardiology and angiology. Together with the Department of Cardiac Surgery, the Division of Pediatric Cardiology, and the Division of Pediatric Cardiac Surgery, the Department of Medicine 2 forms the University Heart Center of Erlangen. The Department is a tertiary referral center offering the full array of inpatient and outpatient diagnostic and therapeutic options for cardiovascular diseases. The Department employs 39 physicians, eight of them with permanent teaching positions at the Faculty of Medicine ("Habilitation"), three biologists, and 122 non-physician nursing or supporting staff. It harbors two large normal care wards, an coronary care unit, two cath lab suites, one hybrid-lab and an outpatient department with several specialized clinics for heart failure, congenital heart disease in adults, arrhythmias, and pacemakers/defibrillators. Furthermore, the Department disposes of a large basic-science laboratory. In October 2012, Prof. Dr. S. Achenbach became Prof. Dr. W.G. Daniel's successor as the director of the Department.

Research

Electrophysiology

Project manager: Dr. M. Arnold

The electrophysiology research group is part of the Leading Edge Cluster „Medical Valley". The project IS 08b is funded by the BMBF. Its aim is to develop an algorithm which predicts the worsening of the clinical condition of heart failure patients. Implantable cardioverter defibrillators with new developed sensors and the Home-Monitoring platform from BIOTRONIC are applied for this study. In the iChart-study, confounding factors that influence the measurement of the intrathoracic impedance were identified. The measurement of the intracardiac impedance is the main focus of the iGraph-study (figure 1). Acute hemodynamic changes in patients are correlated to measurements of the intracardiac impedance. In an accompanying registry, again potentially confounding factors for the intracardiac impedance are documented.

Interventional cardiology

Project managers: Prof. Dr. J. Ludwig, PD Dr. H. Rittger, Dr. M. Arnold

Main focus of the working group was the interventional therapy of coronary artery disease (CAD), especially new treatment modalities and specific aspects of the interventional treatment of stable CAD and acute coronary syndromes in elderly patients.

One main topic was the specific therapy of Instent-Restenosis (ISR) especially in drug eluting stents (DES). In a multicentric, randomized study, we demonstrated that the interventional therapy of DES-ISR with drug coated balloons (DCB) is significantly better than balloon angioplasty alone regarding angiographic and clinical endpoints.

Based on these results, the working group is developing algorithms for the treatment of DES-ISR, since the impact of restenosis patterns on the success of a therapy with drug-eluting balloons (DEB) for DES-ISR has important prognostic significance for the success rate of the repeated intervention and restenosis after DES implantation, making it particularly challenging to treat. Aim is the development of a new classification of DES-ISR and therapy recommendations for the treatment of DES-ISR with the DCB. Another study evaluates the restoration of endothelial function after DCB treatment.

Of further interest is the outcome of elderly patients after interventional treatment of CAD. Based on data of the German ALKK-registry, we showed that there are only minor differences in outcome as compared to younger patient cohorts.

In cooperation with the Chair of Cardiac Surgery, our Department participates in the development of prostheses for transcatheter aortic valve implantations (TAVI). The Department of Medicine 2 was one of the centers where the study for the regulatory approval of the JenaValve® prosthesis was conducted. The Department participates also in international multicenter trials for the evaluation of ballon expandable prosthesis (Prevail, Edwards lifesciences) and an international registry for the documentation of the long term performance of the Edwards-sapein-XT prosthesis® (source XT registry).

Echocardiography

Project manager: PD Dr. O.A. Breithardt

This research group focuses on tissue Doppler and deformation ("strain", "2D strain") imaging, especially in the field of ischemia detection, the identification of heart failure patients who benefit from cardiac resynchronization therapy, and myocardial deformation characteristics in patients with aortic valve disease before and after valve replacement.

Cardiac magnetic resonance tomography

Projekt managers: Dr. M. Schmid, Prof. Dr. S. Achenbach

In collaboration with the Institute of Radiology (head: Prof. Dr. M. Uder) and Siemens Healthcare, Erlangen, the research group focuses on the development and validation of new cardiac magnetic resonance techniques in clinical studies. One field is the prognostic importance of T2 weighted and contrast-enhanced imaging after myocardial infarction and the determination of infarct size as a surrogate endpoint for research studies. Studies of myocardial perfusion with adenosine stress using new high-resolution sequences are another focus of interest. Furthermore, in suspected perimyocarditis, so-called edema-sequences are evaluated to detect the acute inflammatory process and the extent of myocardial involvement. Additional research topics are the non-invasive quantitation of valvular heart disease with comparison to established standards, morphologic and functional MRI imaging in stress cardiomyopathy, and characterization and localization of myocardial fibrosis in dilated cardiomyopathy.

Cardiac computed tomography

Project manager: PD Dr. T. Pflederer

The major focus of the working group Cardiac Computed Tomography is non-invasive coronary CT angiography and imaging of cor-

onary atherosclerosis. Several research projects receive funding - among others - by the BMBF. One research focus is the development and validation of techniques for reducing the associated radiation exposure. Advances in hard- and software now allow non-invasive assessment of coronary arteries in daily routine with effective radiation doses between 1.0 and 2.0 mSv (see figure 2). Furthermore, for the first time, recent studies could achieve - in selected patients - a reduction of effective radiation dose to values less than 0.1 mSv (the average natural background radiation dose in Germany in 2009 was 2.35 mSv per person). Another research focus is the validation of techniques aiming at improving image quality. Advances in the field of "Iterative Reconstruction" allowed reduction of noise and thus a more accurate assessment of the coronary arteries and coronary stents. All the same, studies assessing automated software programs could show a potential benefit in planning the CT scan itself - again for the reduction of radiation exposure - as well as in the subsequent evaluation of coronary artery concerning significant stenoses. In the field of CT-guided planning of transcatheter aortic valve implantation (TAVI), international standards regarding measurement methodology and procedural planning have been established. Moreover, the CT working group cooperates with major national and international registries to further evaluate the prognostic value of CT coronary angiography and is involved as a Core-Lab in international multicenter studies.

Molecular and experimental cardiology

Project manager: Prof. Dr. C. Garlichs

The research projects of the group concentrate on

a) Pathomechanisms of atherosclerosis,

b) Biomarkers in cardiovascular diseases, and

c) The construction of new vessels.

Research questions focus on:

a1) Which role do flow patterns of blood have on atherogenesis and plaque rupture, respectively? How do blood flow patterns interact with inflammatory mechanisms? What specific pathways act in vessel bifurcations?

a2) Which role does the receptor of CRP (c-reactive protein) play within atherogenesis?

a3) Which role play dendritic cells and regulatory T cells in the development of atherogenesis and plaque rupture? The recent work of our group suggests a strong influence of these cells on atherogenesis.

a4) Which influence does sodium have on the development of atherosclerotic plaques?

With regard to biomarkers in cardiovascular diseases, we focus on questions such as:

b1) Which multimarker-profile correlates with atherogenesis, heart failure, or arterial hypertension?

b2) Which multimarker-profile correlates with coronary calcifications as seen in heart computertomography?

Additional projects envision the creation of biological, artificial vessels. As part of the 'Emerging Field Initiative' at the FAU, we currently establish cell lineages as well as culture techniques allowing the construction of three-layered, biological active vessels.

With our projects and biobanks, we participate in national and international projects (e.g. national projection about gen-polymorphisms in coronary artery disease).

Teaching

The Department provides 32 teaching activities (from lecture to practical exercise) per term. Members of the Department repeatedly won the first prize for good teaching of the Faculty of Medicine.

Selected Publications

Achenbach S (2011) Anatomy meets function. Modeling coronary flow reserve on the basis of coronary computed tomography angiography. J Am Coll Cardiol, 58: 1998-2000

Cicha I, Wörner A, Urschel K, Beronov K, Goppelt-Struebe M, Verhoeven E, Daniel WG, Garlichs CD (2011) Carotid plaque vulnerability: a positive feedback between hemodynamic and biochemical mechanisms. Stroke, 42: 3502-10

Gauss S, Achenbach S, Pflederer T, Schuhbäck A, Daniel WG, Marwan M (2011) Assessment of coronary artery remodelling by dual-source CT: a head-to-head comparison with intravascular ultrasound. Heart, 97: 991-7

Marwan M, Taher MA, El Meniawy K, Awadallah H, Pflederer T, Schuhbäck A, Ropers D, Daniel WG, Achenbach S (2011) In vivo CT detection of lipid-rich coronary artery atherosclerotic plaques using quantitative histogram analysis: a head to head comparison with IVUS. Atherosclerosis, 215: 110-5

Raaz-Schrauder D, Klinghammer L, Baum C, Frank T, Lewczuk P, Achenbach S, Cicha I, Stumpf C, Wiltfang J, Kornhuber J, Daniel WG, Garlichs CD (2012) Association of systemic inflammation markers with the presence and extent of coronary artery calcification. Cytokine, 57: 251-7

Rittger H, Brachmann J, Sinha AM, Waliszewski M, Ohlow M, Brugger A, Thiele H, Birkemeyer R, Kurowski V, Breithardt OA, Schmidt M, Zimmermann S, Lonke S, von Cranach M, Nguyen TV, Daniel WG, Wöhrle J (2012) A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEP-CAD-DES study. J Am Coll Cardiol, 59: 1377-82

International Cooperations

Dr. U. Hoffmann, Massachusetts General Hospital, Boston: USA

Dr. S. Voros, Health Diagnostic Laboratory, Richmond: USA

D. Dey, PhD, D.S. Berman, MD, Cedars Sinai Medical Center, Los Angeles: USA

Research Equipment

Siemens Healthcare, Cardiac catheterization lab - angiography (three labs)

St. Jude Medical, OCT-System

Biosense Webster (Johnson & Johnson), Carto 3 Biosense Webster Electroanatomical Mapping System

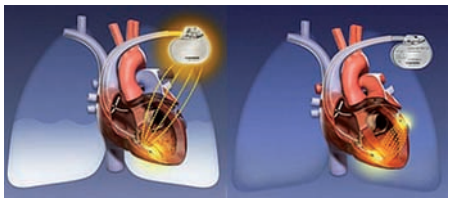

Figure 1: Schematic representation of measurement of intrathoracic impedance (left) and of intracardial impedance (right).

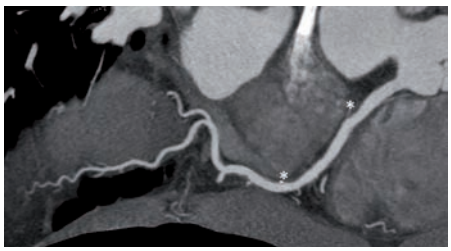

Figure 2: Cardiac computed tomography with an effective dose of 0.6 mSv. The curved multiplanar reconstruction allows to reliably exclude an obstructive coronary artery disease. (*) indicates non-obstructive atherosclerotic plaques.

Department of Medicine 3 – Rheumatology and Immunology

Chair of Internal Medicine III

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Research Focus

- Adipose derived stromal cells for osteoarthritis
- Activation of synovial fibroblasts by microparticles in rheumatoid arthritis (RA)
- Analysis of risk factors and long-term outcome in patients with systemic lupus erythematosus (SLE)
- National and international clinical trials
- Immunogenetics and transplantimmunology
- Immunomodulatory effects of apoptotic and necrotic cells
- Immunodeficiencies and infectious diseases
- Mechanisms for the activation of fibroblasts in systemic sclerosis (SSc)
- Molecular signaling pathways in RA
- Pathogenesis of RPGN in ANCA-associated systemic vasculitides
- Pathomechanisms of bone destruction in RA
- The role of 12/15-lipoxygenase (12/15-LO) in the regulation of innate and adaptive immunity
- Analysis of inflammatory mechanisms in adult onset Still's disease

Structure of the Department

The Department of Medicine 3 covers the fields of rheumatology, immunology, and allergology. It involves the diagnosis and therapy of rheumatologic and immunologic diseases. For the treatment of patients, the Department of Medicine 3 is supplied with inpatient and outpatient wards where patients are cared for.
Our physicians are specialized in recognizing and treating these hard to diagnose diseases. The Department of Medicine 3 is among the few European "Centers of Excellence" according to the guidelines of the European League Against Rheumatism (EULAR) which mirrors its expertise on these fields.

Research

Adipose derived stromal cells for osteoarthritis

Project managers: Prof. Dr. G. Schett, J.-P. David
The FP7-EU-funded ADIPOA wishes to develop efficient mesenchymal stem cell based therapy for the treatment of the osteoarthritis, the most common form of arthritis. Our task is to test the improvement of the treatment efficacy by genetically modifying adipose-derived mesenchymal stem cells in mice.

Activation of synovial fibroblasts by microparticles in rheumatoid arthritis (RA)

Project manager: PD Dr. J. Distler
Microparticles, released from cytokine activated and apoptotic leukocytes, accumulate in high numbers in the involved joints in patients with RA. The group could demonstrate that microparticles represent a novel mechanism for inter-cellular communication. Microparticles might thus play an important 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 a major focus of the group.

Analysis of risk factors and long-term outcome in patients with systemic lupus erythematosus (SLE)

Project manager: Prof. Dr. B. Manger
In a cohort of 410 SLE patients, genetic, serological, and clinical predictors for long-term outcome are analyzed in retrospective and prospective studies. One focus is on the investigation of premature atherosclerosis and ovarian failure in SLE.

National and international clinical trials

Project managers: Dr. J. Rech, Dr. M. Ronneberger, Dr. A. Reisch, Dr. S. Finzel
Various national and international phase Ib-IV studies are conducted, primarily to investigate new treatment approaches in rheumatic diseases. The major focus of the therapeutic trials are on treatments with "biologicals and small molecules" e.g. therapeutic principles which block the proinflammatory cytokine tumornecrosis factor α, IL-6, IL-17, IL-12/23, JAK3-kinase.
Another focus is the initiation and conduction of a multicenter phase II trial in patients erosive finger osteoarthritis. In the course of international multicenter trials, we are conducting standardization seminars for examination techniques in patients with RA.

Immunogenetics and transplantimmunology

Project manager: PD Dr. B. Spriewald
The laboratory provides service for the Eurotransplant area Northern Bavaria with the transplant centers Erlangen-Nürnberg, Würzburg, and Regensburg. The laboratory is accredited by the European Federation of Immungenetics. One research area in collaboration with the experimental cardiac surgery unit is the induction of transplantation tolerance and the 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. Imunogenetic studies analyze polymorphisms of several cytokines and T cell regulatory genes and their association with rheumatic, malignant, and endocrinological disorders.

Immunomodulatory effects of apoptotic and necrotic cells

Project managers: Dr. M. Hoffmann, Prof. Dr. Dr. M. Herrmann
During the execution of apoptosis and necrosis, the cellular surfaces get modified. These changes are the basis for the clearance of the dying cells in vivo. In contrast to the pro-inflammatory clearance of necrotic cells, apoptotic cells are eliminated without inflammation and immune response. This fact has important consequences for both, the etiopathogenesis of autoimmunity and the development of tumor vaccines.

Immunodeficiencies and infectious diseases

Project manager: Prof. Dr. T. Harrer
The Department of Medicine 3 is an important treatment center for patients with immunodeficiencies, a variety of infectious diseases. The major interest of research of the group are various aspects of HIV-infection, such as immunology of HIV-infection, drug resistance, and basic and clinical research on development and evaluation of new therapeutic and diagnostic procedures, such as T cell receptor transfer and immunomonitoring using mRNA electroporation. The Department is working on the development of immunotherapies, such as therapeutic vaccines and immunomodulators. The Department participated in clinical studies including studies for the evaluation of new innovative therapeutics of HIV-infection, such as new antiretroviral drugs and therapeutic vaccines. Other projects are investigating further infectious and immunologic diseases, such as Borrelia burgdorferi infection, chronic fatigue syndrome, and humoral immunodeficiencies.

Mechanisms for the activation of fibroblasts in systemic sclerosis (SSc)

Project manager: PD Dr. J. Distler
SSc is characterized by a progressive accumulation of extracellular matrix components with progressive fibrosis of the involved organs. The fibrosis is mediated by an excessive, uncontrolled production of extracellular matrix by fibroblasts. However, therapies to inhibit selective-

ly the overproduction of extracellular matrix and prevent fibrosis are lacking. The research group investigates novel signaling cascades that lead to activation of fibroblasts and studies potential therapeutic approaches to inhibit the overproduction of extracellular matrix by SSc fibroblasts.

Molecular signaling pathways in RA
Project managers: Prof. Dr. G. Schett, Dr. M. Stock
RA is characterized by perpetuating synovial inflammation and progressive joint destruction based on cartilage damage and bone erosion as a result of an imbalance of formation and resorption of cartilage and bone. Wnt signals appear to link inflammation to this structural damage in arthritis and therefore may play a major role in the pathogenesis of RA. Thus, the group is focused on the Wnt signaling network in rheumatic diseases. In particular the regulation of Wnt signaling is investigated and potentials to interfere with cartilage damage caused by dysregulated Wnt signaling are evaluated.

Pathogenesis of RPGN in ANCA-associated systemic vasculitides
Project manager: PD Dr. J. Zwerina
The group investigates the mechanisms of the activation of intrinsic renal cells and infiltrating immune cells that lead to a massive up-regulation of pro-inflammatory cytokines and proliferation leading to the crescent formation in affected glomeruli. Potential candidate molecules responsible for this deregulation are investigated in kidney biopsies of patients with a RPGN as well as experimental RPGN models.

Pathomechanisms of bone destruction in RA
Project managers: Prof. Dr. G. Schett, PD Dr. J. Zwerina
RA is one of the most common inflammatory rheumatic joint diseases with an estimated prevalence of 1%. Chronic arthritis, if poorly controlled, typically provokes extensive joint damage with the emergence of bone destruction associated with significantly decreased functional capacities. Hence, the project group focuses on the pathophysiology of bone destruction by the use of experimental arthritis models. They investigate the mechanisms leading to increased synovial activation of osteoclasts and decreased ability to repair bone destruction with the help of osteoblasts.

The role of 12/15-lipoxygenase (12/15-LO) in the regulation of innate and adaptive immunity
Project manager: Dr. G. Krönke
12/15-LO is a central arachidonic acid-metabolizing enzyme. The aim of this project is to elucidate the molecular role of 12/15-LO and its metabolites in macrophages and dendritic cells (DC). Moreover, a potential involvement of this enzyme in the phagocytosis of apoptotic cells and during the interaction between DC and T-lymphocytes will be investigated. In addition, the role of 12/15-LO during chronic inflammatory diseases is studied in vivo using 12/15-LO deficient mice and various disease models (TNF-transgenic mice, collagen-induced arthritis).

Analysis of inflammatory mechanisms in adult onset Still's disease
Project managers: Dr. J. Rech, Prof. Dr. B. Manger
Inflammatory mechanisms and cytokine profiles in patients with adult onset Still's disease are analyzed with respect to clinical presentation and outcome to identify therapeutic strategies for this rare disease.

Teaching

The education offered by the Department of Medicine 3 is embedded into the master plan of teaching in the internal medicine with lectures, courses, and internships.
The Graduate School of the SFB 643 is engaged with strategies of cellular immune intervention (see own report).

Selected Publications

Voll RE, Herrmann M, Roth EA, Stach C, Kalden JR, Girkontaite I (1997) Immunosuppressive effects of apoptotic cells. Nature, 390: 350-1

Kiechl S, Willeit J, Schett G (2009) Denosumab, osteoporosis, and prevention of fractures. N Engl J Med, 361: 2188-9; author reply 2190

Schorn C, Frey B, Lauber K, Janko C, Strysio M, Keppeler H, Gaipl US, Voll RE, Springer E, Munoz LE, Schett G, Herrmann M (2011) Sodium overload and water influx activate the NALP3 inflammasome. J Biol Chem, 286: 35-41

Harre U, Georgess D, Bang H, Bozec A, Axmann R, Ossipova E, Jakobsson PJ, Baum W, Nimmerjahn F, Szarka E, Sarmay G, Krumbholz G, Neumann E, Toes R, Scherer HU, Catrina AI, Klareskog L, Jurdic P, Schett G (2012) Induction of osteoclastogenesis and bone loss by human autoantibodies against citrullinated vimentin. J Clin Invest, 122: 1791-802

Schett G, Gravallese E (2012) Bone erosion in rheumatoid arthritis: mechanisms, diagnosis and treatment. Nat Rev Rheumatol, 8: 656-64

Uderhardt S, Herrmann M, Oskolkova OV, Aschermann S, Bicker W, Ipseiz N, Sarter K, Frey B, Rothe T, Voll R, Nimmerjahn F, Bochkov VN, Schett G, Krönke G (2012) 12/15-lipoxygenase orchestrates the clearance of apoptotic cells and maintains immunologic tolerance. Immunity, 36: 834-46

International Cooperations

Prof. Dr. J. Penninger, Prof. Dr. K. Redlich, Prof. Dr. J. Smolen, Institut of Molekular Biotechnology, Vienna: Austria

Prof. Dr. S. Kiechl, Prof. Dr. L. Wildt, Innsbruck Medical University, Innsbruck: Austria

Dr. D. McIlroy, Université de Nantes, Nantes: France

Prof. Dr. C. Jorgensen, CHU Montpellier, Montpellier: France

Prof. Dr. S. Muller, Institut de Biologie Moléculaire et Cellulaire du CNRS, Strasbourg: France

Prof. Dr. B. Autran, Hôpital Pitié-Salpêtrière, Paris: France

Prof. Dr. D. Isenberg, Center for Rheumatology Research, London: UK

Prof. Dr. J. Savill, Prof. Dr. I. Dransfield, The University of Edinburgh, Edinburgh: UK

Prof. Dr. A. Manfredi, Immunologia Clinica, Milano: Italy

Prof. Dr. A. Tincani, Hospital and University of Brescia, Brescia: Italy

Prof. Dr. O.-P. Rekvig, University of Tromso, Tromso: Norway

Prof. Dr. I. Mcinnes, University of Glasgow, Glasgow: Scotland

Prof. Dr. L. Klareskog, Karloniska Institutet, Stockholm: Sweden

Prof. Dr. P.-P. Tak, Academic Medical Center, University of Amsterdam, Amsterdam: The Netherlands

Prof. Dr. J. van de Winkel, University Medical Center Utrecht, Utrecht: The Netherlands

Prof. Dr. A. Vandamme, Prof. Dr. R. Lories, Katholieke Universiteit Leuven, Leuven: The Netherlands

Prof. Dr. T. Huizinga, University Medical Center, Leiden: The Netherlands

Prof. Dr. L. Joosten, Radboud University, Nijmegen: The Netherlands

Prof. Dr. T. Swaak, Erasmus Universiteit Rotterdam, Rotterdam: The Netherlands

Prof. Dr. D.S. Pisetzky, Durham University, Durham: UK

Prof. Dr. B. Walker, Boston Medical Center, Boston: USA

Prof. Dr. G. Firestein, University of California, San Diego: USA

Meetings and International Training Courses

23.-26.03.2011: Fachkongress für Osteologie, Fürth

18.-19.10.2011: Retreat des GRK des SFB 643, Heiligenstadt

10.11.2011: Science meets companies, Erlangen

05.-07.11.2012: Retreat des GRK des SFB 643, Garmisch-Partenkirchen

Research Equipment

Beckman Coulter GmbH, Flow Cytometer Gallios 3L/10C

Scanco Medical AG, XtremeCT in vivo MicroCT Scanner

Scanco MEDICAL samples 1ccm-20ccm, Micro-CT 40

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Research Focus
- The role of miRNAs in B cell maturation and pathogenesis of multiple myeloma
- Nonsense-codon mediated decay of non-functional mRNA
- Molecular control of early B cell differentiation
- Molecular control of peripheral B cell and plasma cell differentiation
- Selection of B cells

Structure of the Department

The Division of Molecular Immunology was founded as an independent section within the Department of Medicine 3 in 1997. The laboratories reside in the NFZ and the Division is headed by Prof. Dr. H.-M. Jäck together with a Professor emeritus (Prof. Dr. Dr. h.c. J.R. Kalden), eight senior postdoctoral scientists who supervise currently four PhD students, five technicians, and various rotation students. The main scientific focus of the Division concentrates on the humoral immune response with a special emphasis on B cell biology. In addition, members of the Division participate in teaching at undergraduate, graduate, and doctoral levels which is reflected by a broad offer of lectures, seminars, and lab courses.
Several research groups within the Division examine molecular mechanisms of development, activation, and differentiation of B cells in cell culture systems and transgenic mouse lines. Methods include state of the art molecular biology, cultivation of primary B cells, flow cytometry with cell sorting, and mouse immunology. Cell culture systems are being used to identify new regulatory factors, e.g. miRNAs, adaptor proteins, and transcription factors. Subsequently, new mouse models are established by homologous recombination in ES cells and blastocysts as well as by pronucleus injections. The Division of Molecular Immunology is well integrated into the Erlangen research environment through its central location in the NFZ and through its leading role in research groups and research training groups (e.g. Research Unit (FOR 832) and GK 1660). Nationally, the Division of Molecular Immunology is an important part of the working committee on Biology of B lymphocytes within the DGfI (Deutsche Gesellschaft für Immunologie).
The overall research activities of the Division of Molecular Immunology focus on molecular aspects of maturation and activation of antibody-producing B cells as well as the pathogenesis of B cell leukemia and autoimmune diseases. B-Lymphocytes express immunoglobulin (Ig) receptors on their surface which allow to recognize foreign antigens and pathogens. Ig receptors consist of two covalently associated identical immunoglobulin heavy (IgH) and two identical immunoglobulin light (IgL) chains which differ from cell to cell in their variable regions. When B cells are activated by contact to pathogen, they develop into either memory B cells or so-called plasma cells, the latter of which then produce huge amounts of soluble antibody molecules. These antibodies then bind to the pathogen, leading to its elimination and/or destruction (figure 1).
B cells emerge from hematopoietic stem cells in the bone marrow. During their maturation process, B cells pass different developmental stages characterized by the rearrangement of Ig gene segments which starts at the IgH locus and later at the IgL locus. Each of these processes need to be carefully and tightly controlled to avoid the generation of self-reactive or leukemic B cells. One part of the first critical checkpoint in early B cell development is the expression of the pre-B cell receptor (pre-BCR) in early progenitor B cells. Only cells that express a functional IgH chain can assemble a pre-BCR and subsequently receive signals for survival, proliferation, and differentiation. During the next developmental stage, rearrangement takes place at the IgL locus, leading to the synthesis of an IgL chain that is then assembled with the IgH chain to form the B cell receptor (BCR). The BCR is then controlled for binding to self structures in the bone marrow environment. B cells with a non-self BCR leave the bone marrow and differentiate via transitional stages into mature antigen-responsive B cells.

Research

The role of miRNAs in B cell maturation and pathogenesis of multiple myeloma

Project managers: Prof. Dr. H.-M. Jäck, Dr. J. Wittmann
One research focus is on the role of microRNAs 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 EBV (Epstein-Barr virus) infection. MiRNAs are small, 22-nt long, non coding RNAs that control the expression of specific target genes at the post-transcriptional level (figure 2). MiRNAs bind to the 3'-untranslated region of mRNAs which results either in a block of translation or an acceleration of the degradation of the target mRNA. MiRNAs play a central role in the regulation of cell fate and cell differentiation processes in animals and plants. Dysregulation of miRNA expression was detected in various tumors. Therefore, we are currently investigating the function of miRNAs 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 miRNAs involved in the B cell maturation and the generation of multiple myeloma or B cell lymphoma (figure 2).

Nonsense-codon mediated decay of non-functional mRNA

Project managers: Prof. Dr. H.-M. Jäck, Dr. J. Wittmann
Another major focus of research is the molecular control of recognition and decay of non functional Ig-mRNAs, a pathway that is termed nonsense-codon mediated decay (NMD) of non-functional mRNA (mRNA surveillance). Nonsense Ig mRNA is encoded from non-productively rearranged Ig genes during B cell development as a consequence of a defective VDJ recombination. As faulty mRNAs can be translated into potentially toxic proteins, the elucidation of control mechanisms and factors involved in mRNA decay is of particular interest for B and T cell maturation. The role of NMD in central B cell maturation is currently analyzed in a mouse line in which a specific NMD factor which was discovered in our lab can be conditionally deleted in developing B cell progenitors. In parallel, immunprecipitation analyses followed by mass spectrometry analyses are carried out to identify novel interaction partners and their role in the degradation of faulty mRNAs and early B cell maturation.

Molecular control of early B cell differentiation

Project managers: Prof. Dr. H.-M. Jäck, Dr. W. Schuh
One major focus is the analysis of mechanisms that control early B cell development and signaling of the pre-B cell receptor. For example, the interaction of the pre-BCR with structures and ligands in the bone marrow microenvironment and its impact on survival and pro-

liferation of progenitor B cells is studied using different mouse models. Using transcriptome- and proteome analyses, we identified various cellular components of the pre-BCR signaling cascade, for example the transcription factor Krüppel-like factor 2 (KLF2) and a number of small non-coding microRNAs (miRNAs). However, investigations of the function of KLF2 in B cell maturation and activation showed that KLF2 cannot be solely responsible for termination of pre-BCR induced proliferation. In future studies, we will analyze further potential target genes of pre-BCR signaling and their role in pre-B cell differentiation.

Molecular control of peripheral B cell and plasma cell differentiation

Project managers: Prof. Dr. H.-M. Jäck, Dr. W. Schuh

Immune responses are strictly dependent on proper positioning of effector cells. KLF2, a target gene of the pre-BCR, plays a dominant role in 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. Future studies should identify the underlying mechanisms by analyses of new and/or known target genes of KLF2.

Selection of B cells

Project manager: PD Dr. D. Mielenz

The unique passport of each single B cell is the B cell receptor (BCR). The BCR allows a specific antigen to select its cognate B cells via binding to the BCR from a pool of billions of B cells. On one hand, this permits an effective and specific immune response; on the other hand, it prevents the activation of potentially dangerous B cells with self-antigens. The specificity of a BCR may furthermore decide which anatomic niche will be populated by a given B cell. Since expression of the BCR per se controls B cell survival, newly formed B cells are positively selected for proper surface expression of the BCR and negatively for self-reactivity. The selected B cell pool, however, should recognize any kind of antigen presented in the blood or on antigen-presenting cell. The diverse requirements that are imposed upon the BCR require thus a fine-tuned intracellular signal transduction machinery whose elements are not fully characterized yet and that are also employed by other receptors on B cells, such as CD40 or toll-like receptors. Therefore, the main goal of this project is to identify new signal elements in B cells. So far, three new adaptor proteins have been identified. The function of these proteins in the proximal and distal signaling pathways of the BCR and CD40 is currently being investigated in cell culture systems and transgenic as well as knock-out mouse lines.

Teaching

The Division participates in undergraduate and graduate education within the bachelor and master programs in biology, life science engineering, and molecular medicine. Students have the opportunity to work on their bachelor and master theses embedded in the research focus of the Division. Furthermore, the Division engages in educating and training doctoral students from GK 1660 and the research group FOR 832 by offering numerous workshops and seminars, like journal clubs or scientific writing and presentation workshops.

Selected Publications

Brandl A, Wittmann J, Jäck HM (2011) A facile method to increase titers of miRNA-encoding retroviruses by inhibition of the RNaseIII enzyme Drosha. Eur J Immunol, 41: 549-51

Lutz J, Heideman MR, Roth E, van den Berk P, Müller W, Raman C, Wabl M, Jacobs H, Jäck HM (2011) Pro-B cells sense productive immunoglobulin heavy chain rearrangement irrespective of polypeptide production. Proc Natl Acad Sci U S A, 108: 10644-9

Vettermann C, Castor D, Mekker A, Gerrits B, Karas M, Jäck HM (2011) Proteome profiling suggests a pro-inflammatory role for plasma cells through release of high-mobility group box 1 protein. Proteomics, 11: 1228-37

Winkelmann R, Sandrock L, Porstner M, Roth E, Mathews M, Hobeika E, Reth M, Kahn ML, Schuh W, Jäck HM (2011) B cell homeostasis and plasma cell homing controlled by Krüppel-like factor 2. Proc Natl Acad Sci U S A, 108: 710-5

Metzner M, Jäck HM, Wabl M (2012) LINE-1 retroelements complexed and inhibited by activation induced cytidine deaminase. PLoS ONE, 7: e49358

Thiele S, Wittmann J, Jäck HM, Pahl A (2012) miR-9 enhances IL-2 production in activated human CD4(+) T cells by repressing Blimp-1. Eur J Immunol, 42: 2100-8

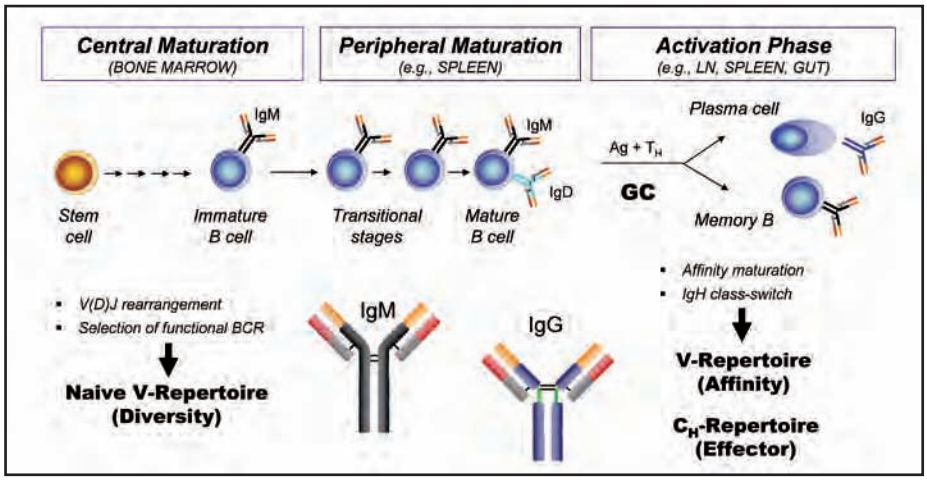

Figure 1: Overview Humoral Immunity

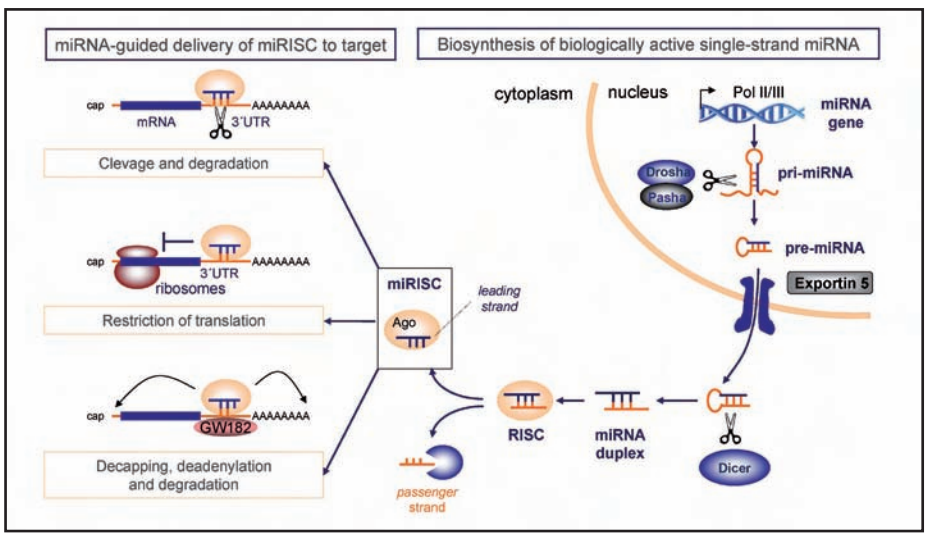

Figure 2: RNA interference by endogenous microRNA

Department of Medicine 4 – Nephrology and Hypertension

Chair of Internal Medicine IV

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Research Focus

- Development and progression of chronic kidney disease
- Pathophysiologic relevance of hypoxia-inducible gene expression
- Pathogenesis of arterial hypertension and hypertensive endorgan damage
- Acute and chronic renal allograft failure
- Systemic consequences of kidney disease and renal replacement therapy

Structure of the Department

The Department of Medicine 4 comprises the Department of Medicine 4 - Nephrology and Hypertension at the UK Erlangen and the Community Hospital in Nürnberg. Together they represent the largest research and treatment center for kidney disease and hypertension in Germany.

More than 90 physicians and basic scientists work in the Department of Medicine 4.

Patient related and experimental research aims at better understanding the pathogenesis of kidney disease and hypertension and their progression and adverse consequences, at identifying novel therapeutic strategies, and at evaluating therapeutic options. Research projects at this Department have played a major role in research networks, such as the Clinical Research Group 106 (Endorgan Damage in Arterial Hypertension) and the SFB 423 (Kidney Injury: Pathogenesis and Regenerative Mechanisms) and contribute significantly to the research focus "Kidney and Circulation Research" of the Faculty of Medicine.

The main clinical areas comprise diagnosis and therapy of kidney diseases, essential and secondary hypertension, renal transplantation, sepsis, and multiorgan failure.

Research

Development and progression of chronic kidney disease

In order to better understand the course of chronic kidney disease and to identify novel risk factors and molecular markers, a national prospective cohort study, the German Chronic Kidney Disease (GCKD) Study, has been initiated. Nine regional centers and several institutes at other universities collaborate with the coordinating center in Erlangen to study 5,000 patients with chronic kidney disease and to follow them for up to ten years. This large consortium is funded by the BMBF and the Foundation for Preventive Medicine of the Kuratorium für Heimdialyse. Studies of the genetic causes of kidney disease play an increasing role.

Besides the observational studies, interventional clinical trials are performed in patients with kidney disease of different etiologies, in particular with certain forms of glomerulonephritis and polycystic kidney disease.

Experimental projects in this research area aim at determining changes in the kidney in conjunction with the initiation of kidney injury and at identifying the mechanisms which result in regeneration or progressive loss of function. To this end, analyses are being performed in isolated cells, human kidney tissue, and animals. Another focus comprises studies determining the influence of renal autonomous innervation on inflammatory processes in the kidney. Projects primarily related to the renal vasculature include studies of the role of oxidative stress in diabetic nephropathy.

Pathophysiologic relevance of hypoxia-inducible gene expression

One pathomechanism which is intensively investigated concerns hypoxia and its relevance for kidney disease. Focus of these studies is the regulation and functional role of the hypoxia inducible transcription factors HIF-1 and HIF-2. Based on studies of the physiological expression of these factors and their regulating enzymes, the activity of the HIF system is being investigated in different types of kidney disease. In addition, experiments are performed to test if kidney disease can be influenced by modulation of the HIF system. It could be shown that inhibitors of HIF degradation result in a marked nephroprotection. This approach is potentially transferable into the clinic in order to prevent acute kidney injury and reduce ischemia reperfusion injury in the context of kidney transplantation. In parallel, the potential long term consequences of hypoxia on renal structure are being analyzed, in particular fibrogenesis, epithelial mesenchymal transition, and the growth of renal cysts.

Pathogenesis of arterial hypertension and hypertensive endorgan damage

A further important research area relates to studies of arterial hypertension. A specific focus in this area lies on target organ damage induced by hypertension in kidneys, heart, eye, and vasculature. In addition, the etiology and pathogenesis of arterial hypertension are being investigated.

This research includes studies on sodium homeostasis which test the hypothesis that stores of non-osmotically active sodium exist in the body and that their capacity has an important impact on blood pressure regulation. Mechanisms in the skin where alterations in sodium content influence lymph-angiogenesis appear to be of particular relevance in this context. Using sodium balance studies during the Mars mission project (MARS 500) and innovative imaging techniques (sodium-MRI), changes in sodium homeostasis and tissue sodium content are analyzed in humans.

Additional experimental projects deal with the role of the renin-angiotensin system and the sympathetic nervous system for the pathogenesis of hypertension and kidney injury. These studies include electrophysiological investigations of ganglion cells, measurements of tissue hormones, and studies in transgenic mice as well as tissue analyses. Electrophysiological measurements of sympathetic nerve activity are not only being conducted in animal models, but - using microneurography - also in humans. In addition, symphathetic outflow to the kidney and endothelial function of renal vessels are indirectly measured through determination of renal perfusion and sodium excretion. Additional studies in patients are dealing with the regulation of endothelial function and in particular the influence of lipids and hormones. In cooperation with the Department of Ophthalmology, perfusion, structure, and endothelial function

of retinal vessels in patients with hypertension are being analyzed.

Acute and chronic renal allograft failure

In cooperation with the Departments of Urology and Surgery, approximately 100 kidney and combined kidney-pancreas transplantations are performed per year, including living donor transplantations. Blood group incompatible living donation is a particular focus.

The research program in this field aims at optimizing long term graft function with particular emphasis on grafts from marginal donors. Several multicenter trials are being conducted to evaluate novel immunosuppressive drugs or their combination.

In parallel to the clinical trials, experimental studies are being performed in a rat transplant model in order to identify novel strategies for the improvement of organ function.

Systemic consequences of kidney disease and renal replacement therapy

More than 10% of the population suffer from chronic kidney disease, as defined by reduced kidney function and/or increased urinary protein excretion. Kidney disease is associated with the risk of progressive loss of renal function as well as a marked increase in cardiovascular risk. Research projects at the Department of Medicine 4 in this context deal with epidemiological questions, aspects of public health care, the causes of an increased cardiovascular risk, and the optimization of renal replacement therapy. Partly in collaboration with the Department of Medicine 2, mechanisms of atherogenesis are being investigated as well as the specific consequences of impaired renal function on vascular pathology. This includes e.g. experimental studies of the role of asymmetric Dimethylarginin (ADMA) and of impaired angiogenesis in kidney disease.

The characteristic systemic consequences of chronic kidney disease include also anemia and disturbances in bone and mineral metabolism which have both been identified as cardiovascular risk factors. The Department participates in several multicenter trials aiming at optimizing management of these complications. A rare complication of treatment with recombinant human EPO is the development of neutralizing antibodies leading to pure red cell aplasia. A therapeutic trial with a novel EPO-mimetic that does not cross react with the antibodies has been initiated.

The AURORA trial and the SHARP trial have been conducted to address the question as to where statins improve the poor cardiovascular prognosis of patients on dialysis.

Additional clinical research deals with acute kidney injury, in particular in the context of sepsis and multiorgan failure. The North Bavarian SepNet Regional Center, located at the Department of Medicine 4 in Erlangen and Nürnberg, participates in several observational and treatment trials.

Teaching

The Department of Medicine 4 with its clinical units in Erlangen and Nürnberg contributes to the entire spectrum of curricular teaching in internal medicine, including main lectures, different courses, and training of final year medical students. In addition, several specialized seminars are being offered as well as optional courses in intensive care medicine, transplantation, kidney and vascular system.

There is also the opportunity for clerkships and short term visits.

Selected Publications

O'Donnell MJ, Yusuf S, Mente A, Gao P, Mann JF, Teo K, McQueen M, Sleight P, Sharma AM, Dans A, Probstfield J, Schmieder RE (2011) Urinary sodium and potassium excretion and risk of cardiovascular events. JAMA, 306: 2229-38

Schley G, Klanke B, Schödel J, Forstreuter F, Shukla D, Kurtz A, Amann K, Wiesener MS, Rosen S, Eckardt KU, Maxwell PH, Willam C (2011) Hypoxia-inducible transcription factors stabilization in the thick ascending limb protects against ischemic acute kidney injury. J Am Soc Nephrol, 22: 2004-15

Schmieder RE, Mann JF, Schumacher H, Gao P, Mancia G, Weber MA, McQueen M, Koon T, Yusuf S, on behalf of the ONTARGET Investigators (2011) Changes in albuminuria predict mortality and morbidity in patients with vascular disease. J Am Soc Nephrol, 22: 1353-1364

Kopp C, Linz P, Wachsmuth L, Dahlmann A, Horbach T, Schöfl C, Renz W, Santoro D, Niendorf T, Müller DN, Neininger M, Cavallaro A, Eckardt KU, Schmieder RE, Luft FC, Uder M, Titze J (2012) (23)Na magnetic resonance imaging of tissue sodium. Hypertension, 59: 167-72

Ritt M, Harazny JM, Ott C, Raff U, Bauernschubert P, Lehmann M, Michelson G, Schmieder RE (2012) Impaired increase of retinal capillary blood flow to flicker light exposure in arterial hypertension. Hypertension, 60: 871-6

Schietke RE, Hackenbeck T, Tran M, Günther R, Klanke B, Warnecke CL, Knaup KX, Shukla D, Rosenberger C, Koesters R, Bachmann S, Betz P, Schley G, Schödel J, Willam C, Winkler T, Amann K, Eckardt KU, Maxwell P, Wiesener MS (2012) Renal tubular HIF-2α expression requires VHL inactivation and causes fibrosis and cysts. PLoS ONE, 7: e31034

International Cooperations

For further information, please visit our homepage: www.medizin4.uk-erlangen.de.

Meetings and International Training Courses

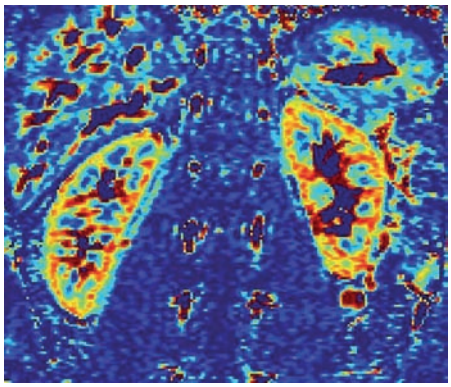
26.02.2011: Intensivsymposium, Klinikum Nürnberg Süd

26.11.2011: Post ASN Fortbildung, Nürnberg

03.03.2012: Intensivsymposium, Klinikum Nürnberg Süd

22.-24.06.2012: Symposium: Molecular Targets in Renal Disease, Bamberg

24.11.2012: Post ASN Fortbildung, München



Magnetic resonance imaging with arterial spin labeling (MRI-ASL): Calculated perfusion map with color encoding.

Department of Medicine 5 – Hematology and Oncology

Chair of Hematology and Oncology

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Research Focus

- T cell based immunotherapy
- Adoptive cell therapy with memory B-lymphocytes for patients after Stem Cell Transplantation (alloSCT)
- CD4+ T cell based immunotherapy
- Immunoregulation of alloSCT
- Immunregulation in cancer biology and SCT
- Immunotherapy and Magnetic Flowcytometry with CD4+ T cells
- Tumor immune escape
- Cellular immunotherapy
- HLA-laboratory

Structure of the Department

The Department of Medicine 5 is the clinic of Hematology and Oncology. As maximum-care hospital, the complete range of diagnostic and therapeutic options for malignancies of the blood, lymphnodes, and solid tumors are offered for both, ambulatory and stationary patients. The clinic focuses on the transplantation of allogeneic and autologous bone marrow stem cells in adults.
The Department has a total of 81 employees (24 on extra-departmental funding). The scientific section counts twelve post-doctoral fellows, ten graduate students, and ten technicians.

Research

T cell based immunotherapy

Project managers: Prof. Dr. A. Mackensen, Dr. M. Aigner, Dr. S. Völkl
The group develops new approaches to generate and improve adoptive T cell therapy against malignant diseases. Main focus of this project is to establish a protocol for the expansion and differentiation of highly functional tumor-specific T cells. The population of human TCRα/β+ CD4- CD8- double-negative (DN) T cells plays a special role in the regulation of immune responses. In this project, the group investigates the immunoregulatory function of human DN T cells. In addition, the role of DN T cells under pathologic conditions as autoimmunity and transplant rejection is currently determined. The long-term goal is to develop a clinical strategy for using DN T cells to treat graft-versus-host disease after allogeneic stem cell transplantation. The projects are funded by DFG and ELAN.

Adoptive cell therapy with memory B-lymphocytes for patients after Stem Cell Transplantation (alloSCT)

Project managers: J. Winkler, Prof. Dr. T. Winkler, Prof. Dr. M. Mach, Prof. Dr. A. Mackensen
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. The development of the technology under GMP-conditions showed that only two-step separations with an CD3-depletion and an enrichment of CD19-B-cells was sufficient for the required purity of B-cells in the cellular product. We showed that B-cells in the product were functional in vitro. In May 2012, we obtained the GMP-certificate for the B-cell product from the regulatory authorities. In the second part of the project, we developed a study protocol for a phase I/IIa clinical trial for the adoptive transfer of allogeneic donor B-lymphocytes for patients five months after alloSCT according to GCP. All necessary documents have been delivered to the Paul-Ehrlich-Institute in February 2013. Funded by BayimmuNet, GCP-Fonds „Clinical Studies" 2009 - 2012.

CD4+ T cell based immunotherapy

Project managers: Dr. A. Kremer, S. Kretschmann
In HLA-matched stem cell transplantation, the beneficial graft versus leukemia (GvL) effect is mediated by donor-derived T-lymphocytes which recognize patient-derived polymorphic peptides. These so-called minor histocompatibility antigens (MiHA) also play an important role in the induction of detrimental graft versus host disease (GvHD). By characterization of the intracellular processing pathways of HLA class II restricted MiHA, we could identify a group of antigens whose presentation is dependent on expression of the non-classical HLA molecule HLA-DO. Based on the selective expression profile of HLA-DO, these results could open the possibility to separate GvL effect and GvHD.
In an additional project, we analyze the CD4+ T cell mediated eradication of HLA class II negative tumors via indirect antigen presentation in mice and involved intracellular mechanisms. These projects are funded by ELAN, IZKF, and Jung-Stiftung.

Immunoregulation of alloSCT

Project managers: Prof. Dr. E. Ullrich, K. Meinhardt, S. Krieg, J. Rothamer
This research group focuses on immunoregulation of GvL and GvH effects in alloSCT. Clinical studies exploiting the impact of innate effector cells on GvHD lead to the suggestion that allogeneic donor NK cells mediate GvL while preventing GvHD. It has been shown that NK cells represent a heterogeneous population of different subsets. Current projects of the research group analyze the specific function of murine and human NK subsets in tumor models and GvHD. The aim of these studies is to further develop NK cell immunotherapeutic concepts in malignant diseases. The preclinical research is funded by the Max Eder Program of the German Cancer Aid and the IZKF. In addition, the Wilhelm Sander foundation supports another project that aims at dissecting the polarization of T-helper cell populations during GvHD.

Immunregulation in cancer biology and SCT

Project manager: Dr. D. Mougiakakos
Our research group is mainly interested in studying the alterations of the immune system due to cancer and after stem cell transplantation. A better understanding regarding the tumor-associated strategies contributing to an immunosuppression will support the development of novel therapeutic strategies. Furthermore, we aim at "learning" from tumors how they specifically weaken immune responses in order to translate these findings into potential experimental approaches for the treatment of rejection reactions (GvHD) following SCT. Our main research interests include studies regarding (I) oxidative stress associated immunosuppression in leukemias, (II) myeloid derived suppressor cells in various tumor entities and following

stem cell transplantation, and (III) the suppressive effects exerted by human mesenchymal stem cells. Supported by ELAN, IZKF, SFB 643, and Deutsche Krebshilfe.

Immunotherapy and Magnetic Flowcytometry with CD4+ T cells

Project manager: Dr. J. Bosch

The main focus of our research group is to develop immunotherapy with CD4+ T cells for treatment of ocular melanoma and to develop a novel magnetic flowcytometry technique. Current research aims at determining which immune cells infiltrate the primary tumor in the immune-privileged eye and if uveal melanoma vaccines activate different subpopulations of CD4+ T cells. The studies on magnetic flowcytometry focus on a novel technique which applies magnetophoresis to perform cell enrichment, focusing, and background elimination in a single step. Time-of-flight measurements are performed with integrated magnetic sensors to detect specifically cancer cells and cell diameters in whole blood. Funded by DFG and WING-program of the BMBF.

Tumor immune escape

Project managers: Prof. Dr. A. Mackensen, Dr. M. Aigner

In the last years, the study of tumor metabolites and their effects on the adaptive immune system moved into the center of interest of tumor immunology. By modulation of their metabolism, tumors are able to generate advantages for growth and proliferation for themselves. Our group focuses on the functions of 5'-Deoxy-5'-methylthioadenosine (MTA) and its degrading enzyme MTAP, as it is known that these molecules play a role in many malignacies. The influence of MTA produced by tumors on the activation, proliferation, and various effector functions of cytotoxic CD8+ T cells is studied by the research unit in cooperation with the Universitätsklinikum Regensburg and funded by the DFG.

Cellular immunotherapy

Project managers: Prof. Dr. A. Gerbitz, Dr. M. Aigner, Dr. H. Bruns, Dr. R. Gary

The "Cellular Immunotherapy" group works on the development of T cell therapies directed against B-cell specific self antigens, such as CD19. Main goal is the development of lymphoma specific T cell therapies in murine models. In addition, the group focuses on the development of virus specific T cells for adoptive transfer in patients after allogeneic stem cell transplantation. Parallel to the development of a GMP grade T cell product, the group established an extended immunomonitoring of patients. Within the collaborative research center SFB 643, the immunomonitoring was extended in collaboration with the Institute of Pathology (Charité Berlin) by single cell TCR analysis using Next Generation Sequencing.

Funded by DFG, Deutsche Krebshilfe, ZIM, and BayImmuNet.

HLA-laboratory

Project manager: PD Dr. B. Spriewald

In recent years, the laboratory was 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 group of experimental heart surgery.

Teaching

A traditional teaching program (lectures, seminars, practica) covering all subjects in the field of hematology and oncology is being offered by qualified staff in an integrated and interdisciplinary fashion. A new internal medicine program in hematology and oncology was introduced. In this comprehensive program, small groups of medical students learn the basics of hematology and oncology in a patient-oriented setting.

Selected Publications

Bosch JJ (2012) Immunotherapy of uveal melanoma. Dev Ophthalmol, 49: 137-49

Gerbitz A, Sukumar M, Helm F, Wilke A, Friese C, Fahrenwaldt C, Lehmann FM, Loddenkemper C, Kammertoens T, Mautner J, Schmitt CA, Blankenstein T, Bornkamm GW (2012) Stromal interferon-γ signaling and cross-presentation are required to eliminate antigen-loss variants of B cell lymphomas in mice. PLoS ONE, 7: e34552

Kremer AN, van der Meijden ED, Honders MW, Goeman JJ, Wiertz EJ, Falkenburg JH, Griffioen M (2012) Endogenous HLA class II epitopes that are immunogenic in vivo show distinct behavior toward HLA-DM and its natural inhibitor HLA-DO. Blood, 120: 3246-55

Le Blanc K, Mougiakakos D (2012) Multipotent mesenchymal stromal cells and the innate immune system. Nat Rev Immunol, 12: 383-96

Aigner M, Feulner J, Schaffer S, Kischel R, Kufer P, Schneider K, Henn A, Rattel B, Friedrich M, Baeuerle PA, Mackensen A, Krause SW (2013) T lymphocytes can be effectively recruited for ex vivo and in vivo lysis of AML blasts by a novel CD33/CD3-bispecific BiTE antibody construct. Leukemia, 27: 1107-15

International Cooperations

R. Kiessling, Cancer Centre Karolinska, Karolinska Institutet, Stockholm: Sweden

J.H.F. Falkenburg, Department of Hematology, Leiden University, Leiden: The Netherlands

L. Zitvogel, Institut Gustave Roussy, Paris: France

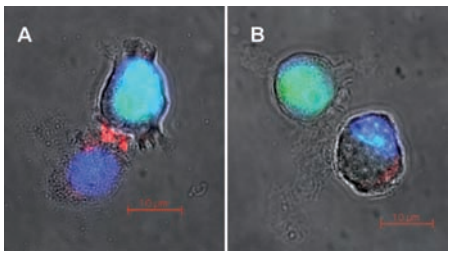
B.R. Ksander, The Schepens Eye Research Institute and Department of Ophthalmology, Harvard Medical School, Boston: USA

Research Equipment

Applied Biosystems, Sequencer AB Genetic Analyser 3130

Becton Dickinson, FACS Canto II

Seahorse Bioscience, XFe96 Analyzer



Human M1 macrophages attack Lymphoma-Cells.
(A) One M1 macrophage secretes a cytotoxic peptide (red), directed against a lymphoma cell (green).
(B) M2 macrophages show no expression of this peptide.

Department of Neurology

Chair of Neurology

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Research Focus
- Intensive care, stroke, emergency care
- Telemedicine and health services
- Epilepsy
- Neuroimmunology
- Pain and functional imaging
- Autonomic nervous system
- Neuromuscular diseases
- Cognitive neurology

Structure of the Department

The Department of Neurology is one of the largest neurological centers in Germany treating 4,500 in-patients and more than 15,000 outpatients each year. Thereby, the Department maintains close collaborations with the Division of Molecular Neurology and the Departments of Neurosurgery and Neuroradiology.
Particularly the emergency unit of the "Kopfklinik", coordinated by our Department, guarantees immediate and best medical treatment and is directly linked to the Department of Neuroradiology. For treatment of in-patients, the Department provides 78 beds altogether. 14 beds are located at one of the largest Stroke-Units in Germany and twelve on the intensive care unit which has been completely remodeled in 2012. The center of Epilepsy (EZE) represents another outstanding facility including a monitoring unit and an interdisciplinary team for surgery in epilepsy. Last but not least a telemedical network for stroke care (STENO) and a number of specialized outpatient services provides university neurological treatment beyond the borders of our region.
The establishment of two endowed chairs for Neuroimmunology and Neurorehabilitation as well as efforts in many other areas further promoted our research activities.
On the basis of this specialized know-how, the Department is able to provide up to date and competent diagnosis and treatment as well as scientific work within all areas of modern clinical neuroscience.

Research

Intensive care, stroke, emergency care
Project managers: PD Dr. M. Köhrmann (Stroke-Unit), PD Dr. H. Huttner (neurocritical care unit), PD Dr. Dr. L. Marquardt (emergency room)
Neurointensive care: Clinical and translational research are major columns of neurointensive care research in Erlangen. Examples include brain edema treatment after ICH, temperature management in subarachnoid hemorrhage cerebral ischemia, intraventricular fibrinolysis and lumbar drainage after intraventricular hemorrhage as well as multimodal monitoring for patients with intracranial pressure.
Emergency room: Each year the initial assessment of about 6,000 patients takes place in the emergency room. After an immediate clinical examination, adequate diagnostic procedures and prompt specific emergency treatment is initiated if necessary. For a multitude of clinical studies, especially vascular ones, screening and inclusion is managed directly in the emergency room.
Stroke-unit: We treat more than 1,000 in-hospital patients on our 14-bed stroke-unit. An extremely high level of medical care (iv-thrombolysis rate > 25%) is combined with state-of-the-art research, including e.g. MRI-based interventions, ECG-monitoring and new oral anticoagulants. Residents are part of an educational curriculum for stroke-care.

Telemedicine and health services
Project manager: PD Dr. Dr. L. Marquardt
For more than five years, the Department of Neurology has been running and coordinating the Stroke Network with Telemedicine with three stroke centers and 17 regional hospitals. Since 2011 the Network has, as the only one of its kind, been certified to the international ISO standard for its rigorous quality management system. The Network is responsible for state-of-the-art stroke care and management in Northern Bavaria and South Thuringia and is part of the regular health care system. Impact and effect of the Network are investigated in scientific studies and the technology is subject to continuous improvement. Amongst other projects with multiple industry and medical collaborators, a very innovative project regarding specialist care for patients with epilepsy in Northern Bavaria will be launched and scientifically evaluated.

Epilepsy
Project manager: Prof. Dr. H.M. Hamer
The Erlangen Epilepsy Center ranks among the top five University Epilepsy Centers in Germany. Scientific hot spots in 2011/2012 included: 1) Changes of the innate immune-system in epilepsy; 2) Epilepsy in CNS-malformations; 3) Pathophysiology of epilepsy: Studies correlating clinical parameters, e.g. neuropsychology, with hippocampal pathology; 4) Magnetoencephlography; the new multichannel MEG system is running; 5) Neuropsychology/Cognition; 6) Quantitative EEG in epilepsy and encephalopathy; 7) Drug monitoring; 8) Historical aspects of epileptology; 9) Socio-economic aspects of epilepsy.
Funding sources are DFG and the Bavarian State Ministry of the Environment and Public Health.

Neuroimmunology
Project manager: Prof. Dr. R. Linker
Activities in the area have been further promoted by the establishment of a W2 endowed chair now held by Prof. Dr. R. Linker. Consequently, the main focus of our interest is a translational approach, bringing experimental knowledge to the patient and vice versa. Apart from the participation in several multicenter trails concerning immunmodulatory therapy of MS, three experimental workgroups have been established very successfully: 1) Immunregulation and new human biomarkers, 2) Neuroprotection and neurodegeneration in the experimental model, as well as 3) T cell immunology and regulation of sodium and water balance. Recent work deals with the regulation of pathogenic Th-17 cell responses by sodium chloride intake. Our group is supported by the Else-Kröner Forschungsstiftung and by several industrial grants.

Pain and functional imaging
Project manager: Prof. Dr. C. Maihöfner
Our research team investigates mechanisms of adaptive and maladaptive sensorimotor plasticity in several diseases (neuropathic pain, headache, and stroke). Employed methods are non-invasive functional brain imaging techniques (fMRI, MEG), neuropsychology, psychophysics, and repetitive transcranial magnetic stimulation (rTMS). Work done by the group

has been awarded several times. Main funding sources are BMBF ("German Research Network on Neuropathic Pain") and DFG ("Determinants and modulators of postoperative pain", KFO 130; see own report).

Autonomic nervous system

Project manager: Prof. Dr. M.J. Hilz

The autonomic research laboratory evaluates cardiovascular autonomic functions of various medical disorders, involving the central and peripheral autonomic network. Moreover, we perform quantitative sensory testing (vibration and temperature sensation) to evaluate polyneuropathy, especially small fiber neuropathy. We investigate the influence of enzyme replacement therapy in lysosomal storage disorders, such as Fabry and Pompe disease, on disease progression.

In patients with familial dysautonomia, we performed polysomnographic sleep recordings in cooperation with the New York University. Furthermore, we evaluated autonomic cardiovascular modulation in patients with stroke, traumatic brain injury, epilepsy, multiple sclerosis, and in professional soccer players after header training.

Neuromuscular diseases

Project managers: Prof. Dr. R. Linker (spokesman), Prof. Dr. R. Schröder

The Neuromuscular Disease Center is an interdisciplinary institute, providing a specialized outpatient clinic and a neuropathological laboratory for diagnostic biopsies and for the investigation of neuromuscular diseases. The neuromuscular research is composed of three task forces with the following key aspects: 1) Examination in immunopathogenesis of autoimmune myositis and Myasthenia gravis, 2) Studies for pathogenesis of myofibrilar myopathy, 3) Works to genetic respectively pathogenesis of hereditary as well as inflammatory neuropathy. A special success was achieved with the extrapolation of the research group FOR 1228, supported by DFG (see own report). The group is managed by Prof. Dr. R. Schröder, not bound to a location.

Cognitive neurology

Project manager: Prof. Dr. T. Schenk

We are interested in visual and movement disorders that occur after selective damage to the brain. We use 3D movement recordings and detailed psychophysicial experiments to gain a better understanding of how the brain uses sensory information to guide our movements. The same techniques are also applied to develop and evaluate new treatment approaches for patients with hemi-blindness and hemispatial neglect. In cooperation with the neuroimmunological group, we examine the cognitive consequences of neuroimmunological disorders. In cooperation with the Institute of Psychiatry, London, we examine the role of the post-traumatic stress disorder in patients' ability to recover after a neurological disease.

Teaching

Between everyday clinical practice and the teachings segment of our Department, the block training gained widespread recognition by the students. Also the clinical course „Einführung in die klinische Medizin" (EKM), giving a short introduction in the everyday clinical practice, as well as the main lecture are appreciated by many students. Due to increased demand, we were not able to integrate all canditates for the final year. A detailed evaluation on scientific basis of teaching activities demonstrated positive results.

Selected Publications

Hilz MJ, Koehn J, Kolodny EH, Brys M, Moeller S, Stemper B (2011) Metronomic breathing shows altered parasympathetic baroreflex function in untreated Fabry patients and baroreflex improvement after enzyme replacement therapy. J Hypertens, 29: 2387-94

Kiphuth IC, Huttner HB, Struffert T, Schwab S, Köhrmann M (2011) Sonographic monitoring of ventricle enlargement in posthemorrhagic hydrocephalus. Neurology, 76: 858-62

Nowak M, Bauer S, Haag A, Cepok S, Todorova-Rudolph A, Tackenberg B, Norwood B, Oertel WH, Rosenow F, Hemmer B, Hamer HM (2011) Interictal alterations of cytokines and leukocytes in patients with active epilepsy. Brain Behav Immun, 25: 423-8

Staykov D, Wagner I, Volbers B, Hauer EM, Doerfler A, Schwab S, Bardutzky J (2011) Natural course of perihemorrhagic edema after intracerebral hemorrhage. Stroke, 42: 2625-9

Birklein F, Maihöfner C (2012) Neglect your back to control your pain? Neurology, 79: 300-1

Kleinewietfeld M, Manzel A, Titze J, Kvakan H, Yosef N, Linker RA, Muller DN, Hafler DA (2013) Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. Nature, 496: 518-22

International Cooperations

X. Wang, Fudan University, Shanghai: China

L. MacDonald, T. Schweizer, Department of Neurosurgery, University of Toronto, Toronto: Canada

Department of cell and molecular biology, Karolinska Institute, Stockholm: Sweden

A. Noble, Institute of Psychiatry, King's College, London: UK

New York University, New York: USA

D. Hafler, Yale University, New Haven: USA

B.S. Chang, BIDMC Harvard, Boston: USA

Meetings and International Training Courses

12.02.2011: Erlanger Schmerz- & Palliativtag, Erlangen

08.-09.07.2011: Symposium Herz & Hirn 2011, Coburg

13.10.2011: 3. Erlanger Telemedizin-Symposium, Erlangen

10.-11.02.2012: Erlanger Schmerz- & Palliativtage, Erlangen

13.-14.04.2012: Comprehensive Epilepsy Course, Erlangen

28.-29.09.2012: Comprehensive Epilepsy Course, Erlangen

15.-16.06.2012: Symposium MS-Zentrum Franken 2012, Nürnberg

11.12.2012: 4. Erlanger Telemedizin-Symposium, Erlangen

Kopfklinikum

Department of Neurology

Division of Molecular Neurology

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Research Focus
- Neurodegenerative diseases
- Translational neuroscience
- Clinical research and development

Structure of the Department

The Division of Molecular Neurology aims at establishing a link between daily patient care towards the neuroscientific development for novel therapies in the field of neurodegenerative diseases. The main focus of the Division is on neurodegenerative diseases, such as Parkinson's disease, Huntington's disease, and hereditary spastic paraplegia. In addition, the Division intends the integration of ongoing clinical projects with the neighboring Departments.
Clinically, a large outpatient clinic for movement disorders is established where the entire spectrum of clinical, electrophysiological, imaging, and genetic diagnostics is provided for patients affected with these diseases. Another focus of the movement disorder outpatient clinic is to assess movements using embedded biosensor systems. This project is jointly developed with an industry partner and the Pattern Recognition Lab.

Research

Neurodegenerative diseases

The scientific focus of the Division emphasizes on adult neurogenesis and neurodegenerative mechanisms in Parkinson's disease, Huntington's disease, and hereditary spastic paraplegia. Neuroregenerative processes with emphasis on adult neurogenesis (generation of new neurons in the adult brain) are assessed in movement disorders, using cell culture and transgenic models of Parkinson's and Huntington's disease. In a complementary approach, neurodegenerative mechanisms in synucleinopathies are analyzed in order to understand the molecular mechanisms in the development of Parkinson's disease and Lewy body dementia. The interaction between neurodegenerative processes and inflammatory pathomechanisms within the CNS has become an additional main focus within the Division.

Translational neuroscience

The Division is interested in the molecular and cellular biology of adult neural stem and progenitor cells in two regions of the adult brain, the subventricular zone and the hippocampus where new neurons are generated throughout the whole life span. Adult neurogenesis is seriously altered in the context of neurodegenerative diseases. Numerous findings indicate that impaired adult neurogenesis may be one of the underlying pathophysiological events in the development of non-motor symptoms, like depression, cognitive impairment, and olfactory dysfunction. These symptoms are likely to reflect the compromised ability of the brain to generate new neurons in the hippocampus as well as the olfactory bulb. Moreover, cell and molecular techniques have been established to delineate and modify pathological mechanisms associated with protein aggregation of α-synuclein in Parkinson's disease and atypical parkinson syndromes. This strategy may lead to a causal therapy of synucleinopathies.
These concepts are currently translated into the generation and characterization of patient derived stem cells that can be isolated from the skin and differentiate into neurons. Based on the initial findings, these patient derived neurons provide for the first time an important tool to study disease processes and define novel interventions.

Clinical research and development

The outpatient clinic for movement disorders (in particular Parkinson's disease, Huntington's disease, and hereditary spastic paraplegia) is offering state of the art diagnostic procedures and long-term care for patients and their caregivers. Furthermore, the integration of scientific projects will be consequently followed up in close cooperation with the Department of Neurology which provides the care for inpatients.
In addition to the clinical and neurobiological activities, deep brain stimulation (DBS) for movement disorders will be established in close cooperation with the Departments of Neurology and Neurosurgery in order to provide the entire spectrum of therapies for movement disorders.
Automated motion and gait analysis systems for stationary and mobile diagnostics are developed in collaboration with the Faculty of Engineering (Pattern Recognition Lab) and with local industry partners (IT Astrum). The goal is to support patients using objective assessment of movement deficits during daily life at home in order to achieve an optimal treatment.

Teaching

The Division of Molecular Neurology is involved in the curricular teaching of Medicine (Department of Neurology) and Molecular Medicine. In addition, internships, bachelor and master thesis as well as medical and natural scientific doctoral theses are supervised.

Selected Publications

Klucken J, Barth J, Maertens K, Eskofier B, Kugler P, Steidl R, Hornegger J, Winkler J (2011) Mobile biosensor-based gait analysis: a diagnostic and therapeutic tool in Parkinson's disease. Nervenarzt, 82: 1604-11

Moessnang C, Frank G, Bogdahn U, Winkler J, Greenlee MW, Klucken J (2011) Altered activation patterns within the olfactory network in Parkinson's disease. Cereb Cortex, 21: 1246-53

Klucken J, Poehler AM, Ebrahimi-Fakhari D, Schneider J, Nuber S, Rockenstein E, Schlötzer-Schrehardt U, Hyman BT, McLean PJ, Masliah E, Winkler J (2012) α-synuclein aggregation involves a bafilomycin A 1-sensitive autophagy pathway. Autophagy, 8: 754-66

Kohl Z, Winner B, Ubhi K, Rockenstein E, Mante M, Münch M, Barlow C, Carter T, Masliah E, Winkler J (2012) Fluoxetine rescues impaired hippocampal neurogenesis in a transgenic A53T synuclein mouse model. Eur J Neurosci, 35: 10-9

May VE, Nuber S, Marxreiter F, Riess O, Winner B, Winkler J (2012) Impaired olfactory bulb neurogenesis depends on the presence of human wild-type alpha-synuclein. Neuroscience, 222: 343-55

Winner B, Regensburger M, Schreglmann S, Boyer L, Prots I, Rockenstein E, Mante M, Zhao C, Winkler J, Masliah E, Gage FH (2012) Role of α-synuclein in adult neurogenesis and neuronal maturation in the dentate gyrus. J Neurosci, 32: 16906-16

International Cooperations

Prof. Dr. L. Aigner, Institute of Molecular Regenerative Medicine, Paracelsus Medical University, Salzburg: Austria

Dr. T.F. Outeiro, Institute for Molecular Medicine - Cellular and Molecular Neuroscience Unit, University of Lisbon, Lisbon: Portugal

Prof. Dr. E. Masliah, Department of Neurosciences, University of California San Diego, San Diego: USA

Prof. Dr. B.T. Hyman, Massachusetts General Hospital - MIND, Harvard University, Boston: USA

Prof. Dr. G. Wenning, Universitätsklinikum Innsbruck, Neurologische Universitätsklinik, Innsbruck: Austria

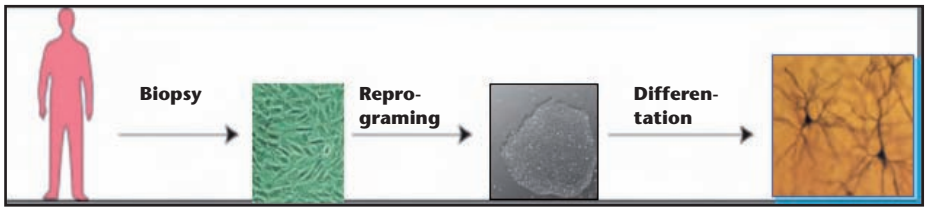
Prof. Dr. T. Wyss-Coray, Stanford School of Medicine, Neuro Immunology and Degeneration, Stanford: USA

Meetings and International Training Courses

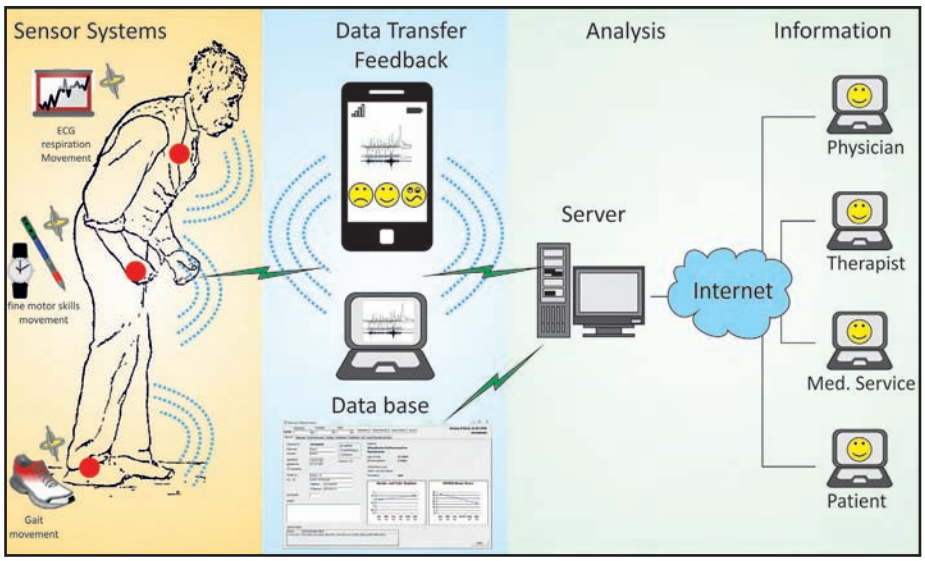
01.01.2011.-31.12.2012: Fortbildungsveranstaltungen im Fortbildungsprogramm der Neurologie, Erlangen

27.-29.10.2011: Jahrestagung der Deutschen Gesellschaft für Neurogenetik, Erlangen

07.12.2012: AMASE: 3. Automated Mobility Analysis Symposium Erlangen, Erlangen



Biopsy derived skin fibroblasts can be reprogrammed into induced pluripotent stem cells and further differentiated into different neural cell types.



Data derived from different body sensors are transferred via IT-network, analyzed server-based, and made available to the patient and therapists.

Department of Neurosurgery

Chair of Neurosurgery

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Research Focus

- Functional Neuronavigation and Intraoperative Imaging
- Neuroendocrinology
- Neurooncology

Structure of the Department

The Department of Neurosurgery of the FAU is one of the largest in Germany. There is a total of 78 beds for inpatients, including ICU beds. The number of outpatients is 4,000 per year. Up to 2,600 patients get inpatient treatment. Caseloads include approximately 2,200 major neurosurgical procedures per year. The range of operations covers the whole spectrum of neurosurgery with a focus in the microsurgical treatment of processes of the skull base, particularly in the sellar region, in eloquent brain areas (e.g. central region, brain stem), the vascular neurosurgery, spine surgery, pediatric neurosurgery, and epilepsy surgery. Aside of modern microsurgical techniques, endoscopic procedure, intraoperative electrophysiological monitoring, neuronavigation, and intraoperative MRI are used. A molecular biological laboratory with an integrated cell culture and a wide range of cellular and molecular biological methods is available for basic scientific issues.

Research

Functional Neuronavigation and Intraoperative Imaging

The research group "functional neuronavigation and intraoperative imaging" is divided in three subgroups that work in part independently, but use the intraoperative 1.5 T MRI-scanner as a common interface.

Subgroup I (intraoperative imaging):
A major effort of this group is the acquisition of all parameters that are connected to intraoperative imaging of pituitary and suprasellar tumors, intra- and extraaxial brain tumors, and epilepsy-associated procedures. The analysis of these data is currently in progress. In addition, the group worked on the visualization of important eloquent brain areas with the implementation of diffusion-tensor-imaging, functional MRI and magnetoencephalography. Moreover, studies of implementation of tractography data in the surgical treatment of brain stem lesions were completed. Two important studies analyzed the connectivity of eloquent brain areas with different DTI algorithms using probabilistic fiber tracking and investigated the amount of susceptibility artifacts in linear registration of fiber tracts.
Subgroup II (functional imaging):
This group made correlative studies for cortical plasticity after resection of gliomas. Also the connectivity of receptive and expressive language areas was investigated with fMRI and DTI following reports of other groups with electrical stimulation.
Subgroup III (metabolic imaging):
Major efforts were 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. Further, we investigate the following topics: Correlation of fluorescence-guided resection of malignant gliomas, utilizing five-aminolevulinic acid (5-ALA) and intraoperative MR imaging, studies of cortical plasticity after gliome resection adjacent to eloquent brain areas and intraoperative MR spectroscopy in gliomas.

Neuroendocrinology

The Department of Neurosurgery represents a nationally and internationally specialized center for the whole spectrum of sellar pathologies. Clinically we investigate the influence of interventional/operative, radiotherapeutic, and pharmacological approaches on normal and hypersecretory pituitary gland function in the course of the "Acrostudy" (treatment and MRI follow-up of the medicinal therapy with Somavert). Also, investigations on Somatostatin analoga and their clinical relevance in the treatment of growth hormone secreting pituitary adenoma represent a central part. Our clinical and laboratory chemical analysis and screening studies are supported by 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 the possibility of control of 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 in the Department of Neurosurgery was established in 2007 in the framework of an endowed professorship for clinical and experimental neuroendocrinology. In cooperation with the Institute of Radiology, body composition, liver and muscle fat content are determined by MRI in patients with various hypothalamic-pituitary diseases (e.g. pituitary deficiency, acromegaly, and M. Cushing). The results are correlated with various metabolic characteristics and with novel parameters involved in the metabolic control. The aims of these studies are to obtain novel insights in the neuroendocrine control of metabolic and energetic processes. Another translational scientific project involves the functional characterization of mutations of the metabotropic calcium-sensing receptor (CaSR) that occur in patients with specific disorders of calcium homeostasis. The CaSR is also expressed in pituitary cells and in hypothalamic nuclei involved in the control of endocrine systems. In this project the patients are screened for clinical evidence of neuroendocrine dysfunction, and clinical and in-vitro data are correlated to define a potential genotype-phenotype relation. Furthermore, agonists and antagonists of the CaSR are tested in vitro whether they can rescue the molecular defect of the mutated CaSR. This potentially offers a therapeutic approach specifically tailored to patient´s molecular CaSR defect (individualized medicine). Further projects investigate various aspects of growth-hormone secreting human adenoma cells in vitro, like the expression of certain membrane receptors (e.g. somatostatin receptors) and the characteristics of signaling cascades (cAMP- and Ca2+-PI-signaling pathway). The in vitro data are related to various clinical data in order to

extract potential prognostic factors concerning therapeutic outcome and to define potential new therapeutic targets.

Neurooncology

Gliomas are the most common primary tumors of the brain, and about 70% of these tumors are malignant gliomas. Currently, there is no promising therapy for the treatment of malignant tumors which targets the high proliferation and diffuse brain invasion. Therefore, investigation and characterization of the molecular mechanisms of glioma growth and invasion are essential steps in developing novel therapeutic strategies. The neurooncology research group deals with the biology and therapy of brain tumors and could demonstrate that malignant gliomas secrete high amounts of the neurotransmitter glutamate which results in neuronal cell death in the peritumoral brain parenchyma and induces perifocal edema. These data correlate with a reduced quality of life of patients suffering from malignant gliomas. Another focus of the group is to decipher the interaction of different brain cells and glioma proliferation. One candidate molecule for tumor-associated cell interaction represents the protein MIF. This cytokine is secreted by glioma cells and interacts with the adjacent parenchyma. The aim of this project is the analysis of MIF effects on immune competent cells in the brain, such as microglial cells, and its role in glioma proliferation and invasion. Moreover, the preliminary data indicate that microglial cells participate at edema formation surrounding malignant gliomas. The presented studies are funded by a grant from the "Wilhelm Sander-Stiftung" and from the "Institut Danone Ernährung für Gesundheit e.V.".

Teaching

Aside of the neurosurgical main lecture with case demonstrations and live broadcasts from the operating theater, neurosurgical diseases are also discussed in smaller groups. As part of the practical course, students learn how to examine neurosurgical patients. Moreover, they have the possibility to participate on clinical routines, such as examination of outpatients, inpatients, and visit the operating theater.

Selected Publications

Savaskan NE, Heckel A, Hahnen E, Engelhorn T, Doerfler A, Ganslandt O, Nimsky C, Buchfelder M, Eyüpoglu IY (2008) Small interfering RNA-mediated xCT silencing in gliomas inhibits neurodegeneration and alleviates brain edema. Nat Med, 14: 629-32

Brandner S, Kleindienst A (2011) Neuroprotection and neuroregeneration: what to expect from a stem cell-based therapy of acute brain injury. Crit Care Med, 39: 2577-8

Savaskan NE, Seufert S, Hauke J, Tränkle C, Eyüpoglu IY, Hahnen E (2011) Dissection of mitogenic and neurodegenerative actions of cystine and glutamate in malignant gliomas. Oncogene, 30: 43-53

Buchfelder M, Schlaffer SM (2012) Intraoperative magnetic resonance imaging during surgery for pituitary adenomas: pros and cons. Endocrine, 42: 483-95

Eyüpoglu IY, Hore N, Savaskan NE, Grummich P, Roessler K, Buchfelder M, Ganslandt O (2012) Improving the extent of malignant glioma resection by dual intraoperative visualization approach. PLoS ONE, 7: e44885

Eyüpoglu IY, Buchfelder M, Savaskan NE (2013) Surgical resection of malignant gliomas-role in optimizing patient outcome. Nat Rev Neurol, 9: 141-51

International Cooperations

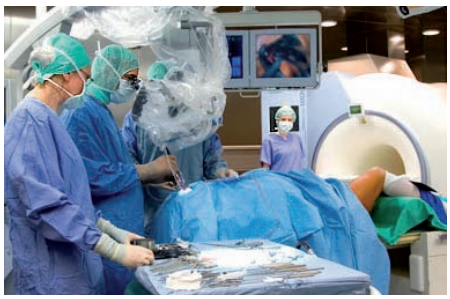
Prof. Dr. T. Lei, Department of Neurosurgery, Huazhong University of Science and Technology, Tongji Medical College, Wuhan: China

Prof. Dr. A. Devin, Cell energy metabolism laboratory, Université Bordeaux, Bordeaux: France

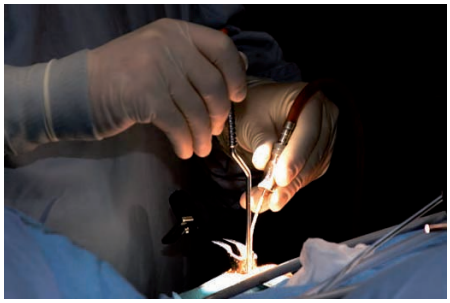
Prof. Dr. I. Shachar, Weizmann Institute of Science, Rehovot: Israel

Prof. Dr. R. Bucala, Department of Medicine, Yale University School of Medicine, New Haven: USA

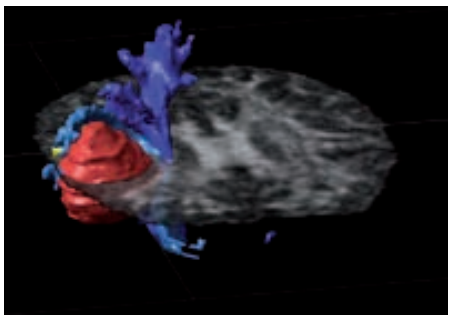
Prof. Dr. D.L. Kleinberg, Department of Endocrinology, New York University Langone Medical Center, New York: USA



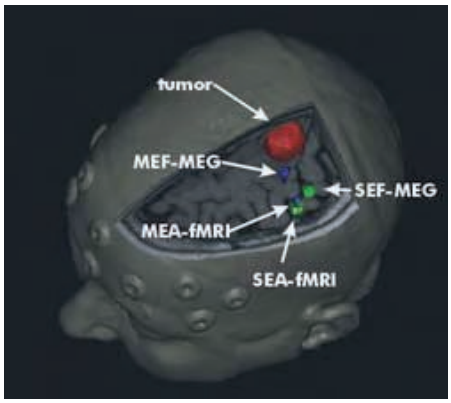
The Department of Neurosurgery



Pituitary surgery



Neurooncology



Functional neuronavigation

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Research Focus
- Correlative Imaging
- Molecular Imaging and Radiochemistry

Structure of the Department

At the Department of Nuclear Medicine, the Chair of Clinical Nuclear Medicine and the Professorship of Radiochemistry and Molecular Imaging, founded in 2010, are established. For patient-oriented clinical research, the hybrid cameras SPECT/spiral-CT and PET/CT are being used in an interdisciplinary setting. Since October 2010, owing to a research cooperation with Siemens Healthcare, the Department has had access to a simultaneous whole-body MR/PET hybrid system that is being operated together with the Institutes of Radiology and Medical Physics. The radiochemical laboratory of the Department is equipped with synthesis modules for synthesizing radiotherapeutics and by a further module for producing PET tracers which is operated under good-manufacturing-practice (GMP) conditions in cooperation with the PETNET GmbH. In the laboratory of molecular imaging of the Department new radiopharmaceuticals are being developed and evaluated. The methodology implemented for this purpose includes chemical, radiochemical, and cell biological facilities. In addition, the laboratory operates a highly resolving autoradiographic detector system and a micro-PET.

Research

Correlative Imaging

The tremendous progress of technology has created a wide array of new ways to image the human body and considerably improved already existing methodology. However, the complexity of the diagnostic process has correspondingly also increased. Therefore, the integration of information from different imaging modalities has become an important issue. Ideally, image datasets from two different modalities are registered to one common coordinate system to allow for true correlative imaging. The manufacturers of medical imaging devices have developed two different solutions to this problem: On the one hand, devices have been designed that unify two cameras of different modalities, the so-called hybrid systems. In particular, hybrid systems combining emission tomographic cameras with X-ray computerized tomographs (CTs) are currently commercially available. On the other hand, user platforms and data structures have been homogenized so that the exchange of image data between different modalities and also the registration of independently acquired images have been facilitated a lot. In cooperation with the Chair of Pattern Recognition of the FAU and Siemens Healthcare, the Department of Nuclear Medicine develops a new methodology of correlative imaging and investigates its clinical value. Currently investigated combinations of modalities are SPECT/CT, PET/CT, and MR/PET.

Molecular Imaging and Radiochemistry

Diagnostic nuclear medicine images the distribution of radioactively labeled substances within the body of patients. This distribution is a consequence of the interaction of the radiopharmaceuticals with functionally relevant proteins. By visualizing this interaction and thus the expressing and activating the proteins, nuclear medicine can bridge the gap between molecular biology and clinical imaging and can correlate imaging results to the specific reason of disease or metabolic disorder. Following this idea and the use of molecular tracers in functional imaging, the term molecular imaging has recently been implemented in this field of research.

The main research area of the professorship of molecular imaging and radiochemistry is the development of new radiochemical labeling methods for the production of radiopharmaceuticals, the preclinical evaluation of novel radiotracers in vitro and in vivo, and the translation of the research results into the clinic. Recent examples for these studies are the development of Ga-68-labeled peptides for the transferrin receptor, the characterization of superagonists of the thyroid TSH receptor in vitro and in vivo, and the translation of [^{18}F] fluoroethyl tyrosine into the clinic for patients with epilepsy. Based on our recent development of a highly effective radiochemical labeling method for the glycosylation of biomolecules that is compatible to the short half life of the positron emitters, a variety of F-18-labeled glycoconjugates is studied in our lab in search for new radiopharmaceuticals. These studies include the development of tracers for imaging angiogenesis with a special focus on the evaluation of the PET method for early detection of therapy response in the preclinical setup. This project is processed in cooperation with the Chair of Pattern Recognition of the FAU (Prof. Dr.-Ing. J. Hornegger) with a special interest in small-animal PET imaging and was supported by the BMBF.

In cooperation with the Chair of Pharmaceutical Chemistry of the FAU (Prof. Dr. P. Gmeiner), this methodology has supported and accelerated the development of tracers for various molecular targets suitable for PET imaging studies. Moreover, radioligands for the D3 and D4 subtype of the dopamine receptor have been evaluated. As yet, radiopharmaceuticals suited to study these receptor subtypes supposed to be implicated in the pathogenesis of several neuropsychiatric disorders are lacking so that this project may be considered to be truly innovative. In 2011 and 2012, this project was supported by the DFG (PR 677/2-3). Further radiopharmaceutical chemistry projects include the development of radiopeptides addressing the neuropeptide-Y receptor and neurotensin receptor that are studied as targets for imaging of mamma and prostate carcinoma in the preclinical setup by small-animal PET. In 2011 and 2012, this research was supported by the DFG (clinical research unit FOR 661, see own report).

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 molecular medicine. He also participates in teaching physiology, pharmacology, and computer sciences. In a broad fashion, the head of

the Department performs postgraduate teaching for physicians in Middle and Upper Franconia. The Professor for Molecular Imaging and Radiochemistry offers practical trainings for students of molecular medicine and provides lectures for students of molecular sciences in the scientific faculty.

Selected Publications

Kasper BS, Struffert T, Kasper EM, Fritscher T, Pauli E, Weigel D, Kerling F, Hammen T, Graf W, Kuwert T, Prante O, Lorber B, Buchfelder M, Doerfler A, Schwab S, Stefan H, Linke R (2011) (18) Fluoroethyl-l-tyrosine-PET in long-term epilepsy associated glioneuronal tumors. Epilepsia, 52: 35-44

Kügler F, Sihver W, Ermert J, Hübner H, Gmeiner P, Prante O, Coenen HH (2011) Evaluation of 18F-labeled benzodioxine piperazine-based dopamine D4 receptor ligands: lipophilicity as a determinate of nonspecific binding. J Med Chem, 54: 8343-52

Merhof D, Markiewicz PJ, Platsch G, Declerck J, Weih M, Kornhuber J, Kuwert T, Matthews JC, Herholz K (2011) Optimized data preprocessing for multivariate analysis applied to 99mTc-ECD SPECT data sets of Alzheimer's patients and asymptomatic controls. J Cereb Blood Flow Metab, 31: 371-83

Reinfelder J, Maschauer S, Foss CA, Nimmagadda S, Fremont V, Wolf V, Weintraub BD, Pomper MG, Szkudlinski MW, Kuwert T, Prante O (2011) Effects of recombinant human thyroid-stimulating hormone superagonists on thyroidal uptake of 18F-fluorodeoxyglucose and radioiodide. Thyroid, 21: 783-92

Wängler C, Nada D, Höfner G, Maschauer S, Wängler B, Schneider S, Schirrmacher E, Wanner KT, Schirrmacher R, Prante O (2011) In Vitro and Initial In Vivo Evaluation of (68)Ga-Labeled Transferrin Receptor (TfR) Binding Peptides as Potential Carriers for Enhanced Drug Transport into TfR Expressing Cells. Mol Imaging Biol, 13: 332-41

Menges M, Uder M, Kuwert T, Schmidt D (2012) 131I SPECT/CT in the follow-up of patients with differentiated thyroid carcinoma. Clin Nucl Med, 37: 555-60

International Cooperations

Dr A.H. Vija, Molecular Imaging, Siemens Medical Solutions, Hoffman Estates, Chicago: USA

Dr. R. Haubner, Department of Nuclear Medicine, Innsbruck Medical University, Innsbruck: Austria

Research Equipment

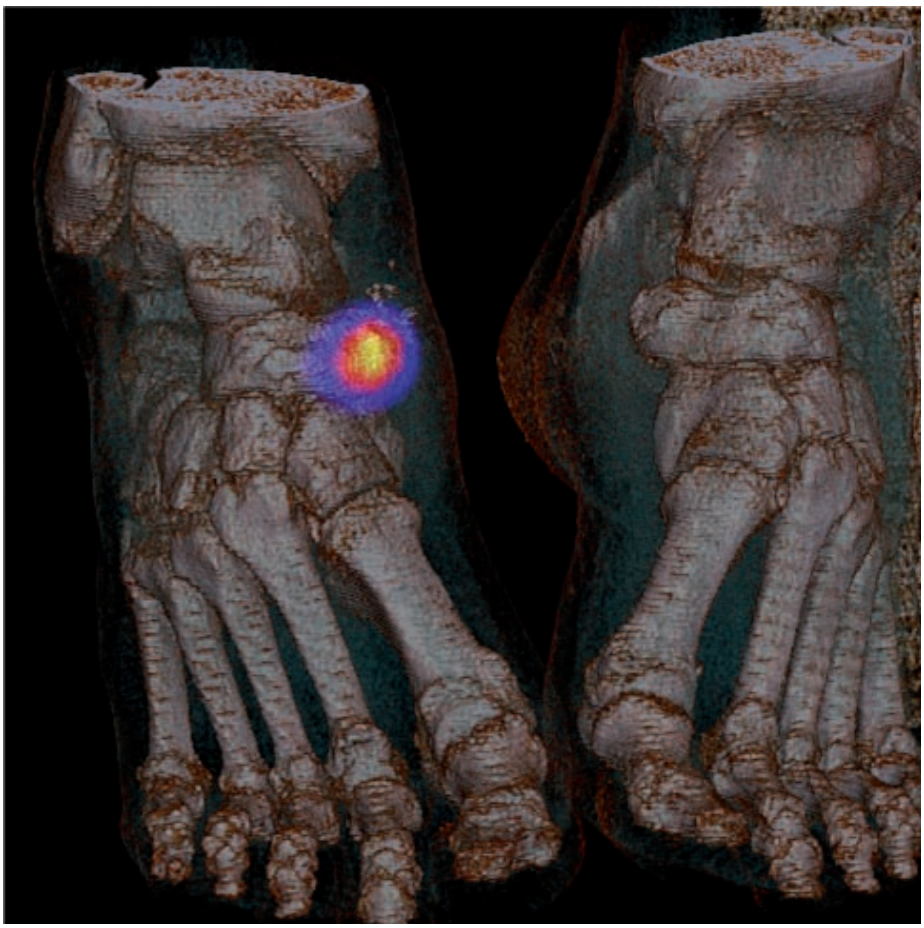
Siemens, mCT (PET/CT)

Siemens, SPECT/CT Symbia T6

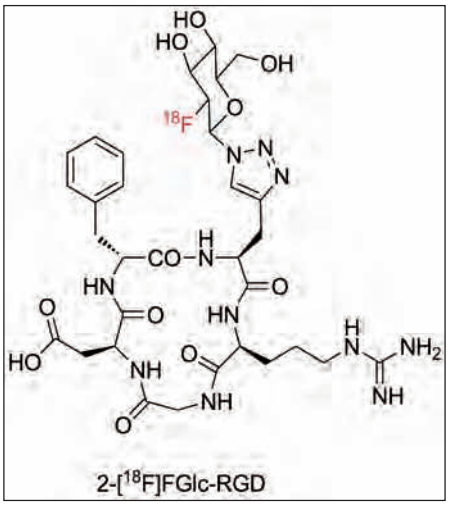
Siemens, SPECT/CT Symbia T2

Siemens, mMR (PET/MR)

Siemens, Animal PET



55-year-old patient four months after bullet injury Focal area with increased uptake indicating an inflammatory lesion (Osteomyelitis) in the Os naviculare.



This image depicts the ^{18}F-labeled cyclic glycopeptide bearing the RGD amino acid sequence that displays high specific binding to newly built blood vessels. Thus, this radiotracer could in principle visualize the process of angiogenesis, e.g. in tumors. This radiopharmaceutical will be further evaluated in preclinical studies in our research laboratory.

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Head of Department
Prof. Dr. med. Matthias W. Beckmann

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Research Focus

- Gynecological oncology (Laboratory for Molecular Medicine, LMM)
- Specialized obstetrics and perinatal medicine
- Clinical Trials (Clinical Trial Center, CTC; Institute for Women's Health, IFG©)
- Gynecological endocrinology and reproductive medicine

Structure of the Department

Following an extensive structural change in the Department of Obstetrics and Gynecology, the three traditional pillars of the field (Gynecology, Gynecologic Oncology, Obstetrics and Perinatal Medicine, and Endocrinology and Reproductive Medicine) are represented clinically and scientifically in the following organizational units:

- University Breast Center Frankonia (UBF),
- Gynecological University Cancer Center Frankonia (GKF),
- University Perinatal Center Frankonia (UPF),
- University Center for Reproductive Medicine Frankonia (UFF),
- University Endometriosis Center Frankonia (UEF).

These centers are certified by the appropriate national and international professional societies and by quality management.

In the clinic, two W2 Professorships for Translational Gynecology and Obstetrics (Prof. Dr. P.A. Fasching) and Experimental Reproductive Medicine (Prof. Dr. R. Dittrich) were established. Interfaces of the scientific work are provided by the Laboratory for Molecular Medicine (LMM) and the associated center for clinical studies (Study Center, Institute for Women's Health, IFG®). In total, more than 40 physicians work in the hospital clinically and scientifically. They are supported by two mathematicians, two scientists, and seven study nurses.

The clinic has an approval of the European Board and College of Obstetrics and Gynecology (EBCOG) as a training clinic for the European physician.

Research

Gynecological oncology (Laboratory for Molecular Medicine, LMM)

Project managers: PD Dr. R. Strick, Prof. Dr. P.A. Fasching, Dr. A. Hein, Dr. C. Rauh, Dr. M. Schrauder, PD Dr. P. Strissel, PD Dr. S.P. Renner

In the LMM, the DNA and tissue bank has been expanded. End of 2012, more than 65,000 blood and DNA samples and more than 41,000 serum samples and - in cooperation with the Institute of Pathology, FAU (Head: Prof. Dr. A. Hartmann) - more than 10,100 tissue samples of benign and malignant tumors have been stored. These samples are utilized for in house research and participation in international consortia, such as the Breast Cancer Associated Consortium (BCAC), the Ovarian Cancer Association Consortium (OCAC), and the NIH-funded networks, like the Genomics and Randomized Trials Network (GARNET) and the Pharmacogenetics Research Network (PGRN).

Cancer research focused on gene variations and their possible correlation with disease risk, detection, and prognosis. Within the BMBF-funded Cluster of Excellence (Spitzencluster) "Integrated Breast Care", a study (Imaging and Molecular Detection in Breast Cancer; iMODE-B) has been conducted that aims at risk prediction and early detection of breast cancer. With regard to molecular detection markers, miRNA in healthy and diseased women have been studied. Using miRNA chips, several miRNA could be identified that are associated with breast cancer. Further cancer detection studies include the development of new imaging methods based on 3D imaging methods (ultrasound, tomosynthesis, MRI) in collaboration with the Institute of Radiology, SIEMENS, and the Erlangen Center for Astroparticle Physics.

In addition, the role of 21 envelope genes of human endogenous retroviruses (HERV) as a oncologic risk factor and their importance for cell invasion and cell-cell fusion was examined. Seven of these envelope genes were significantly overexpressed in endometrial cancer and pre-stages as compared to control tissues. In close cooperation with the Institute of Medical Physics (head: Prof. Dr. B. Fabry), a cell invasion analysis system was established on the basis of collagen. Other preclinical studies in endometrial and breast cancer cells showed that the (de)phosphorylation of AKT and mTOR were differentially activated in these cells.

In an analysis of endometriosis tissue samples, the same cell invasion analysis system was used to examine the different invasion capabilities of fractionated endometriosis versus control endometrium cells. First results show that endometriosis cells have a higher ability to invade matrices. Additional studies are planned to investigate the correlation of invasion and pain.

Specialized obstetrics and perinatal medicine

Project managers: Prof. Dr. T.W. Goecke, Dr. F. Faschingbauer, Prof. Dr. P.A. Fasching, PD Dr. S. Kehl

This group together with the LMM was awarded two DFG-projects to investigate the functional role of specific envelope proteins of human endogenous retroviruses (HERV-family) in the placenta. It was shown that changes of the HERV proteins Syncytin-1, -2, and -3 significantly affected the formation of placental disorders, such as HELLP-syndrome, preeclampsia, and intrauterine growth retardation (IUGR).

In a multicenter study planned with 10,000 pregnant women (Clinical Gravidity Association Trials and Evaluation Program, CGATE) over a longer observation period, possible associations of different factors in pregnancy (including health problems, lifestyle) with the etiology of diseases in later life of the mother and child are studied. One of the study objectives is the detection of valid risk factors that could constitute a basis for preventive measures. Currently, the study has recruited 453 patients and therefore nearly completed the pilot phase. Following a futility analysis, the design of further targets is planned.

Clinical Trials (Clinical Trial Center, CTC; Institute for Women's Health, IFG©)

Project managers: Prof. Dr. P.A. Fasching, PD Dr. F. Thiel, PD Dr. C. Löhberg

Until 2012, over 161 research projects have been carried out in the IFG®. These include clinical phase I-IV studies as well as research on new surgical techniques. The clinical studies

pursue innovative approaches to the etiology, diagnosis, and therapy of breast, ovarian, endometrial, and cervical cancer. In addition to genetic testing and chemotherapy protocols, the current "target therapies" are examined. In line with studies which include both, curative and palliative therapies, so far 1,389 patients received a treatment.

Noteworthy for breast cancer is the Preface study which recruitment phase has ended and was carried out throughout Germany under the guidance of Erlangen. A total of 3,500 patients were included from more than 220 study centers. The Phase-IV study examines pharmacogenetic markers which should predict treatment effects and side effects of aromatase inhibitors. Initial analyses of toxicity have been presented at scientific meetings. With regard to genital cancers, the Department of Obstetrics and Gynecology headed the AGO-cervix-1 study. This Phase-III study was designed to compare the chemotherapy regimens paclitaxel plus topotecan and topotecan plus cisplatin in patients with recurrent, persistent, or metastatic cervical cancer. However, in April 2012 following an analysis of intermediate results, the study was stopped because of sagging recruitment and doubts in reachability of sufficient statistical power.

The work of the clinical trials center is complemented by a preclinical research program with the same substances. Using the breast cancer xenograft mouse models, we could show that the combination with the anti-malaria drug chloroquine activated p53 and weakened the RAD001-induced AKT phosphorylation and could abrogate the resistance mechanism in cancer cells.

Gynecological endocrinology and reproductive medicine

Project manager: Prof. Dr. R. Dittrich

The research in the University Reproductive Center (UFF) includes the cryo-preservation of germ cells, the physiology of movements of the non-pregnant uterus, and the pathology of genital malformations.

Most important, the efforts to restore fertility in young cancer patients after chemotherapy and/or radiotherapy have been crowned with success: In 2011 and 2012, the first two women in Germany gave birth to healthy children at the University Hospital after pregnancies which developed following homologous endoscopic transplantation of cryo-preserved ovarian tissue. Meanwhile, not only the ovary, but also the uterus and the kidneys are a focal point of experiments aimed at cryopreservation of whole organs.

Experiments with an ex-vivo uterus-model showed that seminal plasma from different patients has different potency to induce rhythmical contractions. This capability may be an additional male factor influencing the fertility rate. Thus, the supplementation of substances inducing muscular contractions in sperm preparations for assisted reproductive treatments may increase the pregnancy rate.

Teaching

Since the end of 2010, the specific functional area for undergraduate teaching has been among the first university clinical institutions in Germany to acquire a quality management system especially for medical education. In 2011 and 2012, the structures of practical clinical courses (Blockpraktika) were further improved on this basis and evaluated in respect to the resulting innovations. Aside from this, a study reviewed the efforts to improve medical education at all German university hospitals for Obstetrics and Gynecology. The published results and their discussion are expected to encourage further development.

Selected Publications

Fasching PA, Heusinger K, Haeberle L, Niklos M, Hein A, Bayer CM, Rauh C, Schulz-Wendtland R, Bani MR, Schrauder M, Kahmann L, Lux MP, Strehl JD, Hartmann A, Dimmler A, Beckmann MW, Wachter DL (2011) Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. BMC Cancer, 11: 486

Nik-Zainal S, Strick R, Storer M, Huang N, Rad R, Willatt L, Fitzgerald T, Martin V, Sandford R, Carter NP, Janecke AR, Renner SP, Oppelt PG, Oppelt P, Schulze C, Brucker S, Hurles M, Beckmann MW, Strissel PL, Shaw-Smith C (2011) High incidence of recurrent copy number variants in patients with isolated and syndromic Müllerian aplasia. J Med Genet, 48: 197-204

Schaefer J, Beckmann MW, Frobenius W (2011) Marked Improvements in Training for Students in their Practical Year Developments in German Gynecology Teaching From 2006 to 2010 and the Prospects Geburtsh Frauenheilk, 71: 956-966

Dittrich R, Lotz L, Keck G, Hoffmann I, Mueller A, Beckmann MW, van der Ven H, Montag M (2012) Live birth after ovarian tissue autotransplantation following overnight transportation before cryopreservation. Fertil Steril, 97: 387-90

Faschingbauer F, Beckmann MW, Goecke TW, Yazdi B, Siemer J, Schmid M, Mayr A, Schild RL (2012) A new formula for optimized weight estimation in extreme fetal macrosomia (>= 4500 g). Ultraschall Med, 33: 480-8

Ruebner M, Langbein M, Strissel PL, Henke C, Schmidt D, Goecke TW, Faschingbauer F, Schild RL, Beckmann MW, Strick R (2012) Regulation of the human endogenous retroviral Syncytin-1 and cell-cell fusion by the nuclear hormone receptors PPARγ/RXRα in placentogenesis. J Cell Biochem, 113: 2383-96

International Cooperations

Prof. B. Ponder, Prof. D. Easton, Breast Cancer Consortium, Cambridge, Cambridge: UK

Prof. D. Slamon, MD, PhD, David Geffen School of Medicine, UCLA, Los Angeles: USA

R. Weinshilboum, MD; L. Wang, MD; J. Ingle, MD, Mayo Clinic, Rochester: USA

Meetings and International Training Courses

14.01.2011: Erlanger OP-Workshop Endometriose, Erlangen

25.-28.05.2011: Gemeinsame Tagung der Bayerischen Gesellschaft für Geburtshilfe und Frauenheilkunde (BGGF) und der Österreichischen Gesellschaft für Geburtshilfe und Gynäkologie (OEGGG), Erlangen

22.10.2011: Expertenmeeting: Das fetale Herz, Erlangen

15.02.2012: Fertilitätsprotektion bei Kindern, Frauen und Männern, Erlangen

02.05.2012: Neue Perspektiven in der Primärtherapie der Patientin mit Endometrium- oder Ovarialkarzinom, Erlangen

19.09.2012: Abnorme uterine Blutungen und neue Behandlungsoptionen des Uterus myomatosus, Erlangen

27.10.2012: Das fetale ZNS; Grundlagen und Expertenwissen der interdisziplinären Pränataldiagnostik, Erlangen

In 2011 and 2012, the first two babies in Germany after homologous transplantation of ovarian tissue were given birth.

Department of Ophthalmology

Chair of Ophthalmology

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Research Focus

- Biomorphometry of the optic nerve
- Functional aspects of retinal neurodegeneration
- Retinal physiology
- Clinoco-pathologic 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 and computer-aided-diagnosis & virtual education

Structure of the Department

In total 169 persons are employed at the Department of Ophthalmology. Of these, 43 are physicians and ten scientific staff members. Nine of these are employed as professors. In addition, 78 persons are employed for nursing service and 38 as non-scientific staff (technicians etc.).
The clinical expertise of the Department of Ophthalmology includes the complete spectrum of surgical and conservative ophthalmology.
In the surgical ophthalmology, a diverse spectrum of operations is performed, including surgery of the frontal eye, cornea surgery, reconstructive surgery of the frontal eye, glaucoma surgery, oculoplastic, orbita, tumor, tear gland, and vitreo-retinal surgery.
In the surgical area, innovative surgical procedures are developed and evaluated. These developments include seamless transconjunctival retinal-vitreal surgery (23-gauge-vitrectomy), minimal invasive glaucoma surgery employing implants, refractive surgery with the femtosecond laser, cataract surgery with innovative intraocular lenses, and intraocular injections of compounds to treat age related macular degeneration (AMD).
In the field of the conservative medicine, special consultation areas are established. Special departments (optometry, fluorescence angiography and laser, outpatients department, and the cornea bank) are present. In addition, there is support from different laboratories.

Research

Biomorphometry of the optic nerve
Project managers: Prof. Dr. C. Mardin, PD Dr. R. Lämmer, Dr.-Ing. R. Tornow
Main focus of the research is the development and application of imaging methods for early detection of glaucoma and to quantify progression. Especially the possibilities of the spectral domain OCT to measure retinal layers will be optimized. The developed imaging methods are complemented by functional tests. The findings are also applied to other diseases, like diabetic retinopathy and age related macular degeneration.

Functional aspects of retinal neurodegeneration
Project managers: Prof. Dr. A. Jünemann, Prof. Dr. J. Kremers, Dr.-Ing. F. Horn
In this research center, new electrophysiological and psychophysical techniques are developed to study the functional aspects of retinal degeneration, especially in glaucoma. The responses from different retinal pathways are separated by appropriate stimuli. The stimulation of non-redundant systems allows the early detection of functional glaucomatous damage. Electrophysiological tests have the advantage of objectivity, but they are less sensitive in comparison to the psychophysical tests. The multifocal stimulation, the full-field flash ERG with colored stimuli and temporal contrastsensitivity in perimetric tests are new developments to improve sensory testing of retinal degeneration.

Retinal physiology
Project managers: Prof. Dr. J. Kremers, Prof. Dr. A. Jünemann
The goal of this topic 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.

Clinoco-pathologic concepts in diagnosis and management of ocular diseases
Project managers: Prof. Dr. L. Holbach, Prof. Dr. F.E. Kruse, Prof. Dr. G. Gusek-Schneider, Prof. Dr. A. Bergua
1. Diagnosis and management of orbital diseases - a multidisciplinary approach.
2. Surgical management of periocular malignant tumors using frozen section control and plastic reconstruction - indications, methods, and results.
The aim of this study is the long-term evaluation of surgical results following intraoperative frozen section control and immediate plastic repair regarding recurrence rates and adequacy of reconstructive techniques.
3. Diagnosis and surgical management of epibulbar lesions.
The purpose of this study is to establish correlations between morphologic, biomicroscopic, histologic, and molecular genetic criteria and the long-term results of surgical excision and plastic reconstruction.

Corneal stem cells
Project managers: Prof. Dr. U. Schlötzer-Schrehardt, Prof. Dr. F.E. Kruse
The maintenance of a healthy corneal epithelium and transparent cornea is achieved by a population of stem cells located at the corneal limbus. This research project explores the molecular characteristics of corneal stem and progenitor cells together with their specific niches and their utilization for novel stem cell based therapies for ocular surface reconstruction in patients with limbal stem cell deficiency. The applicability of alternative autologous stem cell sources for corneal epithelial tissue engineering strategies is investigated.

Pseudoexfoliation syndrome/ glaucoma
Project manager: Prof. Dr. U. Schlötzer-Schrehardt
The focus of this research project is the molecular analysis of the generalized matrix process and its causally related glaucoma development. These investigations resulted in new findings contributing significantly to an elucidation of pathogenesis, an improved understanding of

the symptoms, an earlier diagnosis, a reduction of surgical complications, and the identification of novel therapeutic targets. These findings established the group's leading position in basic research on PEX syndrome/glaucoma.

Improvements in corneal transplantation

Project managers: Prof. Dr. F.E. Kruse, Dr. B. Bachmann

The working group seeks for improvements in different surgical techniques for corneal transplantation. Clinical research has lead to an increase in safety, reproducibility, and functional outcome after corneal transplantation by utilizing the lamellar structure of the cornea for the lamellar replacement of diseased corneal tissue.

Circulation of the eye and the visual pathway and computer-aided-diagnosis & virtual education

Project manager: Prof. Dr. G. Michelson

1. Ocular circulation of the eye and the visual pathway

The tissues and vessels of the eye reflect systemic diseases and are a perfect system for the visualization of physiologic processes of the body. Immunological processes, diabetes, and arterial hypertension can be evaluated quantitatively in the eye.

2. Computer-aided-diagnosis & virtual education

Ophthalmology needs new methods for medical information processing to optimize diagnosis and therapy. Automated analysis of ophthalmic images combined with automated classification leads to a fast and bias-free evaluation which is an important prerequisite for screening.

3. Diffusion measurement of the visual pathway based on magnetic resonance images

Neurodegenerative eye diseases often involve the entire visual system. In some cases, they are induced by a cerebral macro- and microangiopathy with subsequent ischemic changes and degeneration of the visual pathway. The new non-invasive technique based on magnetic-resonance imaging provides information about the integrity and orientation of the visual pathway.

Teaching

Results of research are directly implemented in medical student and postgraduate teaching. In the course of the standard curriculum, project leader and research fellows are involved in the regular student education and practical courses. Moreover, they are involved in doctorates' education and training.

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

Kruse FE, Laaser K, Cursiefen C, Heindl LM, Schlötzer-Schrehardt U, Riss S, Bachmann BO (2011) A stepwise approach to donor preparation and insertion increases safety and outcome of Descemet membrane endothelial keratoplasty. Cornea, 30: 580-7

Meyer-Blazejewska EA, Call MK, Yamanaka O, Liu H, Schlötzer-Schrehardt U, Kruse FE, Kao WW (2011) From hair to cornea: toward the therapeutic use of hair follicle-derived stem cells in the treatment of limbal stem cell deficiency. Stem Cells, 29: 57-66

Michelson G, Engelhorn T, Dörfler A (2011) Retinal microangiopathy in arterial hypertension as an early marker of a cerebral macroangiopathy. Dtsch Med Wochenschr, 136: 2355-8

Schrems WA, Laemmer R, Hoesl LM, Horn FK, Mardin CY, Kruse FE, Tornow RP (2011) Influence of atypical retardation pattern on the peripapillary retinal nerve fibre distribution assessed by scanning laser polarimetry and optical coherence tomography. Br J Ophthalmol, 95: 1437-41

Horn FK, Kaltwasser C, Jünemann AG, Kremers J, Tornow RP (2012) Objective perimetry using a four-channel multifocal VEP system: correlation with conventional perimetry and thickness of the retinal nerve fibre layer. Br J Ophthalmol, 96: 554-9

Tourtas T, Laaser K, Bachmann BO, Cursiefen C, Kruse FE (2012) Descemet membrane endothelial keratoplasty versus descemet stripping automated endothelial keratoplasty. Am J Ophthalmol, 153: 1082-90.e2

International Cooperations

Prof. D.S. Fix Ventura, University of Sao Paulo, Sao Paulo: Brazil

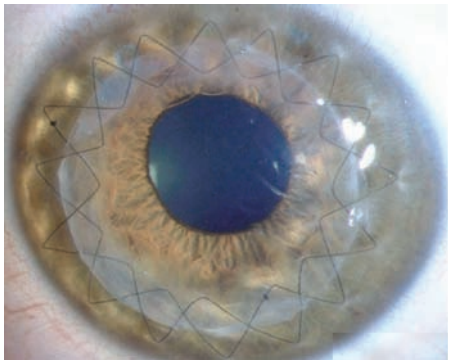
Dr. N. Parry, Royal Eye Hospital, University of Manchester, Manchester: UK

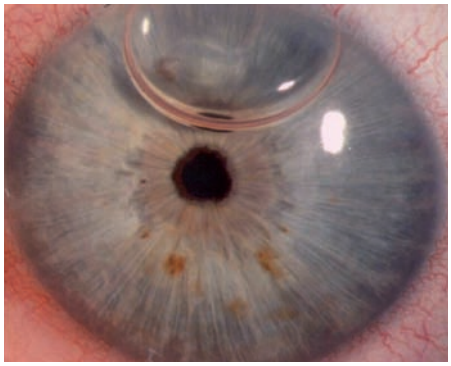
Department of Ophthalmology, Medical University, Lublin: Poland

Department of Ophthalmology, University of Cincinnati, Cincinnati: USA

Dr. S. Kinoshita, Kyoto Prefectural School of Medicine, Kyoto: Japan

Kunming University of Science and Technology, Kunming: China





Top: Old technique corneal transplantation where the graft becomes sutured into the recipients bed.
Bottom: New sutureless technique for corneal transplantation. The lamellar graft becomes attached to the backside of the recipient's corena by a temporary air fill of the anterior chamber.

Department of Oral and Cranio-Maxillofacial Surgery

Chair of Dental, Oral, and Maxillofacial Medicine - especially Oral and Maxillofacial Surgery

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Research Focus
- Infection and inflammation
- Tumor research
- Biomedical technics

Structure of the Department

The Department of Oral and Cranio-Maxillofacial Surgery is responsible for teaching oral and maxillofacial surgery, including dental surgery and dental radiology, research as well as patient care. The Department employs 15 medical doctors/dentists and two biologists. Research mainly focuses on biomedical technology, infection, and inflammation as well as tumors of the head and neck. Topics of particular interest are augmentation of osseous defects by transplantation of autogenous tissues or specific bone substitutes, the pathoetiology of osteonecrosis of the jaw as well as the evaluation of therapeutic options in sites displaying compromised healing, and the identification of indicators of prognosis in patients undergoing resection of oral squamous cell carcinoma. Innovative research focuses on the evaluation and development of laser-assisted surgery. The research laboratory (S1-facility) of the Department allows a wide range of immunohistochemical and molecular biological techniques. For experimental trials concerning bone histology and biomedical technology, a specialized facility is shared with the Department of Prosthodontics. The clinical focus is on the surgery of malformations of the head/neck and cleft lip palate in particular, oncologic and reconstructive surgery for tumors of the head and neck, orthognathic surgery, traumatology of the facial skeleton, esthetic surgery as well as dental implantology.

Research

Infection and inflammation

Research adresses etiology, pathogenesis, and therapeutic options in inflammatory reactions of the facial skeleton. Also the osseous regeneration of bone defects in sites displaying compromised wound healing is being investigated. A relevant focus is on the bisphosphonate-associated osteonecrosis of the jaw (BONJ).
As BONJ is restricted to craniofacial bone structures, research focuses on jaw bone specific signal transduction processes during development, bone remodeling, and disease. Cranial neural crest derived pluripotent progenitor cells are of scientific and clinical interest in experimental approaches to develop regeneration strategies in craniofacial bone structures. In addition, patient-related factors are being evaluated which may promote onset and course of bisphosphonate-associated osteonecrosis of the jaw. An animal model in pigs serves a study to answer the question whether there is an influence of bisphosphonate exposed bone in osseointegration of dental implants.
For functional and esthetic long-term success of dental implants, a sufficient amount of peri-implant hard and soft tissues is indispensible. The research especially focuses on modulation and optimization of peri-implant tissues in the context of rehabilitation of severe atrophic edentulous jaw and jaw segments with implant fixed dentures. This refers particularly to preclinical and clinical examination of new techniques and materials for the augmentation of non-space making vertical bony defects and the long-term stability of vertical bone grafts. Furthermore, research focuses on the regeneration of peri-implant soft tissues and their impact on peri-implant health.
For modeling compromised osseous healing, a diabetic pig model was established. This animal model is currently used for an assessment of regenerative options, using BMP-2 transfected bone substitute in critical size defects.

Tumor research

Research aims at improving function as well as facial esthetics following resection of tumors of the head and neck. In addition, the identification of clinical, immunohistochemical, and molecular indicators of prognosis in patients diagnosed with oral squamous cell carcinoma of the oral cavity is a prime focus.
Oral cancer and its therapy can heavily influence speech intelligibility. An interdisciplinary work group, headed by the Department of Oral and Cranio-Maxillofacial Surgery, FAU, explores the impact of oral cancers and different treatment modalities on speech quality using a special automatic speech analysis system. Technical enhancements of the automatic system, performed by the Division of Phoniatrics and Pediatric Audiology together with the Chair of Pattern Recognition, FAU, now allow for an objective measurement of the word recognition rate of each patient which is automatically analyzed by a computer system. A further development the researchers' group is heading for is the analysis of single distorted phonems. This innovative method will enable the surgeon to identify subtle operation techniques which will preserve function at its best, to support speech quality as elementary part of patients' social life even after the treatment of severe oral cancer.
There is increasing evidence that maintenance, growth, and spread of cancers is driven by a small subpopulation of cancer stem cells (CSC) which are the only cells that are capable of long-term self-renewal. Also current failure of cancer therapies may be due to postulated drug resistance and potential quiescence of these cells, because they will remain vital and may be able to repopulate the tumor. Therefore, new therapeutic strategies, like the immune therapies which are aimed at the destruction of the CSC, are urgently needed. Attractive targets for immunotherapy are Cancer/Testis antigens because of their restricted expression and their high immunogenetic features. Whether oral CSC express these antigens and whether CSC can be eliminated by such therapies in the long run is unknown.
Aim of another research project is to analyze the expression of known stem cell markers in oral tumor cell lines and tissues of OSCC using immunohistochemistry, RTPCR, and flow cytometry. Additionally cell populations with stem cell characteristic features will be enriched by using cell surface markers, e.g. CD133 and a magnetic activated cell sorting system, the efflux of Hoechst dye or the sphere culture system. Afterwards the populations will be characterized on the biomolecular level. Most notably the expression of stem cell markers and CT antigens is to be examined. In the future these studies could lead to more gene specific therapies aimed at the destruction of CSC.

The diagnosis of carcinoma of the oral cavity needs invasive surgery for histopathological examination. Hence, it is the goal of a interdisciplinary project to develop an optical, non-invasive biopsy for oral cancer detection. The research is based on three technical pillars: Diffuse Reflection Spectroscopy, Autofluorescence Spectroscopy, and Raman-Spectroscopy. First results demonstrate a high potency of differentiation between normal and malignant oral mucosa. Further research will focus on the optical identification of different grades of tissue dysplasia to further enhance early cancer detection by monitoring premalignant lesions using the optical biopsy.

Biomedical technics

The focus "biomedical technology" comprises research projects on regeneration of soft and hard tissues, intraoperative imaging, and laser applications.

Bone substitutes promote formation of new bone in pre-existing osseous defects by different biologic mechanisms, including inflammatory and proliferative cellular reactions. As opposed to autogenous bone, the application of anorganic bone substitutes results in a prolongation of the inflammatory phase.

The project aims at creation, application, and evaluation of biomimetic materials and biofunctional surfaces in implant dentistry. Modification of titanium surfaces for adsorption of several cell populations, poly-ether-ether-ketone (PEEK), as well as ceramic materials were applied in in vitro and in vivo experiments.

In cooperation with the Bavarian Laser Center, a sensor-assisted laser system for selective bone ablation was tested in cadaver bone as well as in an in vivo setting. By connecting the Er:YAG laser to a process control for material-specific ablation, the system is able to differentiate cortical and cancellous bone as well as soft tissues. In oral and maxillofacial surgery the selective bone ablation offers a new perspective to preserve nerval structures during surgery, such as the nervus mandibularis during osteotomy of the lower jaw. A second research approach is to transfer the system of optical tissue differentiation towards tumor tissue to allow high selectiv tumor resection in the future.

Teaching

Oral and maxillofacial surgery is a part of both, medical and dental curriculum. The Chair of Oral and Cranio-Maxillofacial Surgery provides compulsory and elective courses for medical and dental students during clinical education. In clinical dentistry, these involve oral and maxillofacial surgery, dental surgery, and dental radiology. Apart from traditional methods of teaching (lectures, lectures with case demonstrations, practical training for medical and dental students), problem based and interdisciplinary approaches are also used. Topics of interdisciplinary education include among others emergency medicine, electivum implantology for dental students (I-LECT), classes as part of the Graduate School in Advanced Optical Technologies (SAOT), and automated analysis of speech disorders in cooperation with the Chair of Pattern Recognition of the Technical Faculty.

Selected Publications

Wehrhan F, Hyckel P, Guentsch A, Nkenke E, Stockmann P, Schlegel KA, Neukam FW, Amann K (2011) Bisphosphonate-associated osteonecrosis of the jaw is linked to suppressed TGFβ1-signaling and increased Galectin-3 expression: a histological study on biopsies. J Transl Med, 9: 102

von Wilmowsky C, Stockmann P, Harsch I, Amann K, Metzler P, Lutz R, Moest T, Neukam FW, Schlegel KA (2011) Diabetes mellitus negatively affects peri-implant bone formation in the diabetic domestic pig. J Clin Periodontol, 38: 771-9

Nkenke E, Vairaktaris E, Bauersachs A, Eitner S, Budach A, Knipfer C, Stelzle F (2012) Acceptance of technology-enhanced learning for a theoretical radiological science course: a randomized controlled trial. BMC Med Educ, 12: 18

Ries J, Agaimy A, Vairaktaris E, Gorecki P, Neukam FW, Straßburg LH, Nkenke E (2012) Detection of MAGE-A expression predicts malignant transformation of oral leukoplakia. Cancer Invest, 30: 495-502

Stockmann P, Park J, von Wilmowsky C, Nkenke E, Felszeghy E, Dehner JF, Schmitt C, Tudor C, Schlegel KA (2012) Guided bone regeneration in pig calvarial bone defects using autologous mesenchymal stem/progenitor cells - A comparison of different tissue sources. J Craniomaxillofac Surg, 40: 310-20

Lutz R, Prechtl C, Nonhoff J, Weisel T, Damien CJ, Schlegel KA (2013) Biofunctionalization of the implant surface with different concentrations of a synthetic peptide (P-15). Clin Oral Implants Res, 24: 781-786

International Cooperations

Dr. E. Felzshegy, Gerichtsmedizinisches Institut, Semmelweiss-University, Budapest: Hungary

Prof. Dr. Dr. E. Vairaktaris, Department of Oral and Maxillofacial Surgery, University of Athens, Athens: Greece

Dr. J. Wolfaardt, PhD, Division of Otolaryngology Head and Neck Surgery, Faculty of Medicine and Dentistry, University of Alberta, Alberta: Canada

Meetings and International Training Courses

15.-18.06.2011: 61. Jahrestagung der Deutschen Gesellschaft für MKG-Chirurgie, Bamberg

Research Equipment

BrainLab, Heimstetten, Neuronavigations system Vector Vision II

Kavo, digital volume tomograph (DVT)

3DSYSTEMS, 3D-printer

KLS-Martin, CO2-Laser (MCO 50+)

Project manager PD Dr. Dr. F. Stelzle (left) and project team member Dr. C. Knipfer (right) during implementation of an optical non-invasive biopsy to identify oral cancer.

Department of Otorhinolaryngology – Head and Neck Surgery

Chair of Otorhinolaryngology

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Research Focus
- Ultrasound and endoscopy
- Computer aided surgery/robotics
- Individual speech processor programming in cochlear implant users
- Neurootology/vestibular laboratory
- Neurophysiology
- Allergology/clinical immunology and rhinology
- Experimental otorhinolaryngology
- Nanomedicine
- Laboratory for sleep disorders/somnology

Structure of the Department

In the Department, altogether 286 people are employed, out of these 86 are engaged in the clinical-scientific and medical-technical area, 13 exclusively within basic research, and 187 in nursing and administration.
Within different scientific groups, clinical-relevant research concerning neurootology, somnology, oncology, ultrasound and endoscopy, allergology, and neurophysiology is performed.

Research

Ultrasound and endoscopy

Studies in imaging of head and neck cancer with the help of high resolution ultrasound remain a key issue. Identification and classification of tissue by visualization techniques (Tissues Harmonic Imaging) were further investigated in their use in the head and neck area.
The Department was able to move into brand new ultrasound and endoscopy facilities. Minimally invasive interventions of the salivary glands and their adjacent duct systems are not only part of the daily routine, but were systematically analyzed regarding clinicial outcome of obstructive gland disease. An endoscopic grading sytem was established enabling disease classification and estimation of prognosis. Salivary duct and gland endoscopy therefore is now finding a growing positive resonance also in the Northern United States where a cooperation (Prof. M.B. Gillespie, MUSC, Charleston, USA) led to interesting aspects of different treatment regimes in salivary gland disease. The international academic workshops in ultrasound and salivary gland surgery again showed growing numbers of participants confirming us to endeavour education and academic projects.

Computer aided surgery/robotics

The group of computer aided surgery and robotics focused its research on the advancement of clinical navigation and robotic procedures. A new software for intraoperative image-update was evalutated and its applicability tested in a clinical setting. Possible errors, misleading procedures as well as advancements were documented. A so far underrepresented field of navigation was evalutated by applying navigation techniques to soft tissues areas of the head and neck. Foreign bodies were removed using navigation procedures. In collaboration with the Department of Neurosurgery, a modification of the Erlangen robot A73 was developed and tested in a preclinical setting.

Individual speech processor programming in cochlear implant users

Today cochlear implants (CI) provide an efficient treatment of profound hearing loss and inner ear deafness. However, individual results vary substantially. The aim of this project is to identify the individual differences by means of cortical auditory potentials and enhance speech and music perception by individual speech processor adjustments.

Neurootology/vestibular laboratory

The neurotology/vestibular laboratory with its up to date equipment inclusive computerized dynamic posturography (Smart Equi Test®, NeuroCom International), videooculography combined to computernystagmography, laser target projector, rotary-/pendularchair system, and static posturography was upgraded at the end of 2010 with a video head-impulse test. This newly developed system allows the physician to objectify a pathologic vestibulo-ocular reflex, even in well compensated patients with so called "covert saccades" which are normally not visible with the pure eye. This helps to differentiate between peripheral and central vestibular disorders.
The emphasis of the neurotology/vestibular laboratory was in particular on the pre- and postoperative diagnostics concerning cochlear implants and octavusneurinomas. Furthermore, the computerized dynamic posturography was used not only to improve the diagnostics of vestibular disturbances, but also very successful regarding the respective therapy of these diseases in cooperation with physiotherapists.

Neurophysiology

The neurophysiology and electromyography (EMG) laboratory focuses on diagnosis and therapy of cranial nerves involved in ENT-procedures.
In paresis or during accordant operations, the function of the facial nerve or the inferior laryngeal nerve is controlled.

Allergology/clinical immunology and rhinology

In patients with ASA intolerance, therapeutic options are the endoscopic sinus surgery and adaptive desensitization to ASA. The diagnostic value of a functional blood test (FET-AIT®) for measuring the eicosanoid dysbalance in patients with sensitivity to ASA is tested. A double-blind, randomized, placebo-controlled trial on clinical and biological effects of oral corticosteroids or doxycycline in patients with nasal polyps focuses on clinical and biological markers. The stimulation of functional intact nasal tissue under in-vitro conditions with the biopsy mucosa oxygenator is used for investigating relevant mediators of inflammation which are then modified pharmacologically. In a multi-centered, double-blind, placebo-controlled study, patients' oral corticosteroids post-operative are evaluated, looking at the rate of recurrences. Study centers: Departments of Otolaryngology, Head- and Neck-Surgery in Kiel, Regensburg, Berlin Charité, Marburg, and Stuttgart. In addition, a clinical study concerning subcutaneous immunotherapy is performed.

Experimental otorhinolaryngology

The research lab experimental otorhinolaryngology focused its research on projects on
1. Central tinnitus and
2. Neuronal plasticity after brain damage in animal models as well as
3. Ex vivo tissue cultures of human nasal mucosa.

Results yielded e.g.:
1. Demonstration of the existence of a central predisposition for the development of subjective tinnitus in an animal model.

2. The description of subcortical reorganization after unilateral lesion of the auditory cortex that enables subcortical regions to replace cortical functions.
3. Using oxygenation, we obtained cytokine expression data from ex vivo tissue cultures of human nasal mucosa stimulated with phyto-therapeutics, cortisone compounds, or conventional antihistamines.

Nanomedicine

Project manager: Prof. Dr. C. Alexiou

The Section for Experimental Oncology and Nanomedicine (SEON) focuses on the targeted local chemotherapy employing magnetic nanoparticles (Magnetic Drug Targeting). Magnetic nanoparticles bound to cytostatic drugs are injected intraarterially close to the tumor and enriched in the tumor region under the presence of an external magnetic field. The research project is supported by the Else Kröner-Fresenius-Foundation and by the BMBF Leading Edge Cluster initiative „Exzellenzzentrum für Medizintechnik". In 2012, two new research projects started: In the project "Nanotoxicology", supported by the Bayerisches Staatsministerium für Umwelt und Gesundheit, systematic toxicological analyses for medical nanoparticles will be performed and risk profiles will be generated. Furthermore, magnetic nanoparticles can be applied to magnetize living cells. Magnetic cells give promise for effective tissue engineering, since they can be grown into three-dimensional structures by application of an external magnetic field which will be done in the project "TOPbiomat" which is supported by the Emerging Fields Initiative (EFI) of the FAU. Such cellular structures are the basic components of multicellular organs and a prerequisite for the engineering of functional tissue.

Laboratory for sleep disorders/ somnology

The projects focus on a surgical treatment of primary snoring and obstructive sleep apnea. Besides the well known nCPAP therapy in obstructive sleep apnea, we try to find alternative treatment options. Therefore we have invented a special nasopharyngeal stent in order to prevent obstruction in patients suffering of obstructive sleep apnea. Results are to be compared to nCPAP therapy. Furthermore we develop a method for wireless sleep stage analysis based on unobtrusive motion sensors. Moreover we analyze pharyngeal tissue reactions and modification of saliva caused by obstructive sleep apnea.

Teaching

Traditional instruction forms (main lecture with case-demonstration and live transmission of operations, block practical courses) are supplemented by interdisciplinary meetings. Furthermore the possibility for hospitation in the outpatient clinic and the operating theater exists althrough the year.

Selected Publications

Gillespie MB, Koch M, Iro H, Zenk J (2011) Endoscopic-assisted gland-preserving therapy for chronic sialadenitis: a German and US comparison. Arch Otolaryngol Head Neck Surg, 137: 903-8

Hornung JA, Brase C, Zenk J, Iro H (2011) Results obtained with a new superelastic nitinol stapes prosthesis in stapes surgery. Otol Neurotol, 32: 1415-21

Tietze R, Rahn H, Lyer S, Schreiber E, Mann J, Odenbach S, Alexiou C (2011) Visualization of superparamagnetic nanoparticles in vascular tissue using XμCT and histology. Histochem Cell Biol, 135: 153-8

Ahlf S, Tziridis K, Korn S, Strohmeyer I, Schulze H (2012) Predisposition for and prevention of subjective tinnitus development. PLoS ONE, 7: e44519

Koch M, Künzel J, Mantsopoulos K, Zenk J, Iro H (2012) Defect closure after oral and pharyngeal tumor resection with the superiorly pedicled myocutaneous platysma flap: indications, technique, and complications. Eur Arch Otorhinolaryngol, 269: 2111-9

Tietze R, Lyer S, Durr S, Alexiou C (2012) Nanoparticles for cancer therapy using magnetic forces Nanomedicine, 7: 447-457

International Cooperations

Prof. C. Bachert, Department of Otorhinolaryngology - Head & Neck Surgery, Ghent University, Ghent: Belgium

Prof. M. Mc Gurk, Salivary Research Unit, Maxillofacial Surgery, Guy's, King's and St. Thomas' Dental Institute, King's College, London: UK

Prof. D.A. Sherris, Department of Otolaryngology, University of Buffalo, Buffalo: USA

Prof. E.J. Moore, Department of Otorhinolaryngology - Head & Neck Surgery, Mayo Clinic, Rochester: USA

Meetings and International Training Courses

13.-14.01.2011: Erlanger Ohroperationskurs, Erlangen

05.02.2011: Jährliche HNO-Fortbildung, Erlangen

17.-20.05.2011: International Course on Aestetic and Reconstructive Rhinoplasty and Otoplasty, Blepharoplasty and Face Lift, Erlangen

01.-02.07.2011: Allergologie Grund- und Aufbaukurse, Erlangen

22.-23.10.2011: Sonographie der Kopf-Hals-Region, Erlangen

12.-13.01.2012: Erlanger Ohroperationskurs, Erlangen

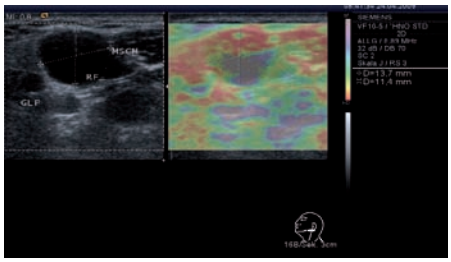
11.02.2012: Jährliche HNO-Fortbildung, Erlangen

13.-16.03.2012: International Course on Aesthetic and Reconstructive Rhinoplasty and Otoplasty, Blepharoplasty and Face Lift, Erlangen

13.-15.06.2012: Internationaler Kurs für Ultraschall und Speicheldrüsenchirurgie, Erlangen

29.-30.06.2012: Allergologie Grund- und Aufbaukurse, Erlangen

13.-14.10.2012: Sonographie der Kopf-Hals-Region, Erlangen



Ultrasound image using ultrasound elastography for measurement of tissue stiffness in different tumor entities.

SEON research laboratory (Angiography system Artis zee, Siemens and electromagnet)

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Division of Phoniatrics and Pediatric Audiology

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Research Focus

- Kinesthetic and auditory feedback during phonation and articulation
- Biomechanical parameterization of vocal fold vibrations
- Modeling of tracheoesophageal voice
- Phonovibrography - objective analysis of vocal fold vibrations
- Differentiated objective analysis of the speech quality of chronically hoarse patients to enhance evidence-based diagnostics
- Fluid Mechanical Basis of the Human Voice

Structure of the Department

Phoniatrics and Pediatric Audiology is a medical field which addresses diseases and disorders of voice, speech, language, hearing, and swallowing. Research deals basically with communication disorders on the perception side (hearing research) and the production side (speech and voice research). The principle contents of the research projects connect the medical field with applied natural sciences and technology. The head of the Division is also member of the Technical Faculty of the FAU and is supervising scientific works in all of these fields. Totally, 21 employees work at the Division, five of them are financed via third-party funds.

Research

Kinesthetic and auditory feedback during phonation and articulation

The precision of the human speech signal is controlled by parallel working feedback processes while speaking. The feedback mechanisms are developed during language acquisition and can be divided into kinesthetic and auditory control. The feedback mechanisms can be affected by voice and speech disorders in different ways.
This project investigates the feedback mechanisms of phonation and articulation of healthy test persons and compares their performance with patients suffering from voice disorders (hyper-, hypotension dysphonia (MTD)) and speech disorder (Apraxia of Speech (AOS)). The synchronous data acquisition (visual and EEG) enables for the first time the analysis of the connection between kinesthetic and auditory feedback processes. Current methods of electrophysiology and quantitative endoscopy are used simultaneously.
The goal of the study is a first understanding of the cooperating auditory and kinesthetic feedback control.

Biomechanical parameterization of vocal fold vibrations

Vocal fold vibrations are captured by applying high speed recordings. Including a laser projection system, the three dimensional displacements can be extracted. By segmentation algorithms, the three dimensional vocal fold trajectories can be determined. The segmented vocal fold oscillations can be analyzed with means of non-linear dynamics by simulating vocal fold motion curves with a biomechanical multi-mass model of the vocal folds. The model simulates the principle properties of vocal fold vibrations with a system of differential equations which establish the temporal process of the vocal fold oscillations. By adapting the model oscillations to the extracted vocal fold vibrations, the asymmetry of vibration patterns as well as tissue properties can be quantified within a 3D parameter domain. In future, different kinds of dysphonia can be quantified within the parameter domain of the biomechanical model. So far, experiments are performed only in vitro models.

Modeling of tracheoesophageal voice

After laryngectomy, the loss of natural voice is the most prominent functional defect. It can be rehabilitated best by means of shunt valves. So far, there is no consensus on how to evaluate tracheoesophageal voice.
In a study funded by the German Cancer Aid Foundation, we objectively analyze the dynamics and the resulting acoustical signal of the remaining pharyngoesophageal segment after total laryngectomy. The goal is to find correlations between dynamics as well as tissue structures and the quality of the resulting acoustic signal. High-speed recordings in combination with a newly developed laser grid projection system are applied. This combination allows a quantitative registration of occurring dynamics. The dynamics are adopted by numerical biomechanical models. The resulting parameters, like damping and swinging masses, are further analyzed and interpreted.

Phonovibrography - objective analysis of vocal fold vibrations

The causes of hoarseness are not yet completely understood. The presumed irregularities of vocal fold oscillation cannot be proven with the conventional investigation instrument (stroboscopy), because this is only designed for periodic events. Owing to funding of the DFG, the novel approach of phonovibrography was developed which enables a visualization and analysis of vocal fold dynamics. In this approach, digital high-speed recordings of vocal fold vibrations, captured at a frame rate of 4000 Hz, are analyzed. For an objective analysis, a specialized image segmentation algorithm was developed which extracts the vibrating vocal fold edges from the high-speed recordings. The results of the procedure were extensively evaluated in a clinical trial. To visualize the relevant vibration information within a single image, the so-called phonovibrogram (PVG) was developed. A PVG image contains the entire vocal fold oscillation pattern and enables a novel classification of vocal fold vibrations. First studies show the robustness as well as the reliability of the new suggested approach. For further quantification, a laser-line projection device was developed which enables a two-dimensional quantification of the image data. Thus, absolute measures of vocal fold elongation and velocities can be performed. In this research area, we closely collaborate with colleagues from the USA.

Differentiated objective analysis of the speech quality of chronically hoarse patients to enhance evidence-based diagnostics

For differentiated diagnostics of functioning and evaluation of distorted voice and speech production, there are currently no validated objective approaches. Voice and speech disorders are usually assessed by perceptive evaluations with only restricted reliability for clinical or scientific use.

Perceptual evaluations are very time consuming and are of limited suitability in clinical routine.
For a differentiated, objective analysis, automatic methods are developed which take this into account. Subjective clinical evaluation criteria are described by objectively computed parameters. The involved patient groups include patients with voice disorders, e.g. chronic hoarseness, partial and total laryngectomy, and patients with articulation disorders, e.g. children with cleft lip and palate and patients with oral squamous cell carcinoma.
The automatic methods analyzed voice parameters as well as speech aspects with a strong focus on a detailed (phoneme) analysis. In this way, the communication problem is not described as one single unit, but phone classes have been identified which are specifically affected by the distortion.
Systems for a detailed phoneme analysis in children with cleft lip and palate and patients with oral squamous cell carcinoma were also established. These systems are based on automatic speech processing techniques, prosodic analysis, phonemic and phonological features.
Additionally, the current topic is the quantification of hoarseness which will also include speech-related parameters for the first time. The objective measurement of nasality without complex and expensive equipment is also part of the research project. In this way, an objective clinical evaluation is created.
The automatic analysis is the basis for future telemedical applications for the control of the progress of voice and speech therapy. Furthermore, this analysis will serve as objective addition to the established subjective voice and speech evaluation in clinical practice. The approach is another important step towards evidence-based diagnostics in phoniatrics.
This project is a cooperation with the Pattern Recognition Lab (Head: Prof. Dr.-Ing. J. Hornegger) of the FAU as well as with the Department of Oral and Cranio-Maxillofacial Surgery (Head: Prof. Dr. Dr. F.W. Neukam).

Fluid Mechanical Basis of the Human Voice

More detailed information is given in the separate report of FOR 894, supported by DFG.

Teaching

Our Division is dedicated to a first-class academic teaching which is of the same value as patient care and scientific research. The offer of lectures follows the clinical focus of the area. Phoniatrics and pediatric audiology is teached during both, the pre-clinical and clinical phase. Complementarily, practical trainings on voice, swallowing, speech, and hearing impairments are given. Additionally, lectures and trainings are given in physiology: "auditory system", "voice, speech, and language" and medical psychology and sociology: "language development in children" and "rehabilitation".
The training of speech therapists takes place at the full-time vocational school speech therapy.

Selected Publications

Dollinger M, Berry DA, Huttner B, Bohr C (2011) Assessment of local vocal fold deformation characteristics in an in vitro static tensile test. J Acoust Soc Am, 130: 977-85

Huttner B, Sutor A, Luegmair G, Rupitsch SJ, Lerch R, Döllinger M (2011) Optical 3-D metric measurements of local vocal fold deformation characteristics in an in vitro setup. IEEE Trans Biomed Eng, 58: 2758-66

Schmidt B, Stingl M, Leugering G, Berry DA, Döllinger M (2011) Material parameter computation for multi-layered vocal fold models. J Acoust Soc Am, 129: 2168-80

Yang A, Stingl M, Berry DA, Lohscheller J, Voigt D, Eysholdt U, Dollinger M (2011) Computation of physiological human vocal fold parameters by mathematical optimization of a biomechanical model. J Acoust Soc Am, 130: 948-64

Döllinger M, Berry DA, Luegmair G, Hüttner B, Bohr C (2012) Effects of the epilarynx area on vocal fold dynamics and the primary voice signal. J Voice, 26: 285-92

Döllinger M, Dubrovskiy D, Patel R (2012) Spatiotemporal analysis of vocal fold vibrations between children and adults. Laryngoscope, 122: 2511-8

International Cooperations

Prof. J.G. Švec, PhD, Department of Experimental Physics, Palacký University, Olomouc: Czech Republic

Y.J. Moon, PhD, School of Mechanical Engineering, Korea University, Seoul: South Korea

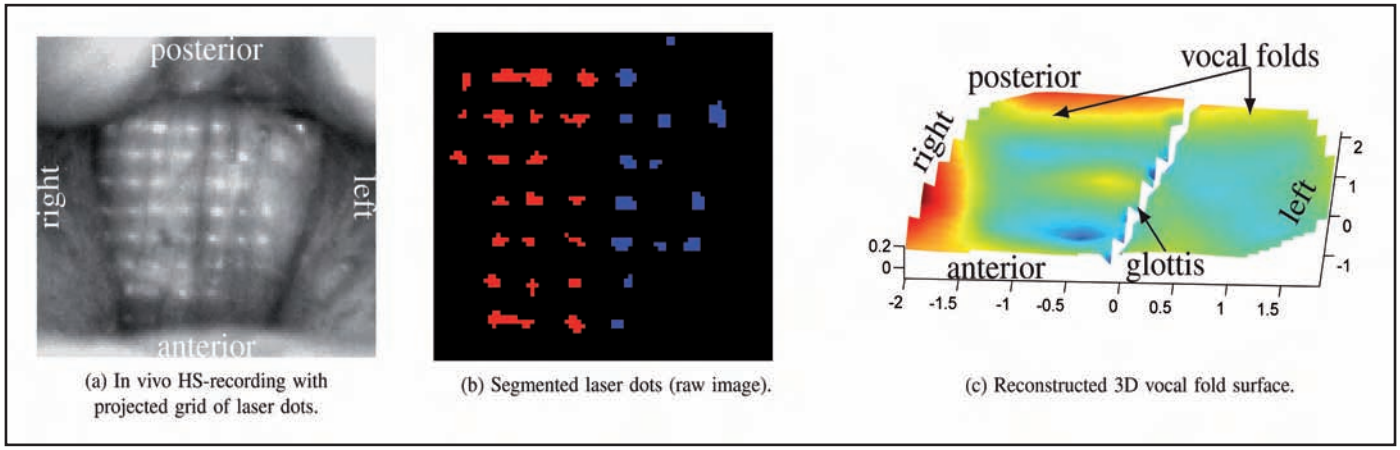
Prof. Dr. R.E. Hillman, Voice Center Research Laboratories, Massachusetts General Hospital, Boston: USA

Prof. D.A. Berry, PhD, Laryngeal Dynamics Laboratory, Division of Head and Neck Surgery, University of California Los Angeles: USA

Prof. T.T. Truscott, PhD, Prof. S.L. Thomson, PhD, Department of Mechanical Engineering, Brigham Young University, Provo: USA

Prof. M. Kunduk, PhD, Department of Communication Science & Disorders, Louisiana State University, Baton Rouge: USA

Prof. R. Patel, PhD, Department of Otolaryngology Vocal Physiology and Imaging Laboratory, Indiana University, Bloomington: USA



(a) Single frame of an in vivo high-speed recording of human vocal folds with projected laser dot grid. (b) Segmented laser dots of the left (blue) and right (red) vocal fold. (c) Reconstructed vocal fold surface basing on the 3D coordinates of the segmented laser dots.

Department of Pediatrics and Adolescent Medicine

Chair of Pediatrics

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Research Focus
- Medication safety
- Determinants of kidney disorders
- Genetic diseases of the neonate
- Genomic aberrations in childhood malignancies
- Pediatric cell therapy
- Perinatal hypoxic brain injury and neuroprotection

Structure of the Department

The Department of Pediatrics and Adolescent Medicine comprises five specialized divisions (Neonatology, Neuropediatrics and Social Pediatrics, Pediatric Oncology/Cell Therapy, Nephrology, and Molecular Pediatrics), an endowed professorship for Pediatric Endocrinology and Diabetology, and a number of specialized outpatient clinics. Academic staff of the Department includes 98 physicians and scientists. Of these, 13 positions are financed by external funds.
Research is focused on the field of perinatal medicine with particular emphasis on molecular and developmental biology. Project coordination and scientific guidance are provided by a professorship for experimental perinatal medicine. Other main research activities are related to pediatric oncology, neuropediatrics, and nephrology. In addition, clinical trials are conducted by all five divisions of the Department and by the section of endocrinology/diabetology (e.g. interventional trials, studies on genetic conditions, infection epidemiology or medication safety, studies investigating long-term effects of surgical interventions, anti-cancer therapy or growth hormone application during childhood). The clinical studies are supported by the hospital's site management organization. Many medical experts work together to bring novel research to the bedsite. Patient care is based on close collaboration with the Divisions of Pediatric Cardiology, Pediatric Surgery, and Cardiac Surgery as well as with various subspecialities, often planned and carried out by interdisciplinary teams (Center for Perinatal Medicine, Center for Epilepsy, Heart Center, Cleft Lip and Palate Center, Transplantation Center).

Research

Medication safety

Project managers: PD Dr. A. Neubert, Prof. Dr. W. Rascher
Newborns and infants are particularly at risk for adverse drug reactions and medication errors due to common off-label use and lack of age-appropriate formulations. We have been working for many years on methods to improve medication safety. To this purpose, data on adverse drug reactions (ADR) have been collected systematically in various mono- and multicenter prospective studies. High-risk medications were detected and particularly vulnerable groups of patients were identified. Furthermore, we evaluated computerized ADR detection and tested methods to improve the specificity of this system. We are currently investigating the impact of electronic prescription on medication safety, aiming at developing evidence-based, structured dosing-information to be integrated into the system. In addition, we actively participate in two EU-funded multicenter pharmacovigilance studies (long-term safety of the iron-chelating agent deferiprone and long-term safety of methylphenidate in children with ADHD).

Determinants of kidney disorders

Project managers: Prof. Dr. A. Hartner, PD Dr. K. Benz
Typical features of progressive kidney diseases are fibrotic changes due to extracellular matrix accumulation and hyperplasia. In this connection, integrins as matrix receptors are known to play a pivotal pathogenetic role. Therefore, we investigate the function of integrins and their ligands which are relevant to the kidney. We were able to show that α8-integrin can regulate cell adhesion, migration, differentiation and proliferation, thereby contributing significantly to the maintenance of renal tissue homeostasis. Further studies aim at clarifying whether these results may provide a basis for the development of new strategies for diagnosis and therapy of renal diseases.
As progression of kidney disorders also depends on the congenital endowment with functional renal tissue that is capable of self-regeneration, we attempt to characterize the impact of prenatal conditions on kidney function and disease progression (fetal programming).

Genetic diseases of the neonate

Project manager: Prof. Dr. H. Schneider
Our primary research goal is to identify pathogenetic mechanisms underlying genodermatoses (hereditary disorders of the skin and its appendages) at a molecular level and to develop appropriate therapeutic approaches. These diseases are rare, but may be associated with life-threatening complications already in the first weeks after birth. In addition to the skin, other organs, such as eye, ear, and lung, are frequently affected by the pathogenetic processes. First systematic studies of patients of different age groups allowed the characterization of genotype-phenotype relationships as a prerequisite for specific therapeutic attempts. In mouse models of epidermolysis bullosa, lamellar ichthyosis, and hypohidrotic ectodermal dysplasia, we have been investigating the feasibility of gene therapy in utero or perinatal protein replacement therapy.
Currently, the first clinical trial in neonates with hypohidrotic ectodermal dysplasia is being prepared, a multicenter interventional study based on the promising preclinical data collected over the last years.

Genomic aberrations in childhood malignancies

Project managers: PD Dr. M. Metzler, Prof. Dr. T. Langer
Modern molecular biology has advanced understanding of the impact of both, heritable and acquired genetic alterations on the development and progression of pediatric tumors. We have been trying to exploit such new information for diagnostic purposes and novel therapeutic approaches, placing emphasis on acute and chronic childhood leukemia, non-Hodgkin lymphoma, Ewing's sarcoma, and other frequent pediatric malignancies. Methods to detect patient-specific aberrations of the tumor genome have been established and employed for quantifying the minimal residual disease, a significant prognostic factor indicating the response to therapy.
In addition to acquired mutations in the tumor genome, the impact of hereditary single nucleotide polymorphisms on the development of late adverse effects of current cancer therapy,

such as hearing loss or cardiomyopathy, is being investigated (LESS study).

Pediatric cell therapy

Project managers: Prof. Dr. W. Holter, Prof. Dr. H. Schneider

Our main goal is to develop immunotherapies directed towards viral infections and malignant disease. Experimental approaches are based on antigen presentation by TLR-matured dendritic cells, the expansion of peptide-specific T cells, and the transfer of chimeric receptors (derived from monoclonal antibodies and NKG2D) into effector cells by RNA-based and lentiviral gene transfer. Furthermore, we study the regulation of apoptosis in dendritic cells and differentiated T cells under the influence of cytokines.

Another research project is focused on the controlled differentiation of cord blood-derived mesenchymal stem cells into osteoblasts, chondrocytes, and myocytes. These cells could be used for autografts, e.g. in the treatment of cleft lip and palate (the most common congenital malformation) to reduce the number of surgical interventions required.

Perinatal hypoxic brain injury and neuroprotection

Project manager: Prof. Dr. R. Trollmann

Aiming at an early detection and prevention of perinatal brain injury caused by acute or chronic hypoxia, we have been analyzing the regulation and function of hypoxia-inducible transcription factors (HIF) in the immature brain. HIF-regulated factors with strong impact on the adaptation to hypoxic conditions have been characterized as placental indicators of severe hypoxic-ischemic CNS injury in term neonates. In a mouse model of perinatal brain hypoxia, gestational age-dependent and cell-specific molecular effects of hypoxia on endogenous neuroprotective mechanisms have been demonstrated. Furthermore, the impact of perinatal hypoxia on early neuronal migration, astrocytic, and blood-brain barrier function has been investigated - as well as experimental approaches to stabilize HIF by pharmacological means.

Teaching

Besides traditional forms of teaching (compulsory lecture series with case presentations, revision course, and hands-on training in pediatrics), special lectures, research seminars, and interdisciplinary courses are offered to medical students. Individual members of the research staff give lectures and practical courses for students enrolled in the Graduate Programs in Molecular Medicine and Medical Process Management. An "emergency care simulator" adapted to the needs of neonatology and pediatric intensive care enables the training of emergency medical procedures and team-work analysis of the management strategies applied. This includes regular reviews of real emergency situations experienced in our clinic.

Selected Publications

Fujiwara H, Ferreira M, Donati G, Marciano DK, Linton JM, Sato Y, Hartner A, Sekiguchi K, Reichardt LF, Watt FM (2011) The basement membrane of hair follicle stem cells is a muscle cell niche. Cell, 144: 577-89

Kuster L, Grausenburger R, Fuka G, Kaindl U, Krapf G, Inthal A, Mann G, Kauer M, Rainer J, Kofler R, Hall A, Metzler M, Meyer LH, Meyer C, Harbott J, Marschalek R, Strehl S, Haas OA, Panzer-Grümayer R (2011) ETV6/RUNX1-positive relapses evolve from an ancestral clone and frequently acquire deletions of genes implicated in glucocorticoid signaling. Blood, 117: 2658-67

Nüsken KD, Schneider H, Plank C, Trollmann R, Nüsken E, Rascher W, Dötsch J (2011) Fetal programming of gene expression in growth-restricted rats depends on the cause of low birth weight. Endocrinology, 152: 1327-35

Pacho F, Zambruno G, Calabresi V, Kiritsi D, Schneider H (2011) Efficiency of translation termination in humans is highly dependent upon nucleotides in the neighbourhood of a (premature) termination codon. J Med Genet, 48: 640-4

Akhmetshina A, Palumbo K, Dees C, Bergmann C, Venalis P, Zerr P, Horn A, Kireva T, Beyer C, Zwerina J, Schneider H, Sadowski A, Riener MO, MacDougald OA, Distler O, Schett G, Distler JH (2012) Activation of canonical Wnt signalling is required for TGF-β-mediated fibrosis. Nat Commun, 3: 735

Oehme AK, Rashed AN, Hefele B, Wong IC, Rascher W, Neubert A (2012) Adverse drug reactions in hospitalised children in Germany are decreasing: results of a nine year cohort-based comparison. PLoS ONE, 7: e44349

International Cooperations

Dr. E. Griesmeier, Department of Pediatrics, Innsbruck Medical University, Innsbruck: Austria

Prof. Dr. I. Wong, Department of Pharmacology & Pharmacy, University of Hongkong, Hongkong: China

Prof. Dr. M. Ohlin, Department of Immunotechnology, Lund University, Lund: Sweden

Prof. Dr. M. Gassmann, Center for Integrative Human Physiology, University of Zurich, Zurich: Switzerland

Dr. C. Tuleu, Centre for Paediatric Pharmacy Research, University College London School of Pharmacy, London: UK

Prof. Dr. T.H. Rabbitts, Institute of Molecular Medicine, University of Leeds, Leeds: UK

Prof. Dr. A. Clarke, Institute of Cancer & Genetics, Cardiff University School of Medicine, Cardiff: UK

Prof. Dr. M. Gibson, Biochemical Genetics Laboratory, University of Pittsburgh, Pittsburgh: USA

Dr. K. Huttner, Edimer Pharmaceuticals Inc., Cambridge: USA

Meetings and International Training Courses

23.01.2012: Spätfolgen und Nachsorge, Erlangen

17.-18.02.2012: Jahrestagung der DEGUM-Sektion Pädiatrie, Erlangen

01.-03.06.2012: 5th International Conference on Ectodermal Dysplasia, Erlangen

23.-25.11.2012: JA-PED-Tagung, Erlangen

Research Equipment

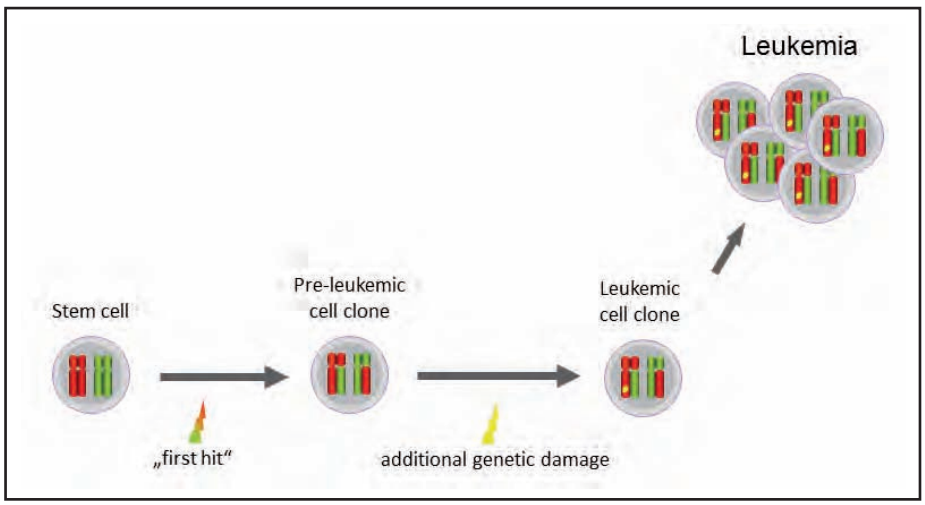
Beckman Coulter, DNA-Sequenzer

Becton Dickinson, FACS Calibur

Applied Biosystems, 2 Tandem-mass spectrometer

Tecan, analyze platform EVO 150

Carl Zeiss, Inverse microscope Axio Observer (Live cell imaging)



Childhood leukemia typically arises from a prenatally established pre-leukemic cell clone. The initial prenatal lesion represents a first, albeit insufficient hit which is followed by additional genetic damage that ultimately leads to leukemia.

Department of Pediatrics

Division of Pediatric Cardiology

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Research Focus

- B-type natriuretic peptide (BNP) in congenital heart disease and acquired heart disease
- 3D-Imaging
- New imaging possibilities in the catheterization laboratory
- Molecular cardiology
- Duchenne muscular dystrophy
- Neutrophil gelatinase-associated lipocalin (NGAL) as a new biomarker for diagnosis of acute kidney damage

Structure of the Department

The independent Division of Pediatric Cardiology was established in July 2007. Clinical work and research activities are performed in close cooperation with the Department of Pediatrics and the Division of Pediatric Cardiac Surgery, founded in September 2008. A total of 19 employed medical doctors are splitting clinical work, teaching, and research. At the moment, there are eleven graduate students studying for a doctorate. Several projects were established to study the genetic mechanisms responsible for congenital heart disease. There is a collaboration with the Competence Network for Congenital Heart Defects in multicenter clinical trials, additionally, we prepare an own multicenter study to evaluate the efficiency of drug treatment for cardiac failure in patients with Duchenne muscular dystrophy.
The clinical focus is on interventional therapy of congenital heart defects in the catheter laboratory, on surgical therapy of congenital heart defects in close cooperation with the Division of Pediatric Cardiac Surgery, and on intensive care after cardiac surgery.

Research

B-type natriuretic peptide (BNP) in congenital heart disease and acquired heart disease

After our own assessment of normal age- and gender-related values for BNP and the N-terminal fragment of its prohormone (NT-proBNP) in healthy children, we now evaluate the diagnostic value of this biomarker in children with congenital heart disease and acquired heart disease. There is a special focus on the diagnostic value in the longterm outcome of patients after corrective and palliative heart surgery and children suffering from cardiomyopathies.

3D-Imaging

Our objective is the processing of pre-procedural data of magnetic resonance imaging (MRI) or computed tomography (CT) for interventions, especially for cardiac interventional procedures. For an optimal planning of safe and effective procedures, the pediatric cardiac surgeon as well as the pediatric cardiologist are provided with three-dimensional volume-rendered images from the cardiac catheterization laboratory. Thus, individually different possibilities to imagine a three-dimensional situs with the help of two-dimensional sectional images can be avoided.
3D-models are generated by different 3D-reconstruction programs in addition to conventional 2D-sectional images to provide the surgeons with information for surgical planning. Furthermore, these models can be used for 3D-navigation in catheter-based interventions by a registered fluoroscopic overlay on a monitor. We evaluate the benefit over conventional imaging techniques. The ideal acquisition techniques for subsequent 3D-reconstructions of the different sectional imaging methods are developed in collaboration with the Institute of Radiology.

New imaging possibilities in the catheterization laboratory

Flat detector computed tomography is an innovative three-dimensional imaging technique generating CT-like images by an interventional angiography system. 3D-data are generated from a rotational angiography with contrast injection during imaging acquisition over five seconds. This data can now be used for reconstruction of a cardiovascular model allowing for diagnostic purposes and planning of catheter interventions or operations. In addition, this three-dimensional model can be used as a three-dimensional map for navigation during interventional procedures. By a 3D-3D-fusion, the data from pre-procedural MRI- or CT-scans can be implemented in the current angiographic examination.
We evaluate the application of this technique mainly in complex anatomy and complicated interventions for the optimal use of the potential of this imaging modality of reduction of radiation exposure, use of contrast dye, and fluoroscopy time.

Molecular cardiology

Project manager: Dr. O. Toka
The investigations of the Molecular Cardiology team focuses on the evaluation of genetic factors and subcellular mechanisms responsible for congenital heart malformation. With good clinical practice, we could establish a comprehensive biomaterial bank for individuals with congenital heart defects which currently counts about 1,500 DNA samples and about 1,500 cardiac tissue samples of all four chambers of the heart. Thus, the biomaterial bank in Erlangen represents one of the largest biobanks for patients with congenital heart defects in the country. Since 2009, a close cooperation and funding through the National Competence-Network has been existing for congenital heart disease. The research projects include mutation detection and expression analysis in familial and sporadic cases of congenital heart disease which are realized by the local research team or national and international cooperation. Another research focus involves comprehensive clinical and molecular-biological investigations on the pathogenesis of the Failing-Fontan physiology. Our collaborators are the Institute for Human Genetics (FAU), the Department of Cardiovascular Genetics (Harvard University, Boston, USA), the Experimental and Clinical Research Center (Charité and MDC Berlin), and the Department for Medical Genetic and Human Genetic (Charité Berlin).
Current projects are:
1. Expression analyses of vasocactive signaling cascades in human aortic tissue of patients with congenital coarctation of the aorta;
2. Exomsequencing in mendalian traits of complex cardiac malformations;
2.1 Exomesequencing and pathway mapping in a cohort of sporadic cases of complex cardiac malformations;

3. CNV-Analyses in patients with coarctation of the aorta. Do chromosomal rearrangements matter?
4. Systemic inflammation as a relevant pathomechanism of the Failing-Fontan physiology.

Duchenne muscular dystrophy

In our study „Effect and safety of preventive treatment with ACE inhibitors and β blockers on the onset of left ventricular dysfunction in Duchenne muscular dystrophy", we are investigating the start of cardiomyopathy and the changes in quality of life in patients with confirmed diagnosis of Duchenne muscular dystrophy. These patients, aged 10 to 14, are so far without any signs of impaired left ventricular function. The study is sponsored by the BMBF and has been initiated in march 2010. The drugs Enalapril and Metoprolol are used in a randomized double-blinded study design and tested against placebo. In current clinical practice, only patients with already impaired ventricular function are treated with anticongestive therapy. The objective of the study is to examine if the time of onset of cardiomyopathy can be postponed by a preventive treatment with ACE inhibitors and beta blockers. Possibly, quality of life for these patients would improve, and perhaps even a prolonged life expectancy may result. This is a nationwide multi-center study with the involvement of eleven centers within the German network of congenital heart disease (Kompetenznetz AHF). Until December 2013, more patients will be included. Methodically, we are using the standard measurements in echocardiography, tissue Doppler, ECG, and Holter ECG and standardized questionnaires for the assessment of quality of life.

Neutrophil gelatinase-associated lipocalin (NGAL) as a new biomarker for diagnosis of acute kidney damage

NGAL has emerged as a new biomarker for early diagnosis of acute renal injury. Impairment of the renal function due to ischemia is a common risk after cardiopulmonary bypass. In a prospective study, we evaluate the significance of this new biomarker in addition to Cystatin C in children with congenital heart disease. Furthermore, we compare the diagnostic impact of these parameters early postoperatively in pediatric patients after cardiac surgery. In the future, primarily the evaluation of Cystatin C and NGAL in the urine might be a helpful diagnostic tool to improve the assessment of acute renal injury in infants and children early after cardiopulmonary bypass.

Teaching

The Division of Pediatric Cardiology takes part in the general teaching program of the Department of Pediatrics (traditional main lecture, compulsory lecture series with case presentations, seminars, hands-on training in pediatrics, practical training courses). Additionally, medical students are taught pediatric cardiology within a specialized training course "optional subject pediatrics". Furthermore, we offer the possibility to perform clinical electives or internships in our Division.

Selected Publications

Koch AM, Dittrich S, Cesnjevar R, Rüffer A, Breuer C, Glöckler M (2011) Plasma neutrophil gelatinase-associated lipocalin measured in consecutive patients after congenital heart surgery using point-of-care technology. Interact Cardiovasc Thorac Surg, 13: 133-6

Glöckler M, Koch A, Halbfaß J, Greim V, Rüffer A, Cesnjevar R, Achenbach S, Dittrich S (2012) Assessment of cavopulmonary connections by advanced imaging: value of flat-detector computed tomography. Cardiol Young, 1-9

Glöckler M, Halbfaß J, Koch A, Achenbach S, Dittrich S (2013) Multimodality 3D-roadmap for cardiovascular interventions in congenital heart disease-A single-center, retrospective analysis of 78 cases. Catheter Cardiovasc Interv: DOI 10.1002/ccd.24646

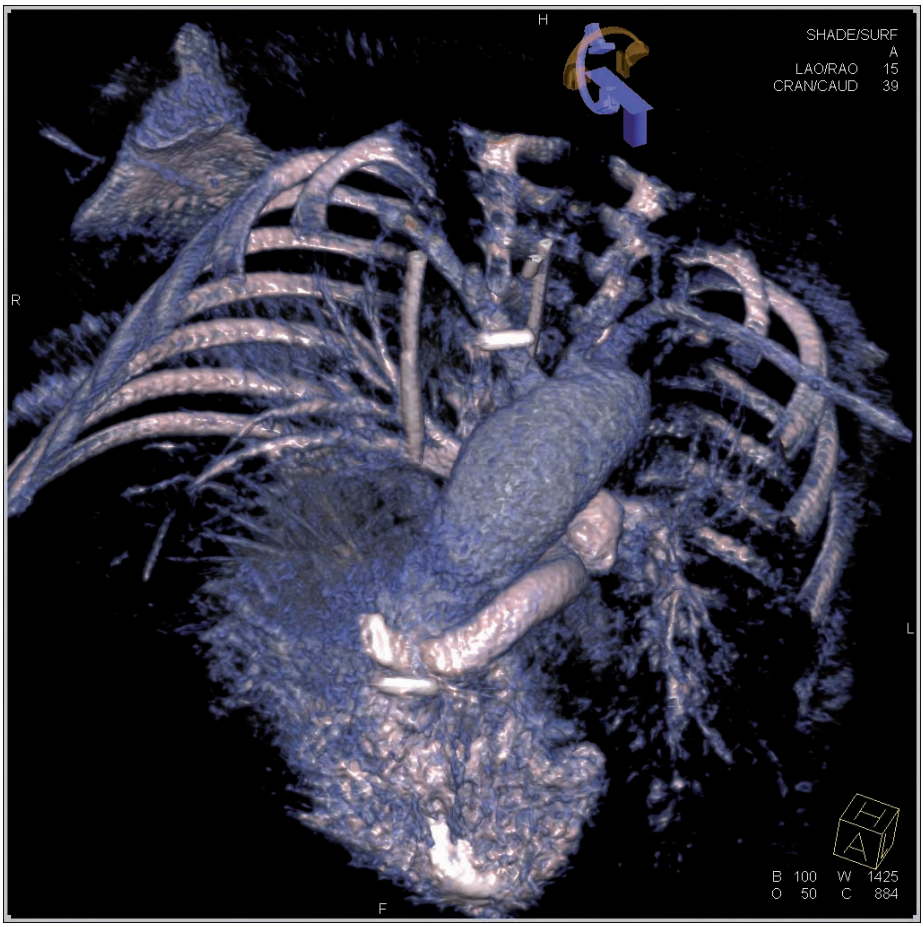
Koch AM, Hammersen G, Rüffer A (2012) Aortopulmonary window. Eur Heart J, 33: 1200

Tagariello A, Breuer C, Birkner Y, Schmidt S, Koch AM, Cesnjevar R, Ruffer A, Dittrich S, Schneider H, Winterpacht A, Sticht H, Dotsch J, Toka O (2012) Functional null mutations in the gonosomal homologue gene TBL1Y are associated with non-syndromic coarctation of the aorta. Curr Mol Med, 12: 199-205

Seitz S, Rauh M, Gloeckler M, Cesnjevar R, Dittrich S, Koch AM (2013) Cystatin C and neutrophil gelatinase-associated lipocalin: biomarkers for acute kidney injury after congenital heart surgery. Swiss Med Wkly, 143: w13744

Meetings and International Training Courses

16.11.2012: 3D-Bildgebung in der Kinderkardiologie, Erlangen



Hypoplastic left heart syndrome after Norwood I-Procedure. Examination with spontaneous breathing, contrast medium administration of 2 ml/kg. Demonstration of the right ventricle, the Sano-Shunt connecting the right ventricle to the pulmonary artery, and the reconstructed aorta.

Department of Plastic and Hand Surgery

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Research Focus

- Artificial dermis for coverage of silicon implants to prevent capsular fibrosis
- The impact of syngenic endothelial progenitor cells on de novo vascular network formation
- Establishment and modulation of a lymphatic network in the AV loop model
- Evaluation of quality of life in postbariatric plastic surgery patients in pre- and post-surgery
- Molecular analysis of ischemia-associated phenomena in extracorporal tissue perfusion in a large animal model
- Optimizing extracorporal tissue preservation by adaptation of conservation parameters in reconstructive plastic surgery
- A retrospective analysis of the operative therapy of advanced Dupuytren's contracture with the Erlangen Distraction Device versus other treatments
- Tissue Engineering of axially vascularized bone in a small animal model
- Tissue Engineering: Skeletal muscle
- Tissue engineering: Generation of axially vascularized tissue in the large animal arteriovenous loop model

Structure of the Department

Under the auspices of the head of the Department of Plastic and Hand Surgery, Prof. Dr. R. Horch, and four attending plastic surgeons, eight residents, two lab technicians, two veterinarian doctors, two scientists, and 16 medical students are working in different groups on various projects including basic science and clinical research. Besides clinical studies and research based on in vitro investigations of clinical samples, different large and small animal models have been established. With these in vivo studies, many key questions are addressed in the field of plastic and reconstructive surgery, especially concerning angiogenesis and tissue engineering.

Research

Artificial dermis for coverage of silicon implants to prevent capsular fibrosis

Project manager: Dr. M. Schmitz

Capsular fibrosis represents a significant complication following implantation of silicone breast implants, necessitating further surgical intervention. Numerous studies investigating methods to prevent capsular fibrosis have been carried out without success so far. In order to reduce foreign body reaction of the surrounding tissue, coverage of silicone implants with acellular dermis has recently been investigated. An experimental animal study will be conducted to investigate if acellular dermis can be used as an envelope for subcutaneous or submuscular silicon implants. Clinical observation as well as histochemistry and immunohistochemistry will be used for evaluation over a period of twelve months.

The impact of syngenic endothelial progenitor cells on de novo vascular network formation

Project manager: Dr. O. Bleiziffer

The aim of this project is to establish and characterize syngenic endothelial progenitor cells (EPC) derived from rat bone marrow. Furthermore, their angiogenic potential and their integration into a newly formed vascular network are being investigated in the AV loop model in the rat.

Establishment and modulation of a lymphatic network in the AV loop model

Project managers: Dr. A.M. Boos, PD Dr. J.P. Beier

An autonomous lymphatic network will be generated in the AV loop model in the rat using lymphatic enddothelial cells and mesenchymal stem cells in combination. This lymphatic network may connect to the vascular network and provide lympathic drainage from the artificially generated tissue. Stimulation by growth factors and transgenic lympathic enddothelial cells may provide the opportunity for therapeutic modulation of the lympathic network and thereby lympathic metastasis in tumor therapy.

Evaluation of quality of life in postbariatric plastic surgery patients in pre- and post-surgery

Project manager: PD Dr. A. Dragu

The S3 Guideline: „Surgery in Adipose Patients" emphasizes the importance of an interdisciplinary approach of the treatment of bariatric patients and discusses the relevance of the contribution provided by postbariatric plastic surgery. In order to generate a high level of evidence, publications are needed providing the development of postbariatric plastic surgery treatment strategies. In the context of this prospective clinical research work, patients will be evaluated using the SF-36 (Short-Form-36-Questionnaire) at defined time points after their postbariatric plastic surgery procedure. The SF-36 evaluates health-associated quality of life, enabling short term as well as long term effects of plastic surgical procedures on the quality of life of this patient cohort as compared to their situation before plastic surgery.

Molecular analysis of ischemia-associated phenomena in extracorporal tissue perfusion in a large animal model

Project managers: Dr. S. Schnürer, PD Dr. A. Dragu

This research project explores the tolerance of the M. rectus Abdominis to ischemia and how it may be improved and increased. A potential relationship with genes associated with apoptosis, inflammation, and adaptation to ischemia will be investigated in muscle tissue samples harvested at different time points.

Optimizing extracorporal tissue preservation by adaptation of conservation parameters in reconstructive plastic surgery

Project managers: Dr. C.D. Taeger, PD Dr. A. Dragu

The aim of this study is to investigate which physiological parameters, including temperature and oxygen tension, have a significant impact on tissue preservation. Muscle tissue of pigs will be connected to an extracorporal maintenance system to adress how adjustment of the above parameters can improve tissue viability.

A retrospective analysis of the operative therapy of advanced Dupuytren's contracture with the Erlangen Distraction Device versus other treatments

Project manager: Dr. M. Schmitz

Dupuytren's contracture may be associated with extreme flexion contractures of the finger

joints that canot be treated with arthrolysis in a satisfactory fashion on the long run. A slow distraction therapy may be a promising alternative. We performed a retrospective study over ten years to evaluate this treatment regimen in comparison with other operative regimens for the treatment of advanced M. Dupuytren of Grade III-IV according to Iselin's classification.

Tissue Engineering of axially vascularized bone in a small animal model

Project managers: PD Dr. A. Arkudas, PD Dr. U. Kneser

Several cooperations have adressed the combination of extrinsic and intrinsic vascularisation in the AV loop model using porous titanium chambers, and axially vascularized bone tissue was succesfully generated using autologous mesenchymal stem cells (MSCs) in combination with BMP-2. A femur defect model in combination with a titanium chamber with an integrated plate osteosynthesis was successfully established to investigate bone formation with the help of transplantation of a pedicled prevascularized bone construct.

Newly designed bioartificial matrices were investigated within the Emerging Fields Initiative Project (EFI) TOPbiomat.

Tissue Engineering: Skeletal muscle

Project manager: PD Dr. J. Beier

We use specially designed functional 3D-scaffolds via electrospun PCL(poly-ε-Caprolacton)/ collagen nanofibers.

In a rat model, additional vascularization and muscle outgrowth of previously raised muscle cells is stimulated by a further development of our established AV loop rat model, i.e. by secondary insertion of an adjacent motor nerve branch for neurotisation. The goal of this combined approach is de novo developing axially vascularized innervated skeletal muscle tissue.

Tissue engineering: Generation of axially vascularized tissue in the large animal arteriovenous loop model

Project managers: Dr. A.M. Boos, Dr. A. Weigand

Using two clinically approved bone substitutes in combination with osteoinductive growth factors as well as autologous mesenchymal stem cells, de novo formation of axially vascularized tissue has already been demonstrated in the large animal sheep model. Ongoing studies are evaluating a load-stable nanocrystalline bone augmentation material and are focused on the acceleration of the vascularization in the AV-loop model in order to allow the generation of transplantable bone tissue in a very short period of time.

Teaching

According to the German "Statutes of the medical act (ÄAppO)", a lecture series of 25 academic hours per term (AHS) is held as part of the general surgery lecture series. It covers general principles of Plastic and Hand Surgery. Additionally, the following teaching courses are conducted regularly by the Department of Plastic and Hand Surgery:

- Lecture series on "Specific Issues in Plastic and Hand Surgery"
- Tutorial "Tissue Engineering"
- Clinical Ward Round of Department of Plastic and Hand Surgery
- Surgical Anatomy of the Hand and Techniques of Hand Examination
- Interdisciplinary Consultation Hour in "Breast Reconstruction"
- Teaching Ward Round and Advanced Course in Plastic Surgery
- Microsurgical Suture Techniques
- Teaching Ward Round and Advanced Course in Reconstructive Microsurgery
- Postbariactric Plastic Surgery Consultation Hour.

Selected Publications

Beier JP, Horch RE, Bach AD (2009) Breast reconstruction after breast-cancer surgery. N Engl J Med, 360: 418-9; author reply 420-1

Bleiziffer O, Hammon M, Naschberger E, Lipnik K, Arkudas A, Rath S, Pryymachuk G, Beier JP, Stürzl M, Horch RE, Kneser U (2011) Endothelial progenitor cells are integrated in newly formed capillaries and alter adjacent fibrovascular tissue after subcutaneous implantation in a fibrin matrix. J Cell Mol Med, 15: 2452-61

Boos AM, Loew JS, Deschler G, Arkudas A, Bleiziffer O, Gulle H, Dragu A, Kneser U, Horch RE, Beier JP (2011) Directly auto-transplanted mesenchymal stem cells induce bone formation in a ceramic bone substitute in an ectopic sheep model. J Cell Mol Med, 15: 1364-78

Arkudas A, Pryymachuk G, Beier JP, Weigel L, Körner C, Singer RF, Bleiziffer O, Polykandriotis E, Horch RE, Kneser U (2012) Combination of extrinsic and intrinsic pathways significantly accelerates axial vascularization of bioartificial tissues. Plast Reconstr Surg, 129: 55e-65e

Dragu A, Kleinmann JA, Taeger CD, Birkholz T, Schmidt J, Geppert CI, Präbst K, Unglaub F, Münch F, Weyand M, Kneser U, Horch RE (2012) Immunohistochemical evaluation after ex vivo perfusion of rectus abdominis muscle flaps in a porcine model. Plast Reconstr Surg, 130: 265e-273e

Horch RE, D'Hoore A, Holm T, Kneser U, Hohenberger W, Arkudas A (2012) Laparoscopic Abdominoperineal Resection with Open Posterior Cylindrical Excision and Primary Transpelvic VRAM Flap. Ann Surg Oncol, 19: 502-3

International Cooperations

Prof. Dr. D. Hutmacher, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane: Australia

Prof. E. Eriksson, MD, PhD, Plastic Surgery Division, Harvard Medical School, Boston: USA

Prof. J. Sun, Department of Plastic and Cosmetic Surgery, Union Hospital, Hubei: China

Research Equipment

Zeiss, 2 Zeiss Surgical Microscopes

Leica, 1 Leica Surgical Microscope

Department of Psychiatry and Psychotherapy

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Research Focus
- Dementia
- Neurophotonics
- Schizophrenia
- Addictive behavior
- Clinical neurochemistry and neurochemical dementia diagnosis

Structure of the Department

The Department of Psychiatry and Psychotherapy combines all psychosocial faculties under one roof regarding organization and location. The clinic encompasses the divisions Psychosomatic Medicine, Child Psychiatry, Medical Psychology, and the Medical Sociology. Content-related networking is supported by the DIN EN ISO 9001:2008 certified quality management system. Medical treatment at our clinic is administered by a highly qualified interdisciplinary team whose dedication and competence assures a speedy recovery of our patients. The cooperation between doctors, care staff, psychologists, social education workers, occupational therapists, and physiotherapists allows for comprehensive diagnoses and selective treatments. Patients may receive treatment on a full or partial inpatient basis or as outpatients. Various stimulatory methods represent a special form of clinical treatment. The research activities of the clinic have a special focus on affective disorders, addiction, schizophrenia, and dementia. The clinic is part of the competence network Demenzen e.V. (KND) where it assumes a leading role as diagnostics center with the focus on early and differential diagnosis. It further participates in ongoing projects on neurodegenerative disorders in Germany and Europe. In the area of addiction research, the FARS (Franconian Alcoholism Research Studies) investigated the neurobiological base of alcoholism in a large patient cohort. The results of this study are currently being integrated into the routine treatment of alcohol addiction. Similarly, results from the nicotine research projects are now part of the quit smoking courses. The Department of Psychiatry and Psychotherapy incorporates the Laboratory for Clinical Neurochemistry and Neurochemical Dementia Diagnostics, the National Reference Center for Neurochemical Dementia Diagnostics within the KND. In addition, the Laboratories for Molecular Neurobiology, the Neurophotonics Laboratory, and a Sensor Laboratory are part of the Department.

Research

Dementia

The focus of research work is on improving the early and progressive diagnosis of disorders surrounding dementia. In the psychometrics branch, a new version of the Resource Utilization in Dementia (RUD) for use in care homes has been developed. This is an instrument which covers the time required to support patients in a care home for helping with activities related to day-to-day issues and supervision and which is suitable for use in health care research studies. In the branch of psychometrics, work is being carried out under the sponsorship of the DFG to further develop a performance test for measuring daily activities on an objective, valid, and economical basis even for mild forms of dementia. It covers tasks from aspects of life including communication, mobility, self-care, and domestic life. So far, only external assessments exist. This test, in contrast, will provide more accurate measurements of therapy success in dementia disorders. The participation of the immune system in mental illnesses with the focus on Alzheimer's dementia is being investigated in cooperation with the Division of Molecular Immunology within the Department of Medicine 3 - Rheumatology and Immunology. In a further project in cooperation with the Department of Medicine 4 - Nephrology and Hypertension, the occurrence of affective and cognitive disorders is being investigated on patients who have undergone a kidney transplant and who are suffering from a suppressed immune system and its connection with soluble and cellular immunological biomarkers.

Neurophotonics

This area of research has seen a number of successful developments during the report period. Thus, it has been possible to show that the drug levels of psychopharmaceuticals (e.g. neuroleptics) are not constant in the brain during chronic treatment (contrary to earlier assumptions), but fluctuate with the activity of the nerve cells. Therapeutically active compounds are accumulated and then released in high concentrations like neurotransmitters by nerve endings during signal transmission. A paper discussing the fundamentals of this subject has been published in a leading specialist journal. On the basis of this highly promising work, the existing research premises now form the Laboratory for Neurophotonics. This laboratory is associated with the Optical Imaging Center Erlangen and networks on an interdisciplinary basis with groups from the Max-Planck-Institute for the Physics of Light and Medical Fundamentals. The laboratory is due to expand in size in the near future in order to enable continuing work to be carried out (e.g. by the Else-Kröner-Fresenius Foundation with more than 200,000 Euro).

Schizophrenia

Following the appointment of Prof. Dr. S.G. Schwab as W2 Chair for Molecular Psychiatry in September 2010, research in the branch of schizophrenia has been considerably enhanced. In cooperation with colleagues in Perth, Australia, and Jakarta, Indonesia, it has been possible to characterize a sample with more than 1,000 patients with schizophrenia and more than 1,000 control persons from Indonesia for chromosomal genomes which had already caused a sensation in conjunction with other genome-wide studies. It is evident that these genomes not only play a role in the origins of schizophrenia in European populations, but also in Asian populations such as the Indonesian population. Furthermore, by cooperating with groups from Europe, the USA, and Australia, it has been possible to obtain for the first time clear signs of genes that play a role in the origin of schizophrenia. This work has been published in leading specialist journals.

Addictive behavior

In the research work focusing on addiction, significant findings have been obtained on genetic fundamentals, biomarkers, and molecular changes in alcohol and nicotine addiction. In the field of alcohol research, the focus was on genetic and molecular mechanisms in the development of addiction. Here, new genetic mutations and downstream molecular circuits have been discovered and described which clearly increase the risk of developing an addiction. In a further focal point, the role of sexual hormones in association with craving has been investigated during alcohol withdrawal. Thus, various polymorphisms were identified in the genes of the sexual hormone axis which are associated with the strength of the craving. Research in the field of nicotine dependence has shown that the con-

sumption of nicotine leads to enhanced activation of intracellular signal cascades. These signal cascades play an essential role in the establishment of addictive behavior. In addition, the effects of nicotine consumption were investigated for the EEG activity and for a modified sensory evaluation of the attractions of nicotine. Smokers were found to have a more positive assessment of S nicotine versus R nicotine. The changes with regard to hedonics were explained by conditioning mechanisms. On a human/experimental basis, it was possible to show an inverse correlation with hedonic estimates in the EEG following olfactory stimulation for the P2 component of the evoked potentials. In cooperation with the Criminological Research Institute Lower Saxony (KFN) and the Hannover Medical School, the problem behavior of binge drinking was investigated involving 45,000 youths in a representative study in Germany. Epidemiological data were evaluated with respect to town and country differences as well as sample differences in consumption as a function of migration background of the youths. Using a theoretical approach, a predictor analysis of binge drinking was carried out which resulted in two statistical and content-relevant protective factors and four risk factors. Later evaluations are planned with respect to the relationships between mental instability and binge drinking. The project is sponsored by external funding (ERAB).

Clinical neurochemistry and neurochemical dementia diagnosis

Project manager: Prof. Dr. P. Lewczuk

The ISO 9001:2008-certified laboratory is an internationally recognized center for neurochemical dementia diagnosis (NDD). The analysis of cerebrospinal fluid offers excellent diagnostic options in several neurological and psychiatric diseases, such as neurodegenerative disorders, stroke, multiple sclerosis and other neuroinflammatory diseases. The head of the laboratory, published two special journal editions as a guest editor in renowned scientific journals in 2012. Furthermore, he received a grant from the BMBF as part of the EU project "BiomarkAPD" of the JPND and coordinates the work package "Certified Reference Material".

Teaching

The Department offers a wide spectrum of courses for students of human and molecular medicine as well as the MPM study program. Evaluation of training regularly places psychiatry among the best clinical subjects. Planning and evaluation of the exams is carried out in accordance with scientific principles. Particular attention is focused on training of communication skills in the doctor/patient interaction. The performance record of this training is assessed by a competence-oriented test, a portfolio. This can be prepared by the students in a flexible time window, thus reducing the work load at the end of the term. It promotes process-based learning thanks to individual feedback and an intensive support by tutors. In 2011, the Erlangen students ranked first in the subject Medical Psychology and Medical Sociology in Part One of the National Medical Licensing Exam in a country-wide comparison.

Selected Publications

Graessel E, Stemmer R, Eichenseer B, Pickel S, Donath C, Kornhuber J, Luttenberger K (2011) Non-pharmacological, multicomponent group therapy in patients with degenerative dementia: a 12-month randomzied, controlled trial. BMC Med, 9: 129

Hollingworth P, Harold D, Sims R, Gerrish A, Lambert JC, Carrasquillo MM, Abraham R, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Jones N, Stretton A, Thomas C, Richards A, Ivanov D, Widdowson C, Chapman J, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Beaumont H, Warden D, Wilcock G, Love S, Kehoe PG, Hooper NM, Vardy ER, Hardy J, Mead S, Fox NC, Rossor M, Collinge J, Maier W, Jessen F, Rüther E, Schürmann B, Heun R, Kölsch H, van den Bussche H, Heuser I, Kornhuber J, Wiltfang J, Dichgans M, Frölich L, Hampel H, Gallacher J, Hüll M, Rujescu D, Giegling I, Goate AM, Kauwe JS, Cruchaga C, Nowotny P, Morris JC, Mayo K, Sleegers K, Bettens K, Engelborghs S, De Deyn PP, Van Broeckhoven C, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwilliam R, Deloukas P, Al-Chalabi A, Shaw CE, Tsolaki M, Singleton AB, Guerreiro R, Mühleisen TW, Nöthen MM, Moebus S, Jöckel KH, Klopp N, Wichmann HE, Pankratz VS, Sando SB, Aasly JO, Barcikowska M, Wszolek ZK, Dickson DW, Graff-Radford NR, Petersen RC, Alzheimer's Disease Neuroimaging Initiative, van Duijn CM, Breteler MM, Ikram MA, DeStefano AL, Fitzpatrick AL, Lopez O, Launer LJ, Seshadri S, CHARGE consortium, Berr C, Campion D, Epelbaum J, Dartigues JF, Tzourio C, Alpérovitch A, Lathrop M, EADI1 consortium, Feulner TM, Friedrich P, Riehle C, Krawczak M, Schreiber S, Mayhaus M, Nicolhaus S, Wagenpfeil S, Steinberg S, Stefansson H, Stefansson K, Snaedal J, Björnsson S, Jonsson PV, Chouraki V, Genier-Boley B, Hiltunen M, Soininen H, Combarros O, Zelenika D, Delepine M, Bullido MJ, Pasquier F, Mateo I, Frank-Garcia A, Porcellini E, Hanon O, Coto E, Alvarez V, Bosco P, Siciliano G, Mancuso M, Panza F, Solfrizzi V, Nacmias B, Sorbi S, Bossù P, Piccardi P, Arosio B, Annoni G, Seripa D, Pilotto A, Scarpini E, Galimberti D, Brice A, Hannequin D, Licastro F, Jones L, Holmans PA, Jonsson T, Riemenschneider M, Morgan K, Younkin SG, Owen MJ, O'Donovan M, Amouyel P, Williams J (2011) Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease. Nat Genet, 43: 429-35

Lenz B, Müller CP, Stoessel C, Sperling W, Biermann T, Hillemacher T, Bleich S, Kornhuber J (2012) Sex hormone activity in alcohol addiction: integrating organizational and activational effects. Prog Neurobiol, 96: 136-63

Levinson DF, Shi J, Wang K, Oh S, Riley B, Pulver AE, Wildenauer DB, Laurent C, Mowry BJ, Gejman PV, Owen MJ, Kendler KS, Nestadt G, Schwab SG, Mallet J, Nertney D, Sanders AR, Williams NM, Wormley B, Lasseter VK, Albus M, Godard-Bauché S, Alexander M, Duan J, O'Donovan MC, Walsh D, O'Neill A, Papadimitriou GN, Dikeos D, Maier W, Lerer B, Campion D, Cohen D, Jay M, Fanous A, Eichhammer P, Silverman JM, Norton N, Zhang N, Hakonarson H, Gao C, Citri A, Hansen M, Ripke S, Schizophrenia Psychiatric GWAS Consortium, Dudbridge F, Holmans PA (2012) Genome-wide association study of multiplex schizophrenia pedigrees. Am J Psychiatry, 169: 963-73

Tischbirek CH, Wenzel EM, Zheng F, Huth T, Amato D, Trapp S, Denker A, Welzel O, Lueke K, Svetlitchny A, Rauh M, Deusser J, Schwab A, Rizzoli SO, Henkel AW, Müller CP, Alzheimer C, Kornhuber J, Groemer TW (2012) Use-dependent inhibition of synaptic transmission by the secretion of intravesicularly accumulated antipsychotic drugs. Neuron, 74: 830-44

Wagner M, Wolf S, Reischies FM, Daerr M, Wolfsgruber S, Jessen F, Popp J, Maier W, Hüll M, Frölich L, Hampel H, Perneczky R, Peters O, Jahn H, Luckhaus C, Gertz HJ, Schröder J, Pantel J, Lewczuk P, Kornhuber J, Wiltfang J (2012) Biomarker validation of a cued recall memory deficit in prodromal Alzheimer disease. Neurology, 78: 379-86

International Cooperations

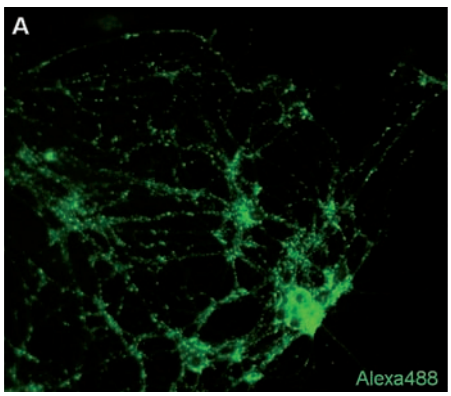
Prof. Dr. D.B. Wildenauer, School of Psychiatry and Clinical Neurosciences University of Western Australia, Crawley: Australia

Prof. Dr. O.M. Lesch, Universität Wien, Wien: Austria

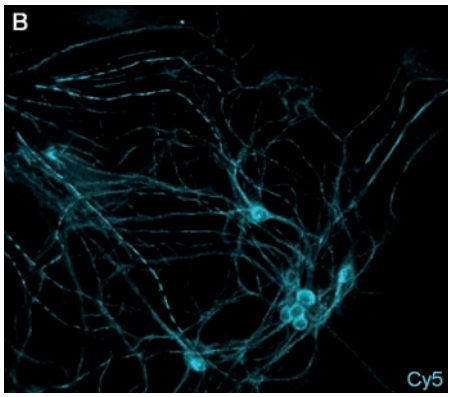
Prof. Dr. M. Barros, Institute of Pharmacology, Brasilia: Brazil

Prof. Dr. S. Trapp, Technical University of Denmark: Denmark

Prof. Dr. G. Schumann, Institute of Psychiatry, London: UK



A: Axon terminals visualized using fluorescence microsopy



B: Corresponding cytoskeleton visualized using fluorescence microsopy

Department of Psychiatry and Psychotherapy

Division of Child and Adolescent Mental Health

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Research Focus

- Neurofeedback
- Attention and inhibition processes in children with ADHD
- Neural processing of emotional and disorder specific stimuli in girls with eating disorders
- Behavioral and neural consequences of prenatal trauma in an animal model

Structure of the Department

The Division of Child and Adolescent Mental Health at the Department of Psychiatry and Psychotherapy is a self-contained division of the UK Erlangen. It is subdivided in the areas research, outpatient division/policlinic, day hospital, and inpatient division. Furthermore, in cooperation with the Fürth City Hospital, another child psychiatric day hospital is operated and professionally directed by Prof. Dr. G. Moll which has been extended to include a family day care for families with children between one and four years.

The clinical focus lies on: Attention deficit/hyperactivity disorder (ADHS), tic disorders, obsessive-compulsive disorders, anxiety disorders, depressive disorders, posttraumatic stress disorders, eating disorders, autistic disorders, reduced intelligence with psychiatric comorbidity, and regulation and behavior disorders in early childhood.

The different research projects of the division aim at better understanding of developmental processes and of the neurobiological basis of emotional and behavioral disorders in children and adolescents as well as gaining further insights into the neural mechanisms underlying therapeutic interventions.

Research

Neurofeedback

In neurofeedback training, participants learn to gain self-control over certain brain activity patterns. In this way, children with ADHD are trained to develop strategies that enable them to improve their attention abilities as well as to better regulate their behavior. In the up to now largest randomized controlled trial that had been conducted in cooperation with the Child and Adolescent Psychiatry at the University Clinic of Göttingen and the Heckscher-Klinik in München, the clinical effectiveness of a neurofeedback training in children with ADHD could be demonstrated and evidence for the mechanisms of action of the standard protocols theta/beta and SCP training was obtained. In the report period, invited reviews including this study were published and perspectives for the application of neurofeedback in ADHD have been discussed.

In a small-scale study on SCP training in children with ADHD, associations of SCP self-regulation skills and clinical reductions of ADHD symptomatology were found. Moreover, tomographic analyses (sLORETA) confirmed that fronto-parietal networks are involved in SCP generation.

A further study in students examined the effects of different variants of neurofeedback training on attentional processes, the motor system and well-being in comparison to a control training. For the different neurofeedback protocols, some specific effects, even though smaller than expected, could be observed. For example, hints were obtained for associations of successful self-regulation of negativity during SCP training and increased amplitudes of the contingent negative variation during an attention task. In addition, hints for increased intracortical inhibition and facilitation in the motor system were observed after theta/beta training. Hence, these studies could contribute to a better understanding of the mechanisms of different neurofeedback protocols.

Attention and inhibition processes in children with ADHD

Children with ADHD show an inhibitory deficit in the motor system. In order to examine this deficit at the neuronal level in more detail, we developed a methodological approach combining transcranial magnetic stimulation (TMS) and event-related potentials (ERPs). In a study comparing children with and without ADHD, altered inhibitory patterns were obtained for children with ADHD depending on the level of hyperactivity/impulsivity. Combining TMS and ERPs revealed a compensatory pattern in children with ADHD. Neurophysiological markers allowed to classify 90% of the children correctly. In further studies attentional processes and their modulation by methylphenidate and atomoxetine (medications for the treatment of ADHD) were examined in children with ADHD. While both medications led to a comparable reduction of the severity of ADHD symptoms, methylphenidate exerted more pronounced effects on attentional processes (with respect to reaction time variability and contingent negative variation).

Neural processing of emotional and disorder specific stimuli in girls with eating disorders

In adolescent girls with eating disorders (anorexia nervosa, bulimia nervosa) and typically developing girls, gaze behavior and central nervous and peripheral physiological responses were studied, e.g. when viewing body scheme pictures of underweight, normal weight, and overweight women. Eating disordered patients showed longer fixation times for unclothed body regions (visual attentional bias towards body shape-related information). At the central nervous level (event-related potentials in the EEG), anorectic patients showed largest responses for pictures of underweight women. In a further study, an assessment battery including standardized pictures of underweight, normal weight, and overweight women as well as pictures of low- and high-caloric food was developed and evaluated in healthy female pupils. The results indicated that especially female adolescents in the age of 16 to 18 years rated underweight women as more attractive than normal weight women.

Behavioral and neural consequences of prenatal trauma in an animal model

We have established an animal model for prenatal trauma which enables us to further examine the mechanisms which lead to a higher risk of developing a psychiatric disorder in children having suffered from a prenatal trauma. In our mouse model, we examine the effects of a prenatal trauma on processes of learning and memory, anxiety and fear, as well as on depres-

sion-like behavior. We measure changes in the neuronal activity of brain structures involved in these processes as well as changes in the activity of the hypothalamic-pituitary-adrenal axis (HPA). Moreover, correlations of the effects of maternal behavior and the phenotype of their offspring are correlated and a differentiation between in utero and postnatal environmental effects is examined.

Teaching

The teachings in the field of child and adolescent psychiatry and psychotherapy are composed of lectures, seminars, case presentations as well as block seminars. These comprise diagnostics and therapy of the clinical disorders as well as the research methods applied in this field. Year-round students of medicine, psychology, education science, and social pedagogy are being educated and supervised. The main lecture "Child and adolescent psychiatry and psychotherapy" is attended by numerous students even though it has not yet been included in the curriculum of the Faculty of Medicine despite its immense importance for the field. However, practical training and seminar are a fixed component of the constantly very successfully evaluated lecture of the Department of Psychiatry and Psychotherapy. Moreover, the subject "Child and adolescent psychiatry and psychotherapy" is offered as a compulsory optional subject for students of medicine (clinical/preclinical term) and as an optional lecture with accompanying seminar within the course of studies in Psychology (Bachelor/Master). Since the summer term 2012, the seminar „school related psychiatric disorders" has offered as an interdisciplinary lecture for both, students and professionals, in the fields of education science, psychology, and medicine.

Selected Publications

Golub Y, Kaltwasser SF, Mauch CP, Herrmann L, Schmidt U, Holsboer F, Czisch M, Wotjak CT (2011) Reduced hippocampus volume in the mouse model of Posttraumatic Stress Disorder. J Psychiatr Res, 45: 650-9

Gevensleben H, Rothenberger A, Moll GH, Heinrich H (2012) Neurofeedback in children with ADHD: validation and challenges. Expert Rev Neurother, 12: 447-60

Hoegl T, Heinrich H, Barth W, Lösel F, Moll GH, Kratz O (2012) Time course analysis of motor excitability in a response inhibition task according to the level of hyperactivity and impulsivity in children with ADHD. PLoS ONE, 7: e46066

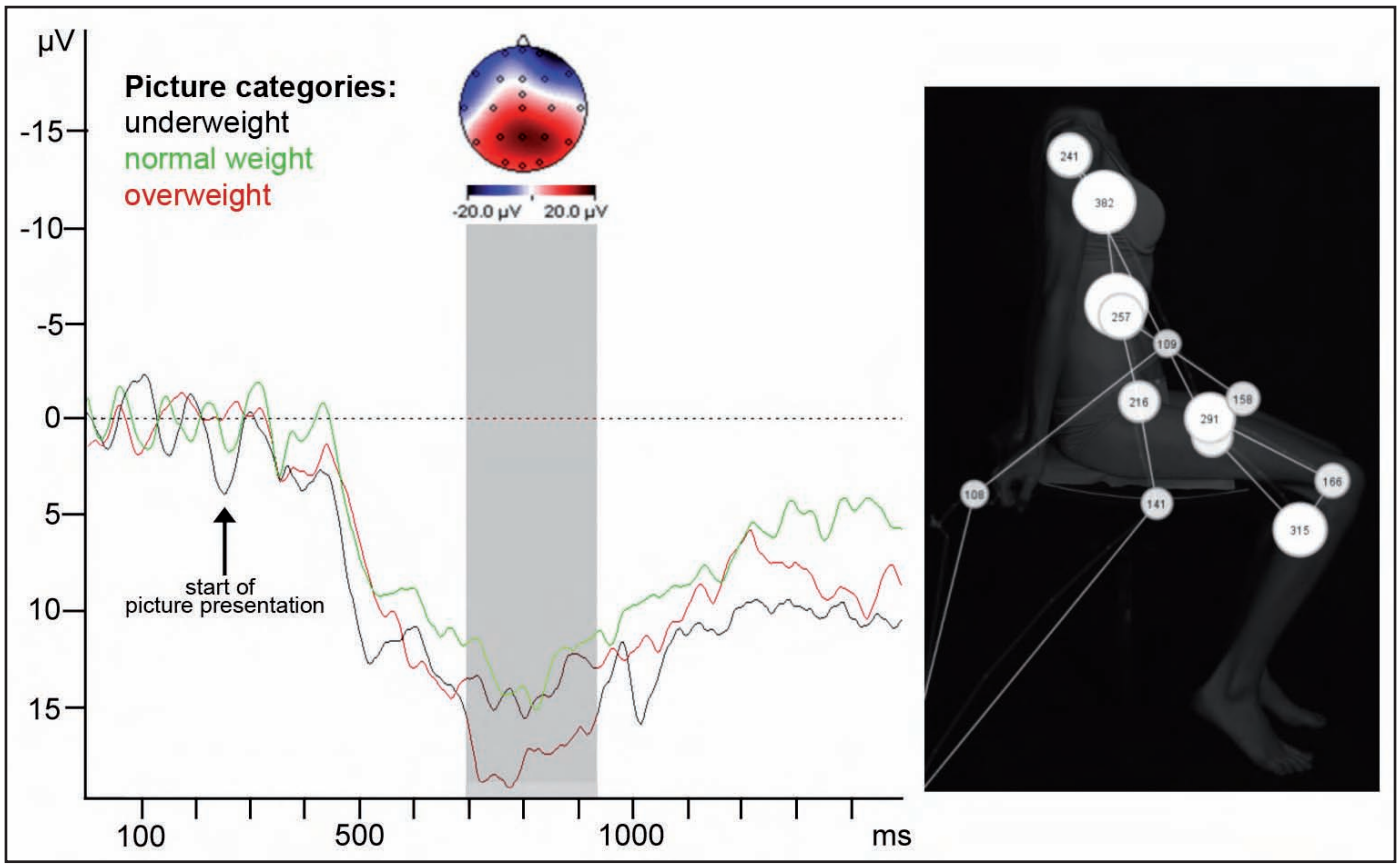
Horndasch S, Heinrich H, Kratz O, Moll GH (2012) The late positive potential as a marker of motivated attention to underweight bodies in girls with anorexia nervosa. J Psychosom Res, 73: 443-7

Kratz O, Studer P, Baack J, Malcherek S, Erbe K, Moll GH, Heinrich H (2012) Differential effects of methylphenidate and atomoxetine on attentional processes in children with ADHD: An event-related potential study using the Attention Network Test. Prog Neuropsychopharmacol Biol Psychiatry, 37: 81-9

Sauerhöfer E, Pamplona FA, Bedenk B, Moll GH, Dawirs RR, von Hörsten S, Wotjak CT, Golub Y (2012) Generalization of contextual fear depends on associative rather than non-associative memory components. Behav Brain Res, 233: 483-93

International Cooperations

Prof. Dr. D. Brandeis, Dr. R. Drechsler, Department of Child and Adolescent Psychiatry, University of Zurich, Zurich: Switzerland



Event-related EEG curve ("late positive potential", electrode Pz, left) and "Attention map" (visualization of fixations, right)

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Research Focus
- Somatoform disorders
- Body dysmorphic disorder
- Eating disorders
- Obesity
- Behavioral medicine
- Psycho-oncology

Structure of the Department

The independent Division could considerably expand its services during the last years. We offer inpatient, day-patient and outpatient treatment, as well as a psychosomatic consultation-liaison service for the patients of the UK Erlangen with a major focus on psycho-oncology. The main clinical focus of the Division surrounds eating disorders. Other areas of activity include obesity, somatoform disorders, pain treatment, and psycho-oncology. The treatment focuses on multimodal and multidisciplinary evidence-based psychotherapy. Prof. Dr. A. Martin, who filled a faculty professorship in "Psychotherapy Research" until 30.09.2012, strengthened the field of behavioral medicine and collaborated successfully with the other departments of the UK Erlangen. With her work, she underlined the importance and impact of psychosomatic medicine as an interdisciplinary medical field.

Research

Somatoform disorders

Project manager: Prof. Dr. A. Martin

The common feature of the somatoform disorders is the presence of physical symptoms that cannot fully be explained by a general medical condition, resulting in considerable impairment and suffering. Our research addresses epidemiology, diagnostic procedures, and etiological aspects of somatoform disorders as well as the development and evaluation of psychological treatment approaches.

1) In cooperation with the Universities of Marburg and Leipzig (DFG grant), a longitudinal survey aiming at clarifying predictors of symptom persistence in somatoform disorders was completed and results on the validity of current classification proposals have been published.

2) Unspecific chest pain: More than 50% of patients in cardiology are found to have no cardiac basis for their persisting chest pain. As a result, patients often suffer from emotional distress and significant restrictions in daily life, both leading to an increased health care utilization. To prevent chronic manifestations of chest pain, a brief and early cognitive-behavioral intervention has been developed and evaluated in a randomized controlled trial. The study has received a grant by ELAN-Fond and is conducted in cooperation with the Departments of Cardiology of the UK Erlangen and the clinic Martha-Maria in Nürnberg. Our analyses show that cognitive processes are relevant in non-cardiac chest pain and that our intervention was well accepted. Results on the longitudinal course of the complaints as well as of the randomized clinical trial can be expected in 2013. In addition, we have developed an experimental design in cooperation with the university of Cologne to investigate cognitive factors in chest pain patients.

Body dysmorphic disorder

Project manager: Prof. Dr. A. Martin

Individuals with body dysmorphic disorder (BDD) are preoccupied with perceived defects or flaws in their physical appearance. These defects or flaws are not observable by others or appear slight to others. BDD is frequently accompanied by feelings of shame and low self-esteem, compulsive checking behaviors (e.g. mirror checking), or attempts to hide the imagined defect (e.g. cosmetic camouflage). The preoccupation with appearance is excessive and causes significant distress or impairment in functioning.

We aimed at identifying disorder-specific characteristics of BDD in comparison with a clinical control group (eating disorders) and healthy controls. Furthermore, we examined body image variables in individuals with BDD in comparison to individuals with major depression and healthy controls. Another project aims at investigating selective visual attention in individuals with BDD.

Eating disorders

Project managers: Prof. Dr. M. de Zwaan (until October 2011), Dr. H. Graap

Prof. Dr. M. de Zwaan coordinates the "Research consortium on psychotherapy of eating disorders (EDNET)", funded by the BMBF. The funding period runs from 2007 to 2013. Within the consortium, five large randomized multi-center psychotherapy trials are conducted, all of which represent international milestone studies. Until the end of 2011, the Division of Psychosomatics and Psychotherapy was the coordinating center of a trial for the treatment of Binge-Eating-Disorder, initiated in 2010. The efficacy of an internet-based, therapist-guided intervention will be compared with individual cognitive-behavioral therapy. As adjunct projects to the psychotherapy trials within EDNET, genetic, epigenetic, and endocrinological studies are conducted.

Besides the engagement in EDNET, we conduct a study concerning an intervention to support the carers of patients with eating disorders. A skills training for carers and reading a selfhelp-guide are compared regarding their impact on carers' quality of life, relationship to the patient, and the course of the eating disorder.

Obesity

Project managers: Prof. Dr. M. de Zwaan (until October 2011), PD Dr. Dr. A. Müller

Prof. Dr. M. de Zwaan is a board member of the Competence Network Obesity which was funded in August 2008 by the BMBF. In addition, she is deputy speaker of the entire Competence Network. The Division of Psychosomatics and Psychotherapy in Erlangen has successfully established the German Weight Control Registry (GWCR) with the goal to determine and examine factors that support better long-term weight loss maintenance. This is taken as a basis for more focused treatments. The registry includes primarily volunteers from the general population who have intentionally lost at least 10% of their initial body weight and have kept it off for at least one year. All participants are subsequently followed-up annually. For data capture, a participant-centered approach with secure data entry directly by the participants is planned. A requirement specification for enhancing existing remote data entry (RDE) sys-

tems to cover for such aspects will be produced by Prof. Dr. H.U. Prokosch and his team from the Chair of Medical Informatics at the FAU.
Another project focused on executive functions in grade 3 obesity. The study examined executive functioning in 150 morbidly obese patients with and without binge eating. The findings suggest a tendency to disadvantageous, risky decisions in obese individuals with regular binge eating.

Behavioral medicine

Project manager: Prof. Dr. A. Martin
Psychosocial factors in congenital chest wall deformity: Patients with funnel or pigeon chest suffer not only from physical restrictions, but also from psychological distress. In a project supported by the ELAN-Fond and in cooperation with the Division of Pediatric Surgery, we have shown that patients with a chest wall deformity suffer from an impaired body image, strongly influencing the self-esteem. The surgical correction of the chest wall deformity results - as expected - in physical improvements, but also in a better body image. Currently, the maintenance and predictors of post-surgical course are further investigated.

Psycho-oncology

Project manager: H. Sinzinger
The establishment of the Comprehensive Cancer Center Erlangen-Nürnberg (CCC), funded by the German Cancer Aid, increases the relevance and importance of research in the area of psycho-oncology. In collaboration with the psycho-oncology services of the other funded CCCs, we intend to investigate the needs and demands of the patients as well as the utilization of psychosocial services.

Teaching

The Division is significantly involved in the curriculum of the Faculty of Medicine. We test new methods of instruction and teaching formats within the practical course offered by the Division in order to teach students basics aspects of a professional doctor-patient-relationship. The Division also participates in several cross discipline teaching efforts ("Querschnittsfächer") within the curriculum of the Faculty of Medicine and also offers courses for psychology students. Medical students can choose Psychosomatic Medicine as a clinical elective ("Famulatur") and as an internship during their final year rotation ("Praktisches Jahr"). The Division also offers courses for advanced training in psychotherapy for psychotherapist with a university degree in psychology. In the study program Medical Process Management, the Division of Psychosomatics and Psychotherapy is responsible for a seminar on "communication and cooperation aspects within the health care system". The Division regularly receives high ratings for the lecture and practical courses based on the evaluation of the medical students.

Selected Publications

Mueller A, Holzapfel C, Hauner H, Crosby RD, Engel SG, Mühlhans B, Kolotkin RL, Mitchell JE, Horbach T, Zwaan MD (2011) Psychometric evaluation of the German version of the impact of weight on Quality of Life-Lite (IWQOL-Lite) questionnaire. Exp Clin Endocrinol Diabetes, 119: 69-74

de Zwaan M, Gruß B, Müller A, Philipsen A, Graap H, Martin A, Glaesmer H, Hilbert A (2011) Association between Obesity and Adult Attention-Deficit/Hyperactivity Disorder in a German Community-Based Sample. Obes Facts, 4: 204-211

Kollei I, Brunhoeber S, Rauh E, de Zwaan M, Martin A (2012) Body image, emotions and thought control strategies in body dysmorphic disorder compared to eating disorders and healthy controls. J Psychosom Res, 72: 321-7

Krille S, Müller A, Steinmann C, Reingruber B, Weber P, Martin A (2012) Self- and social perception of physical appearance in chest wall deformity. Body Image, 9: 246-52

Schroeder S, Achenbach S, Körber S, Nowy K, de Zwaan M, Martin A (2012) Cognitive-perceptual factors in noncardiac chest pain and cardiac chest pain. Psychosom Med, 74: 861-8

de Zwaan M, Gruß B, Müller A, Graap H, Martin A, Glaesmer H, Hilbert A, Philipsen A (2012) The estimated prevalence and correlates of adult ADHD in a German community sample. Eur Arch Psychiatry Clin Neurosci, 262: 79-86

International Cooperations

Prof. Dr. L. Claes, Department of Psychology, Katholieke Universiteit Leuven, Leuven: Belgium

PD Dr. J. Gaab, Clinical Psychology and Psychotherapy, University of Zurich, Zurich: Switzerland

Prof. Dr. J.E. Mitchell, Neuropsychiatric Research Institute and University of North Dakota School of Medicine and Health Sciences, University of North Dakota, Fargo: USA

Department of Radiation Oncology

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Research Focus
- Clinical Trials
- Radiation Biology
- Physical Aspects of Radiation Oncology
- Radiation Immunobiology

Structure of the Department

The Department of Radiation Oncology offers the entire spectrum of modern Radiotherapy at the highest level. Clinical, biological, and physical aspects of radiation oncology are scientifically analyzed. A multimodal radiooncological therapy from one source is applied. The treatment spectrum compasses intensity modulated radiotherapy (IMRT), image guided radiotherapy (IGRT), radiochemotherapy, brachytherapy with its whole spectrum of indications, intensity modulated brachytherapy (IMBT), image guided brachytherapy (IGBT), radiosurgery, hyperthermia (including two deep regional devices, one of it with MR guided thermometry), palliative multimodal concepts, and supportive therapies. Clinical aspects of radiation oncology are predominantly examined within phase I, II, and III trials. This takes place on the ward, in the outpatient department, the therapeutics department as well as the treatment planning department and hyperthermia unit. A total of five senior physicians and 16 residents treat patients and are involved in running the various trials and clinical studies. Coordination of the clinical trials is carried out by the in-house clinical trials office. Besides the administration by three scientific employees, three assistant study nurses as well as a secretary are responsible for this work. Radiotherapy treatments are carried out at one of four linear accelerators and in the department of interventional radiation therapy. The latter is one of the most modern and biggest departments for interventional radiotherapy in Germany. Translational and basic radio(immune)-biological research is carried out by two groups, the classical radiation biology group and the radiation immune biology group. The whole laboratory team consist of two assistant professors, two postdoctoral fellows, three technicians as well as six PhD students and numerous medical doctoral candidates. The "Medical Radiation Physics" group consists of seven doctorate holding co-workers, five doctoral candidates, and three technicians. Since October 2012, the head of this group has been the newly appointed full professor Dr. C. Bert who wants to intensify the physico-medical research. The "Medical Radiation Physics" group prioritizes the power of clinical radiation therapy.

Research

Clinical Trials

Project managers: Prof. Dr. R. Sauer, Prof. Dr. V. Strnad, Prof. Dr. R. Fietkau, PD Dr. O. Ott

1. Phase-III multicenter trial: Preoperative radiochemotherapy and adjuvant chemotherapy with 5-fluorouracil versus preoperative radiochemotherapy and adjuvant chemotherapy with 5-fluorouracil combined with oxaliplatin in patients with locally advanced UICC stage II and III rectal cancer. Funded by Deutsche Krebshilfe.
2. Phase-III multicenter trial: Comparison of partial breast interstitial brachytherapy with external whole breast beam radiotherapy in patients with low risk invasive and in situ breast carcinomas. Cooperation with C. Polgár, Budapest, Hungary; funded by Deutsche Krebshilfe.
3. Phase-III multicenter trial: Reducing total radiation dose in the context of a simultaneous radiochemotherapy of head and neck tumors. Cooperation with Prof. Dr. H. Iro, Department of Otorhinolaryngology, FAU; funded by Deutsche Krebshilfe.
4. Phase-III multicenter trial: Nutritional therapy of patients with head and neck tumors. Funded by Fresenius Kabi AG.
5. Phase II-Study: PDR/HDR interstitial brachytherapy alone in patients with pT1/pT2 pN0 breast carcinomas after breast conserving surgery.
6. Phase II-Study: 3D conformal, external partial breast irradiation in patients with pT1/2 pN0 breast carcinomas after breast conserving surgery.
7. Multi-institutional Phase I/II Study: Neoadjuvant chemoradiation with 5-FU (or capecitabine) and oxaliplatin combined with deep regional hyperthermia in locally advanced or recurrent rectal cancer.
8. Dose-painting-Image-guided interstital PDR-brachytherapy based on HistoScanning in patients with prostatic cancer - Phase II-Study.

The Department further participates in the following externally led phase-III trials:

1. Radiation dose intensity study in breast cancer of young women: Randomized phase-III trial of additional dose to the tumor bed. Principal investigator (PI): Prof. Dr. H. Bartelink, Amsterdam, Netherlands.
2. Multicenter Trial: Effectiveness of Adjuvant Radiotherapy in Patients With Oropharyngeal and Floor of Mouth Squamous Cell Carcinoma and Concomitant Histological Verification of Singular Ipsilateral Cervical Lymph Node Metastasis (pN1-state). PI: Prof. Dr. Dr. W. Wagner, Mainz
3. A randomized two-armed open study on the adjuvant therapy in patients with R0/R1 resected pancreatic carcinoma with Gemcitabine alone versus Gemcitabine plus Cisplatin with regional hyperthermia. PI: Prof. Dr. R. Issels, München.
4. German Hodgkin trials, coordinated by: Deutsche Hodgkin Lymphom Study Group (DHSG), Köln.

In addition, the Department runs a number of phase I and II trials.

Radiation Biology

Project manager: PD Dr. L. Distel

1. Individual sensitivity to radiation. Funded by: Deutsche Krebshilfe. Individual differences in the sensitivity of normal tissues to radiation are the most important determinant for the occurrence of dose-limiting side effects of radiotherapy. In a project run jointly with the University of Würzburg (PD Dr. T. Djuzenova), the usefulness of a bed-side test in determining the β-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.
2. Tumor infiltrating lymphocytes. 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 Department of Pathology at

the FAU (PD Dr. M. Büttner-Herold), the role of CD4, CD8, B-cells, macrophages, and the influence of regulatory T cells is studied in patients with head and neck tumors, gastric cancer, and carcinoma of the rectum.

Physical Aspects of Radiation Oncology

Project manager: Prof. Dr. C. Bert

1. Dosimetric verification and Monte-Carlo based simulation of inhomogeneities in treatment planning for interstitial brachytherapy.
2. MR-spectroscopy for absolute thermometry in hyperthermia; Funding: ZIM, partner: Dr. Sennewald GmbH.
3. Evaluation of a fixed-anode computed tomography concept by multiphysical simulations.
4. Development of a treatment plan verification method by electronic portal imaging (EPID).
5. Developments of algorithms for quality assurance of the treatment geometry via onboard imaging devices.
6. Voxel-based modeling of normal tissue complication rates for treatment planning.
7. Scattering of γ Rays from Concrete Walls in Radiation Treatment Facilities.
8. Development and prototyping of an optical patient-positioning-system (TOPOS), Patents: D, EU, US; partner: cybertechnologies GmbH, Ingolstadt.

Radiation Immunobiology

Project managers: PD Dr. U. Gaipl, Dr. B. Frey

The aim of the Radiation Immunobiology Group is to understand the relationship between targeted (classical radiobiology) and non-targeted (immune mediated) abscopal effects of ionising radiation alone and especially in combination with further immune activation and to identify the underlying immune mechanisms.

The following third-party supported projects are currently handled:

1. Modulation of inflammation in inflammatory mouse models and in patients with inflammatory diseases after therapy with low dose of ionising radiation (LDRT) or exposition to radon; funded by BMBF, GREWIS network.
2. Modulation of inflammation by low and moderate dose of ionising radiation; ModInIr; funded by EU, DoReMi network of excellence.
3. Determination of immune and tumor markers in sera of tumor patients; funded by BMBF, Leading Edge Cluster m4 personalized medicine.
4. Role of interaction of therapy induced dead tumor cells with dendritic cells for the induction of tumor immunity; funded by DFG, GK 1660.
5. Induction of anti-tumor immunity by ionising radiation in combination with the adjuvant AnnexinA5; funded by DFG.
6. Analyses of surface changes of cells after low dose radiation that are relevant for phagocytosis within inflammatory reactions; funded by Doktor Robert-Pfleger Foundation.

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 Erlangen-EMN (CCC). In these lectures, tumors from different organs are considered from different perspectives (surgery, chemotherapy, pathology, epidemiology, medical imaging, radiooncology) or an interdisciplinary discussion revolving around defined tumor settings is held. In the context of this course, a database is being generated that will allow students to familiarize themselves with the interdisciplinary approach by doing clinical case studies. A course in radiation protection including practical teaching sessions for students that is recognized by the BLAEK is held semi-annually. For students doing practical clinical work in their pre-registration year, a complementary teaching program is offered. A new teaching course "prevention, diagnostics, therapy, and after-care of cancer" was offered to the students of the Medical Process Management Masters Degree program. Furthermore, lectures and seminars dealing with problems of tumor immunology are offered. The practical and theoretical training of Bachelor and Master students takes place within the basic training "Infections Immunology" and the specialization module "Immunobiology". Lab rotations are offered for fast track students of GK 1660.

Selected Publications

Brockmann S, Grummich P, Ganslandt O, Fietkau R, Semrau S (2011) Reorganization of functional areas of the brain after brain irradiation. J Clin Oncol, 29: e321-3

Schildkopf P, Frey B, Ott OJ, Rubner Y, Multhoff G, Sauer R, Fietkau R, Gaipl US (2011) Radiation combined with hyperthermia induces HSP70-dependent maturation of dendritic cells and release of pro-inflammatory cytokines by dendritic cells and macrophages. Radiother Oncol, 101: 109-15

Frey B, Stache C, Rubner Y, Werthmöller N, Schulz K, Sieber R, Semrau S, Rödel F, Fietkau R, Gaipl US (2012) Combined treatment of human colorectal tumor cell lines with chemotherapeutic agents and ionizing irradiation can in vitro induce tumor cell death forms with immunogenic potential. J Immunotoxicol, 9: 301-13

Lettmaier S, Lotter M, Kreppner S, Strnad A, Fietkau R, Strnad V (2012) Long term results of a prospective dose escalation phase-II trial: interstitial pulsed-dose-rate brachytherapy as boost for intermediate- and high-risk prostate cancer. Radiother Oncol, 104: 181-6

International Cooperations

For further information, please visit our homepage: http://www.strahlenklinik.uk-erlangen.de

Meetings and International Training Courses

08.-09.04.2011: Grundlagen der Brachytherapie - Interventionelle Radioonkologie, Erlangen

15.-17.09.2011: 14. Interdisziplinäres Symposium, Rothenburg

07.-10.06.2012: 18. Jahrestagung der Deutschen Gesellschaft für Radioonkologie "Qualität schafft Sicherheit", Wiesbaden

09.-10.11.2012: Interdisziplinäre Behandlung, Mammakarzinom, Oligometastasierung, Palliative Radiotherapiekonzepte, Erlangen

12.-13.12.2012: 4D Treatment Planning Workshop 2012, Erlangen

Department of Surgery

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Research Focus

- Evaluation of prognosis of gastrointestinal tumors
- Randomized trials for gastrointestinal tumors
- Anorectal dysfunction
- Sensitive Polyprobe-method for improved prediction of therapy response and determination of prognosis in patients with colorectal carcinoma
- Molecular mechanisms of inflammatory related angiogenesis
- Molecular mechanisms of infection related angiogenesis

Structure of the Department

Research activities are structured into clinical research (clinical trials, clinical diagnosis, and therapy research) and fundamental molecular research (molecular mechanisms of angiogenesis and tumor diagnostic). The clinical trials of the Department of Surgery are largely supervised by the Clinical Trials Office (CCS; see own report) which efficiently initiates and monitors the clinical trials. Since then, numerous trials aiming at improving cancer therapy and surgical techniques and also at establishing new surgical approaches have been conducted. The fundamental molecular research has been conducted at the Division of Molecular and Experimental Surgery (AMEC; head: Prof. Dr. M. Stürzl) which was also founded in 2003. The main focus of AMEC´s research is molecular oncology with particular focus on novel markers of prognosis and the molecular regulation of inflammation-associated angiogenesis in malignant and infectious diseases. In the reported period, the Department consisted of twelve scientific researchers (four post-doctorates, eight postgraduates). Over 80% of funding came from grants from DFG, EU, BMBF, German Cancer Aid, IZKF, and ELAN-awards from the UK Erlangen for equal opportunity for women. The division is heading the colorectal carcinoma research group within the framework of the BMBF-core program for molecular diagnostics. Subprojects are embedded in cooperative research programs of the DFG, including the core program 1130 "Infection of the endothelium", the GK 1071 "Viruses of the immune system", the clinical research group 257 „Moleculare pathogenesis and optimized therapy of chronic inflammatory bowel dieseases", and the SFB 796 "Reprogramming of host cells by microbial effectors". The results of our research ultimately generated revenue following the issuing of a licence for an ELISA by two companies in the USA (Genway Biotech, Quest Diagnostics).

Research

Evaluation of prognosis of gastrointestinal tumors

Project managers: Prof. Dr. Dr. h.c. W. Hohenberger, Prof. Dr. S. Merkel

Since 1978, a Clinical Cancer Registry has been prospectively maintained for organ specific tumor documentation. At present, more than 27,000 patients are registered. The main focus is on colorectal cancer with over 11,500 documented cases. Patients are followed for life with only 1% of patients lost to follow-up. The scientific evaluation of this data focuses on health services research, quality management, the improvement of tumor classification, the identification of prognostic factors, the definition of quality indicators, and quality of life research. The documentation of specific diagnostics and multimodal treatment strategies in many patients results from an interdisciplinary cooperation of clinicians and scientists of numerous medical departments of the UK Erlangen.

Randomized trials for gastrointestinal tumors

Project managers: Prof. Dr. Dr. h.c. W. Hohenberger, Dr. H. Golcher, Dr. K. Öckl, Prof. Dr. J. Göhl

The Department of Surgery respectively the interdisciplinary Colorectal Cancer Centre/Modul Pancreas cancer took part in different multicenter trials about gastrointestinal tumors, inter alia "Comparison of colon-pouch versus side-to-side anastomosis respectively function and quality of life in rectal carcinoma patients", PANTER-study (perioperative chemotherapy for liver metastases in colorectal carcinoma), COMBATAC-study (HIPEC for peritoneal carcinomatosis in colorectal carcinoma), HERFLOT/NEOFLOT (perioperative chemotherapy for gastric cancer). Patients were screened during the interdisciplinary tumorboard for gastrointestinal tumors, assigned to the studies and further attended by the study team (e.g. timely sending of quality of life questionnaires). The trial "Neoadjuvant chemoradiation in resectable pancreatic cancer" was evaluated. The trial "Evaluation of lymphnode dissection for micrometastasis in sentinel node biopsy in malignant melanoma" was performed together with the Department of Dermatology.

Anorectal dysfunction

Project manager: Prof. Dr. K. Matzel

In 1994, the world's first sacral nerve stimulator for treatment of fecal incontinence was implanted at this Department. Since then, the method has been continuously improved. Our patients are participating in an extensive post-operative review program which for the first time allows to document long term follow-up and the sustainability of the therapeutic effects. We repeatedly run workshops on a national and international level which are dedicated to conveying innovative therapeutic methods and initiating international cooperation. Various international studies for the development and evaluation of new treatment procedures for anorectal dysfunction (e.g. constipation and incontinence), e.g. the NASHA/Dx study, have been developed and conducted.

Sensitive Polyprobe-method for improved prediction of therapy response and determination of prognosis in patients with colorectal carcinoma

Project managers: Prof. Dr. M. Stürzl, Prof. Dr. R. Croner

The Polyprobe study is a multicentric interdisciplinary approach of the Medical Centers Erlangen and Frankfurt in cooperation with the industrial partner Siemens Healthcare Diagnostics GmbH. It is the goal of the study to provide new biomarkers for the initiation of combination therapy in the treatment of colorectal carcinoma. 650 patients will be recruited in the study (presently 450 patients are included). The specific target of the Polyprobe

project is the validation of 60 previously identified biomarkers at the mRNA level in order to predict tumor stage, survival, and response to chemo- and radiotherapy of the individual patients (predictive and prognostic molecular diagnosis, prospective diagnostics study). In this framework, a novel technical platform is used which allows automated extraction of RNA from formalin-fixed paraffin-embedded tissue (FFPE). The commercial exploitation of the validated markers will be addressed together with Siemens.

Molecular mechanisms of inflammatory related angiogenesis

Project manager: Prof. Dr. M. Stürzl

In previous studies, the group succeeded in identifying the large GTPase guanylate binding protein-1 (GBP-1) as a central regulator of inflammation-associated angiostasis. It could be shown that GBP-1 can inhibit epithelial cell proliferation via inhibition of β-catenin/TCF-signal pathways which might be of high relevance for the pathogenesis of colorectal carcinoma. In addition, it could be shown that GBP-1 acts as a tumor suppressor protein in colorectal carcinoma cell lines which may be of relevance for immune evasion in colorectal carcinoma. Moreover, an important role of GBP-1 in chronic inflammatory diseases could be substantiated. In this framework, it could be shown that GBP-1 levels are increased in tissues and serum of patients with autoimmune diseases, including lupus erythematosus, systemic sclerosis, and rheumatoid arthritis. The observed increased levels of GBP-1 were associated with vascular defects in accordance with the biologic function of GBP-1.

Molecular mechanisms of infection related angiogenesis

Project manager: Prof. Dr. M. Stürzl

The research on infection-associated angiogenesis focuses on the pathogenesis of AIDS-associated Kaposi's sarcoma (KS), a tumor of endothelial cell origin which is etiologically connected with Kaposi's sarcoma-associated herpes virus (KSHV). In the research period to be reported about, it was systematically analyzed which of the 86 gene products of KSHV are targeted by the regulatory post-translational modification O-GlycNAcylation. It could be shown that predominantly regulatory proteins involved in virus replication are targeted by this modification in infected cells. Moreover, experimentally induced O-GlycNAcylation was found to be associated with inhibition of virus production in infected cells. This suggests that O-GlycNAcylation mediates metabolic effects in KSHV virus replication. In cooperation with the Institute of Clinical and Molecular Virology, ephrin A2 was identified as a cellular receptor of KSHV. Moreover, in the framework of routinely applied quality control analyses, our laboratory could show that the worldwide commonly used model cell line for KS (SLK) is not derived from KS, but is instead a contamination of a renal cell carcinoma cell line. This clearly demonstrates the importance of routinely applied safe quality control analyses in the framework of translationally oriented research work.

Teaching

In the context of the main course, live broadcasts of operations into the lecture hall are arranged for visualization. Moreover, a bed side teaching is included in the internships. To further deepen the acquired knowledge from the main course, we run among other measures intensive preparatory classes. In order to gain a realistic perspective of the clinical routine, small supervised groups are allowed to visit the operating room and the intensive care unit. The Division of Molecular and Experimental Surgery offered during the period under report in total 18 different teaching courses. Among these, a two-week cell biological ground course and a scientific project developing seminar were conducted in the study course molecular medicine. Additional alternating exchange of basic researchers and medical scientists is meant to improve translational research.

Selected Publications

Mulsow J, Merkel S, Hohenberger W (2011) Right colonic transposition technique for pelvic anastomosis. Dis Colon Rectum, 54: e245

Langheinrich MC, Schellerer V, Perrakis A, Lohmüller C, Schildberg C, Naschberger E, Stürzl M, Hohenberger W, Croner RS (2012) Molecular mechanisms of lymphatic metastasis in solid tumors of the gastrointestinal tract. Int J Clin Exp Pathol, 5: 614-23

West NP, Kobayashi H, Takahashi K, Perrakis A, Weber K, Hohenberger W, Sugihara K, Quirke P (2012) Understanding optimal colonic cancer surgery: comparison of Japanese D3 resection and European complete mesocolic excision with central vascular ligation. J Clin Oncol, 30: 1763-9

International Cooperations

Prof. S. Laurberg, Department of Surgery, University of Aarhus, Aarhus: Denmark

Prof. Dr. M. Gariglio, University of Piemonte Orientale, Novara: Italy

Prof. Dr. S. Indraccolo, University of Padova, Padova: Italy

Prof. T. Holm, Colorectal Surgical Unit, Karolinska Institutet, Solna, Stockholm: Sweden

Prof. Dr. M. Heikenwälder, Institut für Neuropathologie, Universitätshospital Zürich, Zurich: Switzerland

Prof. P. Quirke, Institute of molecular medicine and pathology, Leeds: UK

Prof. Dr. D. Ganem, Novartis Institutes for Biochemical Research, St Emeryville: USA

Prof. Dr. A. Nusrath, Emory University School of Medicine, Atlanta: USA

Meetings and International Training Courses

23.-24.05.2011: 6th Advanced Course in Colorectal Cancer Surgery, Erlangen

16.-17.06.2011: Interstim Neuromodulation Academy Colorectal Surgeons & Urologists, Fundamental Training, Erlangen

18.10.2011: Das kolorektale Karzinom - Interdisziplinäre Behandlung in onkologischen Darmzentren, Erlangen

03.12.2011: Arzt-Patienten-Seminar zu Lebertransplantation, Erlangen

21.-22.05.2012: 7th Advanced Course in Colorectal Cancer Surgery, Erlangen

Research Equipment

Bio-Rad Laboratories GmbH, VERSARRAY CHIPWRITER PRO

Leica, TCS-SPE

Fuji, FLA 5000

North/east view of the new Surgical Center. Moving in July 2013.

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Division of Pediatric Surgery

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Research Focus

- Chest wall repair and deficiency in wound healing. Creating an algorithm
- Embryonic remnants and appendicitis. Prospective study
- Implementation of sacral nerve stimulation (SNS) in pediatric surgery

Structure of the Department

The Division of Pediatric Surgery is a self-contained division in the Department of Surgery of the UK Erlangen. Facilities are settled down in the Department of Pediatrics and Adolescent Medicine (Prof. Dr. Dr. h.c. W. Rascher) with ward CK 4 and the Department of Surgery with ward U2, closely connected to the Department of Urology (Prof. Dr. B. Wullich).
There is also a membership in the expert-network of the Perinatal Center of Franconia, located at the Department of Obstetrics and Gynecology (Prof. Dr. M.W. Beckmann) and in the Pediatric Operative Center (KIOZ). There is a close connection, including operative cooperation, to the university teaching hospitals in Bamberg (Prof. Dr. K.-H. Deeg), Bayreuth (Prof. Dr. T. Rupprecht), Schweinfurt (Dr. J. Herrmann) and Fürth/B. (Prof. Dr. J. Klinge).
The medical spectrum comprises the surgical treatment of congenital malformations, especially in the thoracic, abdominal, skeletal, and integumental areas in newborn and children. Acute and chronical diseases are treated in all age groups in cooperation with the pediatrics. Strongest importance is placed on consistent after-care. Traditionally, excellent expertise is known in minimally invasive surgical treatment of chest deformities (Pectus excavatum et carinatum) and in special techniques to resolve recurrences after chest wall repair. There are outstanding experiences in minimally invasive pediatric surgery (laparoscopy, thoracoscopy, rendez-vous procedures) with high-end tissue management and wide-area indications.

Research

Chest wall repair and deficiency in wound healing. Creating an algorithm

Project manager: Dr. S. Schulz-Drost
Deficiencies in wound healing are present in open chest wall repair (pectus excavatum, pectus carinatum) in up to 10% and represent a severe complication. Healing of cartilage and bone structures is compromised by microbial structures. Materials for reconstruction, e.g. metal bars and locking titanium plates, have to be removed in case of an inflammatory event with the result of a functional and cosmetic loss.
Prospectively, patients with deficiencies in wound healing were treated by a vacuum-instillation therapy (V.A.C. instill). At the first step, hard-coded programmed operative revisions and application of periodic instillation with local antiseptic agents (Polihexanid) are achieved. In primary procedures, a standardized strategy takes place:
1. Debridement and necrosectomy,
2. Rinsing with local antiseptic agents,
3. Setting up an instillation system.
At the second step, the programmed revision with
1. Vacuum-wound dressing with instillation until gaining a two-fold negative microbial result of the specimen. Revisions are accomplished repeatedly from three to five days.
2. Debridement, sampling;
3. If applicable, conventional vacuum wound dressing is accomplished until gaining sterile wound situations and sufficient conditioning of wounds;
4. Downsizing the wound.
In a third step, the final wound closure occurs:
1. Final stabilization of wounds, if applicable in a second procedure;
2. Wound closure with a secondary single knot suture.
Until today, open chest wall repair shows early inflammation after 14-30 days postoperatively. With the aid of instillation of local antiseptic agents, all cases showed sterile wound conditions and preservation of implants. Secondary sutures for wound closure were accomplished after an average of 12.6 days. Conventionally, a prolonged wound healing was evident, the secondary closure took place in average after 52.6 days. The evaluation of functional and cosmetic features showed unsatisfactory results (pain, instability, loosening of implants, secondary procedures) in 82.6%.
The preliminary results show the impact of programmed strategy with gaining sterile conditions with the aid of local antiseptic instilled agents in combination with a vacuum wound dressing (V.A.C.).

Embryonic remnants and appendicitis. Prospective study

Project manager: Prof. Dr. R.T. Carbon
In human development, the gastrointestinal tract has a double-curtain mounting with the mesenteric structures: Along the persistent dorsal mesentery, there is a ventral suspensory which should be regressing in utero. From embryonic pathology, peritoneal ligaments are wellknown, e.g. LADD's ligaments, arising from the transverse colon to the right edge of the peritoneal space or connected to the edge of the liver with consecutive compression of small bowel with relevant effects on gastrointestinal passage. Other ligaments are known from Waldschmidt 1990 and are registered at the ileocaecal pole and, depending on position and latitude, they are responsible for perturbance in gastrointestinal transport.
From 1992 to 2012, 1,552 pediatric laparoscopies (aged 1.5 to 21 years, mean 9.2 years) were performed because of "acute lower abdomen/appendicitis" (982 girls, 570 boys). Each case had an appendicectomy and a peritoneal exploration. There were 54 MECKEL's diverticula, 485 hydatides at the fimbrial stem, 232 cystic ovarian structures, 18 carcinoids at the appendix, and 14 embryonic vessels (A. vitellina dextra et sinistra).
Persistent, ventral mesenteries were evident in variable expressions in 1,223 patients: Coloparietal ligaments were present at the right colon in 1,118 patients, in 84 patients at the colon descendens/sigmoideum, and in 21 patients on both sides. Kinking, warping, compression, and constipation were present in 1,178 patients. At any case, there always existed a phlegmoneous finding or a higher grade of appendix's inflammation. "Appendix bags" were discovered in 144 patients - in that situation at least an ulcero-phlegmoneous appendicitis with perforations was present in 88 patients.
The preliminary overview shows a high significance ($p < 0.001$) of correlation "appendix bag"/perforation, because kinking of the appendix leads to consecutive coprostasis and induces inflammation. In comparison to lapa-

roscopic procedures done for the upper abdomen and/or elective reasons, there are highly significant differences in the existence of embryonic remnants of the ventral mesenteries. Those remnants caused by the vental mesenteries induce higher-grade inflammation at the appendix related to local constipation. No high-frequency or radiologic diagnostic device is able to detect such ligaments, so laparoscopic exploration is the choice for both, diagnosis and therapy.

Implementation of sacral nerve stimulation (SNS) in pediatric surgery

Project manager: Dr. M. Besendörfer

The sacral nerve stimulation (SNS) is a low-frequency (15-25 Hz) electric long-time stimulation of sacral ganglion cells - mostly segment S3. The impact of this principle was founded in urology and is a therapeutic option in neurogenic aconuresis. As a side effect in those studies, anal incontinence and constipation were treated just as well. The side effects put focus on an increase of pressure of the anal sphincteric structures and improvement of colonic movement. So it stands to reason to implement SNS in incontinence, constipation, and colon irritable.

Disorders in fecal evacuation in pediatric patients are mostly dismissed and frequently induce psychiatric treatment. That leads to social isloation and disorders in personal development. Especially in children, a high potential of developmental improvement of ganglion activity is evident. "Learning by test-stimulation" gives rise to a long term improvement of quality of life and implantation of a pacemaker is omitted.

The effect of this method is partly explained by the direct stimulation of efferent nerve filaments. In addition to improvement of direct measurable contractions of the sceletal muscles of the anal sphincter, an improvement of the sensor system and the state of feeling the filling of the rectum is noticed. Furthermore, the increase of the tonus of the internal sphincter is evident. It is the belief that neuromodulation changes the function of afferent sensoric nerve filaments, spinal reflexes, and sympathonic and parasympathonic activity. The main goal of SNS is that success of treatment can be estimated after the minimally invasive testing of stimulation. SNS is administered in three steps:

1. Intraoperative test-stimulation. The sacral foramina are punctured with needles. An electric stimulation is maintained. In case of adequate motor response, a test probe is put into the sacral foramen and is fixed by a patch;
2. External pacemaker: Subchronical phase of stimulation; Evaluation and writing a stool-diary;
3. After successful test-phase, the implantation of an internal pacemaker is to be designed.

Aim of the study: Instruments of application adapted to children. Topographic anatomical studies of sacral anatomy and its changing character depending on age.

Teaching

Pediatric surgery is a self-contained surgical speciality and is presented academically as follows:

1. Curricular in the course of IMPP (general guidelines for medical studies in Germany: general and special pediatric surgery in theory and practice) in individual lectures, partly integrated in main lectures on surgery and pediatrics. Cooperative academic events in the course of technical schools at FAU (pediatric nursing, pediatric intensive care medicine, School for operational and technical assistents, physiotherapy, massage)
2. Interdisciplinary (lecture series "Emergency", seminars, boards)
3. Special (postgraduate/diploma students, practical education in phantom-courses for minimally invasive pediatric surgery in skills lab and hands-on courses). An increasing number of trainees and interns (non-local students, ERASMUS-students, students of cooperative universities) is embedded into the curriculum.

Selected Publications

Agaimy A, Stachel KD, Jüngert J, Radkow T, Carbon R, Metzler M, Holter W (2011) Malignant Epithelioid Peripheral Nerve Sheath Tumor With Prominent Reticular/Microcystic Pattern in a Child: A Low-grade Neoplasm With 18-years Follow-up. Appl Immunohistochem Mol Morphol: DOI 10.1097/PAI.0b013e318224751f

Steinmann C, Krille S, Mueller A, Weber P, Reingruber B, Martin A (2011) Pectus excavatum and pectus carinatum patients suffer from lower quality of life and impaired body image: a control group comparison of psychological characteristics prior to surgical correction. Eur J Cardiothorac Surg, 40: 1138-45

Brecht IB, Agaimy A, Besendörfer M, Carbon R, Thiel FC, Rompel O, Osinski D, Langer T, Metzler M, Holter W (2012) Malignant peritoneal mesothelioma in a 16-year-old girl: presentation of a rare disease. Klin Padiatr, 224: 170-3

Naumann-Bartsch N, Carbon R, Klein P, Agaimy A, Holter W, Jüngert J (2012) An unusual thyroid mass in a 5-year-old girl. J Pediatr, 161: 565

Rüffer A, Webinger J, Glöckler M, Purbojo A, Dittrich S, Cesnjevar RA, Carbon R (2012) Pericardial cyst or teratoma? Change of strategy during mediastinal tumor surgery. Thorac Cardiovasc Surg, 60: 488-90

Weikert E, Kraske S, Schott GE, Wullich B, Hirsch K (2012) Umbilical rotation: A new technique for the cutaneous fixation of continent catheterizable vesicostomies. J Pediatr Urol, 8: 87-91

Meetings and International Training Courses

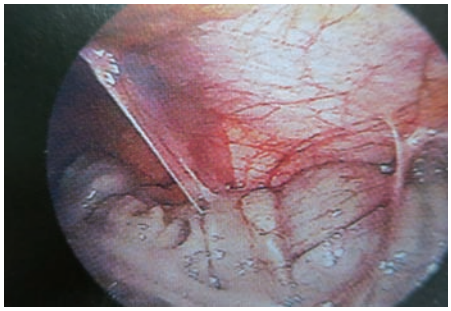
25.07.2012.-27.07.2015: Zystisches Lymphangiom - akutes Abdomen beim Säugling, Regensburg

25.-27.07.2012: Ausgusspräparat des Magens. Rapunzel-Syndrom, Regensburg

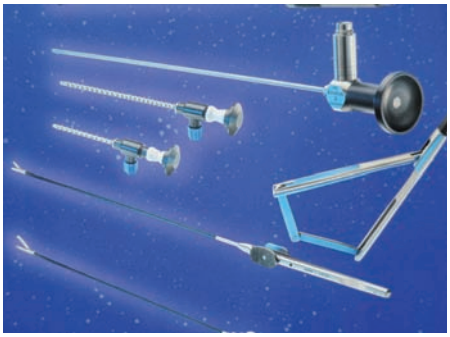
12.-16.09.2012: Bezoar des Magens - Ein Fallbericht, Hamburg

12.-16.09.2012: Mesenteriales Lymphangiom beim Säugling, Hamburg

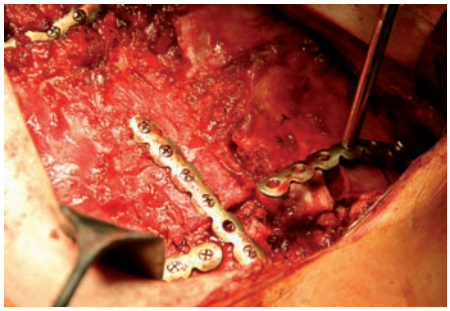
28.-30.11.2012: Stabilizing of the anterior chest wall in recurrent pectus excavatum with sternocostal pseudarthrosis by elastic stable chest repair (ESCR): an innovative fixation device, Dubai, U.A.E.



Fan-like, connective tissue canvas producing warping of the bowel and inducing constipation and inflammation of the appendix.



Prototypes of 1.9 mm-instruments, suitable for pediatric laparoscopy and thoracoscopy.



"Stairway-phenomenon" (sternocostal instability and pseudarthrosis) following open chest wall repair. Implantation of locking-titanium-plates.

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Research Focus

- Surgical therapy of hyperhidrosis - a prospective quality control study
- Surgical management of pulmonary metastases from colorectal cancer
- Deep intrathoracic vacuum therapy for chronic empyema
- Using tracking dogs in early diagnosis for lung cancer
- Imunological and molecular characterization of malignant lung tumors
- Hyperthermic intrathoracic chemotherapy after pleurectomy/decortication in pleural mesothelioma - a phase I study
- Neoadjuvant therapy of locally advanced non-small cell lung carcinoma IIIA; concurrent radiochemotherapy followed by surgery
- Trimodal therapy of malignant mesothelioma
- The value of the systematic extensive lymph node dissection in the operative treatment in non-small cell lung carcinoma

Structure of the Department

The Division of Thoracic Surgery was founded in 2008 and is offering the complete diagnosis and therapy of lung, mediastinal, and chest diseases. Our division is nationwide one of the first academic thoracic surgical divisions. Under the auspices of the head of the Division, Prof. Dr. H. Sirbu, who is Extraordinarius for thoracic surgery, there are working two consultant thoracic surgeons, four residents, and a number of medical students.
In cooperation with the Departments of Medicine 1 and 5, the Department of Radiation Oncology, the Institute of Pathology, the Division of Palliative Medicine, and the Department of Nuclear Medicine, we have founded the Lung Center Erlangen.
Emphasis of our clinical activity concentrates on minimally invasive lung resections (VATS-surgery) and also on interdisciplinary therapy concepts for the advanced lung cancer and other chest diseases. The intensive cooperation with all other oncological field unities and the connection with our Comprehensive Cancer Center (CCC; see ower report) is assuring the best therapy for our patients.
The Division of Thoracic Surgery is actively participating and organizing the activities of the academical study group of the German Society of Thoracic Surgery.

Research

Surgical therapy of hyperhidrosis - a prospective quality control study
Project manager: A. Zdrojek
Videoscopic assisted thoracic sympathectomy is a widely accepted approach in the therapy of palmar and axillary hyperhidrosis. Long term postoperative results are very heterogenous. In this trial, we are analyzing the long term patient satisfaction with a specially designed questionnaire by the Division of Psychosomatics and Psychotherapy.

Surgical management of pulmonary metastases from colorectal cancer
Project managers: Dr. W. Schreiner, Dr. O. Oster
Although resection of solitary lung metastases has been 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.
The Division of Thoracic Surgery is actively organizing and participating in the activities of the academical study group of the German Society of Thoracic Surgery.

Deep intrathoracic vacuum therapy for chronic empyema
Project managers: Dr. W. Schreiner, Dr. O. Oster
Vacuum therapy leads to a significant improvement in the local therapy of infected wounds. The aim of this study is to examine the clinical long and short time results of this therapeutical method in deep infected wounds, e.g. pleural empyema.

Using tracking dogs in early diagnosis for lung cancer
Project managers: Prof. Dr. H. Sirbu, Dr. M. Würfel*, P. Stapel
By using standardized collected breath samplings of patients with lung cancer, tracking dogs of Johanniter Unfallhilfe are trained in different stages to prove how an early detection of lung cancer is possible. The main objective is to provide foundations for a technical gas analysis ("electronic nose") as well as the chemical identification of gas markers with their characteristic ratio in the different stages of cancer.
*Krankenhaus Martha-Maria, Nürnberg

Imunological and molecular characterization of malignant lung tumors
Project managers: Prof. Dr. H. Sirbu, Prof. Dr. S. Finotto, Dr. D. Trufa
The aim of this research project is to investigate immunological and molecular basis. The focus within this project are the malignancies that become visible in the lung, especially non-small cell lung cancer (NSCLC). These parameters are then correlated with the clinical findings.
Before the surgery, the clinical data (age, height, weight, sex, nutritional status, smoking and occupational history, family history, etc.) are acquired. After the surgery, some samples from resected lung tissue and from removed lymph nodes are analyzed in the laboratory.
From the single cell suspension, various cell subpopulations, such as isolated CD4 + or CD8 + T cells, are taken in culture. The cultured cells are then analyzed in different ways (e.g. FACS analysis, ELISA, PCR, etc.). RNA and DNA are isolated, too, which can then be used for epigenetic studies, microarray analysis, and RNA expression analysis. Finally, the proteins can be isolated and analyzed.

Hyperthermic intrathoracic chemotherapy after pleurectomy/decortication in pleural mesothelioma - a phase I study
Project managers: Dr. W. Schreiner, M. Hanika
The end point of this prospective trial is the survival and the disease free interval through the combination of the intrathoracic hyperthermic cisplatin with pleurectomy/decortication in patients with stage I pleural mesothelioma. Through radical pleurectomy/decortication,

an operative tumor reduction is possible. This cytoreduction is improving the efficacy of the intrathoracic chemotherapy. The combination of the intrathoracic perfusion with cisplatin and hyperthermia is improving the needed cytotoxic effect locally. This trial is including patients with advanced age and co-morbidity, resectable mesothelioma masses without lymph node metastasis.

Neoadjuvant therapy of locally advanced non-small cell lung carcinoma IIIA; concurrent radiochemotherapy followed by surgery

Project managers: Prof. Dr. H. Sirbu, Prof. Dr. R. Fietkau

In this trial, we compare the therapy concept of neoadjuvant radiochemotherapy (45Gy/ Cisplatin, Etoposide), followed by surgery with the concept of definitive radiochemotherapy in patients with locally advanced, non-small cell lung carcinoma stadium IIIA.

Trimodal therapy of malignant mesothelioma

Project managers: Dr. W. Schreiner, M. Hanika

The trial is including patients in good clinical condition, younger than 60 years without significant co-morbidity, a resectable tumor mass, and without lymph node involvement. After neo-adjuvant chemotherapy, extended operative tumor resection (pleuropneumectomy with pericardectomy and resection of diaphragma) is performed. Postoperatively, the radiotherapy of the hemithorax is added. The end point of the study is the survival and the disease free interval.

The value of the systematic extensive lymph node dissection in the operative treatment in non-small cell lung carcinoma

Project manager: Dr. W. Schreiner

The purpose of the study is the investigation of the extensive lymph node dissection under consideration of the lymphatic metastasis pathways and the improvement of the lymph node staging. In this study, we have included about 500 patients over a 20 years period.

Teaching

University teaching was completed with the establishment of a professorship for thoracic surgery at the Chair of Surgery. We offer a wide thoracic surgical teaching during the main lectures, the lecture of emergency organized by the Chair of Anesthesiology, and/or lectures during hands-on training.

For advanced students, we additionally offer practical patient bases exercises on thoracic diseases in practical training.

Selected Publications

Fuchs P, Schreiner W, Wolter TP, Autschbach R, Sirbu H, Pallua N (2011) A four-muscle-flap for thoracomyoplasty in patients with sacrificed thoracodorsal vessels. J Plast Reconstr Aesthet Surg, 64: 335-8

Scholz GA, Sirbu H, Semrau S, Anders K, Mackensen A, Spriewald BM (2011) Persisting right-sided chylothorax in a patient with chronic lymphocytic leukemia: a case report. J Med Case Reports, 5: 492

Spillner J, Amerini A, Hatam N, Rex S, Pott F, Goetzenich A, Menon A, Repas T, Steiner F, Autschbach R, Carpi A, Oster O (2011) Pulmono-atrial shunt and lung assist to treat right ventricular failure. Front Biosci, 16: 2342-51

Schmidt J, Irouschek A, Heinrich S, Oster O, Klein P, Birkholz T (2012) Recurrent Laryngeal Nerve Monitoring during Esophagectomy and Mediastinal Lymph Node Dissection: A Novel Approach Using a Single-lumen Endotracheal EMG Tube and the EZ-blocker. World J Surg, 36: 2946-7

Schreiner W, Oster O, Stapel P, Sirbu H (2013) V. A. C. INSTILL® therapy - new option in septic thoracic surgery. Zentralbl Chir, 138: 117-20

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

Meetings and International Training Courses

26.03.2011: 2. Workshop "Arbeitsgemeinschaft Universitäre Thoraxchirurgie" der Deutschen Gesellschaft für Thoraxchirurgie, Erlangen

16.11.2011: Erlanger Thorax-Kolloquien: Aktuelle Aspekte in der Äthiologie und Behandlung des Pleuraempyems, Erlangen

29.02.2012: Erlanger Thorax-Kolloquien: Der Pneumothorax, Erlangen

18.07.2012: Erlanger Thorax-Kolloquien: Die Thorakoskopie, Erlangen

LASER asissted thoracic surgical procedure

Department of Surgery

Division of Transfusion Medicine and Hemostaseology

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Research Focus

- Preparation and characterization of white cell-poor platelet concentrates by apheresis
- Collection of monocytes for the generation of dendritic cells (DC)
- Preparation of dry platelet concentrates and platelet storage in additive solutions
- Clinical research related to hemostaseology
- Clinical research related to hemotherapy
- Mesenchymal stromal cells (MSC)
- Optimization of collection procedures to get regulatory T cells (Tregs)
- Legislation of transfusion
- Platelet-derived growth factors for wound healing and angiogenesis

Structure of the Department

The Division of Transfusion Medicine and Hemostaseology is located at the Department of Surgery of the UK Erlangen. The head of the Division is Extraordinarius for Transfusion Medicine and Hemostaseology.
The Division produces pharmaceutical products from blood and has a widespread manufacturing permit from the local and the federal authorities.
The division offers all laboratory methods in the fields of immunohematology and hemostaseology, organizes the depots of blood preservations and plasma derivates for the treatment of coagulation disorders and the cord blood and stem cell bank of the UK Erlangen.
The quality management system of the Division has been certified according to the DIN EN ISO 9001:2008 standard. Laboratories of the Division have been accredited by the European Federation for Immunogenetics (EFI) and according to the DIN EN ISO 15189 standard by the DAkkS.

Research

Preparation and characterization of white cell-poor platelet concentrates by apheresis

Project managers: PD Dr. J. Zingsem, Prof. Dr. J. Ringwald
Platelet apheresis processing large blood volumes to produce platelet-rich plasma has become a standard procedure. A major research focus is the preparation of extremely white cell-poor platelet concentrates making additional filtration unnecessary. Apheresis procedures were developed for producing concentrates with standardized platelet content, but containing almost no residual white cells. Another research interest is the evaluation of quality control-procedures detecting very low white cell-contaminations of cellular blood components. Additionally, the influence of different blood bags and of component volumes on the quality of stored platelets is examined.

Collection of monocytes for the generation of dendritic cells (DC)

Project manager: Prof. Dr. E. Strasser
Circulating monocytes are precursors of DC which play a key role in the immune system's function by presenting antigens to specific lymphocytes. The collection and cultivation of these cells enables the development of new strategies in the treatment of malignant diseases. Members of the Division of Transfusion Medicine and Hemostaseology cooperate with colleagues from the Department of Dermatology to adjust the collection procedures optimally to the specific clinical and experimental demands of procedures aimed at the cultivation, expansion, and priming of DC.

Preparation of dry platelet concentrates and platelet storage in additive solutions

Project manager: Prof. Dr. J. Ringwald
The preparation of platelet (PLT) concentrates in additive solutions attracts growing attention since there is the possibility to inactivate pathogens that contaminate cellular blood components. Such inactivation procedures presuppose the reduction of the plasma portion in platelet concentrates. Clinically, the reduction of the plasma portion in PLT components may reduce the frequency of adverse reactions, e.g. of allergic reactions. The resuspension of PLT in additive solutions requires the production of "dry platelets" - concentrates containing more than 3000 x 10e+3 per myl. For this purpose, we performed several series of PLT preparations using the TRIMA separator by Caridian. PLT concentrates in the additive solutions PAS II, PAS III, and PAS III M were compared with each other and with platelets in plasma by analyses of the in vitro quality of fresh and stored PLT concentrates.

Clinical research related to hemostaseology

Project managers: Prof. Dr. J. Ringwald, Prof. Dr. E. Strasser
Other research interests include thrombophilia, traveller's thrombosis, and hemostasis dysfunctions resulting in bleeding disorders. Other current study objectives are preanalytical determinants of fibrinolysis tests, hemostasis tests in systemic lupus erythematodes, and other currently relevant topics.

Clinical research related to hemotherapy

Project managers: Prof. Dr. V. Weisbach, Prof. Dr. R. Zimmermann, Prof. Dr. J. Ringwald, Prof. Dr. E. Strasser
Other research interests are the examination of antibodies against red cell antigens, the characterization of factors influencing the quality of stored red cell concentrates, and complex dysfunctions of the coagulation system.

Mesenchymal stromal cells (MSC)

Project managers: Prof. Dr. V. Weisbach, Dr. C. Klein
Mesenchymal stromal cells (MSC) are the predecessors of osteoblasts, chondrocytes, and adipocytes. The term "MSC" especially covers cells cultivated and expanded ex vivo. These cells are a mixture of stem and progenitor cells up to mature stroma cells and are named MSC according to a definition of the International Society of Cellular Therapy. It is excpected that MSC will play a major role in future applications of regenerative medicine. The main focus of the working group is the preparation, characterization, and expansion of MSC especially from placentar tissues.

Optimization of collection procedures to get regulatory T cells (Tregs)

Project managers: Prof. Dr. E. Strasser, Dr. J. Strobel
T cells play an important role in adoptive immune response in many diseases (infectious and inflammatory diseases, tumors). DC act as antigen presenting cells for specific T cells activation. The collection of circulating T cells as well as the culture and expansion of T cells,

especially regulatory T cells (Tregs), enables the development of new strategies for the anti-inflammatory and immunosuppressive therapies. Members of the Division of Transfusion Medicine and Hemostaseology cooperate with colleagues from the Departments of Medicine 1, Dermatology, and Medicine 5 of the UK Erlangen to optimally adjust the collection procedures to the specific clinical and experimental demands of procedures aimed at the cultivation and expansion of Tregs. In the context of cell preparation, analysis of factors responsible for cell damage (cell apoptosis and necrosis) is relevant to optimize the quality of leukocyte products.

Legislation of transfusion

Project manager: Prof. Dr. R. Zimmermann

Under the auspices of the Legal Counsel and Deputy Commercial 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. The focus of the results is the book "Transfusion Law" that has been published by the "Wissenschaftliche Verlagsgesellschaft Stuttgart". The book has become the benchmark in this field of law and has found its way into the jurisdiction of the German Federal High Court of Justice. Alongside, book contributions and articles on different aspects of the legislation and law of blood transfusion are published.

Platelet-derived growth factors for wound healing and angiogenesis

Project manager: Prof. Dr. R. Zimmermann

Platelets contain growth factors which stimulate wound healing, angiogenesis, and possibly bone repair. Thus, these cells do not only initiate coagulation at sites of injury, but induce the processes of healing, too. Possible clinical application of these findings is the local application of concentrated platelets as a source of growth factors for wound healing and bone repair. Additionally, the phenomenon of growth factor release from activated platelets to plasma during procedures with extracorporeal circulation is a focus of research.

Teaching

The Division offers lectures, seminars, and practical hands-on training for students:

- Participation in the principal subject "Laboratory diagnostics" of the German regulation on education in medicine;
- Participation in the practical training course in surgery;
- Further lectures, seminars, and practical trainings according to the university calendar;
- Regular seminars for the Bavarian Medical Council;
- Teaching at the school for assistant medical technicians;
- Teaching for assistant medical technicians and nurses.

Selected Publications

Strasser EF, Weidinger T, Weiss DR, Strobel J, Zimmermann R, Eckstein R (2011) Storage induced apoptosis of peripheral blood mononuclear cells obtained from leucoreduction system chambers. Vox Sang, 101: 106-11

Hauck-Dlimi B, Hammon K, Eckstein R, Ott S, Zimmermann R, Dengler T, Ringwald J (2012) Human platelet antigen genotypes in Turkish and Caucasian blood donors in Germany. Tissue Antigens, 80: 214-8

Ringwald J, Tully S, Geier C, Hauck B, Weiss D, Callaert M, Eckstein R (2012) Effects of immediate or delayed addition of platelet additive solution on the in vitro quality of apheresis platelets. Transfusion, 52: 1237-44

Strobel J, Jörns H, Weisbach V, Ganslandt T, Zimmermann R, Eckstein R (2012) Audit on the usage of plasma derived/recombinant coagulation factor concentrates at a German university hospital. Vox Sang, 103: 122-9

Weiss DR, Eiche C, Hupke C, Schellerer VS, Keller AK, Strasser EF, Ringwald J, Zimmermann R, Eckstein R (2012) The structure of the von Willebrand factor is not altered in patients with colorectal carcinoma. Colorectal Dis, 14: 1500-6

Zimmermann R, Weiss DR, Zingsem J, Ringwald J, Eckstein R (2012) Pooled platelet concentrates and the quality of the red blood cell supply. Clin Lab, 58: 1-6

International Cooperations

Prof. Dr. J. Ringwald, BEST group, International Society of Blood Transfusion (ISBT), Amsterdam: The Netherlands

Meetings and International Training Courses

18.-19.11.2011: Fortbildungsveranstaltung der Bayerischen Landesärztekammer "Qualifikation als Transfusionsverantwortlicher/Transfusionsbeauftragter", Erlangen

09.-10.11.2012: Fortbildungsveranstaltung der Bayerischen Landesärztekammer "Qualifikation als Transfusionsverantwortlicher/ Transfusionsbeauftragter", Erlangen

Stem cell isolation in the GMP laboratory

Department of Surgery

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Research Focus

- Development and validation of a ceramic total knee endoprothesis
- Analysis of soft tissue trauma following surgical care of spine injury
- Mechanisms for the stabilization of the chondrocyte phenotype
- „Molecular" magnetic resonance (MR) imaging of cartilage and joint structures
- Gait and motion analysis
- Biochemical evaluation of cartilage properties in the knee joints of young athletes

Structure of the Department

The Division of Trauma Surgery employs 15 physicians. Beside patient care, clinical and experimental research work is performed together with ten doctoral candidates, one post-doctoral scientist, and two technicians.
The different research groups work on the evaluation and development of novel innovative surgical methods and implants for joint replacement and treatment of skeletal lesions. Furthermore, the research focuses on basic mechanisms of cartilage and bone biology which provides the basis for the development of regenerative strategies for the musculoskeletal system. This also includes imaging and functional non-invasive methods for the analysis of musculoskeletal tissues.
The central research projects are supported by approved fundings, including the DFG, Bayerische Forschungsstiftung, and ELAN.
Besides the clinical and experimental research projects, the Division of Trauma Surgery is closely integrated in the "Trauma Network" and is actively involved in its further development. The aim of this network is the improvement of the nationwide quality of medical care of severly injured patients by improved communication, better coordinated standards of medical care, and quality-based cooperation.

Research

Development and validation of a ceramic total knee endoprothesis

Project managers: Prof. Dr. F. Hennig, Dr. A Mauerer, Dr. M. Blanke, Dr. A. Olk
This interdisciplinary project focuses on the development and validation of a novel total ceramic knee endoprothesis. Long-term load capacity and the biomechanical properties are analyzed under experimental conditions. In these experiments, the total ceramic endoprothesis could meet the standards of established metal endoprotheses. Under long-term loading (alternating load test), the ceramic components withstood 30 million load changes und displayed high reserves in the mechanical strength which exceeded by far the required safety norms. These results demonstrated the applicability of this ceramic material for the broad clinical use.
Further experiments focus on the analysis of the formation of biofilm on the surface of different materials, such as CoCr and Biolox (ceramic). This work is based on microbiological, semiquantitative, and qualitative electronical microscopy methods. The aim is the establishment and evaluation of antiseptic surfaces which are appropriate for endoprotheses.

Analysis of soft tissue trauma following surgical care of spine injury

Project managers: Dr. A. Mauerer, N. Renner, Dr. O. Fuchs
This project investigates if minimally invasive operative treatment of spine injuries will induce less soft tissue trauma than treatment by conventional open surgery. Soft tissue trauma is monitored by the peri- and postoperative monitoring of a set of laboratory parameters, including a broad spectrum of established and potential markers, such as certain muscle enzymes, cytokines, or acute phase proteins. For their validation, these laboratory markers are correlated with clinical scores in the further postoperative clinical course. Besides evaluation of the different surgical strategies, this study aims at the establishment of novel specific marker molecules for soft tissue trauma.

Mechanisms for the stabilization of the chondrocyte phenotype

Project manager: PD Dr. K. Gelse
This project focuses on the mechanisms that induce chondrogenesis and stabilize the unique phenotype of articular chondrocytes. The identification of these mechanisms is finally of central importance for the success of cartilage repair strategies and therapy of osteoarthritis. In a project funded by the DFG, we investigated if the factors Chondromodulin-I (Chm-I) and Thrombospondin-1 (TSP-1) mediate a stabilizing effect on the chondrocyte phenotype. Both factors exerted a strong anti-angiogenic effect in vitro and could prevent inadvertent excessive endochondral ossification in cartilage defects in a cartilage repair model. Both factors efficiently inhibited the terminal chondrocyte differentiation and thus contributed to the stability of the permanent phenotype of articular chondrocytes. Gene expression studies indicated that the observed effects may be mediated by the cell cycle inhibitor p21cip/waf or by inhibition of the expression of GADD45ß. Overexpression of Chm-I did not only efficiently stabilize the chondrocyte phenotype, but was also able to induce chondrogenic differentiation.
Further gene expression analyses (cDNA arrays) demonstrated that a number of inhibitory factors, such as the BMP-inhibitor Grem-1 or FRZB1 and WISP3, are significantly higher expressed in permanent articular cartilage as compared to the transient type of cartilage (e.g. osteophyte cartilage). These observations imply that the generation of hyaline repair cartilage does not solely rely on chondrogenic growth factors, but also on inhibitory-acting factors which may particularly be of immanent importance to prevent inadvertent ossification of repair cartilage tissue. Thus, in future therapeutic settings, it would be useful to load bioactive matrices with a cocktail of specific stimulatory and inhibitory factors for the generation of hyaline repair cartilage and for the inhibition of excessive ossification.

"Molecular" magnetic resonance (MR) imaging of cartilage and joint structures

Project managers: PD Dr. G. Welsch, Dr. M. Pachowsky, PD Dr. K. Gelse
This research project of musculoskeletal magnetic resonance imaging is performed in cooperation with the MR Center of the Department of Radiology of the Medical University of Vien-

na and particularly focuses on the evaluation of articular cartilage (repair tissues and osteoarthritis) as well as other joint tissues, such as meniscus and cruciate ligament.
Goal of the present DFG and Austrian Science Fund (FWF) grant is to validate novel biochemical MR-techniques, such as dGEMRIC, T2 mapping, 23Na(sodium) imaging, T2* mapping, T2d mapping, ultra-short echo-time (UTE) imaging, magnetization transfer contrast (MTC), diffusion-weighted imaging (DWI), and T1ρ by conventional histomorphology and ultra high-field MR-microscopy using two established animal models and to implement the findings into clinical MR-follow-up protocols. In experimental models, healthy articular cartilage was either compared with degenerated articular cartilage or with cartilage repair tissues induced by the microfracture technique or autologous chondrocyte transplantation. Additionally, biochemical MR methods will be used to assess the associated joint structures, including the menisci and anterior cruciate ligament, in a multi-parametric approach.
The aim is to non-invasively attain detailed information on the composition of articular cartilage that closely correlates with histology. Thus, modern MR-imaging is supposed to acquire a high diagnostic predictive value for the analysis of cartilage tissue.
So far, "molecular" MR-imaging allowed adequate characterization of the ultrastructure of cartilage and cartilaginous repair tissue with visualization of the content of proteoglycans, the alignment of collagen fibres, the hydration status of cartilage as well as remodeling processes of repair tissues.
Ongoing studies will assess the correlation to clinical parameters after cartilage therapies with the goal to get a high predictive value reflecting the potential long-term benefit even after a short term follow-up time period.

Gait and motion analysis

Project managers: Prof. Dr. F. Hennig, Dr. M. Blanke, Dr. S. Krinner, PD Dr. G. Welsch
The aim of this research group is to identify the biomechanical forces that interact with the human musculoskeletal system of athletes and patients with endoprotheses. Dynamic forces are not only associated with high strain for the musculoskeletal system, but also set requirements for components of endoprotheses. The biomechanical analysis of these dynamic strains and their integration into proper situations provide the opportunity to increase the safety of endoprotheses and to avoid injury and overuse.

Biochemical evaluation of cartilage properties in the knee joints of young athletes

Project manager: PD Dr. G. Welsch
The aim of this study is to assess the biomechanical behavior of knee cartilage together with clinical scoring and gait analysis. In this prospective and longitudinal study, asymptomatic young professional athletes were enclosed. The knee joints were clinically assessed as well as 3-Tesla-MRI was performed based on biochemical and biomechanical MRI-applications. Measurements also included loading and unloading as well as gait analyses. The results will be implemented in the orthopedic medical care and individual training methods of these young athletes. Furthermore, senso-motoric training is performed with the goal of reducing injuries and helping to prevent early degenerative problems.

Teaching

The comprehensive education comprises the traditional main lecture and the curricular practical courses and additional integrated practical seminars, such as sewing courses and implant workshops, as well as colloquia focusing on interdisciplinary subjects. Interactive courses are also provided as an intensive training for final exams. Furthermore, the division offers the opportunity to participate in clinical rounds and observe in emergency wards and operation rooms.

Selected Publications

Gelse K, Klinger P, Koch M, Surmann-Schmitt C, von der Mark K, Swoboda B, Hennig FF, Gusinde J (2011) Thrombospondin-1 prevents excessive ossification in cartilage repair tissue induced by osteogenic protein-1. Tissue Eng Part A, 17: 2101-12

Klinger P, Surmann-Schmitt C, Brem M, Swoboda B, Distler J, Carl HD, von der Mark K, Hennig FF, Gelse K (2011) Chondromodulin 1 stabilizes the chondrocyte phenotype and inhibits endochondral ossification of porcine cartilage repair tissue. Arthritis Rheum, 63: 2721-31

Welsch GH, Apprich S, Zbyn S, Mamisch TC, Mlynarik V, Scheffler K, Bieri O, Trattnig S (2011) Biochemical (T2, T2* and magnetisation transfer ratio) MRI of knee cartilage: feasibility at ultra-high field (7T) compared with high field (3T) strength. Eur Radiol, 21: 1136-43

Welsch GH, Mamisch TC, Zak L, Mauerer A, Apprich S, Stelzeneder D, Marlovits S, Trattnig S (2011) Morphological and biochemical T2 evaluation of cartilage repair tissue based on a hybrid double echo at steady state (DESS-T2d) approach. J Magn Reson Imaging, 34: 895-903

Gelse K, Ekici AB, Cipa F, Swoboda B, Carl HD, Olk A, Hennig FF, Klinger P (2012) Molecular differentiation between osteophytic and articular cartilage - clues for a transient and permanent chondrocyte phenotype. Osteoarthritis Cartilage, 20: 162-71

Welsch GH, Juras V, Szomolanyi P, Mamisch TC, Baer P, Kronnerwetter C, Blanke M, Fujita H, Trattnig S (2012) Magnetic resonance imaging of the knee at 3 and 7 tesla: a comparison using dedicated multi-channel coils and optimised 2D and 3D protocols. Eur Radiol, 22: 1852-9

Department of Urology

Chair of Urology

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Research Focus

- Establishment of an annotated tumor tissue repository containing urologic tumors
- Systemic tumor therapy, clinical trials
- MRI-guided needle biopsy for the diagnosis of prostate carcinoma
- The role of hypoxia and hypoxia-associated signal transduction pathways in solid tumors
- Tumor genetic research with focus on identification of biomarkers

Structure of the Department

UK Erlangen:
- Outpatients' Clinic and pediatric urology
- Adult renal transplantation unit in cooperation with the Department of Medicine 4 (Prof. Dr. K.-U. Eckardt)
- Pediatric renal transplantation unit in cooperation with the Department of Pediatrics and Adolescent Medicine (Prof. Dr. Dr. h.c. W. Rascher)
- Uro-oncological outpatients' unit for systemic drug therapy (AURONTE) in cooperation with the Department of Medicine 5 (Prof. Dr. A. Mackensen).

Waldkrankenhaus St. Marien gGmbH:
- Adult urology (inpatients' department), private insurance patients (outpatients' department)
- Trial documentation center.

Research

Establishment of an annotated tumor tissue repository containing urologic tumors

Project manager: Prof. Dr. B. Wullich

New insights into the occurrence of malignant tumors and the identification of new and reliable prognostic biomarkers depend upon the molecular characterization of rather large cohorts of tissue samples, since the currently used morphologic criteria only poorly reflect the progression behavior of one patient's specific tumor. To facilitate this research, the collection of tissue samples originating from tumors and corresponding non-tumor tissue as well as blood, serum, and various body fluids, e.g. urine, is of vital importance for translational research projects. A high quality tissue sample repository demands a standardized logistics for the sample transportation from the operating theater to the Institute of Pathology, as well as the careful and standardized preparation of the sample carried out by an experienced pathologist. In close cooperation with the local Institute of Pathology, a repository of urologic tissue samples will be established in which tissue samples of all surgically treated malignant urologic tumors are introduced. This tissue repository is part of the CCC biobank. For the establishment of the required Standard Operating Procedures (SOPs), we have established a close cooperation with the German Prostate Carcinoma Consortium (DPKK) e.V. and could furthermore introduce a web-based tissue database system that relies on the hospital's established clinical information system. All incorporated procedures are consistent with the legal, ethical, technical, and organisatoy regulations of tissue repositories and databases (patients' informed consent, data security, SOPs, and quality management). Our tissue database system is part of the Central Research Infrastructure for Molecular Pathology (CRIP). CRIP is a supervising system for the distribution of tissue samples hosted by the Institute of Biomedical Technology (IBMT) of the Fraunhofer-Gesellschaft e.V.

Systemic tumor therapy, clinical trials

Project manager: PD Dr. P. J. Goebell

The medical care and treatment of patients with uro-oncologic diseases represents an integral part of our urologic expertise. Systemic therapy forms, besides the provision of surgical treatment, are among the fundamental sources of competence in urology. For this purpose, the outpatient center for uro-oncologic diseases (AURONTE) was founded together with the Department of Urology and 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 trails are open to all common patients. Currently open clinical trials mainly focus on new therapeutic options for patients with kidney cancer or prostate cancer:
Registry for advanced kidney cancer,
Registry STAR - TOR,
RCC Switch Study,
Randomized phase III first line trial to evaluate efficacy and safety of sequenced therapy sunitinib/sorafenib versus sorafenib/sunitinib in metastatic kidneys,
RCC Switch 2 Study,
PD-1 CA209-025,
Principal Study,
Everpro Study,
Protect VEG113387,
marC-2 Everolimus Study,
Flipper Study,
Proselica EFC11785,
Firstana EFC11784,
QoLiTime,
JASiMA Study.
Information about open or closed clinical trials can be found at the homepage of the urological trial registry.

MRI-guided needle biopsy for the diagnosis of prostate carcinoma

Project manager: Prof. Dr. D. Engehausen

The magnetic resonance imaging (MRI)-guided biopsy technique is a novel procedure for the generation of diagnostic evidence in the case of a suspected prostate carcinoma. This procedure unites the sophisticated MRI visualization and the guided extraction of prostate biopsy samples. It is a newly developed interdisciplinary technique that incorporates a radiologist (visualization of the target area) and an urologist (targeting the biopsy needle and extraction of the sample), with the patient lying comfortable. Two biopsy samples from every suspect areal and one reference sample are extracted, each with visual control of the biopsy needle. This procedure is intended for patients with persistent suspect for prostate carcinoma after negative transrectal ultrasound (TRUS)-biopsy and shows a very high detection rate in this cohort with 40%, in a subcohort of patients even with 60%. This procedure which is constantly improved is available in only a few centers worldwide (at this time four, including Erlangen) and requires the interdisciplinary cooperation between urologists and radiologists. Before conducting this type of examination, the modalities of payment should be clarified. Presently,

the total cost of about 1,350 Euro according to the medical fee schedule are not approved by the statutory health insurances.

The role of hypoxia and hypoxia-associated signal transduction pathways in solid tumors

Project manager: Prof. Dr. H. Taubert

The lack of oxygen (hypoxia) is a situation seen in many solid tumors. Especially locally advanced malignancies rapidly outgrow the blood vessels that supported their growth. By this, tumor cells are confronted with a lack of oxygen and nutrition. As a consequence, more than 70 genes are activated by the HIF-1 transcription factor. Signal molecules are produced that stimulate the growth of new blood vessels, enzymes are produced that support a survival of cells under hypoxic conditions, and stem cell-associated genes are expressed. We are mainly interested in the regulation of miRNA genes by HIF-1. Because miRNAs themselves regulate numerous target genes, it is obvious that hypoxia has a vital influence on any cell. Using cell culture models we examine the functional consequences of hypoxia on tumor cells.

Tumor genetic research with focus on identification of biomarkers

Project manager: Dr. S. Wach

The identification and characterization of specific biological properties of the prostate carcinoma as well as other malignant tumors, like kidney carcinoma, is the main focus of the biological research projects. By assessing changes in microRNA (miRNA) expression profiles, it is already possible to distinguish between samples of tumor and non-malignant tissue. Furthermore, the prognostic value of miRNA expression profiles is currently examined. MiRNAs directly regulate the expression of numerous other proteins in cells. Therefore, experimental methods for analyzing protein expression are a vital component of our research.

The complete spectrum of molecular cytogenetic techniques, including fluorescence in situ DNA and RNA hybridization, is established in the laboratory. The quantification of miRNA and gene expression as well as the determination of gene copy numbers using real time PCR approaches are a central part of the experimental methods.

Teaching

Medical students are taught in the lecture series of emergency medicine and specialized urological lectures. Students also conduct a practical course in the Department of Urology or one of the associated teaching hospitals. The Department also allows additional education for achievement of the title medical specialist for urology. Additionally, specialized training courses are offered for the fields of andrology and systemic drug tumor therapy. For acquisition and improvement of specialized surgical techniques, the Department of Urology uses patient simulators. These include models for practicing sterile placement of catheters or laparoscopic methods for minimally invasive surgery. In addition, practica for basic and advanced techniques in molecular urology are offered.

Selected Publications

Keller A, Leidinger P, Bauer A, Elsharawy A, Haas J, Backes C, Wendschlag A, Giese N, Tjaden C, Ott K, Werner J, Hackert T, Ruprecht K, Huwer H, Huebers J, Jacobs G, Rosenstiel P, Dommisch H, Schaefer A, Müller-Quernheim J, Wullich B, Keck B, Graf N, Reichrath J, Vogel B, Nebel A, Jager SU, Staehler P, Amarantos I, Boisguerin V, Staehler C, Beier M, Scheffler M, Büchler MW, Wischhusen J, Haeusler SF, Dietl J, Hofmann S, Lenhof HP, Schreiber S, Katus HA, Rottbauer W, Meder B, Hoheisel JD, Franke A, Meese E (2011) Toward the blood-borne miRNome of human diseases. Nat Methods, 8: 841-3

Szczyrba J, Nolte E, Wach S, Kremmer E, Stöhr R, Hartmann A, Wieland W, Wullich B, Grässer FA (2011) Down-regulation of Sec23A protein by miRNA-375 in prostate carcinoma. Mol Cancer Res, 9: 791-800

Burger M, Goebell PJ (2012) Bladder cancer: Validity of the 2004 system for grading Ta bladder cancer. Nat Rev Urol, 9: 126-7

Kunath F, Keck B, Antes G, Wullich B, Meerpohl JJ (2012) Tamoxifen for the management of breast events induced by non-steroidal antiandrogens in patients with prostate cancer: a systematic review. BMC Med, 10: 96

Wach S, Nolte E, Szczyrba J, Stöhr R, Hartmann A, Ørntoft T, Dyrskjøt L, Eltze E, Wieland W, Keck B, Ekici AB, Grässer F, Wullich B (2012) MicroRNA profiles of prostate carcinoma detected by multiplatform microRNA screening. Int J Cancer, 130: 611-21

Keck B, Wach S, Kunath F, Bertz S, Taubert H, Lehmann J, Stöckle M, Wullich B, Hartmann A (2013) Nuclear E-cadherin expression is associated with the loss of membranous E-cadherin, plasmacytoid differentiation and reduced overall survival in urothelial carcinoma of the bladder. Ann Surg Oncol, 20(7):2440

International Cooperations

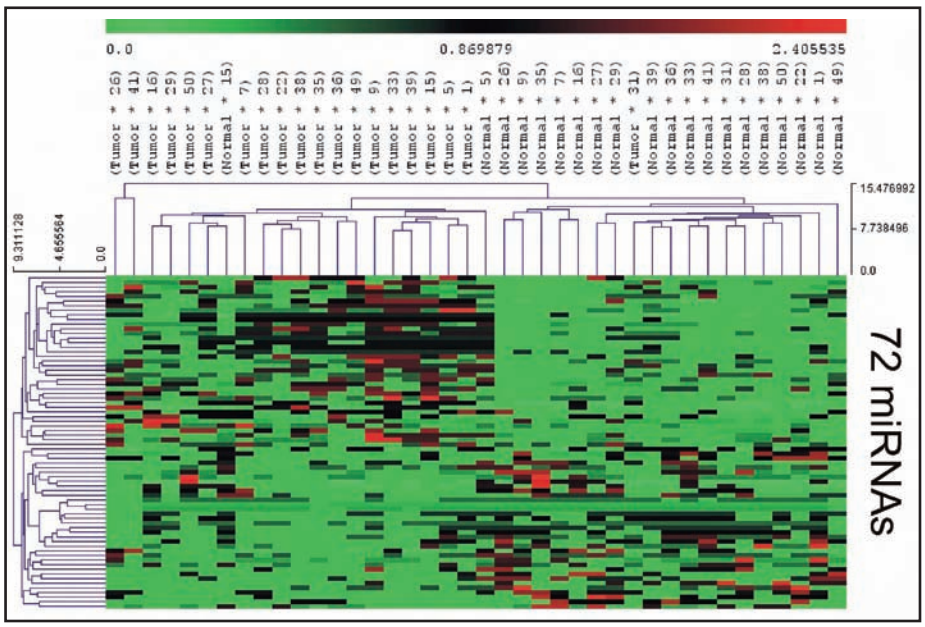
Prof. Dr. G. Yousef, Keenan Research Center, St. Michael's Hospital, Research Center, Toronto: Canada

Prof. Dr. T. Ørntoft, Department of Molecular Medicine, Århus University Hospital, Århus: Denmark

Dr. P.J. Goebell, International Bladder Cancer Network (IBCN), Barcelona: Spain

Meetings and International Training Courses

17.-19.11.2011: 3. Symposium Urologische Forschung der Deutschen Gesellschaft für Urologie, Jena



MiRNA Microarray expression data: Differences between tumor and corresponding non-malignant tissue.

Department of Operative Dentistry and Periodontology

Chair of Dental, Oral, and Maxillofacial Medicine - especially Operative Dentistry, Periodontology, and Pediatric Dentistry

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Research Focus

- Strategies avoiding chipping fractures on zirconia-based frameworks
- Study on direct cusp restoration with plastic resin composites in the load bearing posterior region
- Effects of aging on one-step self-etch adhesives
- HAp nanoparticles as reinforcing fillers for dental adhesives
- Wear analysis of prophylaxis tools on tooth and filling surfaces
- The proficiency of nanosized silica fillers in self-etch dental adhesives
- Prospective clinical study on glassionomercements using the A.R.T.-technique
- Antimicrobial dental products with silver technology

Structure of the Department

The Department of Operative Dentistry and Periodontology employs 56 staff members, thereof six professors and associate professors, 14 assistant professors, 21 dental nurses, and four dental technicians. The Department of Operative Dentistry and Periodontology further hosts a research laboratory with eleven research associates (four by external funding).
The research is generally conducted by three clinically oriented work groups as well as one dental materials, pre-clinically oriented work group. Eight post-doctoral researchers, 55 dental post-graduate and graduate students, and five technical assistants are in charge of the manifold research activities in the lab section. The main focus is on dental materials research with fields of expertise in basic science of operative and periodontal treatment procedures and correlation of experimental findings with clinical outcome. Independent, pre-clinical assessment of dental materials is a further area of interest of the lab section.

Research

Strategies avoiding chipping fractures on zirconia-based frameworks

Project manager: PD Dr. U. Lohbauer
Thermal mismatch between veneer and zirconia core, substructure, surface conditions, and cooling rate will dictate the load to fracture, fracture mode, and reliability of zirconia-based all-ceramic crowns.
The purpose of this study was to identify the factors involved in zirconia crown delaminations via fatigue testing in sliding-motion step-stress fatigue and fractrography analysis and the interaction between them.
Zirconia-based all-ceramic single crowns were fabricated using a zirconium-oxide substructure and two veneer ceramics with different coefficients of thermal expansion in order to result in groups with high and low thermal mismatch between veneer and core ceramic. Veneer ceramics were sintered onto the zirconia substructures as sintered or after being sandblasted. The cooling process was set at a fast or slow cooling rate. Specimens of each group were fractured in a single load-to-fracture compression. Further specimens are submitted to a sliding-motion step-stress fatigue in a chewing simulator. Fracture patterns were fractographically recorded (funded by Forschungsgemeinschaft Dental, FG Dental).

Study on direct cusp restoration with plastic resin composites in the load bearing posterior region

Project manager: PD Dr. U. Lohbauer
Within the last decade, the longevity of dental composite fillings could be significantly improved so that one could think of extending the use to the posterior region. The advantages of using resin composites over metal or ceramic restorations are the preservation of natural dental tissue, the minimally invasive application of the materials, the simplicity of this onsite treatment, and the reduced costs involved.
The study examined the usability of resin composites for the use in load bearing applications in the posterior region.
The expected results should define the minimum requirements for the use of composite materials, allow for appropriate preparation guidelines, and should provide a perspective on the clinical durability of restored cusps in the posterior region. The results of this study will be incorporated into the teaching and practical training at the Department of Operative Dentistry and Periodontology (founded by the ELAN-programm of the Faculty of Medicine).

Effects of aging on one-step self-etch adhesives

Project manager: Dr. M. Taschner
The simplification of adhesive bonding systems are getting more and more advertence in adhesive dentistry. Especially reducing the technique-sensitivity and developing less time-consuming products is playing a major role today. As part of a grant, the influence of different dentin pretreatment-protocols as well as the influence of different aging methods on the adhesive interface between tooth-structure and adhesive systems were evaluated by tensile tests (bond strength) and optical evaluation (nanoleakage).

HAp nanoparticles as reinforcing fillers for dental adhesives

Project manager: Dr. A. Wagner
In collaboration with the University of Jena, we evaluated the effect of adding HAp nanofillers without or with surface modification by silanization into the adhesive resin of a dental adhesive (Adper Scotchbond Multi-Purpose (SBMP), 3M ESPE) on dentin bond strength.
HAp nanoparticles (20-70 nm) were prepared either by biomimetic growth or by hydrothermal processes and incorporated into the adhesive of the SBMP system in 0.2/1/5/10% (wt/vol). Control (unfilled) and experimental groups (filled) were applied onto flat mid-coronal human dentin and composite crowns were built-up. The teeth were cut into beams, fractured in tension, and examined with a scanning electron microscope (SEM) for fractographic analysis. μTBS to dentin changed depending on the fillers and the concentration used. A significant increase of the mechanical strength was obtained for 1% (wt/vol) biomimetic and 5% hydrothermal, silanized HAp particles while the other particle fractions used did not influence μTBS significantly. At high concentrations (10%), nanofiller incorporation had a negative effect on bond strength irrespective of the particle fraction used.
Analysis of nanofiller distribution by transmission electron microscopy revealed nanoparticle dispersion through the adhesive layer, but no deposition on or penetration into the hybrid layer.

Wear analysis of prophylaxis tools on tooth and filling surfaces

Project manager: Prof. Dr. M. Pelka
Removal of supragingival and subgingival plaque and staining is crucial for maintenance of gingival and periodontal health. Dental care personnel usually remove supragingival stain and plaque by means of methods such as scaling, polishing with rubber cups, and

using polishing paste. Air-polishing devices (APD) have come into increased use for easy, fast, and complete removal of supragingival stain and plaque. Air-polishing systems are widely used for effective removal of staining. APDs can remove plaque, but leave the exposed surfaces rougher than before treatment. In vitro test methods were established to test the abrasive potential of APDs, polishing pastes, and dental prophylaxis instruments. The results of these studies showed that the grain size and the chemical composition of the air flow powder have major influence on the amount of wear of the tooth or filling surfaces. It could be shown that even low abrasive substances influence the surface roughness and maybe the subsequent plaque accumulation.

The proficiency of nanosized silica fillers in self-etch dental adhesives

Project manager: PD Dr. U. Lohbauer

This study is probing the proficiency of commercial available nanoscaled silica particles as fillers in self-etch adhesives in terms of mechanical properties and usability.

Experimental self-etch adhesives were filled with nanoparticles in the concentration of 5, 10, 15, and 20 percent by weight and tested subsequently. A microtensile test on bovine teeth revealed the toughening effect of the particles: Bond strengths doubled up to 10 percent by weight as compared to the unfilled adhesive and stayed on the same level when filler concentration was further increased. SEM imaging of the crack plain indicated that the resin tags broke outside of the dentin tubules. The viscosity of the adhesives increased with increasing filler concentration. For more than 10 percent by weight filler, the adhesives can be considered as too viscous to perform properly in clinical applications. Imaging via Confocal Laser Scanning Microscopy confirmed that despite of the increased viscosity, penetration behavior into dentin was comparable for filled and unfilled adhesives. Additionally, filler incorporation prohibited swelling during water uptake.

Therefore, it can be concluded that nanosized silica particles can be used as reinforcing filler particles for self-etch adhesives up to a certain concentration which was found to be 10 percent by weight in this study.

Prospective clinical study on glassionomercements using the A.R.T.-technique

Project manager: Dr. J. Ebert

Glass carbomer cement is taking advantage of the improvement of mechanical values by increased temperature and integrates the tooth component hydroxylapatite into the material. In the course of a prospective clinical study in close cooperation with our partner university in Joinville/Brazil, this innovative glass ionomer cement is examined in comparison to the "gold standard" Fuji IX in proximal defects within deciduous teeth using the "Atraumatic restauration technique" (A.R.T.). The treatment phase of this study took place in spring 2009. Evaluations were undertaken after six months, one year, and two and three years. At the moment, data are analyzed and an ex-vivo model analysis is carried out.

Antimicrobial dental products with silver technology

Project managers: Prof. Dr. A. Petschelt, Dr. J. Zorzin

On restorative materials, adhering biofilms can cause secondary caries. The objective of this cooperative project of the Department of Operative Dentistry and Periodontology with the Department of Dental Prosthetics of the University Hospital of Regensburg and the company BioGate AG is the development of dental materials with silver technology based on antimicrobial properties. The subproject at the Department of Operative Dentistry and Periodontology focuses on the production, exploration of the impact, and effectiveness of antimicrobial dental adhesives and filling materials. It is funded by the support program "Leitprojekte Medizintechnik" (Bayerisches Staatsministerium für Wirtschaft, Infrastruktur, Verkehr und Technologie).

Teaching

The main lectures of the Department of Operative Dentistry and Periodontology focus on basic science in operative dentistry and periodontology as well as on endodontology and pediatric dentistry. In the specific lectures, the most recent international scientific opinions and trends are embedded and controversially discussed, resorting to own measured data and scientific outcome of the dental materials lab.

Besides the conventional lectures, the dental education is highly practically oriented. Therefore, the Department of Operative Dentistry and Periodontology has established practical blockseminars in the graduate courses teaching endodontic treatment strategies (seventh term) and indirect inlay manufacturing skills (tenth term). Students as well as doctoral students are required to report in special seminars on recent scientific trends in restorative dentistry.

Selected Publications

Belli R, Rahiotis C, Schubert EW, Baratieri LN, Petschelt A, Lohbauer U (2011) Wear and morphology of infiltrated white spot lesions. J Dent, 39: 376-85

Lohbauer U, Krämer N, Siedschlag G, Schubert EW, Lauerer B, Müller FA, Petschelt A, Ebert J (2011) Strength and wear resistance of a dental glass-ionomer cement with a novel nanofilled resin coating. Am J Dent, 24: 124-8

Belli R, Monteiro S, Baratieri LN, Katte H, Petschelt A, Lohbauer U (2012) A photoelastic assessment of residual stresses in zirconia-veneer crowns. J Dent Res, 91: 316-20

Schwarz S, Lohbauer U, Petschelt A, Pelka M (2012) Vertical root fractures in crowned teeth: A report of 32 cases. Quintessence Int, 43: 37-43

Taschner M, Krämer N, Lohbauer U, Pelka M, Breschi L, Petschelt A, Frankenberger R (2012) Leucite-reinforced glass ceramic inlays luted with self-adhesive resin cement: A 2-year in vivo study. Dent Mater, 28: 535-40

Zorzin J, Petschelt A, Ebert J, Lohbauer U (2012) pH neutralization and influence on mechanical strength in self-adhesive resin luting agents. Dent Mater, 28: 672-9

International Cooperations

Prof. G. Eliades, University of Athens (UOA), Athens: Greece

Dr. S. Scherrer, University of Geneva, Geneva: Switzerland

Prof. P.F. Cesar, University of Sao Paulo (USP), Sao Paulo: Brazil

Prof. R. Braga, University of Sao Paulo (USP), Sao Paulo: Brazil

Prof. L.N. Baratieri, University of Santa Catarina, Florianopolis: Brazil

Prof. E.W. Schubert, University of Joinville (Univille), Joinville: Brazil

Prof. J. Powers, University of Texas, Houston: USA

Department of Orthodontics and Orofacial Orthopedics

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Research Focus

- 3D-CT evaluation of the asymmetry index by Katsumata/Maeda
- The applicability of the Frankfurt horizontal as reference plane in CT-scans
- Three dimensional efficiency evaluation of aligner treatment
- Erlangen 3D-model analysis for cleft lip and palate newborn - long term documentation
- Face Scan - Stereophotogrammetry
- Material scientific investigations
- Investigation of the reproducibility of skeletal maxillary landmarks in CT-scans
- MSCT and CBCT comparison - an in vitro study

Structure of the Department

The Chair of Dental, Oral, and Maxillofacial Medicine - especially Orofacial Orthopedics is integrated in the department of dentistry with regular, biennial rotation of the head of department.
Altogether, 23 employees are working in the Department of Orthodontics and Orofacial Orthopedics. The research is carried out by ten scientists and 18 postgraduates. Technical assistants are not available.
The prime alignment of our research is the 3D-evaluation of dentofacial anomalies with development of practical 3D-analysis methods. There are internal and external university cooperations concerning this research focus.
Other research projects have their focus on morphology orientated and interdisciplinary themes involving several disciplines of dentistry and medicine.
The clinical main emphasis is the orthodontic treatment of patients of all age groups: babies and small children with cleft lip palates and syndrome malformation, children and adolescents with various tooth misalignments and jaw malpositions, also including craniofacial malformation, and adults with tooth misalignment and complex interdisciplinary problems. We offer an extensive spectrum of international accepted therapy-concepts and modern appliances for the respective age groups.
The Department of Orthodontics and Orofacial Orthopedics is authoritatively involved in the Interdisciplinary Center of Cleft Lip and Palate of the FAU. In this interdisciplinary center, therapy concepts are continuously updated and initiated by the team.

Research

3D-CT evaluation of the asymmetry index by Katsumata/Maeda

So far, skeletal and facial asymmetries were difficult to locate in the orthodontic diagnosis by using cephalograms (lateral and frontal) because of structural superimpositions.
With CT-scans and the use of the CT-software Voxim®, the significance of the asymmetry index by Katsumata/Maeda was evaluated.

The applicability of the Frankfurt horizontal as reference plane in CT-scans

The Frankfurt horizontal (FH) was already preferred by anthropologists to standardize anthropologic-anatomic measurements on the skull in the 19th century. The cephalogram-analysis is based on the orientation of the head according to the Frankfurt horizontal during the scan.
The applicability of a constructed coordinate-reference system using the FH in CT-scans of skeletal asymmetries is to be evaluated.

Three dimensional efficiency evaluation of aligner treatment

Aim of this study was to demonstrate aligner efficiency with Durancasts of the Clear Aligner System for orthodontic treatment.
The treatment outcome of an adult patient with upper frontal crowding by using three-dimensional superimposition of digitized plaster casts (initial, intermediate, set up, and treatment outcome) was evaluated with the software Onyx Ceph™ after scanning the models with the smart optics 3D-Scanner and the activity 201 software (company 3D-Shape, GmbH).

Erlangen 3D-model analysis for cleft lip and palate newborn - long term documentation

Due to the long term and interdisciplinary treatment of CLP patients, it is one of the main goals to establish a consistent and well-arranged documentation. The treatment with presurgical orthopedic appliances in Erlangen takes place in four week intervals until surgical palate closure. During this time, plaster models are made at four defined dates within the first year and later once yearly.
Based on our two dimensional analysis of maxillary models, a simple and clinically applicable minimal documentation analysis for linear and angular measurements on digitized models was developed (company 3D-Shape, GmbH).
The Erlangen 3D-Model analysis can be applied routinely, precisely, and clinically practicable for three-dimensional documentation of changes in growth or treatment. It offers a qualification for standardized documentation and data management.

Face Scan - Stereophotogrammetry

In the field of facial soft tissue diagnostics, our present focus is on the indirect digital measurement of these structures with three-dimensional photographs ("3D-stereophotogrammetry", Face Scan 3D, company 3D-Shape GmbH) and the comparison of these new diagnostic procedures with conventional two-dimensional photography. Clinical relevance is given particularly for therapy planning of malocclusions and craniofacial anomalies.

Material scientific investigations

In order to minimize bracket failure rates during orthodontic treatment, this study investigated the bond strength of orthodontic brackets on enamel (n = 500 extracted teeth) using different bonding materials. The influence of different polymerization devices (LED light-emitting diode, QTH quartz-tungsten-halogen) and polymerization times were tested.

Investigation of the reproducibility of skeletal maxillary landmarks in CT-scans

The skeletal landmarks anterior and posterior nasal spine are showing a high morphological variability.
Aim of the study was to verify the reproducibility of these and other cephalometric maxillary

landmarks in CT-scans in the x-y-z-axis (transverse, sagittal, and vertical). For this study, the CT-examination software Voxim® was applied.

MSCT and CBCT comparison - an in vitro study

The aim of this study was to analyze the imaging accuracy of CBCT data sets compared with MSCT data sets in determining the exact mesio-distal width of unerupted porcine tooth germs and to compare the radiologically obtained results of width measurements with the actual mesio-distal dimension of the tooth germs. In MSCT and CBCT data sets, the largest diameter of 24 tooth germs was determined with the aid of the mesial and distal contact points. The reference method used was mesio-distal width measurement using sliding callipers after the tooth germs had been osteotomized.

Teaching

E-learning platform: Seminar on orthodontic technique

The e-learning platform serves as a complementary support for students of dentistry and goes along with the laboratory processes for the production of orthodontic appliances. Video clips allow individual repetition of dental laboratory technology. Further development and integration, supported by 'Virtuelle Hochschule Bayern (vhb)', shall be conducted in order to facilitate the basic orthodontic seminars in elementary theory and practice.

E-learning platform: Interactive virtual orthodontic case studies

The further development of this platform will establish online tests as a self-control option to intensively prepare for exams and improve knowledge in orthodontic case management. The interactive virtual orthodontic case studies are examples for orthodontic analysis, diagnosis, and treatment planning. The system offers options to add further cases by the supervisors. As additional benefit, all examples can be shared by other universities, supported by 'Virtuelle Hochschule Bayern (vhb)'.

Selected Publications

Medelnik J, Hertrich K, Steinhäuser-Andresen S, Hirschfelder U, Hofmann E (2011) Accuracy of anatomical landmark identification using different CBCT- and MSCT-based 3D images: an in vitro study. J Orofac Orthop, 72: 261-78

Steinhäuser-Andresen S, Detterbeck A, Funk C, Krumm M, Kasperl S, Holst A, Hirschfelder U (2011) Pilot study on accuracy and dimensional stability of impression materials using industrial CT technology. J Orofac Orthop, 72: 111-24

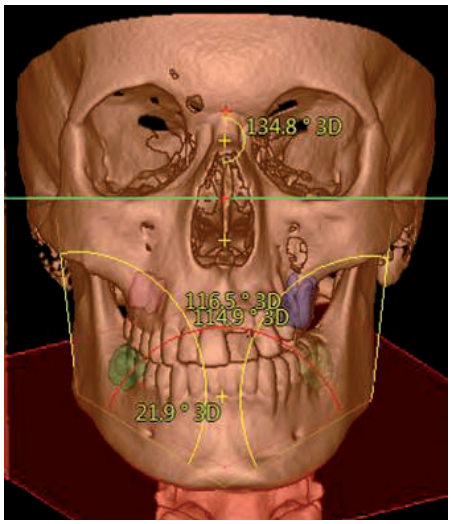
Hanke S, Hirschfelder U, Keller T, Hofmann E (2012) 3D CT based rating of unilateral impacted canines. J Craniomaxillofac Surg, 40: e268-76

Holst AI, Holst S, Hirschfelder U, Seckendorff VV (2012) Retrieval analysis of different orthodontic brackets: the applicability of electron microprobe techniques for determining material heterogeneities and corrosive potential. J Appl Oral Sci, 20: 478-85

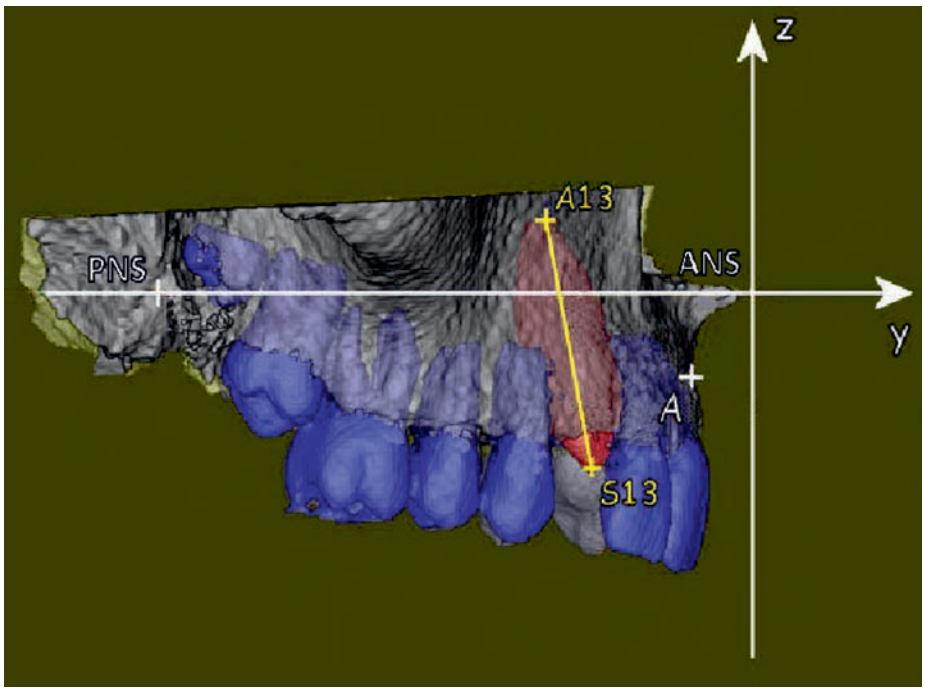
Strobel-Schwarthoff K, Hirschfelder U, Hofmann E (2012) Individualized Erlanger KS-Impression Trays for Infants With Cleft Lip and Palate. Cleft Palate Craniofac J, 49: 237-9

Hofmann E, Medelnik J, Fink M, Lell M, Hirschfelder U (2013) Three-dimensional volume tomographic study of the imaging accuracy of impacted teeth: MSCT and CBCT comparison--an in vitro study. Eur J Orthod, 35: 286-294

A structured-light 3D scan showing soft tissue landmarks on a subject's face.



Development of a CT-based 3D cephalometric analysis preparing stereometric measurements in orthodontics.



Lateral view of the 3D illustration of the image-based CT coordinate system in Voxim® 6.1. The permanent dentition is colored blue and the impacted canine red. The illustration shows the reference landmarks, the canine axis (A13-S13), and the y- and z-axis with the different reference planes: sagittal (y-z) plane, axial, and coronal plane (x-z).

Department of Prosthodontics

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Research Focus
- Dental biomechanics
- Psychogenic influence/quality of life and complementary medical procedures in dental questions
- Optical 3D-measurement technique in dentistry
- CAD/CAM research laboratories

Structure of the Department

The Department of Prosthodontics is responsible for teaching undergraduate students in several areas of fixed and removable prosthodontics, dental laboratory technology, occlusion and TMJ dysfunction, dental implants, CAD/CAM technology and ceramics, as well as maxillofacial prosthodontics. The Department is staffed with 20 full-time academics with a wide range of expertise and a total of 50 employees. The Department is involved in several areas of research, including dental materials, biomechanics, dental implants, and CAD/CAM technology.
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.

Research

Dental biomechanics

Project manager: PD Dr. M. Karl
Dental implants form an integral part of current prosthodontic treatment concepts. The patient's bone quality seems to be a decisive factor for treatment success in that context. However, until now bone quality could only be roughly estimated by radiographic means or by subjective hand feeling during implant site preparation. In order to close this diagnostic gap, principles of hardness testing as applied in dental materials science have been adapted to fit the situation of an implant surgery.
The resulting diagnostic tool "BoneProbe" will allow surgeons to objectively quantify bone quality during implant surgery by means of a compressive test and thus enable them to choose the best surgical protocol, the adequate implant geometry as well as to optimize the loading protocol.
Following thorough computer simulations, prototypes of the BoneProbe were manufactured and tested in bone surrogate materials as well as in bones. Based on the results obtained, application of the BoneProbe in regular patients seems to be realistic. Preliminary trials in an animal model showed that the application of the BoneProbe did not jeopardize osseointegration of the implants.
With bone quality constituting an important factor also in orthopedics and traumatology, future application of the BoneProbe in these areas is currently evaluated.

Psychogenic influence/quality of life and complementary medical procedures in dental questions

Project manager: Prof. Dr. S. Eitner
This area of research is divided in two main focal points. The first focal point evaluates psychogenic influence on treatment planning and outcome of dental disease patterns with a psychogenic background. Among other factors, the subject's appraisal of his own body can influence dental questions. Besides, the etiological correlation of gag reflexes during dental treatment, the influence of stress and clinical pictures on fear, depressive states, and social parameters are evaluated, too.
The second focal point concerns the therapeutic intervention with medical hypnosis and acupuncture in dental treatment and their influence on psycho-social factors as well as pain in above mentioned dental problems.

Optical 3D-measurement technique in dentistry

Project managers: Prof. Dr. S. Holst, PD Dr. M. Göllner
Quantitative assessment of biomechanical effects in vivo intraorally required highly complex research set-ups due to lack of adequate measurement technology in the past.
The aim of the research group is to establish and evaluate full-field three-dimensional (3D) optical inspection systems for clinical application in biomechanic research. The system will allow real time quantitative depiction of biomechanical influences in the oral cavity. 3D-image correlation provides strain measurements in all dimensions which are critical for accurate strain and loading response measurements in objects. The results of these optical measurements are compatible with finite element analysis software and facilitate verification and iteration of models that cannot be used solely to draw general conclusions regarding specific questions related to biomechanics. The system available in the Department of Prosthodontics uses photogrammetric principles. Relevant parameters for future in vivo applications were identified in current and completed studies, and first in vivo applications revealed promising results.

CAD/CAM research laboratories

Project managers: Prof. Dr. S. Holst, PD Dr. M. Karl, PD Dr. J. Schmitt
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.

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, focussing on biologic interactions and material properties. While theoretical knowledge remains integral part of dental education, manual manufacture of dental restoration will be taught only exemplarily.

A unique opportunity for all dental students at the FAU Dental School is the opportunity to participate in a 3-year extra-curricular implant program. The "iLect" program is funded by third parties and provided in cooperation with the Department of Oral and Cranio-Maxillofacial Surgery. The iLect program has become an essential part of the elective and interdisciplinary education of dental students. The first students passed successfully their examination in 2012 and finished their program.

Selected Publications

Winter W, Krafft T, Steinmann P, Karl M (2011) Quality of alveolar bone - Structure-dependent material properties and design of a novel measurement technique. J Mech Behav Biomed Mater, 4: 541-8

Bauer JS, Beck N, Kiefer J, Stockmann P, Wichmann M, Eitner S (2012) Awareness and education of patients receiving bisphosphonates. J Craniomaxillofac Surg, 40: 277-82

Eitner S, Wichmann M, Schlegel KA, Kollmannsberger JE, Nickenig HJ (2012) Oral health-related quality of life and implant therapy: an evaluation of preoperative, intermediate, and post-treatment assessments of patients and physicians. J Craniomaxillofac Surg, 40: 20-3

Krafft T, Winter W, Wichmann M, Karl M (2012) In vitro validation of a novel diagnostic device for intraoperative determination of alveolar bone quality. Int J Oral Maxillofac Implants, 27: 318-28

Matta RE, Schmitt J, Wichmann M, Holst S (2012) Circumferential fit assessment of CAD/CAM single crowns - a pilot investigation on a new virtual analytical protocol. Quintessence Int, 43: 801-9

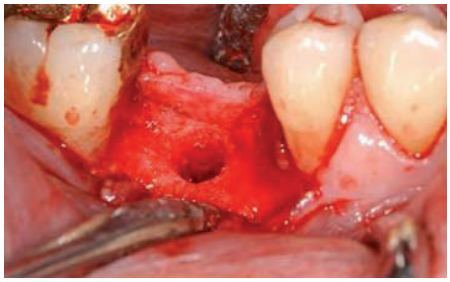
Schmitt J, Goellner M, Lohbauer U, Wichmann M, Reich S (2012) Zirconia posterior fixed partial dentures: 5-year clinical results of a prospective clinical trial. Int J Prosthodont, 25: 585-9

International Cooperations

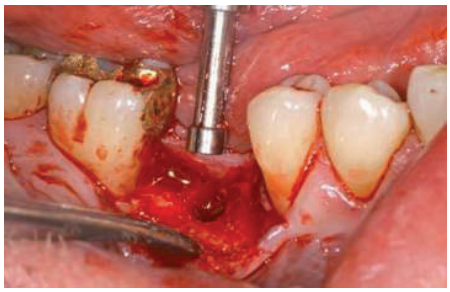
Prof. Dr. M.B. Blatz, University of Pennsylvania, Philadelphia: USA

Prof. Dr. H.P. Weber, Harvard University, Boston: USA

Prof. T.D. Taylor, Prof. J.R. Kelley, PhD, University of Connecticut, Farmington: USA



Clinical situation after implant bed preparation.



Sensing element of the BoneProbe to be inserted in the implant bed for conducting a compressive test.

Total view of a prototypical BoneProbe.

Histologic section of a dental implant placed following application of the BoneProbe.

Institute of Clinical and Molecular Virology

Chair of Clinical Virology

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Research Focus
- Retroviruses
- Beta-herpesviruses
- DNA Tumor Viruses

Structure of the Department

During the past two years, the twelve independent research groups at the Institute of Clinical and Molecular Virology focused on (1) the role of retroviruses in immunodeficiency and oncogenesis, (2) the pathogenesis of Beta-herpesviruses, such as the human cytomegalovirus, and (3) DNA tumor virology. The research groups investigated issues of infection biology, tumor virology, vector development, therapy research, native and adaptive immunity, signaling, and epigenetics, thereby applying a broad range of virological, biochemical, molecular, and cell biological as well as immunological methods. The majority of the staff members are third-party funded PhD students and post docs of biology, molecular medicine, biochemistry, and medicine.

The National Reference Center for Retroviruses (1996 - 2012) comprised on-topic research groups and a large number of services of diagnostic virology (compare own report). The Clinical Diagnostic Section offers a broad range of state-of-the-art diagnostic tests for all relevant viral infections, genotyping, and testing of viral tropism as well as antiviral drug resistance testing for immunodeficiency, herpes, and hepatitis viruses.

The Institute created a large number of subtype panels which are provided nation- and worldwide for both, research institutes and diagnosticians. During the last years, major activities targeted on the further development of molecular diagnostics for respiratory pathogens and gastroenteritis viruses via multiplex PCR, and on the establishment of protocols for the quantification of proviral DNA as a supplement to human oncogenic retrovirus diagnostics.

Research

Retroviruses

Project managers: Prof. Dr. U. Schubert, Prof. Dr. T. Gramberg, PD Dr. B. Schmidt, Dr. Dr. H. Reil, Dr. A. Kreß

Several HIV research groups and one HTLV research group are working at the Institute. The first research group is studying the interaction of host and virus proteins on the molecular level in order to define interface regions of binding partners that can be used as target structures for anti-viral strategies. A major focus of their research encompasses general aspects of HIV-1 biology, including the role of cellular factors in retrovirus assembly. Those studies are focused on the role of the ubiquitine-proteasome-system in late processes of the HIV replication cycle. The second research group investigates innate and intrinsic immunity in retroviral infection. The group focuses on antiviral mechanisms of intracellular restriction factors, such as the proteins of the TRIM family or the recently discovered protein SAMHD1 which can inhibit reverse transcription of retroviruses. The immunopathogenesis in HIV-1 and HSV-1 infections is addressed by the third research group. This group could reveal an essential role of the innate immune defense of plasmacytoid dendritic cells. The fourth research group is engaged in the interference of flavivirus GB Virus C (GBV-C) and immunodeficiency viruses. The main interest of the research group is to elucidate GBV-C specific strategies of HIV replication inhibition and to use this knowledge for the development of new HIV inhibitors. The fifth research group focuses on the molecular mechanisms of the retrovirus HTLV-1 (human T cell lymphotropic virus type 1) and its oncoprotein Tax which can lead to the development of ATLL (adult T cell leukemia/lymphoma). In addition, cell-cell transmission of HTLV-1 is analyzed.

Beta-herpesviruses

Project managers: Prof. Dr. M. Mach, Prof. Dr. T. Stamminger, Prof. Dr. M. Marschall, Prof. Dr. A. Ensser

The characterization of molecular mechanisms of human cytomegalovirus (HCMV) replication and the immune defense against HCMV is another key focus of the Institute. The first research group defines in collaboration with Prof. Dr. T. Winkler (Chair of Genetics, Faculty of Sciences) the key factors providing protective humoral immunity following HCMV infection. In the murine CMV model, the protective mechanisms of antibodies in immunosuppressed host organisms are investigated. For human CMV, antigens which are involved in the induction of neutralizing antibodies are characterized. Their results clearly disprove the so far commonly-received opinion that antibodies do not play any role in the protection from CMV infections in risk groups. The second research group analyzes the functional mechanism of viral regulatory proteins that exert an essential function for efficient viral replication and are thus attractive novel target molecules for antiviral therapy. The group could recently identify a novel intrinsic immune mechanism against herpes viruses that could be relevant for the regulation of herpesviral latency. Furthermore, they are working together with Prof. Dr. S. Ensminger, Department of Cardiac Surgery, on a mouse xenotransplantation model on the mechanism of CMV induced transplant arteriosclerosis. The third research group investigates the role of protein kinases which play an important regulatory role in herpesviral replication and pathogenicity. Specific focus is on the cross-talk between viral and cellular protein kinases involved in complex regulatory processes of herpesviral replication cycles. This area of research aims at developing a new generation of antiviral drugs on the basis of protein kinase inhibitors. In a translational project, the fourth research group develops chimeric immunoreceptors for anti-viral adoptive immunotherapy of CMV infection.

DNA Tumor Viruses

Project managers: PD Dr. F. Neipel, PD Dr. B. Biesinger, Prof. Dr. A. Ensser, Prof. Dr. W. Doerfler

This research focus aims at elucidating the mechanisms of cellular growth transformation by DNA tumor viruses. The Kaposi's sarcoma-associated human herpesvirus type 8 (HHV-8) is associated with certain B-cell lymphomas and Kaposi's sarcoma. The first group focuses on the identification of genes which are involved in tumor development. They identified a new receptor for HHV-8, the ephrin receptor

tyrosine kinase A2 (EphA2). EphA2 is bound to the glycoproteins H and L (gH/gL) of HHV-8. The binding of these viral glycoproteins not only mediates entry of the virus into host cells, but also induces signal transduction pathways known to be involved in the tumorigenic process by vascularization. Thus, HHV-8 encounters and activates cellular genes contributing to oncogenesis at the earliest stages of infection. The second group studies T-cellular signaling pathways regulated by the viral oncoproteins StpC and Tip from Herpesvirus saimiri C488 as well as Tio from Herpesvirus ateles. Analyzing the cell-differentiating proliferative signaling pathways that are stimulated by Tip is also a main focus of the third group within the SFB 796 (see own report). Furthermore, this group investigates the chromatin structure and replication of latent herpesvirus genomes in T and B cells. Novel mechanisms of intrinsic immunity against gamma herpesviruses were revealed in cooperation with Prof. Dr. T. Stamminger. As a visiting professor in the laboratory of Prof. Dr. J.U. Jung, University of Southern California, Los Angeles, Prof. Dr. A. Ensser continued in 2012 collaborative research projects on autophagy and intrinsic immunity involving mutagenesis of KSHV bacmids. DNA methylation and/or histone modification have been documented to affect many biomedical processes via the regulation of gene expression. The fourth group characterizes different aspects of DNA-methylation in HIV-1 proviral genomes, in transgenic cells, and in the human genome.

Teaching

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

Selected Publications

Hahn S, Setz C, Wild J, Schubert U (2011) The PTAP sequence within the p6 domain of human immunodeficiency virus type 1 Gag regulates its ubiquitination and MHC class I antigen presentation. J Immunol, 186: 5706-18

Kress AK, Kalmer M, Rowan AG, Grassmann R, Fleckenstein B (2011) The tumor marker Fascin is strongly induced by the Tax oncoprotein of HTLV-1 through NF-κB signals. Blood, 117: 3609-12

Tavalai N, Adler M, Scherer M, Riedl Y, Stamminger T (2011) Evidence for a dual antiviral role of the major nuclear domain 10 component Sp100 during the immediate-early and late phases of the human cytomegalovirus replication cycle. J Virol, 85: 9447-58

Full F, Reuter N, Zielke K, Stamminger T, Ensser A (2012) Herpesvirus saimiri antagonizes nuclear domain 10-instituted intrinsic immunity via an ORF3-mediated selective degradation of cellular protein Sp100. J Virol, 86: 3541-53

Hahn AS, Kaufmann JK, Wies E, Naschberger E, Panteleev-Ivlev J, Schmidt K, Holzer A, Schmidt M, Chen J, König S, Ensser A, Myoung J, Brockmeyer NH, Stürzl M, Fleckenstein B, Neipel F (2012) The ephrin receptor tyrosine kinase A2 is a cellular receptor for Kaposi's sarcoma-associated herpesvirus. Nat Med, 18: 961-6

Kropff B, Burkhardt C, Schott J, Nentwich J, Fisch T, Britt W, Mach M (2012) Glycoprotein N of human cytomegalovirus protects the virus from neutralizing antibodies. PLoS Pathog, 8: e1002999

International Cooperations

Prof. W. Rawlinson/Dr. G. Scott, University of New South Wales, Sydney: Australia

Dr. Y. Couté, Plateforme d'analyses protéomiques, INSERM U1038/UJF, CEA, Grenoble: France

Prof. B. Ray, University of Burdwan, Bardhaman: India

Dr. V. Ciminale, Department of Oncology and Surgical Sciences, University of Padova, Padova: Italy

Prof. J.A. Levy, University of California, San Francisco: USA

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

Prof. J.U. Jung, Molecular Microbiology & Immunology, University of Southern California, Los Angeles: USA

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

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

Meetings and International Training Courses

11.-17.05.2011: 13th International CMV/BetaHerpesvirus Workshop, Nürnberg

27.03.2012: Cell-based Therapies (Kooperationsforum in Zusammenarbeit mit Bayern Innovativ), Erlangen

14.-16.06.2012: International Symposium Forty Years of Virology at the FAU, Erlangen

Research Equipment

ABI, Prism 3100 Genetic Analyzer and data bank

BD Biosciences, Flow Cytophometer LSR II

Leica, confocal microscope TCS SP5

Institute of Clinical and Molecular Virology

Division of Experimental Therapeutics

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Research Focus

- Comprehenisve phenotyping and therapy in animal models of human neurodegenerative disorders

Structure of the Department

The Division of Experimental Therapy is located in the FPZ and contributes to essential responsibilities of the FPZ. The FPZ is a interdisciplinary facility, responsible for fundamental and preclinical animal research here in Erlangen.
In this context, the Division of Experimental Therapy offers highly standardized methods for the characterization of transgenic animals during preclinical studies in the context of neurodegenerative disorders and immunological research.

Research

Comprehenisve phenotyping and therapy in animal models of human neurodegenerative disorders

The Division of Experimental Therapy deals with comprehensive phenotyping and translational preclinical experimental therapeutic approaches in primarily transgenic rodent models for human neurodegenerative disorders. One goal is to provide models with a high predictivity for the human condition. A present focus is on neurodegenerative processes induced by protein aggregational diseases (polyglutamine disorders, Parkinson´s and Alzheimer´s disease). Various behavioral, neurological, immunological, molecular, and histological techniques are applied to characterize the pathophysiology and to develop new therapies.

Teaching

Seminars contribute to the curricula in clinical and experimental biomedicine, including anatomy, pharmacology, reproductive biology, and laboratory animals sciences. We employ modern educational technologies in several seminars and practical courses which also have been evaluated repeatedly. The seminars are part of the B.Sc./M.Sc. of Molecular Medicine at the FAU and they are integrated in postgraduate research programs.
The following seminars are offered to the students of the study course "Molecular Medicine": "Seminar experimental animals and knowledge of their reproduction" and „System-interactions and neuroendocrine-immunology: From anatomy to pathology". These seminars impart deep knowledge of the structure and function of the nervous-, neuroendocrine- and immune-system. Afterwards the students will have a comprehensive knowledge about the involved physiological pathways, e.g. the classical symptom "fever" as an adaption of the immune-system to pathophysiological processes. These seminars represent a compendium of different medical domains and basic principles to allow a broad understanding on the complexity of somatic processes.
The seminars "Generation of transgenic mice and rats as animal models of human diseases" and „Dealing with Experimental animals" (animal protection law, experimental design, and methods) together with a laboratory training are also offered to students of the master study course „Molecular Medicine".
A further seminar and practical training „Pathophysiological animal models: Pathophysiology and genetic studies" and „Practical training on experimental animals" during the study course „Molecular Medicine" is offered to the students. It imparts knowledge on the phenotyping of experimental animal models. During the practical training, the student will take part in ongoing and routine methods in the context of experimental animal phenotyping together with frequently used methods. Here, the contents and acquired knowledge depend on the teaching and scientific topic of the involved scientists.

Selected Publications

Cong WN, Cai H, Wang R, Daimon CM, Maudsley S, Raber K, Canneva F, von Hörsten S, Martin B (2012) Altered hypothalamic protein expression in a rat model of Huntington's disease. PLoS ONE, 7: e47240

Fink KD, Rossignol J, Crane AT, Davis KK, Bavar AM, Dekorver NW, Lowrance SA, Reilly MP, Sandstrom MI, von Hörsten S, Lescaudron L, Dunbar GL (2012) Early cognitive dysfunction in the HD 51 CAG transgenic rat model of Huntington's disease. Behav Neurosci, 126: 479-87

Lescaudron L, Boyer C, Bonnamain V, Fink KD, Lévêque X, Rossignol J, Nerrière-Daguin V, Malouet AC, Lelan F, Dey ND, Michel-Monigadon D, Lu M, Neveu I, von Hörsten S, Naveilhan P, Dunbar GL (2012) Assessing the potential clinical utility of transplantations of neural and mesenchymal stem cells for treating neurodegenerative diseases. Methods Mol Biol, 879: 147-64

Vlamings R, Benazzouz A, Chetrit J, Janssen ML, Kozan R, Visser-Vandewalle V, Steinbusch HW, von Hörsten S, Temel Y (2012) Metabolic and electrophysiological changes in the basal ganglia of transgenic Huntington's disease rats. Neurobiol Dis, 48: 488-94

Zeef DH, van Goethem NP, Vlamings R, Schaper F, Jahanshahi A, Hescham S, von Hörsten S, Prickaerts J, Temel Y (2012) Memory deficits in the transgenic rat model of Huntington's disease. Behav Brain Res, 227: 194-8

Antonsen BT, Jiang Y, Veraart J, Qu H, Nguyen HP, Sijbers J, von Hörsten S, Johnson GA, Leergaard TB (2013) Altered diffusion tensor imaging measurements in aged transgenic Huntington disease rats. Brain Struct Funct, 218: 767-78

International Cooperations

Prof. A. Petersen, Translational Neuroendocrine Research Unit, University of Lund, Lund: Sweden

Prof. H.-P. Lipp, Institute of Anatomy, ETH Zurich, Zurich: Switzerland

A.P. Osmand, PhD, Research Center - Graduate School of Medicine, University of Tennessee, Knoxville: USA

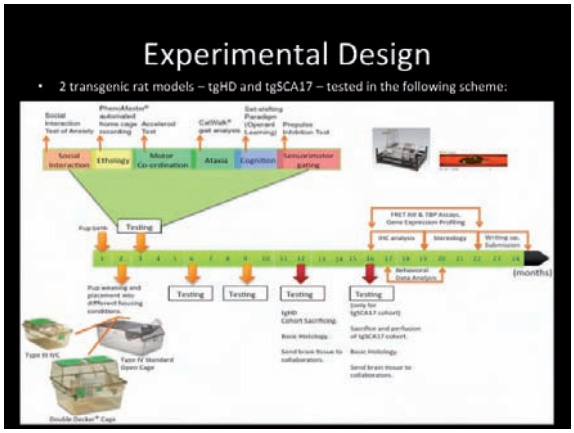
Research Equipment

TSE Systems GmbH, PhenoMaster

New Behavior AG, IntelliCage

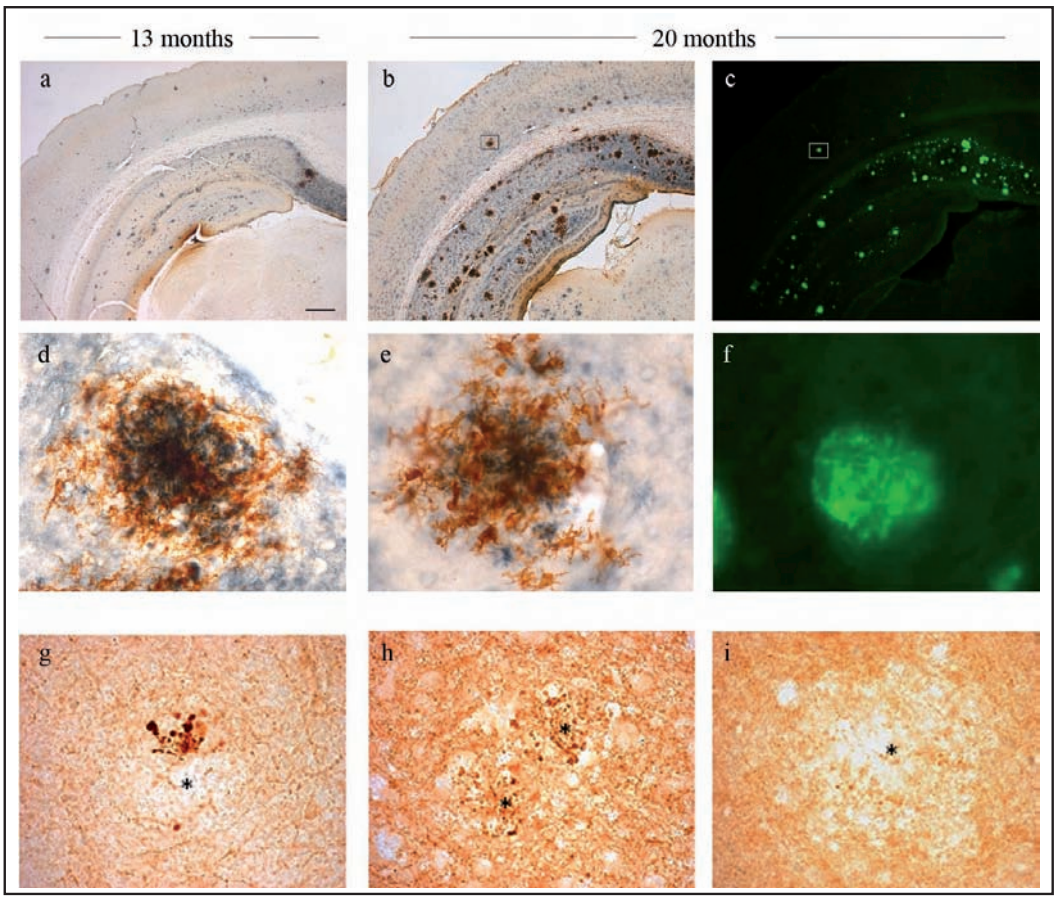
Siemens, Advia 120 Hemolytic Analyzer

BD, FACS Canto II



Example of a possible experimental design used for the characterization of possible beneficial effects of different housing conditions on the behavioral phenotype and cognitive skills of transgenic animal models.

Cognitive skills of laboratory animal models can be characterized by the method of operant learning. It is an automated test system in which animals are positively rewarded for the correct application of operant learning software paradigms which can be personalized with regard to the experimental design.



Amyloid plaque deposition and signs of neuroinflammation and neurodegeneration in the McGill-R-Thy1-APP rats. Sections from 13 (a and d) and 20 (b and e) month-old rats were stained for Aß and MHCII (respectively blue and brown reactions). The dense, fibrillar nature of these plaques was confirmed by thioflavine S staining (c and f). From g to i, the presence of neurodegeneration surrounding the sites of plaque deposition (*) was investigated in the same animal (20 month old): Dystrophic cholinergic (VAChT-IR) (g) and glutamatergic (VGluT-IR) (h), but not GABA-ergic (GAD65-IR) (i) neurites were observed, confirming the differential vulnerability of different neurotransmitter systems to amyloid plaques deposition.
Scale bar = 500μm in panels a - c and =20μm in panels d - i.

Institute of Clinical Microbiology, Immunology, and Hygiene

Chair of Microbiology and Immunology of Infection

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Research Focus

- Bacterial effector proteins
- Microbial phosphatases
- Molecular mycology
- Innate immunity and therapy of leishmaniasis
- Innate immunity, macrophages, arginase, and NO synthase
- Innate immunity, macrophages, and adjuvants
- Innate immunity, granulocytes, and mast cells
- Tissue milieu and the immune response
- Genetic and bacterial factors in chronic inflammation

Structure of the Department

The Institute of Clinical Microbiology, Immunology, and Hygiene is active in research, teaching, and clinical diagnostics. The Institute houses the Chair of Microbiology and Immunology of Infection and, since November 2008, the independent Division of Infection Biology (see own report). 85 employees are working at the Institute, thereof 24 are paid by extramural funding sources. The research is carried out by eleven scientists with a MD or PhD degree, 17 PhD students, und ten technical assistants.

The different research groups of the Institute study the innate and adaptive immune response during infectious diseases, investigate mechanisms of microbial virulence, and analyze the regulation of basic inflammatory processes, using immunological, cell-biological, and molecular techniques. Various infectious disease models are studied which include infections with Coxiella, Listeria, Mycobacteria, Salmonella, Leishmania, and Aspergillus. The Institute is fully equipped with laboratories (BSL2, BSL3), hypoxia chambers for in vitro and in vivo analyses, fluorescence and confocal laser scanning microscopes, real-time PCR machines, analytical fluorescence activated cell sorters (FACS), sequencing and imaging systems.

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

Research

Bacterial effector proteins

Project manager: Dr. A. Lührmann

The pathogenic activity of bacteria is based on the activity of virulence factors. Many Gram-negative bacteria have developed so-called secretion systems which directly inject certain bacterial proteins into the host cell. These effector proteins alter host cells for the advantage of the microbe. The research group studies the function of such proteins using the intracellular bacterium Coxiella burnetii, the causal agent of Q fever, as a model system. A major focus is the analysis of the mechanisms by which C. burnetii prevents the death of the host cells, thereby generating an ideal niche for its own survival and replication.

Microbial phosphatases

Project manager: Dr. D. Soulat (since 01.02. 2012)

Human pathogens have developed numerous strategies to invade their target host organism. One important virulence mechanism relies on the secretion of proteins (e.g. phosphatases) which interfere with cell signaling events during the host-pathogen interaction. Pathogen-secreted phosphatases are highly specific enzymes which are able to hijack the cell response and therefore participate in the creation of a pathogen friendly environment inside the infected host. The research group currently studies phosphatases from two human pathogens: (a) a PIP and tyrosine phosphatase named LipA from the bacteria Listeria monocytogenes and (b) a tyrosine phosphatase secreted by the parasite Leishmania major.

Molecular mycology

Project manager: Prof. Dr. S. Krappmann (since 01.05.2012)

Omnipresent molds of the genus Aspergillus (e.g. A. fumigatus) represent an increasing threat for immunocompromised patients. It is well accepted that pathogenicity of A. fumigatus is a multi-factorial trait. Major efforts in this research group aim at identification of virulence determinants (e.g. the nitrogen and sulfur metabolism) that support the utilization of proteinaceous substrates by A. fumigatus and allow for its propagation inside the susceptible host. Furthermore, the extant sexual cycle of A. fumigatus is investigated. These studies are accompanied by strategies to expand and improve the molecular toolbox of Aspergillus molecular biology.

Innate immunity and therapy of leishmaniasis

Project manager: PD Dr. U. Schleicher

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

Innate immunity, macrophages, arginase, and NO synthase

Project manager: Prof. Dr. C. Bogdan

Nitric oxide which is synthesized from the amino acid L-arginine in macrophages and other cells by the interferon (IFN)-γ inducible NO synthase (iNOS) is essential for the defense against intracellular pathogens and a central regulator of the immune system. In macrophages, the mechanism underlying the suppression of iNOS protein synthesis by L-arginine-deficiency which for example occurs after the induction of the arginine-metabolizing enzyme arginase during an infection will be studied. Both, the host cell arginase 1 as well as the arginase of Leishmania parasites, will be analyzed in this respect. The long-term aim is to unravel whether the host

cell arginase and/or the parasite arginase are critical for the lifelong survival of Leishmania in vivo.

Innate immunity, macrophages, and adjuvants

Project manager: Prof. Dr. R. Lang

The group explores which receptors are used by macrophages to detect pathogenic microorganisms and their products (e.g. the mycobacterial cord-factor trehalose-dimycolate) and how these receptors signal to elicit immune responses. The project aims at elucidating the mechanisms of action of adjuvants. Another research avenue focuses on the question how the inflammatory response of macrophages is terminated in order to prevent collateral tissue damage. In this context, one central aspect is the in vitro and in vivo analysis of the "dual specificity phosphatases". These inhibit various kinases that are essential for the production of proinflammatory cytokines and chemokines.

Innate immunity, granulocytes, and mast cells

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

The group investigates the survival strategies, the immunoregulatory functions, and the production of inflammatory mediators by neutrophils from patients with rheumatoid arthritis. The study aims at characterizing an anti-apoptotic factor and its mechanism of action as well as possible therapeutic applications. A second project analyzes how mast cells interact with B-lymphocytes, modulate the antibody synthesis and thereby optimize the specific immune defense of the host organism.

Tissue milieu and the immune response

Project manager: Dr. J. Jantsch

It is well established that under physiological conditions (e.g. in certain layers of the skin and in the gastrointestinal tract) and in inflamed tissues the oxygen levels may be very low ($pO2 < 0.5\%$). Interestingly, under high-salt diet sodium can accumulate in the skin without simultaneous water retention resulting in interstitial hypertonicity. The group explores the homeostatic role of the immune system in orchestrating the peripheral milieu (i.e. oxygen availability and interstitial tonicity) and studies how an altered milieu (e.g. hypoxia, interstitial hypertonicity) will regulate the immune response and defense against infectious pathogens via the respective transcription factors (e.g. HIF-1α, TonEBP).

Genetic and bacterial factors in chronic inflammation

Project manager: Prof. Dr. J. Mattner

Autoimmune responses and inflammatory processes of the intestine and the liver reflect the result of complex interactions of genetic predisposition and distinct environmental factors. Although the autoantigens targeted by the immune system are often ubiquitously expressed, the inflammatory processes are frequently tissue-specific. In this context, the group investigates the genetic factors that regulate the immune responses in the intestine and the liver. Furthermore, we analyze the role of bacterial antigens in the development of autoimmune responses by applying targeted gene deletion strategies.

Teaching

The employees of the Institute teach students of human medicine, dental medicine, molecular medicine, biology, and pharmaceutical sciences in medical microbiology, immunology, infectious disease research, and in the field of clinical infectious disease diagnostics and tropical diseases. The training takes place in form of seminars, practical courses, lectures, laboratory rotations, as well as bachelor, master, MD, and PhD theses. Together with the Institute of Clinical and Molecular Virology, the Institute organizes an interdisciplinary lecture series on infectious diseases which serves as a continuous medical education program for medical doctors in the region.

Selected Publications

Mohammed JP, Fusakio ME, Rainbow DB, Moule C, Fraser HI, Clark J, Todd JA, Peterson LB, Savage PB, Wills-Karp M, Ridgway WM, Wicker LS, Mattner J (2011) Identification of Cd101 as a susceptibility gene for Novosphingobium aromaticivorans-induced liver autoimmunity. J Immunol, 187: 337-49

Prajeeth Chittappen, Haeberlein Simone, Sebald Heidi, Schleicher Ulrike, Bogdan Christian (2011) Leishmania-Infected Macrophages Are Targets of NK Cell-Derived Cytokines but Not of NK Cell Cytotoxicity Infect Immun, 79: 2699-2708

Wenzel J, Held C, Palmisano R, Teufel S, David JP, Wittenberg T, Lang R (2011) Measurement of TLR-Induced Macrophage Spreading by Automated Image Analysis: Differential Role of Myd88 and MAPK in Early and Late Responses. Front Physiol, 2: 71

Amich J, Krappmann S (2012) Deciphering metabolic traits of the fungal pathogen Aspergillus fumigatus: redundancy vs. essentiality. Front Microbiol, 3: 414

Wiese M, Gerlach RG, Popp I, Matuszak J, Mahapatro M, Castiglione K, Chakravortty D, Willam C, Hensel M, Bogdan C, Jantsch J (2012) Hypoxia-mediated impairment of the mitochondrial respiratory chain inhibits the bactericidal activity of macrophages. Infect Immun, 80: 1455-66

Klingenbeck L, Eckart RA, Berens C, Lührmann A (2013) The Coxiella burnetii type IV secretion system substrate CaeB inhibits intrinsic apoptosis at the mitochondrial level. Cell Microbiol, 15: 675-687

International Cooperations

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

H. Haas, Innsbruck Medical University, Innsbruck: Austria

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

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

O. Mandelboim, The Lautenberg Center for General and Tumor Immunology, The Hebrew University Hadassah Medical School, Jerusalem: Israel

L. Wicker, University of Cambridge, Cambridge: UK

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

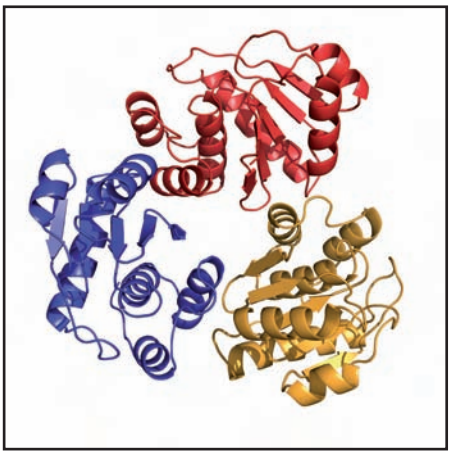

Figure 1: The 3D-structure and -arrangement of the homotrimer of the phosphatase LmjF.16.0230 from Leishmania major was modeled from its human homologs PRL-1. This structural similarity might be an advantage for the parasite to hijack the cellular functions controlled by the human PRL-1.

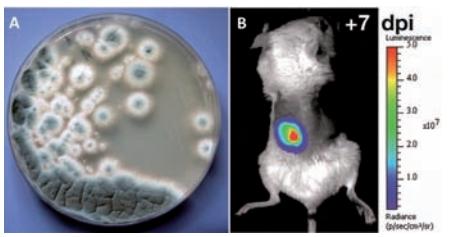

Figure 2: (A) The mould Aspergillus fumigatus. Colonies of mycelia with conidiophores giving rise to the grey-green asexual spores that serve as infectious propagules. (B) Imaging of cutaneous aspergillosis in an animal model by bioluminescence.

Institute of Clinical Microbiology, Immunology, and Hygiene

Division of Infection Biology

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Research Focus

- Immune response against helminths and allergens
- Plasticity of T-helper cells
- IgE response and germinal center reaction

Structure of the Department

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

Research

Immune response against helminths and allergens

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

Plasticity of T-helper cells

We addressed the question whether CD4 T cells that were already differentiated to Th1, Th17, or regulatory T cells (Treg) could be reprogrammed to adopt a Th2 phenotype in vivo. To address this issue, we used T cell receptor transgenic mice in which most CD4 T cells are specific for an epitope derived from chicken ovalbumin. Furthermore, these mice had been crossed to IL-4eGFP reporter mice so that repolarization to Th2 cells could be easily analyzed by flow cytometry. The T cell receptor transgenic cells were first polarized in vitro or in vivo to Th1, Th17, or Treg cells and then purified by cytokine capture assay. The purified Th1, Th17, and Treg cells were then transferred into naïve recipient mice followed by infection with helminths to study the re-programming into Th2 cells. The results indicated that Th1 and Th17 cells show remarkable functional plasticity while Treg cells were largely resistant to repolarization. These findings strengthen the hope that pathogenic Th1 or Th17 cells which often dominate autoimmune responses can be reprogrammed in an antigen-specific manner.

IgE response and germinal center reaction

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

Teaching

The Division of Infection Biology is closely associated to the Institute of Clinical Microbiology, Immunology, and Hygiene. Both institutions offer joined lectures, seminars, and practical courses for students. The teaching activities are dedicated to microbiology and immunology with a special focus on host-pathogen interactions. Scientists of the Division also supervise students that perform their Bachelor- or Master-theses.

Selected Publications

Dudeck A, Dudeck J, Scholten J, Petzold A, Surianarayanan S, Köhler A, Peschke K, Vöhringer D, Waskow C, Krieg T, Müller W, Waisman A, Hartmann K, Gunzer M, Roers A (2011) Mast cells are key promoters of contact allergy that mediate the adjuvant effects of haptens. Immunity, 34: 973-84

Schwartz C, Voehringer D (2011) Basophils: important emerging players in allergic and anti-parasite responses. Bioessays, 33: 423-6

Seidl A, Panzer M, Voehringer D (2011) Protective immunity against the gastrointestinal nematode Nippostrongylus brasiliensis requires a broad T-cell receptor repertoire. Immunology, 134: 214-23

Voehringer D (2011) Basophils in allergic immune responses. Curr Opin Immunol, 23: 789-93

Hoyler T, Klose CS, Souabni A, Turqueti-Neves A, Pfeifer D, Rawlins EL, Voehringer D, Busslinger M, Diefenbach A (2012) The transcription factor GATA-3 controls cell fate and maintenance of type 2 innate lymphoid cells. Immunity, 37: 634-48

Panzer M, Sitte S, Wirth S, Drexler I, Sparwasser T, Voehringer D (2012) Rapid in vivo conversion of effector T cells into Th2 cells during helminth infection. J Immunol, 188: 615-23

International Cooperations

M. Dalod, Center of Immunology of Marseille-Luminy (CIML), Marseille: France

R. Noelle, Dartmouth Medical School, Hanover: USA

L. Muzio, Division of Neuroscience, San Raffaele Scientific Institute, Milan: Italy

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

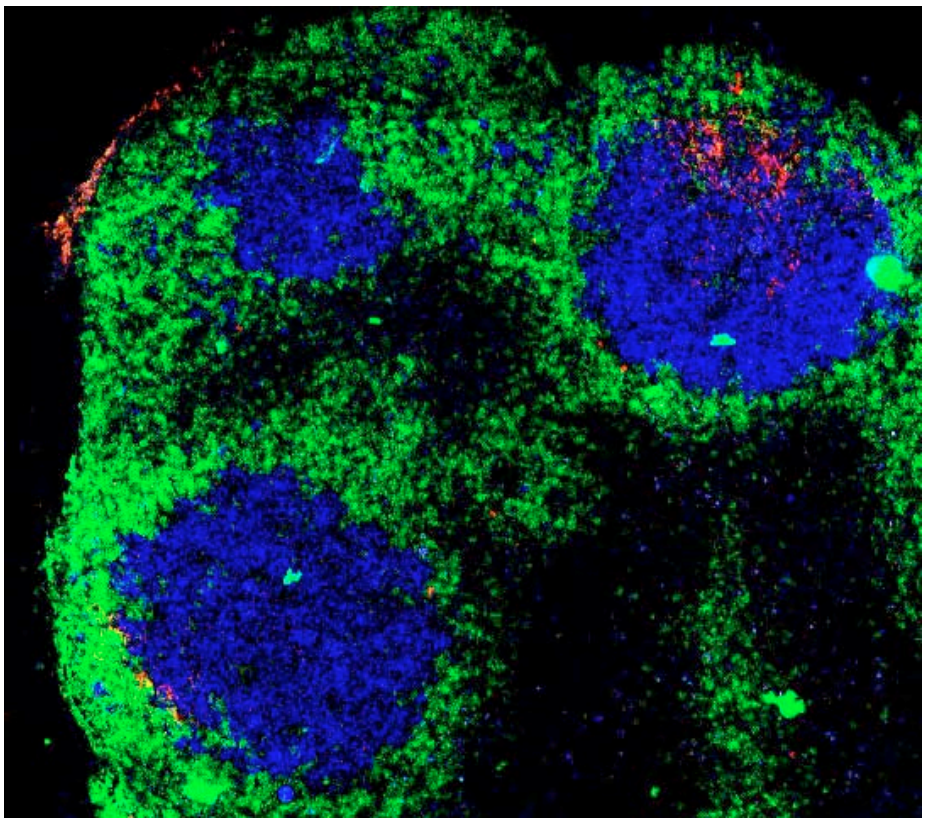
F. Granucci, Department of Biotechnology and Bioscience, University of Milano-Bicocca, Milan: Italy

D. Artis, Department of Microbiology, University of Pennsylvania, Philadelphia: USA

A. Mountford, Department of Biology, University of York, York: UK

Research Equipment

MiltenyiBiotec, MACSquant10



The picture shows three germinal centers in the mesenteric lymph node of helminth infected mice on day 12 after infection. Red: anti-CD35 staining to detect follicular dendritic cells. Blue: anti-GL-7 staining to detect germinal center B-cells. Green: anti-IgD to detect resting B-cells.

Institute of Human Genetics

Chair of Human Genetics

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

Structure of the Department

Members of the Institute are active in teaching, research, and health care provision. At the end of 2012, a total of 51 persons worked at the Institute: 17 scientists and physicians, ten PhD-students, 24 technical and administrative employees as well as eight graduate students. Ten colleagues were funded through grants. The Institute runs a genetic clinic for ambulatory care and genetic counseling of patients as well diagnostic laboratories for highly specialized cytogenetic and molecular genetic investigations. Research activities are organized in research groups. Members of the Institute participate in various collaborative research groups (BMBF and "Forschergruppen"). The head of Institute coordinated a collaborative research network on the genetic basis of mental retardation (MRNET) funded by the BMBF within the National German Genome Research Network (NGFNplus). He is also the Chairman of the University Senate and of the IZKF at the Faculty of Medicine. In addition, he served as president of the German Society of Human Genetics (GfH) in his second term till June 2012. The Institute runs several core units: "Z3 Genomic Platform" for microarray based genomic analyses and "Z4 DNA Extraction Platform (Biobank)" for quality controlled DNA extraction of blood samples, both within IZKF, as well as the interfaculty core unit „Ultradeep Sequencing" for massive parallel sequencing. Another research focus is the clinical and molecular syndromology.

Research

Developmental genetics

Project manager: Prof. Dr. A. Winterpacht
The group is interested in the molecular basis of developmental processes and their individual variability. This includes epigenetic mechanisms and regulatory networks of organogenesis and cell differentiation as well as the identification of variants in specific components of these processes. The projects comprise work on:
1. The gene SPOC1 (PHF13) whose expression is associated with survival time in patients with ovarian cancer. The group was able to show that SPOC1 functions as an epigenetic reader and writer of histone modifications which plays a role in mitosis and in the epigenetic regulation of meiosis as well as spermatogonial stem cell maintenance and differentiation;
2. The nervous system where the group works on the identification of susceptibility genes for post-operative pain perception. This project is carried out in the context of the Klinische Forschergruppe 130 (KFO 130; see own report) and in collaboration with the Departments of Anesthesiology and Surgery.

Genetics of complex diseases

Project manager: Prof. Dr. A. Reis
Complex or multifactorial diseases are caused by a combination of mostly unknown environmental and genetic factors. The group searches for genetic susceptibility factors through association studies with large patient cohorts. The projects were partially funded by BMBF. In a genome wide approach, novel susceptibility factors for psoriasis were identified as part of an international cooperation. Search for rare genetic variants in the previously identified psoriatic arthritis susceptibility gene TRAF3IP2 revealed missense variants which, unlike the frequent variant previously identified, did not affect binding to the interacting molecule TRAF6. Furthermore the initial association of psoriasis to a copy number variable cluster of β-defensins was replicated in larger cohorts. For PEX and PEX-glaucoma syndrome, the group performed a first genome wide association study and identified variants at CNTNAP2 locus as a novel associated gene. In cooperation with Prof. M.K. Wirtz (Portland, USA), the group also identified mutations in ASB10, encoding an important factor for ocular outflow, as a cause of familial open angle glaucoma. Finally, members of the Institute, in collaboration with the Department of Obstetrics and Gynecology, were involved in various studies on genetic factors predisposing to Mayer-Rokitansky-Küster-Hauser (MRKH) Syndrome and ovarian-, breast-, and endometrial cancer.

Genetic factors of intellectual disability

Project managers: PD Dr. R. Abou Jamra, Prof. Dr. A. Reis, Dr. C. Zweier
One of the main scientific topics of the Institute is the elucidation of the molecular basis of intellectual disability. Using homozygosity mapping, the first group studied over 100 families with autosomal recessive intellectual disability and identified AP4 deficiency as a novel syndrome caused by mutations in any of the four members of the AP4 complex. The second group identified heterozygote loss of function mutations in ARID1B, encoding a subunit of the SWI/SNF-A chromatin-remodeling complex, as a relatively frequent cause of unspecific intellectual disability. In the framework of a larger collaborative study, the group further performed whole exome sequencing in 51 patients/parent trios. The detection of pathogenic or most likely pathogenic de novo mutations in 45-55% of cases made a large contribution to the understanding of genetic causes of sporadic intellectual disability. The third group identified and characterized a triplication of the MAPT gene from the microdeletion region 17q21.31, thus contributing to the characterization of genotypes and phenotypes in this region. In addition, the group contributed to the delineation of the Nicolaides-Baraitser syndrome and to the identification of mutations in the causative SMARCA2 gene.

Growth retardation

Project manager: PD Dr. C. Thiel
The velocity of growth as well as growth patterns are fundamentally regulated by genetic factors. The group uses positional strategies to identify and further characterize the genetic basis of idiopathic short stature and skeletal dysplasias. This work was partially funded by BMBF (SKELNET network), ELAN-Fond, and DFG. This approach leads to the identification of nonsense mutations in NEK1 as the underlying cause of short rib-polydactyly syndrome type Majewski. Loss of functional NEK1 protein affects formation and morphology of the pri-

mary cilia (ciliopathy). Moreover, chromosomal breakpoint mapping and functional characterization outlines the histoneacetyltransferase MYST4/KAT6B in a patient with a Noonan-like syndrome phenotype.

Teaching

The Institute is involved in curricular teaching activities in medicine and in the bachelor- and master programs in molecular medicine as well as cellular and molecular biology, respectively. During the report period, 21 diploma or master theses in molecular medicine and cellular and molecular biology were finished at the Institute. In addition, doctoral theses in medical and natural sciences were supervised. Prof. Dr. A. Winterpacht received the best lecturer award for Molecular Medicine in summer terms 2011 and 2012.

Selected Publications

Abou Jamra R, Philippe O, Raas-Rothschild A, Eck SH, Graf E, Buchert R, Borck G, Ekici A, Brockschmidt FF, Nöthen MM, Munnich A, Strom TM, Reis A, Colleaux L (2011) Adaptor protein complex 4 deficiency causes severe autosomal-recessive intellectual disability, progressive spastic paraplegia, shy character, and short stature. Am J Hum Genet, 88: 788-95

Bördlein A, Scherthan H, Nelkenbrecher C, Molter T, Bösl MR, Dippold C, Birke K, Kinkley S, Staege H, Will H, Winterpacht A (2011) SPOC1 (PHF13) is required for spermatogonial stem cell differentiation and sustained spermatogenesis. J Cell Sci, 124: 3137-48

Kraft M, Cirstea IC, Voss AK, Thomas T, Goehring I, Sheikh BN, Gordon L, Scott H, Smyth GK, Ahmadian MR, Trautmann U, Zenker M, Tartaglia M, Ekici A, Reis A, Dörr HG, Rauch A, Thiel CT (2011) Disruption of the histone acetyltransferase MYST4 leads to a Noonan syndrome-like phenotype and hyperactivated MAPK signaling in humans and mice. J Clin Invest, 121: 3479-91

Hoyer J, Ekici AB, Endele S, Popp B, Zweier C, Wiesener A, Wohlleber E, Dufke A, Rossier E, Petsch C, Zweier M, Göhring I, Zink AM, Rappold G, Schröck E, Wieczorek D, Riess O, Engels H, Rauch A, Reis A (2012) Haploinsufficiency of ARID1B, a member of the SWI/SNF-a chromatin-remodeling complex, is a frequent cause of intellectual disability. Am J Hum Genet, 90: 565-72

Pasutto F, Keller KE, Weisschuh N, Sticht H, Samples JR, Yang YF, Zenkel M, Schlötzer-Schrehardt U, Mardin CY, Frezzotti P, Edmunds B, Kramer PL, Gramer E, Reis A, Acott TS, Wirtz MK (2012) Variants in ASB10 are associated with open-angle glaucoma. Hum Mol Genet, 21: 1336-49

Rauch A, Wieczorek D, Graf E, Wieland T, Endele S, Schwarzmayr T, Albrecht B, Bartholdi D, Beygo J, Di Donato N, Dufke A, Cremer K, Hempel M, Horn D, Hoyer J, Joset P, Röpke A, Moog U, Riess A, Thiel CT, Tzschach A, Wiesener A, Wohlleber E, Zweier C, Ekici AB, Zink AM, Rump A, Meisinger C, Grallert H, Sticht H, Schenck A, Engels H, Rappold G, Schröck E, Wieacker P, Riess O, Meitinger T, Reis A, Strom TM (2012) Range of genetic mutations associated with severe non-syndromic sporadic intellectual disability: an exome sequencing study. Lancet, 380: 1674-82

International Cooperations

Prof. M. Tartaglia, Superior Health Institute, University of Rome la Sapienza, Rome: Italy

Dr. A. Barton, arc-Epidemiology Unit, University of Manchester, Manchester: UK

Dr. A. K. Voss, Department of Medical Biology, University of Melbourne, Parkville: Australia

Prof. A. Rauch, Institute of Medical Genetics, University of Zurich, Zurich: Switzerland

Prof. J. Armour, Institute of Genetics, University of Nottingham, Nottingham: UK

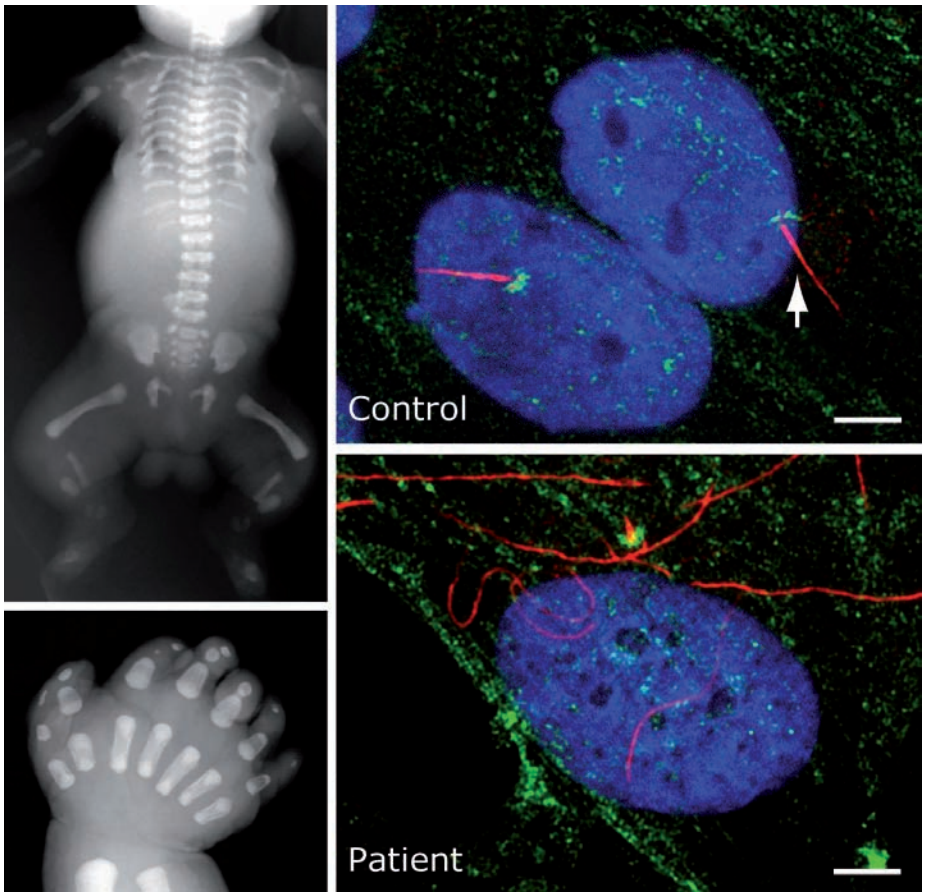
Meetings and International Training Courses

23.-26.06.2012: Tagung der Europäischen Gesellschaft für Humangenetik (ESHG) gemeinsam mit der Jahrestagung der GfH (Tagungspräsident Prof. Dr. A. Reis), Nürnberg

Research Equipment

Applied Biosystems, DNA-Sequencing Automation

Affymetrix, Genomic-Chip-Platform



X-Ray presenting features of skeletal dysplasia in patients with autosomal-recessive Short rib-Polydactyly syndrome caused by identified NEK1 mutations. NEK1 is part of the primary cilium (ciliopathy). Immunofluorescence analysis demonstrates characteristic dysmorphic cilia in the patient cells.

Institute of Neuropathology

Chair of Neuropathology

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

Structure of the Department

Our academic staff and technicians are engaged in studies addressing molecular pathomechanisms of CNS and skeletal muscle disorders. Particular focus is on epilepsy surgery, neuro-oncology, and myopathies. We have established the neuropathological reference center for epilepsy surgery and the European Epilepsy Brain Bank (supported by EU).

Research

Focal human epilepsies and animal models

Project manager: Prof. Dr. I. Blümcke

This research topic addresses drug-resistant focal epilepsies in humans. To unravel the molecular pathogenesis of major entities associated with chronic seizures, e.g. hippocampal sclerosis, glio-neuronal tumors, and focal cortical dysplasias, we performed systematic analysis using surgically resected brain specimens and correlated them with clinical histories and postsurgical follow-up data. Our work helped to settle new international standards for the diagnosis of Focal Cortical Dysplasias. Our group also addresses molecular pathomechanisms of epileptogenesis. We characterize epigenetic chromatin modifications within human surgical specimens as well as using an experimental animal model with 24h video-EEG monitoring which helps to quantitatively examine seizure burden. In this model, we also tested new therapeutic approaches to target DNA methylation. Research of human epilepsies and histopathologically well-characterized surgical specimens obtained from patients with temporal lobe epilepsy opens new avenues to study higher brain function in humans, i.e. the hippocampus plays a major role in memory formation. In addition, our finding of epilepsy-induced neurogenesis in the human hippocampus offers the possibility to unravel molecular signals for the recruitment, proliferation, and differentiation of adult stem cells in the human brain.

Molecular myopathology

Project manager: Prof. Dr. R. Schröder

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

Neuro-oncology

Project manager: PD Dr. R. Buslei

Neuro-oncology plays an important role in our clinico-neuropathological surveillance. With the international reputation of the Department of Neurosurgery in Erlangen and its emphasis on the treatment of neuroendocrine tumors (e.g. pituitary adenomas, craniopharyngeomas), unique collection of surgical tissue samples is available for a systematic molecular-neuropathological examination. Our research topics address three major questions:
(1) Molecular tumorigenesis,
(2) Pathogenesis of brain invasion, and
(3) Molecular genetic analysis as a tool for evaluating prognosis and therapy.
For our biomolecular and genetic analysis, we have access to a tissue bank comprising more than 500 unique tumors of the pituitary gland as well as craniopharyngiomas. Major improvements result from the analysis of β-catenin mutations in craniopharyngiomas and its impact in the differential diagnosis of cystic tumors of the sellar region. Primary cell cultures of craniopharyngiomas were used to unravel the molecular impact of Wnt signaling and EGFR signaling on the pathogenesis and morphology of this peculiar tumor entity. Future work will address the development of novel animal models to identify and verify molecular targets, needed for therapeutic intervention, e.g. EGFR inhibitor gefitinib.

Teaching

Our Institute is enrolled in pathology training and lectures.

Selected Publications

Hölsken A, Gebhardt M, Buchfelder M, Fahlbusch R, Blümcke I, Buslei R (2011) EGFR signaling regulates tumor cell migration in craniopharyngiomas. Clin Cancer Res, 17: 4367-77

Arhzaouy K, Strucksberg KH, Tung SM, Tangavelou K, Stumpf M, Faix J, Schröder R, Clemen CS, Eichinger L (2012) Heteromeric p97/p97R155C complexes induce dominant negative changes in wild-type and autophagy 9-deficient Dictyostelium strains. PLoS ONE, 7: e46879

Blümcke I, Coras R, Miyata H, Ozkara C (2012) Defining clinico-neuropathological subtypes of mesial temporal lobe epilepsy with hippocampal sclerosis. Brain Pathol, 22: 402-11

Clemen CS, Eichinger L, Schroder R (2012) Reply: Hereditary spastic paraplegia caused by a mutation in the VCP gene VCP: A Jack of all trades in neuro- and myodegeneration? Brain, 135: 1-3

Kobow K, Blümcke I (2012) The emerging role of DNA methylation in epileptogenesis. Epilepsia, 53 Suppl 9: 11-20

Mühlebner A, Coras R, Kobow K, Feucht M, Czech T, Stefan H, Weigel D, Buchfelder M, Holthausen H, Pieper T, Kudernatsch M, Blümcke I (2012) Neuropathologic measurements in focal cortical dysplasias: validation of the ILAE 2011 classification system and diagnostic implications for MRI. Acta Neuropathol (Berl), 123: 259-72

International Cooperations

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

Prof. A. El-Osta, Epigenetics in Human Health and Disease Laboratory, and Preclinical Diabetes Division Baker IDI Heart & Diabetes Institute, Monash University, Melbourne: Australia

Prof. G. Wiche, Max F. Perutz Laboratories, University of Vienna, Vienna: Austria

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

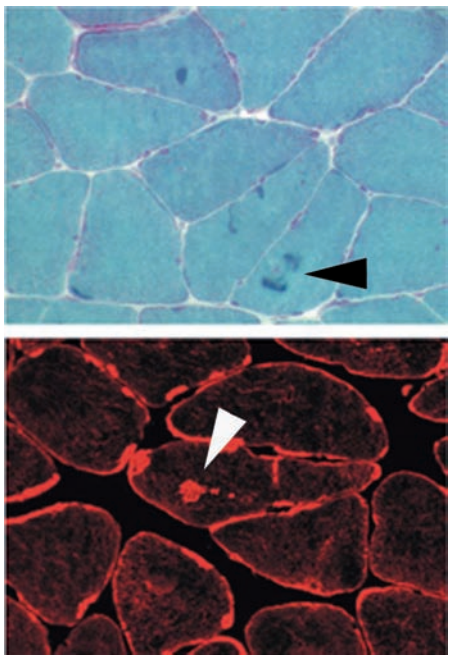
Dr. U. Bartels, Department of Paediatrics, SickKids - Hospital, Toronto: Canada

Prof. A. Pitkänen, Neurobiology Unit and Vice-Dean of Virtanen Institute, University of Eastern Finland, Kupio: Finland

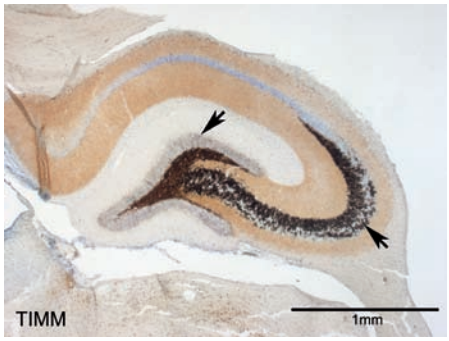
Dr. R. Spreafico, Department of Epilepsy Clinic and Experimental Neurophysiology, IRCCS Foundation Neurological Institute "Carlo Besta", Milano: Italy

Meetings and International Training Courses

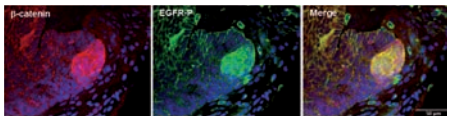
12.-15.09.2012: 57. Jahrestagung der Deutschen Gesellschaft für Neuropathologie und Neuroanatomie (DGNN) 2012, Erlangen



Intracellular protein aggregates (arrowheads) present a characteristic finding in desmin myopathies. Upper image: Gomori staining. Lower image: Fluorescence microscopic analysis of desmin immunoreactivity.



Axonal reorganization in hippocampus of chronic epileptic rat.
Axonal reorganization in the hippocampus of chronic epileptic rats. TIMM staining reveals zinc enriched axons aberrantly invading the supragranular and inner molecular layer of the dentate gyrus of chronic epileptic rats, but also the infrapyramidal band of CA3 (black arrowheads).



Activated EGFR in Craniopharyngiomas
β-catenin (red) and phosphorylated epithelial growth factor receptor (EGFR-P, green) double immunofluorescence staining of an adamantinomatous craniopharyngioma. Cells with an activated Wnt-signaling pathway representing β-catenin accumulations show also an activation of the EGFR signaling pathway as depicted in Merge (yellow). Inhibition of EGFR signaling could be a new therapeutic treatment option as it interrupts tumor cell migration in vitro.

Institute of Pathology

Chair of General Pathology and Pathological Anatomy

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Research Focus

- Diagnostic Molecular Pathology
- Experimental Tumor Pathology
- Clinical and Predictive Molecular Pathology of Urethelial Carcinoma
- Pathology of Immune and Inflammatory Reactions

Structure of the Department

The Institute of Pathology includes also the Division of Nephropathology. A total of 85 members of staff work at the Institute of Pathology, 30 are medical professionals or scientists. Of these, 15 are currently financed by third-party funding.

The Institute of Pathology is responsible for all pathology diagnostics within the UK Erlangen and for more than 30 external hospitals and physicians. The pathology diagnoses are carried out using the latest microscopic, immunohistochemical, and molecular methods. In addition to the histopathological evaluations of approximately 45,000 samples, more than 2,500 molecular pathology investigations are carried out.

The diagnostics specialties of the Institute are urogenital and gynecological pathology as well as breast pathology. Other focuses are the diagnosis of soft part tumors and gastrointestinal tumor pathology. The clinical focuses are very closely linked to the research topics of the Institute of Pathology, with associate professorships in "Experimental Tumor Pathology" and "Diagnostic Molecular Pathology".

Research

Diagnostic Molecular Pathology

Project managers: Prof. Dr. F. Haller, Dr. E.A. Moskalev

The aims of the group which started in Oktober 2011 are development and functional validation of diagnostic, prognostic, and predictive molecular-based markers in soft tissue tumors (Sarcomas and GIST), lung cancer, and breast cancer. There is a strong focus on the establishment of next generation sequencing techniques, such as 454 sequencing which are more sensitive and allow much broader analyses as compared to classical Sanger sequencing. The group is currently establishing tumor-type specific gene panels for simultaneous analysis by 454 sequencing (e.g. EGFR, KRAS, BRAF, and PI3K mutation analysis in lung cancer biopsies). Another aim is the concurrent analysis of DNA mutations, DNA methylation patterns, mRNA, and protein expression profiles in tumor tissues for a better, multidimensional understanding of the functionally relevant signaling mechanisms in cancer.

Experimental Tumor Pathology

Project managers: Dr. T. Rau, C. Geppert, Prof. Dr. R. Schneider-Stock, Prof. Dr. A. Hartmann, Prof. Dr. A. Agaimy, Dr. D. Wachter, Dr. J. Strehl, Dr. K. Brunner, Prof. Dr. R. Rieker

A major focus is the molecular and biochemical characterization of genetic and epigenetic induced changes in tumors and preneoplasias of the gastrointestinal tract. The main focus is on research projects for the molecular regulation of apoptosis in colorectal carcinomas and adeno-carcinomas of the lower oesophagus (Barrett carcinoma).

Furthermore, we focus on the basic molecular principles of chronic gastritis and Barrett metaplasia and the significance of epigenetic changes in malignant tumors as well as on the functional consequences of early epigenetic changes in the intestinal epithelium in colitis ulcerosa.

The molecular characterization of gastrointestinal stroma tumors and malignant mucosal melanomas is to identify new markers for better estimation of the prognosis and therapy response.

The second main focus, in cooperation with the Department of Obstetrics and Gynecology (Prof. Dr. M. Beckmann, Prof. Dr. P. Fasching), the West German Study Group (Prof. Dr. U. Nitz, Dr. O. Gluz), and the Institute of Pathology of the RWTH Aachen (Prof. Dr. E. Dahl), is on the discovery of genetic and epigenetic changes in breast cancer and ovarian carcinomas. The objective of the research here is to discover molecular prognostic markers and to identify molecular markers that could be used in the clinical-pathological differential diagnosis and therapeutic stratification of breast and ovarian cancer.

The subject of a further research project are the molecular changes in tumors of the head and neck region, in cooperation with the Department of Otorhinolaryngology - Head and Neck Surgery (Prof. Dr. H. Iro), and the Department of Oral and Cranio-Maxillofacial Surgery (Prof. Dr. F.W. Neukam, Prof. Dr. Dr. E. Nkenke). This research project has two objectives: One is to compile a molecular-pathological and histopathological classification of salivary gland tumors with low and high risk of relapse and progression, the second is to identify early molecular markers to identify dysplastic changes as tumor precursors in the mucosa of the head and neck region.

An additional research project investigates the molecular pathology of thymoma. The aim of the research in this project is the detection of genetic alterations in these rare tumors and the interaction of these tumors with the immune system.

Clinical and Predictive Molecular Pathology of Urethelial Carcinoma

Project managers: Prof. Dr. A. Hartmann, PD Dr. R. Stöhr, Dr. C. Stöhr, Dr. J. Giedl, Dr. S. Bertz

The research group investigates the basic molecular principles of the development of urethelial carcinoma of the urinary bladder, prostate cancer, and renal cell carcinoma. There is a close cooperation with the Department of Urology at the FAU at the Waldkrankenhaus St. Marien gGmbH and also with numerous national and international cooperation partners. The research group cooperates with several networks of German urology (German Prostate Cancer Consortium, German Research Consortium Renal Cell Carcinoma, German Research Consortium Bladder Cancer). 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 prostate cancer, the main focus is the identification of epigenetic alterations. In addition, one of the priorities of the work is the correlation of clinical-pathological findings with the molecular changes.

Pathology of Immune and Inflammatory Reactions

Project manager: PD Dr. M. Büttner-Herold

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

Teaching

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

Selected Publications

Bertz S, Denzinger S, Otto W, Wieland WF, Stoehr R, Hofstaedter F, Hartmann A (2011) Substaging by estimating the size of invasive tumour can improve risk stratification in pT1 urothelial bladder cancer-evaluation of a large hospital-based single-centre series. Histopathology, 59: 722-32

Fasching PA, Heusinger K, Haeberle L, Niklos M, Hein A, Bayer CM, Rauh C, Schulz-Wendtland R, Bani MR, Schrauder M, Kahmann L, Lux MP, Strehl JD, Hartmann A, Dimmler A, Beckmann MW, Wachter DL (2011) Ki67, chemotherapy response, and prognosis in breast cancer patients receiving neoadjuvant treatment. BMC Cancer, 11: 486

Smith SC, Baras AS, Dancik G, Ru Y, Ding KF, Moskaluk CA, Fradet Y, Lehmann J, Stöckle M, Hartmann A, Lee JK, Theodorescu D (2011) A 20-gene model for molecular nodal staging of bladder cancer: development and prospective assessment. Lancet Oncol, 12: 137-43

Bertz S, Otto W, Denzinger S, Wieland WF, Burger M, Stöhr R, Link S, Hofstädter F, Hartmann A (2012) Combination of CK20 and Ki-67 Immunostaining Analysis Predicts Recurrence, Progression, and Cancer-Specific Survival in pT1 Urothelial Bladder Cancer. Eur Urol, http://dx.doi.org/10.1016/j.eururo.2012.05.033

Rau TT, Rogler A, Frischauf M, Jung A, Konturek PC, Dimmler A, Faller G, Sehnert B, El-Rifai W, Hartmann A, Voll RE, Schneider-Stock R (2012) Methylation-dependent activation of CDX1 through NF-κB: a link from inflammation to intestinal metaplasia in the human stomach. Am J Pathol, 181: 487-98

Tudor CS, Dawson CW, Eckhardt J, Niedobitek G, Büttner AC, Seliger B, Hartmann A, Buettner M (2012) c-Myc and EBV-LMP1: two opposing regulators of the HLA class I antigen presentation machinery in epithelial cells. Br J Cancer, 106: 1980-8

International Cooperations

M. Jasiulionis, Institute of Pharmacology, University Sao Paulo, Sao Paulo: Brazil

S. Jarmalaite, Human Genome Research Centre, Faculty of Natural Sciences, Vilnius University, Vilnius: Lithuania

T. Ornthoft, Aarhus University Hospital Skejby, Department of Molecular Medicine (MOMA), Aarhus: Denmark

E. Zwarthoff, Erasmus MC, Rotterdam: The Netherlands

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

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

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

Meetings and International Training Courses

16.-19.06.2011: 95. Jahrestagung der Deutschen Gesellschaft für Pathologie e.V., Leipzig

31.05.-03.06.2012: 96. Jahrestagung der Deutschen Gesellschaft für Pathologie e.V., Berlin

Research Equipment

Stratifyer, automated DNA-RNA-extraction system

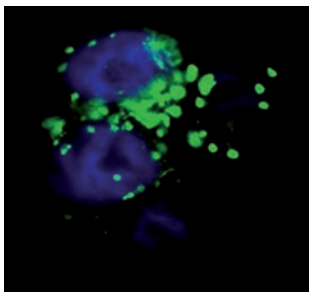
BD Biosciences, Flow Cytometer

Roche, GS Junior, 454 Sequencing technology

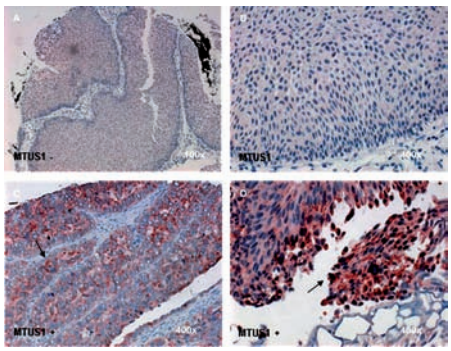
PALM, laser microdissection

Zeiss, laser scanning microscop

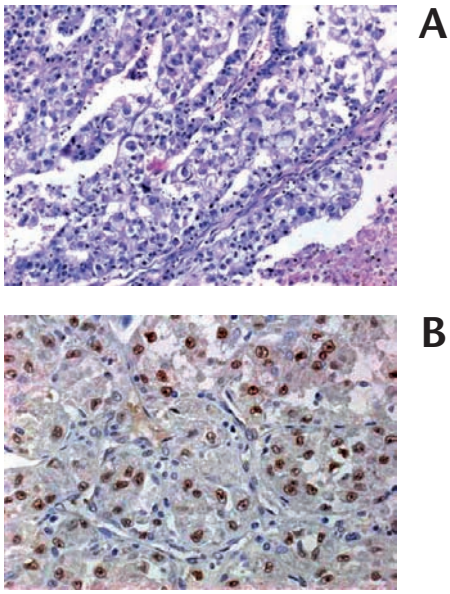
Decon Science Tec GmbH, microscop live-cell-migration unit



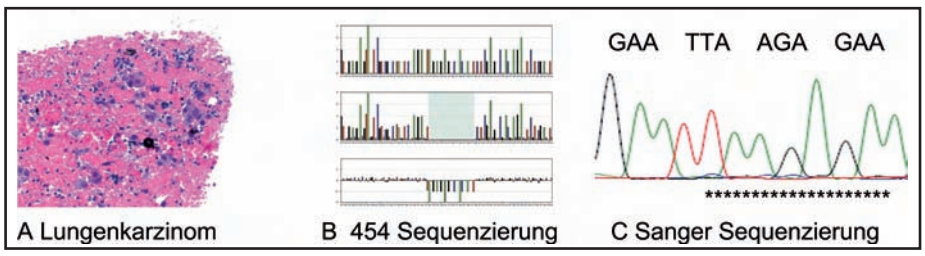
HDAC inhibitor LBH589 induces autophagy in tumor cells (LC3-II punctuates - green, DAPI - blue).



Immunohistochemical staining of papillary bladder tumors with anti-MTUS1-antibody; A and B show tumors with negative staining, C and D show positive, cytoplasmic staining (arrows); MTUS1 (microtubule associated tumor suppressor 1) is a tumor suppressor protein which is located in the cytoplasm in small, punctual aggregations.



Renal cell carcinomas carrying TFE3 translocations frequently demonstrate TFE3 overexpression. A: Hematoxilin and eosin staining of a tumor demonstrating typical features of a TFE3 translocation tumor. B: Staining the tumor with a TFE3-antibody results in clear nuclear positivity which is caused by TFE3 overexpression.



A) Lung cancer specimen, micropapilly type, with a tumor cell content of <10%. B) 454 sequence analysis reveals a therapeutically relevant EGFR exon 19 deletion which is present in 4.3% of all examined alleles, corresponding to 50% of all tumor cells. C) Due to the high amount of non-neoplastic cells, the mutation is not detectable in the classical Sanger sequence analysis of the same DNA isolate.

Institute of Pathology

Division of Nephropathology

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Research Focus

- Clinical and experimental nephropathology
- Proteasome inhibition as a new therapeutic intervention in inflammatory kidney diseases
- Pathomechanisms and modulation of impaired angiogenesis and angioadaption in chronic renal failure
- Podocytes as non-hematopoetic antigen-presenting cells
- Regression of cardiovascular changes by kidney transplantation
- Causes and effects of a reduced nephron number
- The role of CD26 in the manifestation of ischemia/reperfusion injury and acute rejection in the transplanted kidney
- The role of PAR-2 in hypertensive kidney and heart damage

Structure of the Department

The Division of Nephropathology together with the Chair of General Pathology and Pathological Anatomy constitutes the Institute of Pathology. The Division employs a total of 19 members of staff of which seven are financed by third-party funds. Research is carried out by one postdoc, one PhD student and four technical staff. Since October 2012, Prof. Dr. F. Engel has filled the new W2-professorship for "Experimental kidney and circulation research" and has started with two staff members to build up his laboratory.
The Division of Nephropathology is responsible for the kidney biopsy diagnosis of the UK Erlangen (Department of Medicine 4 and Pediatric Nephrology of the Department of Pediatrics and Adolescent Medicine) and of further 90 external biopsy senders. The kidney biopsy diagnosis is carried out using the latest light-microscopic, immunohistological, electron microscopic, and molecular methods. In this field, there are close links with the corresponding structures of the Institute of Pathology.

Research

Clinical and experimental Nephropathology

Project manager: Prof. Dr. K. Amann
Clinical and experimental cooperations are well established with clinical partners (Department of Medicine 4 and Pediatric Nephrology) and several research groups of the UK Erlangen respectively of the FAU 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.

Proteasome inhibition as a new therapeutic intervention in inflammatory kidney diseases

In cooperation with Prof. Dr. R. Voll (Department of Immunology, University of Freiburg) and Prof. Dr. M. Wiesner (Department of Medicine 4, UK Erlangen), it is explored whether proteasome inhibition constitutes a new therapeutic option in the treatment of Lupus-nephritis and also other immuno-complex mediated inflammatory kidney diseases. To test this hypothesis, medical interventions for proteases inhibition in standard models of systemic Lupus erythematodes and other inflammatory kidney diseases are investigated.

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

This project is performed in collaboration with Prof. Dr. K.F. Hilgers (Department of Medicine 4). Mortality rate is still very high in patients with chronic kidney disease (CKD); it is in fact comparable to that of many cancer patients. Death from cardiac causes is the leading cause of death in these patients. Cardiac mortality of young dialysis patients is nearly 1,000-fold greater than in the general population. CKD patients show characteristical cardiovascular structural alterations, like left ventricular hypertrophy with reduced myocardial capillary density, increased intercapillary distance, and reduced myocardial ischemia tolerance as well as peripheral artery disease with higher ischemia susceptibility. 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 address the following questions:
- Is ischemia in CKD associated with lower expression of proangiogenic factors and/or reduced recruitment of hematopoietic stem cells from the bone marrow?
- Does stimulation of angiogenesis in CKD by hypoxic preconditioning or overexpression of VEGF lead to improved capillarisation and perfusion after ischemia?

Podocytes as non-hematopoetic antigen-presenting cells

This project was performed in collaboration with Dr. A. Goldwich (Department of Dermatology, UK Erlangen). Podocytes are highly differentiated epithelial cells of the kidney which can present antigen and can initiate a specific T cell response in vitro and in vivo. As previously shown only for hemopoietic cells, podocytes have the capability to activate naive T cells by MHC class I, MHC class II, and crosspresentation. Thus, podocytes may represent novel targets for immunotherapy of inflammatory kidney diseases and potentially also for prevention of kidney rejection. In this project, we investigate in vitro and in vivo mechanisms of antigen presentation by podocytes.

Regression of cardiovascular changes by kidney transplantation

Patients with CKD represent a disproportionately high prevalence and mortality for cardiovascular diseases leading to a significant clinical problem.
Cardiovascular diseases in these patients are 20 times more common than in age- and gender-matched collective of the general population and up to three times more frequent than in other risk collectives, such as patients with diabetes mellitus. CKD causes characteristic myocardial structural changes, such as left ventricular hypertrophy (LVH), interstitial myocardial fibrosis, artery as well as myocardial wall thickening, and an inadequate low myocardial capillarisation. The latter is accompanied by an increase in intercapillary distances and a reduced blood and oxygen supply contributing to the apparently reduced ischemia tolerance of the myocardium in CKD. So far, it is completely unclear whether the cardiovascular changes, caused by a progressive CKD, are reversible. It is completely unclear whether a kidney transplant can prevent further progression of cardiovascular changes or whether these changes can be regressed. These clinically highly relevant issues will be investigated experimentally in rats with subtotale nephrectomy and subsequent renal transplantation.

Causes and effects of a reduced nephron number

In cooperation with PD Dr. K. Benz (Department of Pediatrics and Adolescent Medicine,

UK Erlangen), we are especially interested in learning whether a structural malformation of the kidney - using an animal model of low nephron number - is pre-conditional for the formation of hypertension and kidney diseases.

The role of CD26 in the manifestation of ischemia/reperfusion injury and acute rejection in the transplanted kidney

In cooperation with Prof. Dr. S. von Hörsten (Division of Experimental Therapeutics, FAU), we examine whether the lack or inhibition of dipeptidylpeptidase IV (DPP4) reduces ischemia/reperfusion injury and acute rejection. In a rat model for kidney transplantation, changes in DPP4 expression and localization as well as alterations in kidney function were investigated by using DPP4 deficient and wild-type rats. Hereby, we try to identify how DPP4 influences pathological changes in ischemia/reperfusion injury.

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

Protease activated receptor-2 (PAR-2) is a G-protein coupled receptor that can be activated by numerous serine proteases which were secreted after tissue injury. In this project, we investigate PAR-2 as a potential target for the treatment of inflammatory and fibrotic organ damage. The pathogenetic role of this receptor will be evaluated using PAR-2 deficient mice in an angiotensin II induced hypertensive model.

Teaching

The Division of Nephropathology participates in the teaching of the Institute of Pathology. In addition, nephropathological conferences with the clinical departments of the UK Erlangen and external biopsy senders regularily take place. Furthermore, twice a year a kidney pathology course takes place for both, staff of the UK Erlangen and staff of external hospitals.

Selected Publications

Amann K, Odoni G, Benz K, Campean V, Jacobi J, Hilgers KF, Hartner A, Veelken R, Orth SR (2011) Sympathetic blockade prevents the decrease in cardiac VEGF expression and capillary supply in experimental renal failure. Am J Physiol Renal Physiol, 300: F105-12

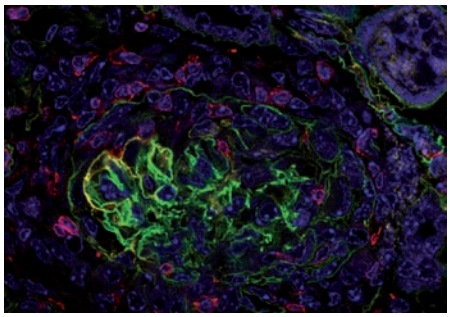
Benz K, Campean V, Cordasic N, Karpe B, Neuhuber W, Mall G, Hartner A, Hilgers KF, Amann K (2011) Early glomerular alterations in genetically determined low nephron number. Am J Physiol Renal Physiol, 300: F521-30

Tyralla K, Adamczak M, Benz K, Campean V, Gross ML, Hilgers KF, Ritz E, Amann K (2011) High-dose enalapril treatment reverses myocardial fibrosis in experimental uremic cardiomyopathy. PLoS ONE, 6: e15287

Buettner M, Xu H, Böhme R, Seliger B, Jacobi J, Wiesener M, Benz K, Amann K (2012) Predominance of TH2 cells and plasma cells in polyoma virus nephropathy: a role for humoral immunity? Hum Pathol, 43: 1453-62

Goldwich A, Steinkasserer A, Gessner A, Amann K (2012) Impairment of podocyte function by diphtheria toxin - a new reversible proteinuria model in mice. Lab Invest, 92: 1674-85

Hainz N, Thomas S, Neubert K, Meister S, Benz K, Rauh M, Daniel C, Wiesener M, Voll RE, Amann K (2012) The proteasome inhibitor bortezomib prevents lupus nephritis in the NZB/W F1 mouse model by preservation of glomerular and tubulointerstitial architecture. Nephron Exp Nephrol, 120: e47-58



After induction of anti-GBM-nephritis, some podocytes (Podocalyxin yellow stain) have direct contact with T cells (CD3 red stain) and were not seperated by a basement membran (Laminin green stain).

Institute of Radiology

Chair of Diagnostic Radiology

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Research Focus
- Methods of dosage reduction in medical imaging
- X-ray induced DNA damages in radiology
- Functional and metabolic MRI
- Imaging of the head and neck
- Interventional radiology
- Cardiovascular imaging
- Breast imaging

Structure of the Department

The Institute of Radiology of the FAU has four subsections (internal medicine, surgery, pediatric radiology, and gynecology). There is an intense cooperation with the Department of Neuroradiology. The staff of the Institute consists of 37 medical doctors (thereof four professors and five assistant professors) and 68 radiographers/assistants (as of end of 2012).
The Institute of Radiology provides the full range of radiological imaging modalities. Furthermore, a variety of interventional procedures, like imaging guided biopsies or angiographic therapies, is performed.
In cooperation with Siemens Healthcare, the Imaging Science Institute (ISI) is operated and integrates new developments in diagnostic imaging and novel IT-solutions into the clinical routine and into the academic research (see own report).
Different study groups and projects evaluate the clinical impact of various imaging procedures or go for new developments. Furthermore, experimental laboratory studies play a well-established role in our scientific activities.

Research

Methods of dosage reduction in medical imaging

Project managers: Prof. Dr. M. Lell, Dr. M. May, Dr. W. Wüst, Dr. A. Eller, Dr. M. Scharf, Dr. M. Brand

The majority of diagnostic and interventional imaging procedures in radiology are associated with radiation exposure. CT is the major contributor to overall medical x-ray exposition. Different strategies are followed to reduce dose while maintaining diagnostic image quality. Current projects include high-pitch scanning, automated anatomy based tube voltage/tube current adaption, as well as organ based tube current adaption. Monte-Carlo-simulations provide volume data of dose distribution that allow for risk evaluation and analysis of dose reduction techniques.
Iterative reconstruction techniques are used and evaluated to reduce image noise which opens the possibility to use less photons for image acquisition and therefore reduce radiation exposure. Metal artifact reduction algorithms are developed and evaluated to reduce artifacts derived from metal hardware (surgical plates, prostheses, dental fillings, etc.).

X-ray induced DNA damages in radiology

Project managers: PD Dr. M. Küfner, Dr. M. Brand, Dr. M. May, PD Dr. S. Schwab, C. Engert, Prof. Dr. M. Uder
Established dose parameters, as DLP or DAP, can detect the physical exposure, but give no evidence about the individual, biological radiation effects. These effects depend on individual factors, like age, body weight, or by the genetic disposition. Double-strand breaks (DSB) are among the most significant radiation induced DNA damages. DSB can be detected by using an immunofluorescence microscopic technique. The sensitive method is based on the phosphorylation of the histone variant H2AX after DSB formation and staining with specific antibodies.
Recent studies have shown a strong correlation between DSB levels and the dose deposed in blood lymphocytes of patients undergoing CT-scans, cardiac-CT, PET-CT, mammography, or angiography. Within 24 to 48 hours after exposure, the number of DNA lesions returned to the baseline levels due to repair. In angiography, DNA damages were also dependent on the anatomic region exposed and the duration/fractionation of the exposure.
In current studies, the influence of new CT-technologies (e.g. Dual-source CT, Flash-CT with high-pitch, Flat-panel CT) and of dose reducing approaches (e.g. risk organ based current modulation or lens protection tools) on the biological dose is investigated in patients and in biological phantom models as well. Furthermore, the potential protective effect of antioxidants/radical binding substances could be proved in vitro and in vivo, and there will be further investigations on this topic.

Functional and metabolic MRI

Project managers: Prof. Dr. M. Uder, PD Dr. R. Janka, Dr. M. Hammon, PD Dr. S. Alibek, Prof. Dr. A. Cavallaro
Diffusion weighted imaging (DWI) visualizes the diffusion of free water molecules in tissue. The physiological amount of diffusion is disturbed in tissue with higher cell density particularly in tumors. The use of DWI develops more and more to the third component of MR imaging beside morphology and contrast enhancement characteristics.
In MRI, perfusion measurements without the use of contrast material are possible. For that purpose, the inflowing (arterial) spins are labeled magnetically and their concentration in the organ of interest can be measured as signal intensity. Our focus of interest is on the kidney where the effect of antihypertensive therapy on the kidney perfusion can be visualized directly.
Sodium can be used to perform MR imaging in a similar way as hydrogen. With sodium MRI, we are able to measure the sodium concentration in tissue non-invasively. Research on this imaging method is focused on its further technical development, its absolute calibration, and the evaluation of possible clinical applications.

Imaging of the head and neck

Project managers: Prof. Dr. M. Lell, Dr. M. Kramer, Dr. M. May, Dr. A. Eller, PD Dr. S. Schwab
Methodological and clinical studies evaluating the use of CT und MRI in morphological and functional imaging of head and neck tumors. Cooperation with the Department of Otorhinolaryngology - Head and Neck Surgery (Prof. Dr. H. Iro), Department of Oral and Cranio-Maxillofacial Surgery (Prof. Dr. Dr. F.W. Neukam), and the Department of Radiation Oncology (Prof. Dr. R. Fietkau).
Methodological and clinical studies evaluating the use of CT and MRI in the preparation and planning of reconstructive surgery in cooperation with the Department of Oral and Cranio-Maxillofacial Surgery (Prof. Dr. Dr. F.W. Neukam).

Interventional radiology

Project managers: Prof. Dr. M. Uder, Dr. A. Schmid, PD Dr. M. Küfner, Dr. M. Heinz, Prof. Dr. M. Lell, PD Dr. R. Janka
Cooperations with the Department of Surgery (Prof. Dr. Dr. h.c. W. Hohenberger), the Department of Vascular Surgery (Prof. Dr. W. Lang), the Department of Medicine 4 - Nephrolo-

gy and Hypertension (Prof. Dr. K.U. Eckardt), the Division of Nephropathology (Prof. Dr. K. Amann), the Department of Medicine 1 - Gastroenterology, Lung Diseases and Endocrinology (Prof. Dr. M.F. Neurath), and the Department of Nuclear Medicine (Prof. Dr. T. Kuwert). The relevance of the recently established endovascular radiofrequency ablation of sympathetic nerve fibres in renal arteries is evaluated in patients with resistant hypertension. In patients with contraindication to the standard percutaneous biopsy of kidney transplants, an alternative transvenous biopsy procedure via a transfemoral approach is established. Selective internal radiotherapy and CT-guided irreversible electroporation are initiated in patients with liver malignancies. New software tools in CT-guided interventions are evaluated.

Cardiovascular imaging

Project managers: PD Dr. K. Anders, PD Dr. R. Janka, Prof. Dr. M. Lell, Dr. M. Scharf, Dr. M. May, Dr. A. Schmid, Dr. W. Wüst

- Pre-clinical and clinical studies in cooperation with the Department of Medicine 2 - Cardiology and Angiology (Prof. Dr. W.G. Daniel, Prof. Dr. S. Achenbach) to evaluate CT and MR for morphological and functional imaging of apparent coronary artery disease;
- Pre-clinical and clinical studies in cooperation with the Department of Medicine 2 - Cardiology and Angiology (Prof. Dr. W.G. Daniel, Prof. Dr. S. Achenbach) in line with the "Excellenzclusteriniative", project BD-02, to evaluate the potential of coronary CT-angiography in early diagnosis of coronary artery sclerosis;
- Pre-clinical and clinical trials to standardize reading and reporting of coronary CT-angiography;
- Pre-clinical and clinical trials in cooperation with the Department of Medicine 2 - Cardiology and Angiology (Prof. Dr. S. Achenbach), the Institute of Medical Physics (PD Dr. W. Kemmler), and the Division of Trauma Surgery (Prof. Dr. F. Hennig) using cardiac MRI (cMRI) to assess physiological myocardial adaptation in recreational and professional athletes in cross-sectional and longitudinal studies;
- Pre-clinical and clinical trials in cooperation with the Divisions of Pediatric Cardiology (Prof. Dr. S. Dittrich) and Pediatric Cardiac Surgery (Prof. Dr. R. Cesnejvar) to evaluate cMRI in the diagnosis of congenital heart disease;
- Clinical trials to optimize contrast use for 3T-MRA.

Breast imaging

Project managers: Prof. Dr. R. Schulz-Wendtland, PD Dr. E. Wenkel, PD Dr. R. Janka, PD Dr. S. Schwab, Dr. B. Brehm, Dr. M. Meier-Meitinger, PD Dr. B. Adamietz

Breast imaging (gynecologic radiology) is an important research domain of the Institute of Radiology. This research team addresses questions in the field of new developments in digital mammography in cooperation with different medical systems manufacturers. On the basis of substantial experimental and clinical studies, their work includes development, implementation, and comparison of different digital mammography systems, including tomosynthesis (hybridsystems). Volumetric analysis of tumors by mammography and (automated) ultrasound and the further characterization of breast masses by sonographic elastography are under investigation. Furthermore, a recently introduced MRI-based method for diagnosing ductal disease is being continuously evaluated. Another main focus in breast MRI lies in the development of new MRI sequences for better differentiation between malignant and benign breast disease.

Teaching

Besides the university standard lectures and practical courses, innovative clinically orientated courses as interactive discussions of clinical cases are offered regularly. In these courses the students are taught a much more analytic and clinical than systematic approach towards the interpretation of radiologic images. A new online course for students to prepare effectively for the state examination was established. Furthermore, we always offer the possibility to perform clinical electives or internships at our Institute. Students wanting a doctor's degree are supervised when writing their experimental or clinical thesis.

Selected Publications

Meier-Meitinger M, Häberle L, Fasching PA, Bani MR, Heusinger K, Wachter D, Beckmann MW, Uder M, Schulz-Wendtland R, Adamietz B (2011) Assessment of breast cancer tumour size using six different methods. Eur Radiol, 21: 1180-7

Eller A, May MS, Scharf M, Schmid A, Kuefner M, Uder M, Lell MM (2012) Attenuation-based automatic kilovolt selection in abdominal computed tomography: effects on radiation exposure and image quality. Invest Radiol, 47: 559-65

Kuefner MA, Brand M, Ehrlich J, Braga L, Uder M, Semelka RC (2012) Effect of antioxidants on X-ray-induced γ-H2AX foci in human blood lymphocytes: preliminary observations. Radiology, 264: 59-67

Lell MM, Meyer E, Kuefner MA, May MS, Raupach R, Uder M, Kachelriess M (2012) Normalized metal artifact reduction in head and neck computed tomography. Invest Radiol, 47: 415-21

May MS, Deak P, Kuettner A, Lell MM, Wuest W, Scharf M, Keller AK, Häberle L, Achenbach S, Seltmann M, Uder M, Kalender WA (2012) Radiation dose considerations by intra-individual Monte Carlo simulations in dual source spiral coronary computed tomography angiography with electrocardiogram-triggered tube current modulation and adaptive pitch. Eur Radiol, 22: 569-78

Anders K, Achenbach S, Petit I, Daniel WG, Uder M, Pflederer T (2013) Accuracy of automated software-guided detection of significant coronary artery stenosis by CT angiography: comparison with invasive catheterisation. Eur Radiol, 23: 1218-25

International Cooperations

Prof. L. Defreyne, University Hospital Gent, Gent: Belgium

Prof. M. Takahashi, National Cancer Center, Tokyo: Japan

Prof. D. Enzmann, University of California UCLA, Los Angeles: USA

Meetings and International Training Courses

25.-27.03.2011: Moderne Mammadiagnostik, Erlangen

30.06.-02.07.2011: MR Compact, Bamberg

24.-25.09.2011: Mammasonokurs, Erlangen

27.-29.04.2012: Moderne Mammadiagnostik, Erlangen

14.-16.06.2012: MR Compact, Bamberg

29.-30.09.2012: Mammasonokurs, Erlangen

Research Equipment

Siemens, Magnetom Verio

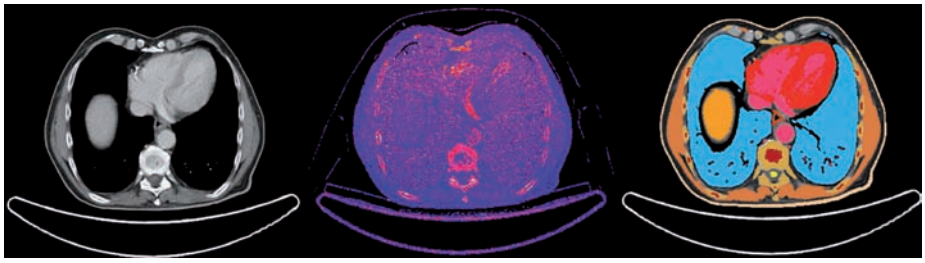
Siemens, Magnetom Aera

Siemens, Somatom Definiton AS+

Siemens, Somatom Definition Flash

Siemens, Artis floor mounted system

Siemens, Mammomat Inspiration



Monte-Carlo-Simulation of dose distribution.
Left: Grayscale image; Middle: Dose distribution; Right: Organ segmentation.

Institute of Radiology

Division of Neuroradiology

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Research Focus

- Clinical and experimental validation of flat-panel volume CT
- Multimodal imaging of cerebrovascular diseases
- Preoperative comprehensive imaging of epilepsy
- Functional and metabolic MR-Imaging
- Quantitative and qualitative assessment of optical fiber tracts in glaucoma patients using diffusion tensor imaging
- Standardization of acquisition and post-processing MRI perfusion techniques (SAPP)
- Multimodal imaging in glioma and validation and development of new interventional therapies
- Simulation of hemodynamics and fluid dynamics in cerebral aneurysms

Structure of the Department

In the Division of Neuroradiology, a total of 39 staff members are employed. Research is performed by twelve medical doctors, five postgraduates, and – externally funded – by a biologist, two physicists, 16 medical technical assistents, two study nurses, and a veterinarian, respectively.

The Division of Neuroradiology performs the neuroradiological work-up for patients of the UK Erlangen and for many patients referred from external hospitals. A special focus is the endovascular therapy of neurovascular diseases, such as acute stroke, aneurysms, stenoses of neck and brain vessels and arteriovenous malformations (AVMs), and the minimal-invasive therapy of spinal pain syndromes.

Research

Clinical and experimental validation of flat-panel volume CT

The project is part of the Leading Edge Cluster Medical Valley, Network „Imaging". In cooperation with the Department of Medical Physics, Siemens Healthcare, and the Department of Computer Science/Institute of Pattern Recognition, we evaluate and further develop intravenous and intraarterial flat-panel volume CT and angiographic techniques and postprocessing algorithms in cerebrovascular disease. Hereby, a focus is set on the optimized visualization of cerebral microimplants, such as stents, coils and clips and new perfusion techniques and 3D visualizations in stroke patients.

Multimodal imaging of cerebrovascular diseases

In cooperation with the Department of Neurology, we participate in several acute stroke studies. Using multimodal MR imaging algorithms, including perfusion- and diffusion-weighted imaging, diffusion tensor imaging, susceptibility-weighted imaging, arterial spin labeling, and contrast-enhanced angiographic imaging, we evaluate the individual indication for acute stroke therapies, such as intravenous thrombolysis, intraarterial thrombectomy, and/or other neuroprotective therapies. Hereby, a main focus is the MR-derived patient selection for mechanical thrombectomy. Another clinical and scientific focus is the evaluation and validation of mechanical devices for revascularization strategies in acute cerebral stroke.

Preoperative comprehensive imaging of epilepsy

In cooperation with the Epilepsy Center/Department of Neurology and the Department of Nuclear Medicine, we evaluate different multimodal imaging strategies in the preoperative work-up of patients with focal seizures refractory to best medical treatment. A major focus is put on high-resolution morphologic and functional MR imaging, i.e. MR spectroscopy, diffusion tensor imaging, functional MRI, perfusion- and diffusion-weighted MRI, and MR volumetry/voxel-based morphometry. Additionally, a dedicated GABA-specific MR spectroscopy sequence is used to evaluate different antiepileptic therapies.

Functional and metabolic MR-Imaging

There are several ongoing research projects in cooperation with different departments and facilities (i.e. Department of Psychiatry and Psychotherapy, Division of Child and Adolescent Mental Health, Division of Psychosomatics and Psychotherapy, Department of Medicine 3 - Rheumatology and Immunology, Department of Neurology, Institute of Physiology and Pathophysiology, Institute of Experimental and Clinical Pharmacology and Toxicology) involving functional and metabolic MR-Imaging (e.g. patients with major depressive disorders, anxiety- and eating disorders, chronic pain syndromes, and rheumatoid arthritis).

Quantitative and qualitative assessment of optical fiber tracts in glaucoma patients using diffusion tensor imaging

In cooperation with the Department of Ophthalmology and Computer Science, we evaluate diffusion tensor imaging (DTI) using 3 Tesla MRI to assess quantitative and qualitative changes within the optical fiber tracts in glaucoma patients at a very early stage. Disorders in optical fiber tracts result in reduced fractional anisotropy (FA) and atrophy of the tracts which can be used for non-invasive and fast screening, staging and to evaluate therapeutical strategies in glaucoma. Moreover, first results indicate that DTI can distinguish at an early stage between different forms of glaucoma that require diverse treatment.

Standardization of acquisition and post-processing MRI perfusion techniques (SAPP)

Broad clinical application of cerebral MR perfusion is limited due to heterogeneous MR protocols used in the investigations published up to date and limited size of study collectives. Therefore an international, prospective, blinded crossover multicenter trial lead by the Department of Neuroradiology was designed in cooperation with Bayer AG und four international Centers (Mailand/Italy, Upsala/Sweden, Ontario/Canada, and Los Angeles/USA). In a first step, the research team developed a standardized MR-perfusion protocol. As next step, a large database will be generated based on sequence and contrast media parameters. Collected data will be investigated by means of technical and radiological parameters and clinical outcome.

Multimodal imaging in glioma and validation and development of new interventional therapies

In cooperation with the DFG Research Group FOR 661 (see own report), the Department of Neurosurgery, the Institute of Experimental and Clinical Pharmacology and Toxicology (Preclinical Imaging Platform Erlangen, PIPE), and the Department of Nuclear Medicine, we evaluate multimodal imaging and new therapy strategies in experimental brain gliomas, using micro-CT, high-field MRI, and micro-PET. Additionally, using an elastase-induced and a surgical aneurysm model, we evaluate different imaging techniques and new materials and techniques for endovascular treatment and follow-up care.

Simulation of hemodynamics and fluid dynamics in cerebral aneurysms

In cooperation with the Department of Computer Science/Institute of Pattern Recognition, Siemens Healthcare, and the Department of Chemical Engeneering/Fluid Mechanics, we evaluate the hemodynamic and fluid dynamics in cerebral aneurysms and malformations. A special focus is put on the effects of different endovascular therapies using different endovascular microimplants, such as stents and coils. Medium-term intention is the development and clinical implementation of a software-platform used by endovascular radiologists.

Teaching

The Department of Neuroradiology is involved in training medical students. We offer a variety of lectures and practical courses, partially in cooperation with the Departments of Neurology and Neurosurgery, Ophthalmology, Computer Science, Medical Engineering, Psychiatry and Psychotherapy, and General Radiology. In addition, we train residents in neuroradiology and general radiology and radiological technicians.

Selected Publications

Engelhorn T, Schwarz MA, Heusch G, Doerfler A, Schulz R (2011) Reduction of cerebral infarct size by dronedarone. Cardiovasc Drugs Ther, 25: 523-9

Kloska SP (2011) CT angiographic source images with modern multisection CT scanners: appropriate injection protocol is crucial. AJNR Am J Neuroradiol, 32: E93; author reply E94

Struffert T, Ott S, Adamek E, Schwarz M, Engelhorn T, Kloska S, Deuerling-Zheng Y, Doerfler A (2011) Flat-detector computed tomography in the assessment of intracranial stents: comparison with multi detector CT and conventional angiography in a new animal model. Eur Radiol, 21: 1779-87

Struffert T, Deuerling-Zheng Y, Kloska S, Engelhorn T, Boese J, Zellerhoff M, Schwab S, Doerfler A (2011) Cerebral blood volume imaging by flat detector computed tomography in comparison to conventional multislice perfusion CT. Eur Radiol, 21: 882-9

Engelhorn T, Michelson G, Waerntges S, Otto M, El-Rafei A, Struffert T, Doerfler A (2012) Changes of radial diffusivity and fractional anisotopy in the optic nerve and optic radiation of glaucoma patients. ScientificWorldJournal, 2012: 849632

Gölitz P, Struffert T, Knossalla F, Saake M, Ott S, Ganslandt O, Doerfler A (2012) Angiographic CT with intravenous contrast injection compared with conventional rotational angiography in the diagnostic work-up of cerebral aneurysms. AJNR Am J Neuroradiol, 33: 982-7

International Cooperations

Prof. C. Strother, Department of Radiology, University of Wisconsin, Madison: USA

Dr. A. Bose, Department of Radiology and Neurology, Lenox Hill Hospital New York, New York: USA

Prof. Dr. I. Wanke, Prof. Dr. D. Rüfenacht, Institute of Neuroradiology, Klinikgruppe Hirslanden, Zurich: Switzerland

Prof. Dr. A. El-Rafei, Faculty of Engineering, Ain Shams University, Cairo: Egypt

Prof. Dr. F.A. Fellner, Dr. J. Trenkler, Institute of Radiology and Neuroradiology, AKH Linz, Linz: Austria

Meetings and International Training Courses

11.-12.02.2011: Workshop "Advanced Neuro-MRI", Erlangen

21.-22.10.2011: Workshop "Advanced Neuro-MRI", Erlangen

02.12.2011: Kursus "Neuroradiologie", Update Neurologie und Psychiatrie, Düsseldorf

09.-10.05.2012: Workshop "Innovations in Interventional Neuroradiology", Erlangen

22.-23.06.2012: Workshop "Advanced Neuro-MRI", Erlangen

11.-12.07.2012: Workshop "Innovations in Interventional Neuroradiology", Erlangen

24.-25.10.2012: Workshop "Innovations in Interventional Neuroradiology", Erlangen

06.-07.11.2012: Workshop "Zerebrale Aneurysmatherapie", Erlangen

07.12.2012: Kursus "Neuroradiologie", Update Neurologie und Psychiatrie, Düsseldorf

Research Equipment

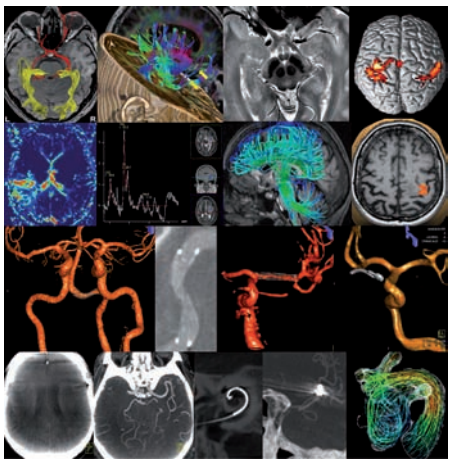
Siemens, 3 Tesla Magnetom TimTrio MRT

Siemens, 1.5 Tesla Magnetom Aera MRT

Siemens, Somatom Definition AS+; 128-Zeilen-CT

Siemens, Axiom Artis dBA

Siemens, Siemens Axiom Artis zeego



The main focus of the Department of Neuroradiology is state-of-the-art imaging of cerebrovascular disease, tumors, and epilepsy and interventional neuroradiology.

Human Medicine

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Aims and Structure

In the winter term 2011/2012, 2,116 students were enrolled in the study program of Human Medicine (185 in the 1st term) and in the summer term 2012 this number was 2,170 (175 in the 1st term). The percentage of women studying Human Medicine decreased as compared to the winter term 2010/2011. In the winter term 2011/2012 62.8% of the enrolled students were female and in the summer term 2012, there were 61.4% female students.
According to statistics of the FAU, for the winter term 2011/2012 and the summer term 2012, 6.9% of the students enrolled in the study program of Human Medicine were foreigners.
Applicants for this degree program are chosen according to the criteria of the "Stiftung für Hochschulzulassung" (foundation for higher education admission, the successor of ZVS) through the corresponding online platform. Applicants are able to improve their chances of receiving a place on the degree program of Human Medicine in Erlangen by taking the so-called "Test für medizinische Studiengänge" (test for medical degree programs). Taking the test is, however, optional. Applicants who decide to take the test can, for the selection process in Erlangen, improve their grade of the final secondary school examinations (Abitur).

Online-Evaluation

Each term, all courses are evaluated online by the students with the help of the online evaluation platform EvaSys. The results of the online evaluation are presented and discussed in the central faculty meeting once per term by the Dean of Student Affairs. A major part of the state funds is distributed in the UK Erlangen according to the results of the online evaluation. Each term the students vote for the best lecturers and monetary sums are awarded to the clinic or institute to which the winners belong. It is noteworthy that teaching awards are financed by the achievement-oriented funds allocation (LOM). Clinics and institutions whose instructors do best in the online evaluation receive grants for good teaching performance. The best three instructors of the clinical part of the degree program (terms 5 – 10) for Human Medicine receive grants of 5,000, 3,000, and 2,000 Euro, respectively. For the degree programs Dentistry, Molecular Medicine, and Medical Process Management, the best instructors receive 5,000 Euro each. Instructors in the pre-clinical or theoretical part of the medical degree program (term 1 - 4) receive certificates only; grants cannot be awarded due to cameralistic accountancy. Additionally, the departments that offer the top ten classes - according to the student evaluations - are awarded a total of 165,000 Euro. A class can, however, only be taken into account for a grant if it has been evaluated by at least 20% of the students in the particular term.

Skills Lab PERLE

The Skills Lab PERLE offers students an opportunity to practice medical examination skills while being instructed by well-trained student-tutors and doctors. Students can practice about 30 different skills, e.g. auscultation, catheterization, taking blood with the help of artificial arm-models, lumbar puncture, suturing, examination of nervous system as well as of eye and ear, preparation for clinical electives (Famulaturen) and the practical year (Praktisches Jahr). Skills Lab PERLE, fully funded by student fees, is a visible enrichment of the medical education in Erlangen. Courses can be attended by all students during the term. Additionally, PERLE offers special courses during the lecture free time. In addition, practicing in PERLE within the frameworks of the Introduction into Clinical Medicine (EKM) course is a part of the Human Medicine curriculum.

Medical State Examination

In the study year 2011/12, the Human Medicine students in Erlangen achieved very good results in the First Medical State Examination (1. Abschnitt der Ärztlichen Prüfung). According to the statistics of the German Institute for Medical and Pharmaceutical Examination Questions (IMPP), the examination results of the Human Medicine students in Erlangen have been ranking among the top results of the medical departments in Germany for many years.

Dentistry

Speaker
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Aims and Structure

The school of dentistry at the FAU admits approximately 110 students per year, despite the fact that our clinical facilities were originally designed to accommodate a maximum enrollment of 100 students. The overall amount of time dedicated to curriculum teaching and examinations at dentistry school is quite considerable, given the extensive role played by practical training, compared to what is the case with students taught at the Faculty of Medicine. New licensing regulations for the practice of dentistry have been formulated, but are not likely to go into effect for the foreseeable future. The fact that new licensing regulations for the practice of 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 first phase of the Faculty of Medicine, the calculation of admission figures for dentistry school 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 dentistry school as opposed to somewhere between three and six students per academic staff member in the Faculty of 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 dentistry school curriculum 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 our dentistry school. 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.

Our Dental Department is equipped with high-quality technical systems in sufficient numbers so that we have no trouble satisfying the demands and needs that arise in connection with dentistry training. National and international quality comparisons show that our standards are very good. All the necessary prerequisites are given for our students to receive modern, clinically oriented training in the field of dentistry.

Phantom head course within the Department of Operative Dentistry: Training at simulation models.

Molecular Medicine

Speaker
Prof. Dr. rer. nat. Michael Wegner

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Aims and Structure

The degree program in Molecular Medicine combines the subjects of experimental medicine and the approaches of molecular biology, biochemistry, and genomics. This program acknowledges the fact that boundaries which traditionally separated biomedical disciplines have long lost their meaning. The Faculty of Medicine offers a future-oriented program for medical scientists interested in research careers in industry, administration, and academics. Nationwide, this program in Molecular Medicine is met by an extraordinary interest. Each academic year 38 students are admitted from more than 1,000 applicants. With the winter term 2007/2008, the diploma program was transformed into a consecutive B.Sc./M.Sc. program which was established according to the guidelines of the Bologna declaration. The first master students graduated in the summer of 2012.

Objectives

The advances in biomedical research continually change our knowledge and understanding of basic biological mechanisms and disease-induced alterations, reflected in new and improved therapies. The consecutive B.Sc./M.Sc. program in Molecular Medicine addresses the necessity to teach both, medical and bioscientific contents. The interdisciplinary curriculum aims at preparing our students for the challenges of medical research and enables them to become independent researchers.
The B.Sc. program spans six terms in which a solid education in all basic disciplines of Molecular Medicine is achieved. The core curriculum in Molecular Medicine is mainly taught by preclinical and theoretical institutes and the NFZ. The first academic year focuses on the basic sciences that are taught by the science faculties (physics, inorganic/physical/organic chemistry). The preclinical aspects are the focus of the second year, while pathology and experimental therapy conclude the curriculum in the last year. The B.Sc. program ends with a scientific thesis.
The main goal of the consecutive two year master program is to convey a deeper understanding of science by working with original publications and extended practical training. Whereas the B.Sc. curriculum teaches the basics of single disciplines, the M.Sc. program focuses on interdisciplinary topics which are taught by the Institutes of Biochemistry, Physiology and Pathophysiology as well as the Departments of Neurology and Psychiatry and Psychotherapy, respectively. The Master program ends with a thesis of six month.
Another focus of the theoretical part of the program is molecular imaging. This module represents another scientific strength of Erlangen, as it puts the program at the interdisciplinary junction between basic science and industrial application.
The first year students in Molecular Medicine are welcomed by an annual symposium, introducing them to the program and the Faculty of Medicine of the FAU. In recent years, these symposia have encountered an extraordinary interest among the new students. Moreover, students are offered support by an academic mentoring program. The mentors are recruited among the lecturers involved in the B.Sc. program, ensuring easy communication between students and faculty. The participation of student representatives in the study committee ensures the active involvement and participation of the students in the further development of the degree program.

Applications, development of student numbers, and implementation of the program

Potential applicants are introduced to the program in Molecular Medicine by the advisory service of the Faculty of Medicine, the central advisory service of the FAU, as well as by brochures and the internet homepage. At present, half of the students enrolled in Molecular Medicine are in-state students from Bavaria, while the other half originate from other German states or are international students. This situation demonstrates the nationwide attractiveness of our study program. Having asked students for their alternative choices in case they would not have been admitted to Molecular Medicine, most students listed medicine, biochemistry, or biotechnology.
Presently, more than 30 applicants compete for one admission slot in Molecular Medicine. For several years, the admission requirements for the program have been constantly at the highly selective grade point average of 1.4. Admission procedures follow federal and state regulations (Bayerische Hochschulzulassungsverordnung). Accordingly, 90% of admissions are based on the Gymnasium grade point average, while another 10% of admissions are granted based on a waiting period.
Following the guide lines from the Bologna declaration, the B.Sc./M.Sc. Molecular Medicine is characterized by close-meshed and course-related exams which are continuously documented in an electronic management system. In the master program, the higher portion of practical courses allows an individualized curriculum. The first two months of the third M.Sc. term are intended as a "mobility window" to facilitate the integration of international internships and industrial placements.

Perspectives

The degree program in Molecular Medicine offers the opportunity to join a high-quality doctoral program at the FAU. Graduates may enrol in a doctoral program (Dr. rer. nat.) offered in collaboration with the Faculty of Sciences. The degree program in Molecular Medicine enables its students to successfully contribute to scientific and practical work in medical research, laboratory diagnostics, and medical biotechnology. A variety of occupational fields in industry, private laboratory, and public institutions are available to the graduates of Molecular Medicine. Industrial employment options include research and development as well as production and quality control, marketing, or administration. Private laboratories, hospitals, and authorities depend on university graduates experienced in molecular diagnostics, DNA and protein diagnostics for medical and biotechnological applications.
The degree program in Molecular Medicine has already proven its concepts through successful professional and academic careers of its graduates which currently have positions in national and international research institutions (e.g. assistant professor at Havard Medical School) and in industry (e.g. Novartis or Roche). Graduates of the first generation are already holding professorships.

Medical Process Management

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Aims and Structure

The degree program in Medical Process Management (MPM) is a non-consecutive M.Sc. program. Lectures are taking place at the FAU. In order to be admitted to this full-time study program, candidates require an academic degree (e.g. bachelor's or master's degree). There is a particular interest in receiving applications by graduates of the following subjects: Natural sciences, computer sciences, engineering, law, economics, social sciences, medicine, dentistry, and molecular medicine.

Participating in this degree program, students are able to gain a thorough knowledge of both, medical contexts and approaches of treating in an integrated manner. Besides, the curriculum offers broadly diversified insights into the structures of the German healthcare system and into business process management in the healthcare sector. Additionally, fundamental questions are dealt with concerning quality and risk management, financial management, medical information technology, and psychology of communication.

All in all, the degree program in MPM connects medicine and healthcare to business process management and information technology. Strengthening patient-orientation approaches, improving the quality of medical care, and increasing efficiency in the healthcare sector are the topics that make up the curriculum's key focus.

Courses are both highly interconnected and interdisciplinary in order to make sure that knowledge and skills are conveyed in a successful manner. Thus, it is not only the Faculty of Medicine that is responsible for 30 different courses of the degree program, but also two other faculties. With reference to the number of European Credit Transfer and Accumulation System (ECTS)-credits, 52% of teaching is done by the Faculty of Medicine. The corresponding figures are 15% for the Faculty of Business, Economics, and Law, and 4% for the Faculty of Engineering, respectively. About one third of the courses are jointly carried out by at least two faculties.

MPM is a "highly application-oriented" degree program. Preparing the students for their future professional life therefore is a pivotal goal. By working as interns in medical facilities or healthcare-related companies for a minimum of twelve weeks, the students get to know the working environment in the healthcare sector.

The degree program starts each October. It is made up of three terms plus the time needed for writing the master's thesis. Generally, students graduate after four terms. A total of 120 ECTS-credits is necessary to successfully complete the degree program. Students graduate as soon as they fulfill the following conditions: Firstly, they must have passed all exams which are written in the course of the first three terms. Secondly, they must have completed their internships. And thirdly, their master's thesis must have been accepted (including a thesis defense). The degree program in MPM has been existing for five years. While it was taken up by 20 students in 2008, already 30 students enrolled one year later, and in 2012, the number amounted to 33 students, respectively.

MPM is more than just a new master's degree program: It is an innovative approach to tackle the challenges faced by healthcare systems in industrialized countries. So far, no other university in Germany offers a comparable study program. The degree program is geared towards the growing demand the healthcare market displays for specialists with analytical expertise in medical issues. Among other things, graduates are capable to analyze, plan, implement, and evaluate processes which take place in an interinstitutional and interprofessional realm. They are thus qualified, for instance, to work as process managers in hospitals and surgeries, as case managers for health insurances, and as network managers for healthcare networks. Furthermore, graduates are able to work for companies belonging to the pharmaceutical and medical engineering industry. The same applies to consulting companies, IT manufacturers and healthcare management organizations. So far, graduates have consistently been able to quickly gain ground on the labor market, having found very good jobs in the healthcare sector.

Speech Therapy

Speaker
Prof. Dr. med. Dr. rer. nat. Ulrich Eysholdt

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Aims and Structure

With the passage of the "Gesetz zur Einführung einer Modellklausel in die Berufsgesetze der Hebammen, Logopäden, Physiotherapeuten und Ergotherapeuten", the B.Sc. degree program Speech Therapy was established at FAU in winter term 2011/12. The program is met by great nationwide interest. Out of 500 applicants, 15 students are admitted every year.
The practical training predominantly takes place at the Institute of Speech Therapy. In order to ensure a sound hands-on clinical education, the training is supervised by teachers of speech therapy. The practical training is enhanced by liaison with collaborative partners as well as internship blocks which comply with the existing quality standards.
External internships deepen the knowledge about the treated speech defects.
As the degree program was developed out of a vocational education (Ausbildung) in a full-time vocational school (Berufsfachschule) and is devised as a model degree program, its students are still required to pass the national exam as speech therapists at the end of the sixth term.

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 therapy. It enables its students to treat their patients independently and with a profound scientific knowledge. It is a full-time degree program that is completed after seven terms with a B.Sc. degree.
Hands-on training and science are complementary and can use synergetic effects resulting from the multidisciplinary nature of speech therapy which bases on the disciplines medicine, linguistics, psychology, and pedagogics.

Application Procedure

Admission requirement for the degree program Speech Therapy is the general qualification for university entrance (allgemeine Hochschulreife) / subject specific qualification for university entrance in Social Studies (13.Klasse). Application procedures follow the regulation "Verordnung über die Zulassung zu den öffentlichen Berufsfachschulen für Logopädie" from 19.12.2005. A preselection of applying students is conducted by drawing lots.

Perspectives

Speech therapists diagnose and treat among others communication and swallowing disorders and counsel patients and their relatives. Within their domain, speech therapists work independently and assume responsibility for their work.
Potential occupational areas for speech therapists are within the health care sector, e.g. in hospitals, rehabilitation centers, centers of speech therapy, their own practice, or as freelancers. Furthermore, they may find employment within the fields of teaching, science, or research.

Interdisciplinary Center for Clinical Research (IZKF)

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Aims and Structure

The Interdisciplinary Center for Clinical Research (IZKF) is a central structure of research development at the Faculty of Medicine. Its mission is to improve the overall quality of clinical research at the Faculty of Medicine, to stimulate interdisciplinary research, to advance the careers of young scientists, and to foster the acquisition of extramural funds. It was established in 1996 under the major topic "Inflammatory Processes: Etiopathogenesis, Diagnostics, and Therapy". During the first eight years (1996-2004) it received regressive funding from the BMBF within the program "Health related research 2000". Since 2004 it has been fully funded by the Faculty of Medicine within the UK Erlangen and the FAU. The initial scientific focus on inflammation research could be further developed to also accommodate all other focal research areas and interdisciplinary fields of the Faculty without sacrificing this distinctive topic. This allows nearly all institutions of the Faculty of Medicine to file applications with IZKF. IZKF activities can be subdivided into three major areas:

Research Grants

The IZKF offers research grants which cover a 30 month period and include one graduate student, one technician, and consumables. If project leaders apply for external funding at the end of the project, funding for another six months is provided. Project leaders are expected to have an active publication record and own external funding. Preliminary results should yield the promise of a successful transfer of the project into external funding after the three years term. Innovative and original ideas and concepts are especially valued; the same applies to the clinical relevance and interdisciplinary approaches.

Core Facilities and Supporting Activities

Modern molecular technologies such as genomics, proteomics, and advanced molecular imaging require very expensive and sophisticated instrumentation and are methodologically very demanding. Core facilities or units are centralized platforms that offer access to these modern methods and technologies to a broad user spectrum. Core units also make sure that smaller groups and those with other methodological focus get access to these technologies. They also ensure that students get direct access to these modern developments. The IZKF offers an initial funding of core facilities covering up to five years.
Supporting activities include the "Visiting Professor Program" and a biennial international scientific meeting.
Various parameters are used to evaluate the performance of the IZKF in advancing clinically oriented research at the Faculty of Medicine. Scientific publications and academic success of young scientists are the most obvious and straightforward parameters. Furthermore, patents, scientific prizes, and offers of professorships are relevant parameters. In 2012, the 40 running projects altogether published 73 original articles with a cumulative impact factor (IF) of 432.2. The high quality of many of these publications is reflected in 55 publications with an IF > 3. Given the fact that IZKF funding starts at an early phase of a project, it can be considered as a high risk funding program. It is nevertheless reassuring that most of the projects are successful and thus likely to be transferred into extramural funding. In this context it seems noteworthy that nearly half of project leaders raise more extramural funds than they receive intramurally by IZKF.

Career Development

Support and development of young scientists has been a central goal of the IZKF since its inception. Two positions for junior research groups housed in the NFZ offer an attractive career development opportunity for outstanding young scientists with a training in medicine or natural sciences, a strong background, and reputation in one of the faculties' main research fields. Over a period of up to six years each junior research group receives funding for the group leader, one postdoctoral and one postgraduate scientist, one technical assistant and consumables. The group of Prof. Dr. J. Titze works on „Immune system as regulator of volume and blood pressure" and the group of PD Dr. B. Winner on "Modeling neurodegenerative diseases using stem cells".
In addition, the IZKF supports six positions for a laboratory rotation and 20 MD-thesis scholarships. Since 2009 the IZKF in collaboration with the ELAN-Fond has offered starting grants to young postdoctoral physicians and scientists up to 35 years of age without previous significant external funding. Candidates should have a visible publication record and projects should be based on an original idea with first tangible results. Project aids include a position for a technician or a doctoral student and consumables for two years. After this time it is expected that successful projects submit an external grant application.

Preclinical Experimental Animal Center (PETZ) of the Franz-Penzoldt-Center (FPZ)

Speaker
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Aims and Structure

The Preclinical Experimental Animal Center (PETZ) belongs to the Faculty of Medicine and is a facility of the Franz-Penzoldt-Center (FPZ) that serves as a state-of-the-art experimental animal facility for basic and preclinical research. The facility resources are primarily meant for users belonging to the Faculty of Medicine, but also offer state-of-the-art and appropriate animal housing with directly associated experimental facilities for other research groups and associations.
The Center is a research-oriented animal facility that provides for customers a modern infrastructure and specific-pathogen-free conditions for preclinical animal experiments. The center offers various research related services, e.g. import of transgenic mouse strains via embryo transfer as well as veterinary advice and supervision for surgical or toxicological studies on large or small animals. Already as early as the time of project application, the team of the PETZ provides competent references in all areas of the application processes and related questions regarding experimental strategy.
With its infrastructure, the PETZ supports effective and optimized science and enables translational medical research in a controlled, standardized environment most appropriate for each of the species. Our center represents a professional and reliable partner on the way from the scientific idea and the consecutive ways ultimately resulting in benefits for the human patients.

Research

The superior goal of the PETZ is the continuous implementation of the principles of reduction, replacement, or refinement (3R's) in experimental research with animals as well as the responsibility of constant optimization of the housing conditions to the benefit of both, animal welfare and quality of scientific results.
Central functions of the PETZ are:
– Providing a responsible and ethical animal treatment in accordance with the local and national law authorities,
– Optimizing and standardizing processes in animal housing,
– Implementing a modern quality assurance,
– Assuring continuous professional development of the scientific and technical personnel,
– Providing state-of-the-art research facilities,
– Establishing and providing core units especially in the area of animal phenotyping in order to assure an effective and standardized application in this highly specialized technical field.
The PETZ provides statutorily regulated areas of operation such as e.g. housing and experimental rooms that meet the safety levels for genetically modified organisms S1 and S2, and the biological safety levels (BSL) for infectious agents BSL I and BSL II. We take care that the experimental work within the facilities is carried out in accordance with the legal regulations of the German Infection Protection Act, Pharmaceuticals Act, Chemicals Act, and Medical Products Acts.
Currently, the PETZ is used as a modern animal facility by 34 academic chairs and 20 independent units of the FAU. Of these users, 49 are members of the Faculty of Medicine.

Teaching

The CU PTZ organizes qualifying professional development courses in laboratory animal science (e.g. FELASA courses), offers the opportunity to learn animal experimental techniques and functions as a training company (Ausbildungsbetrieb) for the recognized occupation requiring formal training "laboratory animal technician" which is certified by the chamber of industry and commerce (IHK). The Center is a competent venue for surgical trainings in students' education as well as in the professional development of experienced practitioners. It places a priority on being a family friendly institution and implements the principles of gender equality in its processes and management to help its staff achieve a work-life-balance.

Center for Clinical Studies (CCS)

Speaker
Prof. Dr. med. Dr. h.c. Wolfgang Rascher

Managing Director
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Aims and Structure

In 2008, the CCS Erlangen was founded as a service shared by the Faculty of Medicine of the FAU and the UK Erlangen. From an organizational point of view, it is affiliated with the UK Erlangen as one of its central facilities. Its tasks comprise:
1. Provision of counseling and support to members of the Faculty of Medicine and staff of the UK Erlangen for the conception, planning, conduct, and analysis of clinical studies, taking into account the relevant legal and regulatory requirements;
2. Administration of the insurance for participants in clinical studies;
3. Administration of the clinical studies database of the Faculty of Medicine;
4. Organization of educational events on all aspects of clinical studies.
Since its inception, the CCS Erlangen was involved in more than 250 clinical research projects of members of the Faculty of Medicine and staff of the UK Erlangen.
The CCS Erlangen comprises the departments of study management and clinical monitoring, quality management, pharmacovigilance, and data management.

Counseling and Support for Clinical Studies

Counseling

Each year, the CCS Erlangen provides a broad range of counseling services, especially in the preparatory phase of clinical studies. The main focus is on so-called investigator-initiated trials (IITs), planned and conducted by members of the Faculty of Medicine and staff of the UK Erlangen. The CCS Erlangen evaluates the feasibility of the research project from an economic and organizational perspective as well as adherence to the relevant legal and regulatory requirements. All counseling services are provided free of charge.

Study management and clinical monitoring

Prior to clinical study start, the CCS Erlangen offers various services, ranging from the generation of the study protocol to obtaining approval from competent authorities and endorsement of the study protocol by ethics committees. This includes multicenter and multinational clinical research projects.
During the conduct of the clinical study the CCS Erlangen provides clinical monitoring, if requested by the sponsor or the project leader.

Quality management

Institutions which assume sponsor responsibilities in clinical studies are required to follow standard operating procedures (SOPs). The CCS Erlangen Quality Management helps identify and develop the SOPs necessary for the fulfillment of sponsor duties.
If requested by the sponsor or the project leader, the CCS Erlangen performs audits of study sites or other institutions involved in a clinical study to assess their compliance with regulatory requirements. On request, the CCS Erlangen provides advice and guidance for inspections by the regulatory authorities and audits by the sponsor.

Pharmacovigilance

For clinical studies subject to AMG or MPG and sponsored by the UK Erlangen, the CCS Erlangen ensures the documentation and timely notification of serious adverse events according to legal and regulatory requirements. For this task the CCS Erlangen uses a dedicated and certified database.

Data management

In close collaboration with the Medical Center for Information and Communication Technology (MIK), the CCS Erlangen develops study-specific electronic case report forms. On demand, additional services such as the development of the data management plan or data cleaning prior to database lock, are available.

Administration of the insurance for participants in clinical studies

The CCS Erlangen administers the insurance for participants in clinical studies initiated by members of the Faculty of Medicine and staff of the UK Erlangen. This comprises obtaining insurance offers and accompanying the project until its conclusion.

Research

Clinical studies database of the Faculty of Medicine

The clinical studies database serves to present the clinical research efforts of the Faculty of Medicine. It contains prospective interventional clinical studies which may be listed according to predefined criteria, providing a survey of the clinical research activities.

Education

At the request of the Faculty of Medicine, the CCS Erlangen in collaboration with the Institute of Clinical Pharmacology and Clinical Toxicology has currently conducted more than 20 educational events for investigators, coordinating investigators, and staff involved in clinical studies. Along with conveying the relevant legal and regulatory requirements, the sessions focus on practical aspects and recommendations which may have a major impact on the feasibility and timely recruitment of clinical studies. Currently more than 400 physicians from the UK Erlangen and the associated academic teaching hospitals have attended the courses.

Comprehensive Cancer Center Erlangen-EMN

Director
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Aims and Structure

The Comprehensive Cancer Center Erlangen – European Metropolitan Region Nuremberg (CCC ER-EMN) is an interdisciplinary center of excellence established to coordinate medical care, research, and teaching. For patients, physicians, and scientific researchers, the CCC ER-EMN is the central contact for all questions connected to cancer diseases.
The center organizes further education and training courses on topics in oncology and coordinates research projects. In addition, the CCC ER-EMN runs a free tumor consultancy service for patients and their relatives.
Nationwide, there are currently only eleven institutions as leading centers for cancer research and treatment, sponsored by German Cancer Aid.
The CCC ER-EMN was founded in December 2007 as the Erlangen University Cancer Center by members of staff at the UK Erlangen and the Faculty of Medicine at the FAU. A cooperation agreement with Bamberg Hospital (Sozialstiftung Bamberg) and Bayreuth Hospital (Krankenhaus Bayreuth, Ltd.) was established in January 2013. The respective oncological centers at the Bamberg and Erlangen sites were certified in accordance with the German Cancer Society (DKG) criteria in 2011. At the Bayreuth site, DKG certification is planned for spring 2013.
Under the aegis of the CCC ER-EMN, there is a total of eleven certified organ cancer centers and 24 interdisciplinary tumor conferences in three oncological centers which are responsible for optimized patient care and multidisciplinary development of clinical pathways according to the most up-to-date standards.

Interdisciplinary treatment based on a clear plan

At the CCC's 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, patients have access to innovative therapeutic approaches.
All treatment decisions are taken jointly by the experts in each specialty, at meetings known as "tumor conferences."

Aims of the CCC ER-EMN

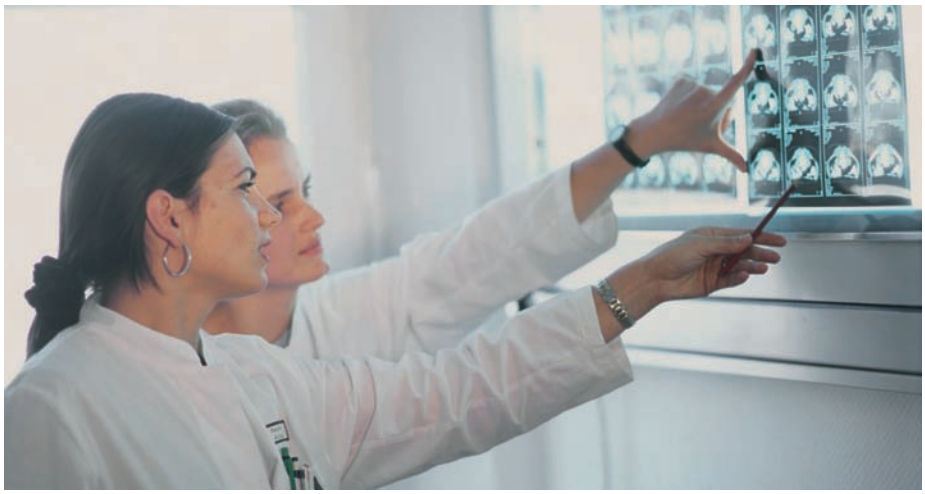
– Interdisciplinary and inter-organizational optimization of care for oncology patients;
– Interdisciplinary and inter-organizational support for cancer research at the level of clinical research, epidemiological research, translational research, and basic research;
– Support for regional collaboration in the field of tumor diagnosis, treatment, and follow-up care together with other hospitals — particularly university teaching hospitals, specialist oncology practices, specialist physicians and family doctors, hospices, and rehabilitation facilities;
– Support for interdisciplinary and inter-organizational teaching in oncology;
– Recruitment of highly talented junior staff for clinical care and research.

Research

If possible, patients are treated in the framework of clinical studies and directly benefit from clinical progress. This means that they can be treated in accordance with the highest safety standards in the context of clinical trials. Links with the Center for Clinical Studies (CCS) at UK Erlangen, with the study coordination offices at the cooperating hospitals and with the Franconia/Southern Thuringia trial network are available for this purpose.
Patient care and clinical research at UK Erlangen are supported by a structured IT approach. This consists mainly of the electronic patient file system Soarian™ and the data warehouse tool Cognos™. Supplementary to these IT systems there are commercial IT solutions for cancer registry, trial management, and biobanking. Data for cancer patients at UK Erlangen are collected in the clinical cancer registry. 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 both, tumor tissue 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.
There are currently major research groups for six different tumor entities at the CCC ER-EMN: breast cancer, leukemia and lymphoma, lung cancer, melanoma, renal cell cancer, and colorectal cancer. Approaches for other tumor entities are also being pursued.

Teaching

The center offers physicians, private medical practices, and hospitals the opportunity to receive further training in the various fields involved in oncology and to consult with experts in difficult treatment cases. In addition, the CCC ER-EMN provides a series of lectures for physicians and scientists in the field of cancer research as well as a further training program in oncology for family practitioners.



Emil Fischer Center (EFC)

Speaker
Prof. Dr. med. Andreas Ludwig

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Aims and Structure

The Emil Fischer Center (EFC) is an association of faculty members from the Faculty of Science and the Faculty of Medicine of the FAU. The center includes full and associate professors from the Chairs of Bioinorganic Chemistry, Biochemistry and Molecular Medicine, Biochemistry and Pathobiochemistry, Clinical Pharmacology and Clinical Toxicology, Pharmacology and Toxicology, Food Chemistry, Pharmaceutical Biology, Pharmaceutical Chemistry, and Pharmaceutical Technology.
The objective of the interdisciplinary center is the promotion and conduction of joint research as well as educational projects between pharmaceutical sciences, food chemistry, chemistry, and molecular medicine. The members' scientific work is interlinked by the EFC which operates a core unit "Bioanalytics" and several basic technical facilities. The EFC represents the members in respect to external contacts, coordinates interdisciplinary fund-raising activities, and serves as a platform for cooperation with partners from the pharmaceutical and food industry. Research and teaching activities at the EFC are supported by several organizations and research collaborations, such as the SFB 583 and SFB 796, KFO 130, FOR 661, the DFG graduate program 1071, the BMBF, the European Union (EU), and the Elite Network of Bavaria.
Interdisciplinary post-graduate training is accomplished by the Emil Fischer Graduate School (EFS; compare own report).

Research and Teaching

Main research topics at the EFC are drugs, drug targets, and bioanalytics. The core unit "Bioanalytics" combines the members' scientific and technical competence on the analysis of the proteome, individual proteins, and low molecular agents. The bioanalytical expertise further covers a variety of molecular biology techniques and functional assays.
The intention behind the research center is to bridge chemistry and biomedical sciences leading to new insights in the physiological function of new bioactive molecules, their interaction with target proteins, and the development of novel therapeutic strategies.
Instrumental analysis at the EFC is based on the following major equipment:
– three LC-ion trap-MS,
– two LC-triple quadrupol- MS/MS,
– one MALDI-TOF-MS,
– one SELDI-TOF-MS,
– two NMR 360 and 600 MHz,
– one CD spectrometer,
– one confocal laser microscope (Zeiss LSM 5),
– NMR for small animals (4,7 Tesla),
– equipment for microinjection and electroporation,
– real-time PCR devices,
– various electrophysiological setups, and
– a computer cluster.

Erlangen Center for Infection Research (ECI)

Speaker
Prof. Dr. med. Christian Bogdan

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Aims and Structure

The Erlangen Center for Infection Research (ECI) was founded as an interdisciplinary center of the FAU on July 28, 2010. The ECI is a consortium of more than 30 professors and lecturers and their research groups which belong to the Faculty of Medicine, the Department of Biology, the Department of Chemistry and Pharmacy, or the Department of Chemistry and Bioengineering. Infectious disease research is one of the key research areas at the FAU and the UK Erlangen.

The ECI focuses on the analysis of the pathogenesis of infections in order to improve the prevention, diagnosis, and therapy of infectious diseases in the long run. Accordingly, the ECI aims at providing a close scientific interaction between medical doctors in the clinics (e.g. specialists for infectious diseases, dermatology, hematology, and oncology) as well as microbiologists, virologists, infectious disease immunologists, pathologists, clinical pharmacologists, pharmaceutical, organic and inorganic chemists, and bioengineers. The necessity for an interdisciplinary and interfaculty cooperation and for combining the diverse scientific strength and know-how in the area of infection research becomes particularly apparent whenever novel anti-infectives, vaccines, or therapeutics for the treatment of immunopathological processes during chronic infections are to be developed. The broad spectrum of expertise of the ECI members in medicine and science will serve to open up new fields of research, such as the design and analysis of redox-active metal compounds for the therapy of infections and chronic inflammatory processes.

The organizational structure of the ECI comprises an executive board of four scientists (Prof. Dr. C. Bogdan, speaker; Prof. Dr. J. Eichler, Prof. Dr. T. Harrer, Prof. Dr. T. Stamminger), a steering committee - consisting of the members of the executive board and five additional faculty members (Prof. Dr. A. Baur, Prof. Dr. A. Burkovski, Prof. Dr. B. Fleckenstein, Prof. Dr. I. Ivanovic-Burmazovic, and Prof. Dr. R. Lang) - as well as the members' assembly.

Research

According to its central tasks and aims, the ECI functions as a platform for innovative research ideas to initiate new collaborative applications for extramural research grants. In summer 2010, the ECI, along with 24 other German universities, participated in a BMBF research competition for the foundation of the German Center for Infection Research (DZI). The ECI's proposal on "Human Immunodeficiency Virus, Herpesviruses and Leishmania: from Mechanisms of Persistence to Novel Preventive and Therapeutic Strategies" which combined projects from 20 key scientists, received a very positive evaluation by the international reviewers in terms of its overall scientific quality. However, the clinical infectious disease arm of the application as well as the potential contribution of Erlangen to the national center were questioned and not ranked high enough which finally resulted in the decision that ECI was not selected as one of the seven sites of the DZI.

Scientists of the ECI are project leaders within the recently reapproved SFB 643 and 796, several GK (e.g. GK 1071 and GK 1660) as well as of the Emerging Field Initiative of the FAU. The initiation of new research consortia in the area of infectious diseases and microbial pathogenesis at the FAU remains the primary goal of the ECI.

Teaching

The researchers of the ECI participate in a number of courses for students and research seminar series. These include not only the interdisciplinary infectious disease and immunology course for medical students (Q4 series), but also the invitation of national and international infectious disease researchers for guest lectures

Selected lectures

01.07.2011
S. Roberts, PhD
Pacific University, School of Pharmacy, Hillsboro, Oregon, USA
"Characterization of the Polyamine Pathway in Leishmania as a Potential Therapeutic Target"

19.07.2011
M. Brigl, MD
Brigham and Women's Hospital, Department of Pathology and Division of Rheumatology, Immunology and Allergy, Harvard Medical School, USA
"Mechanisms that drive NKT cell activation during infections"

21.07.2011
Prof. Dr. N. Gow, PhD
School of Medical Sciences, Institute of Medical Sciences, University of Aberdeen, UK
"The fungal cell wall: Biosynthesis and immune recognition"

15.08.2011
Dr. M. Kvansakul, PhD
Laboratory Head, Department of Biochemistry, La Trobe University, Melbourne, Australia
"Death is not an option - structural studies of virus mediated inhibition of apoptosis"

15.08.2011
J. Tel
Radboud University Nijmegen Medical Centre
"The potency of human plasmacytoid dendritic cells to induce immune responses in melanoma patients: A phase I clinical trial"

13.03.2012
PD Dr. J. Clos
Berhard Nocht Institute for Tropical Medicine
"The Heat Shock Proteins of Leishmania spp. and their Roles in Stress Protection, Signal Transduction, and Immune Evasion"

24.07.2012
Prof. Dr. A. Haas
Institute for Cell Biology, University of Bonn
"Reprogramming of host macrophages by Rhodococcus equi"

Imaging Science Institute (ISI)

Speakers
Prof. Dr. med. Alexander Cavallaro
(Institute of Radiology)
Gerhard Weller (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 of the FAU. Its location within the UK Erlangen allows optimizing in practice modern imaging systems to improve quality and efficient diagnostic analyses and treatment methods. The ISI provides the necessary facilities to transfer new developments regarding the modalities of imaging systems and data-processing systems into a clinical setting. Aside from conducting scientific evaluation, the ISI is responsible for training users and technicians in managing new developments.

ISI partners:
- Siemens AG
  Healthcare Sector
  Industry Sector
- Fujitsu Technology
- Planar Systems, Inc.
- Matrox
- Medtron
- Medrad, INC.
- Barco
- Federal Ministry of Economics and Technology
- BMBF
- Medical Valley EMN e.V.

Research

A wide variety of studies is currently being conducted at the ISI Erlangen.
The research areas comprise not only issues such as the optimization of current imaging systems, but also methods for future systems. Large-scale projects, such as the "Medico Projekt" conducted under the auspices of the Federal Ministry of Economics and Technology, are designed to develop new and intelligent medical databases. With the aid of such programs it will be possible to research and structure medical information in a more intelligent way in order to provide fast and reliable assistance via internet searches during diagnostic and therapeutic decision-making processes in the future. In addition, the ISI plays a pivotal role in the activities of the leading-edge cluster "Center of Excellence for Medical Technology - Medical Valley EMN e.V.", sponsored by the BMBF.
Using the four above-mentioned medical devices, the ISI Erlangen examines many patients every day for its research programs. Only a sufficiently high number of practice-oriented examinations guarantees the relevance of research results.
The ISI Erlangen optimizes medical devices and explores their potential further applications. Ideas for new examination methods and the resultant need for new medical devices are developed in close collaboration between clinical users and developers or technicians from the medical industry. The result of this collaboration is that jointly-owned patents are filed on a regular basis which attests to the great innovative strength and extensive expertise of the ISI Erlangen.

Teaching and advanced training

Offering a range of courses and workshops for doctors, technicians, engineers, and radiographers, the ISI Erlangen enjoys a very high national as well as international reputation thanks to the professional competence of the course instructors and the excellent training conditions. Since the founding of the ISI in 2005, more than 7,500 people have already participated in advanced training courses.

Reference Visits and Public Relations
The ISI Erlangen is also a platform where other medical clinics and the public can bring themselves up to date with the latest developments regarding the research on and application of medical imaging systems. Aside from extensive information on scientific findings, medical professionals and decision-makers working in public health all over the world will also learn about quality improvements and about opportunities to cut costs through the employment of the latest technology.
In the eight years since its establishment roughly 18,000 people from all over the world have visited the ISI Erlangen, among them numerous decision-makers of other clinics as well as representatives of public healthcare systems and politicians.

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 (formerly known as Interdisciplinary Center of Gerontology - ICG) has been active in the fields of biological, medical, psychiatric, psychological, behavioral, humanistic, economic, and technological aging research. The ICA initiates and supports interdisciplinary collaboration on aging research at the FAU. The ICA is also actively collaborating with communal institutions of medical care and with nursing homes of the region. Currently the ICA has 27 members coming from four different faculties and five associated institutions.

Research

Research of the members of the ICA focuses predominantly on health promoting intervention and prevention in the domains of nutrition, physical activity, and social environment. Each area of research addresses specific social, institutional, technological, and environmental conditions and their effects on physical health, autonomy, and personal responsibility.

Field of Research: Nutrition
Quantity and quality of our daily diet are of major importance for health, functionality, and well-being until very old age. With increasing age an adequate nutrition is, however, often impaired by age related factors and changes of the health and living situation. Within the framework of the 'Theo and Friedl Schöller Foundation Professorship of Clinical Nutrition in the Elderly', research is focusing on the relation between different aspects of nutrition and physical as well as mental functionality in very old age. In addition, the development of reliable and valid methods for nutritional assessment in older adults is of interest. Furthermore, in a recent multicenter project nutritional and health situation of older adults receiving home care in Germany has been studied comprehensively.

Field of Research: Physical Activity
Targeted promotion of physical activity can improve function, activities, and participation in the course of life and thus help to maintain independence and autonomy. The aim of physical-activity-related interventions is to induce long-term commitment to physical activity. Applied in rehabilitation, such a behavior-oriented exercise therapy (BET) leads to improved body functions and pain coping competencies and less work incapacity days in patients with chronic back pain (project: PASTOR). Physical-activity-related interventions in the elderly lead to positive effects on physical functioning (muscle strength, balance), the risk of falls, the risk of dementia, and cognitive performance (projects: Sturzprävention im Alter, F.i.A.T, GESTALT I and II). An important aspect of long-term changes in physical activity behavior is the affective attitude towards physical activity (project: KASPADI). The dissemination of BET can successfully be realized in internet-delivered interventions for various indications (projects: Rückenwind (low back pain), ms-intakt, PACE (multiple sclerosis)). A further area of research lies on motor control, especially after injuries or in persons with neurological conditions and/or movement/gait disorders (e.g. Parkinson´s disease, multiple sclerosis). Besides the individual level, organizational and political aspects play a central role in physical activity promotion for the elderly. In order to expand and optimize offers, improving both, internal capacities (e.g. staff training, goal definition, and resource allocation) as well as cross-organizational and inter-sectoral networks in and between sport, healthcare, and social care organizations, is essential. Important means to these ends include structured planning processes and networking between researchers, practitioners, and policy-makers (projects: EUNAAPA, PASEO). Of special interest to gerontology are assets and barriers for the integration of evidence-based, structured interventions for the prevention of dementia into providers' routines (project: GESTALT I). An important focus of this research are difficult-to-reach target groups, such as socially disadvantaged and sedentary older people (project: GESTALT II).

Field of Research: Social Relations
Beyond dispute the quality of an efficient social network plays a major role in maintaining health and a prolonged time of independent living in old age. For example, positive social relationships substantively contribute to improved health and longevity as well as to reduced risks of dementia and frailty. There is also some preliminary evidence suggesting that the association of physical activity and nutrition partly depends on the quality of social and family resources. The situation of care giving relatives with its resulting burdens, challenges, and risks is also of great importance. Additional projects analyze the situation of family caregivers, particularly with respect to the potentials of psychoeducation of family caregivers. Another focus of research is directed on the living conditions and quality of life of seniors living in institutions of residential care concentrating mainly on aspects of social interaction between residents, relatives, and staff.
Interdisciplinary and comprehensive research approaches focus on questions of prevention and interventions strategies with regard to dementia and age-related frailty. Additional non-clinical research is centered round the possibilities of assistive technology for supporting mobility and independent living in later life (e.g. EMN-Moves).

Teaching

The majority of the ICA-members is engaged in the interdisciplinary course offerings of the master's program in gerontology (M.Sc.). Some courses are realized in close cooperation with the associated members of the ICA, especially those related to gerontological practice. A series of lectures (Q7 – medical science of aging) focusing on geriatric and ethical topics are organized by numerous members of the ICA at the medical school of the FAU.
Furthermore, the ICA operates a collective graduate program "gerontology" which provides structured lecturing and special PhD-workshops for PhD students in gerontology as well as in psychology, psychiatry, and sport sciences.

ICA
Interdisciplinary Center for Aging Research

Interdisciplinary Center for Public Health (IZPH)

Speaker
Prof. Dr. med. Hans Drexler
Speaker and Member of Board of the IZPH

Contact
Prof. Dr. med. Peter Kolominsky-Rabas, MBA

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www.public-health.de

Aims and Structure

"Networking across scientific borders" is the unique selling proposition of the Interdisciplinary Center for Public Health (IZPH). The IZPH is a multidisciplinary research center consisting of different faculties of the FAU: The primary objective of the Center is to merge medical, economical, and social sciences and management in order to advance research in public-health and resolve current health care challenges of the aging society.
Within the Nürnberg Metropolitan Region the IZPH bundles all relevant stakeholders of the health care management industry, i.e. medical professionals (doctors, hospitals trusts, outpatient sectors), the different statutory health and care insurance providers, health technology providers (global operating companies like Siemens Healthcare and pharmaceutical manufacturers) as well as patients and their family members acting as research platform for the university.

Research

The research focus of the center is driven by its previous interdisciplinary research in the field of public-health and takes special interest with respect to issues of Health Technology Assessment (HTA) and Market Access, Health Promotion and Preventive Medicine, and Federal Health Monitoring.
During the report period the Center performed a number of large-scale studies addressing research topics as need of care and resource use in chronically ill patients (dementia, cancer, and stroke) as well as assessment of health care services funded externally with 2.3 million Euro.

With its emphasis on Health Technology Assessment (HTA)/Market Access, Health Promotion/ Preventive Medicine, and Federal Health Monitoring, the Center acts as the scientific platform for outcomes research at the FAU and as the main regional promoter.

Teaching

Members of the IZPH are providing interdisciplinary lectures and courses in the field of Public Health, such as Health Economics, Health System Research, Health Promotion, and Prevention. Special focus is also given to lectures on Public Health issues for students of the Faculty of Economics and to the master program "Medical Process Management" (M.Sc.).

Interdisciplinary Center for Ophthalmic Preventive Medicine and Imaging (IZPI)

Speakers
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Aims and Structure

The "Interdisciplinary Center for Ophthalmic Preventive Medicine and Imaging" (IZPI) was founded to increase the intensity and the efficiency of cooperation projects between the Medical and Technical Faculty 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 Medical and Technical Faculty. Embedded in the main research focus "Medical Technology" of the FAU, the IZPI should help to enforce and to improve the scientific excellence in these topics.
The most important purpose of IZPI is the development of novel diagnostic methods in the area of preventive medicine. The goal is to develop new technologies for early detection of risk factors or symptoms of diseases.
Thus, the areas of interest of IZPI are
(1) development of novel technologies and
(2) improvement of well-established technologies by optimizing image acquisition, analysis, and medical prediction.
The analysis of medical images and data comprises all processes which lead to a medical interpretation or a transformation of the medical image in a symbolic description. To extract relevant risk factors from a given medical image, there is the necessity to develop an effective model of the disease. The model will allow elute relevant information from a given image.

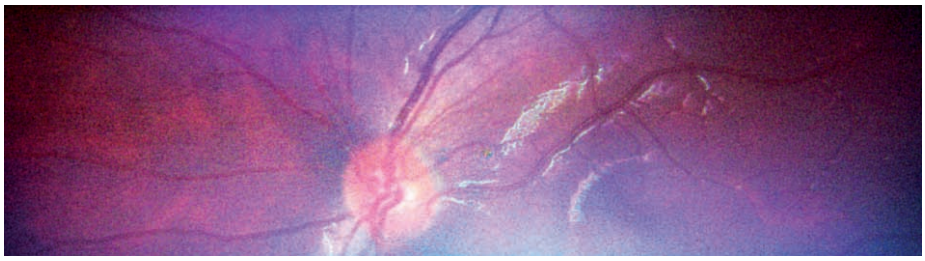
Research

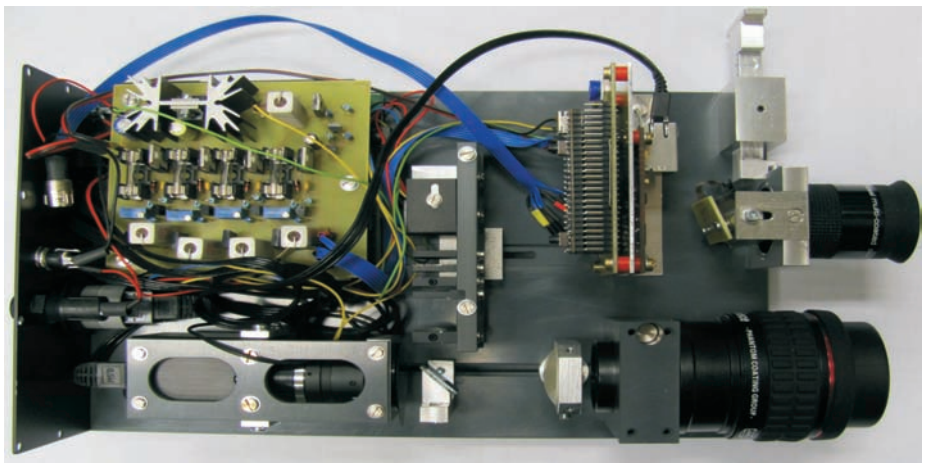
IZPI researchers from the Medical and Technical Faculty cooperate within third-party funded projects of the Center of Excellence for Medical Technology "Medical Valley EMN e.V." and the School of Advanced Optical Technologies "SAOT".

(I) Third-party funded projects of the Center of Excellence for Medical Technology "Medical Valley EMN e.V."
IZPI scientists work on two projects of the "Medical Valley EMN e.V" which deal with telemedical applications in ophthalmology.
(1) Telemedical LowCost-Fundus Camera System: The goal of this project (A04) is the development and clinical validation of a low cost telemedical system for threshold countries for early detection of diabetic retinopathy, hypertensive retinopathy, and glaucoma. We succeeded in generating high-resolution images of the retina by using Superresolution Technology. In 2012 four peer-reviewed articles were published and two patents were accomplished.
(2) E. Atlas: The goal of the project (A02) is the development of novel technologies to run an interactive image database, fully accessible by mobile communication technology. We succeeded in platform-independently publishing of the data base Atlas of Ophthalmology with 6,000 reference images for iOS (Apps iPhone, iPad) and for Windows 8 (Apps for Tablets with Windows 8). In 2012 seven peer-reviewed articles were published.
(II) Third-party funded projects of the School of Advanced Optical Technologies (SAOT)
Several IZPI researchers work on third party funded projects of the SAOT:
(1) 3D-Vision: Within two PhD-projects, a gesture-controlled, interactive system is developed, enabling the measurement and training of the stereo vision capacity. We began a tight cooperation with the University of Kunming (Province Yunnan, China), leading in 2012 to a Visiting Professorship.
(2) MR-DTI imaging of the visual tract: A novel MRI-method (Diffusion Tensor Imaging, DTI, see image) and image pattern analysis allows to quantify the integrity of axons of the cerebral part of the optic tract. By this method, it becomes possible to detect unknown causes of vision impairment. In 2012 four peer-reviewed articles were published.

Teaching

IZPI researchers give lectures within several interdisciplinary frameworks of Medical and Technical Faculty. At the Faculty of Medicine the lecture "retinal microangiopathy as early marker of cardio-vascular diseases" is given as well as lectures for students of the degree program "Medical Engineering". The overall concept of these lectures which are called "Biological and Technical Vision" is to link mechanisms of human vision with the vision of machines. For students of „Medical Engineering", we offer the lectures „Biological and Technical Vision" and "Medical Applications of photonics". In addition, a weekly colloquium "Biological and Technical Vision" is offered to students of the Technical and Faculty of Medicine.





Medical Immunology Campus Erlangen

Speaker
Prof. Dr. med. Christian Bogdan

Scientific Coordinator
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Aims and Structure

The Medical Immunology Campus Erlangen, an interdisciplinary center at the Faculty of Medicine of the FAU, was founded in March 2009 in order to provide a common organizational platform to scientists from all areas of immunobiology and clinical immunology. Since then, several institutes, clinics, clinical divisions, and research groups of the UK Erlangen, the Faculty of Medicine and the Natural Science Faculty of the FAU, the Fraunhofer Institute for Integrated Circuits IIS, and the Max Planck-Institute for the Science of Light have been integrated into the Campus. The Medical Immunology Campus Erlangen organizes scientific seminars and lectures, promotes the research of its members by public relation activities, develops teaching concepts for immunology in the Bachelor's and Master's degree programs of Molecular Medicine, and coordinates the participation in competitive federal funding initiatives. By bundling the available scientific resources in the field of immunology, the Campus is dedicated to strengthen the research focus Immunology and Infection Research of the Faculty of Medicine and, in the long run, to enable the founding of a Leibniz Institute for Translational Immunology and Immunotechnology. Four times a year the Campus publishes a Newsletter on exciting publications, honors, and awards of the Campus' nearly 80 members.

Research

Medical Immunology Campus Erlangen researchers investigate the basic mechanisms of the development, composition, function, and deficiencies of the immune system. By translating the results into clinical approaches, new and personalized methods for the prevention, diagnostic, and therapy of infectious, autoimmune, and inflammatory diseases as well as for neoplasias are developed.
During the reporting period the scientists of the Medical Immunology Campus Erlangen not only received the approval for a third funding period of the SFB 643 "Strategies of cellular immune intervention" (spokesman: Prof. Dr. G. Schuler), but also succeeded in setting up two new DFG research consortia (GK 1660 "Adaptive Immunity", spokesman: Prof. Dr. H.-M. Jäck; Clinical Research Group 257 "Chronische Darmentzündung", spokesmen: Prof. Dr. M. Neurath and Prof. Dr. C. Becker).

Teaching

The members of the Medical Immunology Campus Erlangen are involved in teaching medical students and students of the Bachelor's and Master's degree programs of Molecular Medicine at the Faculty of Medicine as well as students of the life science programs at the Faculty of Sciences. Furthermore, the Campus promotes scientific exchange by hosting national and international speakers of a broad, interdisciplinary range of topics at the weekly Immunological Colloquium. The annual Joachim Kalden Lecture was initiated by the Medical Immunology Campus Erlangen in order to honor outstanding researchers with substantial impact on immunological research, such as the recently deceased Nobel laureate and dendritic cell expert, Prof. Dr. R.M. Steinman, in 2011 and the renowned B cell immunologist, Prof. Dr. K. Rajewsky, in 2012.

Lectures

In 2011 and 2012, the Medical Immunology Campus Erlangen organized 51 research colloquia with distinguished national and international guest scientists. The following compilation is a selection of the complete list, which can be viewed at the homepage of the interdisciplinary center.

11.01.2011 Dr. S. Amigorena, Institut Curie, Paris
„Antigen presentation and T cell activation by dendritic cells"

12.04.2011 Prof. M. Karin, University of California, San Diego
„Control of Tumor Progression and Metastasis by Lymphocyte-Produced Cytokines"

03.05.2011 Prof. B. Malissen, Centre d'Immunologie de Marseille-Luminy
„Disentangling the complexity of the dendritic cell networks present in the skin and the thymus"

31.05.2011 Prof. F. Sallusto, Institute for Research in Biomedicine, Bellinzona, Schweiz
„Dendritic cells and the demanding task of priming T cell responses"

04.07.2011 Prof. Dr. H. Schöler, Max-Planck-Institut für molekulare Biomedizin, Münster
„Induction of Pluripotency: 20 Years of Research"

25.10.2011 Prof. Dr. A. Diefenbach, Universitätsklinikum Freiburg
„Development and Function of Innate Lymphocytes"

15.11.2011 Prof. Dr. E. Latz, Institute of Innate Immunity, Universitätsklinikum Bonn
„Mechanisms of Inflammasome Activation in Inflammatory Diseases"

06.12.2011 Prof. M. Sixt, Institute of Science and Technology Austria, Klosterneuburg
„Mechanisms of Leukocyte Chemotaxis"

17.01.2012 Prof. O. Mandelboim, Hebrew University Hadassah Medical School, Jerusalem
„Inhibition and activation of immune responses by viral and by cellular miRNA"

07.02.2012 Prof. F. Granucci, Department of Biotechnology and Bioscience, University of Milano-Bicocca
„The Multifaceted Roles of CD14 in Innate Immunity"

05.06.2012 Prof. Dr. O. Pabst, Medizinische Hochschule Hannover
„Generating IgA Repertoire Diversity in the Intestine"

19.06.2012 Prof. Dr. T. Hünig, Institut für Virologie und Immunbiologie, Universität Würzburg
„Oligodendrocytes enforce immune privilege of the non-infected brain by deleting the peripheral CD8 T-cell repertoire of auto-reactive cells"

10.07.2012 Prof. A. Hayday, Immunology, Infection and Inflammatory Disease, King´s College London
„Lymphoid stress-surveillance: the benefits and challenges of useful autoimmunity"

16.10.2012 Dr. A. Lehuen, Institut National de la Santé et de la Recherche Médicale, Université Paris Descartes
„Regulatory role of NKT cells in viral infection and autoimmune diabetes"

06.11.2012 G. Eberl, PhD, Lymphoid Tissue Development Unit, Institut Pasteur, Paris
„Innate lymphoid cells and intestinal homeostasis"

27.11.2012 Prof. D. Schendel, Institut für Molekulare Immunologie, Helmholtz Zentrum München
„Selection and use of high-affinity T cell receptors in designer lymphocytes for adoptive cell therapy"

Medical Technology Test and Application Center (METEAN) of the Fraunhofer Institute for Integrated Circuits IIS

Speaker
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Contact
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Aims and Structure

Intention and main focus of METEAN is to combine the research competence in biomedical engineering of the Fraunhofer Institute for Integrated Circuits IIS with the clinical expertise of regional partners from industry, research institutes, and specifically the UK Erlangen in a synergistic way, as to exchange ideas for technical solutions with the medical and clinical needs and hence provide and open perspectives for innovative and market-oriented products. The METEAN is not only located at the Faculty of Medicine inside facilities of the the UK Erlangen, it also hosts technical and medical scientists. The involvement of project partners in decision-making processes of METEAN extends into the active shaping and influencing of strategic, programmatic, and process-related orientation of the scientific research goals.

Research

Computer assisted microscopy

The analysis of cells by means of fluorescent microscopy has been established as a standard within microbiology, virology, and immunology. The research goal of this subproject as part of the SFB 796 is the conception and development of generic image analysis methods that are capable to provide solutions for many similar applications in analysis of fluorescent micrographs. Central problems of automated cell analysis are the detection and segmentation of adequate cells. Various segmentation methods have been developed, implemented, and evaluated for this task which are applicable for fluorescently stained cells with different types of preparations and different applications. After a training phase that is based on some representative images, these methods select the most appropriate features for cell detection and segmentation that can be applied for autonomous and robust segmentation of similar image material.

Decision support systems

The research and development tasks in the field of "Computer-Assisted Diagnosis" (CAD) are focused on the development of "intelligent" systems for computer based detection, analysis, and interpretation of lesions depicted in various medical imaging modalities (endoscopy, colposcopy, mammography). Improved early detection of dysplastic tissue within screening programs as well as an objective differential diagnosis are the main functional purposes of the developed CAD-technology. In cooperation with the Institute of Radiology and funded by the "International Max-Planck Research School for Optics and Imaging" and the "Center of Excellence for Medical Technology – Medical Valley EMN e.V.", we developed and evaluated new methods for computer-assisted characterization and analysis of tissue lesions depicted in digital mammography and tomosynthesis data. As shown in a preclinical study, the CAD-system may improve the diagnosis of micro-calcifications in mammograms.

Analysis and wireless transfer of biosignals of the respiratory and cardiovascular systems

In order to detect and extract therapy-relevant parameters for hemodynamic monitoring, new methods for continuous non-invasive acquisition of biosignals of the respiratory and cardiovascular system are investigated in cooperation with the Department of Medicine 4, the Department of Anesthesiology, and the Max-Schaldach Chair for Medical Technology. A crucial part of this research concentrates on the development of a laboratory prototype which can be applied to the human body for continuous non-invasive long-term acquisition of the central arterial blood pressure under daily standard conditions. A further research goal concentrates on the mathematical modeling of the arterial pulse wave. The information-theoretical characterization of the interaction between the respiratory and the cardio-vascular system yields insights about the physiological-pathophysiological aspects of the bidirectional influence and regulation of these systems.
Goal of the project "KARDIKOM Wireless", funded by the BMBF, is a continuous monitoring of patients with cardiac risk constellations for both, stationary and home care monitoring. After optimization towards a micro-system, the portable vital-sensor system (developed earlier within the project SOMATEK) was certified as medical class II product. Based on this sensor system, two observer studies were conducted in cooperation with the Department of Internal Medicine of the Heidelberg University Hospital and the local Department of Anesthesiology. In Heidelberg, the "KARDIKOM Wireless" system will be tested with respect to clinical use and its integration into a patient data management system, whereas the focus of investigation in Erlangen will be the user acceptance and suitability for home care monitoring.

Teaching

Within METEAN, students of medical and applied informatics, biomedical technology and electronic devices, physics and mathematics of the FAU as well as of the regional universities of applied sciences are educated through assignments and supervision of internships, bachelor- and master theses. Additionally, scientists from METEAN are involved in various lecture units of the Medical and Technical Faculty.

Nikolaus-Fiebiger-Center of Molecular Medicine (NFZ)

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Aims and Structure

The NFZ is a research institution of the Faculty of Medicine. The center harbors the two Chairs of Experimental Medicine I and II (Molecular Pathogenesis Research and Molecular Tumor Research, respectively), a Division of Molecular Immunology as part of the Department of Medicine 3, a division of the Chair of Genetics of the Faculty of Sciences, as well as two junior research groups of the IZKF of the Faculty of Medicine. Additionally, lab space is provided to rotating clinical research groups. The intention of the research center is to strengthen biomedical research in the Faculty of Medicine by stimulating cooperations between basic and clinical researchers and by giving young clinicians the opportunity to carry out our competitive biomedical research projects under the infrastructure of a modern research center.

Research and Teaching

The main research topics at the NFZ comprise different aspects of molecular pathology from tumor biology to connective tissue research including genetic and immunological issues. With the appointment of Prof. Dr. D. Müller as new head of the Chair of Experimental Medicine I in 2011, research was extended to cardiovascular diseases. Since Prof. Dr. D. Müller, however, accepted another position in October 2012, the Chair is vacant again.

The NFZ is well equipped with modern research facilities required for cell and molecular biological research and offers a variety of biochemical, immunological, and cell biological seminars, guest lectures, and common graduate student seminars. Central equipment, such as DNA-sequencing, fluorescence activated cell sorting, confocal laser microscopy, surface plasmon resonance as well as animal facilities, are accessible to all scientists at the center.

Central Institute of Medical Engineering (ZiMT)

Speaker
Prof. Dr.-Ing. Joachim Hornegger

Corporate Executive Committee
Prof. Dr. Ben Fabry
Prof. Dr.-Ing. Joachim Hornegger
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Aims and Structure

Medical technology is one of the scientific focuses of the FAU. About 50 professors and university lecturers are working in this sector linked together in the Central Institute of Medical Engineering (ZiMT). The coordination of responsibilities of numerous cooperation partners as well as international visibility are the important core areas of the ZiMT. It is an organizational unit which sharpens the biomedical engineering profile of the FAU and improves the general conditions for interdisciplinary collaboration in the diversified research area of healthcare engineering.
Head of the ZiMT is an interdisciplinary joint team consisting of Prof. Dr. J. Hornegger (Faculty of Engineering), Prof. Dr. Dr. h.c. J. Schüttler (Faculty of Medicine), and Prof. Dr. B. Fabry (Faculty of Sciences). Operatively, the ZiMT is managed by an office directed by the executive manager Dr. K. Höller.

Research

At the FAU, the scientific focus on "healthcare engineering" is perfectly embedded in an excellent research environment. Especially, the positive decision on the competition "cluster of excellence" of the BMBF for the Center of Excellence for Medical Technology "Medical Valley EMN e.V." had a great impact on Erlangen's profile. The university organization and all project applications were managed by the ZiMT. The close collaboration with Siemens Healthcare, Fraunhofer IIS, and about 50 medical technology enterprises of the metropolitan region complete the excellent research environment at the FAU.
The ZiMT bundles all activities within the university together with representatives of the UK Erlangen. Its mission is the expansion of research networks in the field of healthcare engineering within and around the university. In addition, the institute provides a more transparent visibility of this highly dynamic scientific topic at the FAU. Various chairs of the FAU, especially the Faculties of Engineering, Sciences and Medicine as well as the Department of Economics, deal with research questions of healthcare engineering, such as medical biotechnology, biomaterials, medical imaging and processing, molecular imaging, MR imaging, computational medicine, medical computer science, medical process management, bioinformatics, medical physics, and healthcare management.

Teaching

At the FAU, the relevance of "healthcare engineering" as a scientific focus is not only visible in research, but also in the educational sector. The bachelor program of healthcare engineering was able to show very high numbers of applications right from the start and is, until today, one of the largest study programs at the Faculty of Engineering. The constantly high amount of students and the goal of having as few students dropping out as possible were the reasons for the introduction of a procedure of determining aptitudes for healthcare engineering. Although this takes a lot of extra effort, it enables on the other hand the offer of a valuable individual advisory service before the start of a study program. In particular, courses such as computer science, electrical engineering, electronic engineering, information technology, mechanical engineering, material engineering as well as chemical and biological engineering are embedded in the program of healthcare engineering. Right from the first terms, the basics for mathematics, physics, and medical subjects are set, but also specific references to arts, humanities, and economics are possible. Another specialty about the healthcare engineering program is the high percentage of female students which is more than 50%. Until today, no other engineering study program has reached those numbers.
Since the winter term 2011/2012, the master program in healthcare engineering is offered at the FAU which implements an interdisciplinary engineering education and qualifies students for sophisticated multidisciplinary engineering tasks at the highest level. Offered specializations are medical electronics (electrical engineering), medical imaging and data processing (informatics), and medical instrument and production engineering and prosthetics (mechanical and material engineering).
At the end of 2012, the bachelor as well as the master study program have been internationally certified as an act of quality assurance. Compared to other study programs at the FAU, the healthcare engineering programs were the only ones being certified without any specific additional requirements. This confirms the feasibility of the program and its clearly defined and valid goals which can be realized with the existing concept using the organizational and infrastructural setting at the FAU.

3-D Imaging in Medicine

With the goal of internationally promoting the excellent position in the fields of science, research, and development of our country and strengthening the cooperations with recognized centers of excellence in the field of healthcare engineering throughout the world, the BMBF has launched an initiative to advertise Germany as an excellent research location. Under the motto "Germany – Land of Ideas", the campaign will highlight the attractiveness of Germany and its research environment in important target countries in order to initiate new sector-specific cooperations. Currently, workshops, multiplier events, partnering events, lectures, and presentations at conferences and meetings are being organized. BMBF has selected eight participants that highlight its ideals and goals for initial support. Under the auspices of ZiMT and the topic "3-D Imaging in Medicine – Cutting Edge Research in Germany's Medical Valley", the partners conduct workshops abroad with the aim of establishing international graduate schools and cooperations. Erlangen as a highly innovative location offers unique opportunities for young scientists in the field of medical 3-D imaging.
The expansion of study and research cooperations to internationally attractive and recognized institutions – i.e. the Stanford University and the Johns Hopkins University, USA – and economically important partners like Brazil and China have already been established. Also, student exchange programs with the above mentioned partners in the USA and Brazil as well as an international oriented graduate school with the Peking University and the FAU have been realized.

ZiMT
ZENTRALINSTITUT FÜR MEDIZINTECHNIK

Collaborative Research Center 643: Strategies of Cellular Immune Intervention

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Aims and Structure

The SFB 643 "Strategies of cellular immune intervention" has been existing since July 2004. By the end of 2012 the third funding round (2013 – 2016) was approved by the DFG. The goal of the SFB 643 is the successful implementation of immunological knowledge in treatments that are based on a manipulation of the immune system, i.e. on immune intervention. Immune therapeutic approaches to treat tumors and infectious diseases require the enhancement or stimulation of the immune response. Conversely, innovative treatments of inflammatory diseases, including autoimmune diseases, allergic diseases, and transplantation reactions call for novel and improved immunosuppressive strategies. The SFB 643 is conceptually structured in three closely interconnected project areas: A) basic immunology, B) immune intervention in animal models, and C) therapeutic applications.

Research

Several representative projects will be described shortly.

The project of Prof. Dr. U. Schubert investigates the role of the ubiquitin proteasome system (UPS) for antigen presentation via the MHC class I (MHC-I) pathway.

The research project of PD Dr. U. Schleicher and Prof. Dr. C. Bogdan is focused on natural killer (NK) cells and their effector functions in the immune response against the intracellular parasite Leishmania with the aim to elucidate the mechanism leading to the activation of NK cells.

The project of Prof. Dr. D. Dudziak will translate the strategy concept of in vivo "antigen targeting" of Dendritic Cells (DC) into the human system. Thereby, the work focuses on the production of antigen-conjugated antibodies to analyze T cell responses in tissue culture and the characterization of DC in human tissues. These data will be important for an eventual implementation into the clinic to optimize vaccination.

Prof. Dr. F. Nimmerjahn focuses on antibodies which are essential for defending the body against invading pathogens and show promising results in the therapy of human tumors. In depth knowledge about the cell types involved in phagocytosis and ADCC reactions in vivo is the basis for the generation of novel therapeutic strategies aiming at modulating these reactions.

The project of Prof. Dr. M. Herrmann focuses on the immune modulation by apoptotic cells, necrotic cells, and annexins. Apoptotic cells are considered to be only weakly immunogenic because of their swift recognition and clearance by phagocytes and can even be tolerogenic. The exposure of immature glycoproteins and the phospholipid phosphatidylserine represent signals for the phagocytosis of dead (necrotic) and dying (apoptotic) cells, respectively.

The project of Prof. Dr. T. Winkler and Prof. Dr. M. Mach is concentrating on the adoptive transfer of memory B cells as a new cell based therapy for infection with Cytomegalovirus after transplantation. Support of the patient's immune defense against the virus is a major goal in transplantation medicine. Memory B cell transfer provided long-term protection from the lethal course of the infection that is invariably seen in immunodeficient animals. The data provide evidence that a cell based strategy to support the humoral immune response can be effective to combat infectious pathogens in severely immunodeficient hosts. This is the basis for the planned clinical trial using adoptively transferred CMV-specific memory B cells in stem cell transplanted patients which will take place during the new funding period.

The project of Prof. Dr. L. Nitschke studies the newly developed sialic acid derivatives as high-affinity ligand analogs for CD22, a B cell receptor-associated inhibitory co-receptor, in order to therapeutically manipulate B cells. CD22 can interact with the CD22 ligands on bone marrow endothelial cells which might control the homing of circulating mature B cells and plasma cells into the bone marrow. The therapeutic potential of these modified derivatives will be explored as a novel therapeutic tool to treat patients with multiple Myeloma.

The project of Dr. E. Zinser and Prof. Dr. A. Steinkasserer concentrates on the immunomodulatory potential of the soluble CD83 molecule. Recombinantly expressed soluble CD83 showed a very interesting therapeutic potential and suppressed paralysis associated with experimental autoimmune encephalomyelitis (EAE) which is an animal model for human Multiple Sclerosis and in skin-, heart- as well as cornea-transplant studies in murine models. This represents the basis for further preclinical and clinical developments.

The project of Prof. Dr. J. Siebler and Prof. Dr. M. Neurath deals with the transcriptional regulation and pathogenetic relevance of the IL-28/IL-29 cytokine system in Colitis and Colitis associated colon carcinoma. Thereby, the transcriptional regulation of the IL-28/IL-29 cytokine gene expression will be investigated using murine T cells. The functional role of IL-28/IL-29 for the immunopathogenesis of colitis and colitis-associated colon carcinoma will be characterized in vivo using murine models.

The aim of the project conducted by PD Dr. B. Schuler-Thurner, PD Dr. N. Schaft, and Prof. Dr. G. Schuler is the development of new and innovative immunotherapies based on DC especially for the treatment of patients with cancer (melanoma as a prime model). Several clinical phase I-trials have already been conducted using peptide-loaded DC and now an additional clinical study was concluded that used DC which have been electroporated with defined RNA encoding the tumor associated antigens MAGE-3, MelanA, and Survivin. In addition new and advanced antigen loading strategies have been developed using RNA electroporation.

The project of Prof. Dr. G. Fey and Prof. Dr. W. Hillen dealt with the design and functional testing of novel antibody-derived agents for the treatment of Acute Myeloid Leukemia (AML). Thereby, chimeric proteins carrying a death-effector domain for binding to and elimination of leukemic cells from AML patients have been generated. Human tBid and AIF (apoptosis inducing factor) were used as death-domains. The target antigens were CD33 and CD123 because they are expressed in particularly high density on AML leukemia stem cells (LSCs). This project has led to the funding of the new start-up biotech company SpectraMab which will further develop this approach for the use in humans.

The ability to adoptively transfer T cells to treat cancer is in the focus of the project of Prof. Dr. A. Mackensen. In recent studies the efficacy of adoptive T cell transfer therapies for the treatment of patients with metastatic melanoma has been shown. Effective cell therapy demands in vivo persistence and/or expansion of the transferred TAA-reactive T cells and homing to the tumor. Several strategies will be developed to enhance proliferation, migration, and persistence of infused tumor-reactive T cells. These approaches could improve the efficacy of adoptive T cell therapy for cancer. In the new funding period the adoptive transfer of CMV/EBV-multi-epitope-specific T cells will be tested in a clinical trial in stem cell transplanted patients.

Collaborative Research Center 796: Reprogramming of Host Cells by Microbial Effectors

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Aims and Structure

The long-term goal of the SFB 796 "Reprogramming of host cells by microbial effectors", which started in January 2009, is the understanding of the molecular and ultimately structural basis of pathogen-host interactions as well as the development of novel strategies for immunization and intervention. In order to achieve this goal, interactions between known microbial effector proteins (e.g. bacterial type III secretion machines, viral transport proteins) and host cell structures will be characterized on the molecular level. Furthermore, new virulence factors will be identified and their role during pathogenesis will be studied.

The SFB 796 which was initiated by the Faculty of Science has an interfacultary structure. Groups of the Faculty of Medicine and the Faculty of Science as well as the Fraunhofer Institute for Integrated Circuits (IIS) are involved in the collaborative research. Although the individual research goals of the bio-medical and plant-oriented groups might appear different at first (improved prevention and therapy versus pathogen-resistant and high-yielding crop plants), the underlying basic concepts in pathogen-host interactions are expected to be rather similar, rendering a comparative approach highly appealing. Thus, we expect that the comparative investigation of the reprogramming of central cellular processes (e.g. ubiquitin-mediated protein degradation, vesicular trafficking) in several pathosystems (human and plant pathogenic viruses and bacteria) will enable us to identify general themes that we expect to extend also to pathogens not studied within the SFB 796.

To reach the long-term goal, the SFB 796 incorporates closely cooperating scientists with complementary expertise, as well as a core unit to study structure-function relationships. Presently, the SFB 796 harbors 16 different projects that can be divided into three subgroups that are interconnected:

A) Structural basis of molecular interactions,
B) Reprogramming of cellular processes, and
C) Replication structures and transport processes.

Research

Subgroup A: Structural basis of molecular interactions

Structure-function relationships of already known effector proteins and their interactions with specific cellular targets will be studied in subgroup A. Linear sequence motifs mediating protein-protein interactions are widely used by pathogenic organisms to reprogram cellular processes. The elucidation of the structural requirements for the promiscuity is the focus of several projects of this sub-area.

Subgroup B: Reprogramming of cellular processes

The focus of subgroup B is the elucidation and detailed understanding of mechanisms used by microbial effectors to reprogram cellular processes, including selected signal transduction pathways, intrinsic immune responses, targeted protein turnover, and the primary metabolism.

Subgroup C: Replication structures and transport processes

The focus of subgroup C is the question as to how microbial effectors use, and partially convert, cellular structures for successful microbial colonization and replication.

How viral and bacterial proteins modify the cellular transport is the focus of several projects of this subgroup.

Central project (Z)

Crucial methods for generating novel insight are provided by the central project (Z). The central project will reach into all research areas by offering an integrated and state-of-the-art technology platform supporting all groups of the SFB 796.

Priority Program 1468: Osteoimmunology – IMMUNOBONE – A Program to Unravel the Mutual Interactions between the Immune System and Bone

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Aims and Structure

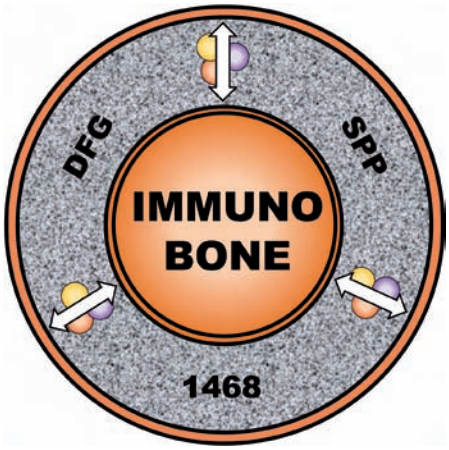
The interdisciplinary project IMMUNOBONE is a priority program (SPP) to unravel the mutual interactions between the immune system and bone. The priority program is funded by the German Research Foundation (DFG) for the first funding period of three years with a total volume of Euro 7.3 million. At the beginning of 2013, the priority program had a positive evaluation for a second funding period for another three years. The interdisciplinary consortium consists of 20 groups of 15 different research institutions of osteologic orthopedics, rheumatology, and immunology.

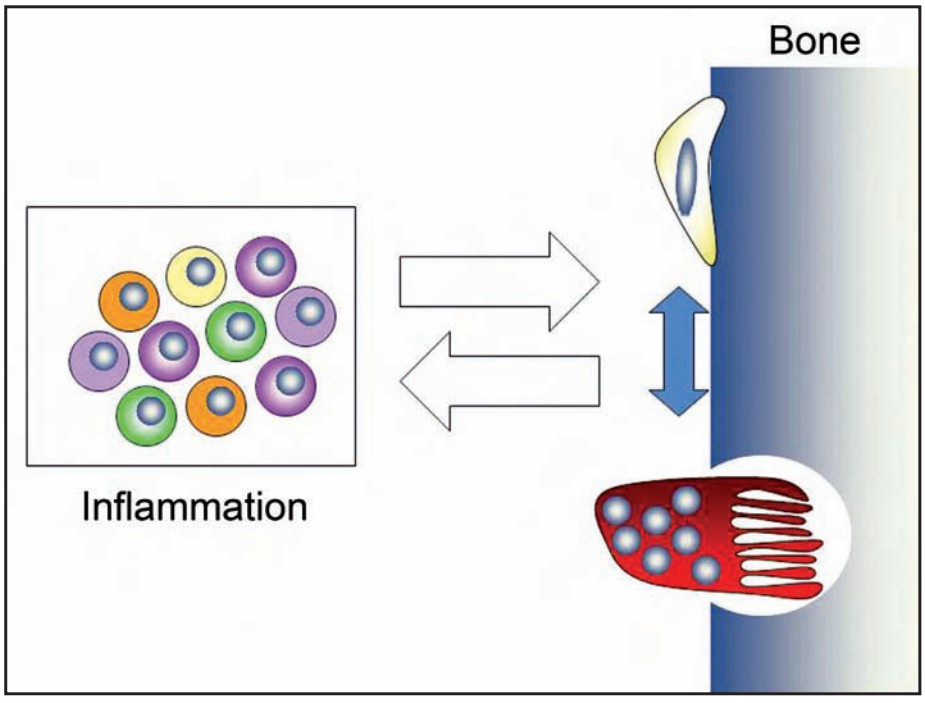
Research

Osteoimmunology is a new field of research calling on the hypothesis that the immune system and the bone are in close relation. Scientists suspect a communication between both systems. It is assumed that the interaction between bone and the immune system has an influence on diseases like osteoporosis and arthrosis. The interaction between bone and the immune system was recognized ten years ago by the discovery of a protein termed Receptor Activator of NF-κ B Ligand (RANKL). Since then, interest in this field has increased substantically and novel insights into the mutual regulation of bone and the immune system have been achieved. It has been shown that molecules located on the surface of immune cells trigger bone metabolism. Moreover, clinical observations support the thesis that activation of the immune system with subsequent inflammatory disease leads to bone damage. The mechanisms by which the immune system influences bones and vice versa are, however, not completely understood.
The IMMUNOBONE consortium investigates which mechanisms and messenger substances trigger overreaching immune reactions. Furthermore, the role of bone as "school of immune cells" will be examined. The bone marrow is the home of the hematopoietic and immune system. Therefore, it can be envisioned that also bone affects the immune cells. Ultimately, the priority program will contribute to improve anti-inflammatory therapies which inhibit bone resorption.

Teaching

The head of the research group is involved in the traditional teaching program (lectures, seminars, practica) covering all subjects in the field of medicine and molecular medicine as well as the PhD/MD programs for basic and translational research.





BMBF Leading Edge Cluster "Center of Excellence for Medical Technology – Medical Valley EMN e.V."

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Aims and Structure

Following its application as a "Center of Excellence for Medical Engineering", the Medical Valley EMN was announced on 26 January 2010 as one of five winners in the Leading Edge Cluster Competition sponsored by the BMBF. The decisive, unique selling feature of the Medical Valley EMN Leading Edge Cluster is the common objective among all industrial and academic cluster partners: Interdisciplinary, research-based further development of products, services, and solutions that help to verifiably improve the effectiveness and efficiency of healthcare.
In July 2012, the substantial progress in implementing the strategy was confirmed through the independent Leading Edge Cluster jury. Central evaluation criteria for the development of the cluster were the progress made in implementing the cluster strategy and the progress in achieving the stated objectives. The Leading Edge Cluster projects accounted for these significant contributions. Within the projects, the respective contribution to increase the efficiency of health care was estimated. For Germany alone a total potential reduction in health expenses of more than 7.5 billion Euro per year is estimated for at the same time unchanged quality of health care. The products and services developed in these projects are very competitive due to their level of innovation and thus likely to gain market share. The estimated sales potential of some of the products and services is almost 500 million Euro annually. The project ideas have already led to more than 50 patents and the results were published in over 100 publications.

Research

To further consolidate its leading position in the global market, the Medical Valley EMN cluster is generating innovative excellence in its core research areas of diagnostic imaging, intelligent sensors, treatment systems, and ophthalmology, as well as horizontal innovations for product and process optimization, a subject with broad application.

Diagnostic imaging

The use of innovative diagnostic imaging technologies results in earlier detection of disease and therefore less invasive, more cost-effective treatment. Diagnostic imaging is equally important for optimizing minimally invasive interventions and determining the effectiveness of treatment. The diagnostic imaging core research area includes projects many of which were performed in cooperation with the Department of Obstetrics and Gynecology, the Institute of Radiology, the Department of Otorhinolaryngology and the Department of Medicine 1.

Intelligent sensors

In conjunction with communication and information technologies, intelligent sensors can contribute significantly to reducing costs in the health system. Within the projects in this core research area, miniaturized sensor modules are being developed that can reliably measure vital care-related data such as breathing and circulation parameters in mobile situations outside hospitals. The modules help optimize the treatment of different illnesses with rapidly growing patient numbers, such as heart insufficiency. The following project of the Department of Medicine 2 associated with this core research area:
"Home monitoring of patients with cardiac insufficiency to avoid decompensation and reduce hospitalization rates".

Treatment systems

Most of the research projects in this area are being carried out in cooperation with the Department of Anesthesiology, the Institute of Experimental and Clinical Pharmacology and Toxicology, the Department of Psychiatry and Psychotherapy, the Institute of Medical Informatics, Biometry, and Epidemiology, the Chair for Technical Thermodynamics, and the Department of Medicine 1. The projects are designed to increase personalization and safety in drug therapy, prove treatment with anti-infective drugs to be more efficient and economic, and develop innovative procedures for early diagnosis and safe treatment.

Ophthalmology

Among diseases of the eye, defective vision such as presbyopia, cataracts, glaucoma, and age-related macular degeneration are by far the most prevalent and economically significant diseases. Together with the Department of Ophthalmology, leading technological companies who operate on a global basis within the Medical Valley EMN cluster are developing laser applications for refractive surgery, artificial lenses, and diagnostic systems in a number of Leading Edge Cluster projects.

Horizontal innovations for product and process optimization

In addition to the core technology research areas, horizontal innovations for product and process optimization are also being generated in the Leading Edge Cluster. With the participation of the Interdisciplinary Center for Public Health, the "ProHTA" project is creating models to simulate the effect of new technologies on the quality of care as well as on direct and indirect costs. At the same time it is supporting the search for potential efficiency levers for new technologies and products.

MEDICAL VALLEY
Europäische Metropolregion Nürnberg

INVENTED IN GERMANY

Federal Ministry of Education and Research

BMBF-Network "Clinics and Pathophysiology of Osteophytes and Ankylosis (ANCYLOSS)"

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Aims and Structure

The ANCYLOSS consortium is funded within the BMBF framework "scientific networks of musculoskeletal diseases". The project was designed to investigate the molecular mechanisms and clinical impact of osteophytes (new bone formations) in joint diseases, such as osteoarthritis (OA), psoriasis arthritis (PsA), and ankylosis spondylitis (AS). The project has been funded with a total amount of 1.5 million Euro by the Deutsches Zentrum für Luft- und Raumfahrt (DLR; national aeronautics and space research center) for the first period of three years in 2010. Within the six different work packages the expertise were bundled from different scientific fields, such as bone biology, lipid metabolism, molecular biology, genetics, animal models, imaging, and clinical research. Three of these projects (WP 1 - 3) concentrate on the pathophysiology of osteophyte formation and joint ankylosis, the other three projects (WP 4 - 6) are more clinically orientated and determine biomarkers as well as imaging tools to better visualize osteophytes.

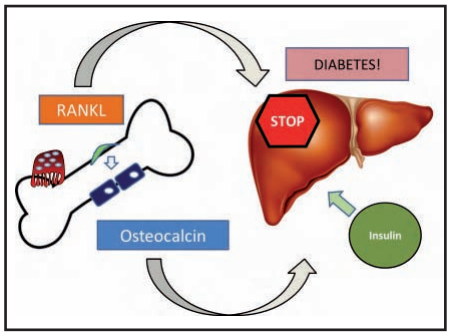
Research

Primary goals of this collaborative project are to understand the mechanisms of osteophyte formation in degenerative and inflammatory rheumatic disease as well as to build concepts and strategies to therapeutically interfere with the onset and progression of such lesions. ANCYLOSS is the first consortium which pursues research on osteophytes by using an interdisciplinary approach. Hitherto the scientific concepts in rheumatic diseases focused on disease aspects such as inflammation, pain, and functional impairment, but did not sufficiently target the structural aspects of rheumatic diseases. The interdisciplinary structure of the project also facilitates the translation of results from laboratory into clinical research. This implementation is achieved by different strategies: Genetic and biomarkers studies will optimize prediction of osteophyte formation and high-resolution imaging will improve the detection of osteophyte formation. The ANCYLOSS consortium focuses the mechanistic and clinical aspects of musculoskeletal diseases and specifically the mechanisms relevant to the crosstalk between inflammation, bone, and the adipose tissue.

One of the exciting findings of the ANCYLOSS project was the observation that diabetes constitutes an independent risk predictor for severe joint diseases. By using a well-documented prospective epidemiological cohort of healthy individuals (Bruneck cohort), we could show that diabetes is associated with later development of severe osteoarthrosis resulting in joint replacement surgery. Importantly, this association was independent from the two other major risk factors for osteoarthrosis, i.e. age and weight. Since its foundation, the consortium has published 34 scientific publications and contributed to improve know-how about musculoskeletal diseases.

Teaching

The interdisciplinary research is particularly suitable for the education of young scientists. The research group leaders supervise basic as well as clinically oriented theses in medicine and biology. The results of the interdisciplinary research will be rapidly implemented in lectures and advance training courses (medicine/molecular medicine/medical physics) in order to raise interest among young scientists to join this project.



BMBF Core Program "Molecular Diagnostics"

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Aims and Structure

Molecular medicine has gained a significant increase in scientific and technological knowledge in the past years. The present challenge is to transfer available knowledge of basic research into clinical application. In this framework, the development of reliable diagnostic and prognostic markers for a powerful molecular diagnostics is still at the very beginning for many diseases. One of the major bottlenecks is the validation of potential biomarkers. Therefore, an improved connection of the results of basic research with clinical findings from well characterized patient cohorts is expected to significantly foster the development and validation of novel markers for individualized treatment in the future. The BMBF has established the core program Molecular Diagnostics to address this point. The primary goal of this program is to support molecular diagnostic research in Germany and to transfer results from basic research to clinically available and economically exploitable products or processes.

Research

The central research topic of the research group headed by Erlangen is colorectal carcinoma. World-wide more than 945,000 colorectal carcinomas are newly diagnosed per year, and 492,000 patients die of them. The goal of the study is the validation and diagnostic application of RNA expression profiles in order to predict the tumor stages and the responses to standard therapies of colorectal carcinoma. The project is sponsored by the BMBF and an industrial partner with a total of two million Euro. Within the frame of this project, different institutes and departments of the clinical centers in Erlangen, Frankfurt, and Bochum in cooperation with clinics of Cologne and Schwabach together with Siemens Healthcare Diagnostic Products GmbH are cooperating. It is a specific clue of this study that all investigations are exclusively carried out on routinely acquired paraffin-embedded and formalin-fixed material. This will foster the spread and commercial exploitation of the potential test in the future. The major innovative components for the project were established in previous studies by members of the consortium.

(1) Predictive and prognostic relevant marker signatures were identified through performing extensive transcriptome analysis on fresh tissues of colorectal carcinomas. Different marker signatures were detected which highly significantly identify metastatic tumor stages (Prof. Dr. R.S. Croner, UK Erlangen) and predict angiogenesis-related survival (Prof. Dr. M. Stürzl, UK Erlangen), as well as responses to chemotherapy (Prof. Dr. W. Brückl, UK Erlangen) and radio-chemotherapy (Prof. Dr. C. Rödel, PD Dr. F. Rödel, Clinical Center Frankfurt).

(2) The industrial partner of the consortium has established a technology for the isolation of RNA from formalin-fixed, paraffin-embedded tissues which are acquired from routine pathological procedures. In this process, the RNA is isolated by silicate-coated magnetic beads which bind nucleic acids with high affinity. Based on this simple, but efficient purification principle, the extraction of RNA from tissue sections could be fully automated. The process has been optimized so that one thin section of a tumor tissue is sufficient to extract RNA amounts sufficiently high enough for quantitative RT-PCR analyses of the expression of more than 1,000 different genes (Polyprobe-test). Siemens Healthcare Diagnostic Products GmbH has established this key technology at the UK Erlangen and in addition has provided the required equipment for the procedure in the course of the cooperation. In the project, 61 different molecular markers which have been identified in previous studies will be validated in an independent patient cohort. Currently, three markers have been identified from previous analysis (n = 80) which correlate significantly with metastasis in independent retrospective (n = 82) and prospective (n = 203) patient cohorts. During further analysis of 177 cases, these three markers showed a significant correlation with survival during a five year follow-up period. Up to the end of the funding period, the predictive power of the

Polyprobe-test for determination of the tumor stage (primary endpoint) and the prediction of response to standard therapy (secondary endpoint) will be evaluated. In the course of a follow-up period (36 months after the end of patient recruitment), it will be investigated whether the established biomarker signatures can also predict disease free survival or total cancer-related survival in the recruited patients. The study is carried out in a non-randomized prospective manner. It is aimed at recruiting 650 patients. Accordingly, this study will be one of the largest studies on this subject worldwide.

SPONSORED BY THE
Federal Ministry of Education and Research

BMBF-Network "Eating Disorders Diagnostic and Treatment Network (EDNET)"

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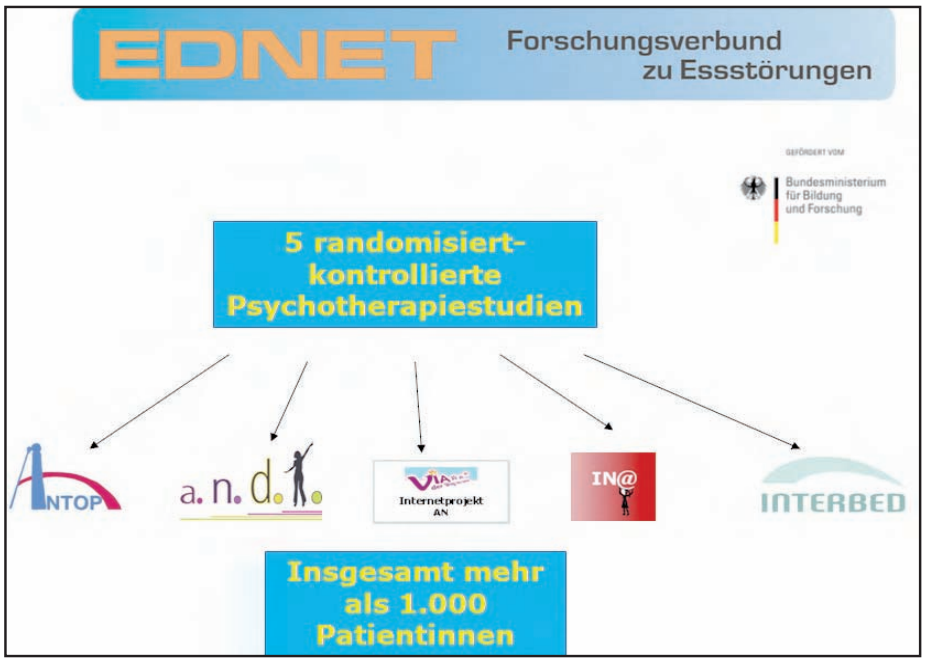
Aims and Structure

The BMBF issued a request for application for „Networks in Research on Psychotherapy". This funding instrument enables for the first time to conduct adequately powered, high-quality, multi-center, randomized, controlled psychotherapy trials in Germany meeting international quality standards. Of the 38 nationwide, multidisciplinary, and disease-specific applications, five networks were selected by international reviewers, including the Eating Disorders Diagnostic and Treatment Network (EDNET). The funding period runs from 2007 to 2013. In this network, the leading eating disorder researchers in Germany collaborate and coordinate their research efforts. The network comprises nine centers which are all university based departments of psychosomatic medicine, child and adolescent psychiatry and clinical psychology, located all over Germany (Aachen, Bochum, Dresden, Essen, Erlangen, Heidelberg, Leipzig, München, Tübingen). The central coordination was located in Erlangen until September 2011 and moved to Hannover Medical School as of October 2011. The Coordination Center for Clinical Trials in Marburg is responsible for randomization and data management of the whole network. This ensures uniformly high quality standards as all studies have to meet GCP criteria. The data monitoring was originally coordinated in Erlangen and has been located in Hannover since October 2011.

Research

Anorexia nervosa (AN) is a severe mental disorder with the highest standardized mortality ratio among all psychiatric disorders. The long-term outcome unfortunately has not improved over the last decades. In regard to treatment efficacy, the evidence to date is judged to be weak and there are virtually no evidence-supported treatment interventions. Therefore, three of the five randomized controlled psychotherapy trials in this network focus specifically on the treatment of AN. The network includes an outpatient treatment trial for AN comparing focal psychodynamic psychotherapy, cognitive-behavioral therapy and treatment as usual (ANTOP), a trial comparing in- and day-patient treatment in adolescents with AN (ANDI), and two internet-based relapse prevention trials for patients with AN (VIA) and BN (IN@) after discharge from inpatient treatment. A further study compares an internet-based guided self-help intervention with a face-to-face cognitive-behavioral therapy for overweight and obese patients with Binge-eating disorder (INTERBED). In total, more than 1,000 patients have been included into the five psychotherapy trials. The long-term success will be investigated in follow-up assessments conducted six months to 1.5 years after the end of the acute treatment phase. Additional funding will enable us to conduct long-term follow-up examinations of up to five years. Overall 35 clinical centers are recruiting and treating patients within the five psychotherapy trials. The treatment phase has already been completed in all studies. The last follow-up examinations are currently ongoing. Associated studies are grouped around the core treatment studies covering neuropsychology, structural as well as functional neuroimaging, genetics, epigenetics, and endocrinology. The Department of Child and Adolescent Psychiatry in Essen is part of an international consortium planning the first genome-wide association study in AN including 4,000 patients. The German group has collected one of the largest AN cohorts world-wide including the DNA samples from the patients of EDNET. To determine moderators and mediators of treatment outcome in psychotherapy trials, a separate proposal using a novel statistical approach has been included. Conceptually, treatment moderators specify for whom and under which conditions the treatment is effected. Treatment mediators identify why and how treatments have effects and identify possible mechanisms (causal links between treatment and outcome) through which a treatment might achieve its effects. Finally, members of the network together with other experts in the field of eating disorders have developed level 3 diagnostic and treatment guidelines for eating disorders. These evidence-based guidelines were published on the webpage of the Association of the Scientific Medical Societies in Germany. The studies in EDNET are highly innovative and will generate unique results justifying the extraordinary effort. These milestone studies will clearly increase our international visibility and competitiveness in this research field and will contribute to our knowledge on the efficacy and mechanisms of change of treatment in patients with eating disorders. The network members have already published numerous papers.



German Chronic Kidney Disease (GCKD-Study): National Cohort Study on Chronic Kidney Disease

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Aims and Structure

Chronic kidney disease is an increasing health problem, affecting approximately 10% of the population. The burden of morbidity and mortality associated with chronic kidney disease derives from progression to end stage renal disease with requirement of dialysis. Patients suffering from chronic kidney disease have a disproportionate risk of cardiovascular diseases including myocardial infarction and stroke.
However, the course of progression of kidney and cardiovascular disease in the setting of renal disease is highly variable and factors determining progression and complication rates are to a large extend unknown.

The number of randomized controlled trials in nephrology lags behind all other medical disciplines.
To address these questions, the FAU is coordinating a large prospective observational cohort study in Germany including the cooperation with the universities of Aachen, Berlin, Freiburg, Hannover, Heidelberg, Innsbruck, Jena, München, Regensburg, and Würzburg and a network of approximately 200 nephrologists from different regions all over Germany.
The study aims at gaining important insights on the heterogeneity of disease courses in observing a large number of patients over a long period of time, opening ways for a more deliberate and focussed application of existing diagnostic and therapeutic procedures and development of novel and more effective therapies.
The GCKD Study is funded by the KfH Foundation of Preventive Medicine and the BMBF.

Research

More than 5,200 patients with impaired kidney function have been included and will be observed over a period of ten years. Observations on the course of the disease, symptoms, and complications will be correlated with genetic information and findings from bioanalytical approaches in blood and urine samples applying modern biostatistical methods of data analysis.
The study aims at establishing valid associations between biomarkers affecting the disease progression and opening insights to the question why patients with kidney disease have a tremendously increased risk and disposition of cardiovascular diseases, including elevated blood pressure, myocardial infarction, and stroke. Another research focus is placed on the implications and consequences of kidney impairment on general health and quality of life.
These findings on disease course and associated complications will open ways for a more deliberate and focused application of diagnostic and therapeutic procedures, improve the overall prognosis, and help to postpone or avoid onset of dialysis.

National Genome Research Network – Mental Retardation Network (MRNET)

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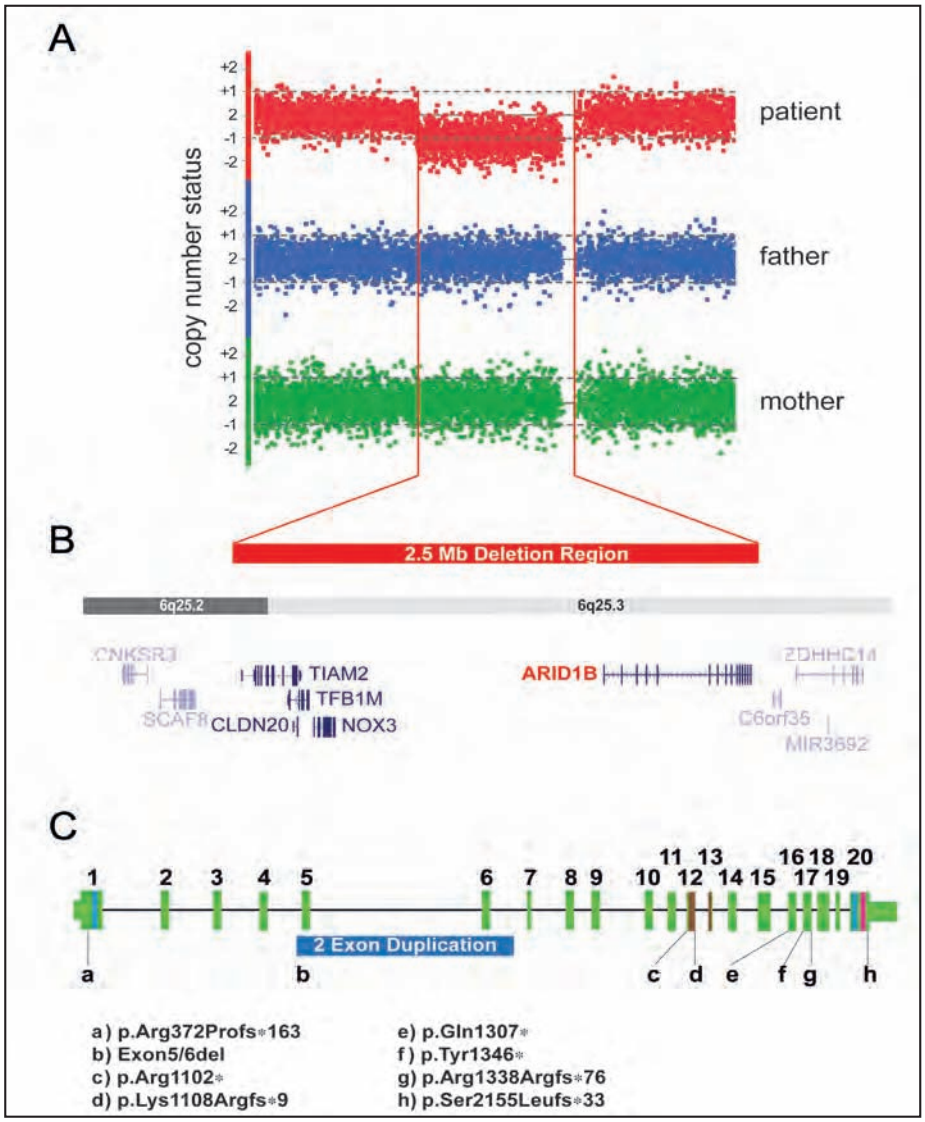
Aims and Structure

Intellectual disability (ID) or mental retardation has a prevalence of about 2% in the general population and is a major unresolved problem in health care. During the last years it became evident that genetic factors play an important role in the etiology of ID. The German Mental Retardation Network (MRNET) is a national network dedicated to the systematic investigation of genetic causes of ID. MRNET was funded from 2008 - 2011 within the medical genome research program (National Genome Research Network, NGFNplus) of the BMBF with a total budget of 6.3 million Euro. The central coordination located in Erlangen brought together the efforts of ten centers distributed throughout Germany and one each in Switzerland and The Netherlands.

Research

The project combines a medical genetic approach with systematic genome analysis. To date more than 2,600 patients were recruited and received a standardized clinical evaluation based on international phenotype ontology. Patient's data were collected in a specially developed, pseudonymized database. Sporadic as well as familial cases were included and several strategies for gene identification were applied. Disease causing submicroscopic aberrations (copy number variants, CNVs) were detected using state of the art micro-array based technologies in about 15% of cases. Patients with similar phenotype to those with the CNV were screened for point mutations in candidate genes from the respective genomic region (figure). In familial cases we studied cosegregation of genetic markers with the disease (linkage analysis) to likewise reveal candidate genes from linked regions. Furthermore, some patients were subject to comprehensive sequencing of the entire coding sequence (exome) with next-generation sequencing technologies. Finally, candidate genes and their respective signaling pathways were functionally investigated using cellular assays and animal models.
Overall, the coordinated research and collaboration between the MRNET members allowed the identification of some 80 genes for intellectual disability. A total of 49 publications in international peer reviewed journals were published, of which 15 were in highly regarded journals with an impact factor >10. Two publications can be highlighted, one in the journal Nature in which 50 novel genes for autosomal recessive ID were described and another paper in the prestigious medical journal The Lancet in which a comprehensive analysis using next generation sequencing of the genetic architecture of severe ID was reported.
In summary, the MRNET results substantially extended the diagnostic options in affected patients and contributed to a better understanding of disease etiology as well as the underlying pathomechanisms. It is now already possible to determine the genetic cause in over 60% of patients with ID. A further important finding was that the majority of mutations found in the patients represent new (de novo) mutations. Therefore, these parents have only a slightly increased recurrence risk.



ARID1B, a frequently mutated gene in intellectual disability.
a) Detection of a 2.5 Mb sumicroscopic genomic deletion in the index patient, chromosomes of both parents are normal.
b) Gene content of the deletion interval.
c) Genomic structure of ARID1B gene with point mutations of different patients with similar phenotype (according to Hoyer et al. Am J Hum Genet 2012).

Bavarian Immunotherapy Network (BayImmuNet): Adoptive Immunotherapy

Speaker
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Aims and Structure

Immunotherapy – the therapeutic interference with the human immune system – is one of the most important cornerstones of modern medical research. One of the current challenges is the translation of innovative therapy approaches from the laboratory into clinical application. In the area of immunotherapy – particularly antibody therapy and cellular therapy – Bavaria has excellent scientific teams and, consequently, a high degree of scientific potential. Many of the projects carried out by those teams are already at a stage in which rapid translation into clinical application can be expected. However, on the part of the university hospitals there is an investment bottleneck that is preventing rapid and efficient translation into clinical application. BayImmuNet, a unique network established by the Bavarian state government in 2008 with a start-up financing of ten million Euro, has set itself the goal of achieving faster translation of new approaches in immunotherapy into clinical application. Five clinical research groups were established at the Universities of Erlangen, Regensburg, Würzburg, and München (LMU and TU München).

Research

Realization that cellular immune reactions, mediated primarily by activated T-lymphocytes recognizing defined antigens, are responsible for the rejection of tumors in experimental models has led to multiple attempts to develop effective immunotherapies for the treatment of cancer patients based on stimulating T cell reactivity against cancer antigens.
Recent success using adoptive transfer of tumor-specific T cells has fueled optimism that this approach may find a place as a targeted therapy for some human cancers. Furthermore, it is well established that the curative potential of allogeneic bone marrow transplantation (BMT) is due to immunocompetent donor T cells inducing potent antineoplastic effects against host tumor cells, the "graft versus tumor" (GvT) reaction.
However, GvT reactions are mostly associated with the graft-versus-host disease (GvHD) which is the major cause of morbidity and mortality after allogeneic BMT.
This project aims at developing new strategies for the priming, selection, and expansion of antigen-specific effector T cells (CTL) under the guidelines of good manufacturing procedures (GMP) that will be used for adoptive T cell therapy in patients with solid and hematologic malignancies. CTLs generated with peptide-pulsed antigen presenting cells are often peptide reactive, but not reactive with tumors that express the gene of interest due to low level expression or impaired antigen processing by the tumor cells.
To circumvent this, we will focus on an approach of full-length proteins or overlapping peptides to generate T cell lines with a broader antigenic repertoire. The focus of another clinical study will be on the comparative analysis of different chemotherapeutic strategies for the induction of lymphopenia before adoptive T cell transfer.
Changing the equilibrium of various immune cell populations may result in a selective advantage being given to adoptively transferred T cells. Successful accomplishment of the aims could yield a new treatment option for patients with certain types of cancer, particularly malignant melanoma and hematologic diseases after allogeneic BMT.
The new building housing the Center for Internal Medicine (INZ) provides clean-rooms within the hematology department for the cGMP complyant production of cellular products. Currently, a quality management handbook for the manufacturing of T cells is generated in order to prepare a clinical study for adoptive T cell therapy of CMV and EBV specific –cells after allogeneic stem cell transplantation. The generation of virus specific T cells is now possible under cGMP conditions and the Department of Medicine 5 has applied for a manufacturing license with the local authorities. In addition, BayImmunNet is financing a phase I study after approval by the federal authorities, the "Paul-Ehrlich Institute", which will supposedly start in 2013.

Teaching

The heads of the clinical research group are involved in the traditional teaching program (lectures, seminars, practica) covering all subjects in the field of medicine and molecular medicine and the PhD and MD program for basic and translational research.

Bavarian Research Cooperation for Adult Neuronal Stem Cells (ForNeuroCell II)

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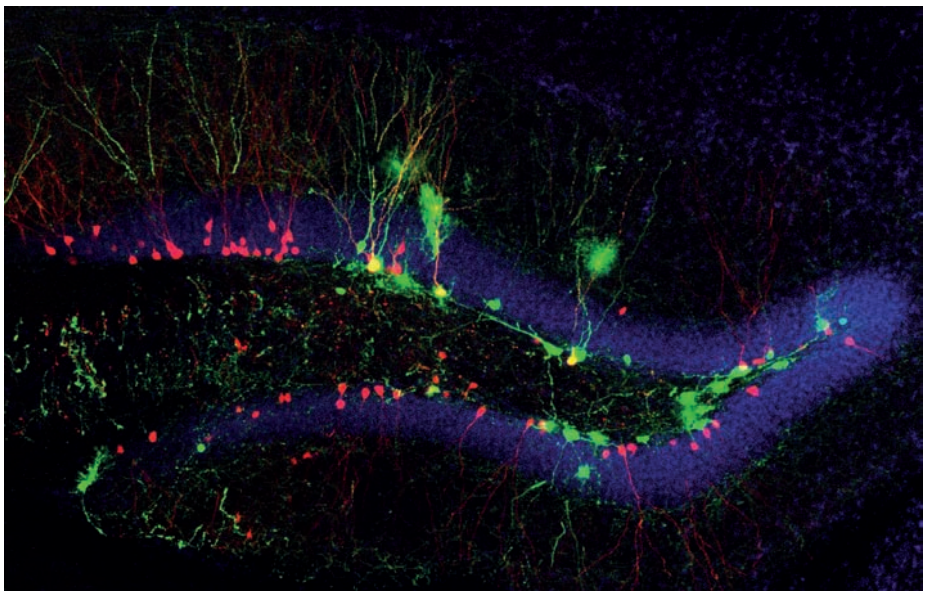

Aims and structure

The research network ForNeuroCell focuses on adult neural stem cells based regenerative strategies for acute and chronic neurodegenerative diseases in order to explore its future potential for clinical implementation. ForNeuroCell links modern neuroscience together with innovative imaging technologies and translational neurobiology. The network is funded for its second period (2009 - 2012). It consists of ten projects located at the Universities of Erlangen, München, Regensburg, Würzburg, and the Helmholtz Center München. The research network covers the following major topics: Molecular and cellular biology of stem cells, stem cell production, stem cell imaging, and preclinical testing of stem cells. This combined approach opens the possibility to implement adult neural stem cell based regenerative approaches for the clinic.

Research

The projects from Erlangen are headed by Prof. Dr. M. Wegner (Institute of Biochemistry), Prof. Dr. I. Blümcke (Institute of Neuropathology), and PD Dr. J. Klucken/Prof. Dr. J. Winkler (Division of Molecular Neurology). The project of Prof. Dr. M. Wegner focuses on the role of distinct Sox proteins during adult oligodendrogenesis. The family of Sox proteins plays a critical role in oligodendrocyte development and myelination. The goal of this project is to investigate the role of these proteins during oligodendrogenesis in preclinical models of neurodegenerative disorders. Prof. Dr. I. Blümcke's project deals with the functional characterization of adult human hippocampal stem cells and their directed differentiation into dopaminergic neurons. The central aim of this project is the characterization of human hippocampal stem cells in patients with pharmaco-resistant temporal lobe epilepsy. In this project, the group succeeded in showing that a close relationship exists between hippocampal plasticity and cognitive performance of epilepsy patients. In addition, adult human hippocampal stem cells are made available to the entire network. PD Dr. J. Klucken's and Prof. Dr. J. Winkler's project characterizes adult neural progenitor cells in Parkinson's disease models. The aim of this project is to redirect adult stem and progenitor cells from the ventricular wall, not only towards the adjacent striatum, but also locally to differentiate these precursors into dopaminergic neurons. Studies of neural progenitor cells from transgenic mouse models of Parkinson's disease illustrate that these cells already show synuclein aggregates interfering with the survival and differentiation of these cells. By analyzing protein aggregation processes together with activation of dopaminergic transcription factors, it remains to be seen whether recruited endogenous progenitors have the potential to obtain a neuronal phenotype. In addition to the projects in Erlangen, basic molecular and cellular research projects at the LMU München and the Helmholtz-Center in München and imaging projects at the University of Regensburg and the Technical University of München are performed within this network. The research network ForNeuroCell also made strong efforts to interact with national and international stem cell networks. The goal of ForNeuroCell is to form a "Bavarian nucleus" for stem cell-based technologies and translational approaches.

Teaching

The administrative core of ForNeuroCell, headed by Dr. R. Lederer together with J. Burczyk, made large efforts to support activities for young undergraduate and graduate students. Travel grants for graduate students and young researchers as well as doctoral seminars with the topics „Biostatistic" and „Grant Writing for Scientists" were organized. In November 2012, an outstanding symposium was held at the Carl-Friedrich-von-Siemens-Foundation (München) with numerous international speakers from the USA and Switzerland.

National Reference Center for Retroviruses

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Aims and Structure

Human immunodeficiency viruses (HIV-1, HIV-2) and human T cell leukemia virus (HTLV) belong to the retrovirus family.
From its foundation in 1996 by the Robert Koch Institute (RKI) until the retirement of the head of the Institute, Prof. Dr. B. Fleckenstein, in October 2012, the National Reference Center (NRC) for Retroviruses was located at the Institute of Clinical and Molecular Virology, FAU. In generally, the main tasks of a NRC are the development, standardization, and improvement of diagnostic and therapeutic procedures, distribution of reference materials, epidemiological surveillance, support in cases of ambiguous laboratory results, and other diagnostic issues as well as advisory service and public relations.

Diagnostic

In the function of a NRC for Retroviruses, our Institute has offered a broad range of methods in all diagnostic fields relating to retroviruses. This service continues even after Prof. Dr. B. Fleckenstein's retirement and will be steadily expanded. It comprises serological antigen and antibody tests and nucleic acid analyses for the detection of retroviral infections as well as methods for the characterization of viruses with respect to subtype, drug susceptibility, and coreceptor tropism. The Institute has vast experience in validating the efficacy of antiretroviral drugs. The range of methods in testing antiretroviral drug susceptibility covers all currently approved antiretroviral drug classes, including integrase inhibitors and CCR5-coreceptor antagonists.
In 2011 and 2012, major activities of the NRC targeted on the further development of methods for HTLV diagnostics. A real-time PCR protocol for the quantification of proviral DNA was established which is used as a parameter of progression of HTLV associated diseases. Additionally, among serology and sequence analyses, this protocol is inevitable for the clarification of infections with unusual clinical manifestations of HTLV infections. Finally, in the beginning of 2012, we successfully performed again a quality control trial for HTLV serology with participants from Germany, Austria, and Switzerland.
In the field of HIV-2 diagnostics, a real-time PCR protocol for the determination of the plasma viral load was established and used for diagnosis and surveillance of antiretroviral HIV-2 therapy. Moreover, in addition to the existing HIV-1 subtype panel, a HIV-2 subtype panel was created, consisting of eight different isolates. As there are no commercial tests available for HIV-2 viral load quantification, this panel (which is measured by three in-house-methods) is one of the best characterized HIV-2 reagents in the world. At the same time, the existing HIV-1 subtype panel was complemented with seven further HIV-1 isolates, including the very rare HIV-1 group N. The HIV-1 and HIV-2 subtype panels can still be provided.
For many years, the identification and characterization of HIV-1 drug resistance associated mutations has been a further topic of the NRC. In addition to the continuous updates of the bioinformatically supported resistance interpretation system geno2pheno, the NRC continued to coordinate a team of clinical virologists generating the German HIV-1 resistance interpretation system HIV-GRADE. Both interpretation tools are freely available online. In 2012, the NRC additionally introduced the SmartGene program for the evaluation of HIV sequence data in routine diagnosis. This program facilitates the comparison of HIV sequence data, e.g. in order to evaluate the development of resistance in different samples of the same person or to rule out contaminations in samples of different persons.
Since 1998, the Retrovirus-Bulletin has been an essential part of public relations. The NRC quarterly published this bulletin to provide scientific and clinical information on HIV, AIDS, and other retroviral infections like HTLV-1/2 (in German). The Bulletin was freely distributed by mail to a broad readership, like specialized clinicians and members of the public health system and of the HIV community.

Research

In addition to epidemiological analysis and evaluation of HIV-1 resistance (which have been performed in close cooperation with the RKI), the detailed analysis of different virus populations has become another important aspect of clinical research. For the detection of resistant viruses which might be present only as a minority in the patient, ultra-deep sequencing has been introduced in order to replace the classical methods (such as allele-specific PCR). In cooperation with the Institute of Pathology, two different platforms have been established. These methods for genotype HIV drug resistance and coreceptor tropism analysis are closely investigated at the moment and are expected to become a routine part of diagnostics. Finally, the efforts of the NRC are broadened by a large number of projects focused on basic and clinical research and addressed by the scientific groups localized at the Institute. These projects are supported by grants from the DFG, BMBF, European Union, and by several industry partners.

Teaching

Due to its task as the NRC for Retroviruses over many years, the Institute offers a broad range of HIV-related seminars to medical students and students of molecular medicine and biosciences. There are lectures about HIV-1 replication, pathogenesis and therapy, and a lecture on tropical medicine, focusing HIV in high prevalence countries. In addition, the HIV seminar addresses recent scientific results of HIV and HTLV research performed by members of the Institute. An experimental training course for retrovirology offers the possibility to learn important methods in the laboratories of the Institute.

Clinical Research Unit 130: Determinants and Modulators of Postoperative Pain

Speaker
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Aims and Structure

The clinical research unit (KFO) 130 was established at the Department of Anesthesiology in August 2005. It was funded by the DFG until the end of the year 2012. Contributing Departments and Institutes were: Anesthesiology, Experimental and Clinical Pharmacology and Toxicology, Physiology and Pathophysiology, Neurology, Human Genetics (all Erlangen), Physiological Psychology (University Bamberg), Pharmacology (University Zurich). The clinical research unit was directed scientifically by Prof. Dr. C. Nau.

Research

The focus of the interdisciplinary research team was postoperative pain that persists beyond the expected healing period. Persistent pain has an incidence of up to 50%, depending on the type and extent of surgery, and is linked to an increased risk for the development of chronic pain. Continuous inflammatory processes or inadvertent intraoperative nerve injuries contribute to the pathobiology of persistent pain. Risk factors for persistent pain are pre-existing pain, repeated surgery, and severe postoperative pain. Largely unknown was the influence of intra- and postoperative applied anesthetics and analgesic drugs, genetic factors, and psychological susceptibility on persistent pain.
In an interdisciplinary and translational approach, modern methods of molecular and cell biology as well as experimental pathophysiology and clinical studies were applied to identify neurobiological, pharmacological, genetic, and psycho-social factors of postoperative pain and to characterize clinical and pathophysiological settings that may facilitate the development of persistent pain.
Many projects also applied functional magnetic resonance imaging (fMRI) in rodents and men. Test subjects and patients were enrolled by the acute pain service as well as by the interdisciplinary pain center of the Department of Anesthesiology. The acute pain service was in charge of all patients that received postoperative pain therapy by means of patient-controlled-analgesia (PCA) techniques. The Department of Anesthesiology also provided physicians and study nurses in charge of enrolling patients and coordinating informed consent.
These are the most important scientific findings achieved by the KFO:

- Anesthetics and analgesic drugs exhibit pro-nociceptive effects by activating the nociceptive membrane proteins TRPV1 and TRPA1.
- HCN2 ion channels play a central role in inflammatory and neuropathic pain.
- Inhibition of a specific glycine receptor subtype (GlyR α3) by PGE2-induced receptor phosphorylation underlies central inflammatory pain sensitization, but not pain after peripheral nerve injury.
- Endocannabinoids, produced upon strong nociceptive stimulation, activate type 1 cannabinoid (CB1) receptors on inhibitory dorsal horn neurons to reduce the synaptic release of GABA and glycine and thus render nociceptive neurons excitable to nonpainful stimuli.
- Targeting spinal GABA(A) receptors containing the α2 and/or α3 subunits leads to pronounced analgesia. The selective activation by an α1-sparing benzodiazepine site ligand is effective against inflammatory and neuropathic pain.
- Medial prefrontal cortex activity is predictive for hyperalgesia and pharmacological antihyperalgesia.
- Noxious electrical stimulation may represent a neurostimulatory paradigm with antihyperalgesic properties.
- fMRI analysis of central pain processing revealed an increased degree of connectivity, clustering, and modularity in the thalamus, periaqueductal gray, and the amygdala of chronic pain (TNFtg) mice.
- Patients with Crohn's disease (CD) require significantly higher postoperative opioid doses than patients undergoing comparable severe abdominal surgery. However, CD patients do not display increased pain sensitivity in terms of lowered thresholds to thermal and mechanical stimuli. Furthermore, common variants in OPRM1 and specific 'high pain sensitivity' COMT haplotypes are not accounting for high opioid needs.
- Hypervigilance and attentional avoiding of negative experiences in patients are predictors of postoperative pain ratings and consumption of analgesics.

Teaching

The KFO provided young scientists and principal investigators with research rotations, thus enabling scientific activity within the projects. The annually hosted "Pain Days" offered inspiration for a more effective translation of preclinical knowledge into clinical practice. In April 2012, the KFO hosted an international symposium which attracted renowned national and international experts in pain research (see pictures).

Clinical Research Unit 257: Molecular pathogenesis and optimized therapy of chronic inflammatory bowel disease (CEDER)

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Aims and structure

Ulcerative colitis and Crohn's disease are prototypes of recurrent chronic inflammation of the intestine. In addition to the inflammatory processes in the gut, patients often suffer from extraintestinal manifestations (e.g. arthritis, erythema nodosum, pyoderma gangrenosum, primary sclerosing cholangitis). Research in recent years has led to the realization that both, environmental and genetic factors and a misdirected activation of the intestinal immune system to the intestinal flora, are key pathogenetic factors for the development of these diseases.
The aim of the Clinical Research Unit (KFO) is to develop and evaluate concepts for the pathogenesis of chronic inflammatory bowel disease (IBD) in order to develop new diagnostic and therapeutic approaches for the clinical management of these diseases. This translational research approach will be conducted in a close interaction between clinically and scientifically active IBD specialists and experienced basic scientists in Erlangen. On the basis of clinical specimens and preclinical models, the research group will develop new strategies and approaches for a more specific molecular or immunologically based therapy of IBD which is already aligned at this time to the development of clinical applications. For example, innovative approaches to influence angiogenesis, mucosal healing, and aberrant immune responses are developed and evaluated experimentally. In addition, methods are established to improve individualized diagnosis and therapy of IBD and the molecular mechanisms of action of established therapies are being researched. Should the KFO 257 succeed in developing preclinical therapy concepts, testing in clinical trials will be sought. The KFO 257 has two positions to allow rotation of clinicians into laboratories.

Research

The KFO 257 is structured into seven projects:

- Project 1: Mechanisms of cytokine-mediated immune pathogenesis of inflammatory bowel disease. Project managers: Prof. Dr. C. Becker/ PD Dr. J. Mudter (Department of Medicine 1 – Gastroenterology, Lung Diseases, and Endocrinology)
- Project 2: Functional analysis of the immunomodulator sCD83 in the pathogenesis and therapy of inflammatory bowel disease. Project managers: Prof. Dr. A. Steinkasserer/Dr. M. Lechmann (Division of Immune Modulation, Department of Dermatology)
- Project 3: Role of the Wnt/-catenin signaling pathway in IBD. Project manager: Prof. Dr. J. Behrens (Chair of Experimental Medicine II (Molecular Oncology))
- Project 4: Immune regulation of angiogenesis in IBD. Project managers: Prof. Dr. M. Stürzl/ Dr. M. Waldner (Department of Surgery/Department of Medicine 1 – Gastroenterology, Lung Diseases, and Endocrinology)
- Project 5: Analysis of the molecular mechanism of action of cyclosporin A in ulcerative colitis. Project managers: Dr. B. Weigmann/ Prof. Dr. R. Atreya (Department of Medicine 1 – Gastroenterology, Lung Diseases, and Endocrinology)
- Project 6: Characterization and expansion of regulatory T cells to establish a cell-based therapy of IBD. Project managers: Prof. Dr. M.F. Neurath/Prof. Dr. G. Schuler (Department of Medicine 1 – Gastroenterology, Lung Diseases, and Endocrinology/ Department of Dermatology)
- Central project: Project to coordinate the scientific program of the KFO 257. Project managers: Prof. Dr. C. Becker/PD Dr. J. Mudter (Department of Medicine 1 – Gastroenterology, Lung Diseases, and Endocrinology)

Teaching

Seminars on IBD:

- Immune pathogenesis and treatment of inflammatory bowel disease (Dr. C. Neufert/Prof. Dr. C. Becker)
- Molecular Medicine (Prof. M.F. Neurath/ Prof. Dr. C. Becker/Dr. I. Atreya)
- Molecular mechanisms of tumor development in the intestine (Dr. C. Neufert/Prof. Dr. C. Becker)
- Physiology and pathophysiology of the gut (Prof. Dr. C. Becker)

Current scientific literature (Topic: Research publications on IBD)
Research progress seminar (Topic: Current research findings of the KFO 257)

Meetings and International Training Courses

21.05.2011 Doctor-Patient-Seminar IBD
30.11.2011 ERIC Erlanger Interdisciplinary IBD Symposium
03.03.2012 Doctor-Patient-Seminar IBD
28.03.2012 ERIC Erlanger Interdisciplinary IBD Symposium

Research Unit 661: Multimodal Imaging in Pre-Clinical Research

Speaker
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Aims and Structure

A team of scientists from different faculties and research areas was supported by the DFG from October 2006 to September 2009 with about 3.5 million Euro in the area "Multimodal Imaging in Pre-clinical Research", with emphasis on computed tomography and small animal imaging. In the final assessment of the DFG, the results of phase 1 were rated as very good. A prolongation for another three years from October 2009 to September 2012 with a funding of about three million Euro was therefore approved by the DFG. In total, six subprojects were prolonged directly from phase 1; another subproject with the topic small animal positron emission tomography was added and integrated into phase 2. The results of phase 2 were presented at the conference "Molekulare Bildgebung (MoBi) 2012" in September 2012 in Erlangen.

Subprojects:
TP1: Contrast, dose, spatial, and temporal resolution in computed tomography focusing on micro CT and small animal imaging (Prof. Dr. Dr. h.c. W.A. Kalender, Institute of Medical Physics)
TP2: 3D and 4D statistical CT image reconstruction (Prof. Dr. M. Kachelrieß, Institute of Medical Physics)
TP3: Multimodal imaging in the acute phase of cerebral ischemia: Micro CT and Micro MR examinations with the focal ischemia model (Prof. Dr. A. Dörfler, Prof. Dr. T. Engelhorn, Department of Neuroradiology)
TP4: Optimized multimodal imaging of the cerebral vessel to improve functional imaging of pain induced activity (PD Dr. A. Hess, Prof. Dr. Dr. h.c. K. Brune, Institute of Experimental and Clinical Pharmacology and Toxicology)
TP5: Development and evaluation of ultrasound imaging modalities for small animal imaging (Prof. Dr.-Ing. H. Ermert, Research group for High Frequency Engineering, Ruhr-University Bochum; Prof. Dr.-Ing. R. Lerch, Chair of Sensor Technology, FAU)
TP6: Combination of optical fluorescence imaging with Micro CT procedures for fusion imaging on small animals (Prof. Dr. A. Langenbucher, Institute of Medical Physics). Prolongation for phase 2 was not granted.
TP7: Interaction between Tumor-Nekrosis-Factor (TNF) and Interleukin-1 (IL-1) in the structural lesion of joints in the context of inflamed joint diseases (Prof. Dr. G. Schett, Department of Medicine 3 – Rheumatology and Immunology; Prof. Dr. K. Engelke, Institute of Medical Physics)
TP8: Molecular imaging with small animal positron emission tomography (µPET) and new PET tracers for arthritis and tumor models (Prof. Dr. O. Prante, Prof. Dr. T. Kuwert, Department of Nuclear Medicine)

Research

Using the field of small animal imaging, a multi-disciplinary team endeavored to improve the assessment of anatomical and functional relationships in the same animal under comparable conditions and in repetitive sequences using Computed Tomography (CT), Magnetic Resonance Tomography (MR), Positron Emission Tomography (PET), and Ultrasound (US), both organ- and pathology-oriented. The combination of biochemical, functional, and morphologic information should improve the possibilities for early non-invasive diagnosis and could finally lead to improved and often more cost-efficient patient care.
It was the central goal of the Research Unit (FOR) 661 to enhance and transfer the recent developments in the field of X-ray CT and to augment them with further efforts in basic CT research and the combination of micro-CT with other slice imaging modalities, such as MR, PET, and US, in order to improve the visualization and evaluation of new therapy methods in chronic pain, stroke, or malignant tumors. The cooperation of the participating institutes and departments offered considerable synergistic effects by the alliance of basic research (TP1, TP2, TP5, and TP8) and clinical application (TP3, TP4, and TP7).
At the Institute of Medical Physics, the projected CT developments, in particular for micro-CT, focused on optimization of image quality at minimal dose, the implementation of dual-energy methods, and the development of tools for dynamic micro-CT. New approaches to CT image reconstruction aimed at maximal low-contrast detectability for a given dose or, as an alternative, at minimal dose for a given level of image quality.
The research group for High Frequency Engineering at the Ruhr University Bochum and the researchers of Sensor Technology at the FAU worked on the application of various ultrasound imaging modalities in small animal imaging, the comparison of these modalities to MRT, micro-CT, and PET. Another research topic was the technical combination of ultrasound and micro-CT in a multi-modal system to make use of the spatial resolution of micro-CT and the contrast resolution of ultrasound.
In the Department of Neuroradiology at the UK Erlangen, the work focus was on the field of medical biological basic research and clinical application. One topic was to scrutinize the sensitivity of micro CT in correlation to a 64 slice CT and a small animal MRT during the acute phase of cerebral ischemia. The intention was to deploy CT to encircle ischemic tissue that is not yet irreversibly damaged and still treatable.
At the Institute of Experimental and Clinical Pharmacology and Toxicology, the researchers focused on the improvement of functional MRI (fMRI) respectively angioplasty by recording and merging data of vascular trees of rodents and optimizing modeling. This work enhanced not only the resolution, but also the understanding of the translation of neuronal activities into signals that are detected in MR.
The Department of Medicine 3 - Rheumatology and Immunology was working on the high resolution imaging of bone damages due to arthritis with micro-CT and micro MR in small animals. The research focus was to be expanded on the quantification of angiogenesis in arthritic inflamed joints in correlation to architecture and extent of the vessel net.
With the subproject of the Department of Nuclear Medicine, the imaging modality PET was also available for functional imaging of arthritis and tumor models on small animals by using new peptide-based PET tracer.

Research Unit 832: Regulators of Humoral Immunity

Speakers
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Aims and Structure

Since 2008, the DFG has sponsored a new interdepartmental research unit (FOR) with the main topic of "Regulators of the Humoral Immune Response" and granted a total volume of two million Euro for it. Seven scientists from the Institute for Biology of the Faculty of Natural Science (three projects) and the UK Erlangen (four projects) are participating in the research unit. Five of the eight participating project leaders which include both, biologists and clinicians, are residing at the NFZ. In close cooperation, the seven projects research the molecular circuits that are involved in the control and regulation of antibody-producing B-lymphocytes. Cell-culture and mouse models are employed. Meetings on a regular basis (such as at the monthly B-Cell Club), a mutual concept for the education of doctoral students analogous to the program of the expired GK 592, the participation in supervisory commissions for doctoral students, as well as scientific colloquia (B-cell retreat), additionally promote the mutual scientific objective.

Research

The B-cell is at the center of attention of FOR 832. During its maturation in the bone marrow, the genes for the antibody molecules are assembled by rearranging the corresponding DNA segments. This process creates millions of B-cells, all of which produce a different type of antibody. This molecule is either directed at a specific pathogen or at a molecular structure that generally signals an attack. The mature B-cell initially carries its antibody to the cell surface, thus allowing to detect an appropriate signal. In this case, the B-cell is activated in the peripheral lymphatic organs and releases large amounts of soluble protective antibodies into the blood. FOR 832 concentrates on these complex regulatory processes during the maturation and activation of B-cells.

On the one hand, congenital disorders of the complex differentiation schema can lead to immune deficiencies – which means to a special susceptibility to conditions ranging from infectious diseases to life-threatening immune defects. However, excessive and misdirected immune responses, such as those of allergies and autoimmune diseases, are caused by disorders in the regulation of the immune response. In autoimmune patients, the immune system frequently develops antibodies that react to structures of their own body instead of pathogens. The research unit directs the focus of its work towards the clarification of such undesirable developments. The approach of the research unit is initially focused on fundamental research because it will only be possible to develop new types of therapy through a better understanding of the molecular circuits and complex cell-cell interactions in the immune defense that is imparted by the antibody.
At the present time, an efficient humoral immune response cannot be adequately reconstructed "in the test tube". The high degree of complexity and the multitude of cellular and molecular interactions between B-cells and other cells of the immune system require studies on the living organism, on both tissue sections and cells that have been isolated from the suitable animal models through appropriate cell-sorting methods. Consequently, one experimental focus of FOR 832 is the use of the mouse as an animal model for the humoral immune response. The research of the previous years has clearly demonstrated that the processes of antibody formation occur in a very similar manner in mice and humans. The possibility of using and also establishing "genetically tailored" mouse models here in Erlangen will be employed by the research unit (compare figure 2), for better understanding molecular and cellular processes during the humoral immune response that cannot be specifically investigated in either the cell cultures or the human being.

Teaching

All project leaders are actively integrated into the supervision of the respective doctoral students as members of the doctoral supervisory commissions. All members of the research unit are also actively involved in public relation (such as the Long Night of the Sciences and supervision of seminar theses for high school students).

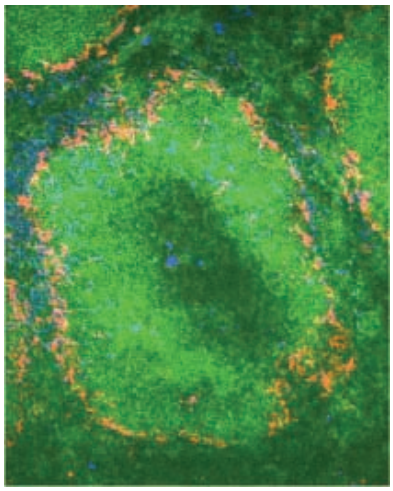

Figure 1: Histology of a B-cell follicle in the spleen

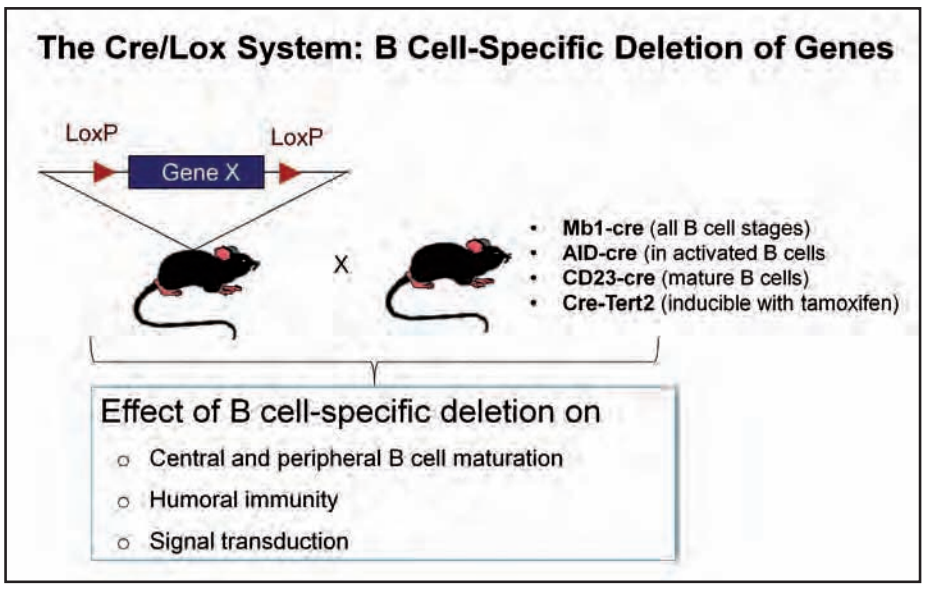

Figure 2: Gene Deletion by the Cre/Lox System

Research Unit 894: Fluid Mechanical Basis of the Human Voice

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Aims and Structure

Participating Institutions: Division of Phoniatrics and Pediatric Audiology, Chair of Applied Mathematics II, Chair of Sensor Technology, Institute for Process Technology and Machinery, Institute of Fluid Mechanics; Institute of Mechanics and Fluid Dynamics (TU Bergakademie Freiberg); Institute of Mechanics and Mechatronics (Vienna University of Technology). Funded since 2008.

Voice production within the larynx is still not entirely understood, neither in normal nor in pathological voice. The goal of the interdisciplinary research unit (FOR) 894 is to substantiate knowledge of normal and pathological vocal fold dynamics and of the resulting acoustic signal. Human voice is the result of a complex process comprising fluid dynamics coupled with moving elastic tissue. Analyzing such complexities necessitates different modeling approaches. Therefore, departments from different research fields are working together to derive a better picture of the entire voice origination process. The different suggested models allow a review and verification of the results and assumptions. In the international fluid dynamics and voice research community, different approaches are still applied and discussed on their own. Hence, FOR 894 is performing pioneer research. To coordinate and lead the interdisciplinary group, the DFG established a W2-professorship on Computational Medicine. Prof. Dr.-Ing. Michael Döllinger is the scientific manager of FOR 894.

Research

The strategy of FOR 894 is the application of different experimental and numerical models, yielding a comprehensive description of voice production. The bases for the models are endoscopic high speed digital video recordings from both, healthy and pathological subjects. At the Division of Phoniatrics and Pediatric Audiology, biomechanical models are fitted to the recorded dynamics for receiving quantitative information on the severity of diseases.

For analyzing fluid mechanical causalities, an air driven physical model has been developed representing a realistic model of human voice production. Vocal folds consisting of a silicon mixture are set into vibration and allow to experimentally analyze the entire chain of fluid-structure-acoustic interaction. The material parameters of the synthetic vocal folds are adapted to human laryngeal tissue by numerical optimization algorithms (Institute of Applied Mathematics II). The model enables the variation of pressure, air flow, and elongation of the synthetic vocal folds (Chair of Sensor Technology). Hence, impacts on dynamics and acoustics can be observed and analyzed. However, irregularities cannot be separated regarding their cause and resulting effect.

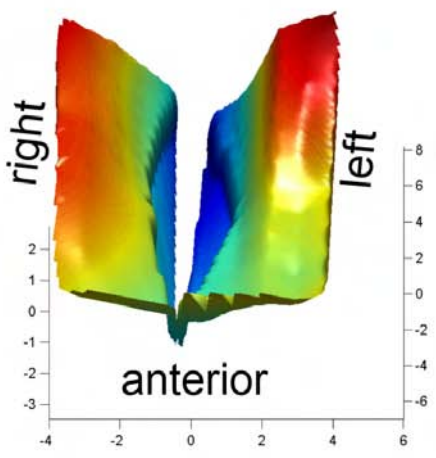
To investigate predefined clinical observed irregularities and their impact on voice quality, a water driven model was developed by the group from Freiberg. Here, the fluid dynamics are easier to observe due to the increased time scale. This model is especially appropriate for observing eddy induced acoustics.

The experimental work is supplemented by a numerical 2d-finite element method model (figure) and a 3d-finite volume model. Thus, fluid volume as well as mechanical induced acoustics can be analyzed directly. However, due to the complexity, these models cause high computational costs.

By these approaches the different acoustic sources can be investigated and analyzed. In the future, conclusions for medical conservative as well as surgical treatments will be driven, based on the cause-and-effect chain.

Teaching

The participating groups in FOR 894 supervise mathematical, technical, and medical theses as well as interdisciplinary master theses and student research projects. The principal investigators of the different projects are involved in lectures in three different faculties: medical, engineering, and natural sciences.



Research Unit 1228: Molecular Pathogenesis of Myofibrillar Myopathies

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Aims and Structure

The multilocation research unit (FOR) 1228 has been funded by the DFG since November 2009. This research unit aims at clarifying the molecular processes that lead to progressive skeletal muscle and cardiac damage in myofibrillar myopathies. FOR 1228 combines the scientific expertise of physicians, biologists, and biochemists and is composed of 13 distinguished groups from the Universities of Erlangen, Bonn, Bochum, Köln, Heidelberg, Ulm, and Vienna. After a positive evaluation in July 2012, FOR 1228 was granted a second funding period until November 2015. The financial support of the DFG sums up to 3.6 million Euro for a six year term of funding.

Research

Myofibrillar myopathies (MFM) are progressive and devastating diseases of human skeletal and cardiac muscles that often lead to premature death. MFM are histopathologically characterized by desmin-positive protein aggregates and myofibrillar degeneration. While about half of all MFM are caused by mutations in genes encoding sarcomeric and extra-sarcomeric proteins (desmin, filamin C, plectin, VCP, FHL1, ZASP, myotilin, and B-crystallin, BAG3, DNAJB6), the other half of these diseases is due to still unresolved gene defects. During the first funding period, FOR 1228 has made substantial contributions to our current understanding of the molecular pathogenesis of desminopathies, plectinopathies, filamin C-, FHL1- and VCP-related MFM. Major joint achievements have been the establishment and validation of MFM-related animal and cell models, the adaptation and refinement of laser microdissection and proteomic analysis of pathological protein aggregates and biochemical approaches to address molecular pathways contributing to the pathogenesis of MFM. In the second funding period, FOR 1228 will focus on the following major goals:

1) Characterization of individual and shared disease mechanisms in myofibrillar myopathies due to pathogenic desmin-, plectin-, filamin C-, and VCP-mutations.
2) Systematic analyses of disease-specific cell and animal models.
3) Validation of cell and animal models for pharmacological treatment strategies.
4) Proteomic characterization of the composition of pathological protein aggregates in skeletal muscle biopsies from patients with genetically proven MFM-causing gene mutations and mouse models.
5) Identification of novel candidate genes that cause human myofibrillar myopathies by laser dissection microscopy followed by proteomic analysis and genomic DNA sequencing.
6) A multi-scale approach addressing biomechanical properties of MFM in myoblasts, myofibers, and whole muscles.

FOR 1228 offers the unique opportunity to unravel the molecular "MFM sequence" that leads to pathological protein aggregation and progressive muscle damage. Currently no causative or ameliorating therapy is available for MFM. The joint work of FOR 1228 will therefore not only provide deeper mechanistic and preclinical insight into the pathogenesis of MFM, but also aims at paving the way to novel targeted treatment concepts. As translational approach we will therefore study the therapeutic effect of drugs and compounds that directly target pathological protein aggregation processes. In addition, gene replacement strategies by AAV-mediated gene transfer will be evaluated.

Teaching

The participating groups of FOR 1228 are supervising PhD and/or medical theses. The principal investigators of individual projects are also actively participating in the teaching of students in the field of medicine, molecular medicine, biology, and biochemistry.

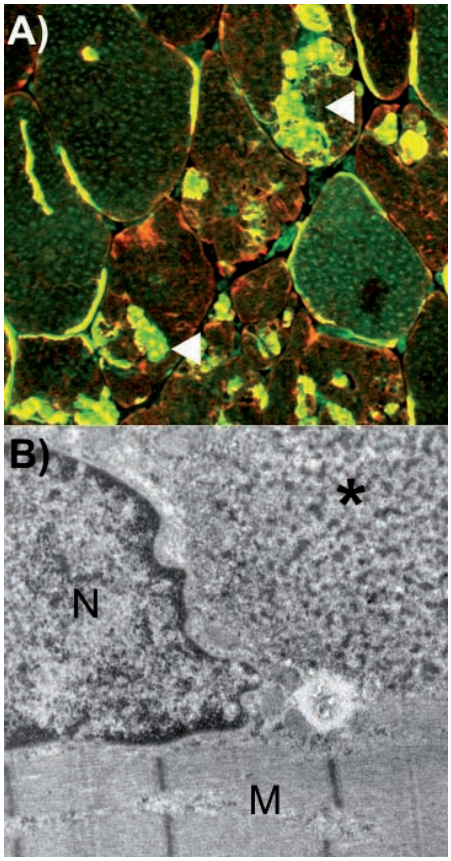

Illustration of pathological protein aggregates in a skeletal muscle biopsy from a patient with myofibillar myopathy by indirect double immunofluorescence and electron microscopy. A: Labeling of pathological protein aggregates by doublestains with antibodies against Desmin and B-Crystallin. B: Ultrastructural visualization of pathological protein aggregates (*) in direct vicinity to a myonucleus (N) and to myofribrills (M).

Project Group of the Academy of Science and Literature, Mainz

Speaker
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Aims and Structure

Persistence and chronic infections of viral pathogens are essential requirements for the development of AIDS and virus induced tumors. The Academy of Sciences and Literature in Mainz supports a project group at the Institute of Clinical and Molecular Virology together with the State of Bavaria which is devoted to investigate persistent and oncogenic viruses of the hematopoetic system.

Research

Section A: Mechanism of the viral interference between GB Virus C and HIV-1

Project leader: Dr. Dr. H. Reil

This research group is studying the phenomenon of viral interference. In HIV patients, persistence of a human non-pathogenic virus, the GB virus C (GBV-C), can result in a delayed AIDS progression. The focus of this project is the clarification of the underlying mechanisms. Here, it could be shown that the GBV-C surface protein E2 is significantly involved. The responsible region could be identified to range from the E2 amino acid 29 to 72. Peptides from this region are able to inhibit HIV entry efficiently (IC50 von 0,1 und 2 µM). The E2 peptides bind directly the HIV transmembrane protein gp41 and suppress entry steps that follow after the HIV receptor binding. The exact E2 binding region could be identified as the disulfide loop of gp41. Cysteine residues within the loop region and the E2 N-terminus turned out to be essential. Bioinformatic analysis revealed a sequence similarity between the N-termini of HIV gp120 and GBV-C E2. Since gp120 interacts with the disulfide loop of gp41 to form functional HIV surface spikes, it is assumed that this structural gp120 mimicry enables E2 to bind the disulfide loop. By this mechanism, the gp120-gp41 interface may be disturbed and the membrane fusion between virus and cell is inhibited.

Section B: Oncogenesis induced by the Kaposi sarcoma associated human herpesvirus 8

Project leader: PD Dr. F. Neipel

This research group is analyzing the early steps of the infection of a cell by human herpesvirus-8 (HHV-8), also termed Kaposi sarcoma associated human herpesvirus (KSHV). Infection of a cell by a herpesvirus is a complex, multi-step process. It involves the interaction of at least three viral glycoproteins with one or more cellular receptors. The highly conserved viral envelope-protein complex formed by glycoproteins H and L (gH/gL) is essential for this process. Using molecular biological methods, the group identified the ephrin receptor tyrosine-kinase A2 (EphA2) as a cellular receptor for KSHV gH/gL. Using a multitude of approaches they could unequivocally show that EphA2 is of crucial importance for the infection of endothelial cells by KSHV. Notably, the observed effects were highly specific for EphA2 and could not be observed with closely related ephrin-receptors. In particular, knock-out of EphA2 on murine cells resulted in complete block of KSHV infection. In summary, the data from the group clearly show that EphA2 - a receptor tyrosine-kinase that is known to play important roles in neovascularization and oncogenesis - is an essential factor for the infection of endothelial cells by KSHV.

Section C: Plasmacytoid dentritic cells, the innate immune defense against Human Immunodeficiency virus Type 1 (HIV-1) and Herpes simplex virus Type 1 (HSV-1) infections

Project leader: Prof. Dr. B. Schmidt

This research group focuses on the role of plasmacytoid dendritic cells (PDC) in virus infections. PDC were identified as main producers of type I interferons in the blood in 1999. The group could show a reduced number and function of PDC in HIV-1 infected patients which results in an impaired immune response to viral and bacterial stimuli. It characterized the chronic immune activation in HIV-1 infection as one of the reasons for the reduced interferon production. On many immune cells, CD40 ligand, a molecule of the TNF family, was found to be upregulated. In parallel, the receptor CD40 was upregulated on the PDC. The enhanced interaction of ligand and receptor leads to a reduced production of type I interferons at physiological levels. To verify the clinical relevance of this model, the group investigated a total of five patients suffering from an immune reconstitution inflammatory syndrome (IRIS). In these patients, a strong increase in CD4+ T cells upon initiation of antiretroviral therapy is accompanied by the occurrence of opportunistic infections. In one patient with a hyperproliferative genital lesion caused by infections with HSV-1 and human papillomavirus type 54, significantly increased levels of CD40 ligand were detected in the plasma for more than a year. The PDC of the patient showed signs of immune activation. These results suggest that the impaired PDC innate immune response contributes to the persistence and reactivation of herpes- and papillomavirus infections. Altogether, the data of the group support important functions of PDC in the immune defense.

Section D: Transformation mediated by human T cell lymphotropic virus type 1 (HTLV-1)

Project leader: Dr. A. Kreß

This research group analyses host cell factors which are deregulated after transformation by Human T cell lymphotropic virus type 1 (HTLV-1) and which contribute to pathogenesis. HTLV-1 is an oncogenic retrovirus which transforms CD4+ T cells via the viral transactivator protein Tax to permanent growth. Moreover, HTLV-1 is the causative agent of adult T cell leukemia/lymphoma (ATLL). After the research group found out that the tumor marker Fascin is a novel, NF-κB-dependent Tax target gene, the studies could be extended to the tumor-virus Epstein-Barr virus and its oncoprotein latent membrane protein 1 (LMP1). Use of several methods revealed that NF-κB signaling is important for LMP1-mediated induction of Fascin in overexpression systems as well as in EBV-transformed lymphocytes. Therefore, NF-κB-dependent induction of Fascin is a common feature of viral oncoproteins encoded by the lymphotropic tumor viruses HTLV-1 and EBV. Thus, induction of Fascin seems to reveal a new quality of virus-induced oncogenesis.

Integrated Research Training Group within Collaborative Research Center 643: Strategies of Cellular Immune Intervention

Speaker
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Aims and Structure

The Research Training Group (GK) is integrated in the SFB 643 "Strategies of Cellular Immune Intervention". It will train the doctoral candidates to become highly qualified scientists. With a structured educational and support program, it will prepare purposefully for the job. Our offer to the students includes a bi-weekly regular meeting, workshops on communication and GMP-production, project-related workshops that allow students to spend time in labs outside of Erlangen. Additionally, each student gets the chance to gain organizational skills, build up scientific networks, and discuss their research with internationally recognized scientists. Finally, the close supervision of the students by three faculty members streamlines and focuses each research project and thus facilitates the completion of the thesis in a timely manner.

Research

The SFB 643 "Strategies of Cellular Immune Intervention" has been existing since July 2004 and is currently in its third funding round. The goal of the research center is the successful implementation of immunological knowledge in treatments that are based on a manipulation of the immune system, i.e. on immune intervention. Immune therapeutic approaches to treat tumors and infectious diseases require the enhancement or stimulation of the immune response. Conversely, innovative treatments of inflammatory diseases, including autoimmune diseases, allergic diseases, and transplantation reactions call for novel and improved immunosuppressive strategies. The research program is conceptually structured in three closely interconnected project areas:

Project area A:
Basic immunology

Project area B:
Immune intervention in animal models

Project area C:
Therapeutic applications.

Teaching

We believe that our structured mentoring and education program will not only result in better trained doctoral students, but will also make them independent scientists early in their career. Our goal is based upon the following mentoring and educational units: Every graduate student will be accompanied by a support-commission. It consists of the direct supervisor and two part-project-leaders of the SFB 643. In a bi-weekly regular meeting the candidates discuss literature, methodical problems, and their own research-data. Internal Report-Symposia and Network-Meetings with other topically relevant and external GK will train the candidates to present their research in front of a larger council. Workshops imparting the following skills are held: Knowledge of the different industrial occupational fields and the improvement of the students' presentation and scientific writing skills. The SFB emphasizes on translating experimental data into clinical practice. Therefore, courses will be offered that deal with the GMP-production of cell based medicine and medical auxiliary material, quality management, certification, and accreditation. Project-related courses, optional visits in external laboratories over the course of several months within the trainee program, and a guest speaker program teach the candidates how to take personal responsibility, establish international networks, and discuss their research projects with international scientist.
We have experienced that especially the intensive scientific exchange does not only educate the candidates to the better, but also helps them to become independent scientists very early in their career. By including the support commission and an intense exchange between the candidates and their mentors, "wrong directions" are detected and the education of the candidates is streamlined.

Integrated Research Training Group within Collaborative Research Center 796: Erlangen School of Molecular Communication

Speaker
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Aims and Structure

The Research Training Group (GK) "Erlangen School of Molecular Communication" forms part of the Collaborative Research Center "Reprogramming of Host Cells by Microbial Effectors" (SFB 796), an interdisciplinary cooperation of groups from the Faculty of Medicine and the Faculty of Natural Sciences of the FAU as well as the UK Erlangen and the Fraunhofer Institute of Integrated Circuits. The GK offers an attractive doctoral program, primarily for students of the natural sciences, but also for medical students. There is a strong emphasis on lively scientific exchange and interdisciplinary work and this is promoted by annual retreats, an engaging series of seminars and a mentoring program. As a special feature, the GK offers now a fast track program. Outstanding students will be given the opportunity to replace the two-year master degree by a one-year curricular phase, thus starting their doctoral studies more quickly.
First funding period: 2009 - 2012
Prolongation: 2012 - 2016

Research

The strong focus on interdisciplinary research at the GK "Erlangen School of Molecular Communication" is both, attractive and challenging. The research within the SFB 796 aims at investigating the dynamic interplay between microbial effectors (viruses and bacteria) and their host cells. This is achieved by examining both, the intrinsic response of plant and mammalian cells and the microbial host cell manipulation at the molecular and cellular level. This research raises the question whether similar structures and mechanisms have developed in the heterogenic host/pathogen interactions during evolution. These general themes may be extended to other pathogens not investigated within the SFB initiative.

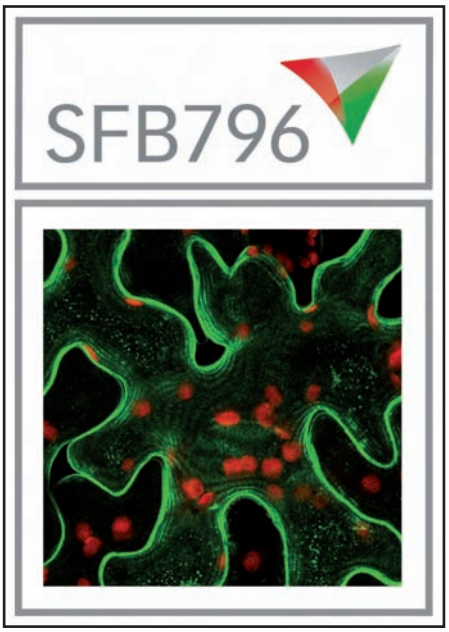
Project area A: Structural basis of molecular interactions
Research in project area A centers on structure/function relationships of previously identified effector proteins and their interactions with specific cellular targets. Major topics include investigation of the HIV regulatory Vpr protein, of HIV mimetic molecules, structural analyses of the potyvirus with plant chaperones and the development of bioinformatic tools for the prediction of protein-protein interactions.

Project area B: Reprogramming cellular processes
The focus of project area B is the detailed elucidation of mechanisms used by microbial effectors to reprogram cellular processes, including selected signal transductions pathways, intrinsic immune responses, targeted protein turnover, and the primary metabolism. Research objects range from viral pathogens (herpesvirus saimiri, herpes-simplex virus 1, human cytomegalovirus) to bacterial pathogens of plant and human cells (Xanthomonas campestris, Corynebacterium diphtheriae).

Project area C: Replication structures and transport processes
Project area C focuses on the question of how microbial effectors use and partially convert cellular structures for successful colonization and replication. A number of different types of host/pathogen interactions are also investigated in this area, namely the role of molecular chaperones during virus replication and spreading in plants, the structure, and function of the nuclear egress complex of the human cytomegalovirus, the influence of the vesicles transport in plants by type III effectors from X. campestris as well as the development of new methods for the expression analysis of Salmonella-virulence proteins.

Teaching

The GK offers structured research training in internationally renowned laboratories. Each doctoral student is supervised by two experienced scientists: The principal investigator of the relevant SFB project and another SFB member. The training program is complimented by scientific and method lectures. Graduate students are given the opportunity to choose the topics for the GK seminars according to their own requirements and were also given responsibility for one session within the first international conference of the SFB in October 2011. Acquisition of soft skills is an important part of the individual development of the students and will support their scientific work and future career. With this in mind, a number of tailor-made workshops are organized to improve presentation and communication skills and writing techniques. In addition to these courses, further training in specific techniques or methods, such as statistics or fluorescence microscopy, are also provided on student request.



Research Training Group 1071: Viruses of the Immune System

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Figure 1: Graduate studies in the GK 1071

Aims and Structure

The GK 1071 "Viruses of the Immune System" provides an internationally oriented, structured training mainly for PhD, but also for MD students. It is based on an established interdisciplinary cooperation among scientists of the Faculty of Medicine and the Faculty of Natural Sciences at the FAU. The special feature of the GK 1071 is an integrated exchange program with Harvard Medical School (HMS). Students holding a diploma or master degree in life sciences or molecular medicine from Erlangen join the laboratory of a participating Harvard faculty member and, upon completion of their thesis, graduate as Dr. rer. nat. from FAU. Joint retreats provide an intense exchange between students and faculty members from Erlangen and Boston. This direct interaction enforces the mentoring program and enables the students to gain insight into the everyday life at one of the leading research institutions. The resulting internationalization should promote the PhD projects and the professional perspectives of the students.
Second funding period: 2009 – 2013.

Research

The scientific focus of the GK 1071 is on the interface of virology and immunology. Current projects mainly concentrate on two groups of persisting lymphotropic viruses, herpesviruses and retroviruses. They are clinically relevant as causative agents of human tumors and AIDS. Research topics include the basis of AIDS pathogenesis and viral oncology as well as therapy and prophylaxis of viral infections. Thus, this network contributes to the research focus on infectiology/immunology at the Faculty of Medicine.

Section A: Viral immunodeficiency
Projects in this field investigate the interactions of Human Immunodeficiency Virus (HIV) with its host cells as well as with other viruses. They aim at the definition of mechanisms relevant to pathogenesis and at potential targets for therapeutic intervention.

Section B:
Basis of Prevention and Therapy
Humoral, cellular, and innate immune responses to viruses are the main topic of projects in this section. Understanding immunological processes controlling infection may lead to novel strategies for specific prevention and therapy.

Section C: Lymphotropic tumor viruses
This research field covers various aspects of viral oncogenesis. The viruses investigated induce various forms of lymphoma which are relevant as human diseases or as model systems for lymphocyte growth transformation.

Teaching

Our program strives for a comprehensive, internationally oriented graduate training that fosters both, scientific and personal skills of the PhD students. To this end, their research projects are accompanied by a mentoring program. An early independence is supported by mandatory research reports at the retreats and by student travel funds that allow for participation in scientific conferences. Personal development is further boosted by activities mediating complementary skills for a career in science or industry. Among these are an autonomous student seminar, workshops on presentation, and writing techniques as well as the organization of scientific and public-oriented events. Particularly, the International GK Symposium in Erlangen is realized together with students of other research training groups and the Long Night of the Sciences is presented at the Institute of Virology by the members of GK 1071.

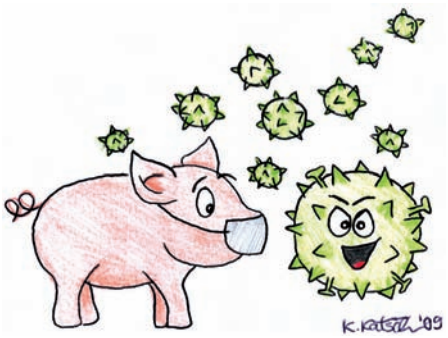

Figure 2: Logo for the Long Night of the Sciences at the Institute of Virology (drawing/copyright Kristin Katsch 2009)

Research Training Group 1660: Key Signals of Adaptive Immune Response

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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 will also accept 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 that runs parallel to the medical school program (figure 1). The doctoral students with a bachelor's degree will first pass through a 1.5-year training program where they will receive extensive training in immunology and related disciplines, participate in three research-oriented laboratory rotations (including one at an external laboratory), and attend communication and softskills workshops. After the training period, they will start their thesis with one of the participating mentors.
The main objective of this new training program is to teach and foster young scientists in the field of adaptive immunity.

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 (figure 2). The main research interest is on the intra- and extracellular signaling factors which 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 physiological activation and regulation of the essential key signals shall be identified. Moreover, 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.

Teaching

During their theses, the doctoral graduate and medical students will participate in the successfully tested core events and activities of the expired GK 592:
(1) A bi-weekly doctoral regular meeting organized by the students,
(2) subject-specific as well as interdisciplinary and softskills workshops,
(3) research symposia and network meetings with members of other external training grants,
(4) external laboratory visits,
(5) and the guest speaker seminar series.
The students will also organize seminars and workshops for the public and high school students and supervise small research projects for undergraduates. The doctoral students will be mentored by a three-member thesis advisory committee. To internationally position our doctoral students, they will organize the 4th International GK Symposium on "Regulators of Adaptive Immunity". Our research and innovative training concept will not only lead to a reduction in the time required to finish a doctoral program, but it will also provide a high-quality training environment for young scientists at an internationally competitive level.

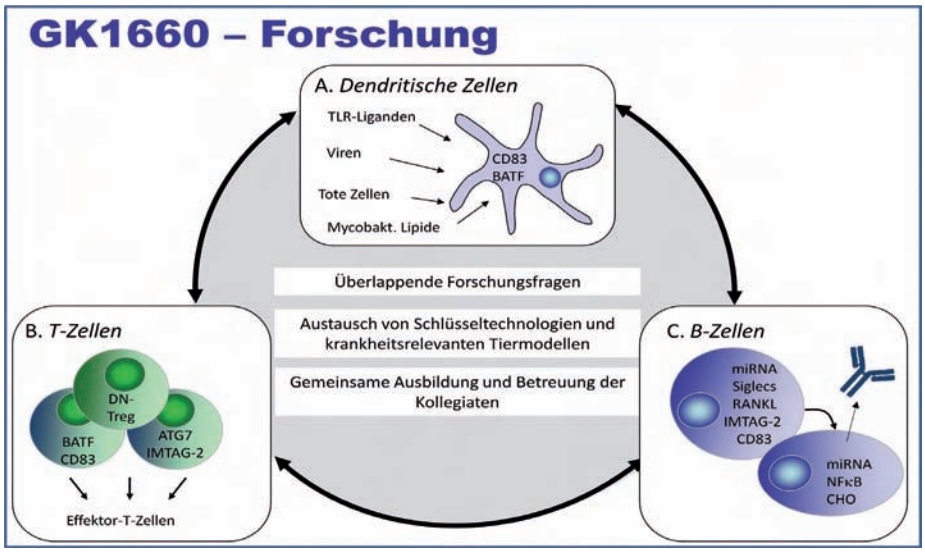

Figure 1: Structure of the training program of the GK 1660

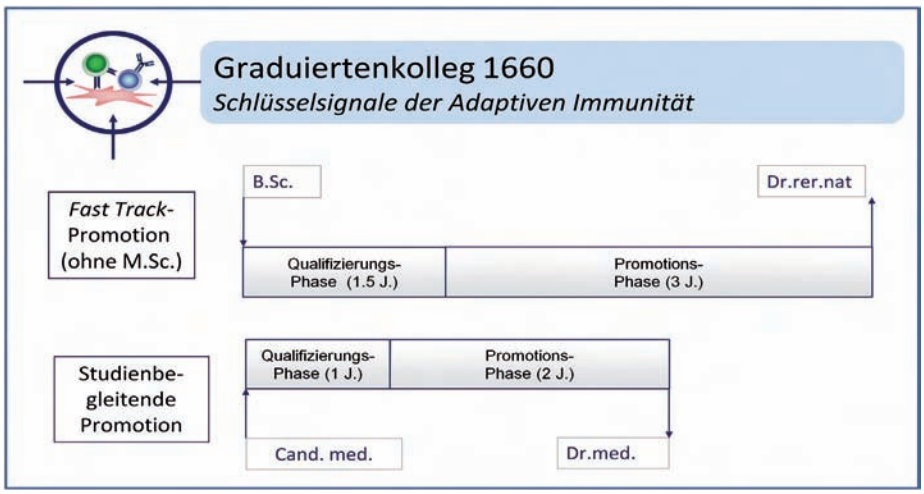

Figure 2: Research focus of the GK 1660

Emil Fischer Graduate Program of Pharmaceutical Sciences and Molecular Medicine (EFS)

Speaker
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Aims and Structure

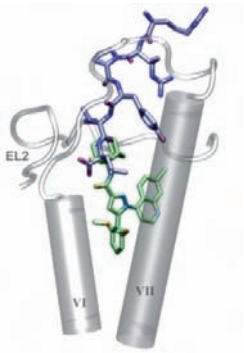
It is the aim of the Emil Fischer Graduate Programme to supply young researchers pursuing their doctoral thesis with an interdisciplinary environment with key qualifications required for a successful career in drug target research and drug development. Main areas of interest are the identification and 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 Natural Science and Medicine:

- Chair of Bioinorganic Chemistry
- Chair of Biochemistry and Molecular Medicine
- Chair of Biochemistry and Pathobiochemistry
- Chair of Clinical Pharmacology and Clinical Toxicology
- Chair of Pharmacology and Toxicology
- Chair of Food Chemistry
- Chair of Physiology
- Chair of Clinical Nuclear Medicine
- Chair of Pharmaceutical Biology
- Chair of Pharmaceutical Chemistry
- Chair of Pharmaceutical Technology.

In 2011, the Chairs of Organic and Pharmaceutical Chemistry at Regensburg University were integrated in the Graduate Programme.

Research and Teaching

The Graduate Program provides a framework of activities including seminars and counseling in order to allow the PhD students to acquire interdisciplinary skills that reach far beyond the particular topic of their PhD thesis. Throughout the Graduate Program, all PhD students are independently counseled by a mentor and a co-mentor. Interdisciplinary seminars provide insights into the research topics and methods of the other groups of the Emil Fischer Center. The PhD students are actively involved in the selection of seminar topics. Additional lectures by high profile speakers from other institutions are provided on a regular basis. The scientific training is complemented by training in soft skills required in the academic environment as well as in the 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, over 70 PhD students have enrolled in the program. Already 25 candidates successfully completed the program with a PhD and a EFS-certificate.



BioMedTec International Graduate School of Science (BIGSS): Lead Structures of Cell Function

Speaker
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Aims and Structure

Involved universities were Bayreuth, Erlangen-Nürnberg, and Würzburg.
Participants from the Faculty of Medicine were:

- Prof. Dr. C.M. Becker, Chair of Biochemistry and Molecular Medicine
- Prof. Dr. B. Fleckenstein, Institute of Clinical and Molecular Virology
- Prof. Dr. C. Korbmacher, Institute of Cellular and Molecular Physiology
- Prof. Dr. U. Schubert, Institute of Clinical and Molecular Virology
- Prof. Dr. T. Stamminger, Institute of Clinical and Molecular Virology
- Prof. Dr. H. Sticht, Professorship of Bioinformatics
- Prof. Dr. M. Wegner, Chair of Biochemistry and Pathobiochemistry.

Funding period: 2004 - 2012.

Research

The International Graduate School BIGSS (BioMedTec International Graduate School of Science) was themed "Lead Structures of Cell Function", indicating that the focus of interest was in the area of biological macromolecular structures. The graduate school applied molecular biology, molecular modeling, bioinformatics, X-ray crystallography, and spectroscopic methods such as nuclear magnetic resonance (NMR) to understand the structure and function of biomolecules. The duration of the individual grants was limited to three years and offered optimal conditions for 19 PhD students. The graduate school resulted from an initiative of the BioMedTec Franken e.V. which forms a network of the Universities of Bayreuth, Erlangen-Nürnberg, and Würzburg. It constituted one out of the ten graduate schools which are embedded into the "Elite Network of Bavaria" (ENB), which in turn was founded in Bavaria in 2004. The fundamental idea of the ENB was to provide the best possible framework for the scientific careers of students with excellent background. For that, primarily a best possible supervision of the projects was necessary. Consequently, the PhD students were supported by theses advisory committees consisting of three supervisors. The privileges of the PhD students included numerous offers to acquire soft skills and a generous travel budget that ensured the possibility to participate at international scientific congresses and workshops. There were, however, also several obligatory yearly events, like written yearly progress report, summer school, seminars, and evaluation by independent international reviewers.
The annual summer school was a highlight with varying topics every year. In 2009, it was held in Erlangen and for the first time organized entirely by the PhD students themselves. The annual Bayreuther Strukturtage, organized in cooperation with the research center for Bio-Macromolecules of the University of Bayreuth, became the main annual meeting of the graduate school.
Taken together, these mechanisms and a first-rate selection of students guaranteed a high degree of interdisciplinarity, a vivid scientific exchange, and high quality dissertations.
The success of the graduate school was reflected by many publications in important journals within the funding period of BIGSS.

Erlangen Graduate School in Advanced Optical Technologies (SAOT)

Speaker
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Aims and Structure

In November 2006, the SAOT was established in cooperation with the Faculty of Medicine at the FAU within the framework of the excellence initiative of the German federal and state governments to promote science and research at German universities and has been continued for another five years in November 2012. SAOT offers a structured, internationally oriented (working language English) and interdisciplinary education program to doctoral candidates. It is hosted by the Faculties of Engineering, Natural Science, and Medicine and is embedded into an international network of distinguished experts in their respective fields of optical technologies. The scientific topics SAOT focuses on are optical metrology, optical material processing, optics in medicine, optics in communication and information technologies, optical materials, and systems and computational optics.

Research

Intensive research work is carried out in each of the different SAOT topics which are in their activities and topics 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. Thus it is inherently interdisciplinary, covering e.g. optical diagnostics as well as optical therapy and surgery. Thus, the further development of optical techniques in medicine demands an intensive and comprehensive exchange and collaboration between the different schools 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 strength. 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 realize these objectives, the Clinical Photonics Laboratory (CPL) was established inside SAOT. The 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 with several medical and clinical research institutes of the FAU. To intensify the interdisciplinary and international collaborations, SAOT organizes international workshops routinely. The "Postdoctoral Medical Research Center", which will be established in 2013 and will be supported by SAOT with personnel, allows doctoral candidates from SAOT and Postdocs from the Faculty of Medicine to work together on joint interdisciplinary research projects.

Teaching

During the terms, SAOT offers standard lectures which are related to the application of optical technologies in medicine. Special SAOT activities related to the educational program comprise seminars, workshops, and academies. Outstanding scientists from international leading institutions are invited to give an one hour talk on specialized themes at the SAOT seminar. Workshops with several speakers of leading international research institutions contributing with a talk to a major subject 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". During the weeklong academies which take place outside Erlangen twice a year, the doctoral candidates are in charge of contributing to the success of the formed group work on a specific focus or have to give short presentations on the activities in their own field. Additionally the successful participation in the entrance academy, which is organized once a year, is mandatory for all SAOT doctoral candidates. At the end of this academy they have to pass the entrance examination which comprises problems covering all scientific topics of SAOT.

Advancement of Women and Gender Research Promotion

Speaker
Prof. Dr. med. Kerstin Amann

Deputies
Prof. Dr. (TR) Yesim Erim
Prof. Dr. rer. nat. Ursula Schlötzer-Schrehardt

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www.frauenbeauftragte.uni-erlangen.de

Aims and Structure

The women's representative of the Faculty of Medicine was placed at the disposal of academic staff of the FAU and UK Erlangen. In October 2007, the Executive Board of the FAU and the Faculty of Medicine concluded a target agreement to support women in science. The targets for 2012 are:

- Increase in the number of habilitated women from 17% (2004/2006) to 25% (2012);
- Increase in the number of female professors from 7% (2006) to 10% (2012).

The actual numbers of academic females within the Faculty of Medicine are shown in the adjoining table.
The target was achieved and the aimed increase reached. The new target agreement (2013 - 2017) was signed on 12th June 2013.

	Status as of winter term 2012
Female students 1st term	**66%** (193/291)
Female students in total	**63%** (2027/3218)
Females graduated	**57%** (368/650)
Females habilitated 2012	**32%** (16/50)
Female professors in total:	**7%** (10/136)
W1	**16%** (1/6)
W2	**10%** (8/80)
W3	**2%** (1/50)

Mentoring program – ARIADNEmed

Project coordinator: Dr. phil. M. Zirngibl
Part of the target agreement is the installation of a mentoring program called ARIADNEmed. It started first in 2008 at the Faculty of Medicine. The core of the program constitutes on individual mentoring/coaching of young female scientists by experienced female and male professors on all strategic questions regarding career development and the implementation of those in concrete steps. The mentoring is combined with a top-class seminar program on career relevant topics, such as Funding, Work-Life-Balance, Bibliometry, and "Appeal"-Coaching. 18 Mentees participate in the current round which started in March 2012 (nine physicians, seven natural scientists and two psychologists). The mentees are supervised by 18 female/male mentors (17 of FAU, one of TU Munich). The mentoring program ends after 18 months in October 2013.

Gender Mainstreaming

Additionally ARIADNE mentees are involved in the appeal committee in a subject oriented consulting manner. To make appeal process more transparent, it is looked after that in addition to the woman's representative one further female expert is elected in the appeal committee, so that a minimum of two women are part of the appeal committee. Furthermore, a member of the Senate of the University takes care of the commission in order to achieve a consequent, systematic, and consistent integration of gender aspects during appeal process.

Headhunting

Headhunting was first started in 2008. We try to raise the number of applicants for professor calls. In 2012 two vacancies for professorships were occupied by headhunted women.

Travel grants and scholarships

Talented postdoctoral students can apply for financial support to attend scientific conferences. The so called travel grant can be applied for once a year and for a maximum of three times in a row. Prerequisite is an active participation at the particular conference, e. g. a poster contribution. In 2012, 14 out 15 applications were supported which amounts to a total funding of € 8,923.

Gender Lectures

The woman's representative introduced the Gender Lectures in order to invite female scientists who can serve as role models and ease the path to make the decision for a scientific university career. Each term three to five guest speakers from the medical sector are invited. The 30-40 minutes lasting Gender Lectures enjoy an increasingly good reputation.

ELAN Program for Supporting Clinical Research and Teaching

Speaker
Prof. Dr. rer. nat. Michael Wegner

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Aims and Structure

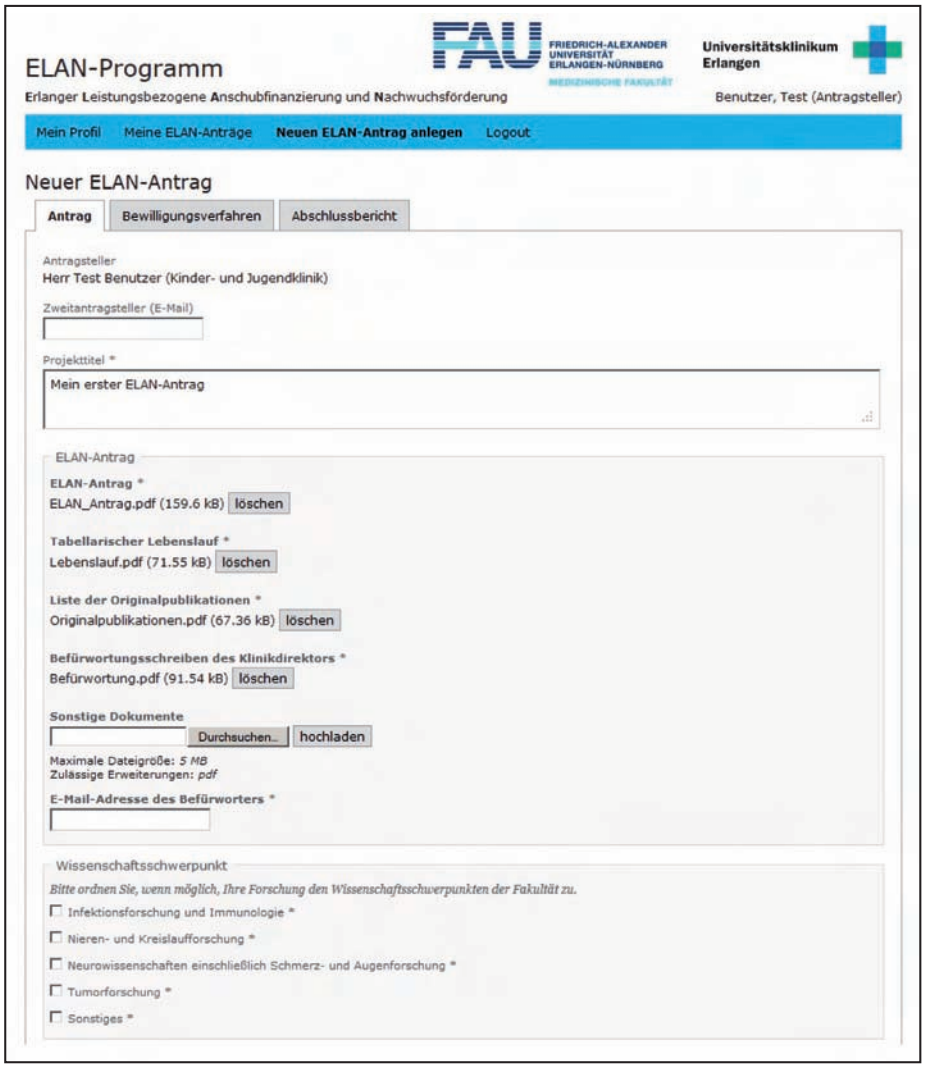
The ELAN program has been designed according to the guidelines of the National Science Council and the Conference of Ministers of Cultural Affairs to support clinical research and teaching. A total of 1.3 million Euro annually is devoted to fund projects for limited periods of time, taking also into account the previous work done by the respective researchers. Decisions on the distribution of funding are made by a committee of faculty members consisting of seven professors from various clinical and preclinical departments, the Dean of the Faculty, the clinical director, and the chairman of the research advisory board. Main purposes of the program are to financially support research projects, promote innovative didactic models, and internationalize clinical teaching as well as its evaluation.

Funding

First and foremost, funding is provided for projects of highly qualified young investigators and newly established groups. Besides this, pilot projects are supported and financial gaps in ongoing investigations are bridged. The best young investigators are additionaly supported by a co-initiated and co-financed "first-application-program" together with the IZKF. It is intended to enable as many qualified investigators as possible to raise further funding from external grant providers. A short term support for personnel and running costs for six to twelve months appears best suited for this purpose in the standard program, whereas an extension of up to 24 month for the "first-application-program" is possible. From mid-1998 until the end of 2012, a total of 826 grant applications has been received (2011: 50, 2012: 52), coming from virtually all clinical departments. The numbers of grant proposals from the respective departments reflects both, their sizes and research activities, although to a different extent. The average funding was about 37,000 Euro in 2011 and increased in 2012 to 38,000 Euro in standard program and about 105,000 Euro in the "first-application-program". The total amount of funding requested was 1.6 million Euro in 2011 and increased in 2012 up to 2.1 million Euro. The total amount of granted money in standard program oscillated around 1.3 million Euro annually reflecting the total available resources. External peer review of grant proposals is required for funding requests above 20,000 Euro. Besides scientific excellence of the project, the committee also considers in its funding decisions compliance with other prime goals of the ELAN program, e.g. start or young investigator support. Since 1998, a total of 565 out of 614 granted projects have been completed, representing a total funding of 13.5 million Euro. From these projects, 298 papers (22 in 2011, 18 in 2012) were published mostly in high ranking or well respected journals. Additionally, 101 (9 in 2011, 3 in 2012) grants were acquired from external funding sources (2.25 million Euro in 2011, 0.6 million Euro in 2012) amounting since 1998 to a total of about 18.1 million Euro.

In conclusion, the ELAN program has successfully stimulated a surge in high quality research projects from all clinical departments. This emphasizes the value of this program as a tool to dynamically improve clinical research within the Faculty of Medicine.

Since summer 2012 applications, peer review, decisions, part of the financial administration, and final evaluation have been handled by a web-based system to increase efficiency and transparency (compare screenshot).



Jakob-Herz-Prize

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

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www.forschungsreferat.med.uni-erlangen.de/e2960/index_ger.html

Aims and Structure

Since 2009, the Faculty of Medicine of the FAU together with the Research Foundation of Medicine has been awarding the Jakob-Herz-Prize for medical research. This prize is named after Prof. Dr. Jakob Herz, the famous physician from Erlangen and the first Bavarian Jewish professor. The award is granted for outstanding scientific success in the whole field of theoretical and clinical medicine. Individual achievements in research can be honored as well as lifetime achievements. The prize is awarded biennial in the course of a ceremony arranged 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. The committee of the Jakob-Herz-Prize consists of the professors of the commission for research and young academics of the Faculty of Medicine who evaluate the proposed candidates. The final decision is made by the faculty council. The prize comprises the amount of 10,000 Euro, a certificate, and a medal with the portrait of Jakob Herz.

History and Funding

This Prize has been designed in honor of the prominent physician and researcher from Erlangen, Prof. Dr. Jakob Herz (1819-1871). Prof. Dr. J. Herz was in due course the leading instructor of pathological anatomy and surgery and is considered as the founder of surgical anatomy. In 1869, Prof. Dr. J. Herz was nominated as the first Jewish professor in the kingdom of Bavaria. At this time he has 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 Erlanger Hugenottenplatz was destroyed by the Nazis. During the National Socialism, his native town Bayreuth removed a memorial plaque at his birthplace and renamed streets which were named after Jakob Herz. 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 principal at that time of the FAU, Prof. Dr. G. Jasper, disclosed a bronze memorial plaque in honor of Jakob Herz at the Hugenottenplatz. In 2011, the well-known scientist Prof. Garret A. FitzGerald, Institute for Translational Medicine and Therapeutics, Philadelphia, USA, was the Jakob-Herz-laureate elected by the Faculty of Medicine for his achievements within the field of cardiovascular diseases (figure). His contributions regarding the comprehension of the role of cyclooxygenase-2 inhibitors for the development of arteriosclerosis, of the significance of the circadian clock for pharmacotherapy and his development of the low-dose aspirin therapy reflect only one part of his scientific achievement which is focused on translational medicine (transferring findings from basic science to clinical practice). Besides many awards, Prof. G.A. FitzGerald was bestowed honorary doctorates by the universities of Edinburgh, Dublin, and Frankfurt (Main).

Prof. Dr. Dr. h.c. J. Schüttler (left), Dean of the Faculty of Medicine, and President Prof. Dr. K.-D. Grüske (right) congratulate Prof. Dr. G.A. FitzGerald. (Photographer: B. Böhner)

Johannes and Frieda Marohn-Foundation

Speaker
Prof. Dr. med. Dr. med. dent. Dr. h.c.
Friedrich W. Neukam

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Aims and Structure

According to the founders' will, the purpose of the Johannes and Frieda Marohn-Foundation is the promotion of new innovative projects of the Faculty of Medicine of the FAU, serving diagnosis, prevention, and therapy of diseases in general. Projects dealing with diseases in the field of gastroenterology, including all liver and pancreatic diseases inclusive diabetes, cancer, and medical data bases shall be supported preferentially. On the other hand, 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 of the FAU.
According to the rules of the Foundation, five members of the Faculty have to be elected for a three years period as members of the scientific board of the Foundation. Five additional members of the Faculty 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 granted. 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 president of the scientific committee. The rules of the Foundation can be provided by the secretary of the Johannes and Frieda Marohn-Foundation.

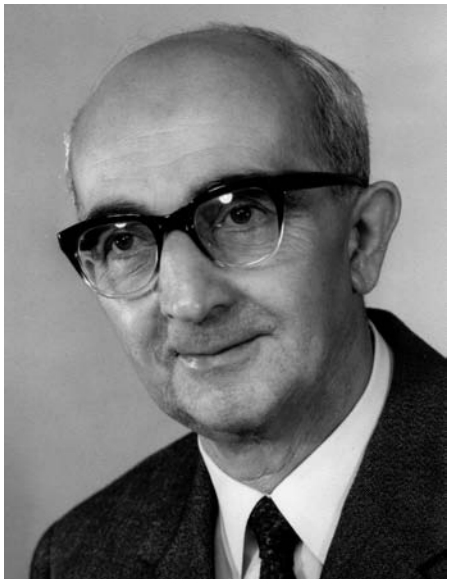
Accepted projects (Time of funding 2011 – 2012)

Financial year	Budget	Number of accepted applications
2011	305.472,20 €	9 = 208.344,00 €
2012	304.389,49 €	8 = 246.563,00 €

Finalized projects (Time of funding 2010 - 2012)

Number of projects	Number of publications	Continued funding by other foundations *
15	12 (from 9 projects)	4 projects

* DFG = 2 projects; other foundations = 2 projects
11 projects could not obtain further financial support



Johannes Marohn

Frieda Marohn

Research Foundation of Medicine

Speaker
Prof. Dr. med. Werner G. Daniel

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Sparkasse Erlangen
IBAN: DE69763500000000062000
BIC: BYLADEM1ERH

Aims and Structure

The Research Foundation of Medicine at the UK Erlangen was founded in December 2007 by an initiative of professors of the UK Erlangen and the Faculty of Medicine of the FAU. The initial capital stock of almost 150,000 Euro was given by 36 founder members - mainly directors of departments and institutes, but also other persons, like the mayor of the city of Erlangen - out of their personal assets. The Research Foundation is intended to be a permanent and stable means of financing in particular medical research, independent from public funding and support. Thus, former patients, alumni, and other patrons can support with their donations individual projects as well as certain medical disciplines or clinics, and also medical research at the UK Erlangen in general. Model for our initiative was the long-lasting successful culture of foundations at the universities in the USA.

Goals

The Research Foundation of Medicine at the UK Erlangen pursues four main goals:
• Advancement of research in all fields of basic and clinical sciences in medicine,
• Advancement of training and further education of students, physician, and scientists,
• Promotion of the public health care system, especially in the fields of prevention and early diagnosis of disease, and
• Benevolence within the medical care of patients in need.

Development

The Foundation provides attractive honors and stimulations for sponsors: donators of 10,000 Euro or more are listed on a special table of honor placed in the main entrance hall of the UK Erlangen, with a fostering sum of 100,000 Euro it becomes possible to establish an own self-named foundation within the Research Foundation, and in certain cases a lecture hall may become named after a particularly generous sponsor (e.g. the "Rudolf-Wöhrl-Hörsaal" named in 2009 after the late Rudolf Wöhrl, the founder of the well-known fashion boutiques who donated a sum of 250,000 Euro for research projects).
Due to the innovative model of the Foundation, many generous sponsors could be found during the last five years. In addition, an appeal to donate not yet changed Deutschemark to the Foundation (and receive the donation receipt on the calculated Euro sum) contributed to the successful development. Thus, in 2012 the Foundation was able to distribute already more than 700.000 Euro for the various projects. This high amount of money became possible also by a "Matching-Funds" concept, established by the UK Erlangen in 2011. It increases all financial supports given by the Research Foundation by the same amount 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. The "Matching-Funds" concept is successfully practiced in countries as USA, Great Britain, and others, and the Foundation hopes that the Bavarian State Government may take over the concept in a modified version for a general use in other foundations at Bavarian universities.
The Research Foundation of Medicine at the UK Erlangen has meanwhile supported numerous projects. This is true for many clinical and basic research projects as well as for the "Erlanger Medizinische Bürgervorlesung", a series of 12 - 14 lectures on up-to-date medical topics, initiated in 2007 and addressed each term to interested citizens. During the last 13 terms, the "Erlanger Medizinische Bürgervorlesung" has reached an audience of 35,000 to 40,000 persons, and it was awarded with the Erlanger Medizinpreis 2012. For the third time, the Research Foundation - together with the Faculty of Medicine - has given the Jakob-Herz-Prize to an outstanding researcher in the field of medicine: In 2011 the prize was given to Prof. Garret A. FitzGerald, Philadelphia, USA, and in 2013 to Prof. Peter J. Ratcliffe, Oxford, England. Furthermore, the Foundation also awards every year a prize for the best dissertation study (thesis) in the field of clinical and basic research, respectively. In 2012, Dr. B. Hohberger (Department of Ophthalmology) and Dr. S. Uderhardt (Department of Medicine 3 – Rheumatology and Immunology) were awarded this prize for their outstanding theses in the fields of clinical research respectively biomedical basic science.

(left to right): The laureates for outstanding doctoral theses in 2012, Dr. S. Uderhardt and Dr. B. Hohberger, together with Prof. Dr. W.L. Neuhuber

(left to right): Press appeal to donate D-Mark with the Bavarian Interior Minister, J. Herrmann, Prof. Dr. B. Fleckenstein, Mayor Dr. S. Balleis, Prof. Dr. Dr. h.c. J. Schüttler, and Prof. Dr. W.G. Daniel.

Poster appealing to donate D-Mark (the appeal is still up to date)

Further Foundations for Research Support

In addition to the ELAN program, the Research Foundation of Medicine, and the Johannes and Frieda Marohn Foundation, more than 20 different foundations and endowments are established at the Faculty of Medicine and support research projects at different levels. Furthermore, there are donations to the Faculty of Medicine (e.g. Dr. Jahn Donation, Elise Pittroff Donation). Science supporting foundations are of particular relevance for the research progress.

The most important foundations that are administrated by the FAU and closely connected to the Faculty of Medicine are mentioned in detail below.

The Dr. Fritz Erler Award for a reputed physician engaged in meritorious surgical medicine is donated every three years by the Dr. Fritz Erler Fund. In 2012 the prize was given to Prof. (em.) Dr. W. Steiner, former director of the Department of Otolaryngology in Göttingen, for his outstanding contributions in the field of "Transoral laser surgery in malignant tumors in otolaryngology". The Dr. Fritz Erler junior prize was given to PD Dr. K. Gelse, Division of Trauma Surgery of the FAU, to appreciate his results in "Cellular and molecular therapy approaches in cartilage defects and arthritis".

The Gottfried and Lieselotte Naumann Fund supports ophthalmology, especially clinical ophthalmo-pathology and contribution to microsurgery of the eye (contact: S. Penschuck). In a four-year rhythm the prize is given to an extraordinary researcher. The next award ceremony will take place in 2014.

The Dr. Norbert Henning Foundation (contact: E. Hoffmann) gives a prize for research in the field of gastroenterology every two years. In 2012, PD Dr. J. Wehkamp, Robert Bosch Hospital Stuttgart, was awarded for his scientific achievements in the field of „Association of a Functional Variant in the Wnt Co-Receptor LRP6 with Early Onset Ileal Crohn´s Disease".

The Dr. Kurt and Margarete Groß Donation supports specific achievements in the field of cardiology, cardiac-physiology, or cardiac surgery. The next award ceremony will take place in 2014.

The Ria Freifrau von Fritsch Foundation (contact: S. Penschuck) was established to support cancer research and to finance the Ria Freifrau von Fritsch Prize for an outstanding research achievement. In 2012, Dr. K. Hildner, Department of Medicine 1 – Gastroenterology, Lung Diseases and Endocrinology, UK Erlangen, was given the prize for his outstanding contributions concerning „Molecular fate mapping of cross presenting dendritic cells via Batf3 reporter mice".

The Sofie Wallner Foundation (contact: S. Penschuck) also supports cancer research; especially travel grants are given to highly gifted young researchers interested in oncology to enable a research project at a guest laboratory in a foreign country. In 2011, S. Lehnert, T. Siller, and J. Wild were awarded, in 2012 L. Wolf, D. Werner, and T. Middendorf were given the Sofie Wallner Prize.

Research projects in environmental medicine can be supported by the Adolf Rohrschneider Foundation (contact: J. Hubert).

The Wilhelm and Helene Dörfler Foundation (contact: Prof. Dr. G. Schett, Department of Medicine 3 – Rheumatology and Immunology, UK Erlangen) offers support for projects in clinical immunology (especially rheumatology).

The Johanna Prey Foundation supports research in the field of Alzheimer's disease, especially by giving grants for doctoral theses (contact: S. Penschuck). In 2011, M. Schindler (Chair of Psychogerontology) was supported.

The Dr. Ernst and Anita Bauer Foundation is an unaffiliated donation with base in Nürnberg. Its aim is to support gifted young physicians originating from the Middle Franconian area. Awards for outstanding research results, benefits for doctoral theses, postdoctoral qualifications, and research projects as well as grants to stay in a foreign laboratory are given by this foundation.

The Luise Prell foundation as well as the Fritz and Maria Hofmann foundation decorate outstanding master and diploma theses (contact: J. Hubert). The Fritz and Maria Hofmann Prize was given to A.K. Wiegers in 2011 and to F. Fröb in 2012 for their excellent diploma theses. F. Winter (2011) and J. Stump (2012) were awarded for their outstanding diploma theses in the reporting period.

The best and most concise postdoctoral qualification (Habilitation) is awarded annually by the Thiersch Prize. PD Dr. K. Zimmermann of the Institute of Physiology and Pathophysiology was the laureate in 2011, and PD Dr. C. Thiel of the Institute of Human Genetics was awarded in 2012.

The most outstanding doctoral theses are awarded by the Staedtler Prize, provided by the Staedtler-Foundation. In 2011, Dr. I. Göhring of the Institute of Human Genetics was awarded with this prize of the Staedtler foundation, and in 2012, Dr. S. Zenk of the Institute of Clinical Microbiology, Immunology, and Hygiene was rewarded for his outstanding graduation.

The Novartis foundation supports especially young investigators at our Faculty of Medicine. In 2011, Dr. F. Full (Institute of Clinical and Molecular Virology) was given the grant, in 2012, Dr. K. Mandery (Institute of Experimental and Clinical Pharmacology and Toxicology) was awarded with this research support.

The Foundation for Teaching was founded to support and improve the education of young clinicians (contact: S. Penschuck). In 2011, Dr. P. Burger (Department of Psychiatry and Psychotherapy) and Dr. K. Singler (Chair of Internal Medicine V) were supported by the Foundation for their postgraduate studies "Master of Medical Education" (MME).

More detailed information can be obtained from the central university administration of the FAU, Division F3 – Körperschaft und Stiftungen.

Physico-Medical Society Erlangen

Corporate Management
Prof. Dr. med. Christian Bogdan (President)
Prof. Dr. Dr. med. h.c. Willi A. Kalender, PhD (Vice-President)
Prof. Dr.-Ing. Dr. rer. med. Ulrich Hoppe (Secretary)
Prof. Dr. med. Thomas Pasch (Treasurer)
Prof. Dr. med. Dr. h.c. Karl-Heinz Plattig (Past Treasurer)

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Aims and Structure

The Physico-Medical Society Erlangen (PMSE), also known as Societas physico-medica Erlangensis, was founded on March 20th, 1808 in order to exchange "ideas, observations, and experiences between all the areas of natural sciences and medicine". These first statutes and articles, defined in the year 1808, are still valid; by amendment of the statutes in 1990, the technical disciplines have also been admitted. On June 18th, 2008, the PMSE celebrated its 200th birthday in a ceremony at the castle of the FAU. In the year of the 200th birthday of the PMSE, the Medical Society, which had separated from the PMSE in 1958 after the 150th birthday celebration of the Societas physico-medica Erlangensis, merged again with the PMSE.
As of December 31st, 2012, the Society has 384 members inside and outside Germany, with four of them being honorary and 36 being corresponding members. Once per year the Society holds a members´ assembly upon invitation by the council.
Every term the Society holds three to four regular meetings with scientific lectures. These are primarily given by invited national and international scientists, but also by members of the PMSE. According to its primary goal, i.e. to promote the scientific exchange between different fields of research, the PMSE preferentially invites guest speakers with outstanding interdisciplinary research approaches and achievements.
From 1984 to 2012, eleven volumes of reports were published, each of them consisting of four single issues. Beside scientific papers, the reports contain recent outstanding academic speeches, for example inaugural or farewell speeches, addresses on the occasion of honorary promotions and the annual graduation ceremony of the Faculty of Medicine of the FAU.

Lectures
02.02.2011
Prof. Dr. med. Dr. sci. nat. C. Klein
Klinik für Pädiatrische Hämatologie/Onkologie, Medizinische Hochschule Hannover
„Novel monogenic disorders of the human immune system: from genetic defects to gene therapy"

04.05.2011
Prof. Dr. med. F. Alves
Universitätsmedizin Göttingen, Max-Planck-Institut für Experimentelle Medizin, Abteilung Hämatologie und Onkologie, Göttingen
„Preclinic evaluation of novel concepts for tumor therapy by near infrared fluorescence imaging and flat-panel computed tomography"

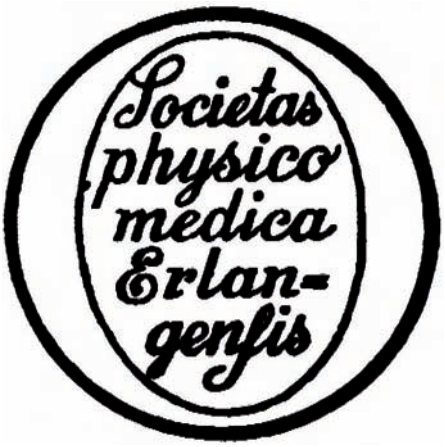
16.11.2011
Prof. Dr.-Ing. Dr. rer. med. U. Hoppe
UK Erlangen, Hals-Nasen-Ohren-Klinik, Audiologische Abteilung
„Elektronische Innenohrprothesen zur Therapie der Schwerhörigkeit und Taubheit: Cochlea-Implantate"

02.05.2012
Prof. P. Ponka, MD PhD
Lady Davis Institute, Department of Physiology and Medicine, McGill University, Quebec, Canada
„The role of iron in health and disease"

06.06.2012
Prof. Dr. rer. nat. P.H. Seeberger
Max Planck Institute of Colloids and Interfaces, Department of Biomolecular Systems, Potsdam
„Using chemical glycomics to understand infectious diseases and to create vaccines against bacteria and parasites: malaria and meningococci as examples"

11.07.2012
Prof. Dr. Dr. h.c. mult. W.A. Kalender, PhD
Institut für Medizinische Physik, FAU
„CTDI and Patient Dose: A European Perspective"

11.12.2012
Prof. I. Batinic-Haberle
Duke University, Durham, USA
„The therapeutic effects of Manganese-containing porphyrins in radiation, cancer and central nervous system injuries"



Selection of Honors and Prizes

2011

Honorary doctorate of the University of Zurich, Switzerland
Prof. Dr. med. Willi A. Kalender

Honorary doctorate of the Grodno State Medical University, Belarus
Prof. Dr. med. Stefan Schwab

Member of the German National Academy of Sciences Leopoldina
Prof. Dr. Karl-Heinz Leven
Director of the Institute of the History of Medicine and Medical Ethics

Member of the AcademiaNet
Prof. Dr. Diana Dudziak
Department of Dermatology

Honorary Member of the German Primate Center
Prof. Dr. Bernhard Fleckenstein
Director of the Institute of Clinical and Molecular Virology

Federal Cross of Merit on the Bond (Bundesverdienstkreuz am Bande)
Prof. Dr. Eberhard Paul, FRCP (Glasg.) a.D., Apl. Prof. at the FAU
Private practice for Dermatology, Nürnberg

Alfred Hauptmann Award
Prof. Dr. Ingmar Blümcke
Head of the Division of Nephropathology

Anton von Tröltsch Award
Prof. Dr. Christoph Alexiou
Department of Otorhinolaryngology – Head and Neck Surgery

Sponsorship Award of the German Cancer Aid
Prof. Dr. Dr. Michael Stürzl, Dr. Elisabeth Naschberger
Department of Surgery

Erlanger Award for Medicine, Technique, and Health
Prof. Dr. Elmar Gräßel und Sabine Pickel
Department of Psychiatry and Psychotherapy

Award for Excellence in Clinical Research 2011
Prof. Dr. Georg Schett
Director of the Department of Medicine 3 – Rheumatology and Immunology

Garabed Eknoyan Award
Prof. Dr. Kai-Uwe Eckardt
Director of the Department of Medicine 4 - Nephrology and Hypertension

Award for brain research in geriatrics, Witten
Prof. Dr. Piotr Lewczuk
Department of Psychiatry and Psychotherapy

1st Award of Clinical Research, Janssen Prize Dermatology/Immunology
Dr. Ulrike Hüffmeier
Institute of Human Genetics

Langener Science Award
Prof. Dr. David Vöhringer
Head of the Division of Infection Biology

Young Investigator Award, 18th Conference of Retroviruses and Opportunistic Infections (CROI), Boston, USA
Dr. Susan Jung
Department of Pediatrics and Adolescent Medicine

2012

Honorary Member of the Chinese Society for Anesthesiology
Prof. Dr. Dr. h.c. Jürgen Schüttler
Director of the Department of Anesthesiology

Honorary Member of the Academia Eurasiana Neurochirurgica
Prof. Dr. Rudolf Fahlbusch
Former director of the Department of Neurosurgery

Honorary Member of the Science Council of Jan-Evangelista-Purkyne University in Ùsti nad Labem
Prof. Dr. Dr. h.c. Karl-Heinz Plattig
Institute of Physiology and Pathophysiology

Safe-Anesthesia-Award of the Foundation German Anesthesiology
Dr. Michael St. Pierre
Department of Anesthesiology

Brocher Award
Prof. Dr. Andreas Frewer
Institute of the History of Medicine and Medical Ethics

Award of the „Alliance of Democracy and Tolerance"
Work Group Medicine and Human Rights
Professorship for Medical Ethics

Award of the German Society of the History of Medicine, Science, and Technology
Dr. Nadine Metzger
Institute of the History of Medicine and Medical Ethics

Rolf Hansen Award
Markus Ries
Institute of Medical Informatics, Biometry, and Epidemiology

Research Fellow 2012 of the Alexander von Humboldt Foundation
Prof. I. Muiznieks, Riga, Lithuania
Institute of Clinical and Molecular Virology

Loeffler-Frosch-Medal of the German Society for Virology
Prof. Dr. Walter Doerfler
Institute of Clinical and Molecular Virology

Fellowship Award of European College of Neuropsychopharmacology (ECNP)
Dr. Davide Amato, M.Sc., PhD
Department of Psychiatry and Psychotherapy

Science Award of the German Society of Plastic, Reconstructive, and Aesthetical Surgery
PD Dr. Andreas Arkudas
Department of Plastic and Hand Surgery

2nd Place Early Researcher Award
Dr. Stephanie Stiel
Division of Palliative Medicine

Young Investigator Award and participation at 19th Conference of Retroviruses and Opportunistic Infections (CROI), Seattle, USA
Sebastian Müller, B.Sc.
Institute of Clinical and Molecular Virology

17. André Schroeder Research Award
Dr. Dr. Cornelius von Wilmowsky
Department of Oral and Cranio-Maxillofacial Surgery

Thieme Teaching Award
Dr. Georg Breuer
Department of Anesthesiology

William D. Wagner Award
Dipl.-Ing. Karl-Heinz Schaller
Institute and Outpatient Clinic of Occupational, Social, and Environmental Medicine

Doctorate Theses, Board Qualifications, Additional Qualifications, Habilitations

Institute of Anatomy
Chair of Anatomy I

Doctorate Theses 2011

Kustermann, Andreas, Dr. med.: Calretinin und Somatostatin als Marker für verschiedene Nervenzellpopulationen in der Submukosa des menschlichen Darms

Doctorate Theses 2012

Beck, Martin, Dr. med.: ChAT und NOS in myenterischen Neuronen des Menschen: Ko-Existenz und Ko-Absenz
König, Sergej, Dr. med.: Lokalisation und Verteilung von GluR2/3-Rezeptorimmunreaktivität im Ösophagus der Maus
Kühn, Mathias, Dr. med. dent.: Typisierung der quergestreiften Muskulatur im Mäuseösophagus
Schuy, Julia, Dr. med.: Quantitative Analyse und chemische Kodierung der ‚spiny Typ I Neuronen' im menschlichen Darm

Institute of Anatomy
Chair of Anatomy II

Doctorate Theses 2011

Peters, Johannes, Dr. med.: Vergleichender Nachweis der Wachstumsfaktoren NGF und ProNGF an der Augenoberfläche und im Tränenapparat

Doctorate Theses 2012

Garreis, Fabian, Dr. rer. nat.: Expression und Regulation antimikrobieller Peptide an der Augenoberfläche und im Tränenapparat des Menschen
Pfütze, Daniel, Dr. med.: Morphologisch-funktionelle Untersuchungen von pro-NGF, NGF und TNF-α an gesunden Zellen und Geweben der Augenoberfläche sowie dem Pterygium oculi
Reiss, Beate, Dr. med.: Nachweis und Funktion der Surfactant - Proteine A, B, C und D in gesundem und degenerativ verändertem Gelenkknorpel
Schicht, Martin, Dr. rer. nat.: Humane Surfactant Proteine - Detektion und Charakterisierung

Board Qualification 2012

Paulsen, Friedrich, Prof. Dr. med.

Institute of Biochemistry – Emil-Fischer-Center
Chair of Biochemistry and Molecular Medicine

Doctorate Theses 2011

Hupfer, Stephan Werner, Dr. rer. nat.: Veränderte Genexpression im ZNS der Calciumkanal-mausmutante Cacna 2d2 ^{entla}

Löhmann, Christian, Dr. med.: Developmental profiling by mass spectrometry of phosphocholine containing phospholipids in the rat nervous system reveals temporo-spatial gradients

Doctorate Theses 2012

Lall, Deepti, Dr. rer. nat.: Transgenic overexpression of glycine transporter 1 and developmental changes in activity of glycine transporters in mouse central nervous system

Institute of Biochemistry – Emil-Fischer-Center
Chair of Biochemistry and Pathobiochemistry

Doctorate Theses 2011

Bremer, Magdalena, Dr. rer. nat.: Impact of the transcription factor Sox10 on Schwann cell homeostasis
Wahlbuhl-Becker, Mandy, Dr. rer. nat.: Analysis of a neural crest-specific Sox10 enhancer in the mouse

Doctorate Theses 2012

Küspert, Melanie, Dr. rer. nat.: Analysis of regulation and molecular function of the transcription factor Sox10 in mouse glial cells

Institute of Cellular and Molecular Physiology
Chair of Physiology (Vegetative Physiology)

Doctorate Theses 2011

Moritz, Andreas, Dr. med.: Zur Interaktion von Sexualhormonen mit Corticosteroiden bei der Regulation des L-Typ $Ca2^+$ Stroms in isolierten linksventrikulären Kardiomyozyten der Ratte
Schütz, Vera, Dr.: Charakterisierung des L-Typ $Ca2^+$-Stroms im linken Ventrikel des Herzens von Gα11-defizienten Mäusen

Doctorate Theses 2012

Frank, Magdalena, Dr. med.: Zur Lokalisation von K^+ Kanaluntereinheiten in Lipid Rafts und dem Einfluss des Cholesterolgehaltes der Zellmembran auf K^+ Ströme in linksventrikulären Kardiomyozyten der Ratte

Board Qualification 2011

Korbmacher, Christoph, Prof. Dr. med.
Wagner, Michael, Dr. med. habil.

Habilitation 2012

Wagner, Michael, PD Dr. med.: Pathophysiologie der Regulation kardialer K^+ und $Ca2^+$ Ströme

Institute of Physiology and Pathophysiology
Chair of Physiology

Doctorate Theses 2011

Tröltzsch, Markus, Dr. med.: Prevalence and association of headaches, temporomandibular joint disorders, and occlusal interferences

Doctorate Theses 2012

Huth, Tobias, Dr. med.: Einfluss von β-site-APP-cleaving enzyme 1 (BACE1) auf neuronale Natriumströme
Kosteletzky, Frauke, Dr. med.: Der Einfluss von Kratzen auf Jucken und die Sympathischen Reflexe induziert durch Cowhage und Histamin
Rückel, Michael, Dr. med. dent.: Mikroneurographische Untersuchung von C-Nervenfasern an Patienten mit Chemotherapie-induzierter Neuropathie
Weller, Konrad, Dr. med.: Neuropeptidfreisetzung aus Axonen des Vagusnerven: Untersuchungen zur Stimulation und Interaktion axonal exprimierter Ionenkanäle und Rezeptoren

Habilitation 2011

Lampert, Angelika, PD Dr. med.: Spannungsgesteuerte Na^+-Kanäle und ihre Bedeutung in der Schmerzentstehung

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

Doctorate Theses 2011

Bär, Barbara, Dr. med.: Influence of carbon disulfide, lifestyle factors, and constitution on blood pressure and serum lipid levels of male employees
Eckert, Elisabeth, Dr. rer. nat.: Development and application of analytical methods for the determination of mercapturic acids in human urine as metabolites of important alkylating agents
Rochlitzer, Ellen, Dr. med.: Analysis made on ECG abnormalities of employees exposed to carbon disulfide referring to the Minnesota code

Doctorate Theses 2012

Hopf, Hans-Georg Michael, Dr. med.: Blood lead levels during corrosion protection work on power poles – influential factors and time course
Lüersen, Lars, Dr. rer. biol. hum.: Study on percutaneous ex vivo penetration of aromatic amines through excised human skin and the influence of skin creams
Penkert, Sabine, Dr. med.: Aromatic amines in the rubber industry – dermal uptake, internal exposure, and strain

Board Qualification 2011

Baumeister, Thomas
Jüngert, Barbara
Straube, Sabine

Board Qualification 2012
Korinth, Gintautas

Institute of Experimental and Clinical Pharmacology and Toxicology
Chair of Pharmacology and Toxicology

Doctorate Theses 2011

Hofmann, Florian, Dr. rer. nat.: Untersuchungen zur Rolle von I_f im hypertrophen Herz der Maus
Milbradt, Anita, Dr. rer. nat.: Konditionelle Gendeletion des Ryanodinrezeptors RyR2 im Herzen der Maus

Doctorate Theses 2011

Mintsioglou, Dimitrios, Dr. rer. nat.: Untersuchung der prädisponierenden Faktoren für die Schmerzverarbeitung bei gesunden Probanden anhand eines experimentellen Schmerzmodells

Board Qualification 2012

Renner, Bertold, Dr. med.

Institute of Experimental and Clinical Pharmacology and Toxicology
Chair of Clinical Pharmacology and Clinical Toxicology

Doctorate Theses 2011

Kindla, Jürgen, Dr. rer. nat.: Organic anion transporting polypeptides (OATPs): Expression und Lokalisation beim Mammakarzinom und ihre Bedeutung für Arzneimittelinteraktionen
Kraft, Michaela, Dr. med.: Expression der Transportproteine OATP2A1 und OATP2B1 im menschlichen Auge und deren funktionelle Bedeutung für die Pharmakokinetik des Antiglaukommittels Latanoprost
Poguntke, Maren, Dr. med.: Transport von Arzneistoffen durch das Breast Cancer Resistance Protein: eine Metaanalyse

Doctorate Theses 2012

Fahrmayr, Christina, Dr. rer. nat.: Aufnahme, Metabolismus und Export von Arzneimitteln in der Leber: tripel- und quadrupeltransfizierte Zelllinien zur Analyse funktioneller Interaktionen
Paulus, Barbara, Dr. med.: ATP-Binding Cassette (ABC)-Transporter im humanen Myokard: Expressionsänderung bei Herzinsuffizienz

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

Doctorate Theses 2012

Braisch, Ulrike, Dr. rer. biol. hum.: Tobacco-associated risk of multiple malignomas

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

Doctorate Theses 2011

Ramming, Thomas, Dr. med.: Elektronische Untersuchungsanforderungen für Labor und Radiologie: Eine Usability-Studie zur Bewertung klinischer Anwendungen
Tech, Hendryk, Dr. med.: Longitudinale Evaluation der Einführung eines Patientendatenmanagement-Systems auf der Interdisziplinären Operativen Intensivstation des Klinikums der Universität Erlangen

Doctorate Theses 2012

Mühlenweg, Martin, Dr. med.: Optimierung des klinischen Prozesses

Habilitation 2012

Schmid, Matthias, Dr. rer. nat.: Erweiterung von Boosting-Verfahren auf neue Modellsituationen hochdimensionaler Daten

Institute of Medical Physics
Chair of Medical Physics

Doctorate Theses 2011

Beister, Marcel, Dr. rer. biol. hum.: GPU-basierte Iterative Bildrekonstruktion und Artefakt-Korrekturen in der Computertomographie
Brauweiler, Robert, Dr. rer. biol. hum.: Design und Erprobung von Perfusions-Modellen in der dynamischen Computertomographie
Chen, Wei, Dr. rer. biol. hum.: Anwendungen von Grafikkarten in der Computertomographie: Monte Carlo Simulationen und Korrekturverfahren
Eisa, Fabian, Dr. rer. biol. hum.: Dynamische kontrastmittelverstärkte Computertomographie im klinischen und präklinischen Einsatz
Jin, Yannan, Dr. rer. biol. hum.: Implementation and optimization of Dual Energy Computed Tomography
Weigel, Michaela, Dr. rer. biol. hum.: Untersuchungen zu dedizierter Brust-Computertomographie
Yohannes, Indra, Dr. rer. biol. hum.: Development of Tissue- and Water-equivalent Materials for Calibration and Quality Assurance in CT and Radiotherapy

Doctorate Theses 2012

Baer, Matthias, Dr. rer. biol. hum.: CT Scatter Simulation and CT Scatter Reduction Methods
Hupfer, Martin, Dr. rer. biol. hum.: Dosisreduktion in der Mikro-Computertomographie
Meyer, Esther, Dr. rer. biol. hum.: Metal Artifact Reduction in Clinical Computed Tomography
Nowak, Tristan, Dr. rer. biol. hum.: Untersuchungen zur Auflösungsverbesserung und Dosisreduktion in der Computertomographie
Ritschl, Ludwig, Dr. rer. biol. hum.: Artefaktkorrekturen in der mobilen Flachdetektor-basierten Kegelstrahl-CT
Sawall, Stefan, Dr. rer. biol. hum.: Preclinical In-Vivo Micro-CT of the Heart
Wilhelmy, Jochen, Dr. rer. biol. hum.: Lossless and Lossy Raw Data Compression in CT Imaging

Institute of the History of Medicine and Medical Ethics
Chair of the History of Medicine

Doctorate Theses 2011

Heinzelmann, Ruth, Dr. med.: Johann Balthasar Erhart (1700-1756) und seine Korrespondenz mit Christoph Jacob Trew (1695-1769)
Holinski, Cornelia, Dr. med.: Friedrich Heinrich Loschge (1755-1840) Leben und Werk
Matentzoglu, Silvia, Dr. med.: Zur Psychopathologie in den hippokratischen Schriften
Mitzel-Kaoukhov, Heidrun, Dr. med.: Die Briefe Johann Heinrich Schulzes (1687-1744) an Christoph Jacob Trew

Institute of the History of Medicine and Medical Ethics
Professorship for Medical Ethics

Doctorate Theses 2012

Graf, Janna, Dr. med.: Weibliche Genitalverstümmelung und die Praxis in Deutschland. Hintergründe-Positionen-Erfahrungen in der Frauenheilkunde
Kolb, Stephan, Dr. med.: Der Ethikkreis der Medizinischen Klinik 4 im Klinikum Nürnberg. Evaluation der Beratungsfälle von 1999-2011 im Kontext der historischen Entwicklung einer patientenzentrierten Medizin
Weisenseel, Nicole, Dr. med.: Behandlungszentren für Folteropfer. Geschichte, Ethik und internationale Kooperation

Nikolaus-Fiebiger-Center of Molecular Medicine
Chair of Experimental Medicine I (Molecular Pathogenesis Research)

Doctorate Theses 2011

Eitzinger, Nicole, Dr. rer. nat.: Etablierung und Phänotypanalyse einer Ucma-defizienten Mauslinie

Nikolaus-Fiebiger-Center of Molecular Medicine
Chair of Experimental Medicine II (Molecular Oncology)

Doctorate Theses 2011

Tanneberger, Kristina, Dr. rer. nat.: Duale positive und negative Regulation des Wnt-Signalwegs durch Amer1/WTX

Doctorate Theses 2012

Pfister, Astrid, Dr. rer. nat.: Funktionelle Charakterisierung von Amer2, ein neuer negativer Regulator des Wnt/β-catenin Signalwegs und ein neuer EB1-Interaktionspartner

Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH

Chair of Orthopedics and Orthopedic Surgery

Doctorate Theses 2011

Köckeritz, Steffen, Dr. med.: Anwendung von Botulinumtoxin A in der Behandlung der spastischen infantilen Cerebralparese
Schramm, Anja, Dr. med.: Orthopädische Therapie der Poliomyelitis acuta anterior

Doctorate Theses 2012

Nowak, Melanie, Dr. med.: Klinische und radiologische Nachuntersuchung einer Kurzschaft-Hüftgelenksendoprothese-Untersuchung 6 Jahre postoperativ
Zingler, Katharina, Dr. med.: Vergleich der kortikalen und spongiösen Knochenreaktion des Beckens nach Implantation einer zementfreien Hüftendoprothese in Abhängigkeit von patienten- und prothesenspezifischen Charakteristika- eine CT- gestützte Knochendichteuntersuchung in vivo

Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH

Division of Orthopedic Rheumatology

Board Qualification 2011

Pauser, Johannes, Dr. med.

Institute for Biomedicine of Aging

Chair of Internal Medicine (Geriatrics)

Doctorate Theses 2011

Kieslich, Barbara, Dr. med.: Nursing home – no return home?
Leikauf, Ruth, Dr. med.: Influence of exercise and food restriction on laboratory parameters of the aging rat

Doctorate Theses 2012

Wehr, Helmut, Dr. med.: Practicality and Relevance of the Frailty Criteria by Fried in a General Practitioner's Office in a Rural Area

Habilitation 2011

Bauer, Jürgen, PD Dr. med.: Body Composition and Functionality in Old Age – Approaches for Therapeutical Interventions

Habilitation 2012

Heppner, Hans-Jürgen, PD Dr. med.: Diagnostik und Therapie schwerer Infektionen beim alten Menschen
Wirth, Rainer, PD Dr. med.: Decision criteria for Enteral Nutrition in Old Age

Department of Anesthesiology

Chair of Anesthesiology

Doctorate Theses 2011

Fischer, Jonas, Dr. med.: Evaluation des postoperativen Verlaufs der Peptide Procalcitonin, midregionales proAdrenomedullin, C-terminales proEndothelin-1, midregionales pro atriales natriuretisches Peptid und C-terminales proArgininvasopressin bei herzchirurgischen Patienten unter besonderer Berücksichtigung systemisch-inflammatorischer und infektiöser postoperativer Komplikationen
Hausmann, Christine, Dr. med.: Einfluss einer zusätzlichen Ketaminmedikation auf Entzündungsreaktion und Katabolierate bei Patienten mit schwerer Sepsis. Eine vergleichende Untersuchung zweier Analgosedierungsverfahren
Niedermirtl, Florian, Dr. med.: Das intravenöse Anästhetikum Propofol aktiviert nozizeptive Neurone über TRPA1-, TRPV1- und GABA A-Rezeptoren
Petterich, Nico, Dr. med.: Einfluss verschiedener Primingdosierungen auf die Anschlagszeit von Cisatracurium an der Kehlkopfmuskulatur und am Musculus adductor pollicis
Pircher, Rebecca, Dr. med.: Vergleich der analgetischen Potenz von Isofluran, Sevofluran und Desfluran im cross-over Design bei der Ratte
Rehner, Dietlinde, Dr. med.: Lokalanästhetika aktivieren und sensibilisieren den Capsaicin-Rezeptor TRPV1
Walz, Florian, Dr. med.: Pharmakodynamische Modellbildung anästhesieassoziierter Veränderungen quantitativer EEG-Variablen und physiologischer Parameter während Desfluranapplikation bei der Ratte

Doctorate Theses 2012

Lieret, Elke, Dr. med.: Identifikation geeigneter EEG-Parameter für das Narkosemonitoring durch Approximation ihres Rausch-Signal-Verhältnisses anhand eines lokalen Polynom-Schätzers
Saßmann, Volker, Dr. med.: Anwendungsbeobachtung zum Nachweis einer analgetischen Wirkung von Dexamethason bei endoprothetischem Hüftgelenkersatz: Vermindert eine Gabe von 8 mg Dexamethason i.v. zur Narkoseeinleitung den postoperativen Schmerzmittelbedarf?
Tiebel, Nils, Dr. med.: Quantitativ-sensorische Testung bei Patienten mit M. Crohn: Unterschiede zwischen Patienten mit hohem und niedrigen postoperativen Opioid-Bedarf
Vogel, Sascha, Dr. med.: Einflussfaktoren einer postoperativ messbaren Skelett- und Herzmuskelschädigung bei mittels Herz-Lungen-Maschine operierten Patienten

Board Qualification 2011

Dexl, Sylvia, Dr. med.
Meyer, Verena, Dr. med.
Plettke, Regina, Dr. med.
Günther, Susanne, Dr. med.

Board Qualification 2012

Kränzlein, Diana, Dr. med.
Kühn, Monika, Dr. med.
Leuthold, Christian, Dr. med.
Mell, Jan, Dr. med.
Pohle, Rebecca, Dr. med.
Reinhardt, Melanie, Dr. med.
Saalfrank-Schardt, Christina, Dr. med.
Tröster, Andreas, Dr. med.
Wagner, Sören, Dr. med.
Wehrfritz, Andreas, Dr. med.
Wilken, Verena, Dr. med.

Additional Qualification 2011

Alt, Christina, Dr. med.: Emergency Medicine
Eisenried, Andreas, Dr. med.: Emergency Medicine
Engelen, Wolf-Christian, Dr. med.: Emergency Medicine
Frank, Paul, Dr. med.: Emergency Medicine
Münster, Tino, PD Dr. med.: Special Pain Therapy
Nau, Carla, Prof. Dr. med.: Intensive Care Medicine
Schneider, Thomas-Michael, Dr. med.: Emergency Medicine
Eisenried, Andreas, Dr. med.: Emergency Medicine

Additional Qualification 2012

Nau, Carla, Prof. Dr. med.: Special Pain Therapy

Habilitation 2012

Birkholz, Torsten, PD Dr. med.: Patientenmonitoring in Risikosituationen

Department of Cardiac Surgery

Chair of Cardiac Surgery

Doctorate Theses 2011

Gebhardt, Julia, Dr. med.: Noninvasive Magnetic Resonance Imaging of Vessels affected by Transplant Arteriosclerosis in an Experimental Mouse Allograft Model
Heim, Christian, Dr. med.: Die Infektion mit murinem Cytomegalie-Virus verstärkt die Ausbildung von Transplantat-Arteriosklerose im experimentellen Mausaortentransplantationsmodell

Board Qualification 2011

Rörick, Olaf, Dr. med.
Rubio-Lopez, Alvaro, Dr. med.

Additional Qualification 2011

Rörick, Olaf, Dr. med.: Emergency Medicine

Habilitation 2011

Harig, Frank, PD Dr. med.: Selektive Retroperfusion

Department of Dermatology

Chair of Skin and Veneral Diseases

Doctorate Theses 2011

Hoffmann, Christian, Dr. rer. nat.: Analyse der TCR Biologie und Entwicklung neuer therapeutischer Strategien bei der HIV-1 Infektion

Doctorate Theses 2012

Böhm, Stefanie, Dr. rer. nat.: Adoptive T-cell-receptor transfer to examine human T-cell immunology in vitro
Bosch-Voskens, Caroline, Dr. med. (MD, PhD): Immunotherapeutic strategies in patients with solid malignancies - Crossing the line between scientific possibility and clinical reality
Epp, Raphael, Dr. med. dent.: Altersentwicklung von Typ IV-Sensibilisierungen auf p-Phenylendiamin und deren klinische Relevanz im Patientenkollektiv der Hautklinik des Universitätsklinikums Erlangen im Vergleich zum Informationsverbund Dermatologischer Kliniken (IVDK)
Hack, Carolin, Dr. med.: CD4+CD25+ regulatorische T-Zellen unter perennialer versus präsaisonaler spezifischer Immuntherapie bei Typ I-Allergie auf Inhalationsallergene
Maronna, Andreas, Dr. med.: Ex vivo Isolation und Charakterisierung von CD4+CD25+ regulatorischen T-Zellen unter perennialer versus präsaisonaler spezifischer Immuntherapie bei Typ I-Allergie auf Inhalationsallergene

Additional Qualification 2012

Heinzerling, Lucie, Dr. med. (MD, PhD): Drug-based Tumor Therapy

Habilitation 2011

Schaft, Niels, PD Dr. rer. nat.: Functional manipulation of T-cells by RNA transfection

Department of Dermatology

Division of Immune Modulation

Doctorate Theses 2012

Seitz, Christine: Production of Recombinant Human Soluble CD83 in an Eukaryotic System and Generation of Tissue-Specific CD83 Knockout Mice
Stein, Marcello, Dr. rer. nat.: Characterization of the CD83 promoter/enhancer complex
Theodoridis, Alexandros: Modulation of dendritic cell migration by herpes simplex virus type 1

Department of Medicine 1 – Gastroenterology, Lung Diseases, and Endocrinology

Chair of Internal Medicine I

Doctorate Theses 2011

Baum, Svenja, Dr. med.: Untersuchungen zur Mortalität bei Blutungen am unteren Gastrointestinaltrakt.
Begemann, Margit, Dr. med.: Spektrum und Komplikationen sonographisch gesteuerter Interventionen an der Medizinischen Klinik 1 Erlangen in den Jahren 2005-2006.
Ertl, Franz, Dr. med.: Spektrum und Komplikationen sonographisch gesteuerter Interventionen an der Medizinischen Klinik 1 Erlangen in den Jahren 2007-2008
Gilsbach, Stefanie, Dr. med.: Medikamentöse Kombinationstherapie bei kolorektalem Karzinom im Metastasenmodell der Ratte.
Grensemann, Sven, Dr. med.: Effekte eines additiven Trainings der Atemmuskulatur bei Patienten mit mittelschwerer COPD.
Jakubaß, Volker, Dr. med.: Einführung eines Behandlungspfades für ambulant erworbene Pneumonie. Bedeutung für Liegedauer und Prognose.
Jugl, Veronika, Dr. med.: ARFI - ein neuer sonographischer Surrogatparameter der Leberfibrosierung.
Kellermann, Carla, Dr. med.: Beeinflussung der TNBS-induzierten Colitis im Tiermodell durch Modulation des Cannabinoidsystems.
Kleye, Christin, Dr. med.: Evaluation einer öffentlich angebotenen Spirometrie als Maßnahme zur Primärprävention von Folgeerkrankungen des Rauchens.
Koucky, Kathrin, Dr. med.: Palliative Erstlinientherapie mit einer wöchentlichen Hochdosisbehandlung aus 5-Fluorouracil und Natriumfolinat als 24h-Infusion (AIO Regime) plus Irinotecan bei Patienten mit metastasierten Adenokarzinomen des Magens und des gastroösophagealen Übergangs gefolgt von sekundärer Metastasenresektion nach Downsizing.
Resheq, Yazid, Dr. med.: Neue immunologische Therapieansätze für den Diabetes mellitus Typ 1 am Non-Obese-Diabetic-Mausmodell unter besonderer Berücksichtigung antigen präsentierender Zellen.
Röhrig, Sandra, Dr. med.: Palliative systemische Kombinationschemotherapie mit Gemcitabin und 5-Fluorouracil als 24h-Infusion bei Patienten mit metastasiertem Pankreaskarzinom
Rus, Crina, Dr. med.: Funktionelle Charakterisierung von Mutationen des Calcium-Sensing-Rezeptors bei Patienten mit familiärer hypokalziurischer Hyperkalzämie: Wirkung des Kalzimimetikum NPS R-568
Walter, Victoria, Dr. med.: Stellenwert der Endosonographie in der präoperativen Diagnostik des Pankreaskarzinoms.
Zenker, Corinna, Dr. med.: Endoskopische Interventionen bei Patienten mit chronisch entzüdlichen Darmerkrankungen.
Zwickel, Philipp, Dr. med.: Entwicklung, Implementierung und Evaluation einer wissensbasierten Entscheidungsunterstützung für die kalkulierte Antibiotikatherapie

Doctorate Theses 2012

Günther, Claudia, Dr. rer. nat.: Regulation of programmed cell death in the intestinal epithelium and its role in intestinal homeostasis
Hagel, Wolfgang, Dr. med.: Evaluation der Doppelballon-Enteroskopie bei der Diagnostik und Therapie von Patienten mit Blutungen im mittleren Gastrointestinaltrakt.
Hauck, Tabea, Dr. med.: Einflüsse einer adäquaten Continuous-Positive-Airway-Pressure Therapie auf die Plasmaspiegel der Peptidhormone Apelin, Obestatin und Leptin bei Patienten mit neu diagnostiziertem Schlafapnoe-Syndrom.
Klein, Matthias, Dr. med.: Doppelballon-Enteroskopie basierte endoskopisch retrograde Cholangiopankreatikographie mit bilio-pankreatischen Interventionen an Patienten mit Zustand nach komplexen Bauchoperationen.
Kraupa, Werner, Dr. med.: Behandlung von okkludierten Gallengangsendoprothesen mit Stoßwellenlithotripsie. Eine experimentelle in-vitro Analyse
Neumann, Florian, Dr. med.: Früherkennung von dysplastischen Kolonläsionen mit Fluoreszenz-Videoendoskopie in Kombination mit Hexaminolavulinat als Photosensibilisator, eine Dosisfindungs- und Machbarkeitsstudie.
Wittkopf, Nadine, Dr. rer. nat.: Regulation of Paneth cell biology in gastrointestinal inflammation

Board Qualification 2011

Albrecht, Heinz, Dr. med.
Ende, Anke, Dr. med.
Janson, Christopher, Dr. med.

Board Qualification 2012

Hildner, Kai, Prof. Dr. med.
Neufert, Clemens, Dr. med.

Additional Qualification 2011

Heide, Roland, Dr. med.: Intensive Care Medicine

Additional Qualification 2012

Janson, Christopher, Dr. med.: Emergency Medicine

Habilitation 2011

Boxberger, Frank, PD Dr. med.: Multimodale Therapie gastrointestinaler Tumore
Frieser, Markus, PD Dr. med.: Radiofrequenzablation als interventionelles Ultraschallverfahren in Lebertumoren
Mudter, Jonas, PD Dr. med.: Bedeutung des Interleukin-6/Interleukin-17 Signaltransduktionsweges bei chronisch entzündlichen Darmerkrankungen und experimenteller Colitis
Zopf, Yurdagül, PD Dr. med.: Indikationen und Komplikationsrisiken bei interventionell-endoskopisch angelegten Sonden bei Patienten mit Mangelernährung

Department of Medicine 2 – Cardiology and Angiology
Chair of Internal Medicine II

Doctorate Theses 2011

Baum, Christina, Dr. med.: Pathophysiologische Relevanz von systemischen Zytokinen für die Entwicklung von Koronarkalk
Böhmer, Kerstin, Dr. med.: Einfluss der Rekonstruktionsparameter auf die Dichte koronarer atherosklerotischer Plaques in der Dual Source CT.
Frick, Maike Veronika, Dr. med.: Is it possible to quantify angles and angle changes at coronary artery bifurcations online?
Geier, Barbara, Dr. med.: Segmentale Synchronität und Volumenänderung des linken Ventrikels während ventrikulärer Schrittmacherstimulation - Ultraschallbasierte Analyse durch Real Time 3D Echokardiographie.
Hagel, Alexander F., Dr. med.: Detektion des rechtsventrikulären Infarktes mittels kardiovaskulärer Magnetresonanztomographie
Regler, Melanie, Dr. med.: Antiathero-sklerotische Eigenschaften von Resveratrol: Molekulare und funktionale Effekte auf humane Endothelzellen und Monozyten
Turan, Nesrin, Dr. med.: Randomisierter Vergleich von transradialer und transfemoraler Koronarangiographie und -intervention bei Patienten über 75 Jahre: Erfolgsrate und prozedurale Daten

Doctorate Theses 2012

Bertogg, Kaja, Dr. med.: Der Einfluss der Herzphase auf die Prävalenz von Bewegungsartefakten beim Koronarkalknachweis mittels Computertomographie
Bietau, Christian, Dr. med.: Sicherheit und Effektivität eines Bare-Metal-Stents der zweiten Generation. Ergebnisse des Coroflex® Blue-Registers der Medizinischen Klinik 2 - Kardiologie und Angiologie des Universitätsklinikums Erlangen.
Roth, Simon-Petrus, Dr. med.: Inflammation und Myokardinfarkt - Die Rolle von FcγRIIa als unabhängiger Risikofaktor für das Auftreten von Komplikationen der Atherosklerose
Schönegger, Carolin, Dr. med.: Kontrastverstärkte kardiale Magnetresonanztomographie zur Risikostratifizierung nach reperfundiertem Myokardinfarkt

Board Qualification 2012

Marwan, Mohamed, Dr. med.
Pflederer, Tobias, PD Dr. med.

Habilitation 2011

Pflederer, Tobias, PD Dr. med.: Diagnostik der koronaren Herzerkrankung mittels Computertomographie

Habilitation 2012

Rittger, Harald, PD Dr. med.: Interventionelle Therapieverfahren bei akutem Myokardinfarkt und stabiler KHK im höheren Lebensalter.

Department of Medicine 3 – Rheumatology and Immunology
Chair of Internal Medicine III

Doctorate Theses 2011

Balzer, Michael, Dr. med.: Peroxisome Proliferator-Activated Receptor γ Coactivator-1 α (PGC-1α) in der Pathogenese der Sklerodermie
Huhn, Konstantin, Dr. med.: Auswirkungen eines Einzelnukleotid-Polymorphismus im Adiponectin-Gen auf Pathogenese und klinische Manifestation der Systemischen Sklerose
Kireva, Trayana, Dr. rer. nat.: Rolle des Transkriptionsfaktors Fra-1
Lang, Veronika, Dr. med.: Resistenz der von Marginalzonen B-Zellen initiierten T-Zell unabhängigen Immunantwort Typ 2 gegenüber dem Proteasomeninhibitor Bortezomib
Müller, Ralf, Dr. rer. nat.: Die Rolle der p38MAPKα und MAPKAPK-2 in einem murinen Modell der anti-Basalmembran Glomerulonephritis
Munoz Becerra, Luis Enrique, Dr. rer. nat.: Dual Role of Clearance Deficiency in the Etiology and in the Pathogenesis of SLE
Schäfer, Valentin, Dr. med.: Risiken von Infektionen und malignen Erkrankungen bei Riesenzellarteriitis
Uderhardt, Stefan, Dr. med.: Molekulare Regulation des Knochenremodeling bei entzündlicher Arthritis

Doctorate Theses 2012

Bergmann, Christina, Dr. med.: Inhibition of glycogen synthase kinase 3β induces dermal fibrosis by activation of the canonical Wnt pathway
Funke, Robin, Dr. med.: Epigenetisches Silencing von endogenen Inhibitoren des WNT-Signalweges durch Promoter Methylierung in der Systemischen Sklerose
Janko, Christina, Dr. rer. nat.: Impact of CRP on dying and dead cells
Schroeder, Kristin, Dr. rer. nat.: Tolerance mechanisms for anit-DNA autoantibodies in the germinal center
Strapatsas, Tobias, Dr. med.: Ungleichgewicht von angiogenen und angiostatischen Faktoren bei Patienten mit Mischkollagenose

Board Qualification 2012

Krönke, Gerhard, Dr. med.
Reisch, Annja, Dr. med.
Ronneberger, Monika, Dr. med.

Department of Medicine 3 – Rheumatology and Immunology
Division of Molecular Immunology

Doctorate Theses 2011

Kroczek, Carmen, Dr. rer. nat.: Functional analysis of Swiprosin-1 in proximal B cell receptor signaling
Porstner, Martina, Dr. rer. nat.: A role for microRNAs during plasma cell differentiation and in multiple myeloma

Doctorate Theses 2012

Brachs, Sebastian, Dr. rer. nat.: Analysis of the function of the murine protein EFhd2/Swiprosin-1 in B cell development and immune response in vivo

Habilitation 2012

Mielenz, Dirk, PD Dr. rer. nat. Dr. habil. med.: Functional analysis of novel adaptor proteins during selection and activation of B cells

Department of Medicine 4 – Nephrology and Hypertension
Chair of Internal Medicine IV

Doctorate Theses 2011

Gimm, Tina, Dr. rer. nat.: Functional role of the hypoxia-inducible protein 2
Heersink, Claudia, Dr. med.: Acid-induced currents in chemically stimulated renal afferents
Knier, Benjamin, Dr. med.: Effect of the plasminogen-plasmin system on hypertensive renal and cardiac damage
Leis, Bastian, Dr. med.: The pressure independent effect of salt on end organ damage in resistant hypertension

Doctorate Theses 2012

Rodionova, Kristina, Dr. med.: Meaning of different populations of dorsal root ganglion neurons in sensory peptidergic renal innervation
Striepe, Kristina, Dr. med.: Comparison of different calcium channel blockers regarding their effect on intrarenal hemodynamics in patients with arterial hypertension
Wiese, Melanie, Dr. rer. nat.: Impact of hypoxia and the influence of the hypoxia-inducible factor HIF-1α on the antibacterial capacity of dendritic cells and macrophages

Board Qualification 2011

Dahlmann, Anke, Dr. med.
Friedrich, Stefanie, Dr. med.
Matheis, Edi, Dr. med.
Ott, Christian, Dr. med.
Raff, Ulrike, Dr. med.
Röseler, Tilmann, Dr. med.
Türk, Tobias, Dr. med.
Weidemann, Alexander, Dr. med.

Board Qualification 2012

Lehmann, Marina, Dr. med.
Ritt, Martin, Dr. med.

Habilitation 2011

Warnecke, Christina, PD Dr. med. vet.: Identification and functional characterization of novel target genes of the hypoxia-inducible transcription factors (HIF)

Habilitation 2012

Bernhard, Wanja, PD Dr. med.: Renal effects of pharmacological induction of hypoxia-inducible transcription factors

Ditting, Tilmann Johannes, PD Dr. med.: The autonomic renal innervation – afferent regulatory mechanisms

Department of Medicine 5 – Hematology and Oncology

Chair of Hematology and Oncology

Doctorate Theses 2011

Gary, Regina, Dr. rer. nat.: Characterization and functional analysis of the transfer of cell components from human antigen-presenting cells onto T cells via antigen-specific trogocytosis

Doctorate Theses 2012

Goldmann, Katja, Dr. rer. nat.: Immunmodulation durch orale Applikation von Antigen kodierenden Chitosan-DNA Nanopartikeln
Meinhardt, Kathrin, Dr. rer. nat.: Isolierung und Charakterisierung muriner NK-Zell-Subpopulationen zur Untersuchung ihrer Rolle während der Graft-versus-Host-Erkrankung

Board Qualification 2012

Erney, Birgit, Dr. med.
Haibach, Martina, Dr. med.
Müller, Andrea, Dr. med.

Habilitation 2012

Ullrich, Evelyn, Prof. Dr. med.: Dendritische Zellen und natürliche Killerzellen in der antitumoralen Therapie und Immunregulation

Department of Neurology

Chair of Neurology

Doctorate Theses 2012

Weiss, Silvia, Dr. med.: Evidence for a progenitor cell population in the human pituitary

Department of Neurology

Division of Molecular Neurology

Board Qualification 2012

Schlachetzki, Johannes, Dr. med.

Department of Neurosurgery

Chair of Neurosurgery

Doctorate Theses 2011

Heckel, Alexandra, Dr. med.: The role of xCT in the progression of malignant gliomas

Doctorate Theses 2012

Schlaffer, Sven-Martin, Dr. med.: Einfluss präoperativer medikamentöser Therapien auf die Proliferationsaktivität von Hypophysenadenomen bei Akromegalie
Schwarz, Marc, Dr. rer. nat.: Interaction of microglia with malignant gliomas

Department of Nuclear Medicine

Chair of Clinical Nuclear Medicine

Doctorate Theses 2011

Sonntag, Christina, Dr. med.: Erfolg der Radioiodablation nach totaler Thyreoidektomie bei differenzierten Schilddrüsenkarzinomen

Doctorate Theses 2012

Kammerer, Sara, Dr. med.: Evaluierung der Aussagekraft und Relevanz nuklearmedizinischer Bildgebung bei Patienten mit Verdacht auf primären Knochentumor
Reinfelder, Julia, Dr. med.: Effects of recombinant human thyroid-stimulating hormone superagonists on thyroidal uptake of 18F-fluorodeoxyglucose and radiodide
Wrubel, Scarlett Margot Annelies, Dr. med.: Biodistribution und Analyse von ^{68}Ga-markierten RGD-Multimeren an tumortragenden Nacktmäusen mit Hilfe der Kleintier-Positronen-Emissions-Tomographie

Department of Obstetrics and Gynecology

Chair of Obstetrics and Gynecology

Doctorate Theses 2011

Brandt, Ina, Dr. med.: Untersuchung der Proliferationshemmung von Brustkrebszellen durch das Bioflavonoid Quercetin in Kombination mit dem mTOR-Inhibitor Everolimus (RAD001).
Cupisti, Dita, Dr. med.: Neuzeitlicher Schwangerschaftsabruch: Vitamin K-Antagonist?
Dilling, Sabine, Dr. med.: Nabelschnurblutentnahmen in der Frauenklinik des Universitätsklinikums Erlangen: Einfluss von maternalen, fetalen und geburtshilflichen Parametern auf das gewonnene Nabelschnurblut und dessen Eignung zur Einlagerung als autologes oder allogenes Stammzellpräparat.
Groh, Nicole, Dr. med.: Untersuchung der Proliferationshemmung von Brustkrebszellen durch Chloroquin in Kombination mit dem mTOR-Inhibitor Everolimus (RAD001).
Henglein, Kathrin, Dr. med.: Vergleich von fünf verschiedenen Hysterektomieverfahren.
Henning, Jens, Dr. med.: In vitro studies on the influence of human seminal plasma on the contractility of the extracorporeally perfused non-pregnant porcine uterus.
Klingsiek, Peter Andreas, Dr. med.: Lifestyle und Endometriose - Ergebnisse aus einer Fall-Kontroll-Studie.
Merk, Sabine, Dr. med.: Lebensqualität und Zufriedenheit nach Hysterektomie - Ein Vergleich von fünf verschiedenen Operationsverfahren.
Rix, Nadine, Dr. med.: Teilnahmerate an einer chemopräventiven Behandlung in der IBIS-II Studie - eine prospektive Kohortenstudie im Rahmen des Mammographiescreenings.
Rübner, Mattias, Dr. rer. nat.: Epigenetic DNA-methylation of the HERV-W promoter in abnormal human placentogenesis and tumorigenesis.
Scheffler, Miriam, Dr. med.: Doppler der Uterinarterien in Kombination mit maternal anamnestischen und biochemischen Faktoren als Screening-Test für Präeklampsie und intrauterine Wachstumsrestriktion am Ende des ersten Trimesters.
Schmid, Monika Stefanie, Dr. med.: Assoziation von anamnestischen und epidemiologischen Faktoren mit der Endometriose - eine krankenhausbasierte Fall-Kontroll-Studie.
Stellwag, Stefanie, Dr. med.: Untersuchung der Bedeutung der genetischen Variation D1853N des ataxia telangiectasia-mutated gene (ATM-Gen) für das Risiko und die Prognose einer Mammakarzinomerkrankung.
Stratmann, Alexandra, Dr. med.: Zufriedenheit von Schwangeren mit der Patient-Controlled-Epidural-Analgesia (PCEA) unter der Geburt am Erlanger Kollektiv in den Jahren 2005-2008.
Tappert, Verena, Dr. med.: Genetische Polymorphismen im methyl-CpG binding domain Protein 4 (MBD4)-Gen beim Mammakarzinom.
Ünlühan, Nesrin, Dr. med.: Neurokinin 1 Receptor Gene Polymorphism might be correlated with recurrence rates in endometriosis.
Walther, Annette, Dr. med.: Expression von Gonadotropin-Releasing-Hormon und Gonadotropin-Releasing-Hormon-Rezeptor in Endometriose-Gewebe.
Weihbrecht, Sebastian, Dr. med.: Assoziationen zwischen Polymorphismen im Topoisomerase Iia Gen mit der Länge des HER2-Amplikons auf Chromosom-17-Implikationen für Mechanismen der Genamplifkation und die Prognose bei Mammkarzinompatientinnen.
Wiesinger, Erika, Dr. med.: Clinical examination and laparoscopy cannot be replaced by imaging techniques when diagnosing the MRKH-syndrome.

Doctorate Theses 2012

Bahnmüller, Bea, Dr. med.: Comparison of laparascopic surgery with open surgery in women with endometrial cancer.
Fru, Chi-Ira, Dr. med.: Investigation of correlation between antioxidant property of seminal plasma and sperm quality.
Geisler, Klaudija, Dr. med.: The perfused swine uterus model: long-term perfusion.
Hochreuther, Christina, Dr. med.: Einfluss der mütterlichen Bindung auf die Entwicklung einer postpartalen Depression. Die MATER-Studie.
Horn, Jasmin, Dr. med.: Marked Improvements in Training for Students in their Pratical Year. Developments in German Gynecology Teaching from 2006 to 2010 and the Prospects.
Schibel, Annika, Dr. med.: Influence of Maternal Smoking during Pregnancy on Oxidant Status in Amniotic Fluid.
Segl, Petra, Dr. med.: Differences in success rates between patients with ectopic pregnancy treated with 30mg methotrexate and those treated by salingotomy.

Board Qualification 2011

Engel, Julia, Dr. med.

Board Qualification 2012

Faschingbauer, Florian, Dr. med.
Jud, Sebastian, Dr. med.
Lermann, Johannes, Dr. med.
Rauh, Claudia, Dr. med.
Ünlühan, Nesrin, Dr. med.

Habilitation 2012

Goecke, Tamme, PD Dr. med.: Untersuchungen zur prä-, peri- und postpartalen Depression.
Löhberg, Christian, PD Dr. med.: Prognostische Relevanz von epidemiologischen und molekularen Risikofaktoren bei Patientinnen mit Mammakarzinom.
Oppelt, Patricia Gerlinde, PD Dr. med.: Hormonelle und anatomische Veränderungen in der Entwicklung und Funktion des weiblichen Genitals.
Thiel, Clemens Falk, PD Dr. med.: Versorgungsaspekte und Gesundheitsökonomie in der gynäkologischen Onkologie.

Department of Ophthalmology

Chair of Ophthalmology

Doctorate Theses 2011

Bellios, Nikolaos, Dr. med.: Überschwellige periphere Stimulation bei präperimetrischen Glaukomen
Hirschmann, Tobias, Dr. med.: Ergebnisse später Therapie von exzentrischer Fixation bei verschiedenen Amblyopieformen.
Hohberger, Bettina, Dr. med.: Frequency dependency of temporal contrast adaptation in normal subjects.
Kleinschmidt, Martin, Dr. med.: Ergebnisse der perforierenden Re-Keratoplastik bei visuslimitierendem Astigmatismus nach Kornea-Transplantation
Raster, Markus, Dr. med.: Der Einfluss der Chloroquineinnahme auf die multifokale Elektroretinographie an einer brasilianischen Population.

Doctorate Theses 2012

Atorf, Jenny, Dr. rer. nat.: Funktionsanalyse der Mausretina mittels Ganzfeld-Elektroretinographie.
Calabrese, Stefano, Dr. med.: Histopathologische Untersuchung von retrocornealen Membranen bei irreversiblem Transplantatversagen
Herold, Elvira, Dr. med.: Therapie der Keratokonjunktivitis sicca mit Augentropfen aus autologem Serum
Pangeni, Gobinda, Dr. rer. biol. hum.: Interpretation von Elektroretinogrammen bei sinusförmig modulierten Stimuli verschiedener Frequenzen und Kontraste.
Riss, Stephan, Dr. med.: Pentacam-based Big-Bubble Deep Anterior Lamellar Keratoplasty (DALK) in Patients with Keratoconus
Schrell, Constanze, Dr. med.: Ciclosporin A 0,05% Augentropfen zur Therapie der Keratokonjunktivitis sicca
Schrems, Wolfgang, Dr. med.: Glaukomdiagnostik mit Scanning Laser Polarimetrie und optischer Kohärenztomographie im Methodenvergleich
Schrems-Hös, Laura, Dr. med.: Einfluss von Papillengröße und Glaukomstadium auf die Glaukomdiagnostik mit dem Heidelberg Retina Tomograph
Stuhlfelder, Konstanze, Dr. med.: Betreuung von Kindern mit septo-optischer Dysplasie (SOD) - Erfahrungen der Augenklinik und der Kinder- und Jugendklinik
Susilo-Sigit, Tina Maria, Dr. med.: Regulation der Expression von LOXL1 und elastischen Mikrofibrillen: Ein in vitro-Modell für das Pseudoexfoliationssyndrom.
Tourtas, Theofilos, Dr. med.: Endotheliale Keratoplastik: Vergleich zwischen Descemet membrane endothelial keratoplasty und Descemet stripping
Zeller, Caterina, Dr. med.: Klinisch-pathologische Korrelationen bei Patienten mit lymphoproliferativen Erkrankungen der okuären Adnexe

Board Qualification 2011

Heindl, Ludwig, Dr. med.
Huchzermeyer, Cord, Dr. med.
Raum, Christoph, Dr. med.
Rössler, Katrin, Dr. med.

Board Qualification 2012

Bellios, Nikolaus, Dr. med.
Brückner-Schmutterer, Kerstin, Dr. med.
König, Yanyan, Dr. med.

Habilitation 2011

Bachmann, Björn, PD Dr. med.: Chirurgische und konservative Therapieansätze zur funktionellen und morphologischen Verbesserung von Hornhauttransplantationen.

Habilitation 2012

Jacobi, Christina, PD Dr. med.: Vaskuläre Erkrankungen der Netzhaut
Lämmer, Robert, PD Dr. med.: Glaukom-Detektion und morphometrische Verfahren zur Progressionsanalyse im Langzeitverlauf

Department of Oral and Cranio-Maxillofacial Surgery

Chair of Dental, Oral, and Maxillofacial Medicine – especially Oral and Maxillofacial Surgery

Doctorate Theses 2011

Adam, Nikola, Dr. med. dent.: Ossäre Regeneration eines experimentellen critical size-Defektes der Schweinekalotte mit einem biphasischen Knochenersatzmaterial (HA/TCP)- Einfluss einer biodegradierbaren Zellulose-Membran auf Ossifikation und Mineralisation
Berner, Alexandra Katharina, Dr. med. dent.: Relevanz von TGF-ß, Smad 2/3, Smad 7 und Galektin-3 für die Bisphosphonat-assoziierte Kiefernekrose
Draschowski, Cornelia, Dr. med. dent.: Immunhistochemische Analyse von Msx1, Rankl und Sox9 bei der terminalen Differenzierung von Osteoblasten unter Bisphosphonatgabe - eine experimentelle Untersuchung
Fitz-Kretschmar, Michaela, Dr. med. dent.: Einfluss von Bisphosphonaten auf die terminale Differenzierung von Osteoblasten: Eine Immunhistochemische, experimentelle Analyse
Göthel, Wolfgang, Dr. med. dent.: Polysaccharid-Template-strukturierte bioaktive Keramiken mit modulierter Oberfläche - eine tierexperimentelle Analyse
Hirschinger, Andreas, Dr. med. dent.: Vergleichende tierexperimentelle Studie zur Anwendung und Osseointegration eines neuartigen bovinen Knochenersatzmaterials im Schweinekiefer
Kassler, Stefan, Dr. med. dent.: Osseo-Integration elektronenstrahlgesinterter Titanimplantate mit und ohne LbL-Pamidronat-Beschichtung - eine tierexperimentelle Studie
Knipfer, Christian, Dr. med. dent.: Speech Intelligibility Enhancement Through Maxillary Dental Rehabilitation with Telescopic Prostheses and Complete Dentures - a Prospective Study Using Automatic, Computer-based Speech Analysis
Lutz, Rainer, Dr. med.: Biofunctionalization of titanium implants with a biomimetic active peptide (P-15) promotes early osseointegration
Möst, Tobias, Dr. med. dent.: Tierexperimentelle Studie zur Knocheneinheilung chemisch oberflächenmodifizierter Implantate im Typ-2 diabetischen Schwein
Rieder, Julia, Dr. med. dent.: Tierexperimentelle Studie zum Osseointegrationsverhalten biofunktionalisierter dentaler Implantate
Rusche, Philipp, Dr. med. dent.: Der Einfluss einer biomimetischen Implantatbeschichtung mit integriertem BMP-2 und VEGF auf die Osseointegration
Stüber, Christopher, Dr. med. dent.: Biofunktionalisierung von Implantatoberflächen mit einer festgelegten Konzentration (200µg/ML) eines synthetisch hergestellten Peptids (P-15) bei diabetischen gegenüber gesunden Versuchstieren
Tima, Dominik, Dr. med. dent.: Biofunktionalisierung von Implantatoberflächen mit unterschiedlichen Konzentrationen der synthetischen Kollagenteilsequenz P-15
Tran-Vinh, Han, Dr. med. dent.: Die Etablierung eines Streptozotocin-induzierten diabetischen Schweines und die Beurteilung der pathologischen Veränderungen des Knochens
Vogel, Melanie, Dr. med. dent.: In-vitro-Untersuchungen zur differentiellen Expression von RANK(L) - Relevanz für die Exklusivität der Bisphosphonat-assoziierten Nekrose im Kieferknochen
Wiesheu, Reinhard, Dr. med. dent.: Vergleichende tierexperimentelle Studie zur Anwendung eines bovinen Knochenersatzmaterials

Doctorate Theses 2012

Döring, Hendrik, Dr. med. dent.: Klinisch vergleichende Studie zur Zufriedenheit von Patienten mit implantatgetragener Unterkiefer-Totalprothese im Vergleich zur totalprothetischen Versorgung im zahnlosen Unterkiefer
Gorecki, Patricia, Dr. med. dent.: Beurteilung der Bedeutung der Expression melanomassoziierter Antigene A (MAGE-A) in Leukoplakien der Mundhöhle für das maligne Entartungsrisiko dieser Läsionen

Lagarie, Sebastian, Dr. med. dent.: Knöcherne Verankerung und Primärstabilität von dentalen Implantaten im Oberkiefer des Menschen. Eine experimentelle Untersuchung
Schlittenbauer, Tilo, Dr. med.: Identifikation genetischer Risikofaktoren bei Patienten mit bisphosphonat-assoziierten Kieferknochennekrosen am Beispiel von HLA-DRB1 und HLA-DQB1

Additional Qualification 2012

Bumiller, Lars, Dr. med.: Plastic Surgery
Stockmann, Philipp, Dr. med. Dr. med. dent.: Plastic Surgery

Habilitation 2011

Stelzle, Florian, PD Dr. med. Dr. med. dent.: Methoden der Hart- und Weichgewebebearbeitung in der Mund-, Kiefer- und Gesichtschirurgie

Department of Otorhinolaryngology – Head and Neck Surgery

Chair of Otorhinolaryngology

Doctorate Theses 2011

Sinzenich, Katharina, Dr. med.: Bluttransfusionen bei Hals-Nasen-Ohren-Patienten

Doctorate Theses 2012

Lang, Anne, Dr. med.: Atypisches Fibroxanthom - Tumorentität und Therapiekonzepte
Velegrakis, Stylianos, Dr. med.: Langzeitergebnisse der endonasalen Chirurgie bei Choanalatresie

Board Qualification 2011

Brase, Christoph, Dr. med.
Scherl, Claudia, Dr. med.

Board Qualification 2012

Birk, Stephanie, Dr. med.
Göderer, Lisa, Dr. med.
Kapsreiter, Markus, Dr. med.
Mantsopoulos, Konstantinos, Dr. med.
Traxdorf, Maximilian, Dr. med.

Additional Qualification 2012

Kirsche, Hanspeter, Dr. med.: Allergology

Department of Otorhinolaryngology – Head and Neck Surgery

Division of Phoniatrics and Pediatric Audiology

Doctorate Theses 2012

Bocklet, Tobias, Dr. rer. biol. hum.: Diagnoseunabhängige Analyse der Sprachverständlichkeit am Beispiel maligner Kehlkopferkrankungen
Kräck, Angelina, Dr. med.: Objective Classification of Organic Voice Disorders using Endoscopic High-Speed Imaging
Tiemann, Melanie, Dr. med.: Static tensile tests using the hemilarynx model: Measuring the local deformation and relaxation behavior of porcine vocal folds
Weigel, Stephanie, Dr. med.: The hemilarynx-model: Reproducibility of the deformation of vocal folds and analysis of the material properties of the vocal folds

Habilitation 2012

Haderlein, Tino, PD Dr.-Ing.: Automatische Messung der Stimmqualität bei laryngealer Heiserkeit

Department of Pediatric and Adolescent Medicine

Chair of Pediatrics

Doctorate Theses 2011

Bani Hashemi-Begerow, Souzan, Dr. med.: Expression Hypoxie-induzierbarer vasoaktiver Faktoren im Gehirn der adulten Ratte unter Einfluss von Hypoxie und chemischen HIF-Stabilisatoren
Geißler, Bettina, Dr. med.: Effekt von Adrenomedullin auf den Verlauf der mesangioproliferativen Glomerulonephritis bei der Ratte
Hermann, Kathrin, Dr. med.: Anti-apoptotischer Einfluss von Syncytin-1 in Staurosporin-behandelten CHO-Zellen
Lukas, Kristin, Dr. med.: Analyse der Arzneimitteltherapie auf einer neonatologischen Intensivstation
May, Julia, Dr. med.: Suppression von Interleukin 8, Cyclooxygenase 2, Prostaglandin E3-Rezeptor und Prostaglandinen durch Parecoxib und Indometacin im Tiermodell der neonatalen B-Streptokokkensepsis
Mölkner, Vera, Dr. med.: Das Anti-Müller Hormon bei Kindern mit kongenitalem adrenogenitalen Syndrom und 21-Hydroxylase-Defekt
Plattner, Erika, Dr. med.: Entwicklungsneurologischer Verlauf bei Hochrisiko-Frühgeborenen der Geburtsjahrgänge 2000-2004
Schulz-Harder, Karoline, Dr. med.: Wirkung von Interleukin-1ß und Transforming Growth Factor ß1 auf den villösen Zytotrophoblasten in vitro
Vehorn, Mareike, Dr. med.: AGS-Risikoschwangerschaften

Doctorate Theses 2012

Albrecht, Andrea, Dr. med.: Entwicklungsneurologischer Langzeitverlauf von Neugeborenen mit perinataler Asphyxie
Bauer, Penelope, Dr. med.: Kardiologische Reihenuntersuchung jugendlicher Sportler
Berk, Susanne, Dr. med.: Etablierung eines Fluoreszenz-Fusionsassays an verschiedenen trophoblastären und Syncytin-überexprimierenden Zellreihen
Kartheuser, Yvonne, Dr. med.: Hyperton-hyperonkotische Kochsalzlösungen und der Einfluss auf die akute Blutdruckregulation durch endokrine Regulationsmechanismen in der pädiatrischen Intensivmedizin
Mückstein-Hupfer, Sieglinde, Dr. med.: Wirkung eines selektiven Interleukin-8-Rezeptorantagonisten auf die pulmonale Hypertonie und die im Rahmen der Inflammation auftretenden Interleukine -8 und -1ß bei Surfactant-depletierten Ferkeln mit akutem Atemnotsyndrom
Münzel, Kathrin, Dr. med.: Gefäßveränderungen nach intrauteriner Wachstumsretardierung
Neukam, Valentin, Dr. med. dent.: Untersuchung des Risikos einer belastungsinduzierten Hyperthermie bei Kindern und Jugendlichen mit hypohidrotischer ektodermaler Dysplasie
Oehme, Ann-Kathrin, Dr. med.: Unerwünschte Arzneimittelwirkungen bei Kindern - ein Vergleich zweier Studien
Offergeld, Ramona, Dr. med.: Bedeutung von Corticotropin-releasing-Hormon für die Leptinexpression und die Synzytialisierung von primären humanen Trophoblasten
Schäfer, Michaela, Dr. med.: Knochendichte bei jungen Frauen mit Ullrich-Turner-Syndrom nach Therapie mit Wachstumshormon
Scheu, Svenja, Dr. med.: Visuell evozierte Potentiale bei Früh- und Reifgeborenen: Reifung und prognostische Bedeutung
Straßer, Katja, Dr. med.: Expression von HIF-regulierten Genen in der Plazenta und im Gehirn der neonatalen Maus unter systemischer Hypoxie

Habilitation 2011

Benz, Kerstin, PD Dr. med.: Nierenstruktur und -funktion bei genetisch bedingter erniedrigter Nephronenzahl im Tiermodell der GDNF-heterozygoten Knockout-Maus
Paulides, Marios, PD Dr. med.: Late effects after oncologic treatment of Ewing's-, osteo- or soft tissue sarcomas in children

Habilitation 2012

Hinkes, Bernward, PD Dr. med.: Hereditäre Formen des nephrotischen Syndromes im frühen Kindesalter - molekulare Grundlagen und ihre klinische Relevanz
Lehner, Manfred, PD Dr. rer. nat.: Dendritische Zellen und genetisch modifizierte T-Zellen für die zelluläre Immuntherapie von Tumoren
Neubert, Antje, PD Dr. rer. nat.: The role of adverse drug reactions in paediatric medication safety
Völkl, Thomas Michael Karl, PD Dr. med.: Neue Therapieziele bei Kindern und Jugendlichen mit adrenogenitalem Syndrom (AGS) durch 21-Hydroxylase-Defekt

Department of Pediatric and Adolescent Medicine

Division of Pediatric Cardiology

Board Qualification 2011

Webinger, Jasmin, Dr. med.

Additional Qualification 2012

Schmidt, Thomas: Emergency Medicine

Department of Plastic and Hand Surgery

Doctorate Theses 2011

Hammon, Matthias, Dr. med.: GBP-1 transgenic EPC in the AV Loop Model
Schnürer, Stefan, Dr. med.: Perfusion Quantification in Pig Muscle

Doctorate Theses 2012

Klumpp, Dorothee, Dr. med.: Muscle Tissue Engineering and Nanomatrices
Yuan, Quan, Dr. med.: HIF 1 α and hypoxia in the AV Loop Model

Board Qualification 2011

Arkudas, Andreas, Dr. med.

Board Qualification 2012

Merz, Katrin, Dr. med.
Saalabian, Ali, Dr. med.
Bleiziffer, Oliver, Dr. med.

Habilitation 2012

Arkudas, Andreas, PD Dr. med.: Replantations of the Upper Extremity
Dragu, Adrian, PD Dr. med.: Postbariatric Plastic Surgery
Polykandriotis, Elias, PD Dr. med.: Models of autonomous vascularization in regenerative medicine: studies on early and late angiogenic phenomena

Department of Psychiatry and Psychotherapy

Chair of Psychiatry and Psychotherapy

Doctorate Theses 2011

Welzel, Oliver, Dr. rer. biol. hum.: Untersuchung heterogener Eigenschaften hippocampaler Synapsen mittels Fluoreszenzmikroskopie

Doctorate Theses 2012

Kleinow, Martina, Dr. rer. biol. hum.: Balanced Scorecard einer psychiatrischen Universitätsklinik: Die Entwicklung und deren Auswirkungen auf die Klinikstrukturen unter Betrachtung der Promotoren Führung, Kommunikation und Qualitätsmanagement

Habilitation 2011

Donath, Carolin, PD Dr. rer. nat.: Versorgungsforschung bei Demenz: diagnostische und therapeutische Versorgung von Patienten und Versorgung von pflegenden Angehörigen mit Unterstützungsangeboten

Habilitation 2012

Lenz, Bernd, PD Dr. med.: Aktivierende und organisierende Sexualhormoneffekte bei Alkoholabhängigkeit: Genetik und Neuroendokrinologie

Department of Psychiatry and Psychotherapy

Division of Child and Adolescent Mental Health

Doctorate Theses 2012

Wangler, Susanne, Dr. med.: Neurofeedback in children with ADHD: Specific event-related potential findings of a randomized controlled trial

Board Qualification 2012

Kupfer, Stefanie, Dr. med.
Wangler, Susanne, Dr. med.
Wichmann, Christa, Dr. med.

Additional Qualification 2011

Vogel, Simone: Child and Adolescent Psychotherapy

Additional Qualification 2012

Busch, Katrin: Child and Adolescent Psychotherapy

Habilitation 2011

Heinrich, Hartmut, PD Dr. sc. hum.: Clinical effects and neurophysiological mechanisms of neurofeedback in children with attention-deficit/hyperactivity disorder

Department of Surgery

Chair of Surgery

Doctorate Theses 2011

Beron, Katja, Dr. med.: Neuentwicklung eines elektronischen Antriebes für ein Koloskop - Ermittlung grundlegender Anforderungen und Messung von Vorschubkräften für eine Sicherheitsabschaltung
Hammon, Matthias, Dr. med.: Untersuchung der angiogenen Eigenschaften von murinen, embryonalen, endothelialen Vorläuferzellen in vitro und in vivo.
Hohnheiser, Annika, Dr. med.: Malignant melanoma of the skin: Long-term follow-up and time to first recurrence
Hörske, Carolin, Dr. med.: Long-term outcomes and quality of life after rectal carcinoma surgery
Hunger, Kordula, Dr. med.: Das Risiko maligner Pleuraergüsse und Thoraxwandmetastasen von intrapulmonalen Malignomen nach perthorakaler Feinnadelpunktion - eine retrospektive Fall-Kontroll-Studie und eine prospektive histologische Untersuchung
Knoch, Miriam, Dr. med.: Langzeitergebnisse der Behandlung der morbiden Adipositas mittels weitenregulierbaren Magenbands
Meyer, Anne, Dr. med.: Kolorektales Karzinom Aktion
Meyer, Jörg, Dr. med.: Sicherheit und Effektivität der präemtiven Strategie zur Behandlung der Zytomegalievirus (CMV) Infektion nach orthotoper Lebertransplantation
Öckl, Karin, Dr. med.: Prognose des Kolonkarzinoms erhoben am Krankengut der Chirurgischen Klinik am Universitätsklinikum Erlangen im Zeitraum 1978-2004
Schuhmann, Sabine, Dr. med.: Therapiemöglichkeiten der Hepatitis C-Reinfektion nach Lebertransplantation mit pegylierten Interferonen und Ribavirin
Tonak, Julia, Dr. med.: Die Evalutation von Humanem Guanylat-Bindungsprotein-1 als Marker im Blutserum für Entzündung und Sepsis
Wunder, Thomas, Dr. med.: Die gastrale Dekompression nach Anlage einer großlumigen PEG-Sonde

Doctorate Theses 2012

Kuhn, Elisabeth, Dr. rer. nat.: Ein neues Chip-basiertes paralleles Transfektionsverfahren für die Analyse parakriner Zellinteraktionen
Löbbert, Marko: Die Etablierung der laparoskopisch assistierten linksseitigen Hemicolektomie bei Divertikulitis
Raabe, Eva, Dr. med.: Gallenwegskomplikationen nach orthotopen Lebertransplantationen - Inzidenz, Risikofaktoren und Therapieverfahren
Villanueva, Marie-Therese: Langzeitlebensqualität bei Patienten nach multimodaler Therapie eines Rektumkarzinoms

Board Qualification 2011

Schildberg, Claus, Dr. med.

Board Qualification 2012

Lux, Philipp, Dr. med.
Zhang, Wei, Dr. med.

Habilitation 2011

Knorr, Christian, PD Dr. med.: Regionale Hyperthermieverfahren als multimodales Therapiekonzept in der chirurgischen Behandlung von lokoregional-metastasierten Malignomen am Beispiel des Malignen Melanoms - Aktueller Stand und Perspektiven
Naschberger, Elisabeth, PD Dr. rer. nat.: Molekulare Mechanismen und klinische Bedeutung der entzündlichen Gefäßaktivierung

Habilitation 2012

Demir, Resit, PD Dr. med.: Hypoxie und maligne Progression von Tumorzellen

Department of Surgery

Division of Thoracic Surgery

Board Qualification 2011

Oster, Oliver, Dr. med.

Department of Surgery
Division of Transfusion Medicine and Hemostaseology

Doctorate Theses 2011

Hollein, Lucie, Dr. med.: Kryokonservierung von Plazentarestblut: Eine vergleichende Studie zwischen unmanipuliertem Vollblut und volumenreduziertem Leukozytenkonzentrat.
Meininghaus, Barbara, Dr. med.: Evaluation des neuen Thrombozytenfunktionsanalysers DiaMed Impact® im Vergleich zur Impedanzaggregometrie mittels Multiplate® bei Patienten unter Therapie mit Acetylsalicylsäure und/oder Clopidogrel
Oremek, Damian, Dr. med.: In-vitro-Qualitätskontrollen bestrahlter und leukozytendepletierter Erythrozytenkonzentrate in der additiven Lösung PAGGS-M
Rießner, Katrin, Dr. med.: Die Bedeutung der Eigen- und Familienanamnese in der Thrombophiliediagnostik
Schmieger, Tobias, Dr. med.: Von-Willebrand Faktor, Faktor VIII sowie frei und zellulär in Thrombozyten zirkulierende Wachstumsfaktoren der Angiogenese vor und nach Resektion eines kolorektalen Karzinoms

Doctorate Theses 2012

Braun, Sabine, Dr. med.: Gepaarte Studie zur Validierung des neuen Thrombozytenaggregotmeters PAP-8® und zur Untersuchung des Einflusses der Einstellung der Thrombozytenkonzentration des plättchenreichen Plasmas auf die Ergebnisse der Thrombozytenaggregationstestung mit PAP-8® und PAP-4®
Dlimi, Afif, Dr. med.: Einfluss der Konzentration unterschiedlicher Zellpopulationen auf die Vitalität kryokonservierter Stammzellkonzentrate.
Eiche, Christian, Dr. med.: Von-Willebrand-Faktor-Aktivität und von-Willebrand-Faktor-Multimerenverteilung bei Patienten mit kolorektalem Karzinom.
Frisch, Andreas, Dr. med.: Bestrahlung leukozytendepletierter Erythrozytenkonzentrate in der additiven Lösung SAG-M aus dem Blutspendedienst Suhl zu verschiedenen Zeitpunkten.
Klein, Caroline, Dr. hum. biol.: Ex vivo Expansion hämatopoetischer Stamm- und Vorläuferzellen aus Nabelschnurblut in Kokultur mit mesenchymalen Stromazellen aus Amnion, Chorion, Whartonscher Sulze, Fruchtwasser, Nabelschnurblut und Knochenmark.
Luther, Romy, Dr. med.: Veränderungen des pH-Wertes in Thrombozytenkonzentraten in Abhängigkeit von Temperatur und dem Verhältnis aus humanem Plasma und additiven Lösungen zur Thrombozytenkonservierung.
Schiffer, Katharina, Dr. med.: Bestrahlung von Babybeuteln aus leukozytendepletierten Erythrozytenkonzentraten in der additiven Lösung SAG-M zu verschiedenen Zeitpunkten
Schoetz, Anna Maria, Dr. med.: In-vitro-Qualitätskontrollen von leukozytendepletierten Erythrozytenkonzentraten in SAG-M nach Bestrahlung mit 30 Gray an Tag +14, +28 oder +35.

Department of Surgery
Division of Trauma Surgery

Doctorate Theses 2011

Krinner, Sebastian, Dr. med.: Vergleich des Verlaufs der neuromuskulären Blockade nach Applikation von Mivacurium bei Schulkindern unterschiedlicher Altersgruppen im Rahmen einer total intravenösen Anästhesie
Pachowsky, Milena, Dr. med.: Diagnostik der linksventrikulären ‚non-compaction' Kardiomyopathie mittels der Magnetresonanztherapie

Board Qualification 2011

Kolvenbach, Carl, Dr. med.
Schulz-Drost, Stefan, Dr. med.

Board Qualification 2012

Dobre, Andra, Dr. med.

Additional Qualification 2011

Mauerer, Andreas, Dr. med.: Special Accident Surgery

Additional Qualification 2012

Gelse, Kolja, PD Dr. med.: Special Accident Surgery

Department of Urology
Chair of Urology

Doctorate Theses 2012

Huppert, Verena, Dr. med.: Tet-regulierte induzierbare Expression von Kandidatengenen in serotonergen Neuronen von transgenen Mäusen
Nolte, Elke, Dr. rer. nat.: The role of microRNAs in prostate carcinoma

Board Qualification 2012

Keck, Bastian, Dr. med.

Additional Qualification 2012

Harlander-Weikert, Eva: Fellow of the European Board of Urology; FEBU: Andrology
Keck, Bastian, Dr. med.: Drug-based Tumor Therapy
Keck, Bastian: Fellow European College of Sexual Medicine; FECSM: Andrology
Dr. Rogenhofer, Michael: Fellow of the European Board of Urology; FEBU: Andrology
Engehausen, Dirk, Prof. Dr. med.: Medical Quality Management
Wullich, Bernd, Prof. Dr. med.: Fellow European College of Sexual Medicine; FECSM: Andrology

Department of Operative Dentistry and Peridontology
Chair of Dental, Oral, and Maxillofacial Medicine – especially Operative Dentistry, Periodontology, and Pediatric Dentistry

Doctorate Theses 2011

Adam, Milan, Dr. med. dent.: Über die Eignung von Phantommodellen zur Testung der Rigidität von Zahntraumaschienen
Auer, Friedrich, Dr. med. dent.: Konstruktion und Evaluation zweier neuer artifizieller Modelle für die Rigiditätsbestimmung von Traumaschienen
Grasser, Andrea, Dr. med. dent.: Polymerisationsspannung und -schrumpf dentaler Füllungskomposite
Kirsten, Maria, Dr. med. dent.: „Gesunde Zähne für Schüler" Kariesvorsorge an Hauptschulen Ergebnisse nach 2 Jahren
Kohlhase, Friedrich, Dr. med. dent.: Mundhygiene und Patientenzufriedenheit von Klinikpatienten einer Universitätszahnklinik
Lauterbach, Madeleine, Dr. med. dent.: Physikalische Eigenschaften eines dentalen Komposits in Abhängigkeit von Verarbeitungstemperatur und Lagerungsdauer
Mackert, Tobias, Dr. med. dent.: Über die Haftkraft von adhäsiv befestigten Faserstiften nach künstlicher Alterung
Meyer, Florian, Dr. med. dent.: Über die Dimensionsstabilität von Wurzelkanalfüllmaterialien auf Guttapercha-Basis
Nagler, Tonia, Dr. med. dent.: Zeitabhängige Putzeffektivität einer neuen Handzahnbürste im Vergleich mit einer ADA-Referenzzahnbürste
Wießner, Jessica, Dr. med. dent.: Über die Entfernung von Kalziumhydroxid aus dem Wurzelkanal (Einfluss des Spülvolumens)
Wießner, Thomas, Dr. med. dent.: Effektivität verschiedener Spültechniken bei der Entfernung von Kalziumhydroxid aus dem Wurzelkanal
Wimmer, Stefan, Dr. med. dent.: Zum Vergleich verschiedener Methoden der Haftkraftmessung von Dentaladhäsiven nach künstlicher Alterung

Doctorate Theses 2012

Franz, Florian, Dr. med. dent.: Einfluss der Klebepunktausdehnung und des Schienentyps auf die Schienenrigidität - Untersuchung mittels der dynamischen Periotestmethode
Henkel, Mario, Dr. med. dent.: Untersuchung des Aushärteverhaltens lichthärtender Füllungskomposite mittels dielektrischer Analyse (DEA)
Khursan, Tamer, Dr. med. dent.: Physikalische Enddaten eines neu entwickelten Kompositmaterials
Knöllinger, Melissa, Dr. med. dent.: Einfluss eines nanogefüllten Schutzlackes auf das Ermüdungsverhalten eines Glasionomerzementes in destillierten Wasser und künstlichen Speichel
Lücking, Julia, Dr. med. dent.: Einfluss von Zementprovisorien und Adhäsivprocedere auf die marginale Adaptation von Kompositrestaurationen

Wimmer, Romana, Dr. med. dent.: Effizienz dreier Prophylaxepulver zur Belagentfernung - eine In-vitro-Untersuchung

Habilitation 2012

Berthold, Christine, PD Dr. med. dent. habil.: Conservative Dentistry after Dento-Alveolar Trauma

Department of Orthodontics and Orofacial Orthopedics

Chair of Dental, Oral, and Maxillofacial Medicine – especially Orofacial Orthopedics

Doctorate Theses 2011

Detterbeck, Andreas Markus Wilhelm, Dr. med. dent.: Von der Kieferabformung zum virtuellen ModOf the jaw impression to the virtual model: A pilot study on accuracy of industrial CT-based measurements of impression materials

Doctorate Theses 2012

Hanke, Sebastian, Dr. med. dent.: Three-dimensional computed tomography based rating of unilateral impacted canines
Prinz, Patrick, Dr. med. dent.: Burnout, depression and depersonalization – Psychological factors and coping strategies among students of dentistry and medicine
Schiller, Peter Johannes, Dr. med. dent.: A new coordinate system based on the Frankfort horizontal and Christa galli for computed tomography analysis of mandibular asymmetry - a comparative study
Wille, Alexander, Dr. med. dent.: Comparison of two-dimensional measurements on the basis of conventional reference points in the respective FRS and mediansagittal projected coordinates in the volume-based CT

Board Qualification 2011

Heckhoff, Uta, Dr. med. dent.

Board Qualification 2012

Hofmann, Elisabeth, Dr. med. dent.
Kunz, Katharina, Dr. med. dent.
Medelnik, Jürgen, Dr. med. dent.
Strobel, Karin, Dr. med. dent.

Department of Prosthodontics

Chair of Dental, Oral, and Maxillofacial Medicine – especially Prosthetic Dentistry

Habilitation 2012

Schmitt, Johannes, PD Dr. med. dent.: The long term outcome of full ceramic dental restorations from the material and biological point of view

Institute of Clinical and Molecular Virology

Chair of Clinical Virology

Doctorate Theses 2011

Adler, Martina, Dr. rer. nat.: Intrinsic immunity against the human cytomegalovirus-characterization of cellular restriction factors and analysis of viral antagonistic mechanisms
De Jong, Sarah Jill, Dr. rer. nat.: Dissecting the Tio- NF-κB signalosome in human T cells
Giede-Jeppe, Antje, Dr. med.: Generation and characterization of recombinant human cytomegaloviruses harboring mutations of the UAP56- and/or RNA interaction domains of the RNA export factor pUL69
Hahn, Sabine, Dr. rer. nat.: Targeting the human immunodeficiency virus type-1 Gag protein into the defective ribosomal product pathway enhances its MHC class I antigen presentation
Kirmaier, Andrea, Dr. rer. nat.: Replication and Persistence of Primate Lentiviruses
Ködel, Yvonne, Dr. rer. nat.: Impact of N-terminal peptides derived from glycoprotein E2 of GB virus C on HIV replication
Kreß, Andrea K., Dr. rer. nat.: The Tax protein of Human T cell lymphotropic virus type 1 (HTLV-1) as a multifunctional oncoprotein
Lohmaier, Jens, Dr. med.: Functional analysis of the HIV-1 rev-protein with heterologous export signals
Mahmoudian, Shohreh, Dr. rer. nat.: Effect of cytomegaloviruses on the development of transplant arteriosclerosis and characterization of potentially associated viral G-protein coupled receptors
Neumann, Liane, Dr. rer. nat.: Structure and function of the HIV-1 gag-protein p6
Ruhland, Wolfgang Christian, Dr. med.: The impact of polymorphisms in the HIV-1 protease on the development of resistance
Schmidt, Katharina Anna, Dr. rer. nat.: Mechanisms and consequences of interferon-γinhibition by the viral interferon regulatory factor 3 (vIRF-3) of Kaposi s sarcoma associated herpesvirus (KSHV)

Doctorate Theses 2012

Dietz, Monika, Dr. rer. nat.: Effector functions of the protective humoral immune response against cytomegalovirus
Heilmann, Andreas, Dr. rer. nat.: Epstein-Barr virus Rta activation of lytic gene promoters and its regulation by the viral LF2 protein
Karbach, Astrid, Dr. rer. nat.: The humoral immune response against glycoprotein B, a major determinant of cytomegalovirus
Katsch, Kristin, Dr. rer. nat.: Modulation of cellular signaling pathways by the oncoproteins of T-lymphotropic herpesviruses
Mazumder, Eman Dey, Dr. rer. nat.: Tyrosine residues Y114 and Y127 of rhadinoviral oncoprotein Tip are central to STAT activation
Naumann, Anja, Dr. rer. nat.: Epigenetic and functional characterization of the 5′-upstream region of the human FMR1 gene
Postler, Thomas, Dr. rer. nat.: The Cytoplasmic Domain of the HIV-1 and SIV Envelope Glycoprotein: Functional Properties and Topology
Pritschet, Kathrin, Dr. rer. nat.: Internalization of human immunodefi ciency virus type 1 in plasmacytoid dendritic cells
Ries, Moritz, Dr. rer. nat.: Endogenous immune activation by cellular DNA in HIV-1 infection
Sommermann, Thomas, Dr. rer. nat.: The role of NFκB in glucose import and the survival of B-cell lymphomas
Sörgel, Stefan, Dr. rer. nat.: Functional and molecular characterization of the HIV-1 accessory protein Vpr with focus on virus – host interaction
Zielke, Barbara, Dr. rer. nat.: The HCMV encoded mRNA-export factor pUL69 – functional conservation within the Betaherpesvirinae and identifi cation of mRNA-targets during infection
Zielke, Katrin, Dr. rer. nat.: The insulator protein CTCF and cohesins are critical for Herpesvirus saimiri genome maintenance

Institute of Clinical Microbiology, Immunology, and Hygiene

Chair of Microbiology and Immunology of Infection

Doctorate Theses 2011

Häberlein, Simone, Dr. rer. nat.: Mechanisms of Transmission and Innate Immune Control of Leishmania Parasites
Wagner, Caroline, Dr. rer. nat.: Characterization of the Salmonella Pathogenicity Island 4-encoded proteins SiiE, SiiA and SiiB: a new mechanism of bacterial adhesion
Wiese, Melanie, Dr. rer. nat.: Impact of hypoxia and the influence of the hypoxia-inducible factor HIF-1α on the antibacterial capacity of dendritic cells and macrophages

Doctorate Theses 2012

Jebran, Fahwad, Dr. med.: In vitro und in vivo Wirkung von pharmazeutischem Natriumchlorid bei der kutanen Leishmaniose

Habilitation 2011

Schleicher, Ulrike, PD Dr. rer. nat.: Mechanismen der angeborenen Immunität bei intrazellulären Erregern

Institute of Human Genetics

Chair of Human Genetics

Doctorate Theses 2011

Uebe, Steffen, Dr. rer. nat.: Identifikation und Charakterisierung neuer genetischer Risikofaktoren für komplexe Erkrankungen

Doctorate Theses 2012

Bezold, Viola, Dr. med.: Identifizierung von Genen für autosomal-rezessiv vererbte mentale Retardierung: Mutationsscreening im TUSC3-Gen und Homozygotiekartierung zur Identifizierung neuer Genloci

Grosch, Melanie, Dr. rer. nat.: Identifizierung und Charakterisierung von Genen mit spezieller Funktion in der Skelettentwicklung
Krumbiegel, Mandy, Dr. rer. nat.: Genetische Faktoren in der Ätiologie und Pathogenese des Pseudoexfoliationssyndroms
Schöb, Dominik, Dr. med.: Homozygotiekartierung bei Kindern mit primärem nephrotischen Syndrom

Facharztausbildung 2012

Hoyer, Juliane, Dr. med.
Zweier, Christiane, Dr. med.

Habilitation 2011

Hüffmeier, Ulrike, PD Dr. med.: Genetische Risikofaktoren für Psoriasis vulgaris und Psoriasis arthritis
Thiel, Christian Thomas, PD Dr. med.: Identifizierung und Charakterisierung genetischer Ursachen von Wachstumsstörungen

Institute of Pathology

Chair of General Pathology and Pathological Anatomy

Doctorate Theses 2011

Benicke, Julia, Dr. med.: Gut differenzierte Barrett-Adenocarcinome werden häufig als „hochgradige intrarepitheliale Neoplasie" unterdiagnostiziert
Gores, Heinz, Dr. med.: Einfluss unterschiedlicher Wurfgrößen auf Glomerulusanzahl und glomerulärem Volumen in einem Modell der intrauterinen Wachstumsrestriktion der Ratte.
Knauth, Solweig, Dr. med.: Kardiale Veränderungen, Atherosklerose und Arteriosklerose in verschiedenen Gefäßprovinzen von Patienten mit chronischer Niereninsuffizienz im Vergleich zu nierengesunden Patienten.
Schwantzer, Anja, Dr. med.: Effekte einer salzreichen Diät auf die Progession der diabetischen Nephropathie im tierexperimentellen Modell der ZDF-Ratte.
Thomas, Susanne, Dr. med.: Effekte der Proteasomeninhibition auf Nierenveränderungen im Mausmodell einer experimentellen Lupusnephritis.
Varga, Ildiko, Dr. med.: Morphologische und immunhistologische Charakterisierung der Gefäßveränderungen bei Patienten mit geringgradig eingeschränkter Nierenfunktion und fortgeschrittener Niereninsuffizienz.
Zemler, Barbara, Dr. med.: Der Grad der Differenzierung, die Häufigkeit der Lymphgefäß- und der Veneneinbrüche von Barrett- Frühcarcinomen sind abhängig von der Tiefeninfiltration

Doctorate Theses 2012

Bott, Simone, Dr. med.: Effekte einer oralen Therapie mit S 18886, einem TP-Rezeptor-Antagonisten, auf kardiovaskuläre Strukturveränderungen im Hypertonie-Modell der doppelt transgenen „human renin-angiotensinogen rats" (dTGR)
Rogler, Anja, Dr. rer. nat.: Role of chromosome 8p-deletions and loss of SFRP1-expression in urothelial carcinoma of the urinary bladder
Röhring, David, Dr. med.: Effekte einer oralen Therapie mit Atorvastatin auf Atherosklerose und Entzündungsmediatoren bei experimenteller Niereninsuffizienz im Tiermodell der ApoE-/-Knock out Maus.

Board Qualification 2011

Söder, Stephan, Dr. med.

Board Qualification 2012

Wachter, David, Dr. med.

Habilitation 2011

Büttner-Herold, Maike, PD Dr. med.: EBV-assoziierte Tumoren in Interaktion mit dem Immunsystem
Schwarz-Furlan, Stephan, PD Dr. med.: Histopathologische Prognosefaktoren von Karzinomen des oberen Aerodigestivtraktes
Stöhr, Robert, PD Dr. med.: Initiating and progression related alterations in human bladder cancer

Institute of Radiology

Chair of Diagnostic Radiology

Board Qualification 2011

Heinrich, Marc, Dr. med.
Heinz, Marco, Dr. med.
Köhler, Julia, Dr. med.

Board Qualification 2012

Meier-Meitinger, Martina, Dr. med.
Schlechtweg, Philipp, Dr. med.

Habilitation 2011

Adamus, Ralf, PD Dr. med.: Development and evaluation of new techniques in the endovascular system
Alibek, Sedat, PD Dr. med.: Improvement in cross sectional imaging in children and adolescents
Anders, Katharina, PD Dr. med.: Computertomographie der Koronarien - Optimierung von Untersuchungstechnik und Patientenselektion
Schwab, Siegfried, PD Dr. med. univ.: Complementary imaging modalities in breast cancer diagnostics

Habilitation 2012

Adamietz, Boris, PD Dr. med.: Elastography of breast tumors
Roemer, Frank, PD Dr. med.: Role of magnetic resonance imaging in cross-sectional and longitudinal evaluation of knee osteoarthritis

Institute of Radiology

Division of Neuroradiology

Additional Qualification 2011

Dölken, Marc, PD Dr. med.: Neuroradiology

Habilitation 2011

Dölken, Marc, PD Dr. med.: High-resolution magnetic resonance imaging and magnetic resonance spectroscopy for diagnosis and therapy of epileptic seizures

APPENDIX

In Memorian

2011

Prof. Dr. med. Wolf-Dieter Keidel
Professor emeritus of the Chair of Physiology

Prof. Dr. med. Walter Kersten
Professor emeritus of the Chair of Biochemistry

Prof. Dr. med. Eberhard Lungershausen
Professor emeritus of the Chair of Psychiatry

Ralph M. Steinman, MD, Henry G. Kunkel Professor and Senior Physician at the Rockefeller University New York
Honorary doctorate of the Faculty of Medicine

Prof. Dr. med. Gerhard Kittel
Former head of the Division of Phoniatrics and Pediatric Audiology at the Department of Otorhinolaryngology

2012

Prof. Dr. med. Dietrich Hohmann
Former head of the Department of Orthopedics at the Waldkrankenhaus

Prof. Dr. med. Dieter Platt
Former director of the Institute for Biomedicine of Aging

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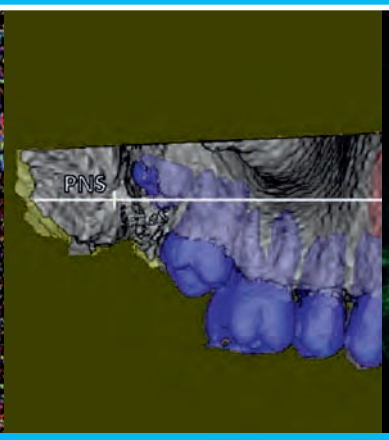
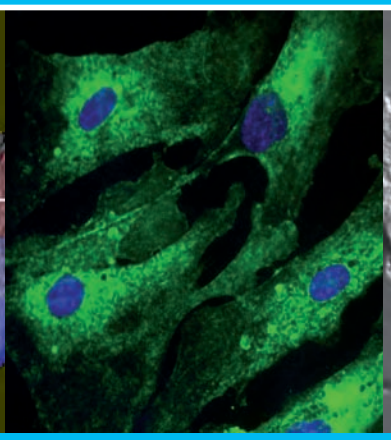
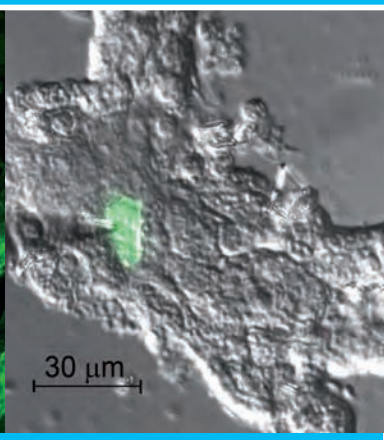
Cover
The cover shows the new medical lecture building (© UK Erlangen) as well as figures of research projects within the Faculty of Medicine.







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