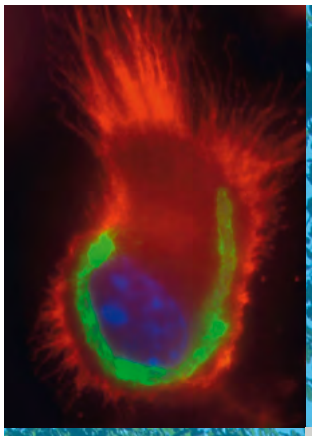
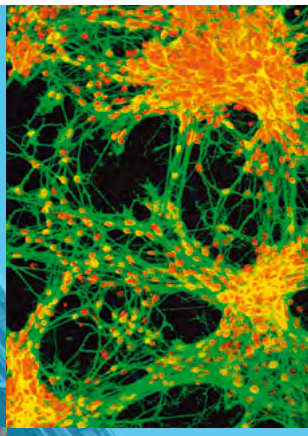
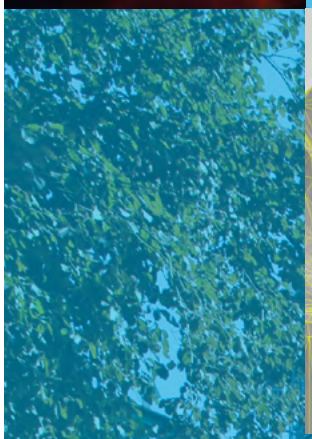
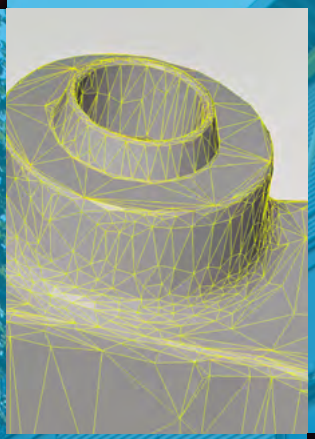
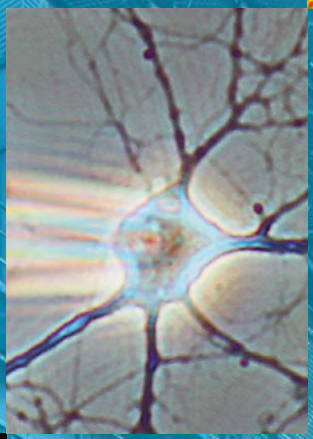
FRIEDRICH-ALEXANDER
UNIVERSITÄT
ERLANGEN-NÜRNBERG

MEDICAL FACULTY

Research Report 2011

Medical Faculty



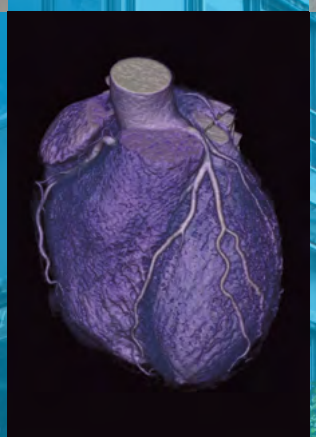




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Table of Contents

RESEARCH TRAINING GROUPS AND PROGRAMS

INTERDISCIPLINARY CENTERS / CENTRAL INSTITUTES / CORE FACILITIES

RESEARCH SUPPORT AND FOUNDATIONS

ACADEMIC SOCIETY

DEGREE PROGRAMS

APPENDIX

Medical Research in Erlangen

This report of the years 2009-2010 gives for the sixth time an overview of the research areas and projects carried out by the various institutes and clinics at the Medical Faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU). The aim is to provide an account of the achievements in basic research as well as in clinical research projects during the report period. It is meant to be read by a wider audience comprised of interested parties both inside and outside the university area. It is intended to serve as a source of information both for internal and interdisciplinary use and to encourage suggestions for future cooperative projects.

The Medical Faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg has established four focal areas of research, all of which were given a high rating by the Science Council in 2006:

1. Immunology and Infection Research
2. Renal and Vascular Research
3. Neurosciences including Pain and Ophthalmology
4. Tumor Research

These research focuses are linked with each other 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 Medical Faculty. 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 to potential research centers. Such focal research areas are characterized by interdisciplinary networks supported by third-party funding provided in the framework of collaborative research centers, graduate research centers, DFG research training groups, as well as network projects funded by the Federal Ministry of Education and Research (BMBF) and the EU. A more detailed account is given in the second part of this report.

Moreover, our Medical Faculty 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 Medical Faculty and the relevant science and engineering departments in the various research networks. The Collaborative Research Center 796, "Reprogramming of Host cells by Microbial Effectors", was given a positive assessment by the DFG Senate and approved for funding in late 2008. How do viruses and bacteria cause diseases? The Collaborative Research Center 796 aims to acquire new knowledge on this pivotal medical problem. In addition to the Medical Faculty, various science and engineering departments at the Friedrich-Alexander-Universität Erlangen-Nürnberg, as well as the Fraunhofer Institute for Integrated Circuits (IIS) in Erlangen are involved in the collaborative research.

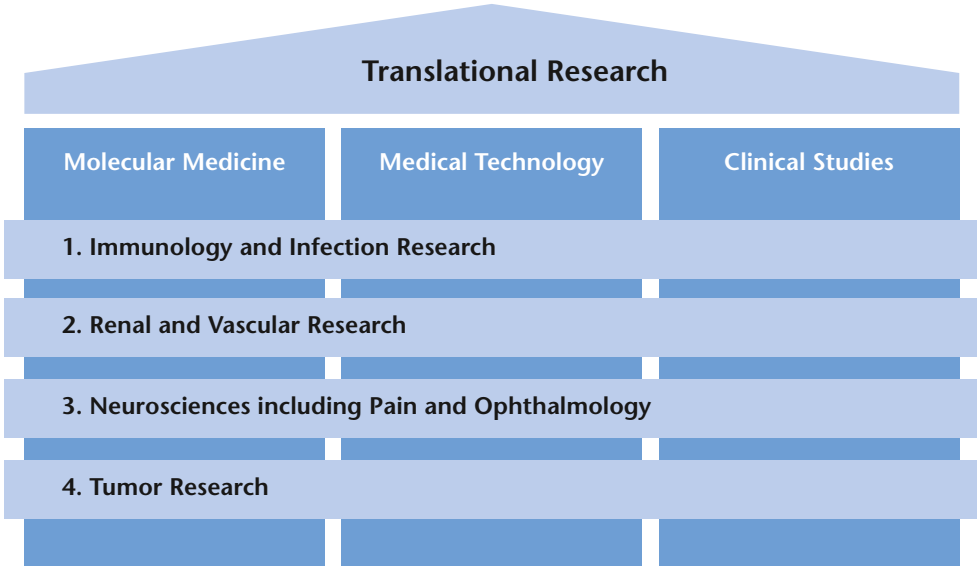
The Dean of the Medical Faculty
Prof. Dr. med. Dr. h.c. Jürgen Schüttler

The third-party funding has been rising continously in the last few years. In the year 2010 the Medical Faculty attracted more than 36 million euro of third-party funding. Therefore, Erlangen ranks far over the average funding of all German medical faculties.

In the course of the report period 2009-2010 a wide range of activities were carried out, aiming at continuing to move forward with the process of enhancing our reputation as an institution and making our achievements as a leading provider of medical research and training more visible to an international audience. The research orientation of our Medical Faculty is reflected by the existence of the Interdisciplinary Center for Clinical Research (IZKF), the Franz Penzoldt Center (FPZ), as well as the newly established Center for Clinical Studies (CCS). The latter will be responsible, among others, for coordinating the legal aspects of bench-to-bedside research projects.

The multitude of outstanding research initiatives require increased lab space. Inventory was taken of the amount of floor space in Medical Faculty facilities dedicated to research. This was documented in a Higher Education Information System (HIS) report on construction planning for teaching and research. The report showed a considerable lack of lab space in the clinical sector. This was a reflection of the large number of excellent research initiatives that have originated in this sector in recent years. On the basis of this report the Medical Faculty has formulated a program aimed at creating space available for research which is to be allocated for limited periods of time on the basis of applications made to the Research Commission. Various building activities have been initiated to cover the need of research facility.

With the Translational Research Center (TRC) – start of the construction in 2010 – the Universitätsklinikum Erlangen will provide an innovative interdisciplinary infrastructure for clinical research of an unprecedented kind on a university location in Germany. The TRC will bring together all those areas from which there is a need to translate research into diagnostic and therapeutic process in an exemplary manner. By this means our Medical Faculty will be able to counteract the much lamented lack of advancement in clinical research and to create new research focuses on the basis of a planned strategy.



Research focuses at the Medical Faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg

Further research facilities have been established at the research campus Hartmannstrasse. Two laboratory modules could be arranged for 3 million euro. Research groups of the Department of Medicine 1 are already working in the first module, research groups of the Department of Dermatology and Immune Modulation, as well as the Devision of Molecular Pneumology and the Department of Urology are currently moving into the second module. A third module is planned as resource for the future. Interdisciplinary collaborations and synergies shall be maxed out at this location to realize new research ideas.

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 which is passed on by the University or the University Hospital to individual clinics or institutes to use at their own discretion for research-related purposes. With the introduction of another lump sum for projects by the BMBF in 2011, these financial means will rise significantly. However, the distribution of funds from the lump sum as well as other research funding and the execution of joint research funding programs have been made difficult by a separation in the Medical Faculty administration of University Hospital budgets from those of non-clinical institutes. It is planned to transfer the preclinical and clinical theoretical institutes into the University Hospital. A university working group on medical facility structures is endeavoring to develop the tools to achieve this goal. The measures are being supported by the administration within a target agreement.

To further strengthen our research focus and to support the establishment of research cooperations, the Medical Immunology Campus Erlangen (MICE) and the Erlanger Center for Infection Research (ECI) were founded as interdisciplinary centers at the FAU. They foster the interdisciplinary and interfaculty cooperation and bundle the local strengths in the field of infection research. Both centers facilitate the development of innovative immunological research. Interdisciplinary and interfaculty cooperation in collaborative reasearch and interdisciplinary centers is a central instrument to strengthen the key research areas of the Medical Faculty. The Medical Technology Test and Application Center (METEAN), which was honored in the year 2008 by the Federal President in the context of the competition "Deutschland – Land der Ideen", is a unique facility in Germany. The Friedrich-Alexander-Universität Erlangen-Nürnberg, the Fraunhofer Institute for Integrated Circuits (IIS) and the Universitätsklinikum Erlangen have committed to making the patients benefit best from new innovative medical engineering by a quick transfer of technologies. This vision was also the base for the application of a "Center of Excellence for Medical Technology" under the roof of the Medical Valley EMN at the Leading-Edge Cluster Competition of the BMBF. In January 2010 a victory could be gained in this highly competitive contest. The aim of the Center of Excellence for Medical Technology is the development of technologies which increase life expectancy, improve quality of life and reduce costs in the public health sector. The Imaging Science Institut (ISI), which was 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 medical technology companies from the metropolitan area complement the outstanding research conditions in Erlangen. Additionaly, in December 2009 the Central Institute of Medical Engineering (ZiMT), a new organizational unit of the university, was founded to advance the interdisciplinary cooperation in the field of medical engineering.

In June 2007 an agreement was concluded between the administration of the Friedrich-Alexander-Universität Erlangen-Nürnberg and the Medical Faculty on the following objectives for the advancement of women in research by the year 2012: to increase the percentage of women who have the formal qualifications for professorial positions from 17 % to 25 % and to increase the percentage of women who hold professorial positions from 7 % to 10 %. The ARIADNE mentoring program, already in place in other divisions of the university, was initiated here in October 2008. The program brings young academic talent (women who have completed their doctorates and are working on a professorial qualification) together with mentors who have accumulated experience in academic careers.

Start-up financing and other forms of funding are provided for young academic talent with a view to helping pave the way to independent research for these persons (ELAN Fund, Johannes and Frieda Marohn Foundation, IZKF Funding for Young Academic Talent, as well as other foundations).

A new permanent platform for research funding, the Medical Research Foundation, was established in Erlangen in December 2007. The founders were the professors and department heads at the Medical Faculty. The Medical Research Foundation also conducts fund-raising activities and in some cases connects the awarding of larger amounts of funding to the temporary dedication of lecture rooms to specific uses.

New developments in teaching

In 2006 the Science Council underscored the transregional activities carried out by our Medical Faculty with a view to promoting further development of teaching. In light of this fact our report contains pertinent items of information on teaching for each institution.

The Medical Faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg currently has degree programs in Medicine Dentistry, Molecular Medicine, and a new master's degree program in Medical Process Management offered since winter semester 2008/2009. Since 2007 the students at the Medical Faculty 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 Medical Faculty has consistently undertaken efforts to seize on and apply new ideas in teaching with a view to maintaining these rankings. A changeover to the bachelor's and master's degree system is not planned for Medicine and Dentistry in Erlangen, given that this is not expected to produce any time advantages in the training of students and, as such, would not make it possible for them to get started any earlier in the medical profession. In a memorandum our Medical Faculty stated its opposition to the general implementation of the "Bologna Process" in medical studies. However, bachelor's and master's degree structures have been firmly established in specialized fields such as Molecular Medicine and Medical Process Management.

In summer semester 2007 a skills lab, PERLE (Practice, Experience and Learning), was created with money taken from tuition fees. Here students are able to improve their skills and prepare for practical examinations with the support of 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 semesters) continues to be pursued.

In 2008 the Bavarian State Ministry for Science, Research and the Arts approved the establishment of a Competence Center for the Teaching of Medicine. In this framework the five medical faculties in Bavaria have each chosen a focal area in which they want to develop special competence in the coming years and then pass on the knowledge gained to the other medical schools. The Medical Faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg has chosen course evaluation as its area of specialization and is working towards the creation of a general system of quality assurance in teaching that can be used by the other medical schools.

On behalf of the Medical Faculty administration I would like to thank all those members of our staff who helped produce this report. Particular thanks go to the Research Director, Dr. Edith Pfitzner for her active involvement in formulating the text. The report can be downloaded from the website of the Office of the Dean of the Medical Faculty (http://www.dekanat.med.uni-erlangen.de).

We hope our readers enjoy the information we have provided on the wide range of research carried out at our Medical Faculty. The scientists involved will be happy to respond to questions sent in by mail or asked in person about their projects.

Erlangen, September 2011

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Dean of the Medical Faculty

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Chair of Anatomy I

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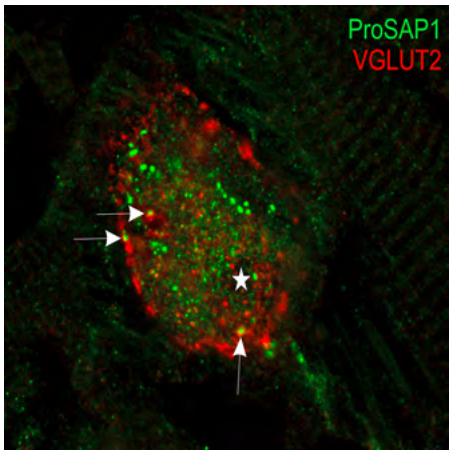
Research Focus
- Innervation of the gastrointestinal tract
- Innervation of the eye
- Nervous system, inflammation and pain
- Cell biology of the NF2 tumor suppressor protein

Structure of the Department

Together with Chair II, Chair I composes the Institute of Anatomy. Altogether, 16 persons are employed, five of them on an external funding basis. Research is conducted by 6 scientists (chairman, senior scientists, postdoctoral fellows), 8 doctoral thesis students (both MD and PhD) and 6 technicians. Chair 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.
Most of the teams investigate various aspects of autonomic innervation, in particular of the gastrointestinal tract and the eye; 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 Experimental Pathophysiology) and *in vitro* preparations of isolated organs as well as molecular biology are applied. Equipment and laboratory facilities are available also for other groups both within and outside the medical faculty.

Research

Innervation of the gastrointestinal tract
Project managers: W. Neuhuber, J. Woerl, M. Raab, A. Brehmer
Demonstration of enteric co-innervation of striated muscle in the human esophagus suggests a possible role of its disturbance in pathogenesis of swallowing disorders. In an *in vitro* vagus nerve-esophagus preparation of the mouse, we were able to further demonstrate a functional role of enteric co-innervation for inhibitory modulation of vagally induced striated muscle contraction. Nitric oxide and various peptides, e.g., neurokinins and galanin, play significant roles in these mechanisms.



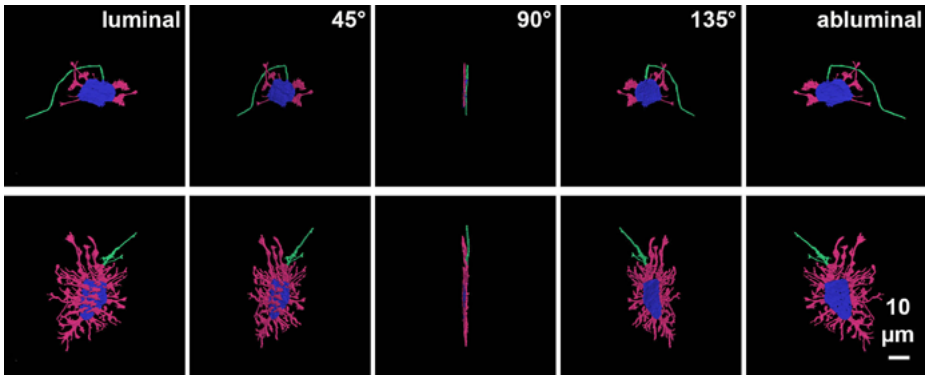
Confocal single section through a myenteric ganglion of the mouse esophagus. IGLEs are labeled with an antibody against VGLUT2 in red and synaptic contacts with an antibody against ProSAP1 in green. Arrowheads point to synapses between IGLEs and enteric neurons. (From Raab et al. 2010)

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 vesicular glutamate transporters (VGLUT1 and 2) and purinergic P2X2/P2X3 receptors. In addition, postsynaptic proteins, e.g., ProSAP 1 and 2 were detected in close relationship to 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. da Silveira (Brasil). This line of research is serving as a paradigm for forthcoming investigations on the enteric nervous system in other gastrointestinal disorders.

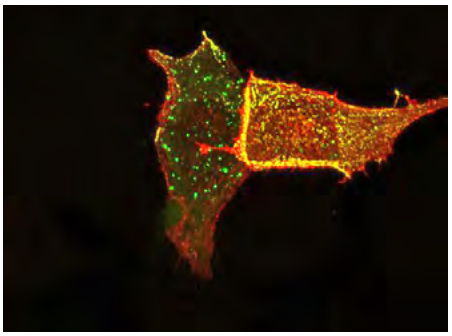
Innervation of the eye
Project manager: F. Schrödl
Knowledge of choroidal innervation is of key importance for understanding ocular homeostasis. Thus, investigation of intrinsic choroidal neurons (ICN) and their connections will provide new insights into various aspects of ocular pathogenesis. These intrinsic neurons were characterized in both humans and birds using immunohistochemistry, electron microscopy, neuronal tracing and electrophysiology. Using novel techniques for complete autonomic denervation of the chicken eye, the role of the autonomic nervous system on eye growth is studied in collaboration with Prof. Nickla (Boston). The physiology and pharmacology of ocular blood flow regulation is investigated together with Prof. Reitsamer (Salzburg).

Nervous system, inflammation and pain
Project manager: W. Neuhuber
In collaboration with the Institute of Experimental and Clinical Pharmacology and Toxicology, investigations on the influence of the autonomic nervous system on experimental liver inflammation were continued. We focused on the role of CGRP, a peptide abundant in sensory neurons. It partly acts antagonistic to substance P, the other landmark sensory neuropeptide, although its effects are more complex. These data may have impact on development of novel therapeutic strategies in hepatitis and other immune liver disorders. In collaboration with colleagues of the Department of Nephrology nerve fiber populations relevant for nephritis pathophysiology were studied. In collaboration with the Institute of Physiology and Pathophysiology neurochemical changes in sensory trigeminal neurons upon nociceptive stimulation of the dura were continued.

Cell biology of the NF2 tumor suppressor protein
Project manager: 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



Three-D reconstruction of two myenteric neurons of the human small intestine. A "stubby" neuron (top) shows dendrites (red) only on the circumference of the cell body (blue), while a "spiny" neuron (bottom) displays dendrites also on its luminal surface. The axon (green) of the stubby neuron projects orally, whereas the axon of the spiny neuron runs anally. These anatomical differences closely correspond to the neurons' chemical makeup: stubby neurons contain enkephalin while spiny neurons utilize VIP and NO as transmitters. (From Lindig et al. 2009, Histochem Cell Biol 131:1-12)



A NF2:MCF7 tumor cell expressing a NF2-mCherry fusion protein (red) together with EGFP-coupled hepatocyte receptor substrate (HRS) protein (green) labeling vesicles of the endolysosomal system. The NF2 protein labels the plasma membrane but is significantly also concentrated in HRS protein positive vesicles in cell processes (yellow). (courtesy M. Kressel)

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 institutes collaborate in teaching anatomy. In particular, Chair 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

Boudaka A, Wörl J, Shiina T, Shimizu Y, Takewaki T, Neuhuber WL (2009) Galanin modulates vagally induced contractions in the mouse oesophagus. Neurogastroenterol Motil, 21: 180-8

Kroeger I, Erhardt A, Abt D, Fischer M, Biburger M, Rau T, Neuhuber WL, Tiegs G (2009) The neuropeptide calcitonin gene-related peptide (CGRP) prevents inflammatory liver injury in mice. J Hepatol, 51: 342-53

Wörl J, Breuer C, Neuhuber WL (2009) Deletion of Pax7 changes the tunica muscularis of the mouse esophagus from an entirely striated into a mixed phenotype. Dev Dyn, 238: 864-74

Brehmer A, Rupprecht H, Neuhuber W (2010) Two submucosal nerve plexus in human intestines. Histochem Cell Biol, 133: 149-61

Raab M, Boeckers TM, Neuhuber WL (2010) Proline-rich synapse-associated protein-1 and 2 (ProSAP1/Shank2 and ProSAP2/Shank3)-scaffolding proteins are also present in postsynaptic specializations of the peripheral nervous system. Neuroscience, 171: 421-33

Stübinger K, Brehmer A, Neuhuber WL, Reitsamer H, Nickla D, Schrödl F (2010) Intrinsic choroidal neurons in the chicken eye: chemical coding and synaptic input. Histochem Cell Biol, 134: 145-57

International Cooperation

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

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

Prof. J. B. Furness, Department of Anatomy and Cell Biology, Universitsy of Melbourne, Melbourne, Australia

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

Dr. M.E. De Stefano, Dipt. di Biologia Celluara e di Sviluppo, University of Rome la Sapienza, Rome, Italy

Prof. Dr. D. Nickla, The New England College of Optometry, Boston, MA, USA

Prof. Dr. M.E. Fitzgerald, Department of Biology, Anatomy and Neurobiology, University of Tennessee, Memphis, TN, USA

Prof. H. Reitsamer, Augenklinik SALK, University of Salzburg, Salzburg, Austria

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

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

Meetings and International Training Courses

04.–06.02.2009: 6th International Course on Diagnostics and Surgery of Salivary Gland Diseases in Consideration of New Techniques (gemeinsam mit HNO-Klinik Erlangen), Erlangen

24.–27.03.2009: 9th International Course Aesthetic and Reconstructive Rhinoplasty (gemeinsam mit HNO-Klinik Erlangen), Erlangen

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Research Focus

- Investigations in glaucoma pathogenesis
- Effector T cell interactions with meningeal vascular structures in an autoimmune encephalomyelitis Lewis rat model
- Mouse models for neurodegenerative changes in retina and optic nerve
- Surface structures in the eye and detection of lacrimal film disorders in the Dry Eye by dynamic light scattering
- Mechanisms of epithelial defense on the surface of the eye
- Effect of Somatostatin on the corneal wound healing

Structure of the Department

The Institute of Anatomy consists of Chair I and Chair II. On the first of April, 2010, Professor Dr. med. Friedrich Paulsen became the new director of Chair II and thus replaced Professor Dr. med. Elke Lütjen-Drecoll, who has gone into retirement. Prof. Dr. F. Paulsen was previously working as Professor of Anatomy at the Martin-Luther University Halle-Wittenberg. Chair II employes 25 members of staff. In the period from 2009 to 2010, Seven positions have been financed with grant money. Eight doctoral researchers (from the field of medical, natural and computer science) contributed to the scientific research. Up to the appointment of Prof. Dr. F. Paulsen, the curriculum of the Anatomical Institute II comprised the functional anatomy of the human body including embryology, microscopic anatomy and neuroanatomy. The scientific focus of the institute under the direction of Prof. Dr. E. Lütjen-Drecoll was on the investigation of the functional anatomy of the eye, the pathogenesis of glaucoma, the basics of presbyopia, the immunprivilege of the eye and the influence of prostaglandins on hair growth. These investigations were performed by the use of immuno-histochemistry, transmission and scanning electron-microscopy, cell cultures, molecular biology and physiological methods. There were close collaborations with the other projects of the Collaborative Research Center (SFB) 539 and long-term international cooperations. The particular scientific focus of Prof. Dr. F. Paulsen is on the anterior eye segment and especially deals with mechanisms of the innate immune response within the tear film, on the surface of the eye and the lacrimal apparatus and limb joints. In particular, proteins and peptides such as antimicrobial peptides, mucines and surfactant proteins are investigated. In addition, the group is working on corneal wound healing and lacrimal gland stem cells. Moreover, a few of the existing projects on the pathogenesis of glaucomas and the functional anatomy of the eye will be continued.

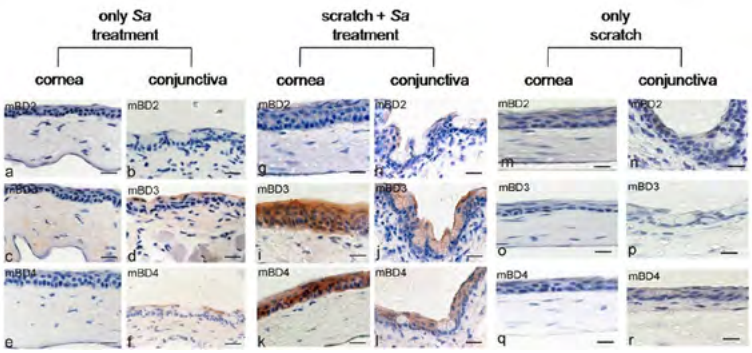
Research

Investigations in glaucoma pathogenesis
Project managers: O. Tektas, E. Lütjen-Drecoll
In collaboration with workgroups from Münster (Germany), New York City (New York) and Wisconsin (Minnesota) we currently investigate in four projects the changes in human and different animal eyes, which occur in glaucoma or experimental drug-induced or laser-induced glaucoma eyes. In a further cooperation with the workgroup of Dr. Heinz, morphological changes in the trabecular meshwork are compared to biochemical changes within the aqueous humor of young patients, which suffer from glaucoma due to juvenile idiopathic arthritis induced uveitis.

Effector T cell interactions with meningeal vascular structures in an autoimmune encephalomyelitis Lewis rat model
Project managers: C. Flügel-Koch, E. Lütjen-Drecoll
Within the central nervous system the blood brain barrier prevents the transgression of cells and most macromolecules from the blood circulation into the brain tissue by specialized vessels. Despite this seemingly absolute seclusion, central nervous system tissues are subject to immune surveillance and are vulnerable to autoimmune attacks. Using intravital two-photon imaging and morphological studies in a Lewis rat model of experimental autoimmune encephalomyelitis, the interactive processes between effector T cells and cerebral structures from their first arrival to manifest autoimmune disease have been analyzed: T cells got arrested to leptomeningeal vessels, crawled preferentially against the blood flow and at places left the luminal surface to scan the abluminal vascular surface and the underlying leptomeningeal (pial) membrane. The contact with phagocytes stimulated the effector T cells to produce pro-inflammatory mediators, triggering further tissue invasion by T cells and the formation of inflammatory infiltrations.

Mouse models for neurodegenerative changes in retina and optic nerve
Project managers: M. Scholz, F. Paulsen
In close cooperation with the Department of Ophthalmology (Prof. Jan Kremers), ERG data of DBA/2J and B6 controls were compared to corresponding IOP measurements and age dependent degenerative changes of the optic nerve in the DBA/2J model. In both strains a decrease in ERG responses with age was observed. In DBA/2J, however, this decrease was considerably higher than in B6. A significant correlation with elevated IOP values in DBA2/J was not found. *In vitro* analyses of aqueous humor components showed that osteopontin was highly increased in aged DBA/2J mice. Moreover, a significant correlation of increased OPN content in the aqueous humor and neurodegenerative changes in the optic nerve was found.

Surface structures in the eye and detection of lacrimal film disorders in the Dry Eye by dynamic light scattering
Project managers: M. Eichhorn, F. Paulsen
Dry Eye is the most common diagnosis of resident ophthalmologists and affects up to 20% of the population in Germany. Although there has been intensive progress concerning the pathogenesis, classification and the characteristics of Dry Eye in the last few years, the diagnosis in the early stages is still very difficult. The “dynamic light scattering” method allows to investigate the surface and viscosity of the tear film according to the different scattering behavior of proteins within the tear film. In addition, different polymers in the anterior eye chamber can be identified according to their dispersion behaviour. Previous findings indicate that hyaluronan could be a possible candidate, playing an important role for the transparency of the cornea and the lens. In a cooperation with the SAOT togehter with Prof. A.P. Fröba



Induction of Mouse-beta-Defensine-2, -3 und -4 (mBD2-4) within a murine "ocular surface scratch" model with and without a pre-treatment with Staphylococcus aureus (Sa). Red staining indicates a strong induction of the Mouse-beta-Defensines.

and Prof. A. Leipertz, Chair of technical thermodynamics, and the Universitätsklinikum together with Dr. C. Jakobi and Prof. Dr. F. Kruse, Director of the Department of Ophthalmology, studies on the diagnostic use of "dynamic light scattering" in the Dry Eye will be carried out, as well as investigations on the possible function of hyaluronan.

Mechanisms of epithelial defense on the surface of the eye

Project managers: F. Garreis, F. Paulsen

Cornea and conjunctiva are characterized by distinct epithelial surfaces, which are constantly in contact with bacteria, bacterial components as well as their "pathogen-associated molecules" (PAMs), but are not infected by them under normal conditions. Our research on "healthy" conjunctiva has shown that in contrast to other epithelial surfaces, different inducible anti-microbial peptides (AMPs) are constitutively expressed. The findings also show that there is a reduced expression of AMPs in cultured corneal epithelial cells under hypoxia. To understand the regulation of AMPs and the effect of PAMs on the eye surface, the influence of different PAMs as well as the influence of hypoxia and ultraviolet light on the production and on the regulation of AMPs on the eye surface will be investigated. To understand the mechanisms of peptide production and secretion, AMPs in the cellular compartment are characterized. The results will contribute to the understanding of various reactions and disorders on the surface of the eye and in addition to the general understanding of the production and regulation of AMPs.

Effect of Somatostatin on the corneal wound healing

Project managers: U. Hampel, F. Paulsen

The peptide hormone Somatostatin is produced by the lacrimal gland and is detectable in the tear film. From this finding, the question arises about the functional significance of this hormone on the surface of the eye. Currently, we clarify how Somatostatin affects the wound healing of the cornea. For that reason the activation of the signaling pathways p38 MAPK, ERK1/2 and SMAD by Somatostatin were investigated. The behavior in proliferation and migration of corneal epithelium cells after Somatostatin stimulation is tested *in vitro*. In addition, *in vivo* findings show that Somatostatin has a positive effect on corneal wound healing in a cornea defect mouse model. As it is known that Somatostatin can inhibit a neovascularization effect of the cornea after insufficient wound healing, analyzes will be done to show the effect of Somatostatin on the expression of VEGF under different conditions. The results will shed light on the role of Somatostatin in the corneal wound healing.

Teaching

In the past years, the Chair II of the Anatomical Institute has been organizing the lectures "functional anatomy" and "functional histology", the accompanying courses "anatomical demonstration" and "microscopic anatomy" as well as the "neuroanatomical seminar". With the recent appointment of Prof. Dr. F. Paulsen a more intense focus will be set on teaching functional and clinical anatomy of the musculosceletal system (bones, ligaments and joints). The present concept of lectures in microscopic anatomy will be transferred into an extended model which takes advantage of the virtual histology. This model should also be closely intertwined with the lectures in neuroanatomy. In this context, there is already a close cooperation with the Fraunhofer-Institute for integrated circuits and the Virtual University of Bavaria. All lectures and courses are attended by the students of human medicine, dentistry and molecular medicine. In addition, students of Medical Process Management will be instructed in human anatomy. Prof. Eichhorn and Prof. Dr. F. Paulsen are involved in the subject matter of the MAOT and SAOT graduate schools.

Selected Publications

Bartholomäus I, Kawakami N, Odoardi F, Schläger C, Miljkovic D, Ellwart JW, Klinkert WE, Flügel-Koch C, Issekutz TB, Wekerle H, Flügel A (2009) Effector T cell interactions with meningeal vascular structures in nascent autoimmune CNS lesions. Nature, 462: 94-8

Harazny J, Scholz M, Buder T, Lausen B, Kremers J (2009) Electrophysiological deficits in the retina of the DBA/2J mouse. Doc Ophthalmol, 119: 181-97

Birke MT, Neumann C, Birke K, Kremers J, Scholz M (2010) Changes of osteopontin in the aqueous humor of the DBA2/J glaucoma model correlated with optic nerve and RGC degenerations. Invest Ophthalmol Vis Sci, 51: 5759-67

Garreis F, Schlorf T, Worlitzsch D, Steven P, Bräuer L, Jäger K, Paulsen FP (2010) Roles of human beta-defensins in innate immune defense at the ocular surface: arming and alarming corneal and conjunctival epithelial cells. Histochem Cell Biol, 134: 59-73

Paulsen FP, Eichhorn M, Bräuer L (2010) Virtual microscopy-The future of teaching histology in the medical curriculum? Ann Anat, 192: 378-82

Tektas OY, Lütjen-Drecoll E, Scholz M (2010) Qualitative and quantitative morphologic changes in the vasculature and extracellular matrix of the prelaminar optic nerve head in eyes with POAG. Invest Ophthalmol Vis Sci, 51: 5083-91

International Cooperation

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Paul Kaufman, Madison, WI, USA

Monica Berry, Bristol, UK

Robert Sack, New York, NY, USA

Yolanda Diebold, Valladolid, Spain

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Research Focus

- Receptors and receptor associated diseases of the nervous system
- Structure and function of synaptic signaling complexes in the central nervous system
- Mass spectrometry: Analysis of molecular heterogeneities
- Bioinformatics of biomolecular interactions

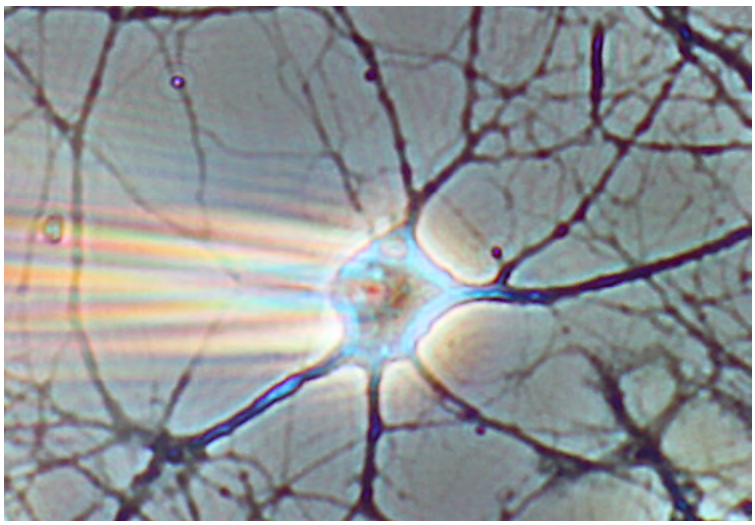
Structure of the Department

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 Medical Faculty and the Institute of Pharmaceutical Chemistry of the Science Faculty.
The Chair has a total of 40 employees (half of them funded by grants), including 17 scientists, 19 postgraduate students and 10 technicians.

Research

Receptors and receptor associated diseases of the nervous system
Project managers: C.-M. Becker, C. Kluck, C. Villmann, N. Vogel, V. Eulenburg
Glycine is the most important inhibitory neurotransmitter in the human spinal cord and brain stem. Upon binding of glycine to the postsynaptically localized glycine receptor (GlyR, a member of the Cys-Loop receptor superfamily), an intrinsic chloride channel opens, eventually causing neuronal inhibiton. Mutations within the human GlyR-gene are associated with neuromotor-disorders, such as hyperekplexia, leading to enhanced startle reactions and episodic muscle stiffness. The GlyR is a pentameric ion channel comprising 2 alpha- and 3 beta-subunits. Every subunit encloses a large extracellular ligand binding domain (LBD) followed by four transmembrane domains each conntected to its neighbor via loops. Our group is especially interested in investigating the pathomechanisms of GlyR channelopathies as well as in identifying structurally important domains and their functional interactions. *In vitro* studies combined with MALDI-TOF mass spectrometry revealed the existence of a GlyR-specific disulfide bond in addition to the superfamily-specific bond within the LBD. This disulfide bond has been shown to be crucial for protein maturation. Mutation of one of the bond-forming cysteine residues lead to intracellular retention and loss of function of the GlyR.
Human hyperekplexia is being inherited either dominantly or recessively with incomplete penetrance. The dominant mutations found within the ion channel pore and adjacent loops directly influence channel function whereas recessive mutants display altered biogenesis and impaired stability. Known recessive mutations within the first transmembrane domain reduce channel activity caused by impaired surface expression of the receptor. Mutations affecting important intracellularly localized arginine residues lead to endoplasmatic retention and accelerated proteasomal degradation of the receptor. Murine models carrying mutations within the GlyR display a similar phenotype compared to humans. The oscillator mouse lacks functional GlyRs due to a microdeletion leading to truncation of the protein. By means of *in vitro* complementation studies, we recently succeeded in restoring receptor function. Thereby we identified an intracellularly localized basic motif playing an important role for surface expression and functionality of the GlyR. The multi-functionality of this basic domain becomes manifest by also influencing subunit-specific cellular receptor trafficking as well as by being part of a nuclear localization signal.
Neurotransmission with high temporal and spatial resolution requires a fast termination of signal transmission. At glycinergic synapses, this is achieved by the reuptake of the neurotransmitter glycine into the nerve terminal or the surrounding glial cells by the high affinity transporters GlyT1 and GlyT2. Using advanced genetic approaches combined with biochemical and behavioural analysis we could show that *in vivo* GlyT1 that is expressed by neurons and glial cells respectively has different functions depending on the cell-type expressing the transporter. Inactivation of GlyT1 expression in glial cells resulted in a severe hypotonic movement disorder, whereas loss of neuronal GlyT1 expression resulted in impairment of higher brain functions like learning and memory. These results enhance our understanding how these transporters influence synaptic transmission.

Structure and function of synaptic signaling complexes in the central nervous system
Project managers: R. Enz, 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 app. 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.



Patch-clamp technique on hippocampal neurons

Mass spectrometry: Analysis of molecular heterogeneities

Project managers: A. Seebahn, N. Vogel, W. Xiang

MALDI-TOF MS (matrix-assisted laser desorption/ionization time-of-flight mass spectrometry) allows for the determination of molecular masses of virtually any biopolymer. Genetic polymorphisms influence the individual susceptibility to certain diseases and therefore can serve as markers for disease-associated loci. We develop methods for the MALDI-TOF MS-based diagnosis of molecular heteogeneities for hyperekplexia, mitochondrial myoencephalopathies and other diseases. The application of MS to a mixture of two nucleic acid species discerned by a single nucleotide exchange permits us to quantify the relative proportion. We also focus on the characterization of post-translational modifications of proteins using MALDI-TOF MS as well as electrospray-ionization (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 ESI-MS/MS. In oxidative stress, elevated levels of free radicals can be observed, eventually leading to increased modification of amino acids. These can be efficiently monitored using MS and are analyzed for example in hemoglobin and alpha-synuclein. Neurodegenerative diseases also change the cell membrane lipid composition as evident from lipid profile analysis using MALDI-TOF MS and ESI-MS/MS performed by our group. Furthermore, our group investigates neuronal cell death using the snake venom beta-Bungarotoxin in neuronal cell culture experiments.

Bioinformatics of biomolecular interactions

Project manager: H. Sticht

Protein-protein interactions play a crucial role for the transduction of information in biological signaling pathways. The computational identification of the underlying principles 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.

Molecular dynamics simulations are used to study the dynamics of viral proteins (e.g. HIV protease) and the conformational transitions of human proteins (e.g. Alzheimer Abeta-Amyloid). 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 interaction motifs in pathogenic proteins.

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 modules of neuroscience and molecular pathomechanisms. The professorship of bioinformatics teaches in the course program of molecular medicine and computer sciences.

Selected Publications

Villmann C, Oertel J, Ma-Högemeier ZL, Hollmann M, Sprengel R, Becker K, Breitinger HG, Becker CM (2009) Functional complementation of Glra1(spd-ot), a glycine receptor subunit mutant, by independently expressed C-terminal domains. J Neurosci, 29: 2440-52

Vogel N, Kluck CJ, Melzer N, Schwarzinger S, Breitinger U, Seeber S, Becker CM (2009) Mapping of disulfide bonds within the amino-terminal extracellular domain of the inhibitory glycine receptor. J Biol Chem, 284: 36128-36

Eulenburg V, Retiounskaia M, Papadopoulos T, Gomeza J, Betz H (2010) Glial glycine transporter 1 function is essential for early postnatal survival but dispensable in adult mice. Glia, 58: 1066-73

Horn AH, Sticht H (2010) Amyloid-beta42 oligomer structures from fibrils: a systematic molecular dynamics study. J Phys Chem B, 114(6): 2219-26

Löhmann C, Schachmann E, Dandekar T, Villmann C, Becker CM (2010) Developmental profiling by mass spectrometry of phosphocholine containing phospholipids in the rat nervous system reveals temporo-spatial gradients. J Neurochem, 114: 1119-34

Urbanczyk A, Jünemann A, Enz R (2010) PKC-ζ-interacting protein ZIP3 is generated by intronic polyadenylation, and is expressed in the brain and retina of the rat. Biochem J, 433: 43-50

International Cooperation

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Research Equipment

Bruker Daltonik Autoflex 1 MALDI-TOF MS

Bruker Daltonik Esquire 6000 ESI-IT 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
- beta-Thymosins, Substrates of Transglutaminases during Blood Coagulation, Angiogenesis, Wound Healing, and Apoptosis

Structure of the Department

The Chair of Biochemistry and Pathobiochemistry and the Chair of Biochemistry and Molecular Medicine constitute the Institute of Biochemistry. They are furthermore part of the Emil-Fischer-Center which in addition harbours 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 beta-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: 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: 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: 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.

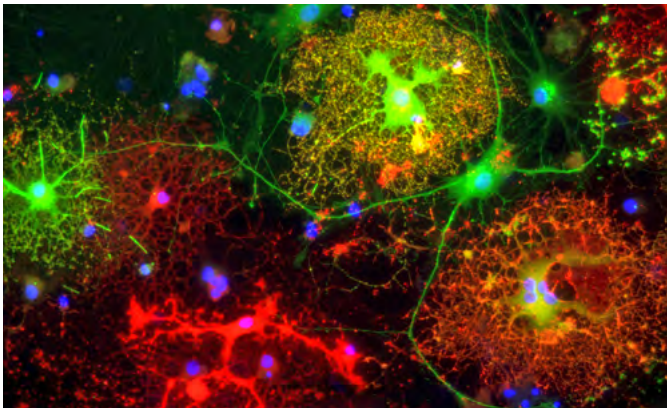
In the central nervous system, Sox9 and Sox10 regulate several steps in gliogenesis. Sox9 is responsible for the specification of neural stem cells into oligodendrocytes, whereas Sox10 guides terminal differentiation and myelination in oligodendrocytes as a direct activator of myelin genes. During the 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.

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: 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 10 candidates, Erbin and CK2 as binding partners of MuSK. Protein kinase CK2 furthermore bound MuSK via its beta subunit, phosphorylates MuSK and thereby regulates the stability of acetylcholine (AChR) clusters. Muscle-specific CK2beta-deficient mice are myasthenic. To identify the cause for the destabilization of AChR aggregates in CK2beta-deficient muscles, their phenotype is compared with the one of CK2alpha/CK2alpha'-deficient muscles. Behavioural tests and electrophysiological studies



Immuncytochemical staining of differentiating glial cells in culture

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

GCM proteins as switches in organ development

Project manager: 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.

beta-Thymosins, Substrates of Transglutaminases during Blood Coagulation, Angiogenesis, Wound Healing, and Apoptosis

Project manager: E. Hannappel

Thymosins were originally isolated from thymus, but do not represent thymic hormones. Thymosin beta-4 is now regarded as the main intracellular G-actin sequestering peptide in most mammalian cells. Domains of thymosin beta-4 were identified which are important for the interaction with G- and F-actin. Apart from this intracellular function of thymosin beta-4, this peptide seems to be a player in wound healing and inflammation. Beta-thymosins are substrates of transglutaminases. Glutaminyl residues of beta-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 beta-4. During aggregation of blood platelets, thymosin beta-4 is cross-linked by factor XIIIa to the fibrin clot. This research thus also provides insight on how small, soluble peptides can be fixed to extracellular structures by transglutaminases to promote further physiological effects.

beta-Thymosins can be labeled by fluorescent derivatives of cadaverine. The fluorescent beta-thymosins are comparable to the natural beta-thymosins with respect to their G-actin sequestering ability. Therefore, these fluorescent peptides are novel tools to study the interaction of beta-thymosins with other proteins as well as their intracellular distribution in living cells. Surprisingly, thymosin beta-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 beta-4 was expected to freely diffuse through the nuclear pore complex into the nucleus. However, when thymosin beta-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 beta-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 jointly 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

Stolt CC, Schlierf A, Lommes P, Hillgärtner S, Werner T, Kosian T, Sock E, Kessaris N, Richardson WD, Lefebvre V, Wegner M (2006) SoxD proteins influence multiple stages of oligodendrocyte development and modulate SoxE protein function. Dev Cell, 11: 697-709

Batista-Brito R, Rossignol E, Hjerling-Leffler J, Denaxa M, Wegner M, Lefebvre V, Pachnis V, Fishell G (2009) The cell-intrinsic requirement of Sox6 for cortical interneuron development. Neuron, 63: 466-81

Bhattaram P, Penzo-Méndez A, Sock E, Colmenares C, Kaneko KJ, Vassilev A, Depamphilis ML, Wegner M, Lefebvre V (2010) Organogenesis relies on SoxC transcription factors for the survival of neural and mesenchymal progenitors. Nat Commun, 1: 9

Finzsch M, Schreiner S, Kichko T, Reeh P, Tamm ER, Bösl MR, Meijer D, Wegner M (2010) Sox10 is required for Schwann cell identity and progression beyond the immature Schwann cell stage. J Cell Biol, 189: 701-12

Potzner MR, Tsarovina K, Binder E, Penzo-Méndez A, Lefebvre V, Rohrer H, Wegner M, Sock E (2010) Sequential requirement of Sox4 and Sox11 during development of the sympathetic nervous system. Development, 137: 775-84

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

International Cooperation

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Research Focus

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

Structure of the Department

The institute comprises one chair and two professorships for physiology with their work groups, two further groups are associated with an Academic Directorate and a professor emeritus. In addition, the institute houses collaborating work groups of the Nephrological, Anesthesiological, and Neurological Hospitals, guest researchers of the Medical Hospital as well as from Romania, the Czech Republic, Hungary and the US.
Altogether 86 persons work in the institute, 15 of them funded by grants. The research is done by 21 PhD/MD scientists, 41 doctoral students and 19 technical assistants.
The institute has successfully integrated new work groups that study synapses and ion channels of central nervous neurons using electrophysiological and histochemical means and bringing new biophysical and molecular biological expertise. Many common interests and technical-methodical synergies are arising with the established groups that are focusing on pain physiology and predominantly work on primary and secondary sensory neurons. Their research spectrum covers cellular and molecular biological questions and extends over behavioral physiology towards microneurography, functional imaging, and psychophysics in healthy humans and chronic pain patients.

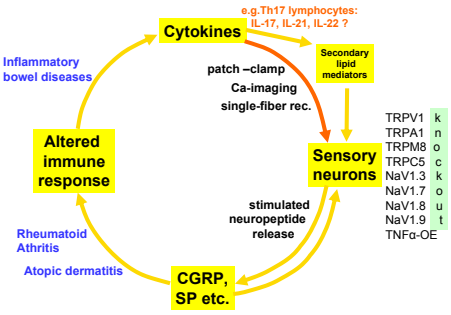
Research

Properties of peripheral human C-fibers
Project manager: 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 is on properties of nociceptors and mechanisms which contribute to genesis of pain, in particular neuropathic pain. The methods include non-invasive techniques like assessment of Axon reflexes and psychophysical studies as well as microneurography. Microneurography examines single action potentials of C-fibers and their discharge patterns in awake humans. The main research topics are:
1) Acquisition of data samples of physiological properties of nociceptors in aging healthy subjects to understand the causes of a higher prevalence of pain in ageing humans.
2) Development of a technique to diagnose small fiber neuropathy objectively and non-invasively with the help of axon reflexes. The new technique was validated by correlation with nerve fiber density in skin biopsies.
3) Evaluation of the possibility to translate the results obtained in the pig to human nociceptors.
4) Microneurographic assessment of C-fiber properties in patients with painful and painless neuropathies and in patients with genetic mutations which cause pain.

Functional imaging of brain activity by fMRI
Project manager: 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. Our group uses this method to identify brain regions involved in the central processing of pain and itch. Here we also focused on areas of the brainstem. 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 together with the clinics of Psychiatry and Psychotherapy analyze the central changes induced by psychogenic or emotional stress, or by addiction.

Neurophysiologic principles of higher brain functions / Biophysics and function of voltage-dependent ion channels
Project manager: 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 basic neural processes which are essential for cognitive functions and affective behavior and the impairment of which might cause neuropsychiatric disorders. In particular, we are studying the following topics:
1) Role of muscarinic acetylcholine receptor subtypes in synaptic plasticity, learning and memory.
2) Role of activin, a member of the Transforming Growth Factor β superfamily, as a "master molecule" tuning glutamatergic and GABAergic neurotransmission and its impact on cognition, emotions and neuroprotection.
3) Interaction between BACE1, a crucial enzyme in the amyloid cascade of Alzheimer's disease, and properties and expression of Na^+ and K^+ channels.

Transduction, integration, plasticity in primary nociceptive neurons
Project manager: P.W. Reeh
Research on primary nociceptive neurons, their electrophysiological and neurochemical responses to noxious 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. The aim is to elucidate nociceptive transduction and integration of stimuli as well as possible pharmacological interventions. A specific topic is sensitization by tissue acidosis and inflammatory mediators as well as their intracellular signal transduction. Transgenic mouse strains lacking different metabotropic and ionotropic receptors or thermally activated ion channels (TRPV1) are studied. Voltage-controlled ion channels (NaV, 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.



A possible vicious cycle of neuroimmune interactions that may participate in chronic inflammatory diseases.

Trigeminal nociception and headache generation

Project manager: K. Messlinger

Our group is working on nociceptive processes in the rat cranial dura mater, the trigeminal ganglion and the spinal trigeminal nucleus as neurobiological basis for the generation of headaches. Neuronal tracing is employed to follow the course of nerve fibers from the trigeminal ganglion to the cranial dura mater, extracranial structures and the central nervous system. Extracellular recordings from single afferent fibres in the isolated rat dura mater are made to study their sensitivity and response properties to mechanical, thermal and chemical stimulation with substances like prostaglandins, serotonin or histamin, which are assumed to be involved in the generation of headaches in humans. In a similar tissue preparation we examine by which mechanisms neuropeptides and prostaglandin are released from the cranial dura mater. Using immunohistochemical and molecular biological methods, we work on detecting the intracellular signal mechanisms that are induced by these substances. In collaboration with the Clinic of Neurosurgery and the Institute of Neuropathology we also use these techniques to examine the mechanisms that underlie headaches caused by meningiomas. To study the central processes of headache generation, we examine the response properties of neurons in the spinal trigeminal nucleus and the effects of potential headache therapeutics like CGRP receptor antagonists.

Teaching

In the context of theoretical education for students of medicine and dentistry as well as to Bachelor and Master students of Molecular Medicine the institute teaches neurophysiology. Beside the classical teaching methods, which are lectures, practical courses and seminars, also internet based seminars are provided. Half of the practical courses are given as a course block which has been positively rated by the students. This positive rating is further supported by the modernization of the experimental setups which was funded by the students' fees. Colleagues from the clinics are regularly invited to complement actual topics from a clinical point of view which they often do with the presentation of a patient.

Furthermore, interdisciplinary lectures are given for students of natural and technical sciences and for students of psychology who selected medicine as a subsidiary subject or a main focus. For them, not only neurophysiology but all topics of physiology are given. Special lectures and practicals are also provided to students of Pharmaceutical Chemistry.

Selected Publications

Namer B, Barta B, Ørstavik K, Schmidt R, Carr R, Schmelz M, Handwerker HO (2009) Microneurographic assessment of C-fibre function in aged healthy subjects. J Physiol, 587: 419-28

Sixt ML, Messlinger K, Fischer MJ (2009) Calcitonin gene-related peptide receptor antagonist olcegepant acts in the spinal trigeminal nucleus. Brain, 132: 3134-41

Zheng F, Adelsberger H, Müller MR, Fritschy JM, Werner S, Alzheimer C (2009) Activin tunes GABAergic neurotransmission and modulates anxiety-like behavior. Mol Psychiatry, 14: 332-46

Zimmermann K, Hein A, Hager U, Kaczmarek JS, Turnquist BP, Clapham DE, Reeh PW (2009) Phenotyping sensory nerve endings in vitro in the mouse. Nat Protoc, 4: 174-96

Fuchs D, Birklein F, Reeh PW, Sauer SK (2010) Sensitized peripheral nociception in experimental diabetes of the rat. Pain, 151: 496-505

Weigelt A, Terekhin P, Kemppainen P, Dörfler A, Forster C (2010) The representation of experimental tooth pain from upper and lower jaws in the human trigeminal pathway. Pain, 149: 529-38

International Cooperation

J. Olesen, Glostrup Hospital, Copenhagen, Denmark

P. Kemppainen, Institute of Dentistry, University of Turku, Turku, Finland

G. Pethö, University of Pécs, Pécs, Hungary

L. Negri, University of Rome la Sapienza, Rome, Italy

J. Sato, RIEM, Nagoya University, Nagoya, Japan

N. Suzuki, Department of Neurology, Keio University, Tokyo, Japan

Y. Suzuki, Aichi University, Nagoya, Japan

A. Ikoma, Department of Dermatology, University Hospital, Kyoto, Japan

E. Jørum, Department of Clinical Neurophysiology, University of Oslo, Oslo, Norway

A. Babes, University of Bucharest, Bucharest, Romania

C. Belmonte, Department of Neuroscience, Miguel Hernández University of Elche, Alicante, Spain

S. Werner, Institute of Cell Biology, ETH Zurich, Zurich, Switzerland

P. McNaughton, University of Cambridge, Cambridge, UK

J. N. Wood, University College London, London, UK

G. Kobal, Altria Client Services, Richmond, VA, USA

C. Woolf, Harvard University, Boston, MA, USA

M. Ringkamp, Department of Neurosurgery, Johns Hopkins Hospital, Baltimore, MD, USA

R.H. LaMotte, Department of Anesthesiology, Yale University, New Haven, CT, USA

H. van Brederode, University of Washington, Seattle, WA, USA

Institute of Cellular and Molecular Physiology

Chair of Physiology (Vegetative Physiology)

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Research Focus
- Renal epithelial ion channels
- Cardiac ion channels

Structure of the Department

The Department of Cellular and Molecular Physiology (Chair of Systems Physiology) is housed in a teaching and research building in a central location 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 department 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 department is headed by the Chair of the department, Prof. Dr. med. Christoph Korbmacher, the additional cardiac physiology research group is headed by an Associate Professor, Prof. Dr. med. Tilmann Volk.
The research focus of the Department 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. This research focus fits very well into the broader context of research activities in Erlangen known to have a strong renal and cardiovascular research focus as evidenced e.g. by the DFG funded centre research grant SFB 423 entitled 'Kidney pathology: Pathogenesis and regenerative mechanisms'.
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, sorting, 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: C. Korbmacher
In the kidney and in other epithelial organs 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 can 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 loosing 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 above 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, the 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 of Prof. Korbmacher investigates the molecular 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 of Prof. Korbmacher 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, they investigate 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.
The research projects are funded by grants from the German Research Foundation (DFG) in the context of the center research grant SFB423 ('Kidney pathology: Pathogenesis and regenerative mechanisms') and from the IZKF (Interdisciplinary Center for Clinical Research).

Cardiac ion channels

Project manager: T. Volk
The key interest of Prof. Volk's 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, al-

though 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.
In order to understand the mechanisms underlying this region-specific effect of cardiac hypertrophy, Prof. Volk's group investigate 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 repolarisation 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 repolarisation, 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 repolarisation and hence prevent the development of malignant arrhythmia.

Teaching

The Chair of Physiology (Department of Physiology and Pathophysiology) and the Chair of Systems Physiology (Department 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 Department 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 department 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 plenary lectures which are supplemented by interactive small group seminars. These seminars reinforce the topics of the plenary lecture and emphasize relevant clinical aspects. In practical classes, theoretical concepts are illustrated by experiments and the students have the opportunity to acquire practical skills. The practical course covers 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. These exams are routinely evaluated and conform to quality criteria recommended for medical exams, e.g. by the 'Kompetenzzentrum für Prüfungen in der Medizin – Baden-Württemberg'.

Selected Publications

Haerteis S, Krueger B, Korbmacher C, Rauh R (2009) The δ-subunit of the epithelial sodium channel (ENaC) enhances channel activity and alters proteolytic ENaC activation. J Biol Chem, 284: 29024-40

Loffing J, Korbmacher C (2009) Regulated sodium transport in the renal connecting tubule (CNT) via the epithelial sodium channel (ENaC). Pflügers Arch, 458: 111-35

Svenningsen P, Bistrup C, Friis UG, Bertog M, Haerteis S, Krueger B, Stubbe J, Jensen ON, Thiesson HC, Uhrenholt TR, Jespersen B, Jensen BL, Korbmacher C, Skøtt O (2009) Plasmin in nephrotic urine activates the epithelial sodium channel. J Am Soc Nephrol, 20: 299-310

Rauh R, Diakov A, Tzschoppe A, Korbmacher J, Azad AK, Cuppens H, Cassiman JJ, Dötsch J, Sticht H, Korbmacher C (2010) A mutation of the epithelial sodium channel associated with atypical cystic fibrosis increases channel open probability and reduces Na^+ self inhibition. J Physiol, 588: 1211-25

Wagner M, Riepe KG, Eberhardt E, Volk T (2010) Open channel block of the fast transient outward K^+ current by primaquine and chloroquine in rat left ventricular cardiomyocytes. Eur J Pharmacol, 647: 13-20

Wagner M, Rudakova E, Schütz V, Frank M, Ehmke H, Volk T (2010) Larger transient outward K^+ current and shorter action potential duration in $G_{\alpha 11}$ mutant mice. Pflugers Arch, 459: 607-18

International Cooperation

Prof. Nigel Bunnett, Center for the Neurobiology of Digestive Diseases, UCSF, San Francisco, USA

Prof. Jean-Jacques Cassiman & Prof. Harry Cuppens, Center of Human Genetics, Katholieke Universiteit (KU) Leuven, Belgium

Prof. David I. Cook Department of Physiology, University of Sydney, New South Wales, Australia

Prof. Mike Edwardson, Department of Pharmacology, University of Cambridge, Cambridge, UK

Prof. Johannes Loffing, Anatomisches Institut, Universität Zürich, Schweiz

Prof. Bernard C. Rossier & Prof. Edith Hummler, Department of Pharmacology & Toxicology, University of Lausanne, Switzerland

Prof. Ole Skøtt, Physiology and Pharmacology, Institute of Medical Biology, University of Southern Denmark, Odense, Denmark

Prof. Jacques Teulon, Centre de Recherche Biomédicales de Cordeliers, Université Pierre et Marie Curie (Paris 6), Paris, France

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
- Dermatotoxicology
- Molecular markers of exposure to hazardous substances
- 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. The Institute employs 38 employees (16 of them financed by third-party funds). Research is carried out by 11 PhD scientist, 5 PhD students and 11 technical assistants.
Different work groups develop molecular markers of exposure to hazardous substances as well as procedures to quantify skin penetration of hazardous substances and to standardize diagnostical premedical findings. Furthermore, the Institute examines work-related exposure of employees and the exposure of the general population.
The department of the university's medical officers belongs to the Institute. It carries out the preventive medical checkups of all the university's employees and the students. It also gives advice to the head of the university and the university hospitals regarding occupational health protection and offers actions 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 German Research Foundation (DFG). The Institute also 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 international quality assessment schemes.

Research

Work related health research
Within field studies, taking into account the workplace conditions, it is aimed for the detection of physiological and pathophysiological changes before manifest diseases appear. Diseases as a response to an exposure in workplaces of the last decades are still a scientific field of activity of clinical occupational medicine. For example, substantial social-medical problems can result from asbestos-induced malignoms of the respiratory tract system. Current questions always arise when new technologies or working materials are introduced. Exemplarily, new welding techniques used in the aluminium processing industry, or the replacement of classical solvents with alternative solvents with a higher risk of skin irritation of the exposed employees are named. Furthermore, allergically mediated diseases at the workplace, even with clearly improved hygienic conditions, are still a problem. Therefore, the assessment of exposure and effect of toxic, mutagenous and sensitizing working materials in Germany and abroad is an important topic for the Institute. Many field studies qualitatively assess the uptake which can be absorbed percutaneously by taking into account the workplace conditions. These studies are often fostered by the 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 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, plasticizers in pharmaceuticals or toys, aromatic amines in fabric. These studies are often fostered by local authorities, the Bavarian State Ministry of the Environment and Public Health and the German Federal Environment Agency.

Dermatotoxicology
At the Institute different research projects deal with procedures to determine dermal penetration of chemicals and to standardize preclinical skin damages.
All the scientific projects focusing on skin penetration examine influence factors to dermal penetration by using *in vitro* models (static diffusion chamber, microdialysis on freshly excised human skin) and *in vivo* models (microdialysis of volunteers). These projects are substantially promoted by the DFG and the employer's liability insurance associations. Furthermore, scientists of the Institute participate in the evaluation of skin penetration for the establishment of occupational medical threshold limit 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 can penetrate via skin. The DFG work group is responsible for labeling chemical substances with a skin designation in Germany.
Additionally, procedures to early diagnose preclinical skin damages and irritations like the Erlanger Haut-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 (dose monitoring), for the disposition for hazardous substances in the metabolism (susceptibility monitoring) and the effects of hazardous substances (biological effect monitoring). The research is mainly promoted by the DFG. 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 specificity, sensitivity and toxicokinetic behaviour of the different parameters.
An important prerequisite for sensitive and specific biomonitoring is the use of very sensitive and molecular-structural distinguishing analyzing techniques. The Institute therefore possesses very good technical equipment which is modernized on a regular basis. Gas chromato-

graphic techniques as well as high performance liquid chromatographic systems belong to the equipment which are particularly connected to one-dimensional and multi-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).

Quality assurance of Biomonitoring methods

On behalf of the German Association for Occupational and Environmental Medicine (DGAUM), the Institute currently organizes worldwide external quality assessment schemes for the evaluation of occupational and environmental biomarkers. The 46th round robin test of G-EQUAS was finished within the report period. At the moment G-EQUAS comprises 123 analysis parameters; worldwide 150 to 200 laboratories take part in G-EQUAS every six months, 2/3 of them are international.

Quality assurance of health promoting actions

This research area develops concepts to examine the effectivity and sustainability of health promotion in companies and uses them in practice. The network "Erlangen model of workplace health promotion" aims at initiating a sustainable culture in the enterprises. Health promotional behaviour is to be brought not only temporarily limited into companies and should, after an initiation phase, be preserved in the entire enterprise. Carriers of the current network are public health authorities, the city of Erlangen, the Siemens health insurance, as well as different clubs and associations. Participating companies are divisions of large-scale companies, as well as small and medium-sized companies of the region. The Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine and the Interdisciplinary Institute for Philosophy and History of Science evaluate the network. Task of the evaluation is to verify the goals of the initiative on its consistency and feasibility and to judge the assigned means for the objectives fitness and efficiency, as well as the whole network for its sustainability. The evaluation results are communicated regularly to the carriers and participants of the network and continuously serve as a quality control and further project optimization.

Specimen collector for recording skin exposure in practice

Teaching

Professor Drexler has been the Dean of Students in the clinical phase since 2006. The lessons in the Occupational-, Social- and Environmental Medicine (lectures, practical courses and E-learning) are carried out according to the statutes of the medical act.

Selected Publications

Kütting B, Göen T, Schwegler U, Fromme H, Uter W, Angerer J, Drexler H (2009) Monoarylamines in the general population--a cross-sectional population-based study including 1004 Bavarian subjects. Int J Hyg Environ Health, 212: 298-309

Kütting B, Schettgen T, Schwegler U, Fromme H, Uter W, Angerer J, Drexler H (2009) Acrylamide as environmental noxious agent: a health risk assessment for the general population based on the internal acrylamide burden. Int J Hyg Environ Health, 212: 470-80

Kütting B, Weistenhöfer W, Baumeister T, Uter W, Drexler H (2009) Current acceptance and implementation of preventive strategies for occupational hand eczema in 1355 metalworkers in Germany. Br J Dermatol, 161: 390-6

Baumeister T, Weistenhöfer W, Drexler H, Kötting B (2010) Spoilt for choice--evaluation of two different scoring systems for early hand eczema in teledermatological examinations. Contact Dermatitis, 62: 241-7

Eckert E, Drexler H, Göen T (2010) Determination of six hydroxyalkyl mercapturic acids in human urine using hydrophilic interaction liquid chromatography with tandem mass spectrometry (HILIC-ESI-MS/MS). J Chromatogr B Analyt Technol Biomed Life Sci, 878: 2506-14

Kütting B, Baumeister T, Weistenhöfer W, Pfahlberg A, Uter W, Drexler H (2010) Effectiveness of skin protection measures in prevention of occupational hand eczema: results of a prospective randomized controlled trial over a follow-up period of 1 year. Br J Dermatol, 162: 362-70

International Cooperation

Alain LeBlanc, Institut National de Santé Publique du Québec, INSPQ, Centre de Toxicologie, Québec, Canada

Nadine Fréry, Environmental Health Department, Institut de Veille Sanitaire, St. Maurice, France

Tamar Berman, Department of Environmental Health, Israel Ministry of Health, Jerusalem, Israel

John Cocker, Health and Safety Laboratory (HSL), Buxton, UK

Patrick J. Parsons, Department of Health (DOH), State of New York, Albany, NY, USA

Research Equipment

Sciex API 2000 LC-MS/MS-System

Agilent GC-MS/MS System 7000

Agilent ICP-MS System 7500 cx

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Research Focus

- Molecular characterization of drug transporters
- Expression and function of uptake transporters in the gastrointestinal tract
- Pharmacogenomics
- Molecular and clinical characterization of therapeutic targets in the L-arginine-NO-nitrate pathway
- 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-Professorship of 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. A. Ludwig) and the Chair of Clinical Pharmacology and Clinical Toxicology (Prof. M. Fromm) on a two-year basis.
32 persons are working at the Chair with 13 of them being funded by extramural sources. In July 2008 a Professor of Clinical Pharmacology (W2) was appointed. 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 Universitätsklinikum Erlangen and for external physicians.
The following topics, which are funded e.g. by the German Research Council (DFG), the German Cancer Aid, the German Federal Ministry of Health (BMG) and the German Federal Ministry of Education and Research (BMBF), are in the focus of our studies: uptake and efflux transporters for drugs, genetic determinants of drug effects (pharmacogenomics), drug metabolism, drug uptake in tumors, cardiovascular pharmacology and risk factors, alterations of the L-arginine-NO-metabolism, safety in drug therapy.

Research

Molecular characterization of drug transporters

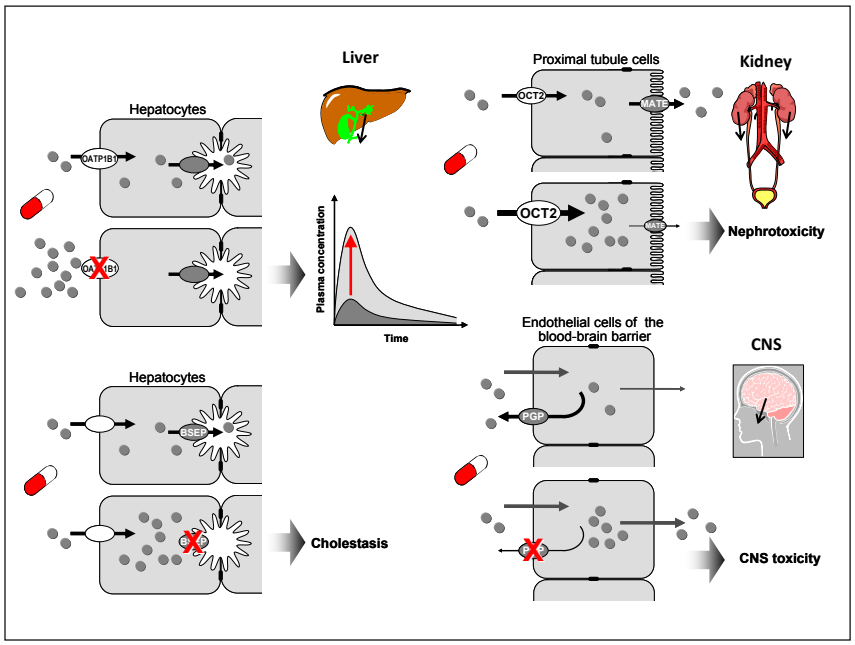
Project managers: J. König, M.F. Fromm
Transport proteins located in distinct plasma membrane domains are important for the uptake, the distribution and the final excretion of drugs and drug metabolites. Therefore, modulation of transport function may result in adverse drug reactions (ADR). Two molecular mechanisms can account for such modulations of transport function. On the one hand, variations in transporter genes (polymorphisms) may result in mutated transport proteins with altered transport kinetics. Secondly, one drug can influence the transport kinetics of a second coadministered drug if both are substrates for one transport protein (transporter-dependent drug-drug interactions). The molecular characterizations of both processes together with expression studies are in the focus of our studies, which are funded by the DFG and the German Cancer Aid.
In cooperation with the Clinic of Gynecology and Obstetrics and the Institute of Pathology of the Universitätsklinikum Erlangen we analyzed the expression and localization of uptake transporters of the OATP family (organic anion transporting polypeptides) in normal breast tissue and breast cancer tissue. In normal breast tissue, OATP3A1 and OATP5A1 localized to the plasma membrane of epithelial cells of the lactiferous ducts whereas in breast cancer tissue these transporters are highly expressed in the plasma membrane as well as intracellularly. Since hormones and hormone metabolites are substrates of OATPs and since it has been shown that hormones may promote tumor growth, these findings may be relevant for studies on tumor progression as well as for cancer treatment using anticancer agents which are substrates for these uptake transporters.
The functional consequences of genetic variations have been studied in cooperation with the University of Paris. It was shown that the variant OATP1B1*5 shows reduced transport of metabolites of the immunosuppressant mycophenolic acid and that mycophenolic acid tolerance is influenced in renal transplant recipients by this polymorphism.

Expression and function of uptake transporters in the gastrointestinal tract

Project manager: H. Gläser
The knowledge about the clinical relevance of OATP uptake transporters for drug absorption, physiology and pathophysiology in the human gastrointestinal tract is still limited. With the performed studies, which are funded by the DFG, it was shown that the prostaglandin transporter OATP2A1 is localized in parietal cells of human gastric mucosa. Interestingly, the function of OATP2A1, which specifically transports prostaglandins, can be modified by NSAIDs. Some of these drugs are able to inhibit the function of OATP2A1, whereas others lead to a stimulation of OATP2A1 transport activity. Such functional modifications may contribute to NSAID-induced side effects such as ulceration or bleeding in the human gastric mucosa. Currently, we are investigating the influence of OATP2A1 on the local prostaglandin effects in human gastric mucosa.
In further *in vitro* studies a possible relevance of the drug uptake transporters OATP1A2 and OATP2B1, which are expressed in human intestine, for drug-drug interactions was investigated. It was demonstrated that the OATP1A2- and OATP2B1-mediated cellular uptake of fexofenadine (antihistaminic drug) and atorvastatin (HMG-CoA reductase inhibitor) is inhibited by naturally occurring flavonoids such as apigenin, kaempferol and quercetin. Considering the broad abundance of flavonoids in herbal drugs and food, inhibition of OATP1A2 and OATP2B1 may be a relevant mechanism for drug-drug and/or food-drug interactions.

Pharmacogenomics

Project managers: O. Zolk, M.F. Fromm
Frequently marked differences in treatment effects between individual patients are observed leading to treatment failure or enhanced toxicity. In this project variations in genes involved in drug transport or metabolism that give rise to differing response to drugs are investigated. A collaborative project with the Heart Cen-



Schematic illustration of major mechanisms underlying adverse drug reactions due to alterations of drug transport. Grey circles: drug molecules, ovals: drug transporters

ter Bad Krozingen focuses on the association of polymorphisms in drug metabolizing enzymes (CYP2C19) with the inhibitory effect of the frequently used drug clopidogrel on platelet aggregation. Moreover, the impact of polymorphisms in drug transporter genes for the pharmacokinetics of the oral antidiabetic drug metformin was investigated. Another clinical study focused on the impact of gender and differences in genes involved in transport and metabolism of drugs on the pharmacokinetics of the diuretic torasemide.

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

Project manager: R. Maas

A major focus of the group is the experimental and clinical characterization of new cardiovascular risk factors as potential targets for therapeutic intervention. Presently we study the regulation of the L-arginine-NO-nitrate pathway by endogenously formed compounds such as 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 Medizinische Klinik 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. Complementing studies are conducted in cooperation with the partners at the Institute of Bio-Medicine of the National Research Council in Italy and at the Ohio State University, USA.

Safety in drug therapy

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

An important research focus is safety in drug therapy. Here we are partners in a project funded by the German Ministry of Health (BMG) to implement and evaluate measures to improve therapeutic safety in an emergency ward. As a partner in the German Federal Ministry of Education and Research (BMBF) funded cluster "Medical Valley Europäische Metropolregion Nürnberg" therapeutic systems project we currently work on new software and chemoinformatic databases to improve drug safety.

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 are welcome to work with us during their final year.

Selected Publications

Birkenfeld AL, Jordan J, Hofmann U, Busjahn A, Franke G, Krüger N, Igel S, Mürdter T, Drescher S, Shi S, Engeli S, Schwab M, Eichelbaum M, Luft FC, Fromm MF (2009) Genetic influences on the pharmacokinetics of orally and intravenously administered digoxin as exhibited by monozygotic twins. Clin Pharmacol Ther, 86: 605-8

Maas R, Xanthakis V, Polak JF, Schwedhelm E, Sullivan LM, Benndorf R, Schulze F, Vasan RS, Wolf PA, Böger RH, Seshadri S (2009) Association of the endogenous nitric oxide synthase inhibitor ADMA with carotid artery intimal media thickness in the Framingham Heart Study offspring cohort. Stroke, 40: 2715-9

Franke RM, Kosloske AM, Lancaster CS, Filipski KK, Hu C, Zolk O, Mathijssen RH, Sparreboom A (2010) Influence of Oct1/Oct2-deficiency on cisplatin-induced changes in urinary N-acetyl-beta-D-glucosaminidase. Clin Cancer Res, 16: 4198-206

Hochholzer W, Trenk D, Fromm MF, Valina CM, Stratz C, Bestehorn HP, Büttner HJ, Neumann FJ (2010) Impact of cytochrome P450 2C19 loss-of-function polymorphism and of major demographic characteristics on residual platelet function after loading and maintenance treatment with clopidogrel in patients undergoing elective coronary stent placement. J Am Coll Cardiol, 55: 2427-34

Mandery K, Bujok K, Schmidt I, Wex T, Treiber G, Malfertheiner P, Rau TT, Amann KU, Brune K, Fromm MF, Glaeser H (2010) Influence of cyclooxygenase inhibitors on the function of the prostaglandin transporter organic anion-transporting polypeptide 2A1 expressed in human gastroduodenal mucosa. J Pharmacol Exp Ther, 332: 345-51

König J, Zolk O, Singer K, Hoffmann C, Fromm M (2011) Double-transfected MDCK cells expressing human OCT1/MATE1 or OCT2/MATE1: determinants of uptake and transcellular translocation of organic cations. Br J Pharmacol, 163: 546-55

International Cooperation

Prof. Mikko Niemi, Department of Clinical Pharmacology, University of Helsinki, Helsinki, Finland

Prof. Laurent Becquemont, Service de Pharmacologie, Hopital Bicetre, Le Kremlin Bicetre Cedex, France

Prof. Ramachandran Vasan, Framingham Heart Study, Framingham, MA, USA

Prof. Arturo Cardounel, Ohio State University, Internal Medicine and Pharmacology, Columbus, OH, USA

Research Equipment

Applied Biosystems API 4000 MS/MS System Package

Zeiss Confocal Laser Scanning Microscope LSM 5 Pascal

Institute of Experimental and Clinical Pharmacology and Toxicology

Chair of Pharmacology and Toxicology

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Research Focus
- Mechanisms of cardiac pacemaking
- Ventricular Ion channels
- HCN-channels in neurons
- 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-Foundation Professorship 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. A. Ludwig) and the Chair of Clinical Pharmacology and Clinical Toxicology (Prof. M. Fromm) on a two-year basis.
The chair has a staff of 31 employees. Research is carried out by 8 PhD graduates, 7 postgraduate student and 6 research technicians.
Main areas of research are the function of various ion channels (HCN pacemaker channels, calcium channels, ryanodine receptors) in the heart and in the nervous system, in particular in pain generation. Another research field is small animal imaging, focusing mainly, but not exclusively, on mechanisms of pain processing. These areas are explored by combining methods from molecular biology, mouse genetics, electrophysiology, whole-animal studies and functional MRI. Research is supported by various grants from the DFG, EU and BMBF.
Together with the chair of Clinical Pharmacology and Clincal Toxicoloy a drug information service is provided for clinicians of the Universitätsklinikum Erlangen as well as for physicians in private practice.

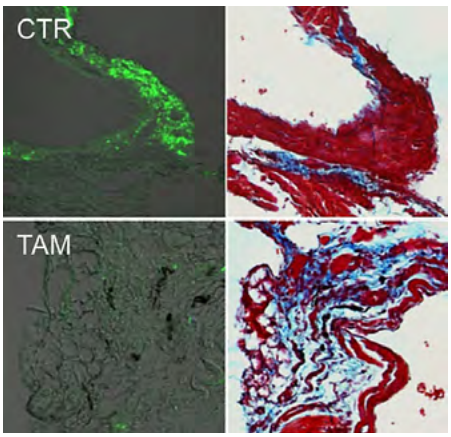
Research

Mechanisms of cardiac pacemaking
Project managers: J. Stieber, S. Herrmann, A. Ludwig
The complex mechanisms of cardiac pacemaking in the sinoatrial node are analyzed by using a variety of knock-in and knock-out mouse models. We generated the first mouse model for age-dependent sick-sinus syndrome. Sinoatrial cells were deleted by using our sinus node-specific and inducible KiT-Cre line. The resulting animals developed typical arrhyhtmias. Unexpectedly, sufficient atrial pacemaking was detected in the absence of any sinoatrial node cells. In addition, the role of If for cardiac pacemaking was analyzed. By generating a triple-knockout (HCN1/2/4), sinoatrial If was completely deleted resulting in severe bradycardia and lethality. Other projects examine the function of voltage-gated calcium channels and ryanodine receptors in the cardiac pacemaking and conduction system.

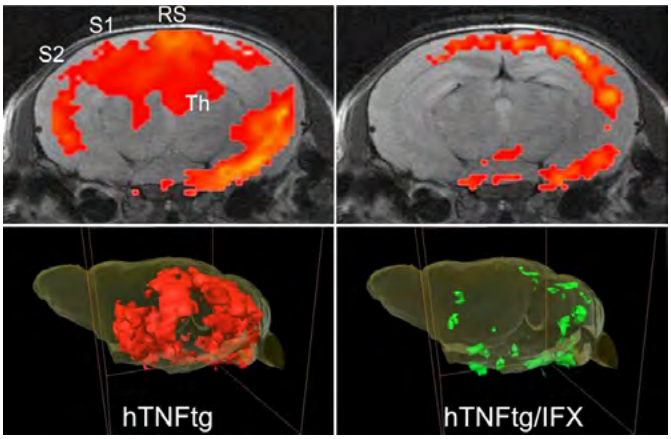
Ventricular Ion channels
Project managers: S. Herrmann, A. Ludwig, J. Stieber
Ventricular arryhthmias are frequently observed in cardiac diseases including heart failure and hypertrophie. The contribution of ventricular If to these arrhythmias is unclear. By inducing left ventricular hypertropyh in mice it could be shown that this current is increased in hypertrophied ventricular myocytes. Unexpectedly, cardiac-specific deletion of HCN2+4 demonstrated that HCN channels contribute to the prolongation of repolarization observed in the hypertrophied heart. These results directly demonstrate that increased HCN channel activity augments the arryhthmic potential of hypertrophied hearts.
Another project used conditional mouse mutants to study the role of ryanodine receptors (RyR2) in different cardiac cell types. Lack of the channels in ventricular myocytes resulted in a severe dilatative cardiomyopathy. The selective deletion in the sinoatrial node leaded to sinus bradycardia with impared heart rate modulation and low basal Ca^{2+}-levels in pacemaking cells.

HCN-channels in neurons
Project managers: S. Herrmann, A. Ludwig
The detection und propagation of painful stimuli in the dorsal root ganglion involves several ion channels. We studied the potential role of HCN channels in this process by the generation and analysis of nociceptor-specific HCN1- and HCN2 deletion mutants. These animals exhibit reduced pain responses in models of neuropathic and inflammatory pain. Single-fibre analysis in collaboration with the group of Prof. Reeh, Physiology, point in the same direction. The results suggest that HCN channels play an important role in the generation of pain signals in nocicteptors.
The role of HCN4 in thalamic regions is examined in a collaboration with the University of Münster by analysing a brain-specific HCN4 deletion mutant.

Pharmacological imaging and image analysis
Project manager: A. Hess
The group uses non-invasive magnetic resonance tomography (fMRT) to study plastic nociceptive processes in the central nervous system of rodents and humans. The successful application of this technique to transgenic mice allowed for the first time the combination of modern genetic techniques with functional imaging. This achievement results in a unique position of the group documented by high-ranking publications. Together with the group of J. Penninger from the Institute of Molecular Biotechnology in Vienna it could be shown that an isoform of an accessory calcium channel subunit (alpha2delta3) contributes to the processing of nociceptive signals in the thalamus (Cell 2010). Another collaboration with the group of G. Schett, Medical Clinic 3 analyzed transgenic mice which overexpress human TNFalpha resulting in severe arthritis. It could be shown that treatment with the antibody infliximab alters the processing of pain signals in the central nervous system of the animals and thereby reduces painful conditions. In addition, similar effects were observed in the brain of patients with arthritis by using functional MRT imaging (PNAS 2011). The ability to perform non-ivasive imaging in laboratory animals under minimal stress together with the development of image analysis techniques allowed acquistion of several research grants (DFG FG 661, DFG KFO 130, BMBF 3R, Baxter). Several different cooperations resulted in a variety of publications. In ad-



Sick sinus-mouse model: After induction with tamoxifen (TAM) sinoatrial node cells are completely eliminated



Infliximab (IFX) reduces the enhanced neuronal activity in the brain of TNF-transgenic mice (hTNFtg)

dition, the core-unit "Small animal imaging" of the IZKF was finished with several publications.

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 tutorial. Students of molecular medicine are trained by lectures, a seminar focusing on the molecular mechanisms of drug actions and 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 and several seminars and laboratory internships.

Selected Publications

Heindl-Erdmann C, Axmann R, Kreitz S, Zwerina J, Penninger J, Schett G, Brune K, Hess A (2010) Combining functional magnetic resonance imaging with mouse genomics: new options in pain research. Neuroreport, 21: 29-33

Hofmann F, Ludwig A, Herrmann S (2010) The proarrhythmogenic role of I-f in cardiac hypertrophy. Naunyn Schmiedebergs Arch Pharmacol, 381: 49-49

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 alpha2delta3 as an evolutionarily conserved pain gene. Cell, 143: 628-38

Stieber J, Ludwig A (2010) Complete deletion of I-f in the sinoatrial/AV-node results in lethal bradyarrhythmia in mice. Naunyn Schmiedebergs Arch Pharmacol, 381: 51-51

Herrmann S, Fabritz L, Layh B, Kirchhof P, Ludwig A (2011) Insights into sick sinus syndrome from an inducible mouse model. Cardiovasc Res, 90: 38-48

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-alpha rapidly inhibits pain responses in the central nervous system. Proc Natl Acad Sci U S A, 108: 3731-6

International Cooperation

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

Prof. X. Wehrens, Molecular Physiology, Baylor College of Medicine, Houston, TX, USA

Prof. C. Zuker, Columbia University, New York, NY, USA

Prof. H. Sakano, Department of Biophysics and Biochemistry, University of Tokyo, Tokyo, Japan

Prof. R. Shigemoto, National Institute for Physiological Sciences, Okazaki, Japan

Prof. L. Cervetto, Dipartimento di Scienze Fisiologiche, University of Pisa, Pisa, Italy

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

Dr. M. Lei, School of Medicine, University of Manchester, Manchester, UK

Dr. M. Mangoni, Institut de Genomique Fonctionnelle, Universite de Montpellier I et II, Montpellier, France

Research Equipment

Bruker 4,7 Tesla Small Animal MRT

Zeiss Confocal Laser Scanning Microscope LSM 5

Institute of Experimental and Clinical Pharmacology and Toxicology

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Research Focus
- Non-invasive functional imaging
- Analgesics

Structure of the Department

This professorship is one of three full professorships implemented at the Institute of Experimental and Clinical Pharmacology and Toxicology. The acting directorship is rotating among the professors.
The Doerenkamp professorship will be ending on June 30, 2012. Funds, donated by the person the professorship 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 close collaboration of this chair with researchers of the other two professorships. Together with these senior scientists, grants finance up to 3 post-doctoral and 5 doctoral collaborators.
The research goals of the Doerenkamp professorship are pursued in close collaboration with Prof. Dr. Burkhard Hinz (formerly senior scientist at the institute, presently chairman of the Department of Toxicology and Pharmacology at the University of Rostock), PD Dr. Andreas Pahl (formerly member of the Chair of Pharmacology and Toxicology, presently head of a research division of Nycomed, Hamburg) and PD Dr. Andreas Hess (member of the Chair of Pharmacology and Toxicology at the institute). In collaboration with these senior co-workers, the following results were achieved.

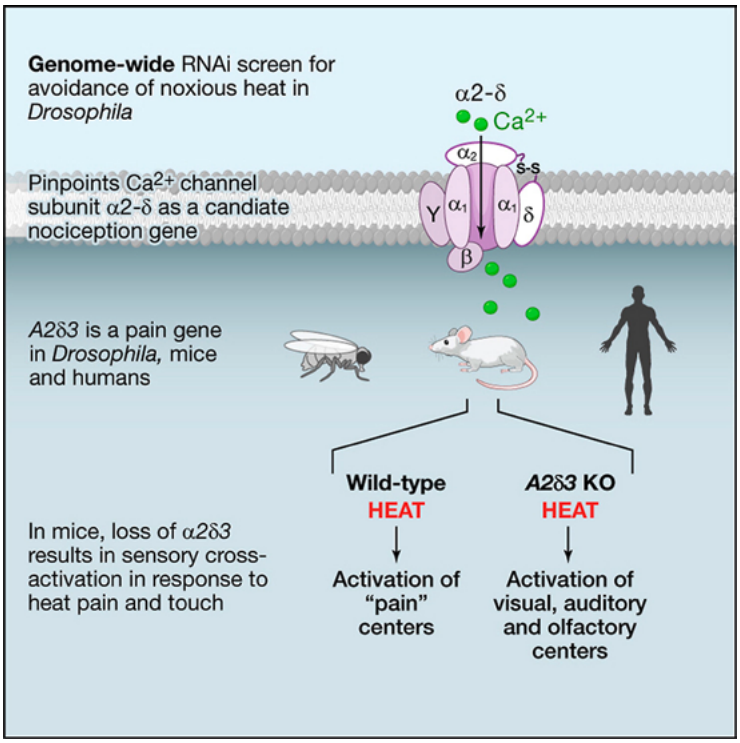
Research

Non-invasive functional imaging
One of the central aims of the Doerenkamp-Professorship was to establish non-invasive imaging techniques in experimental pain research. This approach turned out to be extremely successful. Together with H.U. Zeilhofer (Zurich), we could identify the role of glycinergic receptors in the spinal cord for pain control (Knabl et al, 2008). Together with J.M. Penninger (Vienna) and C.J. Woolf (Boston), we could employ this technology to identify pain controlling genes which had been identified in a drosophila assay system (Neely et al, 2010). 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 TNFalpha), we could show that anti-TNFalpha-treatment in mice (overexpressing TNFalpha) and men (rheumatoid arthritis patients) instantaneously relieves pain in experimental animals and men (Hess A et al, PNAS 2011).
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 M. Uder, who has taken over the administrational control of the unit diverted to employ imaging techniques in experimental research involving animals. There is hope that this division will continue to flourish.

Analgesics
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 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 arguments 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 atherosclerosis in certain patients. Using NTproBNP, a new biomarker, we could show that determing the NTproBNP 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.

Teaching

The engagement of Prof. 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. 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 Department. He is a member of the Executive Committee of IUPHAR (International Union of Basic and Clinical Pharmacology).



Searching for „pain genes": A Ca-channel, expressed in drosophila, mouse, and man, controls heat-avoidance, pain, and synesthesia

Acute and chronic pain affects 20% of the adult population. Using genome-wide neuronal-specific RNAi knockdown in Drosophila, we report a global screen for an innate behavior and identify hundreds of genes implicated in heat perception, including the alpha2delta family calcium channel subunit straightjacket (stj). Mice mutant for the stj ortholog CACNA2D3 (alpha2delta3) also exhibit impaired behavioral heat pain sensitivity. In addition, in humans, alpha2delta3 SNP variants associate with reduced sensitivity to acute noxious heat and chronic back pain. Functional imaging in alpha2delta3 mutant mice revealed impaired transmission of thermal pain-evoked signals from the thalamus to higher-order pain centers. Intriguingly, in alpha2delta3 mutant mice, thermal pain and tactile stimulation triggered strong cross-activation, or synesthesia, of brain regions involved in vision, olfaction, and hearing.

Selected Publications

Knabl J, Witschi R, Hösl K, Reinold H, Zeilhofer UB, Ahmadi S, Brockhaus J, Sergejeva M, Hess A, Brune K, Fritschy JM, Rudolph U, Möhler H, Zeilhofer HU (2008) Reversal of pathological pain through specific spinal GABAA receptor subtypes. Nature, 451: 330-4

Brune K, Hinz B, Otterness I (2009) Aspirin and acetaminophen: should they be available over the counter? Curr Rheumatol Rep, 11: 36-40

Brune K, Renner B, Hinz B (2010) Using pharmacokinetic principles to optimize pain therapy. Nat Rev Rheumatol, 6: 589-98

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 alpha2delta3 as an evolutionarily conserved pain gene. Cell, 143: 628-38

Renner B, Zacher J, Buvanendran A, Walter G, Strauss J, Brune K (2010) Absorption and distribution of etoricoxib in plasma, CSF, and wound tissue in patients following hip surgery--a pilot study. Naunyn Schmiedebergs Arch Pharmacol, 381: 127-36

Research Equipment

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

Institute of the History of Medicine and Medical Ethics

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Research Focus

- Galen – Compendium and Catalogue of Galenic Writings
- The Nuremberg Sondersiechenalmosen 1394–1664
- Later Ancient and Early Byzantine Psychopathology
- Leprosy and Vagrancy in Southern German Free Imperial Cities
- Early 18th Century Medical Practice: Physician Johann Christoph Götz (1688–1733) from Nuremberg
- 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 Department of Gynecology and Obstetrics

Structure of the Department

Together, the Chair for History of Medicine and the Professorship for Medical Ethics (see separate article in this report) constitute the Institute for 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 consist of 16 members, 14 are academic personnel with 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 Medical Faculty Erlangen, medical ethics in Germany after 1945).

Research

Galen – Compendium and Catalogue of Galenic Writings
Project manager: K.-H. Leven
The Greek physician Galenus of Pergamum (129–ca. 210 AD) figures as the most influencal medical author of the Roman imperial period. A very prolific writer, the extent of his oeuvre 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 in and out of antiquity for which renowned international experts have been gathered. It aims at both consolidating existing knowledge and venturing into new ground. On the other hand an annotated catalogue of all remaining Galenic writings (ca. 400) is devised to provide a much needed reference work for scholars in the field.

The Nuremberg Sondersiechenalmosen 1394–1664
Project manager: F. Dross
The Nuremberg Sondersiechenalmosen, a charity founded in 1394 by three wealthy patrician women, provided food, clothing and temporary shelter for foreign lepers not endowed with the privileges of Nuremberg residents. Restricted to three days of Holy Week, this charity was in existence for more than 250 years. In the 15th century Nuremberg saw hundreds of lepers gathering for this occasion at the appointed days; by the 16th century there are up to several thousand recipiants reported by reliable sources. The domestic lepers, in contrast, were provided for in four municipal Siechköbel outside the city walls throughout the year. This extensive institutional care for lepers in late mediaeval and early modern times places Nuremberg as outstanding in this regard. Despite this prominent position, concise and comprehensive treatment of the subject is still a desideratum of present international scholarship.

Later Ancient and Early Byzantine Psychopathology
Project manager: N. Metzger
In their descriptions of mental illnesses, the later ancient and early byzantine medical authors show much more diverse sources and originality than their much attested founding on Galenism would lead to suspect. The medical compendia by physicians like Oribasius, Aetius, Paulus Aegineta, Paulus Nicaeus and Alexander of Tralles (4th–9th century AD) surpass Galenic psychopathology by including diseases unlisted by Galen, drawing their knowledge from preceding authors otherwise lost. Although these authors mostly aim to preserve the medical knowledge of their predecessors, it can be observed – by comparing with sources from outside the medical sphere – how changing cultural and social realities leave their mark. Excerpting in their own way, these medical encyclopedists convey new meanings to old words, nudge medical concepts according to their needs and in the meantime shape them with lasting effects for the subsequent medical tradition.

Leprosy and Vagrancy in Southern German Free Imperial Cities
Project managers: F. Dross, 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 so far entirely wanting. Neither amount nor behaviour nor strategies of these individuals are known yet. Furthermore, by posing these questions 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 Nuremberg
Project manager: 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. Michael Stolberg, Würzburg). It is dedicated to quantitative and qualitative analysis of the early 18th century medical records by the hand of Johann Chris-

toph Götz which have fortunately been preserved in the Trew Collection of the local University Library Erlangen. Consisting of seven volumes, originating from the years 1716 to 1726 and predominantly in Latin, these records enable a close look into every-day practice as noted down by Götz. His patients, their ailments and social status, furthermore his arrangements and contemporaneous medical knowledge can be brought to surface. Besides database driven analysis the project focuses on Götz's patients. Although their perspectives are unmistakably hard to obtain, selected case stories especially rich in detail are closely scrutinized. Götz's journal sparks additional interest because its author was closely connected to the influential physician and publicist Christoph Jacob Trew from Nuremberg and promises new insights into early public health measures.

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

Project managers: K.-H. Leven, Ph. 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 to outline 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. These physicians, constituting the core unit of nazi persecution and genocide policies, originated from the heart of the German academic upper middle class, a social group regarded with particular esteem by their contemporaries. After 1945, the question remains open to what extend these persons lost their status in face of the severe charges laid against them or whether they continued their careers undisturbed by public and political repercussions. 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 Department of Gynecology and Obstetrics

Project managers: F. Dross, W. Frobenius

The Bavarian Society for Gynecology and Obstetrics ("Bayerische Gesellschaft für Geburtshilfe und Frauenheilkunde" [BGGF]) has been established in 1912 by an united meeting of both the former Franconian and Munich societies. On the occasion of its centenary a historical research project is analyzing the Society with special respect on how it worked out professional policy on the background of the social history of 20th century Western Germany. The role of the society and its members within Nazi Germany will be highlighted as well as its way to deal with this matter afterwards.

Teaching

The Institute of the History of Medicine and Medical Ethicsis is responsible for teaching the following courses according to medical curriculum: Medical Terminology (first semester students in human medicine/dentistry); Querschnittsbereich Q 2 "History, Theory and Ethics of Medicine" (seventh semester medicine) and "History of Science and Ethics" (degree program in molecular medicine). Furthermore, it contributes to 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; this includes basic understanding of Latin grammar and vocabulary necessary for anatomical terms, furthermore Greek for clinical usage. At the same time it aims to place medicine in its social and historical context.

History, Theory and Ethics of Medicine includes lectures dedicated to the basic principles of medical humanities while the specific skills 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 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.

Moreover, several recurring seminars offer further insight into historical and ethical subjects to students with special interest in the medical humanities (Wahlpflichtfach). In collaboration with the Chair of Anatomy I a seminar on

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

"Death and Dying in Cultural Perspective" is held by the Chair of History of Medicine. Each semester, a group of interested students is introduced to methods and objectives of medical historiography. Seminars on selected topics close to current research interests are offered each semester, in certain cases in conjunction with the Master Program "Mittelalter- und Renaissance-Studien" and/or colleagues in the Philosophical Faculty.

The lecture series "Über den Tellerrand" caters current research topics to a wider audience. During lunch hour, members of staff present selected tidbits about historical and ethical matters. Invited medical historians from outside give insight into their work in the monthly "Medizinhistorische Vortragsreihe".

Selected Publications

Dross, F. / Salimi K. (Hrsg.): Jacob Henle. Bürgerliches Leben und „rationelle Medicin". Eine Ausstellung im Klinikum Fürth 10.7.2009 bis 10.9.2009, Fürth 2009 [Katalog].

Dross, F.: Patterns of Hospitality: Aspects of Institutionalisation in 15th & 16th Centuries Nuremberg Healthcare. In: Hygiea Internationalis 9 (2010), Nr. 1, S. 13-34

Leven, K.-H.: „Das Wesen des Meeres ist aus dem Tropfen nicht ersichtlich". Bernadette Soubirous (1844-1879) und die Wunderheilungen in Lourdes. In: Deutsche Medizinische Wochenschrift 135 (2010), S. 2588-2592.

Rauh, P./Quinkert, B./Winkler, U. (Hrsg.): Krieg und Psychiatrie, 1914-1950. (Beiträge zur Geschichte des Nationalsozialismus, Bd. 26). Göttingen 2010.

Meetings and International Training Courses

10.07.–10.09.2009: Ausstellung: Jacob Henle. Bürgerliches Leben und „rationelle Medicin", Klinikum Fürth, Deutschland

Institute of the History of Medicine and Medical Ethics

Professorship for Medical Ethics

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Research Focus
- Clinical Ethics and Ethics Counseling
- Medicine and Human Rights
- Philosophy of Medicine and Enhancement

Structure of the Department

Together, the Professorship for Medical Ethics and the Chair of History of Medicine (see separate report) constitute the Institute for 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 8 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 Medical Faculty Erlangen, medical ethics in Germany after 1945).
30 doctoral theses are being supervised at the Professorship of medical ethics and 10 academic book series are being edited.
The main areas of research are clinical ethics and ethical 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. This topic is unique at a medical faculty 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: A. Frewer, F. Bruns.
A main field of expertise of the professorship of 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 (F. Bruns; A. Frewer) and the evaluation of ethical counseling (A. Frewer; T. Ramsauer) belong to this field of enquiry. Files of patient's advocates are being dealt with in the project "Clinical Ethics from the Patient's Perspective" (F. Bruns; I. Emrich; A. Frewer; B. Friedrich; L. Fröhlich-Güzelsoy).
A further field of research are end of life conflicts, e.g. projects on ethical counseling, cultures of dying and advance directives (B. Friedrich; A. Frewer; M. Rothhaar). As part of this field of research an annual "Ethics Day" and an Intensive Course "Clinical Ethics" (BMBF) is being organized, the "Yearbook Ethics in Clinics" and the book series "Clinical Ethics" are being edited (A. Frewer et al.).

Medicine and Human Rights
Project managers: A. Frewer, H. Furtmayr.
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. From a theoretical perspective the possibilities and limits of a rights-based medical ethics and bioethics are considered and several dimensions of the concepts of human dignity and human rights are investigated in this context (M. Rothhaar; S. L. Sorgner). 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 (H. Furtmayr; A. Frewer), but also the participation of physicians in human rights violations (M. Mylius, S. Kolb). 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 (J. Graf; K. Krása). 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: A. Frewer, S. L. Sorgner.
The field of enquiry "Philosophy of Medicine and Enhancement" deals with questions concerning the notion "disease" and human aging (A. Frewer; M. Rothhaar), moral evaluations of various aspects of human enhancement, preimplantation diagnosis (PGD) and deep brain stimulation (S. L. Sorgner). 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 for History of Medicine and Medical Ethics is responsible for teaching the following courses according to medical curriculum: Medical Terminology (1st semester students in human medicine/dentistry); Querschnittsbereich (cross-sectional area) Q 2 "History, Theory and Ethics of Medicine" (7th semester 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, fur-

thermore Greek for clinical usage. At the same time it aims to place 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" to "Intercultural Communication", 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 "Über den Tellerrand" ("Beyond one's own Nose") are being offered.

Selected Publications

Frewer, A./Fahr, U./Rascher, W. (Hrsg.) (2009) Patientenverfügung und Ethik. Beiträge zur guten klinischen Praxis. Jahrbuch Ethik in der Klinik 2. Würzburg.

Frewer A (2010) Human rights from the Nuremberg Doctors Trial to the Geneva Declaration. Persons and institutions in medical ethics and history. Med Health Care Philos, 13: 259-68

Frewer, A./Bruns, F./Rascher, W. (Hrsg.) (2010) Hoffnung und Verantwortung. Herausforderungen für die Medizin. Jahrbuch Ethik in der Klinik 3. Würzburg.

Furtmayr H, Frewer A (2010) Documentation of torture and the Istanbul Protocol: applied medical ethics. Med Health Care Philos, 13: 279-86

Wittwer, H./Schäfer, D./Frewer, A. (Hrsg.) (2010) Sterben und Tod. Geschichte – Theorie – Ethik. Ein interdisziplinäres Handbuch. Stuttgart.

International Cooperation

Prof. M. Grodin, M.D., Boston University School of Public Health, Boston University, Boston, MA, USA

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

Meetings and International Training Courses

22.07.2009: Hierarchie und Ethik. Entscheidungskultur im Krankenhaus, Erlangen, Deutschland,

30.09.–01.10.2009: GENerell krank oder chronisch gesund? Neue ethische Implikationen des Krankheitsbegriffs, Erlangen, Deutschland,

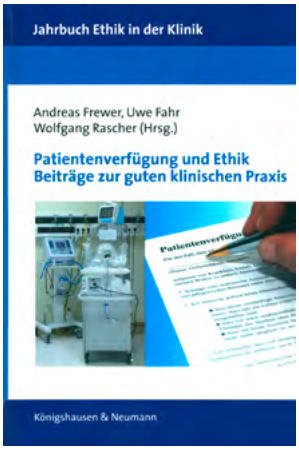
17.10.2009: 8. Ethiktag des Klinischen Ethikkomitees und der Professur für Ethik in der Medizin: "Hoffnung und Verantwortung in der klinischen Praxis", Erlangen, Deutschland,

12.–19.09.2010: Erlanger Sommerkurs „Klinische Ethik": BMBF-Klausurwoche mit zahlreichen Foren und Expertenvorträgen, Leitung: Prof. A. Frewer, Erlangen, Deutschland,

18.09.2010: 9. Ethiktag des Klinischen Ethikkomitees und der Professur für Ethik in der Medizin: "Ethik in der Medizin zwischen Empathie und Ökonomie", Erlangen, Deutschland,

Persistent Vegetative State Baby: Ethics Committee and Professorship of Clinical Ethics advise the Gynaecological Hospital in the case of the "Boy from Erlangen". Press conference 14.10.2009

Persistent Vegetative State Baby: Dialogue partner at the main press conference (from left to right): Prof. Dr. med. Dr. h.c. Wolfgang Rascher, director of the pediatric and youth clinic; Prof. Dr. med. Andreas Frewer, M.A., medical ethics; Andrea Maywald, nurse in the gynecological hospital; Prof. Dr. med. Matthias W. Beckmann, director of the gynecological hospital; Dr. med. Julia Engel, physician in the gynecological hospital



The professorship of medical ethics and the ethics committee published the case study entitled "Pregnancy, Heart Attack, Brain Damage" on the "Boy from Erlangen". Herein, the medical background and the ethical challenges get described from the perspective of the team of physicians. These contributions are being followed by interdisciplinary comments from medical ethics/ethics council, neonatology/paediatrics, nursery, internal medicine/diabetology and law.

Institute of Medical Informatics, Biometry and Epidemiology

Chair of Medical Biometry and Epidemiology

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Research Focus
- Contribution to Sonderforschungsbereich 539: Glaucoma including pseudoexfoliation syndrome
- Computational Biostatistics
- Dermatoepidemiology
- Cooperative epidemiological and clinical studies

Structure of the Department

The department comprises the Chair of Medical Informatics (Prof. H.-U. Prokosch) and the Chair of Biometry and Epidemiology. The staff of the Chair of Biometry and Epidemiology includes 16 scientists (8 post-docs, 8 doctoral students) and 3 further employees. 50% of the staff is 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 33 nodes is available as infrastructure for computer-intensive biostatistical simulation studies.

Research

Contribution to Sonderforschungsbereich 539: Glaucoma including pseudoexfoliation syndrome

Project managers: W. Adler, O. Gefeller
With the aim of improving early diagnosis of glaucoma new approaches of machine-based learning are evaluated and further developed. Data from cross sectional and longitudinal studies (in particular FDT, HRT, GDx, colour image (Kowa), OCT data) contribute to new and improved classification rules. In a multi-disciplinary project with the Department of Ophthalmology and the Department of Informatics a computer based system for the diagnosis "suspected glaucoma", based on image analysis and other data, is being developed.

Computational Biostatistics

Project managers: M. Schmid, 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 respect to their general performance as a feature selection method. Feature selection in boosting methods was investigated from a theoretical perspective, and a framework for unbiased selection was suggested.

Dermatoepidemiology

Project managers: A. Pfahlberg, 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, www.ivdk.org), maintained by an institute at the University of Göttingen, has been established. Pooled data collected in the participating allergy departments is 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 fragrances and essential oils. Moreover, the network "ESSCA" (www.essca-dc.org) is collecting and analyzing such data on a European level since 2002, with the data center at the IMBE.
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.

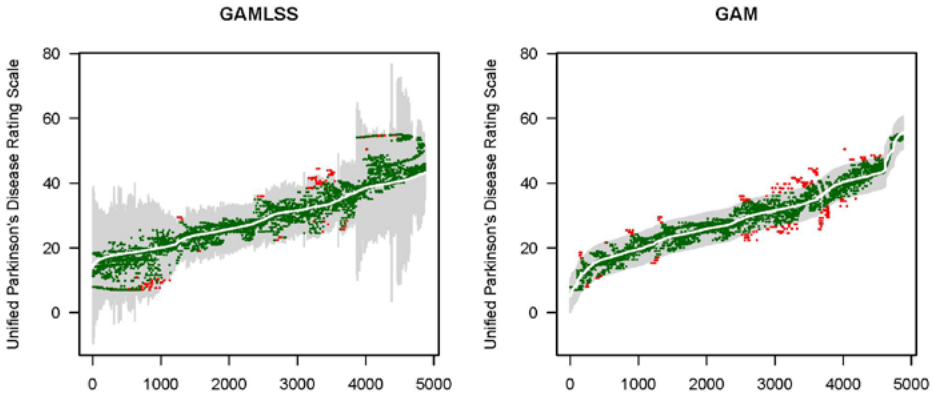
Cooperative epidemiological and clinical studies

Project managers: various
This area of activity comprises diverse research topics addressed in cooperation with different departments. Usually, biometrical aspects of study design and statistical analysis have been performed by the IMBE in these cooperative projects. The most important projects in the reporting period include:
• a follow-up study in the field of occupational medicine addressing the effectiveness of an intervention program targeting skin protection in the metal working industry,
• international study coordinated by the Institute of Biomedicine of Aging/Chair of Geriatrics regarding re-design of the "Mini Nutritional Assessment" and diagnostics and prevention of frailty,
• multi-centric European studying on "Accelerated Partial Breast Irradiation" (www.apbi.uni-erlangen.de), 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 Radiotherapy of the Universitätsklinikum Erlangen,
• biostatistical support of the ENT department in studies on the therapy of nasal polyps, diagnostic value of different CT and ultrasound methods, perfusion imaging in tumors of the parotis and of contrast enhanced ultrasound measurement of perfusion dynamics in cervical lymph nodes,
• the multi-centric "German Chronic Kidney Disease Study (GCKD)" funded by the BMBF and the "Kuratorium für Heimdialyse",
• implementation of the "German Weight Maintenance" registry (http://www.gewicht-halten.de) and biostatistical support of a multi-

center study on the therapy of eating disorders (INTERBED), chaired by the Department of Psychosomatic Medicine and Psychotherapy of the Universitätsklinikum Erlangen.

Teaching

In the context of curricular teaching the chair contributes to the "multidisciplinary field I" (medical informatics, biometry and epidemiology) for medical students (lecture and seminars in small groups, 1 SWS each). Moreover, this introduction to biometry and epidemiology (lecture and seminars in small groups, 1 SWS each) is part of the bachelor phase of the course on "molecular medicine" together with a seminar on the practice of data analysis (2 SWS) which teaches basic programming knowledge in the statistical program "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, 3SWS). 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 is part of an introductory seminar for students of information science specialising in medical informatics.



Improved prediction, with 95% prediction intervals, of the clinician's Parkinson's disease symptom score (UPDRS) comparing the flexible GAMLSS approach and conventional GAM. The solid white line represents point predictions, prediction intervals are shaded gray. Observed values are colored green if they are covered by the intervals, otherwise they are red. For better readability, the sample was ordered by the respective point estimate - thus, the ordering is different between the two images

Selected Publications

Adler W, Lausen B (2009) Bootstrap estimated true and false positive rates and ROC curve. Comput Stat Data Anal, 53: 718-729

Gefeller O (2009) Invited commentary: Recall bias in melanoma -- much ado about almost nothing? Am J Epidemiol, 169: 267-70; discussion 271-2

Radespiel-Tröger M, Meyer M, Pfahlberg A, Lausen B, Uter W, Gefeller O (2009) Outdoor work and skin cancer incidence: a registry-based study in Bavaria. Int Arch Occup Environ Health, 82: 357-63

Uter W, Frosch PJ, Becker D, Schnuch A, Pfahlberg A, Gefeller O (2009) The importance of context information in the diagnostic rating of digital images of patch test reactions. Br J Dermatol, 161: 554-9

Uter W, Rämsch C, Aberer W, Ayala F, Balato A, Beliauskiene A, Fortina AB, Bircher A, Brasch J, Chowdhury MM, Coenraads PJ, Schuttelaar ML, Cooper S, Corradin MT, Elsner P, English JS, Fartasch M, Mahler V, Frosch PJ, Fuchs T, Gawkrodger DJ, Gimènez-Arnau AM, Green CM, Horne HL, Jolanki R, King CM, Krêcisz B, Kiec-Swierczynska M, Ormerod AD, Orton DI, Peserico A, Rantanen T, Rustemeyer T, Sansom JE, Simon D, Statham BN, Wilkinson M, Schnuch A (2009) The European baseline series in 10 European Countries, 2005/2006--results of the European Surveillance System on Contact Allergies (ESSCA). Contact Dermatitis, 61: 31-8

Schmid M, Potapov S, Pfahlberg A, Hothorn T (2010) Estimation and regularization techniques for regression models with multidimensional prediction functions. Stat Comput, 20: 139-150

International Cooperation

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

Prof. Geir E. Eide, Haukeland Hospital, University of Bergen, Bergen, Norway

Prof. Ana-Maria Giménez-Arnau, Hospital del Mar, IMAS, Autonomous University of Barcelona, Barcelona, Spain

Institute of Medical Informatics, Biometry and Epidemiology

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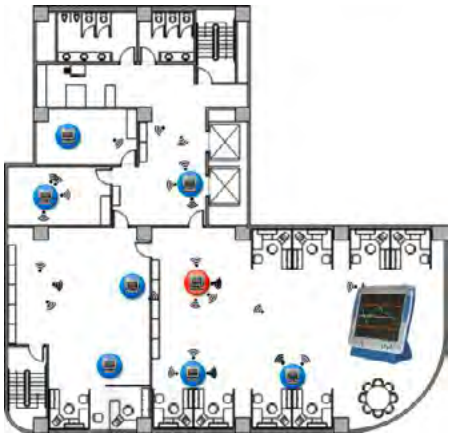
Research Focus
- Architecture of health information systems
- Analysis, assessment and visualization of medical databases
- Evaluation of health information systems
- IT-infrastructure applications for medical research
- Medical ontologies and medical knowledge processing

Structure of the Department

The Chair for Biometry and Epidemiology and the Chair for Medical Informatics together constitute the Department of Medical Informatics, Biometry and Epidemiology within the Medical Faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg. Furthermore, the Chair for Medical Informatics has a secondary affiliation within the Technical Faculty, named Research Group Medicine.
The Chair for Medical Informatics has 14 staff members, half of them are funded by research grants. A wide spectrum of research projects is pursued by 6 post-doctoral researchers, 9 doctoral candidates and 2 medical documentalists. Those 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 inter-sectoral 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.



Application of Smart Object technology for the localisation of medical equipment

The head of the Chair for Medical Informatics, Professor Hans-Ulrich Prokosch is (as Chief Information Officer (CIO) of the Universitätsklinikum Erlangen) also responsible for the University Hospital´s routine operative business and its strategic information processing development.

Research

Architecture of health information systems
Project manager: H.-U. Prokosch
Research concerning the design, implementation and management of Hospital Information Systems (HIS) is currently in a transition phase. For many years the major issue was optimization of communication processes and the integration of heterogeneous departmental systems into a comprehensive HIS. Meanwhile, we are faced with new challenges. 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. Current research topics therefore concern integration of clinical guidelines and clinical pathways into daily practice as well as enhanced electronic networking between hospitals and general practitioners. Further important topics are mobile appliances such as tablet PCs, ePen etc. and their integration into routine hospital processes. In this context, the design and the evaluation of the VMobile system is especially noteworthy, as it provides electronic and mobile support of doctor's rounds and at present is the basis for nearly 100% paperless patient charts in the Department of Obstetrics and Gynecology. Hospital-wide image data management is no more restricted only to radiology departments but has to consider image generating, image processing and image distribution in departments such as cardiology, nuclear medicine, dermatology, pathology and other areas in hospital where images and movies are used for diagnostics and therapy. Here as well, optimized clinical workflows are required and must be considered when establishing IT support.
The Chair for Medical Informatics of Erlangen-Nuremberg University deals with these research topics within pilot projects embedded in the SOARIAN® hospital information system environment, in connection with the OPAL-HEALTH project for RFID / Smart Object-technologies in hospitals (supported by the German Federal Ministry of Economics and Technology), and within various health telematics projects.

Analysis, assessment and visualization of medical databases
Project manager: T. Ganslandt
An increasing amount of data is documented electronically in clinical IT systems during routine patient care. To avoid information overload or, even worse, overlooking of essential facts, appropriate and flexible visualization methods for the clinician are urgently required. 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 (Prof. Isaac S. Kohane) the i2b2 (informatics for integrating biology and the bedside) platform has been integrated into the Universitätsklinikum Erlangen Clinical Data Warehouse and has been extended with functions supporting improved administration, semantic integration between databases and timeline-based visualization methods.

Evaluation of health information systems
Project manager: T. Bürkle
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 at-

titudes towards such new technologies, by user-unfriendly interfaces and by insufficient usability in general. When evaluating health IT, issues of health economics as well as socio-technological issues have to be considered as well. The Chair for Medical Informatics has initiated evaluation projects before and after introducing a new patient data management system into several intensive care units. Further studies have used ThinkAloud and Cognitive Walkthrough methods and a small mobile usability laboratory to evaluate the usability of different order entry systems of the Universitätsklinikum Erlangen with the formative goal to develop better user interfaces for such systems. Finally, the Chair for Medical Informatics participated in a study financed by the Barmer Health Insurance to evaluate the usage of a personal electronic health record.

Prospective Evaluation is a new and promising research area which uses simulation tools to assess the potential impact of future, not yet existing technologies and their potential innovation return on invest before development of such technologies is even started. Here, the Chair for Medical Informatics participates in a very innovative new research project ProHTA (prospective health technology assessment) within the German governments "cluster of excellence" initiative to promote research in regions with outstanding industrial focus.

IT-infrastructure applications for medical research

Project manager: H.-U. Prokosch, T. Ganslandt

Today, medical research is often pursued within interlinked multi-center structures with the urgent need for appropriate efficient and safe IT-infrastructures.

The Chair for Medical Informatics has assumed responsibility to provide such IT infrastructures as internet portals for secure research communication and collaboration as well as study databases for eCRF (electronic case report forms) for local and remote documentation of study data for within multi center medical research projects such as the EB (Epidermolysis Bullosa) Research Network, the Polyprobe study, the German Weight Control Registry and the nation-wide Registry for Chronic Kidney Diseases GCKD.

Current activities comprise IT infrastructures to support biobanking and single source reuse of clinical patient data for clinical research.

The Chair for Medical Informatics is member and active in many working groups of the TMF (German Platform for Technology and Methods in Medical Research Networks) and has promoted the foundation of the new GMDS working group "Use of electronic patient records for clinical research".

Within the project "HIS-based patient recruitment for clinical trials" we study optimization possibilities for patient recruitment in clinical studies using functions provided within clinical information systems.

Medical ontologies and medical knowledge processing

Project manager: R. Sojer / T. Bürkle

Clinical decision support systems (CDSS) in medicine strive to optimize the quality of medical care by means of decision support and decision monitoring. Numerous studies have shown the potential of CDSS, e.g. in the field of medication therapy and drug induced adverse events. In this context, the Chair for Medical Informatics pursues research activities to improve knowledge modeling for drug therapy data within ontologies and to implement standardized (Arden Syntax) logic modules to support appropriate high quality drug therapy.

To make those CDSS efforts available within many components of the Erlangen information system of the Universitätsklinikum Erlangen, a CDSS framework has been established consisting of an Arden-MLM-library, an Arden engine and the drug ontology as core components. Routine CDSS applications based on this framework have been implemented in the commercial patient data management system of the hospital's intensive care units as well as for the systematic assessment of adverse drug events in projects within and outside the Universitätsklinikum Erlangen. A drug safety research project founded by the German Federal Ministry of Health is conducted at the central emergency unit of the nearby City of Fürth Hospital to examine adverse drug events in patients with emergency admission in cooperation with the University Institute for Pharmacology. Here, the goal is to quantify the effect of a variety of measures including CDSS upon the amount of adverse drug events in a three phase longitudinal study.

Teaching

The Chair for Medical Informatics is teaching medical students in the cross-sectional subject medical informatics, biometry and epidemiology. It offers courses for computer science students of the technical faculty in medical informatics and has a considerable teaching part in the new Master Course Medical Process Management of the medical faculty, as well as the Bachelor program Medical Devices Technology of the technical faculty. Besides, the Chair for Medical Informatics has mentored 11 master and diploma theses as well as 6 preparatory in 2009 and 2010.

All lectures are based on the concept of blended learning. The Chair for Medical Informatics introduced and evaluated the e-learning system Moodle for its course materials in 2008, paving the way for the rollout of this system for the complete Faculty of Medicine. Meanwhile, system administration of this campus wide installation has been handed over to the Dean's office. The design, implementation and procurement of a web-based portal for searching and navigating medical image data bases was another research activity of the Chair for Medical Informatics.

Selected Publications

Gräßel E, Bleich S, Meyer-Wegener K, Schmid U, Kornhuber J, Prokosch HU (2009) [The Internet as an Information Source for Family Caregivers of Dementia Patients.]. Psychiatr Prax, 36: 115-118

Kammerer FJ, Frankewitsch T, Prokosch HU (2009) Design of a web portal for interdisciplinary image retrieval from multiple online image resources. Methods Inf Med, 48: 361-70

Prokosch HU, Ganslandt T (2009) Perspectives for medical informatics. Reusing the electronic medical record for clinical research. Methods Inf Med, 48: 38-44

Suc J, Prokosch HU, Ganslandt T (2009) Applicability of Lewin s change management model in a hospital setting. Methods Inf Med, 48: 419-28

Dugas M, Lange M, Müller-Tidow C, Kirchhof P, Prokosch HU (2010) Routine data from hospital information systems can support patient recruitment for clinical studies. Clin Trials, 7: 183-9

Prokosch HU, Beck A, Ganslandt T, Hummel M, Kiehntopf M, Sax U, Uckert F, Semler S (2010) IT Infrastructure Components for Biobanking. Appl Clin Inform, 1: 419-29

International Cooperation

Prof. Dr. Klaus-Peter Adlassnig, Section for Medical Expert and Knowledge-Based Systems, Medical University of Vienna, Vienna, Austria

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

Prof. Dr. Patrice Dégoulet, Hôpital Européen George Pompidou, Paris, France

Prof. Isaac Kohane, M.D., Ph.D., i2b2 National Center for Biomedical Computing, Boston, MA, USA

Institute of Medical Physics

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Research Focus

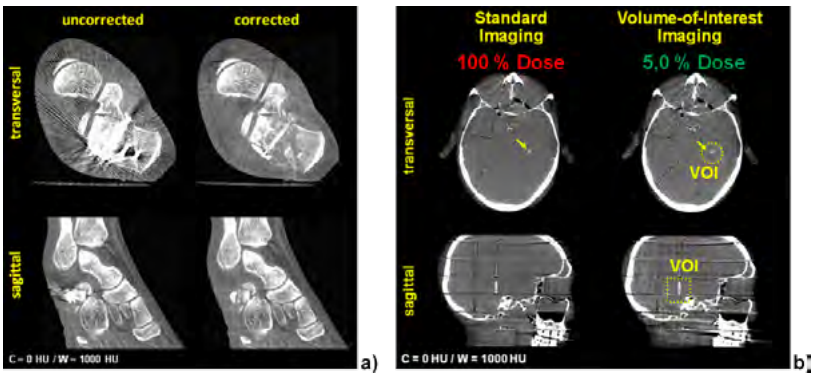
- Development and application of imaging procedures in medical diagnosis and image-guided therapy

Structure of the Department

In addition to the chair and full professorship of Medical Physics, the Institute of Medical Physics comprises the professorship of Medical Imaging (held by Prof. Dr. M. Kachelrieß since 07/2005), the professorship of Medical Optics (held by Prof. Dr. A. Langenbucher from 11/2005 to 07/2009) and the professorship of Magnetic Resonance Imaging (held by Prof. Dr. Harald H. Quick since 10/2009).
In all, the Institute employs 71 persons, whereof 52 are financed by third-party funds. The researchers, 32 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
- Computer-Assisted Surgery
- Dosimetry and Radiation Protection
- Magnetic Resonance Tomography
- Medical Imaging
- Medical Image Processing
- Medical Optics
- Osteoporosis Research
- Radiation Therapy.

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

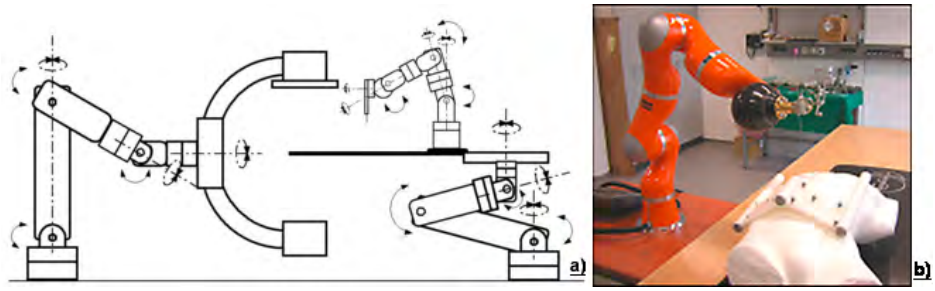


Two examples for image quality optimization and dose reduction. (a) Metal artefact reduction for the improvement of image quality of datasets containing orthopedic implants [Prell, 2009]. (b) Volume-of-Interest imaging to enable high-resolution scans with simultaneously reduced dose [Kolditz, 2010].

Research

Development and application of imaging procedures in medical diagnosis and image-guided therapy
In the focus of the more than 40 ongoing research projects and cooperations are the development and the application of imaging procedures in medical diagnosis and image-guided therapy. In particular the achievements in the field of computed tomography (CT) receive great recognition; the institute has gained a world-wide leading position here. Three selected research projects are described in the following:
From July 2005 to December 2010 the German Federal Ministry of Research and Technology (BMBF) supported a major project dedicated to minimal invasive surgery methods in orthopedics (orthoMIT - Orthopedic Operating Room of the future; reference number 01EQ0425). The main objective of the project was to develop an integrated platform for the "gentle" surgical therapy in orthopedics and traumatology with particular emphasis on hip, knee and spinal column surgery. The Institute of Medical Physics (project director: W.A. Kalender) participated in the orthoMIT project by working on the implementation of 3D CT imaging in minimally invasive interventions. The aim of this subproject was to develop image quality improvements as well as dose reduction and new applications for the intra-operative CT imaging in the treatment room.
Within the project a robot-controlled C-arm system was installed at the Institute of Medical Physics that allows all X-ray examinations from fluoroscopy to CT scanning which are necessary in the treatment room, with only one device. For image quality improvements special methods were developed for the correction of misalignment, scatter and truncation [Kalender, 2007]. The development of a metal artifact reduction technique improved the image quality of datasets containing orthopedic implants significantly [Prell, 2009].
For dose optimization a volume-of-interest imaging technique was developed, for which the robot-controlled C-arm system is used to perform a low-dose overview scan and a successive high-dose detail scan of a structure of interest [Kolditz, 2010]. Respective possibilities are enabled for the first time by the robot-controlled C-arm system; this procedure has been protected internationally by patent application early on, which meanwhile were granted for Germany and the USA*. This method can be used for a number of medical applications that require high image quality at low dose which were not available so far with conventional scanning because of technical or dose considerations.
Furthermore, new applications were developed and evaluated which again use the advantages and flexibility of the robot-controlled C-arm system. By the increased rotation speed of the C-arm a better temporal sampling was realized whereby the acquisition of perfusion parameters was enabled. A dedicated perfusion phantom was used for the evaluation which enabled reliable and repeatable measurements and the assessment of perfusion curves.
In the 7th Research Framework the European Union supported the research on dedicated CT of the female breast with 2.05 million Euros from 01/2008 to 06/2010 (Euratom/FP 7-213153; project director and speaker: W. A.

The C-arm system allows almost unlimited freedom of movements. (Foto: Kurt Fuchs, IMP, Erlangen)



a) Concept of using robots in medical imaging and surgical interventions. [Kalender, 2007] b) Implementation of a KUKA light weight robot in experiment in a navigation and robot-assisted intervention at the IMP

Kalender). Three academic partners representing internationally renowned and well established centers for modern radiological imaging at the universities of Erlangen-Nürnberg, Leuven and Rotterdam and one industrial partner, CT Imaging GmbH from Erlangen, worked together on the development of a special device for scanning the female breast with computed tomography (CT) with focus on feasibility and optimisation and in comparison to competing imaging modalities.

Considering the incidence rate of breast cancer in women accurate diagnosis of this disease at an early state is a pending challenge. Digital x-ray mammography is considered today's state of the art in diagnosis although severe insufficiencies are acknowledged. It is a so called projection procedure in which structures and details along the ray are displayed interfering with each other in the image. For this reason findings are often missed – this corresponds to low sensitivity. On the other hand there are findings suspected as malignant although they are not – in this case we speak of low specificity. Significant advantages are expected from superposition-free 3D imaging of the female breast as is generally acknowledged. In eight different subprojects the potential of a dedicated CT scanner for the female breast was scrutinized and its performance features were characterized. Besides the specification of a dedicated breast CT scanner, another aim was to evaluate the role of the different competing methods to diagnose breast cancer. The main objective was, above all, to make breast tumors detectable as early as possible. From this point of view the different alternative imaging procedures had to be explored and evaluated. Since 10/2006 the German Research Foundation has been supporting the Research Unit 661: "Multimodal Imaging in Pre-clinical Research" (Speaker: W.A. Kalender). More information on this project is offered in the section describing special research areas or major research projects funded by the German Research Foundation.

*Kalender, W.A.: Method for recording images of a definable region of an examination tomography facility. DE 10 2006 044 783; US 2008/007525

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 optics, medical imaging and medical image processing and of osteoporoses research.

An essential part of the education program at the Institute is the supervision of diploma theses in different fields and of doctoral studies to graduate as Dr. rer. biol. hum.

Selected Publications

Kalender WA, Kyriakou Y (2007) Flat-detector computed tomography (FD-CT). Eur Radiol, 17: 2767-79

Kalender WA, Deak P, Kellermeier M, van Straten M, Vollmar SV (2009) Application- and patient size-dependent optimization of x-ray spectra for CT. Med Phys, 36: 993-1007

Prell D, Kyriakou Y, Beister M, Kalender WA (2009) A novel forward projection-based metal artifact reduction method for flat-detector computed tomography. Phys Med Biol, 54: 6575-91

Vollmar SV, Kalender WA (2009) Reduction of dose to the female breast as a result of spectral optimisation for high-contrast thoracic CT imaging: a phantom study. Br J Radiol, 82: 920-9

Deak PD, Smal Y, Kalender WA (2010) Multisection CT protocols: sex- and age-specific conversion factors used to determine effective dose from dose-length product. Radiology, 257: 158-66

Kolditz D, Kyriakou Y, Kalender WA (2010) Volume-of-interest (VOI) imaging in C-arm flat-detector CT for high image quality at reduced dose. Med Phys, 37: 2719-30

International Cooperation

Prof. Dr. Hilde Bosmans, Radiologie, Katholieke Universiteit Leuven, Leuven, Belgium

Prof Jean-Denis Laredo, Assistance Hôpitaux Publique de Paris, Paris, France

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

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

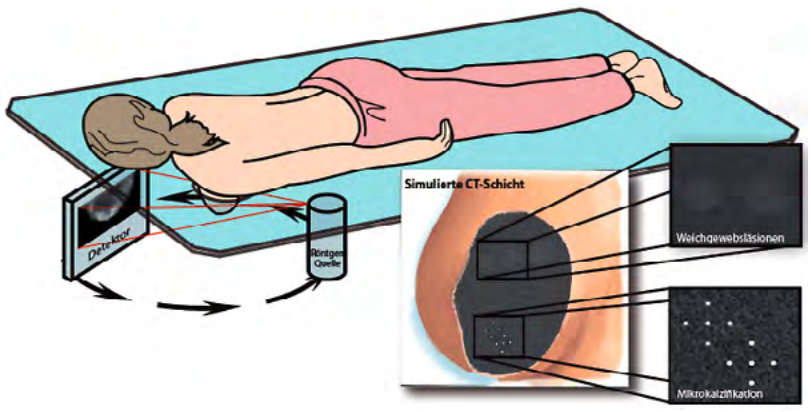
Profs. S Napel, G Rubin, Dep artment of Radiology, Stanford University, Palo Alto, CA, USA

Research Equipment

Siemens SOMATOM Definition Flash

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

Siemens Biograph mMr



In dedicated breast CT a multitude of projection images from all directions on a circular path are taken with low x-ray dose. Calculations indicated that we will be able to display microcalcifications as well or even better than standard mammography does. However, in addition we will be able to clearly see soft tissue lesions which are often obscured by overlying tissue in mammography. Fig.: Inst. f. Med. Physik

Institute of Forensic Medicine

Chair of Forensic Medicine

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Research Focus

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

Structure of the Department

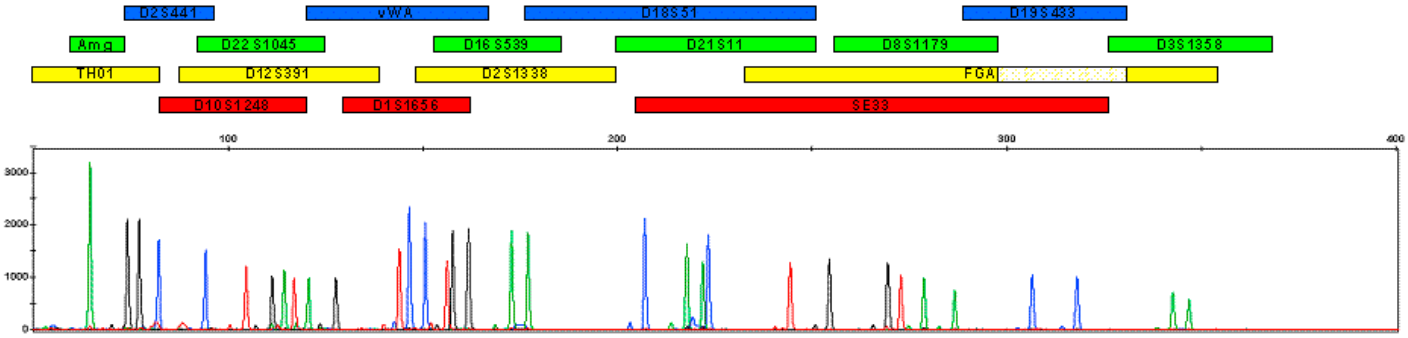
The Institute of Forensic Medicine with its divisions forensic medicine, forensic genetics and forensic toxicology belongs to the clinical theoretical institutes of the Friedrich-Alexander-Universität Erlangen-Nürnberg. Beside responsibilities in the field of research and education, official expertises 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: T. Lederer
Since the beginning of the development of molecular methods for forensic stain analysis and paternity testing in 1985, in particular the PCR-based typing of STR-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-mutliplex systems were established which allow the simultaneous amplification of up to 12 autosomal STR markers. It could be shown that all multiplexes are robust and reliable typing tools for a diversity of forensic specimen and are well suited in the case of paternity testing.
It has already been mentioned that national and international databases for genetic profiles and a cross-national usage of these data are an important tool of investigations by the police. A European-wide standardization and extension of the respective databases as well as the establishment of new typing systems is in the focus of current discussions and developments. Therefore, within our work the existing multiplex systems was 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: 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: I. Doering
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 the case may be 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.



Signal pattern after amplification of 16 polymorphic STR-Markers and the gender-specific locus Amelogenin. This genetic profile includes, amongst others, all European Standard System (ESS) for forensic databases

The purchase of an UPLC/MS-MS instrument leads to 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 (AeAppO) 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

Seider T, Fimmers R, Betz P, Lederer T (2010) Allele frequencies of the five miniSTR loci D1S1656, D2S441, D10S1248, D12S391 and D22S1045 in a German population sample. Forensic Sci Int Genet, 4: e159-60

Research Equipment

Applied Biosystems DNA-Sequenzierautomat

Waters UPLC/MS-MS

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Research Focus
- General research
- Molecular mechanisms of endochondral ossification and skeletal development

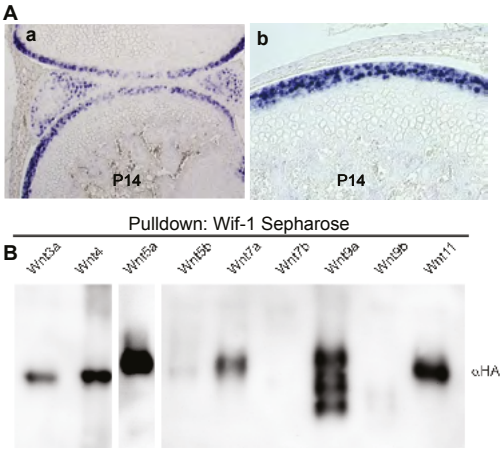
Structure of the Department

The Chair of Experimental Medicine I is located in the Nikolaus-Fiebiger Center of Molecular Medicine and is, together with the Chair of Experimental Medicine II, responsible for the organisation and administration of the Center. In 2007-2008 about 15 persons were involved in research and teaching at the Department of Experimental Medicine I, among them five postdoctoral and senior scientists, three graduate students, three undergraduate students and four technicians. Half of the staff was financed by grants.
After the retirement of Prof. von der Mark, Prof. Dominik N. Müller has been chairman since 1.4.2011.

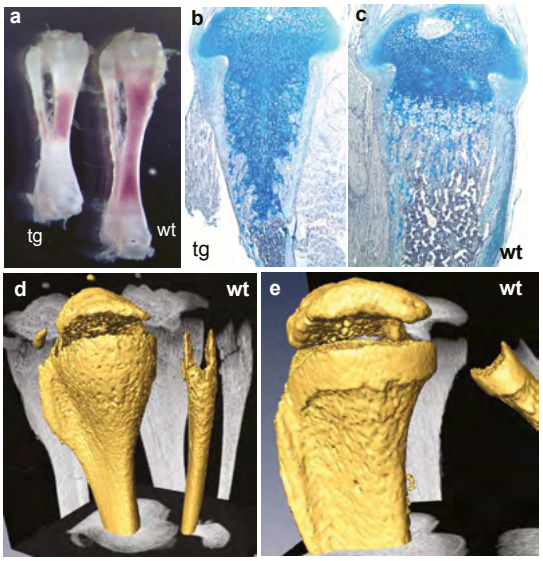
Research

General research
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 organs culture systems and transgenic mouse models is currently the major focus of the workgroup of Prof. von der Mark.

Molecular mechanisms of endochondral ossification and skeletal development
Coordinated turnover of fetal cartilage and its replacement by bone in the growth plate long bones, ribs and vertebrae requires a precise control by numerous growth factors and their receptors. In order to investigate the specific role of growth factors, receptors and transcription factors identified in growth plate cartilage, we generated various transgenic mouse models in which selected factors such as TSG, UCMA and Wif1 were specifically overexpressed in cartilage under the collagen II promoter Col2a1. 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 beta-catenin mice (R. Kemler, Freiburg) with floxed catenin alleles resulted in transgenic mice lacking trabecular bone in the suchondral zone of the diaphysis. Several cooperation were started with laboratories in Vienna (C. Hartmann), Boston (B. Lanske) and in Houston (B. de Crombrugghe) and Freiburg (B. Zabel) for specific gene inactivation studies of the hypertrophic zone using the Col10-Cre deleter mouse.



The Wnt-inhibitor Wif-1 is strongly expressed in the upper zone of articular cartilage (14 d mouse knee joint), suggesting a protective function against degenerative actions of Wnt factors



Overexpression of Sox9 in hypertrophic chondrocytes of the growth plate under a BAC Col10promoter causes substantial retardation of bow marrow formation in transgenic (tg) mice (a), impairs resorption of hypertrophic cartilage (b,c) and bone growth (d,e ; MicroCT image: A. Hess, Pharmacology, Friedrich-Alexander-Universität Erlangen-Nürnberg)

Teaching

The Departments 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

Park J, Bauer S, Schlegel KA, Neukam FW, von der Mark K, Schmuki P (2009) TiO2 nanotube surfaces: 15 nm--an optimal length scale of surface topography for cell adhesion and differentiation. Small, 5: 666-71

Park J, Bauer S, Schmuki P, von der Mark K (2009) Narrow window in nanoscale dependent activation of endothelial cell growth and differentiation on TiO2 nanotube surfaces. Nano Lett, 9: 3157-64

Surmann-Schmitt C, Widmann N, Dietz U, Saeger B, Eitzinger N, Nakamura Y, Rattel M, Latham R, Hartmann C, von der Mark H, Schett G, von der Mark K, Stock M (2009) Wif-1 is expressed at cartilage-mesenchyme interfaces and impedes Wnt3a-mediated inhibition of chondrogenesis. J Cell Sci, 122: 3627-37

Surmann-Schmitt C, Widmann N, Mallein-Gerin F, von der Mark K, Stock M (2009) Stable subclones of the chondrogenic murine cell line MC615 mimic distinct stages of chondrocyte differentiation. J Cell Biochem, 108: 589-99

Hattori T, Müller C, Gebhard S, Bauer E, Pausch F, Schlund B, Bösl MR, Hess A, Surmann-Schmitt C, von der Mark H, de Crombrugghe B, von der Mark K (2010) SOX9 is a major negative regulator of cartilage vascularization, bone marrow formation and endochondral ossification. Development, 137: 901-11

von der Mark K, Park J, Bauer S, Schmuki P (2010) Nanoscale engineering of biomimetic surfaces: cues from the extracellular matrix. Cell Tissue Res, 339: 131-53

International Cooperation

Christine Hartmann, Institute of Molecular Pathology, IMP, Vienna, Austria

Takako Hattori, Graduate School of Dentistry and Medicine, Okayama University, Okayama, Japan

Benoit de Crombrugghe, MD Anderson Cancer Center, Texas University, Houston, TX, USA

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Research Focus
- Molecular oncology of nt signaling
- Role of conductin in centrosome separation
- Tumor suppressor APC
- Functional genomics of renal cell carcinoma

Structure of the Department

The Chair of Experimental Medicine II is situated at the Nikolaus-Fiebiger-Center for Molecular Medicine. There are 16 staff members, 9 of them scientists financed by third-party funds. During the reported period there were 6 PostDocs, 6 PhD students, 3 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 beta-catenin in cytoplasm and nucleus by binding to frizzled and LRP receptors. Beta-Catenin interacts with TCF transcription factors and activates target genes. The destruction of beta-catenin is induced by phosphorylation in a multi-protein complex, which consists of the scaffold component conductin, the serine/threonine kinase GSK3beta and the tumor suppressor APC (Adenomatous Polyposis Coli). The Wnt signal inhibits phosphorylation of beta-catenin and thereby leads to its stabilization. In colorectal tumors, mutations of APC or conductin, or mutations of the serine/threonine phosphorylation sites of beta-catenin lead to stabilization of beta-catenin and trigger constitutive signaling to the nucleus. Such beta-catenin mutations are also found in a multitude of other tumor types suggesting that aberrant activation of wnt signaling is a key mechanism of oncogenic transformation. During the report period we have investigated the consequences of APC mutations on Wnt signaling in tumors, and we have identified a new interaction partner of APC which recruits APC to the plasma membrane. In addition, we have found a surprising role of the negative Wnt regulator conductin in centrosomal separation.

Role of conductin in centrosome separation

We found that conductin/axin2, a negative regulator of beta-catenin, localizes at the centrosomes by binding to the centriole-associated component C-Nap1. Knockout or knockdown of conductin leads to premature centrosome separation termed splitting which is abolished by knockdown of beta-catenin. Conductin promotes phosphorylation of the amino-terminal serine (Ser 33/37) and threonine (Thr 41) residues of centrosome-associated beta-catenin. Beta-catenin mutated at these residues causes centrosomal splitting, whereas a phosphomimicking mutant of beta-catenin does not. Importantly, beta-catenin-induced splitting is not inhibited by blocking beta-catenin-dependent transcription. Treatment with Wnts and inhibition of glycogen synthase kinase 3 block beta-catenin phosphorylation and induce centrosomal splitting. These data indicate that Wnt/beta-catenin signaling and conductin regulate centrosomal cohesion by altering the phosphorylation status of beta-catenin at the centrosomes (M. Hadjihannas, M. Brückner).

Tumor suppressor APC

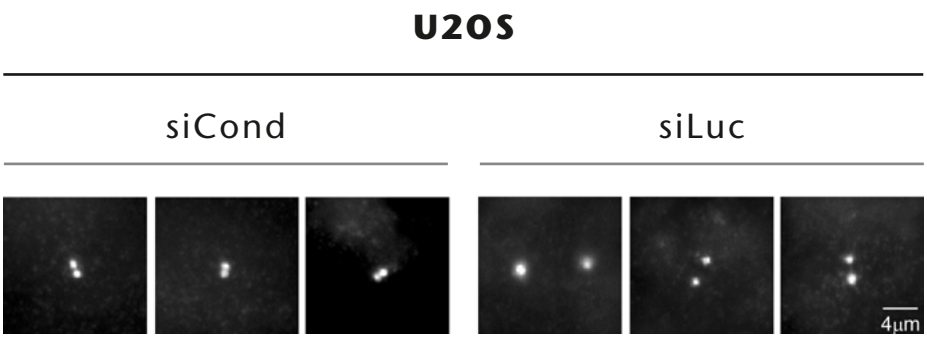
Mutations of the APC gene result in truncations of the APC protein. The "Mutation Cluster Region (MCR)" is located approximately in the middle of the APC gene and overlaps with the region that binds to beta-catenin. To investigate the functional relevance of truncated APC proteins, we have introduced tumor-associated mutations into the APC cDNA and analyzed the effects on the binding to beta-catenin and on beta-catenin destruction. We found that in most cases truncated APC retains reduced, but still significant binding to beta-catenin as well as the capacity of negative regulation of Wnt signaling. We could demonstrate that beta-catenin binding to the so-called 15 amino acid repeats (15R) is necessary and sufficient to target beta-catenin for degradation. The first 15R displays the highest affinity for beta-catenin in the 15R module. Biallelic mutations of the APC gene lead to colon cancer in familial adenomatous polyposis coli (FAP) and result in the synthesis of truncated products lacking domains involved in beta-catenin degradation but still having a minimal length. The analysis of the distribution of truncating mutations along the APC sequence in colorectal tumors from FAP patients revealed that the first 15R is one target of the positive selection of mutations that lead to tumor development. Furthermore, upon closer analysis we found that a domain within the MCR is essential for the activity of the APC fragments. Deletion of this domain, which we have called beta-catenin inhibitory domain (CID), results in a complete loss of APC activity. Our data also indicate that a certain control of activity of Wnt signaling needs to be retained in colon tumors to allow for "just-right-signaling" (Jean Schneikert, Eva Kohler).

Functional genomics of renal cell carcinoma

We have established gene expression patterns of renal cell carcinomas (RCC) using DNA microarrays in order to identify genes relevant for the tumor biology and clinical course of this disease. The von Hippel Lindau tumor suppressor is mutated in clear cell renal carcinoma, which leads to constitutive activation of hypoxia inducible factor (HIF) transcription factors and to expression of its target genes. We found that Activin B, a member of the TGFbeta family, is highly overexpressed in kidney tumors as compared to normal kidneys. Furthermore, expression of Activin B is stimulated by hypoxia via HIFs and repressed by VHL. Functional studies showed that Activin B reduces adhesion of RCC cells to extracellular matrix and promotes invasion of tumor cells *in vitro*. Importantly, knock-down of Activin B inhibited tumor growth of kidney tumor cells in nude mice. Collectively, the data show that the loss of Activin B has similar consequences as the reconstitution of wildtype VHL in kidney tumor cells. Our results indicate that Activin B is a major oncogenic factor in kidney tumors (I. Wacker, M. Sachs).

Liprin-alpha1 to liprin-alpha4 constitute a family of cytoplasmic proteins, which have been found in various multiprotein complexes. For

liprin-alpha1 roles in synapse formation and cell spreading were described but other liprin family members are not well characterized. We found that liprin-alpha4 is upregulated in human clear cell renal cell carcinomas as compared to normal kidney tissue. Liprin-alpha4 expression is downregulated by the von Hippel-Lindau tumor suppressor and upregulated by hypoxia in RCC cell lines. The liprin-alpha4 gene promoter is directly activated by binding of the hypoxia-inducible factor 1 alpha (HIF-1alpha) to HRE consensus binding sites as shown by reporter assays and chromatin immunoprecipitations. RNAi mediated knockdown of liprin-alpha4 leads to reduced E-cadherin and beta-catenin levels at cell junctions and to dissociation of epithelial cell contacts. Our data describe for the first time liprin-alpha4 as a hypoxia-induced gene potentially involved in cell-cell adhesion in kidney tumors (S. Mattauch).



Loss of conductin leads to centrosome splitting. Gamma-tubulin staining to visualize duplicated centrosomes in human osteosarcoma U2OS cells transfected with siRNAs against conductin (left panels) and luciferase (right panels) as control. Note the increased distance between centrosomes after knockdown of conductin.

Teaching

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

Selected Publications

Kohler EM, Chandra SH, Behrens J, Schneikert J (2009) Beta-catenin degradation mediated by the CID domain of APC provides a model for the selection of APC mutations in colorectal, desmoid and duodenal tumors. Hum Mol Genet, 18: 213-26

Wacker I, Sachs M, Knaup K, Wiesener M, Weiske J, Huber O, Akçetin Z, Behrens J (2009) Key role for activin B in cellular transformation after loss of the von Hippel-Lindau tumor suppressor. Mol Cell Biol, 29: 1707-18

Hadjihannas MV, Brückner M, Behrens J (2010) Conductin/axin2 and Wnt signaling regulates centrosome cohesion. EMBO Rep, 11: 317-24

Kohler EM, Brauburger K, Behrens J, Schneikert J (2010) Contribution of the 15 amino acid repeats of truncated APC to beta-catenin degradation and selection of APC mutations in colorectal tumors from FAP patients. Oncogene, 29: 1663-71

Mattauch S, Sachs M, Behrens J (2010) Liprin-alpha4 is a new hypoxia-inducible target gene required for maintenance of cell-cell contacts. Exp Cell Res, 316: 2883-92

International Cooperation

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

Research Equipment

Dako Cytomation MoFlo - Cell Grader

Applied Biosystems Genetic Analyzer ABI 3130

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Research Focus

- Clinical Nutrition in the Elderly
- Sarcopenia and Frailty
- Malnutrition in Nursing Home Residents
- Validation and Modification of the MNA Short-form
- Impact of Long Term High Fat Diets on the Development of Sarcopenia
- Influence of Obesity in Immuno Senescence and Inflamm-aging

Structure of the Department

The Institute for Biomedicine of Aging (IBA) of the Friedrich-Alexander-Universität Erlangen-Nürnberg is characterized by its close cooperation with the Internal Medical Clinic 2, Clinical Center Nürnberg, which includes the Acute Geriatric Hospital and the Geriatric Day Hospital. Professor Cornel C. Sieber is Head of the Chair of Internal Medicine - Geriatrics, the Institute as well as the Clinic. Scientific projects with a medical focus can be realized in close cooperation between experts of the institute and the clinic. The different research groups are mainly funded by third-party funds. The main research topics are clinical pharmacology and toxicology in old age, quality assurance and outcome parameters for geriatric treatment, rehabilitation in old age, health care and allocation of resources in the elderly, metabolism in the elderly, cellular aging, sarcopenia – frailty and nutrition in geriatrics. In order to examine problems of malnutrition in the elderly, the Theo and Friedl Schoeller Endowed Chair for Clinical Nutrition in Geriatrics was established in 2009. Thereby, the research on malnutrition is not only focused on inpatients but also on nursing home residents. For this purpose a close collaboration with the municipal nursing homes of Nuremberg including a geriatric rehabilitation unit was established in 2006.

Research

Clinical Nutrition in the Elderly

Project manager: D. Volkert

With the establishment of the Professorship of Clinical Nutrition in the Elderly, at the Institute, supported by the Theo and Friedl Schöller Foundation, research questions on nutrition in elderly people in different situations of life have been investigated in several projects since 2009.

Following up on ongoing projects on frailty of the elderly, a monocentric cross-sectional study covering usual diet and physical performance is being carried out on 200 voluntary, independent senior citizens living in private households with different levels of frailty. The aim of the study is to investigate the relationship between nutrition and frailty in detail and to identify dietary patterns associated with frailty. The collected data are evaluated on a nutrient and food level. Initial results show that the probability of being frail with a more Mediterranean-based diet is much lower than with a less Mediterranean diet. Moreover, it was shown that an existing risk of malnutrition as well as unintentional weight loss is already associated with functional limitations, and therefore requires observation.

In a further study, the effectiveness of a particularly small volume of energy and nutrient-dense oral nutritional supplement (ONS) in nursing home residents with malnutrition or risk of malnutrition was investigated in cooperation with Caritas. In general, the addition of ONS is found to be effective in prevention and treatment of malnutrition in the elderly; positive effects in terms of nutritional status and mortality are well documented. In the nursing home setting, however, the data situation is poor. In particular, the impact on functionality and morbidity are unclear. 87 residents from six nursing homes in Nuremberg were included in a 3-month randomized controlled intervention study with subsequent evaluation after an additional 3 months. Nutritional status, functionality and medical (history) data were collected at the beginning of the study, after 3 and 6 months in standardized form. Compliance and tolerability were recorded daily. The present results confirm the efficiency of ONS for nursing home residents to improve the nutritional status. However, no evidence has been found to favorably affect functionality. Severe impairment of cognitive and physical functions, however, limits the examination of the functional status and thus the validity of the data. By low compliance the positive effects on the nutritional status were reduced. Gastrointestinal symptoms and immobility were identified as limiting factors, on the other hand high compliance was observed in residents with malnutrition. To improve the efficiency of ONS these aspects should be more taken into account in future.

Sarcopenia and Frailty

Project managers: J. M. Bauer, M. Drey

The working group carried out several externally funded projects in the last two years. The FiAT study (fit in old age by professional training) was supported by the Robert Bosch Foundation in cooperation with the Institute for Sports Science and Sports of the FAU. The aim was to compare traditional strength training with power training in older adults with existing functional deficits, with regard to clinically relevant improvement.

In addition, a method was established with external partners to investigate the degree of sarcopenia, using a serum marker. The analyses focus on the substance of agrin, which is cleaved by the enzyme Neurotrypsin at the neuromuscular junction. In this context, we started electromyographic measurements for the individual determination of the number of motor units in specific muscle groups.

The working group also examined possible links between metabolic changes and decreasing functionality on nearly 200 participants. The observation of appetite-regulating hormones such as ghrelin, leptin and insulin was also included in the analysis.

Malnutrition in Nursing Home Residents

Project manager: R. Diekmann

The Else Kroener-Fresenius Foundation sponsored a follow-up study investigating the nutritional status of nursing home residents with regard to prevalence of under- and malnutrition as well as the influence on functional parameters and mortality. Blood samples of 186 nursing home residents between 65 and 100 years of age were analyzed at baseline and after 12 months regarding vitamins and numerous micronutrients. The highest prevalence of blood level deficiency was shown for vitamin D. Several studies lead to comparable results for the

same age group. Retinol deficiency was detected more often in men than in women. Nearly one third of the investigated population showed low albumin status. After 12 months the blood level of residents with vitamin D supplements increased significantly while the blood level of participants without such supplement decreased significantly. Also retinol levels decreased significantly during the study period. Tube-fed residents showed significantly higher vitamin D and folate levels as well as more favourable cholesterol/tocopherol ratios than their non tube-fed counterparts. Vitamin D was positively associated with several parameters of functionality and survival in the investigated cohort.

Validation and Modification of the MNA Short-form

Project manager: M. J. Kaiser

The Mini Nutritional Assessment (MNA®) is among the most frequently used tests for evaluation of nutritional status in older people. The MNA is available as full version featuring 18 items and as short-form using six items. In the present project which was supported by Nestlé the MNA short-form was validated and modified for facilitated practical applicability using an international dataset from studies conducted in eight different countries. Statistical analyses were made in cooperation with the Institute for Medical Informatics, Biometry and Epidemiology of the FAU. In the validation process the present combination of items within the MNA short-form was confirmed as one of the best item combinations possible. In an alternative approach a combination of items was chosen which allowed for completion of the MNA short-form by using the calf circumference (CC) without having to determine the body mass index (BMI), which can be strenuous in immobilized older people. The weighting of the CC item was increased to provide identical cut-offs and total score for both alternative short-forms with BMI and CC, respectively. In analogy to the full MNA an additional third scoring category termed "risk of malnutrition" was introduced and its optimal cut-offs points calculated. A high agreement between the MNA short-forms and the full MNA was demonstrated.

Impact of Long Term High Fat Diets on the Development of Sarcopenia

Project manager: C. Bollheimer, in collaboration with C. Fellner, Institute of Radiology, University of Regensburg

Sarcopenia denotes the exceeding decline of muscle mass, strength and performance with age. 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 mechanims by which obesity might be linked with sarcopenia. Employing MRI and MRS techinques 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.

Influence of Obesity in Immuno Senescence and Inflamm-aging

Project manager: C. Bollheimer, in collaboration with G. Pongratz, Dept. of Internal Medicine I, University of Regensburg

The immune system changes with age which results not only in a global down-regulation (so-called immuno senescence) but also leads to an up-regulation of certain immunological features (so-called inflamm-aging). Also fat enriched diets and obesity are supposed to profoundly influence the immune system. In our study, we address the question as to how the aging immune system – especially the T-cell independent B-cell activation – might be modulated by dietary induced changes of the production of adipo(-cyto-)kines such as Leptin and IL-1ß.

Teaching

"Instant Aging" is a simulation model of aging. It was integrated in the practial geriatric training of the Medical Clinic 2, Clinical Center Nürnberg. "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

Kaiser MJ, Bauer JM, Ramsch C, Uter W, Guigoz Y, Cederholm T, Thomas DR, Anthony P, Charlton KE, Maggio M, Tsai AC, Grathwohl D, Vellas B, Sieber CC, MNA-International Group (2009) Validation of the Mini Nutritional Assessment short-form (MNA-SF): a practical tool for identification of nutritional status. J Nutr Health Aging, 13: 782-8

Bauer JM, Kaiser MJ, Sieber CC (2010) Evaluation of nutritional status in older persons: nutritional screening and assessment. Curr Opin Clin Nutr Metab Care, 13: 8-13

Kaiser MJ, Bauer JM, Rämsch C, Uter W, Guigoz Y, Cederholm T, Thomas DR, Anthony PS, Charlton KE, Maggio M, Tsai AC, Vellas B, Sieber CC, Mini Nutritional Assessment International Group (2010) Frequency of malnutrition in older adults: a multinational perspective using the mini nutritional assessment. J Am Geriatr Soc, 58: 1734-8

Kaiser R, Winning K, Uter W, Volkert D, Lesser S, Stehle P, Kaiser MJ, Sieber CC, Bauer JM (2010) Functionality and mortality in obese nursing home residents: an example of 'risk factor paradox'? J Am Med Dir Assoc, 11: 428-35

Muscaritoli M, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, Boirie Y, Bosaeus I, Cederholm T, Costelli P, Fearon KC, Laviano A, Maggio M, Rossi Fanelli F, Schneider SM, Schols A, Sieber CC (2010) Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr, 29: 154-9

Wirth R, Bauer JM, Willschrei HP, Volkert D, Sieber CC (2010) Prevalence of percutaneous endoscopic gastrostomy in nursing home residents - a nationwide survey in Germany. Gerontology, 56: 371-7

International Cooperation

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

Prof. Bruno Vellas, GerontoNet, Toulouse, France

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Research Focus

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

Structure of the Department

14 medical doctors work in the departement of orthopedic surgery. The research is accomplished by 6 postdoctorate medical doctors, 14 graduate students and 2 technical assistants.
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 osteodensitometry and radiostereoanalysis (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 focus of our clinic are: total hip-, knee- and shoulderarthroplasty, spine surgery, pediatric orthopedics, foot surgery, tumor-surgery, arthroscopic operations.

Research

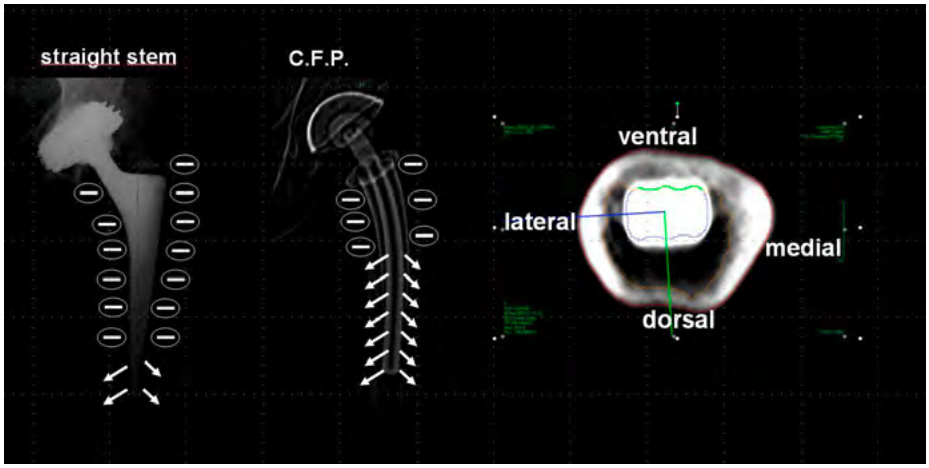
Computer-assisted surgery of the hip joint
The aim of this study is to develop a navigation system for total hip arthroplasty and to use it for the surgery process as well as to test the accuracy of the system with integrated modules. The sytem works with three-dimensional CT-data. The received data 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: R. Forst, 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 computed tomography (CT) – assisted bone density measurement *in vivo*. A special software tool is used (CAPPA postOP, CAS Innovations AG, Erlangen) which allows 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).

Neuromuscular disorders
Project managers: J. Forst, A. Fujak, 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 optimizing of orthopedic treatment, improvement of the medical care and of the 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 - to date there is no causal therapy of Duchenne muscular dystrophy (DMD) - the most common neuromuscular disease. The natural history of this disease includes beside the obligatory restrictive respiratory insufficiency and 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 developed.
In close co-operation 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 department of children cardiology and department of radiology the participation of the heart musculature in DMD is examined.

Radiostereoanalysis for quality control in total hip arthroplasty
Project manager: R. Forst, L. Mueller
Recent studies lead to the conclusion that a measurement of migration at 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. Radio stereo analysis (RSA) has proved 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 micrometer and 0.03°-0.6°. Altogether, 200 patients have been supervised with radiostereometric analysis 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 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.



CT-osteodensitometry: distribution of forces after femoral neck-conserving vs. standard hip endoprothesis

Teaching

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

Selected Publications

Mueller LA, Schmidt R, Ehrmann C, Nowak TE, Kress A, Forst R, Pfander D (2009) Modes of periacetabular load transfer to cortical and cancellous bone after cemented versus uncemented total hip arthroplasty: a prospective study using computed tomography-assisted osteodensitometry. J Orthop Res, 27: 176-82

Fujak A, Kopschina C, Forst R, Gras F, Mueller LA, Forst J (2010) Fractures in proximal spinal muscular atrophy. Arch Orthop Trauma Surg, 130: 775-80

Fujak A, Kopschina C, Forst R, Mueller LA, Forst JX (2010) 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

Fujak A, Kopschina C, Gras F, Forst R, Forst J (2010) Contractures of the upper extremities in spinal muscular atrophy type II. Descriptive clinical study with retrospective data collection. Ortop Traumatol Rehabil, 12: 410-9

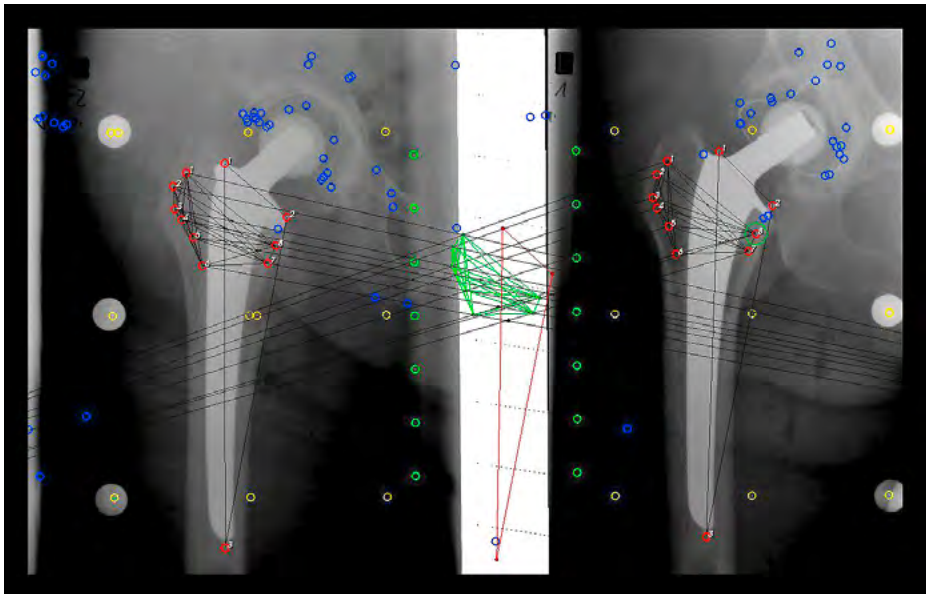
Mueller LA, Nowak TE, Haeberle L, Mueller LP, Kress A, Voelk M, Pfander D, Forst R, Schmidt R (2010) Progressive femoral cortical and cancellous bone density loss after uncemented tapered-design stem fixation. Acta Orthop, 81: 171-7

Müller LA, Wenger N, Schramm M, Hohmann D, Forst R, Carl HD (2010) Seventeen-year survival of the cementless CLS Spotorno stem. Arch Orthop Trauma Surg, 130: 269-75

International Cooperation

Institute Duchenne de Boulogne, Poitiers, France

Gaetano Conte Academy, Naples, Italy



The X-ray-Stereo-Analysis 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 micrometer and 0.03°- 0.6°.

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Research Focus

- Arthroscopic Synovectomy
- Dynamic pedobarography
- Cellular and molecular basis of cartilage degeneration and regeneration
- The role of anti-angiogenic factors for regeneration and homeostasis of articular cartilage
- Endoprostheses for degenerative and inflammatory joint diseases

Structure of the Division

The Division of Orthopedic Rheumatology is an independent institution of the Friedrich-Alexander-Universität Erlangen-Nürnberg which is integrated into the Department of Orthopedics.
Clinical activities focus on the treatment of patients with degenerative and inflammatory joint diseases. The head of the department is also speaker of the Arthritis Center of Erlangen, 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 is on the mechanisms of induction and progression of osteoarthritis. Projects are funded by the DFG and the IZKF. A better understanding of osteoarthritis will help to develop new therapeutic approaches like tissue engineering.
The scientific projects are accompanied by two M.D.s, which are also involved in patient care, and one technician. Another scientist and two technicians are funded by the DFG and the IZKF.

Research

Arthroscopic Synovectomy
Project manager: PD Dr. med. H.-D. Carl
We investigated the results from synovectomy in studies comprising patients with juvenile and adult-onset rheumatoid arthritis.
A study on open hip joint synovectomy in Juvenile idiopathic arthritis (JIA) patients was performed in collaboration with the Orthopädische und Unfallchirurgische Klinik Rummelsberg. Evaluating a series of sixty-seven open hip-joint synovectomies carried out in fifty-six patients with juvenile rheumatoid arthritis, we showed that open hip synovectomy in patients with juvenile rheumatoid arthritis is a safe procedure that can improve hip-joint function for up to five years.
Recent studies addressed the long-term outcome of combined arthroscopic and radiation synovectomy of the knee joint in rheumatoid arthritis. We found that this treatment leads to a stable improvement of knee function for a minimum of five years but surgical re-interventions are frequently observed at the 14-year assessment and challenge the long-term benefit of the procedure. Patients with no interventions had a significantly shorter (7 vs 11 years) history of disease.

Dynamic pedobarography
Project managers: PD Dr. med. H.-D. Carl (Dr. Robert Pfleger-Foundation), Dr. med. J. Pauser
Several studies were conducted using dymamic pedobarography as a computer-based tool for plantar pressure measurement. One of the studies aimed to evaluate the effectiveness of two different types of forefoot-relief shoes frequently used after surgery, especially their safety against unintentional forefoot load. Two different shoe designs (i: short heel-short sole, ii: short heel-complete sole) were compared in two trials each with appropriate and inappropriate use (attempting to put weight on the forefoot). According to our results, forefoot-relief shoes are effective in reducing both mean and peak plantar pressures, but shoes with a nonsupported midfoot and forefoot may be safer with inappropriate use than shoes with a complete sole.
Recent investigations focus on the accuracy of a physical strain trainer for the limitation of weight bearing after surgical interventions (submitted) and the effect of limited knee joint range of motion for foot loading characteristics.

Cellular and molecular basis of cartilage degeneration and regeneration
Stabilization of chondrocyte phenotype by HIF-1a (IZKF A36)
Project manager: PD Dr. K. Gelse
This work demonstrated the importance of hypoxia and the transcription factors HIF-1/-2 for the induction and maintenance of the chondrocyte phenotype *in vitro* and *in vivo*. In a miniature pig model, we could demonstrate that the generally observed problem of insufficient chondrogenesis within superficial layers of cartilage repair tissue correlates with a lack of activity of the transcription factors HIF-1/-2. Instead, chondrogenic differentiation was promoted within the hypoxic deep layers. HIF-1/-2 was shown to transactivate a number of chondrogenic genes including Sox9 and the cell cycle inhibitor p21. Overexpression of HIF-1 and HIF-2 constructs revealed the importance of the oxygen-dependent degradation domain (ODD) for a proper transcriptional activity. Deletion of ODD gave rise to degradation resistant HIF-variants (HIF-1 alpha ODD, HIF-2 alpha ODD) that translocated into the nucleus even under normoxic conditions. However, these constructs had a significantly reduced transcriptional activity. The transcriptional activity was instead pertained in HIF-constructs that exhibited only point mutations at the three hydroxylation sites within the ODD region, which outlines the important role of the N-terminal transactivation site.
In order to yield high transcriptional activity of HIF-1/-2 within cartilage repair tissue, we focused on a concept to induce and maintain avascularity and thus promote hypoxia.

The role of anti-angiogenic factors for regeneration and homeostasis of articular cartilage
(DFG GE 1975/2-1)
Project manager: PD Dr. K. Gelse
In contrast to hyaline articular cartilage, which is physiologically rich in the anti-angiogenic factors Thrombospondin-1 (TSP-1) and Chondromodulin-I (Chm-I), cartilage repair tissue is lacking these proteins. We could demonstrate that a deficiency in these proteins within cartilage repair tissue was associated with vascu-

lar invasion, terminal chondrocyte differentiation and endochondral ossification. The overexpression of TSP-1 and Chm-I using self-complementary AAV-vectors significantly inhibited the angiogenic activity of endothelial cells. In a miniature pig model, administration of TSP-1 or scAAV-mediated overexpression of Chm-I within cartilage defects that were treated by the microfracturing technique, completely inhibited vascular invasion into the cartilage repair tissue and provided an hypoxic milieu that stabilized the permanent chondrocyte phenotype and resisted endochondral ossification. Further *in vitro* studies and gene expression analyses revealed that TSP-1 and Chm-I upregulate factors involved in the cell cycle arrest including p21 and p27, and downregulate pro-hypertrophic genes such as GADD45ß. These data are the basis for continuing projects focusing on the role of cellular quiescence for the survival and phenotypic stability of chondrocytes.

Endoprostheses for degenerative and inflammatory joint diseases

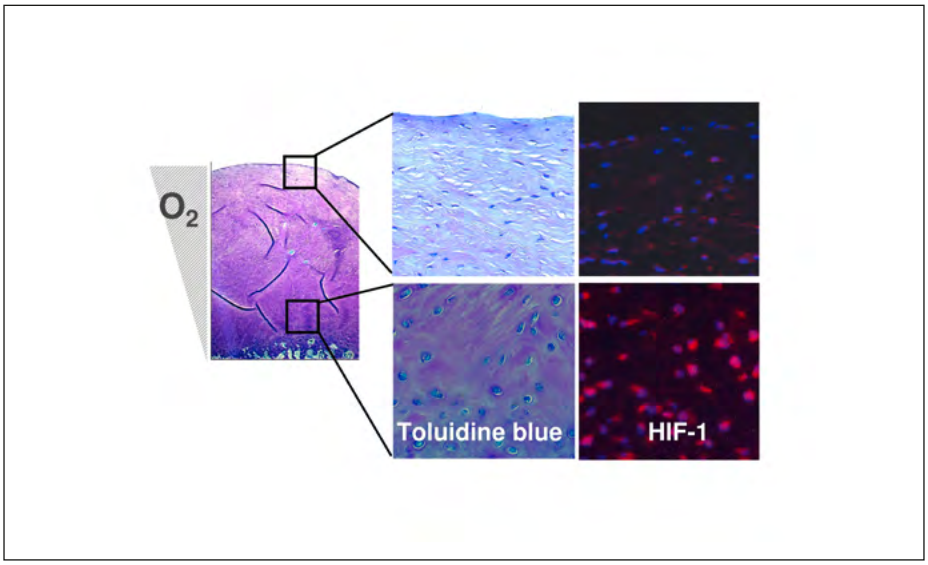
Project manager: B. Swoboda

The aim of this observational study is to identify differences in the treatment of patients with degenerative and inflammatory joint diseases undergoing joint replacement surgery. Preoperative findings, intraoperative differences as well as the patients' satisfaction will be documented. Since joint replacements in rheumatoid patients are frequently done at an early age, a focus will be long-term results after joint replacement, especially of the knee.

Teaching

Staff of the Division of Orthopedic Rheumatology is active in the curriculum for general orthopedics. Specialized lectures are 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 OR when doing surgery on rheumatoid patients.



Role of hypoxia for the maintenance of the chondrocyte phenotype in cartilage repair tissue in a minipig model. In deep hypoxic layers of the cartilage repair tissue, the BMP-2-induced chondrocytic phenotype of mesenchymal stem cells could be maintained even 26 weeks after their transplantation. However, in more superficial layers with higher oxygen levels, the transplanted cells tended to dedifferentiate into fibroblasts. The maintenance of the chondrocyte phenotype correlated with a high activity of the transcription factor HIF-1.

Selected Publications

Blanke M, Carl HD, Klinger P, Swoboda B, Hennig F, Gelse K (2009) Transplanted chondrocytes inhibit endochondral ossification within cartilage repair tissue. Calcif Tissue Int, 85: 421-33

Gelse K, Brem M, Klinger P, Hess A, Swoboda B, Hennig F, Olk A (2009) Paracrine effect of transplanted rib chondrocyte spheroids supports formation of secondary cartilage repair tissue. J Orthop Res, 27: 1216-25

Gelse K, Olk A, Eichhorn S, Swoboda B, Schoene M, Raum K (2010) Quantitative ultrasound biomicroscopy for the analysis of healthy and repair cartilage tissue. Eur Cell Mater, 19: 58-71

Carl HD, Ploetzner J, Swoboda B, Weseloh G, Mueller LA (2011) Cementless total hip arthroplasty in patients with rheumatoid arthritis using a tapered designed titanium hip stem minimum: 10-year results. Rheumatol Int, 31: 353-9

Carl HD, Rech J (2011) [Large-joint synovectomy in the era of biological therapies]. Z Rheumatol, 70: 9-13

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

International Cooperation

Prof. Dr. T. Kirsch, PhD, Department of Orthopedic Surgery, Director of the Musculoskeletal Research Center, New York, NY , USA

Meetings and International Training Courses

09.05.2009: Das dicke Knie, Kollegienhaus FAU Erlangen-Nürnberg, Deutschland,

26.06.2010: Rheuma- häufige Symptome in der täglichen Praxis, Waldkrankenhaus St. Marien, Erlangen, Deutschland,

Department of Anesthesiology

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Research Focus

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

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 Universitätsklinikum 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 of the Universitätsklinikum with 25 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 region of Erlangen-Höchstadt and the location of Herzogenaurach. 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 Friedrich-Alexander-Universität Erlangen-Nürnberg (Chair and Chairman of the department: Prof. Dr. Dr. med h.c. Jürgen Schüttler) as well as the extra Ordinariates for Experimental Anesthesiology (Prof. Dr. Dr. rer. nat. Helmut Schwilden) and Anesthesiology / Pain Research (Prof. Dr. med. Carla Nau) are located at the Department of Anesthesiology. An autonomous unit with an Extraordinariate for Molecular Pneumology (Prof. Dr. Dr. Susetta Finotto) was affiliated to the Chair of Anesthesiology in 2009 and an endowed chair for palliative medicine was established in 2010. The Anesthesiology Department employs 108 medical doctors and 9 scientific members with responsibilities in research and teaching.

Research

Pain research: determinants and modulators of perioperative and palliative pain
Since 2005, an interdisciplinary clinical research unit (DFG KFO 130) has been focusing on postoperative pain that persists beyond the expected healing period. The interdisciplinary team investigates which mechanisms in the peripheral and central nervous system contribute to postoperative pain sensitization and in which way anesthetic and analgesic substances influence these mechanisms, in which cortical and sub-cortical 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 employs basic, disease-, and patient-related methods of pain research.
Other funded projects investigate hypnotic and analgesic effects of anesthetic and analgesic substances and mechanisms of opioid-induced hyperalgesia by means of psycho-physical methods and functional imaging, the function and pharmacology of nociceptor-specific ion channels, and single nucleotide polymorphisms in nociceptor-relevant genes and their role in acute and chronic pain.
Pain research in palliative medicine focuses on the improvement of pain therapy of inpatients and outpatients with cancer.

Medical technology of diagnostic and therapeutic procedures
In the field of hemodynamic monitoring we assessed the precision and accuracy of continuous non-invasive measurements of peripheral arterial pressure (AP). Particularly, the applicability of the technology for clinical use in patients with different ASA physical status was investigated in comparison with simultaneously recorded invasive measurements of AP. Pulse waves of AP have been automatically extracted for modeling the effect of anesthetics on parameters of wave morphology that have been shown to correlate with left ventricular function or vascular status.
In cooperation with the Chair of Medical Informatics we analyzed the medical engineering requirements of a patient data management system (PDMS) for implementation on intensive care units of our university hospital. A pilot version of PDMS has successfully been implemented. The aim of the medical investigation was to develop a consistent reproduction of the medical work flow, whereas the technical system analysis focused the feasibility of implementation of PDMS and its integration in the existing electronic data processing system.

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.
Concerning neuromuscular blocking agents new pharmacodynamic models have been developed to describe the impact of disease progression on the neuromuscular blocking effect of mivacurium and rocuronium in children and adolescents suffering from Duchenne muscular dystrophy and its implication for the dosing of these compounds.
Methods analyzing populations were used to determine the pharmacokinetics of the alpha2-agonist dexmedetomidine during long term sedation in intensive care patients. This study was performed in cooperation with the Department of Anesthesiology, University Turku, Finland, giving special focus on the influence of individual variability and covariates.
Validity and usability of the unitary theory of narcosis for inhalational anesthetics were investigated in rats in a cross-over trial with three different inhalational agents. By using cluster analysis of the spontaneous EEG power spectra of all three compounds, primarily rather similar types of EEG spectra can be found which may

be considered as an indication of the validity of the unitary theory.

Research projects furthering the curriculum and the medical education

The Anesthesiology Department 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, and the patient education:

Our clinic is among the leading parties responsible in accomplishing a national list of learning targets for anesthesiology on behalf of the German Society for Anesthesiology and Intensive Care Medicine. Additionally, we have been commissioned by the Society for Medical Education to make important contributions for the authority-based, national list of learning targets for medicine. Our focus for this contribution is to provide the work packages "acute emergencies" and "practical skills". In order to broaden the range of teaching, the clinic set up several innovative teaching projects, like the elective subject "perioperative medicine" and an internship in the emergency rescue service. We have been very successful in launching preparatory courses for assistant physicians in the fields of emergency and intensive medicine. Before young physicians start working on an intensive care unit or as emergency physician, they have to pass a hybrid curriculum, consisting of simulation and theory modules.

Another focus in the research on medical education is the study within a virtual environment. With the help of initial funding by ELAN, the Department of Anesthesiology together with the Chair for Educational Psychology set up a research project studying the learning process in a situational simulated environment with the focus on the determining factors of each type.

In addition to these projects, we started a research project in close collaboration with the interdisciplinary Pain Center studying patient training in the field of multimodal pain therapy for outpatients in 2010. In a multi-level approach we studied the long-term sustainability and approach. Together with the Competence Center for Medical Didactics (University of Regensburg) we performed interventions to improve the outpatient curriculum.

Besides teaching students and educating physicians, the simulation and training center serves research projects furthering the curriculum and the medical education.

Teaching

The cross-sectional area Emergency medicine accounts, in addition to the lecture "clinical anesthesiology", for the main part of the teaching curriculum in anesthesiology. Professional lecturers and instructors of the Department of Anesthesiology organize this cross-sectional area and are firmly committed to applying new concepts of teaching, such as the use of teaching simulators installed in the simulation and training center of the Department of Anesthesiology. The cross-sectional area Q12 rehabilitation has a focus in pain therapy at the Medical Faculty and is organized by the Department of Anesthesiology. The classes are designed as interdisciplinary and interactive lectures. Additionally, the department offers 6 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

Ihmsen H, Schmidt J, Schwilden H, Schmitt HJ, Muenster T (2009) Influence of disease progression on the neuromuscular blocking effect of mivacurium in children and adolescents with Duchenne muscular dystrophy. Anesthesiology, 110: 1016-9

Pernía-Andrade AJ, Kato A, Witschi R, Nyilas R, Katona I, Freund TF, Watanabe M, Filitz J, Koppert W, Schüttler J, Ji G, Neugebauer V, Marsicano G, Lutz B, Vanegas H, Zeilhofer HU (2009) Spinal endocannabinoids and CB1 receptors mediate C-fiber-induced heterosynaptic pain sensitization. Science, 325: 760-4

Birkholz T, Irouschek A, Labahn D, Klein P, Schmidt J (2010) Electromyographic response persists after peripheral transection: endorsement of current concepts in recurrent laryngeal nerve monitoring in a porcine model. Langenbecks Arch Surg, 395: 121-5

Jeleazcov C, Krajinovic L, Münster T, Birkholz T, Fried R, Schüttler J, Fechner J (2010) Precision and accuracy of a new device (CNAPTM) for continuous non-invasive arterial pressure monitoring: assessment during general anesthesia. Br J Anaesth, 105: 264-72

Leffler A, Reckzeh J, Nau C (2010) Block of sensory neuronal Na+ channels by the secreolytic ambroxol is associated with an interaction with local anesthetic binding sites. Eur J Pharmacol, 630: 19-28

Wilhelm IR, Tzabazis A, Likar R, Sittl R, Griessinger N (2010) Long-term treatment of neuropathic pain with a 5% lidocaine medicated plaster. Eur J Anaesthesiol, 27: 169-73

International Cooperation

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

Prof. G. Simonnet, Laboratoire Homeostasie-Allostasie-Pathologie, Univesité Bordeaux, Bordeaux, France

Prof. G. K. Wang, Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women´s Hospital and Harvard Medical School, Boston, USA

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

Meetings and International Training Courses

21.02.2009: 9. Erlanger Schmerztag, Erlangen

06.–07.11.2009: Pain and Fear Days - Autumn School, Erlangen/Bamberg

27.11.2009: 2. Erlanger Schmerztag für Pflegekräfte, Erlangen

27.–28.11.2009: 14. Erlanger Notfallmedizinische Tage "Präklinische Notfallversorgung - Entwicklung und Trends", Erlangen

12.–13.02.2010: 10. Erlanger Schmerz- und Palliativtage "Schmerztherapie und Palliativmedizin - Forschung und Klinik", Erlangen

19.–22.06.2010: Deutscher Anästhesiecongress DAC, Nürnberg, DGAI

12.11.2010: Pain Day, Erlangen

26.–27.11.2010: 15. Erlanger Notfallmedizinische Tage "Kleiner Patient, große Not - Kinder-Notfälle im Rettungsdienst", Erlangen

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Research Focus
- Immunopathogenesis of Lung Tumor and Allergic Asthma

Structure of the Division

The Institute of Molecular Pneumology consists of thirteen employed persons currently supported from the Institute, a grant from the SFB 643 (Role of NFAT family members in lung tumor and allergic asthma), a DFG grant (Role of Interleukin (IL)-28/Interferon Lambda (IFN) in allergic asthma and lung tumor) and a European grant (Role of Virus infection in asthma in Children).
Research is conducted by twelve scientists: the Chairman, one postdoctoral fellow, six doctoral thesis students (PhD) and four technicians. The team investigates the immunological responses present in experimental lung tumor and allergic asthma. This comprises the 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. Sirbu and the Institute of Pathology (Prof. Dr. Hartmann und Prof. Dr. Rieker) at the Friedrich-Alexander-Universität Erlangen-Nürnberg and Prof. H. A. Lehr at the University-Hospital in Lausanne (Switzerland), our department analyzes the tissue proteins and mRNA derived from lung resection obtained from patients with tumor, to identify important genes involved in the pathogenesis of lung tumor and to set up experimental molecular therapeutic strategies to cure lung adenocarcinoma.
In addition, we recently received support from the European Community to investigate the immunological response in asthmatic and non asthmatic children after rhinovirus infection. For this study, we collaborate with several groups in Europe and with the Department of Pediatrics at the Friedrich-Alexander-Universität Erlangen-Nürnberg (Prof. Dr. Zimmermann, pulmonology and allegology). A variety of molecular and cellular methods are applied to investigate isolated and purified lung immuno-competent cells.
We are grateful to several collaborations from different scientific departments around the world for providing us with updated material to advance our understanding and improvement of the therapy of these two widespread lung diseases.

Research

Immunopathogenesis of Lung Tumor and Allergic Asthma
With research focus on the immunopathogenesis of lung tumor the laboratory identified in the last five years some genes which play a protective or pathogenetic role in the immunoregulation of lung cancer development.

Some examples of those genes we are investigating are described below:
EBV-induced gene 3 (EBI-3) codes for a soluble type I receptor homologous to the p40 subunit of interleukin (IL)-12 that is expressed by antigen presenting cells (APC) following activation. In a recent study we demonstrated that targeting EBI-3 leads to a T-bet-mediated anti-tumor CD8-positive T cell response in the lung. T-bet (T.´-Box expressed in T cells) is a transcription factor expressed by T cells and controls interferon gamma production. Regarding lung adenocarcinoma T regulatory cells are also known as T suppressor cells because they inhibit the immune response and as such are increased in tumor. It is therefore the aim of our research to set up therapeutic 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 signature of the T regulatory cells is Forkhead box P-3 (FoxP-3). We have also recently described the reduction of Nuclear Factor of Activated T cells 2 (NFATc2) mRNA expression in the lungs of patients with bronchial adenocarcinoma. We found that engagement of Glucocorticoid-Induced Tumor Necrosis Factor-Receptor (GITR) with an agonistic antibody suppressed T regulatory cells and expanded effector T cells, in NFATc2 (-/-) mice. This treatment also induced the IFN-gamma levels in the airways and reversed the suppression by T(reg) cells, and costimulated effector and memory T cells resulting in the abrogation of the carcinoma progression. Such therapeutic approach delineates new possible strategies to turn on an immunoresponse in lung cancer.
We and others recently described that targeted deletion of T-bet (T.´-Box expressed in T cells), the main transcription factor inducing IFN-gamma, 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 the anti tumor immunological disregulation 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-17 we are investigating the role of IL-6 and TGF-beta, two Th17 inducing cytokines in lung adenocarcinoma.
Allergic asthma is a disease characterized by an imbalance of the CD4+ T helper cell subsets Th2/Th1 cytokines and transcription factors with a pathological expansion of the Th2 cells and 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. This resulted in an inhibition of inflammation, airway hyper-responsiveness 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 alpha chain of the interleukin-6-receptor resulted in local expansion of positive $CD4^{+}CD25^{+}FoxP3^{+}$ Tregs with increased immunosuppressive capacities. 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, we recently discovered that Tyrosine Kinase 2 (Tyk-2) signaling is involved in IL-17 production. 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 started analyzing the molecular mechanism involved in this disregulation.

Teaching

The Institute is teaching basic immunology at the Institute of Molecular Medicine and at the Microbiology Institute of the Friedrich-Alexander-Universität Erlangen-Nürnberg. Seminars using electronic media are given at a weekly basis to train new students in the institute.

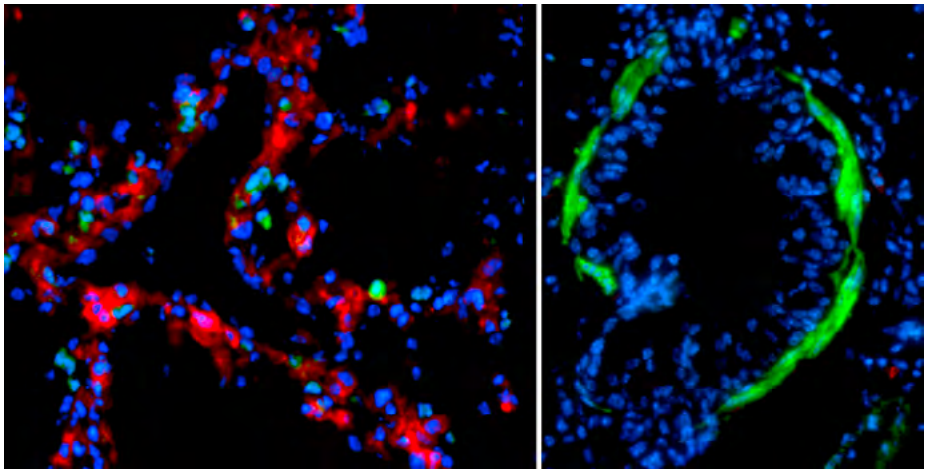
Selected Publications

Finotto S, Neurath MF, Glickman JN, Qin S, Lehr HA, Green FH, Ackerman K, Haley K, Galle PR, Szabo SJ, Drazen JM, De Sanctis GT, Glimcher LH (2002) Development of spontaneous airway changes consistent with human asthma in mice lacking T-bet. Science, 295: 336-8

Maxeiner JH, Karwot R, Sauer K, Scholtes P, Boross I, Koslowski M, Türeci O, Wiewrodt R, Neurath MF, Lehr HA, Finotto S (2009) A key regulatory role of the transcription factor NFATc2 in bronchial adenocarcinoma via CD8+ T lymphocytes. Cancer Res, 69: 3069-76

Neurath MF, Finotto S (2009) Translating inflammatory bowel disease research into clinical medicine. Immunity, 31: 357-61

Hausding M, Tepe M, Ubel C, Lehr HA, Röhrig B, Höhn Y, Pautz A, Eigenbrod T, Anke T, Kleinert H, Erkel G, Finotto S (2011) Induction of tolerogenic lung CD4+ T cells by local treatment with a pSTAT-3 and pSTAT-5 inhibitor ameliorated experimental allergic asthma. Int Immunol, 23: 1-15



Increased Immunostaining of myofibroblasts in the airways of T-bet deficient mice (right panel) compared with that in the airways of WT mice (left panel). Staining for T-bet (red) and alpha smooth muscle actin (green) is shown (Finotto S. et al. Science 2002).

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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 (DKH 107509; DKH 108726)
- Quality Management in Palliative Care in Germany
- Desire for hastened death in patients receiving palliative care (DFG: PAK 158)
- Health care research

Structure of the Division

The Division of Palliative Medicine and its chair are associated with the Department of Anesthesiology of the Friedrich-Alexander-Universität Erlangen-Nürnberg. The Division of Palliative Medicine provides care to patients suffering from advanced or terminal disease and aims to improve quality of life for patients and their relatives (Coordination: Dr. C. Klein). The holistic approach of care requires flexible and individual concepts of different professionals.
The Division of Palliative Medicine is located in the center of the Universitätsklinikum in the ancient building of the obstretics ward. It provides ten beds in six single and two double rooms. Besides the director of the division, Prof. Dr. med. Christoph Ostgathe, the team consists of four physicians, eleven nurses, two psychologists and one physiotherapist, chaplain and social worker, each with a different focus, employed in clinical practice, education and research.
The palliative care consultation team (physician, nurse, and psychosocial team member) offers advice in the field of Palliative Medicine to other departments in the Universitätsklinikum Erlangen. Symptom relief, palliative nursing principles, psychosocial mentoring, adaptation of treatment goals, information and education of patients, and advance planning of care can be promoted.
Outpatient general practitioners, medical specialists, other hospital and health care services or patients themselves approach the Division of Palliative Medicine for admission to the inpatient unit. In case of acute urgency, patients are taken care by the medical emergency unit first. Fees are covered by the individual health care insurance. Furthermore, patients and their relatives may get support from outpatient consultations.

Research

Research is 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.
According to the holistic approach of palliative care, the research team of the Division of Palliative Care of the Universitätsklinikum Erlangen is supported by physicians, psychologists and nursing staff. (Coordination: Dr. S. Stiel)

Outcome Criteria and Quality Indicators in Palliative and Hospice Care in Germany (funding: DKH 107509; DKH 108726)
During the last few years, there has been an increased public and academic awareness of the significance of health care outcome indicators and outcome assessment. To ensure quality of care (a) a consensus of outcome criteria and indicators and (b) validated and applicable outcome assessment instruments in palliative and hospice care are needed. This approach aims at evaluating central outcome measures and assessment instruments in palliative care practice. A discourse analysis of the definitions, a focus group and a systematic review of the literature are performed to further develop a framework for comprehensive concepts. Potential quality indicators will be identified and evaluated.

Quality Management in Palliative Care in Germany
The discussion about suitable quality indicators in palliative care and nationwide quality management is one of the hottest research topics in Germany.
Therefore a standardized basic documentation tool (Hospice and Palliative Care Evaluation HOPE) for palliative care patients in Germany was developed and is recommended by the German Association for Palliative Care 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. In 2010 scientific analyses of data on symptoms burden of non-cancer patients in palliative care and patients with primary and secondary brain tumors were performed. (Prof. Dr. Christoph Ostgathe)

Desire for hastened death in patients receiving palliative care (DFG: PAK 158)
A multicentre study funded by the German Research Foundation (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).
Patients who wish to die anticipate their own future and seem to be led by fear of suffering and by their own personal images of the dying process. These expectations cause a high uncertainty for patients. Life changes during the disease trajectory imply loss of autonomy which in turn calls for more sense of control. The wish to die is the attempt to find a solution for the tension between the uncertainty and the wish for autonomy by gaining control over the time of death. Thus, in the patients` view, opting for palliative care does not contradict the wish for euthanasia. (Dr. Stephanie Stiel)
b) To be able to study the desire for hastened death 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) the desire for hastened death (DhD) in patients with little burden, (2) the character-

istics and intensity of the desire to hasten death 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 the DhD has to be differentiated into actual and non-actual DhD. (Prof. Dr. Christoph Ostgathe)

Health care research
There are several approaches in health care research that aim at implementing recommendations of the World Health Organization (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. (Prof. Dr. Christoph Ostgathe)

Teaching

Academic education (coordination: Dr. J. Buekki) in Palliative Medicine is meant to enable students to improve and reflect their knowledge, skills and attitudes towards incurable diseases, dying, death and bereavement. Central aspects of education are symptom relief, planning of care, communication with terminally ill patients and their relatives as well as learning about the limitations of physicians` roles, the management of ethical dilemmas and end-of-life issues and decisions. Different methodological approaches help to achieve these goals. Teaching is performed by a multiprofessional staff.
In 2010 a series of voluntary lectures was given. Additionally, a seminar which was originally initiated by the Department of Anaesthesiology was held in the monastery of Vierzehnheiligen covering the treatment of dyspnoea, care in the dying phase, hospice care, ethical issues as well as team work, palliative nursing and psychosocial support. Additionally, students are invited to attend clinical ward rounds and interdisciplinary team conferences. A seminar on "Physicians at limits" in cooperation with the Institute of History and Ethics of Medicine addressed students in their final year. Public lectures and a variety of smaller presentations on specific topics were delivered to a broader audience to raise awareness of Palliative Care issues in other medical specialties and in interested laypersons.
Parallel to the further installation of Palliative Medicine services a mandatory class for medical students is currently under development (QB 13 Palliativmedizin). This new approach will be evaluated and studied continuously.

Selected Publications

Stiel S, Bertram L, Neuhaus S, Nauck F, Ostgathe C, Elsner F, Radbruch L (2009) Evaluation and comparison of two prognostic scores and the physicians' estimate of survival in terminally ill patients. Support Care Cancer, :

Gaertner J, Wolf J, Scheicht D, Frechen S, Klein U, Hellmich M, Ostgathe C, Hallek M, Voltz R (2010) Implementing WHO recommendations for palliative care into routine lung cancer therapy: a feasibility project. J Palliat Med, 13: 727-32

Ostgathe C, Gaertner J, Kotterba M, Klein S, Lindena G, Nauck F, Radbruch L, Voltz R, Hospice and Palliative Care Evaluation (HOPE) Working Group in Germany (2010) Differential palliative care issues in patients with primary and secondary brain tumors. Support Care Cancer, 18: 1157-63

Pastrana T, Radbruch L, Nauck F, Höver G, Fegg M, Pestinger M, Ross J, Krumm N, Ostgathe C (2010) Outcome indicators in palliative care--how to assess quality and success. Focus group and nominal group technique in Germany. Support Care Cancer, 18: 859-68

Stiel S, Pestinger M, Moser A, Widdershoven G, Lüke U, Meyer G, Voltz R, Nauck F, Radbruch L (2010) The use of Grounded theory in palliative care: methodological challenges and strategies. J Palliat Med, 13: 997-1003

Voltz R, Galushko M, Walisko J, Pfaff H, Nauck F, Radbruch L, Ostgathe C (2010) End-of-life research on patients' attitudes in Germany: a feasibility study. Support Care Cancer, 18: 317-20

International Cooperation

OPCARE9: "European collaboration to optimise research and clinical care for cancer patients in the last days of life"

Meetings and International Training Courses

06.10.2010: 1. Multiprofessional Symposia "Network for Palliative- and Hospice Care in Erlangen", Erlangen

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Research Focus

- Biomorphometry of the optic nerve
- Functional aspects of retinal neurodegeneration
- Clinoco-pathologic concepts in diagnosis and management of ocular diseases
- Corneal stem cells
- Retinal physiology
- Ocular hem- and lymphangiogenesis and their relevance for corneal transplant immunology and tumor metastasis
- Pseudoexfoliation syndrome/glaucoma
- Circulation of the eye and the visual pathway and computer-aided-diagnosis & virtual education

Structure of the Department

In total 168 Persons are employed at the Eye Hospital. Of these, 42 are physicians and ten scientific staff member. Seven of these are employed as professor. 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.
At the outpatient department surgical procedures are performed (ambulant surgical center, cataract operation, laser coagulation, surgery of the eye lids using CO2 laser, refractive surgery and retino-vitreal surgery). New clinical developments include the multidisciplinary patient care with the electronic patient dossiers available for all departments.

Research

Biomorphometry of the optic nerve
Project managers: C. Mardin, 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: A. Juenemann, J. Kremers, 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.
By using neuronal feedback one can make the system particularly sensitive to the appropriate stimuli. Electrophysiological tests have the advantage of objectivity, but they are less sensitive in comparison to the psychophysical tests.
The combination of multifocal LED stimulation and cyclic summation in the pattern-reversal ERG and the photopic negative response in the full-field flash ERG with coloured stimuli are new developments to improve electrophysiological testing of retinal degeneration.

Clinoco-pathologic concepts in diagnosis and management of ocular diseases
Project managers: L. Holbach, F. Kruse, G. Gusek-Schneider, A. Bergua
1. Diagnosis and management of orbital diseases – a multidisciplinary approach.
The goal of this study is to further improve the multidisciplinary approach in diagnosis and management.
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: U. Schloetzer-Schrehardt, F. 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.

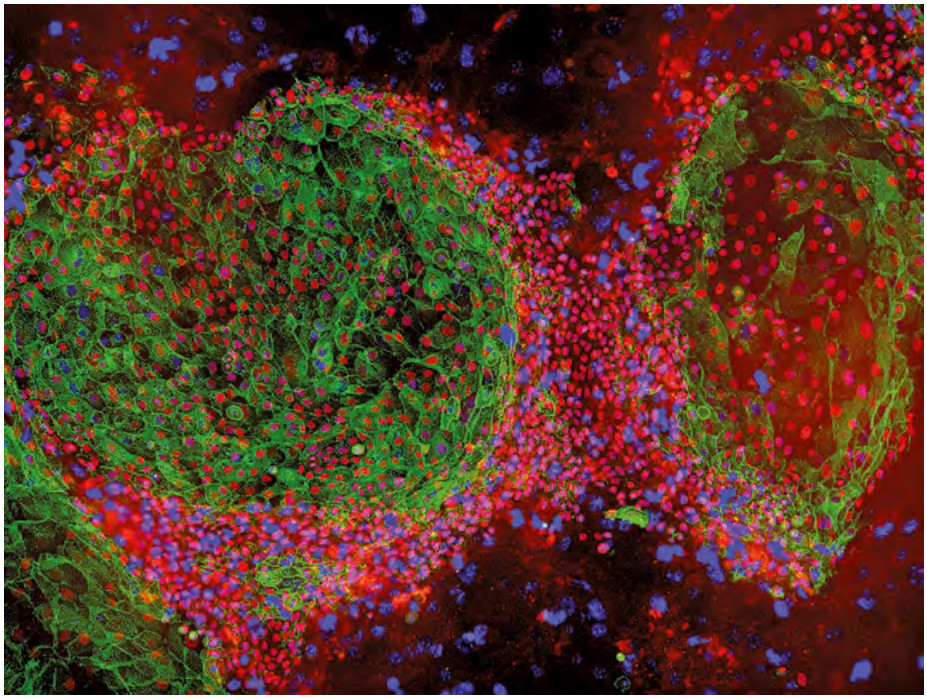
Retinal physiology
Project managers: J.Kremers, A.Juenemann
The goal of this topic is to study the function of the normal and diseased retina. To reach that goal, we record electrophysiological responses of the retina of rodent models of human diseases. In addition, we perform electrophysiological and 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.

Ocular hem- and lymphangiogenesis and their relevance for corneal transplant immunology and tumor metastasis
Project manager: C. Cursiefen
The relevance of pathologic hem- and lymphangiogenesis for corneal transplant immunology after corneal grafting is evaluated. Novel anti(lymph)angiogenic therapies are evaluated and translated by performing several phase II and III clinical trials. The laboratory is the morphometric reading center of several multicenter antiangiogenic trials. The role of pathologic lymphangiogenesis for tumor metastasis of ocular tumors is examined.

Pseudoexfoliation syndrome/glaucoma
Project manager: U. Schloetzer-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.

Circulation of the eye and the visual pathway and computer-aided-diagnosis & virtual education
Project managers: G. Michelson, S.Waerntges, M. Scibor
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.



Cultivation of corneal stem cell clones containing differentiated cells (green fluorescence) in the center and undifferentiated cells (red fluorescence) in the periphery on a feeder cell layer (blue fluorescence).

3. Diffusion measurement of the visual pathway based on magnetic resonance images.
Neurodegenerative eye diseases often involve the entirevisual system and may induce by cerebral macro- and microangiopathie and 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. There are several medical and biologic PhD students in the laboratory.
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

Cursiefen C, Bock F, Horn FK, Kruse FE, Seitz B, Borderie V, Früh B, Thiel MA, Wilhelm F, Geudelin B, Descohand I, Steuhl KP, Hahn A, Meller D (2009) GS-101 antisense oligonucleotide eye drops inhibit corneal neovascularization: interim results of a randomized phase II trial. Ophthalmology, 116: 1630-7

Heindl LM, Hofmann TN, Knorr HL, Rummelt C, Schrödl F, Schlötzer-Schrehardt U, Holbach LM, Naumann GO, Kruse FE, Cursiefen C (2009) Intraocular lymphangiogenesis in malignant melanomas of the ciliary body with extraocular extension. Invest Ophthalmol Vis Sci, 50: 1988-95

Schlötzer-Schrehardt U (2009) Molecular pathology of pseudoexfoliation syndrome/glaucoma--new insights from LOXL1 gene associations. Exp Eye Res, 88: 776-85

Kremers J, Rodrigues AR, Silveira LC, da Silva Filho M (2010) Flicker ERGs representing chromaticity and luminance signals. Invest Ophthalmol Vis Sci, 51: 577-87

Mayer MA, Hornegger J, Mardin CY, Tornow RP (2010) Retinal Nerve Fiber Layer Segmentation on FD-OCT Scans of Normal Subjects and Glaucoma Patients. Biomed Opt Express, 1: 1358-1383

Meyer-Blazejewska EA, Kruse FE, Bitterer K, Meyer C, Hofmann-Rummelt C, Wünsch PH, Schlötzer-Schrehardt U (2010) Preservation of the limbal stem cell phenotype by appropriate culture techniques. Invest Ophthalmol Vis Sci, 51: 765-74

International Cooperation

Dr. Andrew Zele, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia

Prof. Dora Fix Ventura, University of São Paulo, São Paulo, Brazil

Dr. K. Maruyama,, Kyoto Prefectural School of Medicine, Kyoto, Japan

Claude Burgoyne, Discoveries in Sight Research Laboratories, Devers Eye Institute, Legacy Health, Portland, OR, USA

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Research Focus
- Clinical trials office
- Clinical cancer registry
- Anorectal Dysfunction
- Clinical-experimental research
- 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, founded in 2003, which efficiently initiates and monitors the clinical trials. Since then, numerous trials aiming to improve cancer therapy and surgical techniques, and also to establish new surgical approaches have been conducted.
The fundamental molecular research has been conducted at the Division of Molecular and Experimental Surgery (AMEC), 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 German Research Foundation (DFG), BMBF, Deutsche Krebshilfe, IZKF and ELAN-awards from the Universitätsklinikum Erlangen for equal opportunity for women. This department is heading the colorectal carcinoma research group within the framework of the BMBF-core program for molecular diagnostics. Subprojects of the DFG have a focus on "Infection of the endothelium" (1130) and Graduiertenkolleg 1071 "Viruses of the immune system". 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

Clinical trials office
Project managers: W. Hohenberger, H. Golcher
Gastrointestinal tumors: Based on earlier findings, the study "Neoadjuvant chemo radiotherapy and adjuvant chemotherapy with 5-fluorouracil (5-FU) and oxaliplatin versus 5-FU alone in locally progressed rectal cancer of UICC stages II and III" (CAO/ARO/AIO – 04) was launched in 2006 in close collaboration with the Department of Radiotherapy. On 26th February 2010 the trial was closed due to complete inclusion of all 1200 patients (87 patients from Erlangen University)(Prof. Hohenberger, Prof. Goehl).
A prospective-randomized, multi-center phase III trial investigated whether preoperative chemoradiation of resectable tumors of the pancreatic head leads to better median overall survival (ISRCTN78805636) (Prof. Hohenberger, Dr. Golcher).
Further multi-center trials investigating malignant melanoma, gastrointestinal stromal tumors and colon carcinoma are underway. Additionally, clinical trials are underway in patients with anorectal dysfunction and acute cholecystitis, in the prevention of incisional hernias and in patients undergoing resection of deviating ileostomies (Prof. Hohenberger, Prof. Matzel, Dr. Golcher).

Clinical cancer registry
Project managers: W. Hohenberger, S. Merkel
Since 1978 a Clinical Cancer Registry has been prospectively maintained for organ specific tumor documentation. At present more than 25.000 patients are registered. The main focus is on colorectal cancer with over 10.000 documented cases. Patients are followed for life with only 0.5% of patients lost to follow-up.
The scientific evaluation of this data focuses on health services research, 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 therapeutical strategies administered in many patients results from an interdisciplinary cooperation of clinicians and scientists of numerous medical departments.

Anorectal Dysfunction
Project manager: K. Matzel
In 1994, the world's first sacral nerve stimulater combined with graciloplasty for treatment of fecal incontinence was implanted at this clinic. 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 us to document sustainable 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. the NASHA/Dx study have been developed and conducted.

Clinical-experimental research
Project manager: R. Croner
The objective of this study group is the individualization of the multi modal therapy for gastrointestinal tumors based on molecular predictors and factors for prognosis. In cooperation with our partners, high-throughput methods (e.g. genetic expressional analysis, proteomic analysis) for the identification of molecular predictors are applied. With the help of microarray analysis it was possible to identify a group of 50 predicting genes for the lymph node metastasis from primary colorectal carcinoma (Croner et al., 2008). After patent registration by the university, the identified markers are currently being validated prospectively in clinical studies and in cooperation with industry. The functional characterization of the identified genes is currently being conducted through collaborative projects (PD Croner, Prof. Stuerzl).

Molecular mechanisms of inflammatory related angiogenesis
Project manager: M. Stuerzl
In studies conducted previously, the study group identified the large GTPase guanylate binding protein 1 (GBP-1) as the main regulator of the inflammatory related angiogenesis inhibition. New studies on the mechanism of action of GBP-1 have shown that GBP-1 inhibits the migration and invasion capability of en-

dothelial cells through integrin mediated signal processes (Weinlaender et al., 2008).
Initial results suggest that this activity may contribute to an improved survival of colorectal carcinoma patients with Th1-like inflammatory stroma reactions. In order to study the epigenetic effects of inflammatory stroma reactions on the angiogenic behaviour of tumor vascular endothelial cells, we cultured for the first time vital microvascular endothelial cells from more than 20 different colorectal carcinomas. In addition, endothelial cell cultures from unaffected healthy colorectal tissue in the same patients were established. Comparison of gene expression by microarray detected significant differences between the two groups of cell samples (Schellerer et al., 2007). Most interestingly, the isolated tumor endothelial cells also showed a differential gene expression according to the immunologic tumor microenvironment. It is likely that these differences are due to epigenetic imprinting according to the different tumor microenvironments. The relevance of these findings for antiangiogeneic therapy is presently being investigated in a project sponsored by the German Cancer Aid.

Molecular mechanisms of infection related angiogenesis

Project manager: M. Stuerzl
In order to investigate infection associated angiogenesis, an investigation of the pathogenesis of AIDS associated Kaposi's sarcoma (KS) is currently the focus of our attention. This sarcoma is an endothelial tumor which is triggered by the human herpesvirus-8 (HHV-8). The goal of the study is to determine by systematic analyses which of the 86 genes that comprise HHV-8 plays a key function in the angiogenic activation of KS and how different genes may cooperate in the context of the development of KS. For these studies new systems biology approaches were established for high throughput analyses of gene functions. Using these approaches it was possible as a first step to map out the intracellular localization of all HHV-8 coded proteins (Sander et al., 2008). Knowledge of the intracellular localization of herpes viral proteins constitutes an important starting point for the determination of pathogenic functions. Further studies enhance this systems biology approach for the high-throughput analysis of viral gene effects on cellular signal transduction. Comparative proteomic analysis for viral gene effects in endothelial cells complements this approach.

Prof. Hohenberger and OA Dr. Weber

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, smaller, supervised groups are allowed to visit the operating room and the intensive care unit. The Division of Molecular and Experimental Surgery conducts a practical course in high-throughput methods for comparable proteomic and genomic functional analysis for students of molecular medicine over a 3-week period. Alternating exchange of basic researchers and medical scientists should improve translational research.

Selected Publications

Croner RS, Förtsch T, Brückl WM, Rödel F, Rödel C, Papadopoulos T, Brabletz T, Kirchner T, Sachs M, Behrens J, Klein-Hitpass L, Stürzl M, Hohenberger W, Lausen B (2008) Molecular signature for lymphatic metastasis in colorectal carcinomas. Ann Surg, 247: 803-10

Konrad A, Wies E, Thurau M, Marquardt G, Naschberger E, Hentschel S, Jochmann R, Schulz TF, Erfle H, Brors B, Lausen B, Neipel F, Stürzl M (2009) A systems biology approach to identify the combination effects of human herpesvirus 8 genes on NF-kappaB activation. J Virol, 83: 2563-74

Matzel KE, Lux P, Heuer S, Besendörfer M, Zhang W (2009) Sacral nerve stimulation for faecal incontinence: long-term outcome. Colorectal Dis, 11: 636-41

Meyer A, Merkel S, Brückl W, Schellerer V, Schildberg C, Campean V, Hohenberger W, Croner RS (2009) Cdc2 as prognostic marker in stage UICC II colon carcinomas. Eur J Cancer, 45: 1466-73

Hammon M, Herrmann M, Bleiziffer O, Pryymachuk G, Andreoli L, Munoz LE, Amann KU, Mondini M, Gariglio M, Airó P, Schellerer VS, Hatzopoulos AK, Horch RE, Kneser U, Stürzl M, Naschberger E (2010) Role of guanylate binding protein-1 in vascular defects associated with chronic inflammatory diseases. J Cell Mol Med

Hoerske C, Weber K, Goehl J, Hohenberger W, Merkel S (2010) Long-term outcomes and quality of life after rectal carcinoma surgery. Br J Surg, 97: 1295-303

International Cooperation

Univ.-Prof. Dr. Hannes Stockinger, Division of Molecular Immunology, Medical University of Vienna, Vienna, Austria

Prof. Dr. Christine Hohenadel, Veterinärmedizinische Universität, Vienna, Austria

Prof. S. Laurberg, Department of Surgery, University of Aarhus, Aarhus, Denmark

Prof. Dr. Stefano Indraccolo, University of Padova, Padova, Italy

Prof. T. Holm, Colorectal Surgical Unit, Karolinska Institutet, Solna, Stockholm, Sweden

Prof. Quirke, Institute of molecular medicine and pathology, Leeds, UK

Dr. Terry Robins, Quest Diagnostics, Madison, WI, USA

Prof. Dr. Asma Nusrath, Emory University School of Medicine, Atlanta, GA, USA

Meetings and International Training Courses

18.–19.05.2009: 4th International Symposium and Workshop: Advanced Course in Colorectal Surgery, Erlangen

10.–11.05.2010: 5th International Symposium and Workshop: Advanced Course in Colorectal Surgery, Erlangen

18.–19.10.2010: Interdisziplinäre Therapie von Lebermetastasen in modernen onkologischen Versorgungsstrukturen, Erlangen

Research Equipment

SIEMENS AG MEDICAL SOLUTIONS OR1

STORZ INSTRUMENT GmbH AESOP ROBOTERSYSTEM

Bio-Rad Laboratories GmbH VERSARRAY CHIPWRITER PRO

SIEMENS AG MEDICAL SOLUTIONS ROE ARCADIS VARIC

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Research Focus

- Biomechanical features of pectus excavatum - characteristics in recurrences
- Chest wall deformities: Attentional and emotional mechanisms and post-operative pain
- Sealing in minimally invasive pediatric surgery

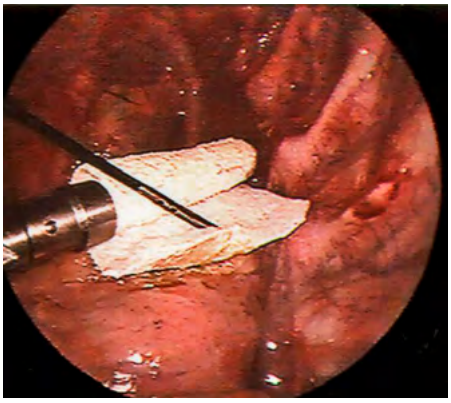
Structure of the Division

The Division of Pediatric Surgery is a self-contained division in the Department of Surgery of the Universitätsklinikum Erlangen. Facilities are settled down in the Department of Pediatric (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 in the Department of Obstetrics and Gynecology (Prof. Dr. M. 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) 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. Most of importance is put on consistent after-care. Traditionally, excellent expertise is known in minimally invasive surgical treatment of chest deformities (Pectus excavatum et carinatum). There are outstanding experiences in minimally invasive pediatric surgery with high-end tissue management and wide-area indications.

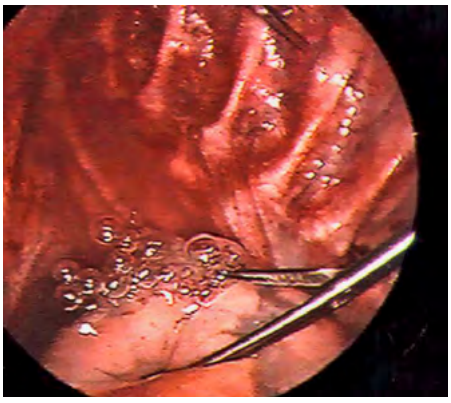
Research

Biomechanical features of pectus excavatum - characteristics in recurrences
Project manager: Dr. S. Schulz-Drost
Correction of chest wall deformities is a challenge in a physiological and biomechanical reconstruction. The main part of the reconstruction is held by the implants and/or techniques of sternal reunification of osteochondral structures.
There were early and late recurrences of pectus excavatum-repair using transsternal metal bar implants caused by costosternal shift and posterior displacement. The affected patients always suffered from tremendous sternal pain, dyspnea and the feeling of chest instability. Computed-3D-reconstructions constantly showed costosternal pseudarthrotic alterations, mostly in hypertrophic shape. Thereby significant mediastinal masses, pleural, pericardial and diaphragmatic adhesions were caused and due to the clinical findings.
The biomechanical model showed the effectiveness of the metal bar implants in sternal elevation and approved the equilibrium of forces in sternal elevation/side load of implant. However, shearing forces of the ribs V-VII themselves were always higher than the contact pressure gained by the costosternal sutures – even multiple chondrotomias were performed to reduce tension. An exceptionally high rate of step-like, to the retrosternal area drifted pseudarthroses is maintained by early degradation of the suture material.
The sternal, median fixation of the metal bar implant was released in another biomechanical model and the fixation was switched to the lateral costal compartment. In that way the implant gained a convex shape which is due to the desired future shape of the chest wall. The costosternal reunion can be carried out free of shearing forces like a puzzle, approximated to the "dome" with the aid of chevron-stabile screws connections after performing multiple costal notchings and wedgings. Appropriately the piles in the costal area of rib V-VII are reconstructed.
The change of implants showed elastic and stabile conditions at the chest wall especially in the areas of costal and sternocostal approximation leading to an enhancement of healing by calming down shearing forces and avoiding pseudarthroses in that way.
Preliminary results from complex recurrent pectus excavatum-repair (n=10) endorsed the innovative principle of chest wall reconstruction. Undisturbed osteochondral healing and an elastic and stabile thorax free of pain are the main endpoints. Secondary benefit is an early mobilization causing less impairment postoperatively.

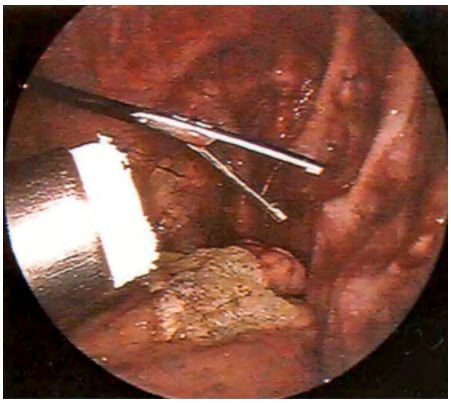
Chest wall deformities: Attentional and emotional mechanisms and post-operative pain
Project manager: S. Lautenbacher
A prospective longitudinal study on chronic postoperative pain was conducted to assess the predictive power of attentional and emotional variables specifically assumed to augment pain, such as pain hypervigilance, pain-related anxiety, pain catastrophizing and attentional biases to pain. Their relevance was determined in comparison with other psychological and physiological predictors (depression, anxiety, somatization, cortisol reactivity, pain sensitivity). In 84 young male patients the predictor variables were assessed one day before surgery (correction of chest malformation). Postoperative outcome (subjective pain intensity and pain-related disability) was assessed three (N=84) and six months (N=78) after surgery. Patients were classified into good and poor outcome groups. Patients with high pain intensity three (25%) or six months (14%) after surgery, differed significantly from those low in pain with regard to their preoperative performance in the dot-probe task (high attentional bias towards positive words). A sizeable portion (54%) of the patients still felt disabled due to pain after three months and a few patients after six months (13%). These patients were those with high preoperative ratings in the Pain Vigilance and Awareness Questionnaire. The few subjectively disabled patients after six months could be identified in addition by low pressure pain and high cold pain thresholds before surgery. An attentional bias towards positive stimuli prior to surgery may indicate a maladaptive coping style, which avoids necessary confrontation with pain and predisposes patients to chronic postoperative pain. Lasting subjectively felt pain-related disability occurs predominantly in



Thoracoscopic, selective leak closure by minimally invasive fleece-bound sealing, MIS-applicator (12-yrs old, cystic fibrosis, recurrent pneumothorax)



Pleural leakage in cystic fibrosis



Minimally invasive sealing of apical lung in cystic fibrosis

patients with high levels of pain hypervigilance before surgery.

Sealing in minimally invasive pediatric surgery

Project manager: R.Carbon

Sealing as a tool of tissue-management seems to be minimally invasive and is due to techniques in pediatric surgery. Especially minimally invasive pediatric surgery [MIPS: laparoscopy, thoracoscopy] seems to show additive effects in procedures for selective leak closure [SLC] (bleeding, chylus, air) and consecutively augment socio-economic effects (demand of drainage, analgetics, time to discharge). High impact is shown by an adequate tool for application.

Following material-science evaluation of liquid sealants on the base of fibrin fleece materials had been evaluated and impregnation of those material by biological two-component-sealing materials (fibrinogen, thrombin) tested. Practicability of such technology is serving an important clinical role.

A rotatable, swizzling 12 mm device was developed which is able to contain rolled-up fleeces up to a size of 10 x 5 cm.

SLC is performed during MIPS-procedure through a 12 mm trokar. The fibrinogen & thrombin impregnated fleece from equine collagen is placed on the target area as a carpet roll. Air and liquid tightness is gained by compression taken to the sealing compound. Appropriately to the compound's elasticity the application is due to "elastic" organs, e.g. lung, or swelling organs, e.g. liver, spleen, gut.

SLC was used in the Department of Pediatric Surgery in MIPS during 1432 procedures [2000-2009] in 344 patients and herewith 385 sealings. Leading indications were pneumothorax, chylothorax, hematothorax, ruptures of liver and/or spleen. In contrast to conventional surgical procedures demand of drainages, time of drainages, stay on ICU and compliations could be cut down significantly. Socio-economic benefit is evident in MIPS-procedures and aims to an advanced method of application and professional sealing systems.

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 of surgery and pediatrics. Cooperative academic events in the course of technical schools at FAU (pediatric nursing, 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)

Selected Publications

Fröhlich T, Richter M, Carbon R, Barth B, Köhler H (2010) Review article: percutaneous endoscopic gastrostomy in infants and children. Aliment Pharmacol Ther, 31: 788-801

Geissler B, Agaimy A, Jüngert J, Hartmann A, Carbon R, Knorr C (2010) Tumoral calcinosis of the gluteal region in a 14-year-old girl with juvenile polyarthritis. Eur J Pediatr Surg, 20: 421-3

Lautenbacher S, Huber C, Schöfer D, Kunz M, Parthum A, Weber PG, Roman C, Griessinger N, Sittl R (2010) Attentional and emotional mechanisms related to pain as predictors of chronic postoperative pain: a comparison with other psychological and physiological predictors. Pain, 151: 722-31

Nüsken E, Dittrich K, Carbon R, Dötsch J (2010) Considering laparoscopic salvage options--is pre-emptive omentectomy necessary in paediatric peritoneal patients? Klin Padiatr, 222: 252-4

International Cooperation

A. Fisher, Biochemical Center of Research, Weizman Institute of Science, Rehovot, Israel

G. Berci, Endoscopic Research, Cedars-Sinai Medical Center, Los Angeles, CA, USA

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Research Focus
- Clinical Research

Structure of the Division

The Division of Thoracic Surgery was founded in 2008 and is offering the complete diagnosis and therapy of lung, mediastinal and chest diseases. Our division is one of the first academic thoracic surgical divisions in Bavaria and also nationwide. Under the auspices of the head of the division, Prof. Sirbu, who is Extraordinarius for thoracic surgery, there are working one consultant thoracic surgeon, one attending physician, two residents and a number of medical students.
In cooperation with the internal medicine departments 1 and 5, the departments of radiotherapy, pathology, palliative care and 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 co-operation with all other oncological field unities and the connection with our Comprehensive Cancer Center 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

Neoadjuvant therapy of locally advanced non small cell lung carcinoma IIIA; concurrent radiochemotherapy followed by surgery
Project managers: H. Sirbu, 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.

Surgical management of pulmonary metastases from colorectal cancer
Project managers: W. Schreiner, 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.

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 our psychosomatic division.

Hyperthermic intrathoracic chemotherapy after pleurectomy/decortication in pleural mesothelioma - a phase I study
Project managers: 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.

Trimodal therapy of malignant mesothelioma with neoadjuvant chemotherapy, pleuropneumectomy, pericardectomy and resection of diaphragma and postoperative radiotherapy of the hemithorax.
Project managers: 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: W. Schreiner
The purpose of the study is the investigation of the extensive lymph node dissection under consideration to 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.

Deep intrathoracic vacuum therapie for chronic empyema
Project managers: W. Schreiner, 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.

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, in practical training we additionally offer practical patient bases exercises on thoracic diseases.

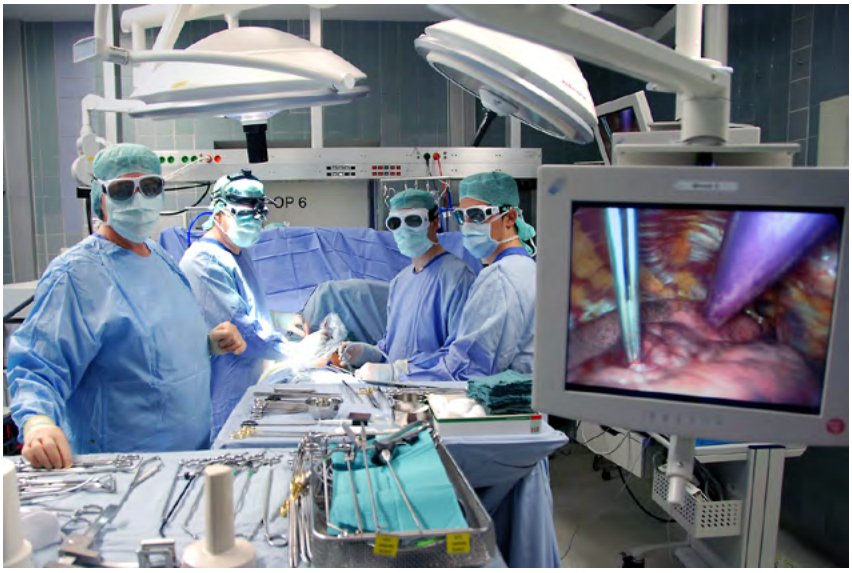
Selected Publications

Sirbu H, Busch T, Aleksic I, Schreiner W, Oster O, Dalichau H (2001) Bronchopleural fistula in the surgery of non-small cell lung cancer: incidence, risk factors, and management. Ann Thorac Cardiovasc Surg, 7: 330-6

Sirbu H, Schreiner W, Dalichau H, Busch T (2005) Surgery for non-small cell carcinoma in geriatric patients: 15-year experience. Asian Cardiovasc Thorac Ann, 13: 330-6

Schreiner W, Fuchs P, Autschbach R, Pallua N, Sirbu H (2010) Modified technique for thoracomyoplasty after posterolateral thoracotomy. Thorac Cardiovasc Surg, 58: 98-101

Sirbu H, Fuchs F (2010) Invited comment. A single-center experience with partially covered expandable stents for the management of "benign tracheobronchial stenosis". Thorac Cardiovasc Surg, 58: 256-7



LASER asissted thoracic surgical procedure

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Research Focus

- Preparation and characterization of white cell-poor platelet concentrates by apheresis
- Preparation of dry platelet concentrates and platelet storage in additive solutions
- Separation of progenitor cells from peripheral blood or cord blood
- Collection of monocytes for the generation of dendritic cells
- Optimization of collection procedures to get regulatory T-cells (Tregs)
- Platelet-derived growth factors for wound healing and angiogenesis
- Autologous blood donation and hematopoiesis
- Clinical research related to hemostaseology
- Clinical research related to hemotherapy
- Legislation of transfusion

Structure of the Divison

The Division of Transfusion Medicine and Hemostaseology is located at the Department of Surgery of the Universitätsklinikum Erlangen. The head of the Division is Extraordinarius for Transfusion Medicine and Hemostaseology.
The department produces pharmaceutical products from blood and has a widespread manufacturing permit by 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 university hospital.
The quality managment system of the department has been certified according to the DIN EN ISO 9001:2008 standard. Laboratories of the department 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: J. Zingsem, 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.

Preparation of dry platelet concentrates and platelet storage in additive solutions
Project manager: 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 PLTs in additive solutions requires the production of "dry platelets" – concentrates containing more than 3000 x 10e+3 per µl. 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.

Separation of progenitor cells from peripheral blood or cord blood
Project manager: J. Zingsem.
Hematopoietic progenitor and stem cells can be identified among bone marrow cells and circulating white blood cells. Another interesting source of progenitor cells is cord blood. A major focus of research is the isolation of hematopoietic progenitor cells in children. Main research interests are the adaptation of apheresis procedures to clinical problems of the isolation of progenitor cells in pediatric patients with small total blood volume and flow cytometry as method of quality control and improvement. In the recently opened cord blood bank, research is focused to cord blood derived-hematopoietic progenitor cells in cooperation with the departments of pediatrics, gynecology and obstetrics and other departments of the hospital.

Collection of monocytes for the generation of dendritic cells
Project manager: E. Strasser.
Circulating monocytes are precursors of dendritic cells 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 Department of Transfusion Medicine 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 dendritic cells.

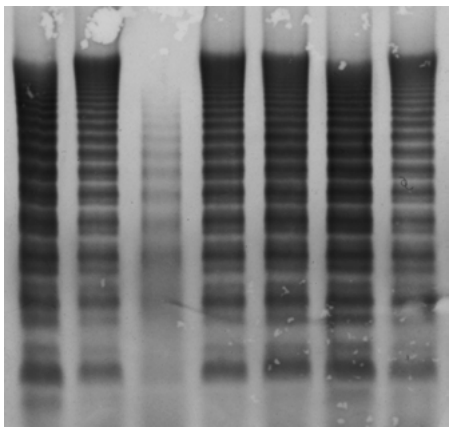
Optimization of collection procedures to get regulatory T-cells (Tregs)
Project managers: E. Strasser, J. Strobel.
T-cells play an important role in adoptive immune response in many diseases (infectious and inflammatory diseases, tumors). Dendritic cells (DCs) act as antigen presenting cells for specific 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 Department of Transfusion Medicine cooperate with colleagues from the Department of Medicine 1, the Department of Dermatology and the Department of Internal Medicine 5 of the Universitätsklinikum Erlangen, to adjust the collection procedures optimally to the specific clinical and experimental demands of procedures aimed at the cultivation and expansion of regulatory T-cells (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.

Platelet-derived growth factors for wound healing and angiogenesis
Project manager: R. Zimmermann.
Platelets contain growth factors which stimulate wound healing, angiogenesis and possibly bone repair. Thereby, 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.

Autologous blood donation and hematopoiesis
Project manager: V. Weisbach.
The preoperative donation of autologous blood is a procedure with a substantial, albeit not yet quantifiable risk for the patient. The compensatory erythropoiesis after repeated autologous blood donation shows marked interindividual variability. Patients with a weak erythropoietic response have an elevated risk to need homologous blood. It is a main focus of this work group to explore the mechanims underlying this variability and to investigate measures to enhance the power of compensatory erythropoiesis after autologous blood donation.

Clinical research related to hemostaseology
Project managers: J. Ringwald, 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
Other research interests are the examination of antibodies against red cell antigens (V. Weisbach), the characterization of factors influencing the quality of stored red cell concentrates (V. Weisbach, R. Zimmermann) and complex dysfunctions of the coagulation system (J. Ringwald, E. Strasser).



High-resolution imaging of von-Willebrand-factor (vWF) multimers; Line 3: von-Willebrand syndrome type 3

Legislation of transfusion
Under the auspices of the Legal Counsel and Deputy Commercial Director of the Universitätsklinikum Erlangen, Dr. jur. Albrecht W. Bender, the Department of Transfusion Medicine and Hemostaseolgy 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 first edition of this book was printed in 2001, the second in 2007. 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.

Teaching

The department 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 for nurses

Selected Publications

Ringwald J, Strobel J, Eckstein R (2009) Travel and oral anticoagulation. J Travel Med, 16: 276-83

Weiss DR, Juchem G, Kemkes BM, Gansera B, Nees S (2009) Extensive deendothelialization and thrombogenicity in routinely prepared vein grafts for coronary bypass operations: facts and remedy. Int J Clin Exp Med, 2: 95-113

Zimmermann R, Wintzheimer S, Weisbach V, Strobel J, Zingsem J, Eckstein R (2009) Influence of prestorage leukoreduction and subsequent irradiation on in vitro red blood cell (RBC) storage variables of RBCs in additive solution saline-adenine-glucose-mannitol. Transfusion, 49: 75-80

Ringwald J, Zimmermann R, Eckstein R (2010) Keys to open the door for blood donors to return. Transfus Med Rev, 24: 295-304

Strasser EF, Eckstein R (2010) Optimization of leukocyte collection and monocyte isolation for dendritic cell culture. Transfus Med Rev, 24: 130-9

Weiss DR, Juchem G, Eblenkamp M, Kemkes BM, Gansera B, Geier M, Nees S (2010) Search for optimized conditions for sealing and storage of bypass vessels: influence of preservation solution and filling pressure on the degree of endothelialization. Int J Clin Exp Med, 3: 10-27

International Cooperation

PD Dr. Jürgen Ringwald, BEST Working Party, International Society of Blood Transfusion (ISBT), Amsterdam, The Netherlands

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Research Focus

- Development of a ceramic knee endoprothesis
- Biomechanical studies of a minimally invasive internal fixation method
- Factors and molecular mechanisms of chondrocyte differentiation and cartilage repair
- „Molecular" Magnetic Resonance Imaging
- Bone physiology and its pharmacokinetics
- Early diagnosis and monitoring of osteoarthritis

Structure of the Division

The Division of Trauma Surgery of the Universitätsklinikum Erlangen employs 14 physicians. Besides patient care, clinical and experimental research work is performed together with 10 doctoral candidates, 1 post-doctoral scientist and 1 technician.

The different research groups work on the evaluation and development of novel innovative surgical methods and implants for joint replacement and fracture treatment. 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 cartilage repair tissue. Another research focus investigates methods for the early diagnosis and characterization of osteoarthritis by magnetic resonance imaging.

The central research projects are supported by approved fundings including the German Research Foundation (DFG), "Bayerische Forschungsstiftung", Interdisciplinary Center for Clinical Research (IZFK), German Association of Orthopedics and Orthopedic Surgery (DGOOC), and ELAN.

Besides the clinical and experimental research projects, the Division of Trauma Surgery is closely integrated in the recently founded "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 severely injured patients by improved communication, better coordinated standards of medical care and quality-based cooperation.

Research

Development of a ceramic knee endoprothesis

Project manager: F.F. Hennig

This project, which is based on a research corporation with Rotec Medizintechnik, Peter Brehm Chirurgie-Mechanik and the Department of Glass & Ceramics of the Friedrich-Alexander-Universität Erlangen-Nürnberg, focuses on the development of an innovative ceramic knee endoprothesis. This project is supported by the "Bayerische Forschungsstiftung". Compared with conventional metal-implants of CoCr-alloy, the fundamental advantages of ceramic materials are an even further reduced wear of friction and the completely non-allergic properties. The main criteria for the acceptance of ceramic implants are based on the reliability of their fixation into bone following cementation in comparison to conventional metal-implants. The technical specifications, including the reliability of fixation and the functional requirements of a specific implantation equipment, were defined and monitored throughout development and prototype construction, including the evaluation and verification in cadaver surgical approaches. First preliminary results were pomising with respect to functionality and operability.

Biomechanical studies of a minimally invasive internal fixation method

Project managers: A. Olk, M. Blanke

Injuries of the pelvis are often associated with a disrupture of the symphysis. Such injuries are often considered instable and need surgical stabilization. Such lesions can be treated by various surgical approaches which often coincide with considerable trauma by the surgical approach. However, the surgical stabilization can also be performed using an internal fixateur system, which can be applied by minimally invasive principles. The duration of surgery can be significantly reduced with a lower surgical risk for the patient. So far, no extensive biomechanical studies on the stability and reliabilty of this implant for this approach have been published. Therefore, this internal fixateur system was evaluated for its resistance and fixation stability in the pelvis in experimental settings and compared with the current gold standard of conventional plate osteosynthesis.

Preliminary results demonstrate that, with respect to biomechanical properties, the minimally invasive internal fixateur system is comparable to the more invasive plate osteosynthesis.

Factors and molecular mechanisms of chondrocyte differentiation and cartilage repair

Project manager: K. Gelse

Chondrocytes are physiologically well adapted to the severe hypoxic conditions within articular cartilage. We could show that hypoxia is even essential for the induction and maintenance of the chondrocyte phenotype. For example, in cartilage repair tissue, spontaneous chondrogenic differentiation of transplanted mesenchymal stem cells was only present in deeper hypoxic layers of the tissue. The formation of cartilaginous repair tissue of high quality in superficial, less hypoxic tissue layers could only be induced by additional stimulation of transplanted cells by gene transfer of certain growth factors (e.g. BMP-2). We could demonstrate that BMP-2 induces similar effects as hypoxia, including the increase in the activity of the transcription factor HIF-1alpha which is crucial for chondrocyte metabolism.

Further experiments showed that rib chondrocyte spheroids represent an endogenous source of growth factors and, thus, exert therapeutically useful paracrine effects on mesenchymal stem cells. The role of hypoxia and the reservoir of endogenous therapeutically useful factors for cartilage and bone regeneration remains the main focus of the current projects supported by the DFG and IZKF.

„Molecular" Magnetic Resonance Imaging

Project manager: G. Welsch

The research project of musculoskeletal magnetic resonance imaging are performed in cooperation with the MR Center of the Department of Radiology of the Medical University of Vienna and particularly focuses on the evaluation of cartilage repair tissues. Multi-modal-/ multi-parametrical approaches were estab-

lished for diagnosis, therapy and follow-up of focal cartilage defects under consideration of orthopedic-traumatological and radiological aspects of cartilage repair. The aim is to non-invasively attain detailed information on the composition of articular cartilage that closely correlate with histological examination. 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. The content of proteoglycans, the alignment of collagen fibres, the hydration status of cartilage as well as remodeling processes of repair tissues could be visualized and quantified leading to important additional information on the properties of cartilage.

Bone physiology and its pharmacokinetics
Project manager: J. Gusinde
This project investigates the bone affinity of various drugs and their pharmacokinetics in osseous tissue. From a therapeutical point of view, the accumulation of drugs in bone tissue can either be desired or inadvertant. For example, bone infections are a dreaded complication which requires efficient antibiotic therapy. In this study, Moxifloxacin proved to be an antibiotic drug with a high bone affinity resulting in effective drug levels within osseous tissue. This study also investigates other drugs that may accumulate within bone and which may negatively affect bone metabolism. With respect to hematogenic distribution, additional animal studies are performed to further characterize microvascularization of bone tissue.

Early diagnosis and monitoring of osteoarthritis
Project manager: M. Brem
Risk factors for the development of osteoarthritis and their monitoring were evaluated by MR imaging methods in cooperation with the Department of Radiology of the Harvard Medical School. A novel method for quantitative determination of cartilage morphology could be developed. The project investigated longitudinal changes in surface characteristics and volume of articular cartilage in early stages of osteoarthritis.
Furthermore, the role of bone marrow edema for the process of osteoarthritis was investigated by MR imaging. It could be shown that the bone marrow edema is not a mandatory phenomenon in early stages of knee osteoarthritis. Its localization and extent is rather variable and does not closely correlate with the process of osteoarthritis. Bone marrow edema rather seems to be associated with physical activity and local inflammatory processes.

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 divison offers the opportunity to participate in clinical rounds and attend in emergency wards and operation rooms.

Selected Publications

Blanke M, Carl HD, Klinger P, Swoboda B, Hennig F, Gelse K (2009) Transplanted chondrocytes inhibit endochondral ossification within cartilage repair tissue. Calcif Tissue Int, 85: 421-33

Landersdorfer CB, Kinzig M, Bulitta JB, Hennig FF, Holzgrabe U, Sörgel F, Gusinde J (2009) Bone penetration of amoxicillin and clavulanic acid evaluated by population pharmacokinetics and Monte Carlo simulation. Antimicrob Agents Chemother, 53: 2569-78

Welsch GH, Trattnig S, Domayer S, Marlovits S, White LM, Mamisch TC (2009) Multimodal approach in the use of clinical scoring, morphological MRI and biochemical T2-mapping and diffusion-weighted imaging in their ability to assess differences between cartilage repair tissue after microfracture therapy and matrix-associated autolo. Osteoarthritis Cartilage, 17: 1219-27

Welsch GH, Zak L, Mamisch TC, Resinger C, Marlovits S, Trattnig S (2009) Three-dimensional magnetic resonance observation of cartilage repair tissue (MOCART) score assessed with an isotropic three-dimensional true fast imaging with steady-state precession sequence at 3.0 Tesla. Invest Radiol, 44: 603-12

Gelse K, Olk A, Eichhorn S, Swoboda B, Schoene M, Raum K (2010) Quantitative ultrasound biomicroscopy for the analysis of healthy and repair cartilage tissue. Eur Cell Mater, 19: 58-71

Welsch GH, Mamisch TC, Zak L, Blanke M, Olk A, Marlovits S, Trattnig S (2010) Evaluation of cartilage repair tissue after matrix-associated autologous chondrocyte transplantation using a hyaluronic-based or a collagen-based scaffold with morphological MOCART scoring and biochemical T2 mapping: preliminary results. Am J Sports Med, 38: 934-42

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Research Focus
- Laboratory for Molecular Medicine (LMM) and gynecological oncology
- Specialized obstetrics and perinatal medicine
- Clinical Trial Center (CTC) and Institute for Women's Health (IFG®)
- Gynecological endocrinology and reproductive medicine

Structure of the Department

Following an extensive structural change in the women's clinic, 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. Peter A. Fasching) and Experimental Reproductive Medicine (Prof. Dr. rer. nat. Ralf 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

Laboratory for Molecular Medicine (LMM) and gynecological oncology
In the LMM (Leader: PD Dr. rer. nat. Reiner Strick) different research approaches are being pursued. The DNA and tissue bank has been expanded. End of 2010 more than 35,200 blood and DNA samples from patients and in cooperation with the Institute of Pathology, Universitätsklinikum Erlangen (Head: Prof. Dr. Arndt Hartmann) more than 8,200 tissue samples of benign and malignant tumors have been stored. The research groups are members of the International Breast Cancer Associated Consortium (BCAC), which has data of more than 30,000 breast cancer patients with appropriate controls.
The cancer research in the LMM (Prof. Dr. Fasching) focused on the search for gene variations and their possible correlation with disease risk and prognosis. The latter appears also to be influenced by microRNA (miRNA). Studies of this new research approach revealed several specific miRNA deregulations in the blood of breast cancer patients using miRNA chips (Dr. Michael Schrauder, PD Dr. Strick).
The continuation of a project about the different effects of tamoxifen on endometrial and breast cells showed that the signaling pathways of AKT and mTOR in these cells were differentially activated. Especially, protein phosphatases were identified as particularly important (PD Dr. Strick, PD Dr. Pamela Strissel, PhD).
The mTOR-kinase inhibitor RAD001 is an established representative of the "targeted therapies" for breast cancer treatment with promising properties. However, it also induces AKT phosphorylation, which leads to the development of resistance. Using the breast cancer MCF7 xenograft mouse model, we could show that the combination with the anti-malaria drug chloroquine (CQ), for which we have already demonstrated breast cancer protective effects, weakened the RAD001-induced AKT phosphorylation and could abrogate the resistance mechanism in cancer cells (Dr. Christian Löhberg).
The research regarding ovarian and endometrial cancer (Prof. Dr. Fasching, Dr. Thiel) in cooperation with the Ovarian Cancer Association Consortium (OCAC) aims for the identification of cancer associated gene variations. A disease-specific locus could be identified for both malignancies in studies with more than 10,000 patients. In addition the role of 14 human endogenous retroviruses (HERV) as a risk factor and importance for cell invasion and cell-cell fusion was examined. In close cooperation with the Institute of Medical Physics Erlangen (Head: Prof. Dr. Ben Fabry) a cell invasion model was established on the basis of collagen. Initial results show that Syncytin-1 (HERV-W) and the neuron-restrictive silencer factor (NRSF) regulate tumor cell invasion in an opposite manner (PD Dr. Strick, PD Dr. Strissel).
In an analysis of endometriosis tissue samples (PD Dr. Stefan P. Renner, PD Dr. Strissel) using the chip technology over 3,900 genes were found to be significantly deregulated. Above all, muscle-regulating genes showed large differences in expression. Additional studies are planned to investigate the activation of pain.

Specialized obstetrics and perinatal medicine
The groups Special Obstetrics and Perinatal Medicine (Dr. Tamme W. Goecke) together with the LMM (PD Dr. Strick) were 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 close cooperation with the Clinic of Children and Adolescents (Director: Prof. Dr. Dr. h.c. Wolfgang Rascher) a continuation of studies of the role of the placenta in fetal programming took place. It was shown that in placentas of small for gestational age neonates (SGA-children), a decreased gene expression of cortisol-activating and -inactivating enzymes occurred simultaneously. In children with intrauterine growth retardation (IUGR) an inverse correlation between placental gene expression of 11-β-hydroxysteroid dehydrogenase 2 and the growth rate in the first year of life was shown.
In a multicenter study planned with 10,000 pregnant women (Clinical Gravidity Association Trials and Evaluation Program, CGATE) over a longer period of observation 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 (Prof. Dr. P. Fasching, Dr. T. Goecke, Dr. F. Faschingbauer). One of the objectives of the study is the detection of valid risk factors that could constitute a basis for preventive measures. Currently, the study is in the run-in phase, in which 500 patients will be introduced. Following a futility analysis, the design of further targets is planned.

Clinical Trial Center (CTC) and Institute for Women's Health (IFG®)

Since 2001 over 150 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 1,200 patients received a treatment.

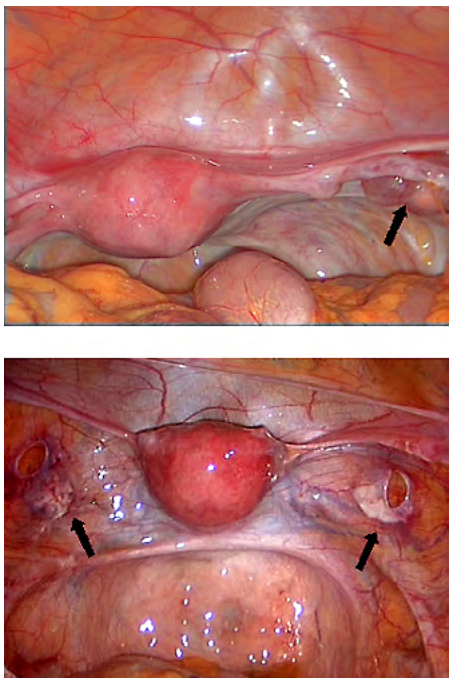
Noteworthy for breast cancer is the Preface study (LKP: Prof. Dr. Fasching), which recruitment has ended and was carried out throughout Germany under guidance of Erlangen. A total of 3500 patients were included from more than 220 study centers. The Phase-IV study examines pharmacogenetic markers, which should predict treatment effects and side effects of aromatase inhibitors. Initial analysis of toxicity are expected 2011. In regard to genital cancers the Women's Hospital (LKP: Dr. F. Thiel) heads the AGO-cervix-1 study. This Phase-III study (expected to end 2011) compares the chemotherapy regimens paclitaxel plus topotecan and topotecan plus cisplatin in patients with recurrent or persistent cervical cancer.

Gynecological endocrinology and reproductive medicine

The research in the University reproductive center (UBF) has included the cryo-preservation of germ cells, the physiology of movements of non-pregnant uterus and the pathology of hyperandrogenism.

In an effort to restore fertility in young cancer patients after chemotherapy and / or radiotherapy, a pregnancy after homologous endoscopic transplantation of cryo-preserved ovarian tissue was achieved for the first time in Germany. Experiments with an *ex vivo* uterus-model showed that seminal plasma has a high potential to trigger contractions, which could be modulated by progesterone and estradiol. The perfusion with appropriate protectives resulted in the maintenance of contractility of the whole uterus during cryopreservation.

In one of the largest retrospective evaluations on polycystic ovary syndrome (PCOS), it could be shown that the current definition of PCOS is not suitable for identifying patients with metabolic risk factors (Prof. Dr. Andreas Müller, Prof. Dr. Ralf Dittrich, PD Dr. Susanne Cupisti, Dr. Patricia G. Oppelt).



Oncofertility: Reconstruction of ovarian function by transplantation of cryopreserved ovarien tissue (arrows indicate the transplanation sites on the pelvic wall)

Teaching

After the implementation of a specific functional area (2008), the upgrading of quality management (QM) was further developed (PD Dr. W. Frobenius, Master of Medical Education; PD Dr. Susanne Cupisti). The aim was a certification according to DIN EN ISO 9001:2008, issued by the Management Service of the TÜV Süd in October 2010 after an appropriate audit. The Erlangen Department of Obstetrics and Gynecology is hence one of the first University Clinical Institutions in Germany, which has acquired a QM-certificate specifically for teaching.

Selected Publications

Dittrich R, Mueller A, Maltaris T, Hoffmann I, Magener A, Oppelt PG, Beckmann MW (2009) Hormonal and histologic findings in human cryopreserved ovarian autografts. Fertil Steril, 91: 1503-6

Frobenius W, Ganslandt T, Junger J, Beckmann MW, Cupisti S (2009) Effectivity of Peer Teaching for Gynecological and Obstetrical Skills Training. Geburtsh Frauenheilk, 69: 848-855

Schroth W, Goetz MP, Hamann U, Fasching PA, Schmidt M, Winter S, Fritz P, Simon W, Suman VJ, Ames MM, Safgren SL, Kuffel MJ, Ulmer HU, Boländer J, Strick R, Beckmann MW, Koelbl H, Weinshilboum RM, Ingle JN, Eichelbaum M, Schwab M, Brauch H (2009) Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. JAMA, 302: 1429-36

Bolton KL, Tyrer J, Song H, Ramus SJ, Notaridou M, Jones C, Sher T, Gentry-Maharaj A, Wozniak E, Tsai YY, Weidhaas J, Paik D, Van Den Berg DJ, Stram DO, Pearce CL, Wu AH, Brewster W, Anton-Culver H, Ziogas A, Narod SA, Levine DA, Kaye SB, Brown R, Paul J, Flanagan J, Sieh W, McGuire V, Whittemore AS, Campbell I, Gore ME, Lissowska J, Yang HP, Medrek K, Gronwald J, Lubinski J, Jakubowska A, Le ND, Cook LS, Kelemen LE, Brook-Wilson A, Massuger LF, Kiemeney LA, Aben KK, van Altena AM, Houlston R, Tomlinson I, Palmieri RT, Moorman PG, Schildkraut J, Iversen ES, Phelan C, Vierkant RA, Cunningham JM, Goode EL, Fridley BL, Kruger-Kjaer S, Blaeker J, Hogdall E, Hogdall C, Gross J, Karlan BY, Ness RB, Edwards RP, Odunsi K, Moyisch KB, Baker JA, Modugno F, Heikkinenen T, Butzow R, Nevanlinna H, Leminen A, Bogdanova N, Antonenkova N, Doerk T, Hillemanns P, Dürst M, Runnebaum I, Thompson PJ, Carney ME, Goodman MT, Lurie G, Wang-Gohrke S, Hein R, Chang-Claude J, Rossing MA, Cushing-Haugen KL, Doherty J, Chen C, Rafnar T, Besenbacher S, Sulem P, Stefansson K, Birrer MJ, Terry KL, Hernandez D, Cramer DW, Vergote I, Amant F, Lambrechts D, Despierre E, Fasching PA, Beckmann MW, Thiel FC, Ekici AB, Chen X, Australian Ovarian Cancer Study Group , Australian Cancer Study (Ovarian Cancer) , Ovarian Cancer Association Consortium , Johnatty SE, Webb PM, Beesley J, Chanock S, Garcia-Closas M, Sellers T, Easton DF, Berchuck A, Chenevix-Trench G, Pharoah PD, Gayther SA (2010) Common variants at 19p13 are associated with susceptibility to ovarian cancer. Nat Genet, 42: 880-4

Goecke TW, Ekici AB, Niesler B, Loehberg CR, Hammer C, Rappold G, Schanze D, Straub V, Altmann HH, Strissel P, Strick R, Beckmann MW, Fasching PA (2010) Two naturally occurring variants of the serotonin receptor gene HTR3C are associated with nausea in pregnancy. Acta Obstet Gynecol Scand, 89: 7-14

Ruebner M, Strissel PL, Langbein M, Fahlbusch F, Wachter DL, Faschingbauer F, Beckmann MW, Strick R (2010) Impaired cell fusion and differentiation in placentae from patients with intrauterine growth restriction correlate with reduced levels of HERV envelope genes. J Mol Med, 88: 1143-56

International Cooperation

Prof. Bruce Ponder, Prof. Doug Easton, Breast Cancer Consortium, Cambridge, Cambridge, UK

R. Weinshilboum, MD; L. Wang, MD; J. Ingle, MD, Mayo Clinic, Rochester, MN, USA

Prof. D. Slamon, MD, PhD, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA

Meetings and International Training Courses

05.–07.02.2009: Intensivkurs-Süd für Gynäkologie Endokrinologie und Reproduktionsmedizin, München

18.03.2009: Die Frau mit Mammakarzinom 2009, Erlangen

04.07.2009–05.07.0009: Erlanger Kolposkopie 2009, Erlangen

20.–21.11.2009: IV. Bayern-Seminar 2009 für Gynäkologie und Geburtshilfe, Erlangen

17.03.2010: Update Mammakarzinom, Erlangen

20.–21.03.2010: Kolposkopie Workshop, Erlangen

10.–12.06.2010: 84. Tagung Bayerische Gesellschaft für Geburtshilfe und Frauenheilkunde, Erlangen

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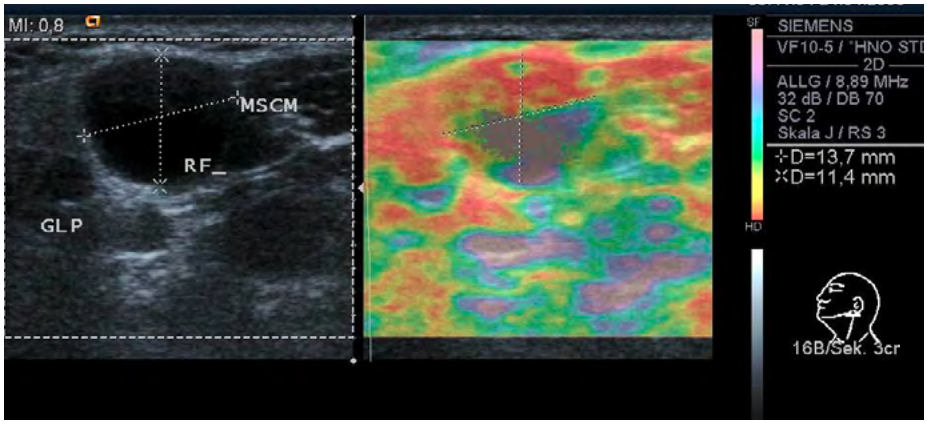
Research Focus
- Nanomedicine
- Allergology/clinical immunology and rhinology
- Computer aided surgery/robotics
- Experimental otolaryngolgy
- Individual speech processor programming in cochlear implant users
- Neurootology/vestibular laboratory
- Neurophysiology
- Laboratory for sleep disorders/somnology
- Ultrasound and Endoscopy



Ultrasound image using ultrasound elastography for measurement of tissue stiffness in different tumor entities

Structure of the Department

In the Department altogether 270 people are employed, out of these 44 are engaged in the clinical-scientific area, eight exclusively within basic research and 218 in nursing and administration.
Within different scientific groups clinical-relevant research concerning neurootology, somnology, oncology, ultrasound and endoscopy, allergology and neurophysiology is performed.

Research

Nanomedicine

In a countrywide and competitive announcement for a W3-Professorship for Nanomedicine of the Else Kröner-Fresenius-Stiftung the Medical Faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg and Prof. Dr. Christoph Alexiou accomplished successfully and since July 1st, 2009 he owns this Professorship. In this position he works as an assistant medical director at the ENT-clinic and leads the Section for Experimental Oncology and Nanomedicine (SEON). An emphasis of his scientific work is the local chemotherapy with magnetic nanoparticles (Magnetic Drug Targeting), which is a new and innovative therapeutic regime. Magnetic nanoparticles bound to cytostatic drugs are injected close to the tumor into the supporting vessels and are enriched under the presence of an external magnetic field in a certain body compartment (e.g. tumor). These particles serve as vehicles for concentrating the bound chemotherapeutic agents (e.g. Mitoxantrone) over the blood way in the desired target area which is in the focus of an appropriate external magnetic field. In the laboratory of SEON extensive work is accomplished for the synthesis of biocompatible nanocarrier systems and their application in animal models. The aim of these basic research studies is to lay the foundations for human trials ("Translational Cancer Research").

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 polyp tissue under *in vitro* conditions with the biopsy mucosa oxygenator is used for investigating relevant mediators of inflammation. In a multicentered double-blind placebo-controlled study patients oral corticosteroids post-operative are evaluated, looking at the rate of recurrences. Study centers: Dpt.s of Otolaryngology, Head- and Neck-Surgery in Kiel, Regensburg, Berlin Charite, Marburg and Stuttgart.

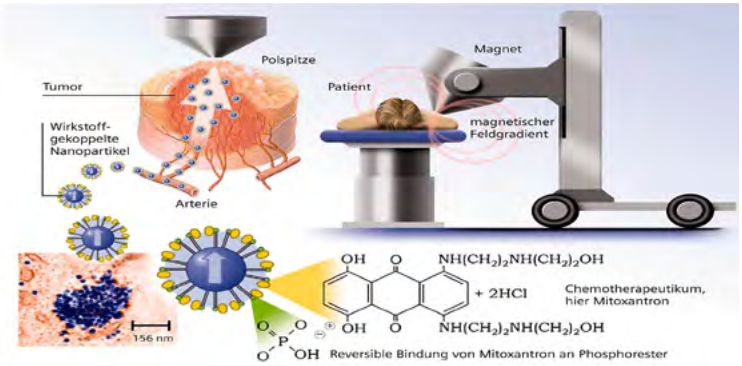
Computer aided surgery/robotics

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.

Experimental otolaryngolgy

The research lab experimental otolaryngology focused its research on projects on 1. inner ear biology 2. central tinnitus and 3. hearing impairment in animal models. Results yielded e.g.:
1. The first characterization of the developmental expression of glycine transporters (GlyT1 and 2) in the cochlea. Their localization suggests a participation in inner ear signal transduction.
2. Cortical correlates of central tinnitus development in an animal model that point to the neuronal mechanisms that underlie the development of a tinnitus percept.

with Magnetic Field to the Tumor



Schematical drawing: Magnetic Drug Targeting
Enrichment of the nanoparticles in the tumor is shown in the left part of the picture

3. The description of cortical effects of hearing aid use in hearing impaired animals that point to a loss in dynamic range (rate-level-functions) of auditory neurons.

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 Int.), 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. Further the computerized dynamic posturography was used not only to improve the diagnostics of vestibular disturbances but also very successfully to 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.

Laboratory for sleep disorders/somnology
The projects focus on a surgical treatment of primary snoring and obstructive sleep apnea. Besides the well known nCpap therapie in obstructive sleep apnea we try to find alternative treatment options. Therefore we are inventing a special nasopharyngeal stent in order to prevent obstruction in patients suffering of obstructive sleep apnea. Results are to be compared to nCpap therapy.
Concerning the treatment of primary snoring we are comparing a coblation assisted palatoplasty to general uvulopalatopharyngoplasty or other surgical methods such as laser assisted uvuloplasty.

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.
Using state of the art ultrasound devices, 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. A 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) 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.

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 all the year.

Selected Publications

Hornung JA, Brase C, Bozzato A, Zenk J, Iro H (2009) First experience with a new titanium clip stapes prosthesis and a comparison with the earlier model used in stapes surgery. Laryngoscope, 119: 2421-7

Zenk J, Koch M, Iro H (2009) Extracorporeal and intracorporeal lithotripsy of salivary gland stones: basic investigations. Otolaryngol Clin North Am, 42: 1115-37, Table of Content

Alexiou C, Tietze R, Schreiber E, Lyer S (2010) [Nanomedicine : Magnetic nanoparticles for drug delivery and hyperthermia - new chances for cancer therapy]. Bundesgesundheitsblatt Gesundheitsforschung, Gesundheitsschutz, 53: 839-45

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Lyer S, Tietze R, Jurgons R, Struffert T, Engelhorn T, Schreiber E, Dörfler A, Alexiou C (2010) Visualisation of tumor regression after local chemotherapy with magnetic nanoparticles - a pilot study. Anticancer Res, 30: 1553-7

Moeller CK, Kurt S, Happel MF, Schulze H (2010) Long-range effects of GABAergic inhibition in gerbil primary auditory cortex. Eur J Neurosci, 31: 49-59

International Cooperation

Prof. Mc Gurk, Salivary Research Unit, Maxillofacial Surgery, Guy's, King's and St. Thomas' Dental Institute, King's College, London, UK

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Research Focus
- Auditory evoked cortical potentials
- Biomechanical parameterization of vocal fold vibrations
- Modeling of tracheoesophageal voice
- Phonovibrography - objective analysis of vocal fold vibrations
- Quantitative evaluation of speech
- Principles of voice production

Structure of the Division

Phoniatrics and Pediatric Audiology is a medical field which addresses diseases and disorders of voice, speech, language, hearing and swallowing. Research deals basically with communication disorders on the perception side (hearing research) and the production side (speech and voice research). The principle contents of the reserach 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 Friedrich-Alexander-Universität Erlangen-Nürnberg and is supervising scientific works in all of these fields. Totally, 21 employees work at the department, four of them are financed via third-party funds.

Research

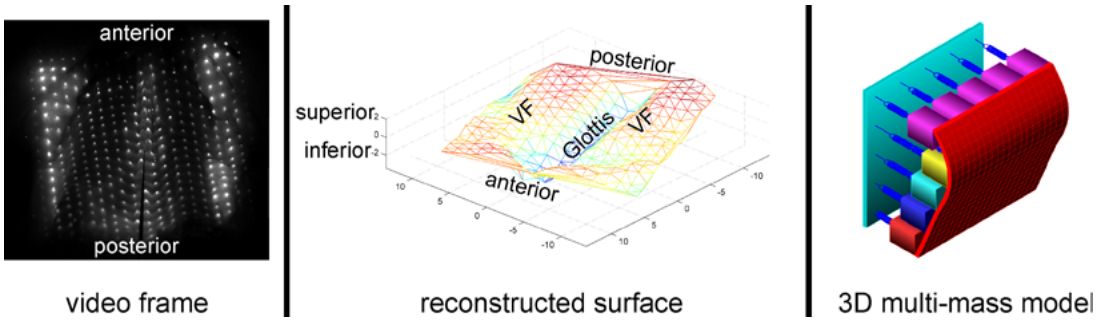
Auditory evoked cortical potentials
Processing, perception, and analysis of heard speech is an enmeshed, partly hierarchical process chain, in which numerous serial, parallel, and distributed neural networks are participating. An impairment of this process chain affects the linguistic development of children adversely. Focus of our workgroup is the development of objective tests for the auditory processing of speech, which are independent of the patients' state of attention. As an approach auditory evoked potentials were used, whereat event related voltage deflections are derived from the scalp (EEG). It was investigated, how far the discrimination ability of speech relevant stimulus features can be assessed electrophysiologically. In fact, potentials could be evoked (mismatch negativity), whose occurrence correlated with behavioural determined auditory functions.

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 on *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 German Reserach Foundation (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 work very closely together with colleagues from the US.

Quantitative evaluation of speech
For the evaluation of speech disorders objective, validated and simple evaluation methods are missing. Speech disorders are usually assessed by a perceptive evaluation with only restricted reliability for clinical or scientific use.
Automatic speech analysis is used in order to provide an objective and cost-reducing diagnostic method for the therapist. The correlation between automatic analysis and perceptive rating by a panel of speech experts was enhanced during the projects. The involved patient groups comprised partially laryngectomized persons, patients with benign chronic hoarseness, and children with cleft lip and palate. The automatic methods analyzed voice parameters, such as in the established roughness-breathiness-hoarseness (RBH) scheme, and speech aspects, such as intelligibility. Ad-



Left: An excised larynx with projected laserdots. Middle: Reconstructed three-dimensional surface of the vocal folds. Right: this numerical 3D-model is fitted towards the extracted vocal fold vibrations.

ditionally, the voice over the telephone is subject of the experiments since the telephone has a very important role in communication society. For all scenarios, high human-machine correlations showing the validity of the approaches were achieved.
The projects are in cooperation with the Department on Pattern Recognition (Head: Prof. Dr.-Ing. J. Hornegger) of the Friedrich-Alexander-Universität Erlangen-Nürnberg as well as with the clinics for oral and maxillofacial surgery (Head: Prof. Dr. Dr. F. W. Neukam).

Principles of voice production
Voice production within the larynx is still not entirely understood neither in normal nor in pathological voice. The goal of the interdisciplinary DFG research unit FOR894/1 is to get substantiated knowledge on normal and pathological vocal fold dynamics and on 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. On the one hand, experimental approaches have been applied: nearly realistic *in vitro* excised larynx experiments, an air driven channel containing polyurethane vocal folds, and a water driven channel. Those experimental approaches motivated numerical models like multi-mass-models, 2D-FEM as well as 3D-FVM models. New findings regarding the Coanda effect, airflow, and acoustical outcome were achieved.
In the international fluid dynamics and voice research community, different approaches are still applied and discussed on their own. Hence, the research unit FOR894/1-2 is performing highly frontier research. The FOR894 hosted the 9th International Conference on Advances in Quantitative Laryngoscopy in Erlangen (2010). For coordination and leading the interdisciplinary group, a DFG funded research W2-professorship was established.

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 for logopedics.

Selected Publications

Burger M, Hoppe U, Lohscheller J, Eysholdt U, Döllinger M (2009) The influence of temporal stimulus changes on speech-evoked potentials revealed by approximations of tone-evoked waveforms. Ear Hear, 30: 16-22

Doellinger M, Lohscheller J, McWhorter A, Kunduk M (2009) Variability of normal vocal fold dynamics for different vocal loading in one healthy subject investigated by phonovibrograms. J Voice, 23: 175-81

Petermann M, Kummer P, Burger M, Lohscheller J, Eysholdt U, Döllinger M (2009) Statistical detection and analysis of mismatch negativity derived by a multi-deviant design from normal hearing children. Hear Res, 247: 128-36

Luegmair G, Kniesburges S, Zimmermann M, Sutor A, Eysholdt U, Döllinger M (2010) Optical reconstruction of high-speed surface dynamics in an uncontrollable environment. IEEE Trans Med Imaging, 29: 1979-91

Voigt D, Döllinger M, Braunschweig T, Yang A, Eysholdt U, Lohscheller J (2010) Classification of functional voice disorders based on phonovibrograms. Artif Intell Med, 49: 51-9

Yang A, Lohscheller J, Berry DA, Becker S, Eysholdt U, Voigt D, Döllinger M (2010) Biomechanical modeling of the three-dimensional aspects of human vocal fold dynamics. J Acoust Soc Am, 127: 1014-31

International Cooperation

Melda Kunduk, PhD, Department of Communication Science & Disorders, Louisiana State University, Baton Rouge, LA, USA

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Research Focus

- Dendritic cell (DC) subpopulation and T-cell response
- Vaccination with dendritic cells (predominantly malignant melanoma)
- RNA electroporation to improve dendritic cell vaccines and to generate antigen-specific T-cells
- Signal transduction and intercellular communication in the tumor microenvironment

Structure of the Department

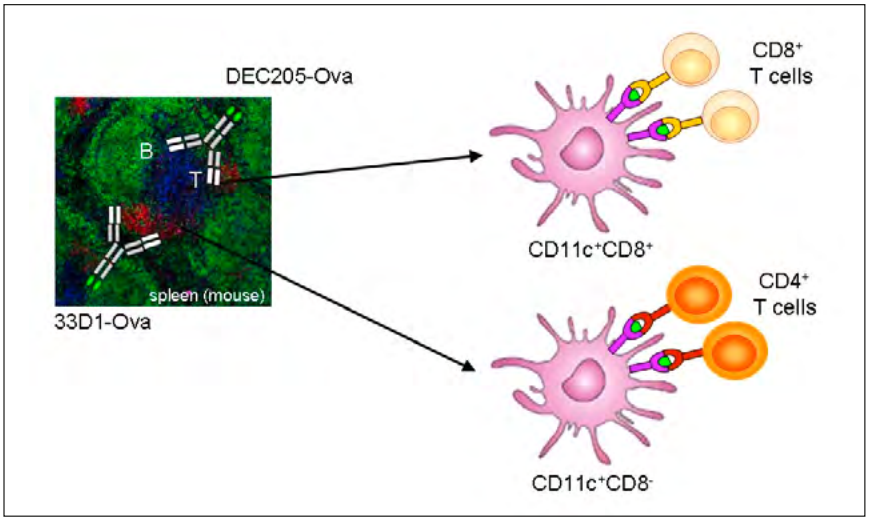
More than 70 medical doctors and scientists are working at the department. Scientific projects are grouped in three main areas, namely "experimental immunotherapy", "Cancer biology and signal transduction" and "biology of dendritic cells (DC) and T cells". All three areas are tightly interconnected and aim at improving therapy and diagnostics of malignant melanoma and understanding the mechanisms in the tumor microenvironment. All research activities are centered around the development and clinical testing of innovative immunotherapies based on the *ex vivo* generation of DC. So far several clinical studies have been performed using peptide-loaded DC and more than 200 patients have been treated so far. Most recently a major grant application has been approved by the BMBF for the development of an individualized DC vaccine. The development of this third generation vaccine will be performed in close collaboration with the biotech company Miltenyi and the Helmholtz Center for Immunology in Munich. A second scientific focus is the molecular and immunological analysis of human DC and T cells as well as the tumor microenvironment. In addition, in 2009 the department has established the new "Toponome" research group setting up a novel automated technique able to stain a single tissue section with multiple antigens. All projects are funded by grant money as for example by the SFB643 "strategies of cellular immune intervention".

Research

Dendritic cell (DC) subpopulation and T-cell response
The Emmy-Noether and BayGene research group of Prof. Dudziak focuses on the characterization of dendritic cell subpopulations in mouse and man. In mouse experiments, the group of Prof. Dudziak was able to show that antigens can be targeted by antigen-coupled antibodies against C-type lectin and endocytosis receptors to DCs *in vivo*. Depending on the DC subpopulation, the group found that the T-cell response could be directed and was either a CD4 T-helper response when CD11c+CD8- DCs presented the antigen or a prominent cytotoxic T-cell response, when CD11c+CD8+ DCs were targeted (Dudziak et al., Science, 2007). This approach allows the maintenance or initiation of antigen-specific tolerance as well as the implementation of immunity. At the time, with help of the Ria-Freifrau von Fritsch Award, the group of Prof. Dudziak is analyzing if the DC subset induced immune responses are strong enough to protect mice from melanoma. Moreover, the strategy concept of '*in vivo* antigen targeting' of DC subsets shall be translated into the human system. Thus, work has been started to characterize DC subpopulations of human peripheral blood and lymphoid organs. We have successfully developed protocols for the preparation of single cell suspension from the tissues. With this established method as well as with confocal microscopy and FACS studies, FACS-sorts and microarray analysis, we have been able to analyze the tissues for distinct DC subpopulations. With help of newly identified human targeting receptors, antigen targeting antibodies will be produced and T-cell responses analyzed in tissue culture. These data will be important for a future implementation into the clinic.

Vaccination with dendritic cells (predominantly malignant melanoma)
The major aim of the "Experimental Immunotherapy" group is the development of new and innovative immunotherapies based on DC. DC, primarily those generated from monocytic precursors, are currently used to vaccinate patients against cancer (melanoma as a prime model). The production of the vaccines is carried out in specialized clean room laboratories under GMP (Good Manufacturing Practice) standards. In 2007 and 2008 the "Experimental Immunotherapy" group was especially engaged in extending the manufacturing authorization (with the collaboration of Dr. Uwe Koch and Dr. Jan Dörrie) for DC from peptide-loaded DC to those loaded with autologous tumor-RNA. Moreover we were preparing for a randomized, multi-centric phase III trial for the indication uveal melanoma (with the collaboration of Prof. Kämpgen). In addition a clinical trial, using DC loaded with defined RNA for the tumor antigens MAGE-3, MelanA and Survivin was carried out for the treatment of patients suffering from metastasized melanoma. The medical care of study patient is intimately connected with the dermatooncology group managed by Prof. Dr. Eckhart Kämpgen.
The RNA-project group (Dr. Schaft and Dr. Dörrie) markedly improved the RNA transfection approach to load DC not only with antigens, but also to endow them with functional proteins ("designer DC"). For example, a chimeric E/L-selectin fusion molecule which allows DC to migrate into all lymph nodes after intravenous injection, was introduced into DC by RNA electroporation. This approach could enhance vaccine efficacy and is currently clinically tested. Moreover, the RNA-group initiated the transfer of T-cell receptors (TCR) to bulk T-cells by RNA transfection. TCR, specific for several epitopes (e.g. tumor antigens gp100, MAGE-A3, MelanA and viral antigens HIV-gag, HIV-pol) were successfully transferred by this technique.

RNA electroporation to improve dendritic cell vaccines and to generate antigen-specific T-cells
Research field 1 aims at the optimization of vaccination against melanoma by targeted modulation of mRNA-transfected dendritic cells (DC). To achieve this optimization, two strategies were pursued. On the one hand, the tumor-antigen-loading of DC was improved by using chimeric protein constructs consisting of a tumor antigen and a binding moiety which binds the endocytosis receptor DEC-205 on DC. This antigen-loading strategy turned out to be more effective than mRNA transfection



Antigen targeting to murine Dendritic cell subpopulations in vivo

or peptide pulsing. On the other hand, the immunogenicity of DC was improved by: i) providing a help signal to the DC by electroporation of mRNA encoding CD40L, ii) providing maturation and help signals to the DC by electroporation of mRNA encoding CD70, CD40L and constitutively active TLR4, and iii) manipulating the NFkappaB-signaling pathway in the DC by electroporation of mRNA encoding constitutively active mutants of elements of this signaling pathway. All three approaches led to a clear improvement of the DC-stimulation capacity of tumor-antigen-specific T-cells. Approach i) and ii) have already been tested in a small clinical trial.

Research field 2 aims at the direct generation of tumor-specific T cells, which can be used for adoptive immunotherapy. The RNA-group successfully transferred full-length T-cell receptors (TCRs), specific for tumor antigens and viral antigens and chimeric antigen receptors (CARs) specific for tumor proteins to T cells by RNA electroporation. These cells displayed the redirected specificity, produced cytokines and lysed target cells. Moreover, the RNA-group established a fast and robust method to clone and functionally validate new TCRs. The group now works on carrying this technique from the bench to bedside

Signal transduction and intercellular communication in the tumor microenvironment

Project manager: A. Baur

The research group analyzes and compares new forms of intercellular communication in the microenvironment of malignant melanoma and HIV-infected T cells. In this context patches of cell membranes and associated molecules are transferred from one cell to the other, a process termed trogocytosis. In addition, microvesicles are secreted and received and cellular proteins and associated vector functions are spread throughout the microenvironment. The functional consequences of this transfer, as well as its molecular basis, are not understood. We hypothesize that these mechanisms serve the tumor immune escape and are regulated at least in part by a MAP kinase dependent signal transduction pathway. The preliminary data supporting our hypothesis are based on findings obtained through the functional and molecular analysis of the Nef protein of HIV-1. As a result of these studies we found that an hnRNP-K-depend formation of a signaling complex leads to the activation of MAP kinase and subsequently to increased secretion of microvesicles and activation of trogocytosis.

With respect to the analysis of these mechanisms, we made significant progress in 2009-2011. We detailed the molecular events behind microvesicles secretion. We found that the process is initiated by an integrin-dependent mechanism, in which the signaling proteins Paxilin, Pak1 and Pak2 play crucial roles (manuscript in preparation). Likewise the function of the released microvesicles could be determined, at least partially. It turned out, that the Integrin-initiated process leads to the activation and shuttling of matrix metalloproteinases into microvesicles. Such equipped microvesicles subsequently stimulate recipient cells to secrete those cytokines being substrates of the proteinases.

Teaching

The co-workers of the clinic teach students of human medicine, dental medicine, molecular medicine and biology in the field of dermatology and genital diseases, as well as in molecular and cellular immunology including translational applications (GMP facility). The training takes place in form of seminars, practical courses, lectures, laboratory rotations as well as bachelor, master, M.D. and Ph.D. theses. The clinic organizes interdisciplinary dermatological lecture series which serve as continuous medical education program of medical doctors in the region. In addition, the clinic coordinates the Collaborative Research Center (SFB) 643 (strategies of cellular immune intervention).

Selected Publications

Wolf D, Witte V, Clark P, Blume K, Lichtenheld MG, Baur AS (2008) HIV Nef enhances Tat-mediated viral transcription through a hnRNP-K-nucleated signaling complex. Cell Host Microbe, 4: 398-408

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Birkholz K, Hombach A, Krug C, Reuter S, Kershaw M, Kämpgen E, Schuler G, Abken H, Schaft N, Dörrie J (2009) Transfer of mRNA encoding recombinant immunoreceptors reprograms CD4+ and CD8+ T cells for use in the adoptive immunotherapy of cancer. Gene Ther, 16: 596-604

Muratori C, Cavallin LE, Krätzel K, Tinari A, De Milito A, Fais S, D'Aloja P, Federico M, Vullo V, Fomina A, Mesri EA, Superti F, Baur AS (2009) Massive secretion by T cells is caused by HIV Nef in infected cells and by Nef transfer to bystander cells. Cell Host Microbe, 6: 218-30

Thomas S, Klobuch S, Heemskerk MHM, Stolle D, Besold K, Plachter B, Schaft N, Theobald M, Voss RH, Herr W (2009) Generation of CMV Specific T Cells From CMV Seronegative Donors by T Cell Receptor RNA Transfer. Blood, 114: 1386-1386

Birkholz K, Schwenkert M, Kellner C, Gross S, Fey G, Schuler-Thurner B, Schuler G, Schaft N, Dörrie J (2010) Targeting of DEC-205 on human dendritic cells results in efficient MHC class II-restricted antigen presentation. Blood, 116: 2277-85

Department of Dermatology

Department of Immune Modulation

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Research Focus

- Characterization of the human CD83 promoter
- The intracellular signal transduction of CD83 in dendritic cells
- Immune modulation by TSLP und CD83
- Interaction of dendritic cells und viruses
- Immune modulation by soluble CD83

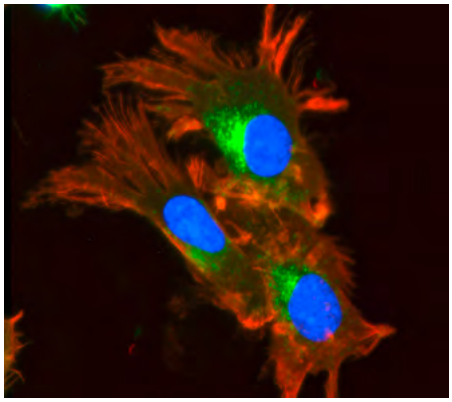
Structure of the Department

In the Department of Immune Modulation, which is headed by Prof. Dr. Alexander 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 Department. 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, Graduate Schools and scientific foundations.

Research

Characterization of the human CD83 promoter

The major aim of the research group, headed by Ilka Knippertz, 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 currently one of the best known markers for human mature DCs. Since CD83 is not expressed on immature DC, 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 DCs 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 the patients) under the control of the cell type- and stadium specific CD83 promoter. Initially, the characterization of the human CD83 promoter was accomplished by a ChIP-chipTM Microarray analysis, by which, in addition to the minimal promoter, a short enhancer sequence was identified. Further, bioinformatical analysis identified an additional promoter region, which was shown to build a ternary promoter-complex together with the minimal promoter and the enhancer. Moreover, we have demonstrated that this ternary promoter-complex is not only highly inducible, but it is also cell type- and maturation specific. Finally, we have identified the transcription factors involved in this process.



Immune-fluorescence staining of mature dendritic cells

The intracellular signal transduction of CD83 in dendritic cells

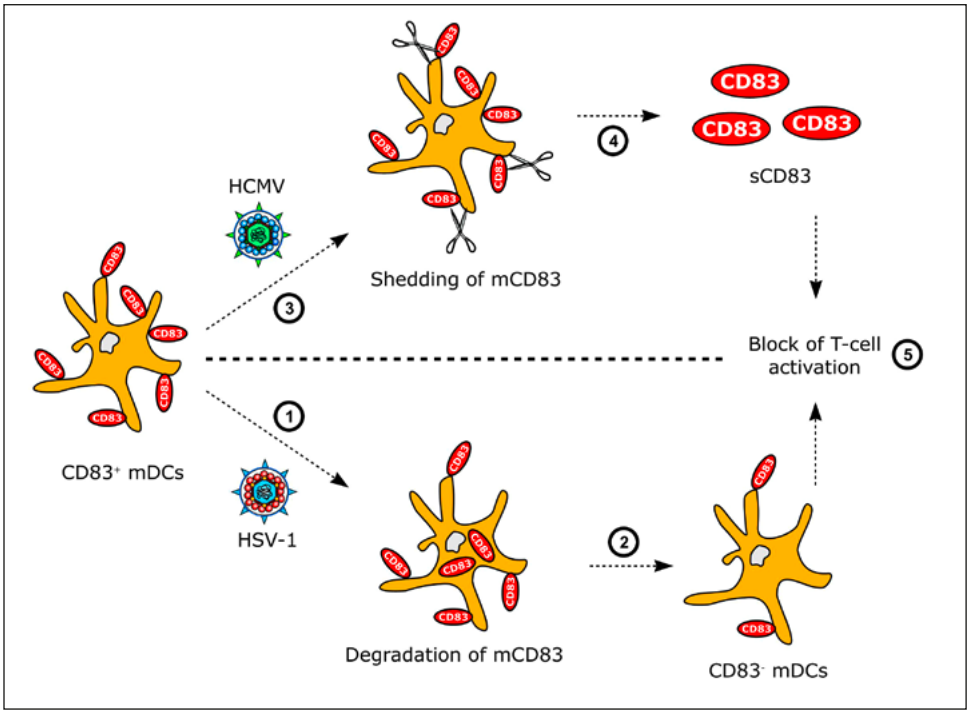
The main research focus of the project, headed by Katja Blume, concentrates on structural and signal transduction pathway analyses of the membrane bound CD83 molecule. Specific binding domains and partners have been identified using a yeast two hybrid screen. Site directed mutagenesis, transfection,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

Immune modulation by TSLP und CD83

The research group, headed by Dr. Matthias Lechmann, is on the one hand interested in the regulatory mechanisms balancing TH1/TH17-TH2 immune responses and on the other hand in the development and activation of regulatory T cells *in vivo*. They are focusing on two modulators of the immune system, namely the thymic stromal lymphopoietin (TSLP) and CD83. TSLP is thought to be the "missing link" between DC activation and allergic responses. To further analyze the role of TSLP *in vivo*, a TSLP KO-mouse has been generated. Using this KO-mouse the function of TSLP will be addressed in different inflammatory and infectious disease models as well as in models for autoimmunity. In the second project the CD83-specific reporter mouse has been generated, which now allows us to carry out *in vivo* monitoring of CD83 expressing cells. In this project the expression and function of CD83 in T cell subpopulations is of particular interest. With regard to the therapeutic application of sCD83, a pilot study in an animal model of inflammatory bowel disease, i.e. the DNBS-induced colitis, has been performed. Interestingly sCD83 treatment ameliorated DNBS-induced colitis, whereby these animals showed less severe progress of disease and significant faster recovery.
In addition, a rapid and highly specific aptamer-based screening technology for the detection of biomarkers on living cells has been established. One aim using this technique is to isolate specific aptamers for T cell epitopes of known tumor antigens. Furthermore, new tumor targets will be identified to improve tumor-specific DC-vaccination strategies.

Interaction of dendritic cells und viruses

The project group "DC and viruses" (heads: Dr. Mirco Kummer, Dr. Andreas Goldwich) analyzes the interaction between DC and viruses, whereby 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 infect-



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

ed 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 IFN-gamma-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 viruses 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 essential step in order to induce potent antiviral immune responses.

Immune modulation by soluble CD83

The project group headed by Dr. Elisabeth Zinser, 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- and skin transplants could be prevented by the use of sCD83. 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 relvance also in tumor patients. In the long run, sCD83 will be developed as a new therapeutic option also for humans.

Teaching

The employees of the department teach students of molecular medicine and biology in the field of molecular and cellular immunology. The training takes place if term of lectures, seminars, practical courses as well as bachelor, master and PhD thesis. In addition, the Collaborative Research Center (SFB) 643 (strategies of cellular immune intervention) is coordinated together with the department of dermatology.

Selected Publications

Lechmann M, Shuman N, Wakeham A, Mak TW (2008) The CD83 reporter mouse elucidates the activity of the CD83 promoter in B, T, and dendritic cell populations in vivo. Proc Natl Acad Sci U S A, 105: 11887-92

Hock BD, Fernyhough LJ, Gough SM, Steinkasserer A, Cox AG, McKenzie JL (2009) Release and clinical significance of soluble CD83 in chronic lymphocytic leukemia. Leuk Res, 33: 1089-95

Zinser E, Rössner S, Littmann L, Lüftenegger D, Schubert U, Steinkasserer A (2009) Inhibition of the proteasome influences murine and human dendritic cell development in vitro and in vivo. Immunobiology, 214: 843-51

Ge W, Arp J, Lian D, Liu W, Baroja ML, Jiang J, Ramcharran S, Eldeen FZ, Zinser E, Steinkasserer A, Chou P, Brand S, Nicolette C, Garcia B, Wang H (2010) Immunosuppression involving soluble CD83 induces tolerogenic dendritic cells that prevent cardiac allograft rejection. Transplantation, 90: 1145-56

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

International Cooperation

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

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

Meetings and International Training Courses

07.12.2009: System biology approaches to elucidate immune functions, Erlangen

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Chair of Cardiac Surgery

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Research Focus

- Chronic rejection of allografts (transplant arteriosclerosis)
- Therapy of end-stage heart failure: heart transplantation or support with a left- or right ventricular assist device
- Neuropeptide release of the heart
- Hospital-economics and management
- Tissue Engineering of cardiovascular implants

Structure of the Department

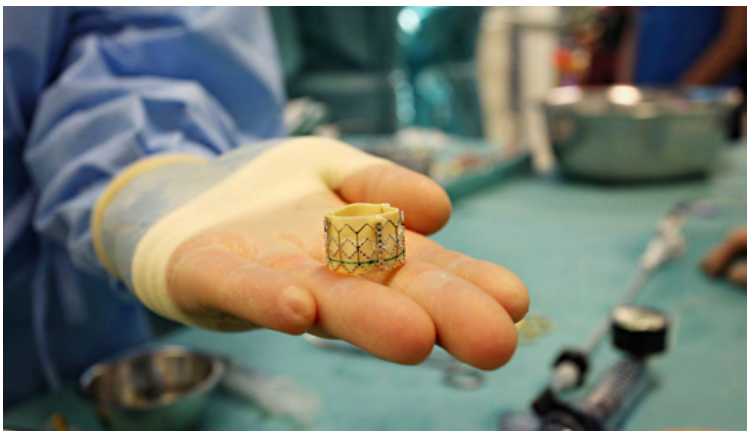
20 medical doctors work in the departement of cardiac surgery. The research is accomplished by all medical doctors, 7 graduate students and 2 technical assistants.

Research

Chronic rejection of allografts (transplant arteriosclerosis)
Project manager: S. Ensminger
Our group is a collaboration between the Department of Cardiac Surgery (Prof. Ensminger) and the Department of Medicine 3 and Medicine 5 (PD Dr. Spriewald, M. Poehner, pharmacist) and is interested in the underlying pathological mechanisms leading to the development of transplant arteriosclerosis. 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. Currently the only definite treatment of transplant arteriosclerosis is re-transplantation, which is associated with a significantly poorer survival rate and an increased overall complication rate. Transplant arteriosclerosis is the main reason for late graft failure and develops in all other vascularized organ transplants such as livers and kidneys.
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 (kindly provided by Professor Foerster, Hannover) 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. Since Mai 2003 Prof. Ensminger and Dr. Spriewald supervise a graduate student (M. Poehner) working on the project "Preventing transplant arteriosclerosis using chemokine- and costimulatory-receptor modulating IgG-fusion proteins" which is part of the post graduate program 750 "Vaskuläre Schäden an Herz und Niere" of the German Research Foundation (DFG). The aim of this project is to develop fusion proteins to costimulatory molecules such as CTLA4-Ig, ICOS-Ig and PDL1-Ig to modify and influence T-cell activation. In addition, a joint project with Dr. Lechmann and Prof. Steinkasserer from the Department of Dermatology regarding the effect of CD83 modulation on the development of transplant arteriosclerosis just started in November 2003. Recent findings implicate an important role of human cytomegalovirus infection (HCMV) for the development of inflammatory-proliferative vascular lesions in transplanted vascularized allografts. Therefore, the major aim of this project is to develop a human peripheral blood lymphocyte (hu-PBL)/severe combined immunodeficiency (SCID) mouse xenograft-model to investigate the immunological and pathological mechanisms of HCMV in the modulation and progression of transplant arteriosclerosis. This project called "Investigations into the role of cytomegalovirus in the development of transplant arteriosclerosis using a Hu-PBL/SCID mouse model" is funded for 3 years by the IZKF of the Universität of Erlangen-Nürnberg.

Therapy of end-stage heart failure: heart transplantation or support with a left- or right ventricular assist device
Project managers: M. Weyand, R. Tandler, M. Kondruweit
The survival rate of patients with end stage heart failure (prevalence approx. 0.1%) with optimized medical therapy is 0.4 to 0.8 for 1 year and 0.1 to 0.5 for 5 years. Orthotopic cardiac transplantation is the therapy of choice for these patients. Due to an increasing shortage of donor organs, a considerable number of patients die on the waiting list. If necessary, these patients can be bridged with an implantable ventricular assist device until a suitable donor organ is available. In our heart-failure clinic patients are evaluated if they are suitable candidates for transplantation. In some cases heart disease has already progressed to such an extent that the patients need to be stabilized ('bridged') with a left ventricular assist device (LVAD) or in case of additional right heart failure with a biventricular assist device (BIVAD) until the day of transplantation.

Neuropeptide release of the heart
Project manager: Th. 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-delta- 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 cardioprotective and reduced the infarct size of myocardial infraction.
The aim of our project 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 is planned by using tissue from the right ventricle or ascending aortic tissue.



Transkatheter Aortic Valve Implantation (TAVI) transapikal/transfemoral

Hospital-economics and management
Project manager: R. Feyrer
This group is a collaboration between the Department of Cardiac Surgery (PD Dr. Feyrer) and the competent office of Healthcare Resource Groups (DRGs) (U. Kunzmann). One of the main tasks of this group is to face the changes in hospital reimbursement from retrospective payment to a prospective flat rate payment since the introduction of the DRGs. 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 Centre in Berlin we are trying to set up a database regarding long-term costs of patients on cardiac assist devices.

Tissue Engineering of cardiovascular implants
Project managers: M. Weyand, O. Roerick
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 with only RGD. These experiments were extended to the peptide sequences SIKVAV, RYVVLPR (both laminin) and DGEA (collagen) also known from the literature as 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, whereby SMC did not show any difference.

Teaching

Beside the traditional teaching forms (main lecture and practical courses), hospitations and fellowships can be undertaken anytime. Monday's seminars to actual clinical and experimental topics take place in our hospital.

Selected Publications

Abele S, Spriewald BM, Ramsperger-Gleixner M, Wollin M, Hiemann NE, Nieswandt B, Weyand M, Ensminger SM (2009) Attenuation of transplant arteriosclerosis with clopidogrel is associated with a reduction of infiltrating dendritic cells and macrophages in murine aortic allografts. Transplantation, 87: 207-16

Ensminger SM, Abele-Ohl S, Ohl L, Spriewald BM, Ramsperger-Gleixner M, Weyand M, Förster R (2009) Unaltered levels of transplant arteriosclerosis in the absence of the B cell homing chemokine receptor CXCR5. Transpl Immunol, 20: 218-23

Abele-Ohl S, Leis M, Mahmoudian S, Weyand M, Stamminger T, Ensminger SM (2010) Rag2-/- gamma-chain-/- mice as hosts for human vessel transplantation and allogeneic human leukocyte reconstitution. Transpl Immunol, 23: 59-64

Eckl S, Heim C, Abele-Ohl S, Hoffmann J, Ramsperger-Gleixner M, Weyand M, Ensminger SM (2010) Combination of Clopidogrel and Everolimus Dramatically Reduced the Development of Transplant Arteriosclerosis. J Heart Lung Transplant, 29 Suppl. : 343 -

Heim C, Abele-Ohl S, Eckl S, Ramsperger-Gleixner M, Mahmoudian S, Weyand M, Stamminger T, Ensminger SM (2010) Murine cytomegalovirus infection leads to increased levels of transplant arteriosclerosis in a murine aortic allograft model. Transplantation, 90: 373-9

Hoffmann J, Bohm M, Abele-Ohl S, Weyand M, Ensminger SM (2010) Reduced Transplant Arteriosclerosis after Treatment with MMF and MMF in Combination with Ganciclovir in a Mouse Aortic Transplant Model. J Heart Lung Transplant, 29 Suppl. : 382 -

International Cooperation

Prof. Kathryn J. Wood, Nuffield Department of Surgery, John Radcliffe Hospital, University of Oxford, Oxford, UK

Prof. Marlene Rose, National Heart and Lung Institute, Imperial College, Harefield Hospital, School of Medicine, Harefield, UK

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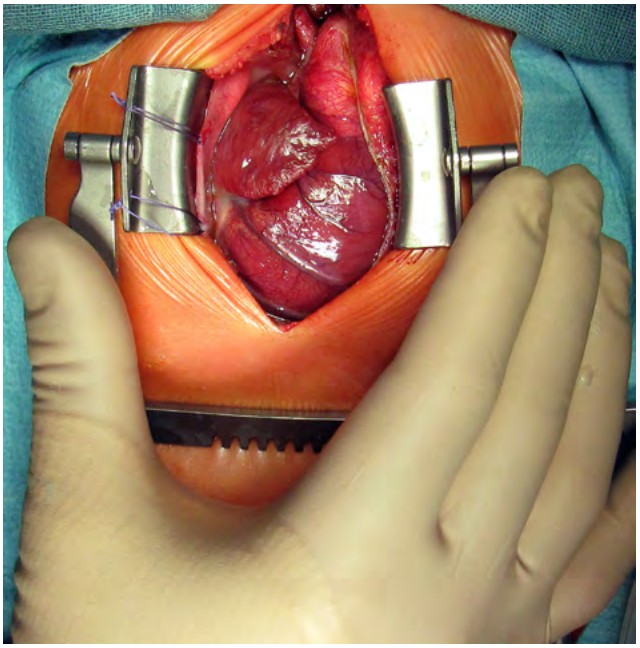
Research Focus

- Biomaterial bank for congenital heart disease
- Role of thymic tissue in immune cell differentiation
- Aortic arch surgery
- Development of new surgical procedures and treatment of strategies for the univentricular heart
- Reconstruction of the right venricular outflow tract



Heart with hypoplastic left heart syndrome in comparison with the surgeons hand

Structure of the Division

Four doctors cover the medical service in the newly established Division of Pediatric Cardiac Surgery. Patient care is carried out 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 four medical students are involved in scientific projects.

Research

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 Department of Pathology and is preserved for further studies afterwards. Erlangen has the largest tissue sample database for children with congenital heart disease. Dr. Toka has been awarded for this project by the "German Foundation for Cardiac Research".

Role of thymic tissue in immune cell differentiation
In cooperation with the Department of Dermatology (Prof. Dr. D. Dudziak) and Department for 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-Fonds of the Medical Faculty.

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-Fonds of the Medical Faculty.

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 department is to lower the operative risk to the level of common neonatal cardiac surgery. The first surgical step (Norwood I) carries a mortality risk of about 30% in Europe. In conjunction with the Department of Pediatric Cardiology, we have established processes to lower the risk of mortality to about 15% for hypoplasts. In paral-

View in the operating theater

lel, we have developed a novel surgical technique for the first step in the treatment of patients with hypoplastic left heart syndrome in December 2010. It was approved by the ethics committee for 2011. Informed consent of parents is requested with a special consent form. The first case will probably be performed by beginning of 2011.

Reconstruction of the right venricular 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 cardiology (Prof. Dr. Garlichs, 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.

Teaching

Four doctors cover the medical service in the newly established Division of Pediatric Cardiology. Patient care is carried out 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 four medical students are involved in scientific projects.

Selected Publications

Rüffer A, Danch AM, Lacour-Gayet F, Hraska V, Weil J, Cesnjevar R (2009) Early Glenn is Crucial for Successful Completion to the Fontan Pathway Following Norwood Procedure with a Right Ventricle to Pulmonary Artery Conduit. Clin Res Cardiol, 98: 594-594

Rüffer A, Danch A, Gottschalk U, Mir T, Lacour-Gayet F, Haun C, Hraska V, Reichenspurner HC, Cesnjevar RA (2009) The Norwood procedure - does the type of shunt determine outcome? Thorac Cardiovasc Surg, 57: 270-5

Zimmermann WH, Cesnjevar R (2009) Cardiac tissue engineering: implications for pediatric heart surgery. Pediatr Cardiol, 30: 716-23

Rüffer A, Purbojo A, Cicha I, Glöckler M, Potapov S, Dittrich S, Cesnjevar RA (2010) Early failure of xenogenous decellularised pulmonary valve conduits--a word of caution! Eur J Cardiothorac Surg, 38: 78-85

International Cooperation

Professor Dr. Marc Roger De Leval, Cardiothoracic Unit, Great Ormond Street Hospital, London, UK

Professor Dr. Alistair Philips, Professor Dr. John Cheatham, Nation Wide Children´s Hospital, Columbus OH, USA

Institute of Human Genetics

Chair of Human Genetics

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Head of Institute
Prof. Dr. med. André Reis

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Research Focus
- Molecular basis of monogenic traits and genotype-phenotype correlation
- Genetics of complex diseases
- Developmental genetics

Structure of the Institute

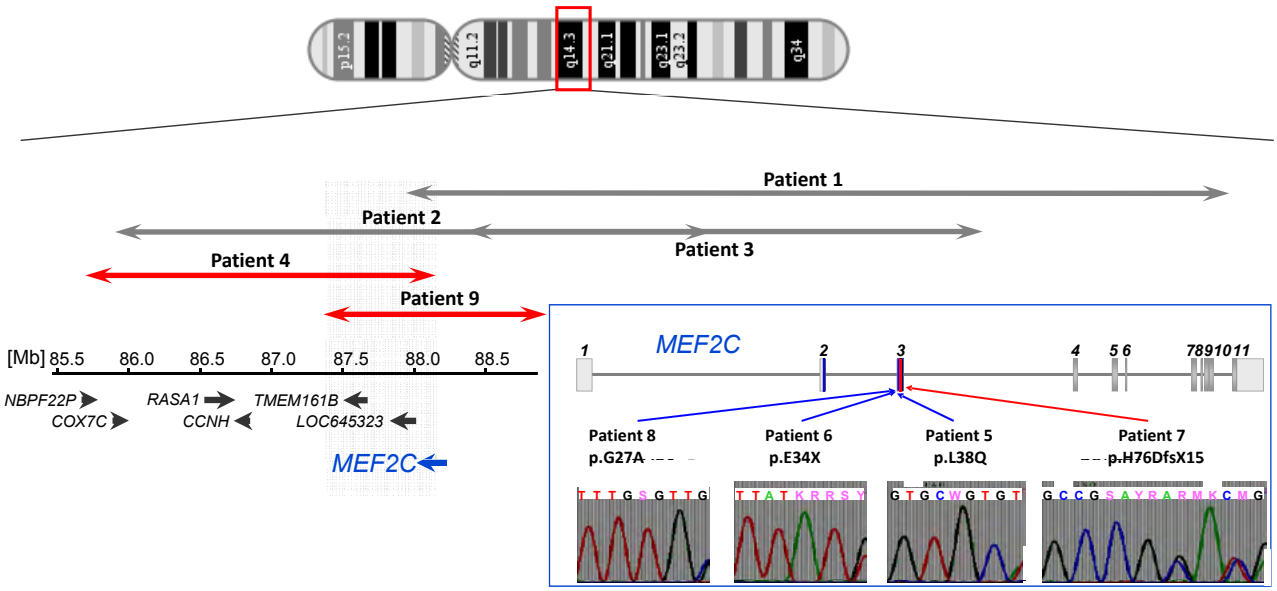
Members of the institute are active in teaching, research and health care provision. At the end of 2010 a total of 55 persons worked at the institute: 17 scientists (natural scientists and physicians), 13 PhD-students, 25 technical and administrative employees and 12 graduate students. 20 colleagues were funded through grants. The institute runs a genetic clinic for ambulatory care and genetic counselling of patients as well as diagnostic laboratories for highly specialized cytogenetic and molecular genetics investigations. Research activities are organized in research groups. Members of the institute participate in various collaborative research groups (SFBs and "Forschergruppen"). The head of the institute, Prof. Reis, coordinates a collaborative research network on the genetic basis of mental retardation (MRNET) funded by the Federal Ministry of Research (BMBF) within the National German Genome Research Network (NGFNplus). He is also the speaker of the Interdisciplinary Center for Clinical Research (IZKF) at the Medical Faculty. In addition, he was reelected president of the German Society of Human Genetics (GfH) in 2010. The institute runs the IZKF-core units "Z3 Genomic Platform" for microarray analysis and "Z4 DNA Extraction Platform (Biobank)" for quality controlled DNA extraction of blood samples, especially for clinical studies and the interfaculty core unit „Ultradeep Sequencing" for massive parallel sequencing analysis. In 2009 two members of the institute were appointed to faculty chairs: Prof. Dr. A. Rauch obtained the chair of Medical Genetics at the University of Zürich und Prof. Dr. M. Zenker obtained the chair of Human Genetics at the Otto-von-Guericke-University Magdeburg.

Research

Molecular basis of monogenic traits and genotype-phenotype correlation
Project managers: Prof. Dr. med. A. Rauch, Prof. Dr. med. A. Reis, Prof. Dr. M. Zenker, Dr. med. C. Thiel, Dr. med. C. Zweier
The main scientific focus of the institute is on the elucidation of the molecular basis of inherited disease. Major methodological approaches used include positional cloning strategies and the detection of copy number variants using molecular karyotyping. With this approach the groups of Prof. Rauch and Prof. Reis identified MEF2C mutations underlying a form of severe intellectual disability in children (Fig. 1). Furthermore mutations in GRIN2A and GRIN2B were associated with intellectual disability and behavioural anomalies with and without epilepsy. Both genes code for subunits of NMDA-receptors, ion chanels in the central nervous system involved in synaptic plasticity, learning and memory. Furthermore, mutations in CNTNAP2 und NRXN1 were identified in individuals with severe intellectual disability. Functional studies in drosophila revealed that the gene products of both genes are involved in the architecture and function of synapses (Dr. Zweier, Prof. Rauch).
The group of Prof. M. Zenker mainly focused on the molecular basis of Noonan syndrome. Spearheading a large international collaboration, the group succeeded in identifying germline NRAS mutations conferring enhanced stimulus-dependent activation of MAP-kinase pathway. In addition, the group published findings on genotype-phenotype correlation for this disease.

Genetics of complex diseases
Project manager: Prof. Dr. med. A. Reis
Complex or multifactorial diseases are caused by a combination of mostly unknown environmental and genetic factors. The group of Prof. Reis carries out genetic association studies with large patient cohorts, especially for psoriasis vulgaris, psoriatic arthritis and glaucoma with and without pseudoexfoliation syndrome. The projects were partially funded by SFB 539 and IZKF. In a genome-wide association study on psoriatic arthritis the group identified the NFKB-regulator ACT1, encoded by the gene TRAF3IP2, as a risk factor for psoriasis. This gene had not been previously found associated with either psoriasis or any other autoimmune disease. A strongly associated variant was found to diminish binding of the protein to other members of the IL-17 pathway and thus most probably represents the causative risk variant at this locus. For secondary glaucoma with pseudoexfoliation, the group performed association studies of functional candidates and identified clusterin as a novel associated gene. In collaboration with Prof. Schlötzer-Schrehardt (Department of Ophthalmology) it could be demonstrated that clusterin is a principal component of abnormal exfoliation deposits. The group also identified mutations in NTF4, encoding a neuronal ganglion cell survival factor as a possible cause of open angle glaucoma. Finally, members of the institute, in collaboration with the Gynecology Department, were involved in various studies on genetic factors predisposing to ovarian- and breast cancer.

Developmental genetics
Project manager: 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 plays a role in mitosis and in the epigenetic regulation of spermatogonial stem cell maintenance and differentiation; 2. the nervous system, where the group focuses on cognitive processes, which are investigated using the Wolf-Hirschhorn syndrome as a model disease. In the context of the "Klinische Forschergruppe 130 (KFO 130)" and in collaboration with the Departments of Anesthesiology and Surgery, the group works on the identification of susceptibility genes for post-operative pain perception; 3. the skeletal system. This project aims at the global and systematic identification and molecular characterization of novel genes and gene networks involved and cartilage/bone formation.



Overlapping microdeletions on chromosome 5q14.3 in patients with severe intellectual disability define a critical segment (highlighted in grey) around the MEF2C gene. Sequence analysis of further patients revealed point mutations in 4 cases (blue box).

Teaching

The institute is involved in curricular teachings at the Medical Faculty and in the diploma, bachelor- and master programs in Molecular Medicine as well as Cellular and Molecular Biology, respectively. During the report period, 16 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.

Selected Publications

Pasutto F, Matsumoto T, Mardin CY, Sticht H, Brandstätter JH, Michels-Rautenstrauss K, Weisschuh N, Gramer E, Ramdas WD, van Koolwijk LM, Klaver CC, Vingerling JR, Weber BH, Kruse FE, Rautenstrauss B, Barde YA, Reis A (2009) Heterozygous NTF4 mutations impairing neurotrophin-4 signaling in patients with primary open-angle glaucoma. Am J Hum Genet, 85: 447-56

Zweier C, de Jong EK, Zweier M, Orrico A, Ousager LB, Collins AL, Bijlsma EK, Oortveld MA, Ekici AB, Reis A, Schenck A, Rauch A (2009) CNTNAP2 and NRXN1 are mutated in autosomal-recessive Pitt-Hopkins-like mental retardation and determine the level of a common synaptic protein in Drosophila. Am J Hum Genet, 85: 655-66

Cirstea IC, Kutsche K, Dvorsky R, Gremer L, Carta C, Horn D, Roberts AE, Lepri F, Merbitz-Zahradnik T, König R, Kratz CP, Pantaleoni F, Dentici ML, Joshi VA, Kucherlapati RS, Mazzanti L, Mundlos S, Patton MA, Silengo MC, Rossi C, Zampino G, Digilio C, Stuppia L, Seemanova E, Pennacchio LA, Gelb BD, Dallapiccola B, Wittinghofer A, Ahmadian MR, Tartaglia M, Zenker M (2010) A restricted spectrum of NRAS mutations causes Noonan syndrome. Nat Genet, 42: 27-9

Endele S, Rosenberger G, Geider K, Popp B, Tamer C, Stefanova I, Milh M, Kortüm F, Fritsch A, Pientka FK, Hellenbroich Y, Kalscheuer VM, Kohlhase J, Moog U, Rappold G, Rauch A, Ropers HH, von Spiczak S, Tönnies H, Villeneuve N, Villard L, Zabel B, Zenker M, Laube B, Reis A, Wieczorek D, Van Maldergem L, Kutsche K (2010) Mutations in GRIN2A and GRIN2B encoding regulatory subunits of NMDA receptors cause variable neurodevelopmental phenotypes. Nat Genet, 42: 1021-6

Hüffmeier U, Uebe S, Ekici AB, Bowes J, Giardina E, Korendowych E, Juneblad K, Apel M, McManus R, Ho P, Bruce IN, Ryan AW, Behrens F, Lascorz J, Böhm B, Traupe H, Lohmann J, Gieger C, Wichmann HE, Herold C, Steffens M, Klareskog L, Wienker TF, Fitzgerald O, Alenius GM, McHugh NJ, Novelli G, Burkhardt H, Barton A, Reis A (2010) Common variants at TRAF3IP2 are associated with susceptibility to psoriatic arthritis and psoriasis. Nat Genet, 42: 996-9

Zweier M, Gregor A, Zweier C, Engels H, Sticht H, Wohlleber E, Bijlsma EK, Holder SE, Zenker M, Rossier E, Grasshoff U, Johnson DS, Robertson L, Firth HV, Cornelia Kraus , Ekici AB, Reis A, Rauch A (2010) Mutations in MEF2C from the 5q14.3q15 microdeletion syndrome region are a frequent cause of severe mental retardation and diminish MECP2 and CDKL5 expression. Hum Mutat, 31: 722-33

International Cooperation

Prof. Marco Tartaglia, Superior Health Institute, University of Rome la Sapienza, Rome, Italy

Prof. Yves Barde, Biocenter , University of Basel, Basel, Switzerland

Dr. Anne Barton, arc-Epidemiology Unit, University of Manchester, Manchester, UK

Prof. John Armour, Institute of Genetics, University of Nottingham, Nottingham, UK

Meetings and International Training Courses

29.09.–01.10.2010: „Internationaler Kongress zur Genetik und Neurobiologie der mentalen Retardierung" gemeinsam mit der Jahreskonferenz der Nationalakademie Leopoldina,

29.09-01.10.2010 in Erlangen (Tagungspräsident Prof. André Reis), Erlangen

Research Equipment

Applied Biosystems DNA-Sequenzierautomat

Affymetrix Genomik-Chip-Plattform

Department of Pediatrics

Chair of Pediatrics

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Research Focus
- Perinatal programming
- Perinatal hypoxic brain injury and neuroprotection
- Genetic diseases of the neonate
- Genomic aberrations in childhood malignancies
- Pediatric cell therapy
- Progression of kidney disorders

Structure of the Department

The Department of Pediatrics 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 93 physicians and scientists. Of these, 12 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 5 divisions of the department and by the section of endocrinology/diabetology (e.g. studies on prenatal programming, genetic conditions or infection epidemiology, 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

Perinatal programming

Project managers: J. Dötsch, W. Rascher
The term "perinatal programming" refers to permanent modifications of physiological processes by the intrauterine or early postnatal environment. Although the phenomenon has been well described also in humans, its mechanisms have remained unclear. Using different animal models as well as data from a prospective, multi-center clinical study (FIPS study), we have been exploring possible pathogenetic mechanisms of perinatal programming, which may allow preventive strategies to be established.
Our results show that fetal growth restriction may induce programming of the expression of genes with metabolic relevance strongly depending on the cause of growth restriction.

Perinatal hypoxic brain injury and neuroprotection

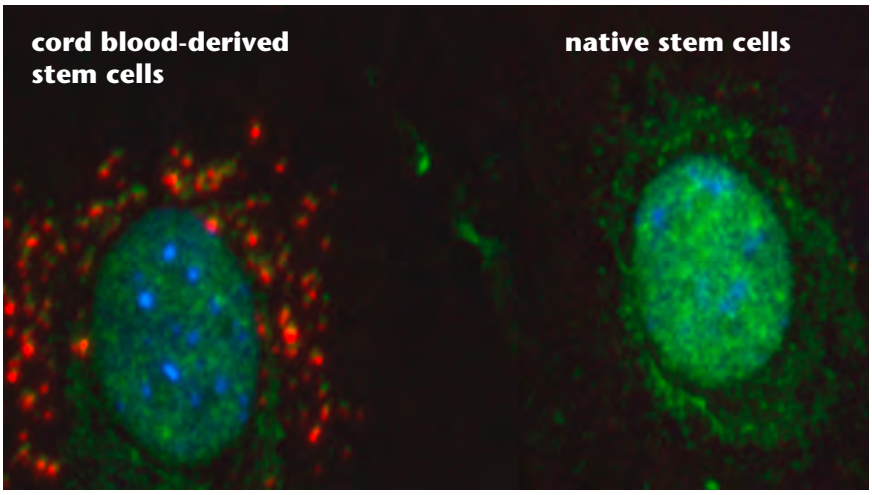
Project manager: R. Trollmann
Aiming at an early detection and prevention of perinatal brain injury caused by acute or chronic hypoxia, we have been analyzing the regulation and function of hypoxia-inducible transcription factors (HIF) in the immature brain. HIF-regulated factors with strong impact on 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 stabilizing HIF by pharmacological means.

Genetic diseases of the neonate

Project managers: H. Schneider, H. Köhler
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 pathogenic 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.
Another area of interest is in gastrointestinal diseases based on genetic defects predisposing to diarrhea. Current investigations focus on hereditary factors contributing to necrotizing enterocolitis of preterm neonates.

Genomic aberrations in childhood malignancies

Project managers: M. Metzler, 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.



Chondrogenic differentiation of cord blood-derived stem cells: CD133-positive stem cells isolated from human cord blood and labeled with the DiI cell tracker (red) were shown by immunofluorescence staining to express Sox9, a marker of chondrogenesis (green). Cell nuclei were counterstained with DAPI (blue). AG Schneider 2009.

Pediatric cell therapy

Project managers: W. Holter, 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.

Progression of kidney disorders

Project managers: A. Hartner, C. Plank

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 alpha8-integrin can regulate cell adhesion, migration, differentiation and proliferation, thereby contributing significantly to the maintenance of renal tissue homeostasis. Further studies aim to clarify whether these results may provide a basis for the development of new strategies for diagnosis and therapy of kidney diseases.

Because progression of renal 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.

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 Program in Molecular Medicine. 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 hospital.

Selected Publications

Hartner A, Klanke B, Cordasic N, Amann K, Schmieder RE, Veelken R, Hilgers KF (2009) Statin treatment reduces glomerular inflammation and podocyte damage in rat deoxycorticosterone-acetate-salt hypertension. J Hypertens, 27: 376-85

Park J, Setter V, Wixler V, Schneider H (2009) Umbilical cord blood stem cells: induction of differentiation into mesenchymal lineages by cell-cell contacts with various mesenchymal cells. Tissue Eng Part A, 15: 397-406

Jung R, Jacobs U, Krumbholz M, Langer T, Keller T, De Lorenzo P, Valsecchi MG, van der Velden VH, Moericke A, Stanulla M, Teigler-Schlegel A, Panzer-Gruemayer ER, van Dongen JJ, Schrappe M, den Boer ML, Pieters R, Rascher W, Metzler M (2010) Bimodal distribution of genomic MLL breakpoints in infant acute lymphoblastic leukemia treatment. Leukemia, 24: 903-7

Plank C, Nüsken KD, Menendez-Castro C, Hartner A, Ostreicher I, Amann K, Baumann P, Peters H, Rascher W, Dötsch J (2010) Intrauterine growth restriction following ligation of the uterine arteries leads to more severe glomerulosclerosis after mesangioproliferative glomerulonephritis in the offspring. Am J Nephrol, 32: 287-95

Trollmann R, Rehrauer H, Schneider C, Krischke G, Huemmler N, Keller S, Rascher W, Gassmann M (2010) Late-gestational systemic hypoxia leads to a similar early gene response in mouse placenta and developing brain. Am J Physiol Regul Integr Comp Physiol, 299: R1489-99

Schneider H, Hammersen J, Preisler-Adams S, Huttner K, Rascher W, Bohring A (2011) Sweating ability and genotype in individuals with X-linked hypohidrotic ectodermal dysplasia. J Med Genet, 48: 426-32

International Cooperation

Prof. Dr. Mats Ohlin, Department of Immunotechnology, Lund University, Lund, Sweden

Prof. Dr. Mike Gibson, Biochemical Genetics Laboratory, University of Pittsburgh, Pittsburgh, PA, USA

Dr. Simon Waddington, Department of Haematology, University College London, London, UK

Prof. Dr. Max Gassmann, Center for Integrative Human Physiology, University of Zurich, Zurich, Switzerland

Dr. Kenneth Huttner, Edimer Pharmaceuticals Inc., Cambridge, MA, USA

Dr. Elke Griesmeier, Department of Pediatrics, Innsbruck Medical University, Innsbruck, Austria

Prof. Dr. Terence H. Rabbitts, Institute of Molecular Medicine, University of Leeds, Leeds, UK

Dr. Ornella Parolini, Fondazione Poliambulanza, Brescia, Italy

Meetings and International Training Courses

07.–08.05.2010: Gemeinsames Symposium der Gesellschaft für Neonatologie und Pädiatrische Intensivmedizin und der Gesellschaft für Pädiatrische Nephrologie, Iphofen

02.–04.12.2010: 7. Fortbildungskurs der Süddeutschen Gesellschaft für Kinder- und Jugendmedizin, Erlangen

Research Equipment

Applied Biosystems Tandem Mass Spectrometer

Beckman Coulter DNA Sequencer

Becton Dickinson FACS Calibur

Carl Zeiss Inverse Microscope Axio Observer (Live cell imaging)

Tecan Analysis Platform EVO 150

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Research Focus

- B-type natriuretic peptide as a diagnostic and prognostic tool for patients with congenital heart defects
- Flat-detector computed tomography during catheterization of congenital heart disease
- Investigations in the field of molecular cardiology
- Clinical course in the intensive care unit after on-pump coronary bypass surgery of children with congenital heart failure
- Impact of cardiologic and genetic parameters on the quality of life and neuropsychological status of patients with tetralogy of Fallot after surgery
- Duchenne Muscular Dystrophy
- Early measurment of urine and plasma neutrophil-associated lipocalin for screening of acute renal injury after congenital cardiac surgery

Structure of the Division

The independent Division of Pediatric Cardiology was newly established at July 1st 2007. Clinical work and research activities are performed in close cooperation with the Department of Pediatrics and the Division of Pediatric Cardiac Surgery founded at the 1st of September in 2008. A total of 15 employed medical doctors are splitting clinical work, teaching, and research. At the moment, there are nine graduate students studying for a doctorate. Several projects were established to study the genetic mechanisms responsible for congenital heart malformation. 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 efficiancy 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 as a diagnostic and prognostic tool for patients with congenital heart defects

B-type natriuretic peptide (BNP) and the N-terminal fragment of its prohormone (NT-proBNP) are established sensitive markers for the diagnosis and prognosis of heart failure. We have assessed normal values of both BNP and NT-proBNP from infancy to adolescence and examined the distribution of both peptides according to the age. Based on these data we investigate prospectively the diagnostic validity of plasma BNP on pediatric patients with acquired and congenital heart disease. There are several prospective studies on BNP in patients with myocarditis, cardiomyopathy, arrythmias and additionally, in patients with congenital heart defects before and after corrective surgery. Moreover, studies were assessed to elucidate the diagnostic role of BNP in the long-term follow-up of patients with systemic right ventricle, with functional univentricular heart after total cavopulmonary connection, or after surgical repair of tetralogy of Fallot.

Flat-detector computed tomography during catheterization of congenital heart disease

The use of flat-detectors (FD) in the interventional catheter-suite of congenital heart-diseases is a new modality and allows a CT-like imaging.
Mainly the long scanning time raises the question, whether this technique is suitable in the catheterization of congenital heart disease. Particular the possibility to acquire 3D vascular volumes in high quality by the rotational angiography with the option to have a sight from any angle on the region or volume of interest and to display the spatial anatomical relationships will help to plan surgical interventions.
Our first results in Erlangen:
FD-CT in the department for pediatric cardiology in 2010:

- 303 Patients in the cath lab 2010,
- 175 (58%) of them had an interventional procedure. In 68 cases we performed a FD-CT,
- 32 times during an interventional catheter
- Overlaid 3D-image on fluoroscopy was always performed in these cases.
- in 9% the FD-CT was exclusive.

The aim will not only be to facilitate an intervention, but also to reduce of required position controls by angiographies and a diminished fluoroscopy time is accomplished by this technique.

Investigations in the field of molecular cardiology

The evaluation of genetic factors and subcellular mechanisms responsible for congenital heart malformation are in the focus of Dr. Toka's investigations. With good clinical practice, we could established a comprehensive biomaterial bank for individuals with congenital heart defects, which currently counts about 700 DNA samples and about 750 cardiac tissue samples of all four chambers of the heart. Thus, the biomaterial bank in Erlangen represents one of the largest biomaterial banks for patients with congenital heart defects in the country. The focus of our research involves mutation detection and gene expression analyses with traditional techniques of PCR amplification, Sanger Sequencing and TaqMan analysis but also array technology for the analyses of single nucleotide polymorphisms, gene copy number variations and linkage studies. In one of our current projects we investigate a familial form of complex cardiac malformations with mendelian inheritance by exome capturing and next generation sequencing. Our collaborators are the Institute for Human Genetics, FAU Erlangen, the Department of Cardiovascular Genetics, Harvard University, Boston, USA and the Experimental and Clinical Research Center, Charité and MDC Berlin.
Current projects are:

- A gonosomal candidate gene approach for sporadic coarctation of the aorta
- The congenital coarctation of the aorta, a structural but also functional alteration of the aortic isthmus; expression analysis in human tissue.
- Genome wide analyses in a familial form of complex conotruncal heart defects with mendelian inheritance by exome capturing and next generation sequencing.

Clinical course in the intensive care unit after on-pump coronary bypass surgery of children with congenital heart failure

The clinical course of pediatric patients in the intensive care unit is mainly determined by the intraoperative used analgetic and its applicated lot. The necessary dose of fentanyl (opioid) can be reduced by co-using of remifentanil (opioid). The postoperative potentially remaining analgesic power of fentanyl has been evaluated in overall 50 patients with congenital heart failure since january 2011 via different clinical parameters and measurement of concentrations in blood. The accumulation of fentanyl in contrast to remifentanil might cause a prolonged effect and might become relevant in hemodynamically and respiratory aspects. The analysis of clinical signs, concentrations of fentanyl and of the entire clinical course in the intensive care unit should enable a further optimization of the intraoperative analgesia and inpatient treatment.

Impact of cardiologic and genetic parameters on the quality of life and neuropsychological status of patients with tetralogy of Fallot after surgery

The interdisciplinary study – together with the Department of Psychiatry – aims to investigate the influence of cadiologic and genetic factors on the quality of life and neuropsychological variability of adult patients with tetralogy of Fallot after cardiac surgery. For the evaluation of cardiologic problems of acute or chronic nature, we performed an echocardiography, a stress ECG and a normal ECG. The assessment of the quality of life and neuropsychological status was accomplished by a variety of well established psychological tests. An additional cerebral MRI is essential to rule out brain abnormalities caused by perioperative injury. Further genetic disorders, which are commonly associated with congenital heart failure, for example the microdeletion 22q11.2. and genetic variability of the APOE-genotype (Apolipoprotein E), which is are marker for an increased vulnerability of neurons of the brain are detected.

Duchenne Muscular Dystrophy

Since March 2010 we have established a double-blind, placebo-controlled clinical trial under the title "Effect and safety of preventive treatment with ACE-inhibitor and beta blocker in patients on the onset of left ventricular dysfunction in DMD patients".

The research is financed through the German Federal Ministry of Education and Research (BMBF) and works in participation with the pediatric neurological MD-Network and the competence network for congenital heart defects.

The study is planned to include a total of 130 male patients which are diagnosed with Duchenne disease between 10 and 14 years with normal left ventricular function. Patients can be recruited until 2012 and the study has an expected duration of 6 years.

The Cardiological Center of Erlangen is the leading center of this multicenter study carried out in 11 pediatric cardiological centers all over Germany.

Another clinical study was carried out in 2009/2010 to evaluate the pattern of cardiomyopathy in DMD patients using cardiac MRI with late Gadolinium enhancement, 12-lead ECG, Holter ECG and BNP.

It was concluded that the cardiomyopathy in those patients didn't present itself in the expected typical dilative cardiomyopathy, but with decreasing physical inactivity manifested decreased volumes and dimensions of the left ventricle exactly in opposite to athletic heart disease. Independent of the global pump function of the heart, a sinus tachycardia and anatomic imbalance was evident by decreased heart rate variability (HRV).

A consecutive follow up MRT clinical study will investigate the course and prognosis of cardiomyopathy in those 39 patients.

In the near future it is planned to establish a cross sectional study, which is intended to expand the concept of prevalence of myocardial dysfunction in different age groups of DMD patients, together with the possible influencing factors such as drugs and ventilation.

Early measurment of urine and plasma neutrophil-associated lipocalin for screening of acute renal injury after congenital cardiac surgery

Neutrophil gelatinase-associated lipocalin (NGAL) has emerged as a new biomarker for acute renal injury and can be measured in urine and plasma. In a prospective study we compare the diagnostic impact of the urine NGAL and the plasma NGAL measurement in pediatric patients after cardiac surgery in daily clinical practice. In the future this biomarker might be a helpful diagnostic tool to detect acute renal injury in infants and children early after cardiopulmonary bypass.

Teaching

The department takes part in the general teaching program of the Division 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 department.

Selected Publications

Koch A, Zink S, Dittrich S (2009) Plasma levels of B-type natriuretic peptide in children and adolescents with high degree atrioventricular block. Int J Cardiol, 134: 429-30

Nir A, Lindinger A, Rauh M, Bar-Oz B, Laer S, Schwachtgen L, Koch A, Falkenberg J, Mir TS (2009) NT-Pro-B-type Natriuretic Peptide in Infants and Children: Reference Values Based on Combined Data from Four Studies. Pediatr Cardiol, 30: 3-8

Ruffer A, Purbojo A, Glockler M, Toka O, Cicha I, Seeliger T, Zink S, Koch A, Dittrich S, Cesnjevar R (2009) Early Failure of Decellularized Pulmonary Valve Conduits - A Word of Caution! Clin Res Cardiol, 98: 591-592

Koch AM, Zink S, Glöckler M, Seeliger T, Dittrich S (2010) Plasma levels of B-type natriuretic peptide in patients with tetralogy of Fallot after surgical repair. Int J Cardiol, 143: 130-4

Teekakirikul P, Eminaga S, Toka O, Alcalai R, Wang L, Wakimoto H, Nayor M, Konno T, Gorham JM, Wolf CM, Kim JB, Schmitt JP, Molkentin JD, Norris RA, Tager AM, Hoffman SR, Markwald RR, Seidman CE, Seidman JG (2010) Cardiac fibrosis in mice with hypertrophic cardiomyopathy is mediated by non-myocyte proliferation and requires Tgf-β. J Clin Invest, 120: 3520-9

Toka O, Maass PG, Aydin A, Toka H, Hübner N, Rüschendorf F, Gong M, Luft FC, Bähring S (2010) Childhood hypertension in autosomal-dominant hypertension with brachydactyly. Hypertension, 56: 988-94

Department of Medicine 1 – Gastroenterology, Lung Diseases and Endocrinology

Chair of Internal Medicine I

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Research Focus
- Inflammatory Bowel diseases
- Endocrinology
- Experimental hepatology
- Immunosuppressive strategies for the treatment of chronic inflammatory diseases
- Clinical and experimental pneumology
- Molecular endoskopy
- Molecular gastroenterology
- Ultrasound
- Celiac disease

Structure of the Department

The Department of Medicine 1 covers research in the fields of gastroenterology, hepatology, endocrinology, pneumology, intensive care medicine, infectious diseases, endoscopy and ultrasound. Several research groups investigate these fields in clinical and experimental approaches.
In 2009 and 2010 the research division of the Department of Medicine 1 was substantially reorganized. In addition to clinical research, especially clinically oriented basic research was strengthend and new research groups were established. In the course of these reorganization efforts, two new W2-professorships and two W1-juniorprofessorships were created.

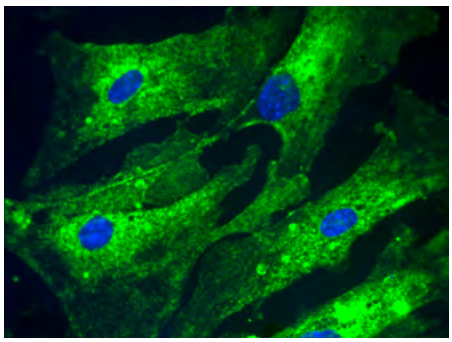
Research

Inflammatory Bowel diseases
Project managers: R. Atreya, J. Mudter
The "Inflammatory Bowel Diseases" working group aims at analyzing the immunopathogenic mechanisms involved in ulcerative colitis and Crohn's disease. The following projects are currently being investigated:
- Immunpathogenic role of cytokine mediated signaling pathways and transcription factors
- Characterization of the molecular mechanism of action of immunosuppressive therapies
- Innovative endoscopic procedures
- Establishing therapy-specific predictors of response
- Characterization of the influence of specific pathogens on the immunpathogenesis of IBD

Endocrinology
Project manager: C. Schöfl
The Calcium-Sensing-Receptor (CaSR) is pivotal for calcium homeostasis. Mutations of the CaSR cause hyper- and hypocalcemic disorders and Bartter-Syndrome Type V. Our group characterizes inactivating and activating CaSR mutations and tests how the detrimental effects of these mutations can be corrected pharmacologically. These results provide novel treatment options for patients with CaSR associated disorders, contribute to the individualized therapy of rare diseases and are the basis for CaSR based therapeutic approaches of more common diseases such as osteoporosis, nephrolithiasis or arteriosclerosis.

Experimental hepatology
Project managers: S. Wirtz, J. Siebler
We are interested in the role of cytokines for development of liver-fibrosis, a consequence of most chronic diseases of the liver. In ongoing studies, we comprehensively adress the functional role of the novel cytokine IL-33 that is upregulated in liver-fibrosis and induces strong hepatic alterations when overexpressed. In this translational research project we want to identify new molecular mechanisms of liver pathophysiology and clear up, whether IL-33 could be a potential prognostic marker or therapeutic target in chronic liver disease.

Immunosuppressive strategies for the treatment of chronic inflammatory diseases
Project manager: I. Atreya
Immunosuppressive strategies for the treatment of chronic inflammatory diseases represent our main focus. We monitor the effects of clinically established or innovative immunosuppressive compounds on intracellular signaling cascades and the overall pro-inflammatory capacity of immune cells. The project aims at the identification of new molecular mechanisms of action of immunosuppressive agents. A detailed understanding of the underlying mechanism might help to optimize existing immunosuppressive strategies or might even enable us to identify new target structures for innovative therapeutic attempts.



Hepatic Stellate Cells

Clinical and experimental pneumology
Project managers: F. Fuchs, K. Hildner
The main clinical field of research is the evaluation of new imaging methods during bronchoscopy. First results show the possibility of cellular visualization of malignant lesions *in vivo* by confocal laser-endomicroscopy. Our aim is to evaluate this method for routine use.
Our translational studies focus on the molecular and functional analysis of the immune response pattern within malignant airway lesions of lung cancer patients and in murine lung tumor models. Our goal is to identify novel prognostic markers and therapeutic target molecules to improve treatment options for our patients.

Molecular endoskopy
Project manager: 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.
The 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.

In 2010 the Department of Medicine 1 moved into the laboratories of the new research facility in the Hartmannstrasse

Molecular gastroenterology
Project manager: Ch. Becker
The research focuses on the immunological and molecular mechanisms that lead to the development of infection, chronic inflammation and cancer within the gut.
Experimental data have shown that independent from each other, defects in the intestinal epithelial barrier as well as an unregulated immune response can lead to a breakdown of immune homeostasis in the gut. A consequence of this can be the development of inflammatory bowel disease (Crohn's disease and ulcerative colitis) and colon cancer. Our research has helped to understand the pathogenesis of these diseases on a cellular and molecular level. With these scientific findings we ultimately aim at the development of future therapeutic options for patients suffering from inflammatory bowel disease and colon cancer.

Ultrasound
Project manager: D. Strobel
Research is focused on contrast-enhanced ultrasound (CEUS), elastography (ARFI) and interventional ultrasound (radiofrequency ablation of liver tumors)
Current activities:
- Monitoring of antiangiogenetic therapy in hepatocellular carcinoma (CEUS),
- Quantitative CEUS in focal liver lesions,
- Quantitative CEUS in inflammatory bowel disease,
- Liver metastasis detection with CEUS in colorectal cancer and pancreatic cancer (DEGUM Multicenter trials).
- Ultrasound guided interventions in abdomen (DEGUM Multicenter trial),
- Elastometry (ARFI) in chronic liver diseases and focal liver lesions,
- Elastometry (ARFI) in extrahepatic pathologies

Celiac disease
Project manager: W. Dieterich
The group of Dr. W. Dieterich is interested in celiac disease, a glutensensitive enteropathy, which is caused in genetically predisposed individuals by glutens from wheat, rye and barley. Although nearly 20-25% of the European possess these genetic markers, the prevalence data only reaches 1% . Interestingly, we showed that glutens were able to mature and stimulate the antigen presenting cells in all individuals, independent of their genetic background. That's why we are interested to study the impact of further factors in developing celiac disease. Furthermore, we are looking for receptor molecules for glutens on antigen presenting cells and their signal transduction.

Teaching

The Department of Medicine 1 contributes to curricular teaching for medical students from 2nd 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

Neurath MF, Finotto S (2009) Translating inflammatory bowel disease research into clinical medicine. Immunity, 31: 357-61

Waldner MJ, Neurath MF (2009) Novel cytokine-targeted therapies and intestinal inflammation. Curr Opin Pharmacol, 9: 702-7

Letz S, Rus R, Haag C, Dörr HG, Schnabel D, Möhlig M, Schulze E, Frank-Raue K, Raue F, Mayr B, Schöfl C (2010) Novel activating mutations of the calcium-sensing receptor: the calcilytic NPS-2143 mitigates excessive signal transduction of mutant receptors. J Clin Endocrinol Metab, 95: E229-33

Neurath MF, Wittkopf N, Wlodarski A, Waldner M, Neufert C, Wirtz S, Günther C, Becker C (2010) Assessment of tumor development and wound healing using endoscopic techniques in mice. Gastroenterology, 139: 1837-1843.e1

Waldner MJ, Neurath MF (2010) The molecular therapy of colorectal cancer. Mol Aspects Med, 31: 171-8

Wirtz S, Nagel G, Eshkind L, Neurath MF, Samson LD, Kaina B (2010) Both base excision repair and O6-methylguanine-DNA methyltransferase protect against methylation-induced colon carcinogenesis. Carcinogenesis, 31: 2111-7

Meetings and International Training Courses

Please visit our internet page to find an overview on the various meetings and continuing education topics at the department: www.medizin1.uk-erlangen.de/e114/e195/index_ger.html

Research Equipment

Becton Dickinson GmbH - Fortessa 15 parameter multicolor flow cytometer

Intas GmbH - Maestro Fluorescence in vivo Imaging System

Caliper Life Sciences - IVIS Lumina II Bioluminescence in vivo Imaging System

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 is the internal medicine department focusing 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 in-patient and out-patient diagnostic and therapeutic options for cardiovascular diseases, including advanced techniques like ablation therapy of atrial fibrillation or interventional aortic valve replacement. The department employs 37 physicians, eight of them with permanent teaching positions at the Medical Faculty (habilitation), three biologists, and 118 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 out-patient 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.

Research

Electrophysiology
Project managers: M. Wilhelm, S. Kuly
The electrophysiology research group participates in several multicenter studies of new technology implemented in implantable defibrillators (ICD). In the ACTION study, heart failure patients undergo home monitoring during an individualized physical exercise training program. In a further project, candidates for cardiac resynchronization therapy are pre-operatively analyzed by cardiac computed tomography with regard to their asynchrony. In patients undergoing ablation therapy of atrial fibrillation by cryo-balloon, 3-dimensional fusion imaging based on electro-anatomical mapping and cardiac computed tomography is being developed and refined. Finally, professional football players are systematically evaluated by ECG and other non-invasive techniques.
The working group is part of the Center of Excellence for Medical Technology "Medical Valley e.V.". The project IS 08b is funded by the German Ministry of Science and Education (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.

Interventional cardiology
Project manager: J. Ludwig
The main fields of interest of this research group are the interventional treatment of coronary artery disease and interventional aortic valve replacement in the elderly. In the first field, advanced techniques for treatment of coronary bifurcation are being developed using on-line 3D quantification of coronary anatomy. A further focus lies on treatment of the acute coronary syndrome by improving coronary microcirculation through pharmacologic modulation of free radicals to ultimately minimize infarct size and thus improve patient prognosis. Together with the department of heart surgery, transapical and percutaneous aortic valve replacement (Fig.1b) is evaluated One major focus is the evaluation of periprocedural cerebral insults. In cooperation with the division of neuroradiology cerebral MR images are correlated to clinical events. Furthermore, the changes in quality of life are studied, efforts are made to identify special groups of patients who benefit more than others from transcatheter aortic valve implantation and the costs related to the effectiveness of the procedure are analyzed.

Echocardiography
Project managers: F.A. Flachskampf, O.-A. Breithardt
The echocardiography 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 characteristiscs in patients with aortic valve disease before and after valve replacement. Further topics are the technical foundations for ultrasound thrombolysis, echocardiography (including contrast echocardiography) in small-animal models of myocardial infarction (together with the Institute for Clinical Pharmacology and Toxicology) and in the application of engineered heart tissue as a therapeutic option in experimental heart failure. Several members of the internationally renowned group were voted members of the board of the European Association of Echocardiography. The group holds a yearly workshop on new echocardiographic techniques.

Cardiac magnetic resonance tomography
Projekt managers: M. Schmid, S. Achenbach
In collaboration with the Institute of Radiology (Head Prof. Uder) and Siemens Medical Solutions, 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 (tako-tsubo) and characterization and localization of myocardial fibrosis in dilated cardiomyopathy.

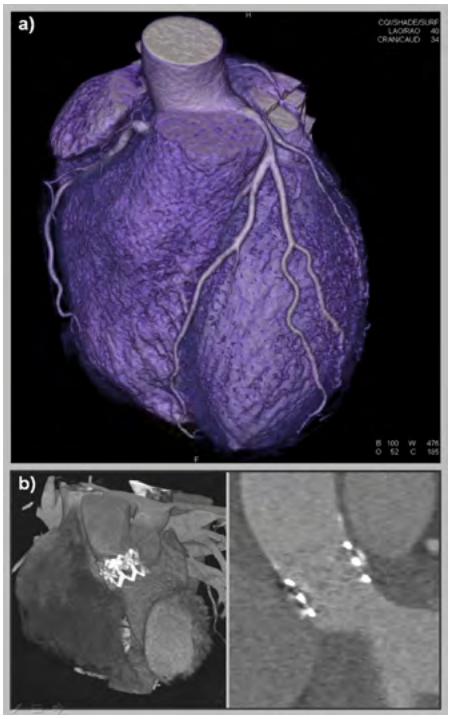

Fig. 1: Cardiac computed tomography.
a) 3D high-resolution coronary CT angiography with effective dose < 1.0 mSv
b) Transcatheter aortic valve implantation (TAVI): 3D- and sectional image

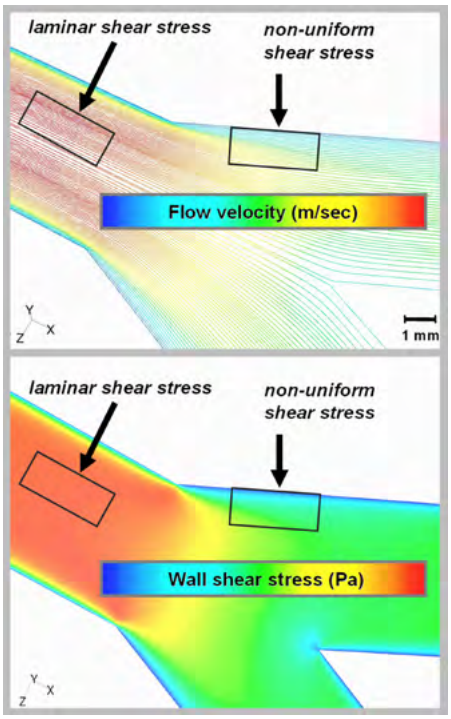

Fig. 2 Shear stress patterns and flow velocities in bifurcating slides

Cardiac computed tomography

Project manager: S. Achenbach

The major focus of the working group "Cardiac Computed Tomography" is non-invasive coronary CT angiography and imaging of coronary atherosclerosis. Several research projects, receive funding by the federal government. Next to clinical studies, technology development and validation of new techniques mainly concern new low-dose acquisition protocols. The group presented the first studies that demonstrated the ability to perform high-resolution coronary CT angiography with an estimated effective dose of less than 1.0 mSv (see Fig.1a). Further, the group conducts extensive trials concerning the characterization of coronary atherosclerotic plaques by CT. The group has a leading role in national and international registries which clarify the prognostic relevance of coronary CT angiography. Erlangen also serves as a core lab for large, international multi-center trials. A further area of work is CT imaging in the context of cardiac and coronary interventions, including transcatheter aortic valve implantation (see Fig.1b).

Molecular and experimental cardiology

Project manager: C. Garlichs

The research projects of the group focus on new pathomechanisms of atherosclerosis as a chronic inflammatory disease in order to identify innovative strategies for its treatment and prevention. a) Inflammatory / immunological mechanisms play an essential role in atherogenesis. Recently, C-reactive protein and its receptor moved into the focus of atherosclerosis research. Collecting a large patient databank enabled us to examine the role of C-reactive protein (CRP) and its receptor in the initiation, progression and destabilization of coronary plaques. In parallel with clinical investigations, the pro-inflammatory effects of CRP and its receptor on human endothelial cells has been characterized. b) CRP has a damaging effect on vessels and myocardium. In the rat model of myocardial infarction (MI) we investigate the effect of human CRP on myocardial necrosis. We will determine the possibility of limiting the deleterious effect of CRP on myocardium by using the specific neutralizing anti-CRP antibodies. c) Dendritic cells (DC) play an important role in atherosclerosis. Our previous studies showed that DC participate in plaque destabilization and MI, and that their functions can be modulated by statins. The present studies focus on the role of DC in coronary artery disease, restenosis and stroke, the long-term aim being establishing DC as potential candidates for therapeutic interventions. d) Calcification and stenosis of aortic valves bears important similarity to atherosclerosis. Our micro-array analyses of stenosed valves detected a number of differentially expressed pro-inflammatory genes. The role of these genes in development of aortic valve stenosis is currently under investigation. e) Using bifurcating flow-through cell culture slides which mimic *in vivo* shear stress patterns, we investigate the impact of laminar and disturbed flow on important atherogenesis-related endothelial functions, such as recruitment of leukocytes and platelets, expression of inflammatory proteins, and release of cytokines (Fig.2). f) C-kit+/CD34-/CD45- adult cardiac progenitor cells were found to be part of the physiological regeneration process of the myocardium in animal studies. We experimentally analyze the presence and distribution of adult cardiac progenitor cells in hearts from terminal heart failure cases. g) In patients with arterial hypertension and chronic heart failure, the association of inflammatory biomarkers with the extent of disease has been investigated. h) Analyses of differential expression of cytokines and chemokines in order to predict coronary calcifications and coronary stenoses in patients undergoing cardiac CT.

Teaching

The department provides 29 teaching activities (from lecture to practical exercise) per semester. Members of the department repeatedly won the first prize for good teaching of the Medical Faculty.

Selected Publications

Cicha I, Beronov K, Ramirez EL, Osterode K, Goppelt-Struebe M, Raaz D, Yilmaz A, Daniel WG, Garlichs CD (2009) Shear stress preconditioning modulates endothelial susceptibility to circulating TNF-alpha and monocytic cell recruitment in a simplified model of arterial bifurcations. Atherosclerosis, 207: 93-102

Achenbach S, Marwan M, Ropers D, Schepis T, Pflederer T, Anders K, Kuettner A, Daniel WG, Uder M, Lell MM (2010) Coronary computed tomography angiography with a consistent dose below 1 mSv using prospectively electrocardiogram-triggered high-pitch spiral acquisition. Eur Heart J, 31: 340-6

Arnold M, Schulz-Heise S, Achenbach S, Ott S, Dörfler A, Ropers D, Feyrer R, Einhaus F, Loders S, Mahmoud F, Roerick O, Daniel WG, Weyand M, Ensminger SM, Ludwig J (2010) Embolic cerebral insults after transapical aortic valve implantation detected by magnetic resonance imaging. JACC Cardiovasc Interv, 3: 1126-32

Marwan M, Pflederer T, Schepis T, Lang A, Muschiol G, Ropers D, Daniel WG, Achenbach S (2010) Accuracy of dual-source computed tomography to identify significant coronary artery disease in patients with atrial fibrillation: comparison with coronary angiography. Eur Heart J, 31: 2230-7

Schmid M, Daniel WG, Achenbach S (2010) Cardiovascular magnetic resonance evaluation of the patient with known or suspected coronary artery disease. Heart, 96: 1586-92

International Cooperation

Thomas J.Brady, Massachusetts General Hospital, Harvard University, Boston, MA, USA

Dr. Zahi Fayad, Mount Sinai School of Medicine, New York, NY, USA

Damini Dey, Daniel Berman, Cedars Sinai Medical Center, Los Angeles, CA, USA

Dr. Ravi Bathina, Care Medical Center, Hyderabad, India

Dr. Kristian Ovrehus, Vejle Hospital, Vejle, Denmark

Prof. JU Voigt, UZ Gasthuisberg, Katholieke Universiteit Leuven, Leuven, Belgium

Research Equipment

Siemens Healthcare Intracardiac Catheter Angiography Facility (3 Labs)

GE Healthcare Vivid 7 (2 devices)

Philips Echo Cardiography Device ie33

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

Department of Medicine 3 – Rheumatology and Immunology

Chair of Internal Medicine III

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Research Focus

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

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 one of 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

Pathomechanisms of bone destruction in rheumatoid arthritis (RA)
Project managers: G. Schett, J. Zwerina
Rheumatoid arthritis 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.

Immunomodulatory effects of apoptotic and necrotic cells
Project managers: M. Herrmann, R. Voll
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.

Regulation of NF-kB
Project managers: R. Voll, M. Herrmann
This transcription factor serves a major role in the transcriptional regulation of many genes which are involved in inflammation and immune response. Furthermore, NF-kB-activation induces various anti-apoptotic factors. The latter are able to prevent cell death. Due to the central role of NF-kB for inflammation and immune response a targeted inhibition of NF-kB is supposed to be a very efficient new principle for the therapy of inflammatory diseases.

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

Analysis of inflammatory mechanisms in adult onset Still´s disease
Project managers: J. Rech, 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.

Mechanisms for the activation of fibroblasts in systemic sclerosis (SSc)
Project manager: 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 selectively 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.

Activation of synovial fibroblasts by microparticles in rheumatoid arthritis (RA)
Project manager: 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.

Pathogenesis of RPGN in ANCA-associated systemic vasculitides
Project manager: 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 in-

vestigated in kidney biopsies of patients with a RPGN as well as experimental RPGN models.

The role of 12/15-lipoxygenase (12/15-LO) in the regulation of innate and adaptive immunity

Project manager: 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. Moreover, a potential involvement of this enzyme in the phagocytosis of apoptotic cells and during the interaction between DCs and T-lymphocytes will be investigated. In addition, Dr. G. Kroenke studies the role of 12/15-LO during chronic inflammatory diseases *in vivo* using 12/15-LO deficient mice and various disease models (TNF-transgenic mice, collagen-induced arthritis).

National and international clinical trials

Project managers: J. Rech, M. Ronneberger, A. Reisch, S. Finzel

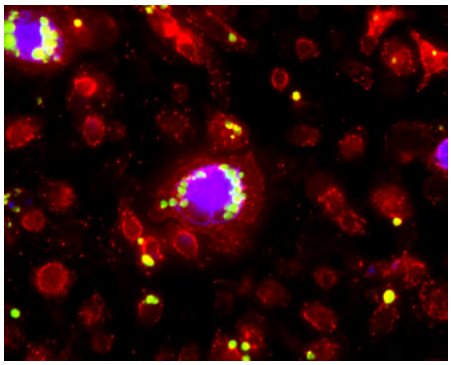
Various national and international phase Ib-IV studies were conducted, primarily to investigate new treatment approaches in rheumatic diseases. The major focus of the therapeutic trials are on treatments with "biologicals and small molecules" e.g. therapeutic principles which block the proinflammatory cytokine tumor necrosis factor alpha, IL-6, IL-17, IL-12/23, JAK3-kinase.

Another focus is the initiation and conduction of a multicenter phase II trial in patients with erosive finger osteoarthritis. In the course of international multicenter trials we are conducting standardization seminars for examination techniques in patients with RA.

Immunodeficiencies and infectious diseases

Project manager: 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 clinic is working on the development of immunotherapies such as therapeutic vaccines and immunomodulators. The clinic 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.



Differential phagocytosis of apoptotic cells by distinct macrophage subpopulations

Immunogenetics and transplant-immunology

Project manager: 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.

Molecular signaling pathways in rheumatoid arthritis (RA)

Project managers: G. Schett, M. Stock

Rheumatoid arthritis (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 signalling are evaluated.

Teaching

The education offered by the Department of Medicine 3 is enbedded 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.

Speaker: Prof. M. Herrmann

Selected Publications

Diarra D, Stolina M, Polzer K, Zwerina J, Ominsky MS, Dwyer D, Korb A, Smolen J, Hoffmann M, Scheinecker C, van der Heide D, Landewe R, Lacey D, Richards WG, Schett G. Dickkopf-1 is a master regulator of joint remodeling. Nat Med. 2007;13:156-163. IP: 27.136

Neubert K, Meister S, Moser K, Weisel F, Maseda D, Amann K, Wiethe C, Winkler TH, Kalden JR, Manz RA, Voll RE (2008) The proteasome inhibitor bortezomib depletes plasma cells and protects mice with lupus-like disease from nephritis. Nat Med, 14: 748-55

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

Maurer B, Busch N, Jüngel A, Pileckyte M, Gay RE, Michel BA, Schett G, Gay S, Distler J, Distler O (2009) Transcription factor fos-related antigen-2 induces progressive peripheral vasculopathy in mice closely resembling human systemic sclerosis. Circulation, 120: 2367-76

Hakkim A, Fürnrohr BG, Amann K, Laube B, Abed UA, Brinkmann V, Herrmann M, Voll RE, Zychlinsky A (2010) Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis. Proc Natl Acad Sci U S A, 107: 9813-8

Schramek D, Leibbrandt A, Sigl V, Kenner L, Pospisilik JA, Lee HJ, Hanada R, Joshi PA, Aliprantis A, Glimcher L, Pasparakis M, Khokha R, Ormandy CJ, Widschwendter M, Schett G, Penninger JM (2010) Osteoclast differentiation factor RANKL controls development of progestin-driven mammary cancer. Nature, 468: 98-102

International Cooperation

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

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

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

Prof. S. Muller, Institut de Biologie Moléculaire et Cellulaire du CNRS, Strassbourg, France

Prof. D. Isenberg, Center for Rheumatology Research, London, GB

Prof. J. Savill, Prof. I. Dransfield, The University of Edinburgh, Edinburgh, GB

Prof. Y. Shoenfeld, Sheba Medical Center, Tel-Hashomer, Israel

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

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

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

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

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

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

Prof. G. Firestein, University of California, San Diego, CA, USA

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

Prof. B. Walker, Boston Medical Center, Boston, MA, USA

Prof. M. Wabl, University of California UCSF, San Francisco, CA, USA

Prof. J. B. Imboden, University of California, San Francisco, CA, USA

Prof. Ch. Jorgensen, CHU Montpellier, Montpellier, France

Prof. L. Klareskog, Karolinska Institutet, Stockholm, Sweden

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

Meetings and International Training Courses

04.–07.03.2010: 30th European Workshop for Rheumatology Research, Bamberg, Deutschland

Research Equipment

Beckman Coulter GmbH – Throughput Cytometer Gallios 3L/10C

Scanco Medical AG - XtremeCT in vivo MicroCT Scanner

Department of Medicine 3 – Rheumatology and Immunology

Division of Molecular Immunology

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Research Focus

- The role of microRNAs (miRNAs) in B cell maturation and pathogenesis of multiple myeloma
- Nonsense-Codon Mediated Decay (NMD) of non-functional mRNA (mRNA Surveillance)
- Molecular control of early B cell differentiation
- Molecular control of peripheral B cell and plasma cell differentiation
- Signal transduction in B cells

Structure of the Division

The Division of Molecular Immunology was founded as an independent section within the Department of Internal Medicine 3 in 1997. The laboratories reside in the Nikolaus-Fiebiger-Center and the division is headed by Prof. Dr. Hans-Martin Jaeck together with six senior postdoctoral scientists, who supervise currently four PhD students, four 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 the 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 miRNAs, adaptor proteins and transcription factors for instance. Subsequently, new mouse models are being 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 Nikolaus-Fiebiger-Center and through its leading role in research groups and research training groups (e.g., Research Unit FOR 832 and the graduate program GK592). Nationally, the Division of Molecular Immunology is an important part of the study group (Arbeitskreis) Biology of B lymphocytes within the DGfI (Deutsche Gesellschaft fuer 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 allows them 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 (Fig. 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 microRNAs (miRNAs) in B cell maturation and pathogenesis of multiple myeloma

Project managers: H.-M. Jaeck, 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 (Fig. 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. (Fig. 2)

Nonsense-Codon Mediated Decay (NMD) of non-functional mRNA (mRNA Surveillance)

Project managers: H.-M. Jäck, 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 analy-

ses 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: H.-M. Jäck, W. Schuh

One major focus is the analysis of mechanisms that control early B cell development and signaling of the pre-B cell receptor. For example, the interaction of the pre-BCR with structures and ligands in the bone marrow microenvironment and its impact on survival and proliferation of progenitor B cells is studied using different mouse models. Using transcriptome and proteome analyses, we identified various cellular components of the pre-BCR signaling cascade, for example the transcription factor Krueppel-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 can not 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: H.-M. Jäck, 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.

Signal transduction in B cells

Project manager: 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 mouse lines.

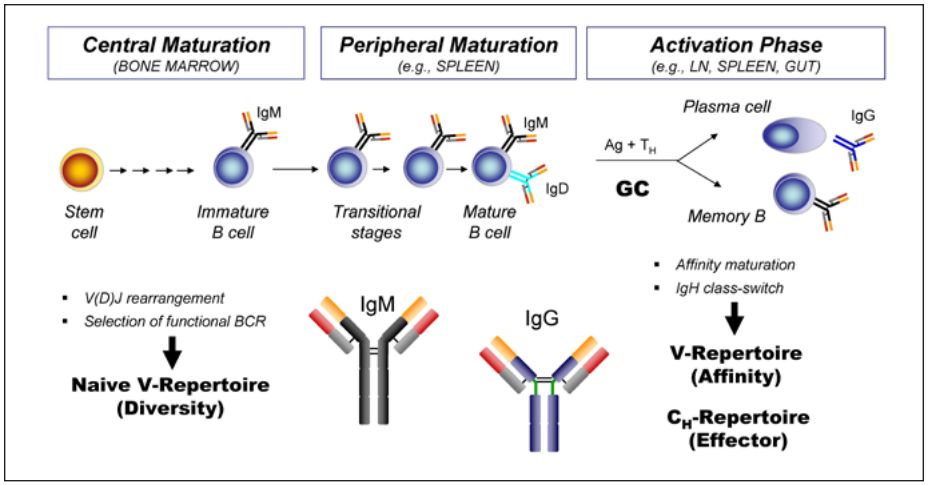

Fig. 1: Overview Humoral Immunity

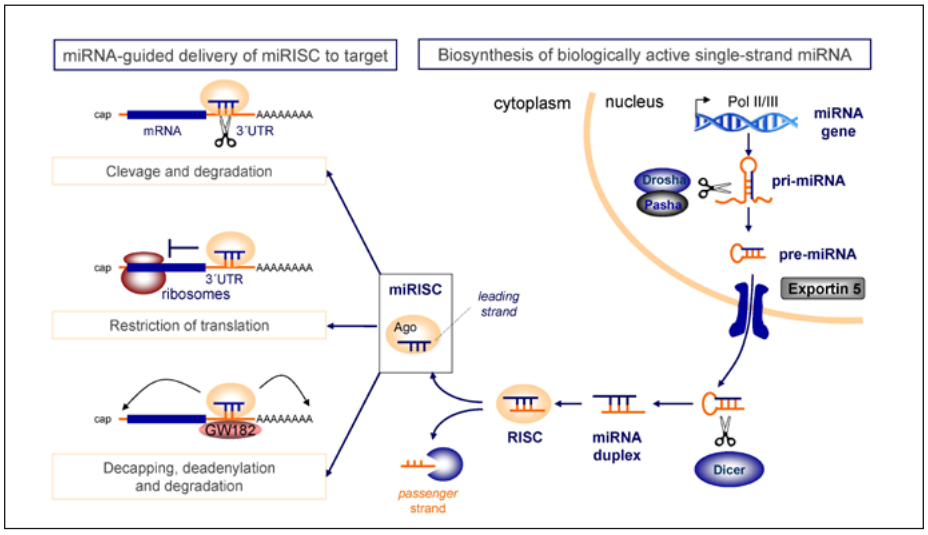

Fig. 2: RNA interference by endogenous microRNA

Teaching

The division participates in undergraduate and graduate education within the bachelor and master programs in biology 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 of doctoral students from the DFG training group GK 592 and the research group FOR 832 by offering numerous workshops and seminars, like journal clubs or scientific writing and presentation workshops.

Selected Publications

Beck-Engeser GB, Eilat D, Harrer T, Jäck HM, Wabl M (2009) Early onset of autoimmune disease by the retroviral integrase inhibitor raltegravir. Proc Natl Acad Sci U S A, 106: 20865-70

Eberle AB, Herrmann K, Jäck HM, Mühlemann O (2009) Equal transcription rates of productively and nonproductively rearranged immunoglobulin mu heavy chain alleles in a pro-B cell line. RNA, 15: 1021-8

Kroczek C, Lang C, Brachs S, Grohmann M, Dütting S, Schweizer A, Nitschke L, Feller SM, Jäck HM, Mielenz D (2010) Swiprosin-1/EFhd2 controls B cell receptor signaling through the assembly of the B cell receptor, Syk, and phospholipase C gamma2 in membrane rafts. J Immunol, 184: 3665-76

Metzner M, Schuh W, Roth E, Jäck HM, Wabl M (2010) Two forms of activation-induced cytidine deaminase differing in their ability to bind agarose. PLoS ONE, 5: e8883

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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

Meetings and International Training Courses

15.–17.10.2010: 3. Internationales GK Symposium Regulatoren der Adaptiven Immunität, Erlangen, Deutschland,

Department of Medicine 4 - Nephrology and Hypertensiology

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 Internal Medicine IV comprises the Medical Clinic 4 (Nephrology and Hypertension) at the Universitätsklinikum 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 Internal Medicine IV.
Patient related and experimental research aims to better understand the pathogenesis of kidney disease and hypertension and their progression and adverse consequences, to identify novel therapeutic strategies and to evaluate therapeutic options. Research projects at this institution have played a major role in research networks, such as the Clinical Research Group 106 (End Organ Damage in Arterial Hypertension) and the Collaborative Research Center 423 (Kidney Injury: Pathogenesis and Regenerative Mechanisms) and contribute significantly to the research focus "Kidney and Circulation Research" of the Medical Faculty.
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 (www.gckd.org). Nine regional centers and several institutes at other universities cooperate with the coordinating center in Erlangen to enrol 5000 patients with chronic kidney disease and to follow them for up to 10 years. This large consortium is funded by the BMBF and the Foundation for Preventive Medicine of the Kuratrium für Heimdialyse (KfH).
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 to determine changes of in the kidney in conjunction with the initiation of kidney injury and to identify the mechanisms which result in regeneration or progressive loss of function. To this end, analyzes are being performed in isolated cells, human kidney tissue and animals. One focus in this area includes the growth and migration pattern of glomerular and tubular cells and the influence of cytokines, cell cycle regulators and their respective inhibitors, as well as the role of integrin receptors. 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.

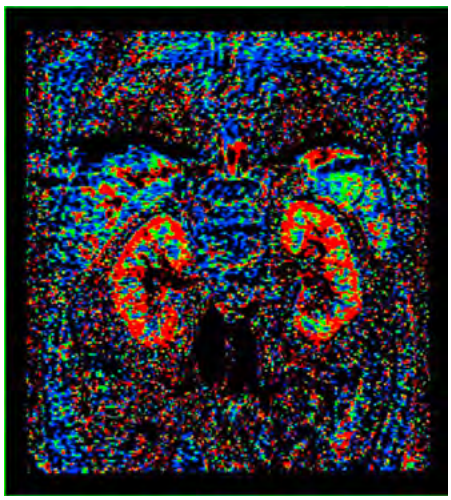
Pathophysiologic relevance of hypoxia-inducible gene expression
One pathomechanism, which is intensively investigated, concerns hypoxia and its relevance for kidney disease. Focus of these studies is the regulation and functional relevance of the hypoxia inducible transcription factors HIF-1 and HIF-2.
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 avoid 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 mesenchial 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. Of particular relevance in this context appear to be mechanisms in the skin, where alterations in sodium supply influence lymph-angiogenesis. Using sodium balance studies during the Mars mission project (MARS 500) and novel 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, chemical 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 is 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 Ophtal-

mology, 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 80 to 100 kidney and combined kidney-pancreas transplantations are performed per year, including living donor transplantations.
The research program in this field aims at optimizing long term graft function with particular emphasis on grafts from marginal donors. To this end, the clinic actively participates in several multicenter trials evaluating 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 measured 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 Medical Clinic 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 Medical Clinic 2, mechanisms of atherogenesis are being investigated and 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 clinic participates in several multicenter trials aiming to optimize management of these complications. Of particular relevance is the recently published TREAT trial of anemia management in patients not on dialysis. 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.



Magnetic resonance imaging with arterial spin labeling (MRI–ASL): calculated perfusion map with color encoding.

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 Medical Clinic 4 in Erlangen and Nürnberg participates in several observational and treatment trials.

Teaching

The Department of Internal Medicine IV 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 and optional courses in Intensive Care Medicine, Transplantation, Kidney and Vascular System.
There is also the opportunity for clerkships and short term visits.

Selected Publications

Bernhardt, WM, Gottmann, U, Doyon, F, Buchholz, B, Campean, V, Schödel, J, Reisenbuechler, A, Klaus, S, Arend, M, Flippin, L, Willam, C, Wiesener, MS, Yard, B, Warnecke, C, Eckardt, KU. Donor treatment with a PHD-inhibitor activating HIFs prevents graft injury and prolongs survival in an allogenic kidney transplant model. Proc Natl Acad Sci U S A 2009 106: 21276-21281.

Fellström BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Grönhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Süleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wüthrich RP, Gottlow M, Johnsson E, Zannad F, AURORA Study Group (2009) Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med, 360: 1395-407

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Walz G, Budde K, Mannaa M, Nürnberger J, Wanner C, Sommerer C, Kunzendorf U, Banas B, Hörl WH, Obermüller N, Arns W, Pavenstädt H, Gaedeke J, Büchert M, May C, Gschaidmeier H, Kramer S, Eckardt KU (2010) Everolimus in patients with autosomal dominant polycystic kidney disease. N Engl J Med, 363: 830-40

International Cooperation

Please find further information on our website:
www.medizin4.uk-erlangen.de

Meetings and International Training Courses

07.03.2009: Sepsis und Multiorganversagen, Klinikum Nürnberg-Süd, Deutschland

06.03.2010: Sepsis und Multiorganversagen, Klinikum Nürnberg-Süd, Deutschland

08.–10.10.2010: 3. Internationales SFB 423 - Symposium, Bamberg, Deutschland

22.–23.10.2010: Leben ohne neue Niere? Organtransplantation als gesellschaftliche Herausforderung, Germanisches Nationalmuseum Nürnberg, Deutschland

Department of Medicine 5 - Hematology and Oncology

Chair of Hematology and Oncology

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Head of Department
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Research Focus

- T-cell based immunotherapy
- Cellular immunotherapy
- CD4+ T helper cells in uveal melanoma disease and therapy
- Adoptive immunotherapy with memory B-lymphocytes after allogeneic stem cell transplantation
- Natural killer (NK) cells
- Tumor immune escape
- HLA-Laboratory

Structure of the Department

The Department of Medicine 5 is the department 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 70 employees (18 on extra-departmental funding). The scientific section counts ten post-doctoral fellows, 13 graduate students and ten technicians.

Research

T-cell based immunotherapy
Project managers: A. Mackensen, M. Aigner, S. Völkl
The Collaborative Research Center (SFB) 643 focuses on new approaches for cellular immune intervention. In project C8 the group of Prof. Mackensen / Dr. Aigner develops new strategies for the in vitro generation of tumor-antigen-specific T-cells for adoptive T-cell therapy. The population of human TCRalpha/beta+ CD4- CD8- double-negative (DN) T-cells plays a critical role in the regulation of immune responses. In a project funded by the DFG Prof. Mackensen and Dr. Voelkl investigate the immunoregulatory function of human DN T-cells. Furthermore, the role of DN T-cells under pathologic conditions such as autoimmunity and transplantation rejection is currently investigated. The long-term goal is to develop a clinical strategy for using DN T-cells as a cellular therapy for treatment of graft-versus-host disease after allogeneic stem cell transplantation.

Cellular immunotherapy
Project managers: A. Gerbitz, M. Aigner, H. Bruns
The group "Cellular Immunotherapy" works in two separate areas: (i) development of murine preclinical models for T-cell-therapy of high grade lymphoma and (ii) implementation of clinical adoptive T-cell therapy under GMP conditions.
(i) Using a model antigen, we could show in a murine model of high grade B-cell lymphoma that T-cell mediated rejection is possible and dependent on the presence of IFN-gamma which acts on the stroma. In future we will therefore focus on the role of tumor stroma with respect to immune escape. In collaboration with the Helmholtz-Center Munich, we showed that murine CD19 functions as rejection antigen. These studies will be extended to human CD19 as preclinical model.
(ii) Within the BayImmuNet consortium and in collaboration with the CCS of the Friedrich-Alexander-Universität Erlangen-Nürnberg we are in the process of preparing a clinical study for adoptive transfer of CMV- and EBV-specific T-cells after allogeneic stem cell transplantation. Currently documents for application of manufacturing license are in preparation. An extended immunomonitoring of patients was established within two clinical studies.
Funding for various projects of the group comes from DFG, Deutsche Krebshilfe, Wilhelm-Sander-Stiftung, ZIM and IZKF/ELAN.

CD4+ T helper cells in uveal melanoma disease and therapy
Project managers: J. Bosch, S. Rödel.
We are developing immunotherapy with CD4+ T-cells as an alternative or adjunctive treatment for metastatic uveal melanoma. Uveal melanoma may be particularly responsive to T-cell-based immunotherapy because of its origination in the immune-privileged eye. The location of the primary tumor in the immune-privileged eye excuses the tumor cells from continuous immunological pressure. This may render primary uveal melanoma more immunogenic than tumor cells from non-privileged sites and allow for expression of novel tumor antigens to which the patient's endogenous T-cell repertoire is not tolerized. To facilitate the activation of tumor-specific CD4+ T-cells we have generated cell-based vaccines consisting of primary and metastatic uveal melanoma cells that are genetically modified to express CD80 costimulatory molecules and HLA-DR alleles that are syngeneic to the patient. Current research aims to determine whether HLA-DR+/CD80+ primary and metastatic uveal melanoma cells activate different CD4+ T-cells, which cytokines are necessary for CD4+ T-cell activation and which subpopulations of CD4+ T-cells are activated. Finally, we demonstrated that transfection of uveal melanoma cells with the gene encoding the costimulatory molecule CD80 prevents PDL1-mediated immune suppression by tumor cells and restores T-cell activation. Supported by the ELAN program, DFG-SFB643-C8, SFB643-GRK (SR) and Interdisciplinary Clinical Research Center (IZKF).

Adoptive immunotherapy with memory B-lymphocytes after allogeneic stem cell transplantation
Projekt managers: J. Winkler (1), M. Mach (2), A. Mackensen (1), T. H. Winkler (3).
The project is performed in collaboration with (1) the Department of Internal Medicine 5, Hematology/Oncology, (2) the Institute for Clinical and Molecular Virology and (3) the Institute for Biology, Chair of Genetics, Hematopoesis Unit at the Friedrich-Alexander-Universität Erlangen-Nürnberg.
Human cytomegalovirus viremia (CMV) and disease are a major cause of morbidity and mortality following allogeneic hematopoietic stem cell transplantation. We have recently used the murine model of CMV as a preclinical model to investigate the potential of a novel cell-based strategy to support the humoral antiviral immune response. These preclinical data provided evidence that a cell-based strategy supporting the humoral immune response might be effective in a clinical setting of post-HSCT immunodeficiency. The aim of the proposed project is to develop a novel cell-based therapy on the basis of adoptive transfer of memory B-lymphocytes from the SCT donor in patients after allogeneic SCT. Supported by BayimmuNet, GCP Fonds and CCS.

Natural killer (NK) cells

Project managers: E. Ullrich, I. Kröger, M. Meinhardt.

The research group of Prof. Dr. Evelyn Ullrich mainly focuses on the role of natural killer (NK) cells in antitumor responses and bone marrow transplantation (BMT).

Although BMT provides curative graft-versus-leukemia (GVL) effects, the graft-versus-host disease (GVHD) is an often lethal complication. A great challenge of current research on allogeneic BMT attempts to prevent the undesirable GVHD complications. Recently, clinical studies exploiting the impact of innate effector cells on GVHD lead to the suggestion that allogeneic donor NK cells mediate GVL effects and support immune reconstitution, while preventing GVHD.

It has now been shown that NK cells represent a heterogeneous population of functionally different subsets. Our current projects focus on the characterization of different subpopulations of murine and human NK cells and aim to analyze the immunoregulatory functions of different NK- and DC-subsets in tumor models and in GVHD upon allogeneic BMT. Understanding the role of NK and DC immune cell subsets in GVL and GVHD will improve the implementation of cellular therapies in the treatment of human malignancies.

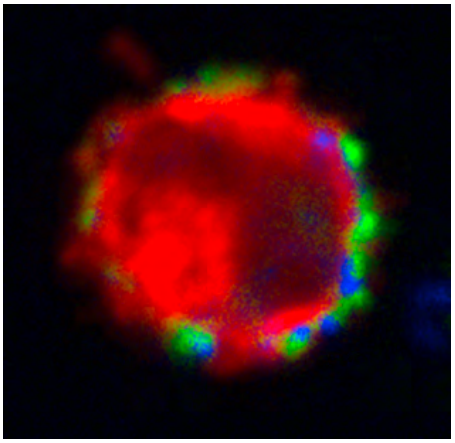
The preclinical research is funded by the Max-Eder-Program of the German Cancer Aid and the project characterizing human NK cell subsets is supported by the IZKF.

Tumor immune escape

Project managers: A. Mackensen, M. Aigner, K. Singer, R. Gary

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. The influence of metabolites produced by tumors on the activation, proliferation and various effector functions of cytotoxic CD8+ T-cells is studied by the group of Prof. Mackensen/Dr. K. Singer in a project funded by the IZKF.

T-cell dependent immune responses are initiated via antigen recognition of peptide-MHC complexes by specific T-cell receptors. During this interaction, T-cells acquire membrane fragments and surface molecules from their target cells in a process called trogocytosis. The importance of this phenomenon for the formation of a strong antitumor immune response is to be characterized by Prof. Mackensen/Dipl. Biol. R. Gary in a project funded by the DFG.



Human CD8⁺ T cell (red) after trogocytosis: membrane fragments (green) and PD-L1 (blue) were acquired from mature dendritic cells

HLA-Laboratory

Project manager: 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. Supported by the IZKF.

Teaching

A traditional teaching program (lectures, seminars, practica) covering all subjects in the field of hematology and oncology is being offered by qualified faculty 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

Bruns H, Meinken C, Schauenberg P, Härter G, Kern P, Modlin RL, Antoni C, Stenger S (2009) Anti-TNF immunotherapy reduces CD8+ T cell-mediated antimicrobial activity against Mycobacterium tuberculosis in humans. J Clin Invest, 119: 1167-77

Hoves S, Aigner M, Pfeiffer C, Laumer M, Obermann EC, Mackensen A (2009) In situ analysis of the antigen-processing machinery in acute myeloid leukaemic blasts by tissue microarray. Leukemia, 23: 877-85

Voelkl S, Moore TV, Rehli M, Nishimura MI, Mackensen A, Fischer K (2009) Characterization of MHC class-I restricted TCRalphabeta+ CD4- CD8- double negative T cells recognizing the gp100 antigen from a melanoma patient after gp100 vaccination. Cancer Immunol Immunother, 58: 709-18

Guettinger Y, Barbin K, Peipp M, Bruenke J, Dechant M, Horner H, Thierschmidt D, Valerius T, Repp R, Fey GH, Stockmeyer B (2010) A recombinant bispecific single-chain fragment variable specific for HLA class II and Fc alphaRI (CD89) recruits polymorphonuclear neutrophils for efficient lysis of malignant B lymphoid cells. J Immunol, 184: 1210-7

Singer K, Kastenberger M, Gottfried E, Hammerschmied CG, Büttner M, Aigner M, Seliger B, Walter B, Schlosser H, Hartmann A, Andreesen R, Mackensen A, Kreutz M (2010) Warburg phenotype in renal cell carcinoma: High expression of glucose-transporter 1 (GLUT-1) correlates with low CD8(+) T-cell infiltration in the tumor. Onkologie, 33 Suppl. : 128-128

Winkler J, Rech D, Kallert S, Rech J, Meidenbauer N, Roesler W, Mackensen A (2010) Sorafenib induces sustained molecular remission in FLT3-ITD positive AML with relapse after second allogeneic stem cell transplantation without exacerbation of acute GVHD: A case report. Leuk Res, 34: e270-2

International Cooperation

L. Zhang, Departments of Lab Medicine and Pathobiology, University of Toronto, Toronto, Canada

M. Nishimura, Department of Surgery, Medical University of South Carolina, Charleston, SC, USA

M. Oelke, School of Medicine, Johns Hopkins University, Baltimore, MD, USA

S. Ostrand-Rosenberg, Department of Biological Sciences, University of Maryland, Baltimore, MD, USA

B.R. Ksander, The Schepens Eye Research Institute and Dept. of Ophthalmology, Harvard Medical School, Boston, MA, USA

C.J.M. Melief, Dept. of Immunohematology and Bloodtransfusion, Leiden University, Leiden, The Netherlands

L. Zitvogel, Institut Gustave Roussy, Paris - Villejuif, France

Meetings and International Training Courses

19.–20.03.2009: 5th International Symposium on the Clinical Use of Cellular Products, Nürnberg

Research Equipment

Becton Dickinson FACS Canto II

Applied Biosystems Sequencer AB Genetic Analyser 3130

Institute of Microbiology – Clinical Microbiology, Immunology and Hygiene

Chair of Microbiology and Immunology of Infection

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Research Focus

- Bacterial virulence factors
- Innate immunity, granulocytes and mast cells
- Innate immunity and antimicrobial proteins
- Innate Immunity, macrophages and NO synthase
- Innate immunity, macrophages and adjuvants
- Innate immunity and natural killer cells
- The immune system and milieu factors in the tissues
- Infection – induced autoimmunity
- Signal transduction of interleukin-4 receptor signaling

Structure of the Department

The Institute of Microbiology is active in research, teaching and clinical diagnostics. The institute houses the Chair of Microbiology and Immunology of Infectious Diseases and, since November 1, 2008, the newly installed independent Division of Infection Biology (see there). The institute employs 84 coworkers, of which 26 are payed by extramural funding sources. The research is carried out by 16 scientists with a M.D. or Ph.D. degree, 17 Ph.D. students und 12 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 Borrelia, Coxiella, Mycobacteria, Salmonella, Pseudomonas and Leishmania. The institute is fully equipped with BSL2- and BSL3-laboratories, 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. For bacteriological, serological and mycological diagnostic procedures the diagnostic section of the institute (head: OA Dr. med. Dipl. Chem. C. Schoerner) functions as reference center for the nationwide quality control and proficiency tests.

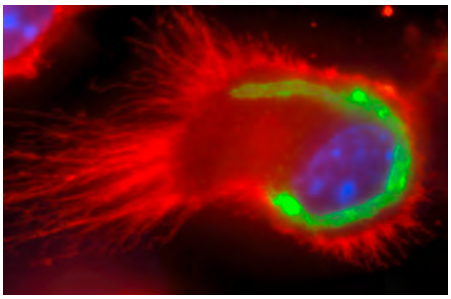

Fig. 1: MHC class II-positive dendritic cells (from the bone marrow of B6 mice; red with blue nucleus) were infected with Legionella pneumophila delta-flaA bacteria, which express and inject the antiapoptotic Coxiella burnetii effector protein AnkG (green) into the host cell thereby promoting its survival

Research

Bacterial Virulence factors
Project manager: A. Lührmann (since 01.10.2009)
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 C. burnetii, the causal agent of Q fever, as a model system. A major focus is the analysis of the mechanisms by which Coxiella promotes the viability of the host cells, thereby generating an ideal niche for its own survival (Fig. 1).

Innate immunity, granulocytes and mast cells
Project manager: 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 to characterize 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.

Innate immunity and antimicrobial proteins
Project manager: M. Schnare (until 30.09.2009)
Antimicrobial proteins are essential components of the immune response against infectious pathogens. The focus of the project is the analysis of the function and the regulation of antimicrobial proteins by toll-like receptors (TLR). Emphasis will be given to the "bactericidal/permeability-increasing protein" (BPI), which facilitates the phagocytosis and the lysis of Gram-negative bacteria. The phenotype of BPI-deficient transgenic mice will be characterized. Finally, the expression of TLR and antimicrobial proteins in trophoblasts and placental tissue is investigated in order to gain novel insights into the immunsuppressed status and susceptibility to infection of fetuses and newborns.

Innate Immunity, macrophages and NO synthase
Project manager: C. Bogdan
Nitric oxide, which is synthesized from the amino acid L-arginine in macrophages and other cells by the interferon (IFN)-gamma 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* (Fig. 2).

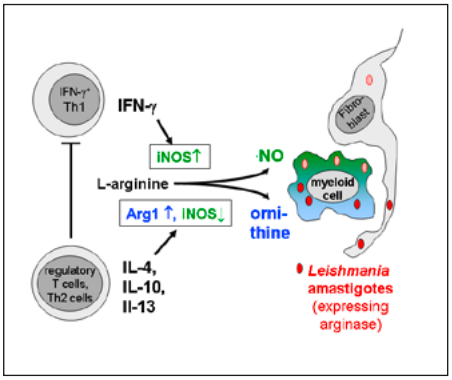

Fig. 2: The iNOS-dependent control of Leishmania during the chronic phase of infection might be impeded via the arginase 1 of myeloid cells (macrophages, dendritic cells) and/or the arginase of the parasite thereby allowing for the lifelong persistence of Leishmania

Innate immunity, macrophages and adjuvants

Project manager: 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 reponses. The project aims to eludicate 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 and natural killer cells

Project manager: U. Schleicher

The early phase of Leishmania infections is characterized by the rapid activation of natural killer (NK) cells. The group investigates, which signals (receptors, cytokines and myeloid cell types) are required for NK cell activation. As activated NK cells contribute to the control of pathogens, experiments are carried out to unravel the underlying direct (i.e. cytolytic) or indirect (i.e. immunoregulatory) effector mechanisms. For the functional analysis of NK cells during cutaneous (L. major) and visceral leishmaniasis (L. infantum) a transgenic mouse model, which allows for the selective deletion of NK cells, the transfer of NK cells or NK target cells and novel NK cell activators will be applied.

The immune system and milieu factors in the tissues

Project manager: J. Jantsch (since 01.01.2010)

It is well established that the oxygen levels of certain layers of the skin and of cells in the gastrointestinal tract and inflamed tissues may be very low (p02 < 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-1alpha, TonEBP).

Infection – induced autoimmunity

Project manager: J. Mattner (since 01.04.2010)

Autoimmune responses result from complex interactions of genetic predisposition and environmental factors. Although the autoantigens are often ubiquitously expressed, the autoimmune attack is frequently tissue-specific. The group investigates the microbial and immunological causes of Primary Biliary Cirrhosis (PBC), a chronic inflammatory liver disease. Using a congenic mouse model we evaluate 1) the genetic factors that favor the destruction of small intrahepatic bile ducts and 2) the role of bacterial antigens for the development of autoimmune responses by applying targeted gene deletion strategies.

Signal transduction of interleukin-4 receptor signaling

Project manager: A. Gessner (until 30.09.2010)

T-helper lymphocytes exist as different subtypes and therefore contribute both to the control as well as to the pathogenesis of infectious diseases. For the induction and function of type 2 T-helper cells interleukin (IL)-4 is of pivotal importance. Using various biochemical approaches as well as a number of newly established knock-out and knock-in mice the signalosom that is recuited to the IL-4 receptor as well as the subsequent signaling cascades will be defined. For functional *in vivo* analyses, the elucidation of inflammatory processes and the evaluation of novel immunotherapeutic approaches infectious disease mouse models will be used (Leishmania, Borrelia, Pseudomonas).

Teaching

The coworkers of the institute teach students of human medicine, dental medicine, molecular medicine, biology and pharmaceutical sciences in clinical and molecular microbiology, in immunology, in 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, M.D. and Ph.D. theses. Together with the Institute of Clinical and Molecular Virology the institute organizes an interdisciplinary lecture series on the diagnosis and treatment of infectious diseases, which serves as a continuous medical education program of medical doctors in the region.

Selected Publications

Mattner J, Savage PB, Leung P, Oertelt SS, Wang V, Trivedi O, Scanlon ST, Pendem K, Teyton L, Hart J, Ridgway WM, Wicker LS, Gershwin ME, Bendelac A (2008) Liver autoimmunity triggered by microbial activation of natural killer T cells. Cell Host Microbe, 3: 304-15

Fritzsche C, Schleicher U, Bogdan C (2010) Endothelial nitric oxide synthase limits the inflammatory response in mouse cutaneous leishmaniasis. Immunobiology, 215: 826-32

Haeberlein S, Sebald H, Bogdan C, Schleicher U (2010) IL-18, but not IL-15, contributes to the IL-12-dependent induction of NK-cell effector functions by Leishmania infantum in vivo. Eur J Immunol, 40: 1708-17

Lührmann A, Nogueira CV, Carey KL, Roy CR (2010) Inhibition of pathogen-induced apoptosis by a Coxiella burnetii type IV effector protein. Proc Natl Acad Sci U S A, 107: 18997-9001

Schoenen H, Bodendorfer B, Hitchens K, Manzanero S, Werninghaus K, Nimmerjahn F, Agger EM, Stenger S, Andersen P, Ruland J, Brown GD, Wells C, Lang R (2010) Cutting edge: Mincle is essential for recognition and adjuvanticity of the mycobacterial cord factor and its synthetic analog trehalose-dibehenate. J Immunol, 184: 2756-60

Wiese M, Castiglione K, Hensel M, Schleicher U, Bogdan C, Jantsch J (2010) Small interfering RNA (siRNA) delivery into murine bone marrow-derived macrophages by electroporation. J Immunol Methods, 353: 102-10

International Cooperation

Eric Cambronne, Department of Molecular Microbiology & Immunology, Oregon Health & Science University, Portland, OR, USA

M. Eric Gershwin, University of California, Davis, CA, USA

Peter Murray, St. Jude Children´s Research Hospital, Memphis, TN, USA

Paul Savage, Brigham Young University, Provo, UT, USA

Linda Wicker, University of Cambridge, Cambridge, UK

Marsha Wills-Karp, Cincinnati Children´s Hospital Medical Center, Cincinnati, OH, USA

Meetings and International Training Courses

10.–11.12.2010: Immunopathogenesis and novel treatment strategies of cutaneous leishmaniasis, Erlangen, supported by German Federal Ministry for Education and Research (BMBF)

Research Equipment

Applied Biosystems DNA-sequencer

Applied Biosystems ABI Prism 7900 sequence detector

BD Biosciences FACS Canto II

Institute of Microbiology – Clinical Microbiology, Immunology and Hygiene

Division of Infection Biology

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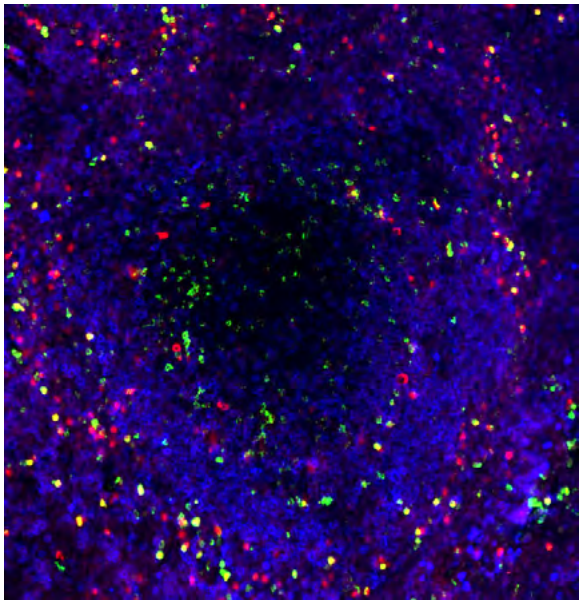

The picture shows a stained section from the spleen of a N. brasiliensis infected mouse with B cells (blue), IgE-producing plasma cells (red), basophils (yellow) and IL-4 producing cells (green).

Research Focus

- Immune response against helminths and allergens
- Characterization of alternatively activated macrophages
- Plasticity of T helper cells

Structure of the Division

The Division of Infection Biology was founded in 2009 as an independent department at the Institute of Clinical Microbiology, Immunology and Hygiene. The department is headed by Prof. David Vöhringer, who was recruited in October 2010 as W2 professor by the Friedrich-Alexander-Universität Erlangen-Nürnberg. The department employs 3 scientists with Ph.D. degree, 2 Ph.D. students and 2 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 the helminth *Nippostrongylus brasiliensis* 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 Department of Infection Biology during the last year could demonstrate that basophils play an important role for protective immunity against *N. brasiliensis*. It further became apparent that basophils are essential for chronic allergic inflammation of the skin. On the other hand, the previously proposed roles of basophils as antigen-presenting cells for Th2 cells or mediators of IgG1-induced passive anaphylaxis could not be confirmed.

Characterization of alternatively activated macrophages

Another project characterized the inhibitory activity of so-called "alternatively activated macrophages" (AAM) against T cells. AAM develop in the presence of interleukin (IL)-4 or IL-13, two cytokines that are mainly produced by Th2 cells. The results demonstrate that expression of PD-L2 on the cell surface of AAM is required and sufficient to confer inhibition against T cells which express the inhibitory receptor PD-1.
It was further observed that activation of macrophages by chitin, a major component of the cell wall in yeast and in the exoskeleton of crustaceans and arthropods, leads to expression of PD-L1 which binds to PD-1 on T cells and suppresses their proliferation. Whether pathogenic fungi use this mechanism to inhibit the immune response remains to be determined.

Plasticity of T helper cells

The T cell response against helminths was studied in two different projects. It could be shown that Th2 polarization after infection of mice with *N. brasiliensis* is only induced in antigen-specific T cells and not in bystander T cells. Analysis of the T cell receptor (TCR) repertoire revealed that the immune response was based on polyclonal T cell activation. In fact, mice with a restricted TCR repertoire could not expel the worms. The second project 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*. 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 could be reprogrammed in an antigen-specific manner.

Teaching

The Division of Infection Biology is closely associated to the Institute of Clinial Microbiology, Immunology and Hygiene and 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 department also supervise students that perform their Bachelor- or Master-thesis.

Selected Publications

Gründemann C, Schwartzkopff S, Koschella M, Schweier O, Peters C, Voehringer D, Pircher H (2010) The NK receptor KLRG1 is dispensable for virus-induced NK and CD8+ T-cell differentiation and function in vivo. Eur J Immunol, 40: 1303-14

Hinterberger M, Aichinger M, da Costa OP, Voehringer D, Hoffmann R, Klein L (2010) Autonomous role of medullary thymic epithelial cells in central CD4(+) T cell tolerance. Nat Immunol, 11: 512-9

Huber S, Hoffmann R, Muskens F, Voehringer D (2010) Alternatively activated macrophages inhibit T-cell proliferation by Stat6-dependent expression of PD-L2. Blood, 116: 3311-20

Ohnmacht C, Schwartz C, Panzer M, Schiedewitz I, Naumann R, Voehringer D (2010) Basophils orchestrate chronic allergic dermatitis and protective immunity against helminths. Immunity, 33: 364-74

Ohnmacht C, Voehringer D (2010) Basophils Protect against Reinfection with Hookworms Independently of Mast Cells and Memory Th2 Cells. J Immunol, 184: 344-350

Wagner CJ, Huber S, Wirth S, Voehringer D (2010) Chitin induces upregulation of B7-H1 on macrophages and inhibits T-cell proliferation. Eur J Immunol, 40: 2882-90

International Cooperation

David Artis, Department of Microbiology, University of Pennsylvania, Philadelphia, PA, USA

Randy Noelle, Dartmouth Medical School, Hanover, NH, USA

Richard Locksley, University of California San Francisco, San Francisco, CA, USA

Adrian Mountford, Department of Biology, University of York, York, UK

Luca Muzio, Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy

Francesca Granucci, Department of Biotechnology and Bioscience, University of Milano-Bicocca, Milan, Italy

Marc Dalod, Center of Immunology of Marseille-Luminy (CIML), Marseille, France

Department of Oral and Maxillofacial Surgery

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Research Focus
- Infection and inflammation
- Tumor Research

Structure of the Department

The Department of Oral and Maxillofacial Surgery is responsible for teaching oral and maxillofacial surgery, including dental surgery and dental radiology, research, as well as patient care. The faculty includes fifteen 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 Dept. of Oral and Maxillofacial Surgery allows a wide range of immunohistochemical and molecular biological techniques. For experimental trials concerning bone histology and biomedical technology, a specialized facility is shared with the Dept. 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

Project managers: F.W. Neukam, E. Nkenke, K.A. Schlegel, F. Wehrhan, P. Stockmann

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. The outcome of surgical therapy (i.e. osteotomy and primary wound closure) was recorded in a prospective cohort of patients.

For modeling compromised osseous healing the clinical and histologic changes following high-dose irradiation were determined in an experimental trial. External hypofractionated irradiation with a total dose of 60 Gy was shown to be feasible in rats and yielded all histologic changes attributed to osteoradionecrosis after a follow-up of six weeks. The animal model is currently used for an assessment of regenerative options (e.g. implantation of BMP-2 transfected bone marrow stromal cells) in critical size defects.

Tumor Research

Project managers: F.W. Neukam, E. Nkenke, F. Stelzle, J. Ries

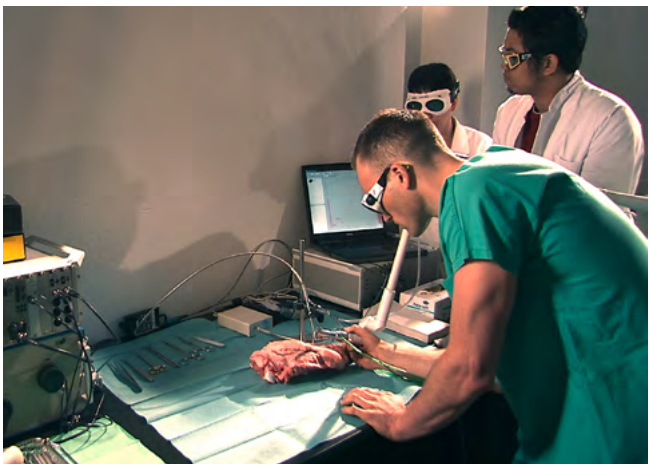
Research aims at improving function as well as facial esthetics following resection of tumors of the head and neck. In addition, the identification of clinical, immunohistochemical and molecular indicators of prognosis in patients diagnosed with oral squamous cell carcinoma of the oral cavity is a prime focus.

Oral cancer and its therapy can heavily influence speech intelligibility. An interdisciplinary work group, headed by the Department of Oral and Maxillofacial Surgery, Friedrich-Alexander-Universität Erlangen-Nürnberg, 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 Department of Phoniatry and Paedaudiology together with the Chair of Pattern Recognition, Friedrich-Alexander-Universität Erlangen-Nürnberg, now allow for an objective measure 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 (CSCs) 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 CSCs express these antigens and whether CSC can be eliminated by such therapies in the long run, is unknown.

Aim of a reasearch 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.

Detection of oral squamous cell carcinoma (OSCC) at an early stage improves the five-year patient survival rate from 50% to approximately 80%. Therefore, early diagnosis is the most effective approach for reducing morbidity and mortality. Furthermore, approximately 67% of all carcinomas are based on precancerous lesions like leukoplakia (LP) which progress into cancer in 1 to 18% of the cases. At present biopsies are histopathologically grad-



Project manager Dr. Dr. Stelzle during the tissue-specific laser ablation at an ex vivo animal model

ed for dysplasia to assess the risk of progression, but this grading is somewhat subjective and of limited use. However, an early identification of oral lesions with a high risk of malignant transformation and an early diagnosis of malignancies developing from them is of highest clinical importance for an improvement of the healing prospect.

Multiple MAGE-A expression analysis may be a very sensitive method for diagnosis of OSCC, since at least one of these genes is expressed in 93% of all tumor samples. On the other hand they are not provable in normal oral mucosa. Due to these characteristics they may allow a distinction between malignant and healthy tissues and an early diagnosis for the disease ($p > 0{,}001$).

Additionally the working group could show that a high risk of malignant transformation of LP is correlated with the expression of MAGE-A ($p > 0{,}001$). 85.4% of all examined LP proceeding into an OSCC pointed out a MAGE-A expression, whereas no antigen could be proven in all 50 LPs, which did not develop a malignancy within five years.

In the future, expression analysis of MAGE-A genes may be a valuable additional method for early diagnosis and for assessment of the malignant potential of oral precancerous lesions. Additionally alternative diagnostic methods like exfoliative cytology and planning of individual therapies could be improved. All these starting points could crucially contribute to the improvement of the survival rate of patients suffering from OSCC.

Teaching

Oral and maxillofacial surgery is a part of both, medical and dental curriculum. The Chair of Oral and 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) there are also problem based and interdisciplinary approaches used. Topics of interdisciplinary education include among others emergency medicine, 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

Fenner M, Vairaktaris E, Nkenke E, Weisbach V, Neukam FW, Radespiel-Tröger M (2009) Prognostic impact of blood transfusion in patients undergoing primary surgery and free-flap reconstruction for oral squamous cell carcinoma. Cancer, 115: 1481-8

von Wilmowsky C, Bauer S, Lutz R, Meisel M, Neukam FW, Toyoshima T, Schmuki P, Nkenke E, Schlegel KA (2009) In vivo evaluation of anodic TiO2 nanotubes: an experimental study in the pig. J Biomed Mater Res B Appl Biomater, 89: 165-71

Lutz R, Srour S, Nonhoff J, Weisel T, Damien CJ, Schlegel KA (2010) Biofunctionalization of titanium implants with a biomimetic active peptide (P-15) promotes early osseointegration. Clin Oral Implants Res, 21: 726-34

Stelzle F, Tangermann-Gerk K, Adler W, Zam A, Schmidt M, Douplik A, Nkenke E (2010) Diffuse reflectance spectroscopy for optical soft tissue differentiation as remote feedback control for tissue-specific laser surgery. Lasers Surg Med, 42: 319-25

Stockmann P, Vairaktaris E, Wehrhan F, Seiss M, Schwarz S, Spriewald B, Neukam FW, Nkenke E (2010) Osteotomy and primary wound closure in bisphosphonate-associated osteonecrosis of the jaw: a prospective clinical study with 12 months follow-up. Support Care Cancer, 18: 449-60

Wehrhan F, Hyckel P, Ries J, Stockmann P, Nkenke E, Schlegel KA, Neukam FW, Amann K (2010) Expression of Msx-1 is suppressed in bisphosphonate associated osteonecrosis related jaw tissue-etiopathology considerations respecting jaw developmental biology-related unique features. J Transl Med, 8: 96

International Cooperation

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. U. Thams, Chair for Animal Pathology II, University of Complutense, Madrid, Spain

Prof. Dr. K. Smetana, Institut of Anatomy, Charles University in Prague, Prague, Czech Republic

Research Equipment

BrainLab, Heimstetten Neuronavigationsgerät Vector Vision II

Kavo Digitaler Volumentomograph (DVT)

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Research Focus
- Neuroendocrinology
- Neurooncology
- Functional Neuronavigation and Intra-operative Imaging

Department of Neurosurgery

Structure of the Department

The Department of Neurosurgery of the Friedrich-Alexander-Universität Erlangen-Nürnberg is one of the largest in Germany. There are a total of 78 beds for inpatients, including ICU beds. The number of outpatients is 4000 per year. Up to 2600 patients get inpatient treatment. Caseloads include approximately 2200 major neurosurgical procedures per year. The range of operations covers the whole of neurosurgery with a focus on 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 are available for basic scientific issues.

Research

Neuroendocrinology

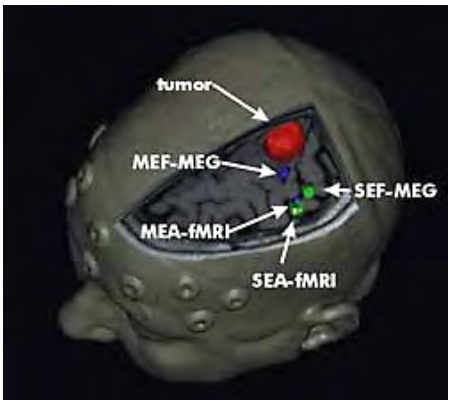
The Department of Neurosurgery represents a nationally and internationally specialized center for the whole spectrum of sellar pathologies. Clinically we investigate the influence of interventional/operative, radiotherapeutic, and pharmacological approaches on normal and hypersecretory pituitary gland function. Also, investigations on Somatostatin analoga and their clinical relevance in the treatment of growth hormone secreting pituitary adenoma represent a central part. The efficacy of novel intra-operative technologies in pituitary adenoma surgery and craniopharyngiomas are 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.

In another 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 does not exist any 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.

Pituitary Surgery



Functional Neuronavigation

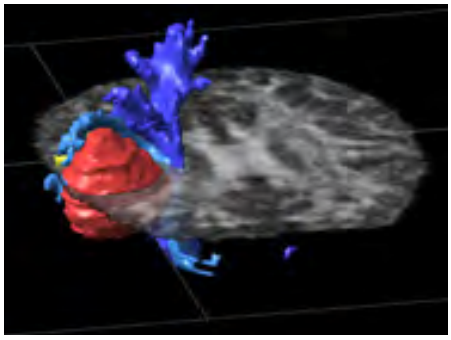
Functional Neuronavigation and Intraoperative Imaging

The reseach 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 were 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.



Neurooncology

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

Buchfelder M, Weigel D, Droste M, Mann K, Saller B, Brübach K, Stalla GK, Bidlingmaier M, Strasburger CJ, Investigators of German Pegvisomant Observational Study (2009) Pituitary tumor size in acromegaly during pegvisomant treatment: experience from MR re-evaluations of the German Pegvisomant Observational Study. Eur J Endocrinol, 161: 27-35

Engelhorn T, Savaskan NE, Schwarz MA, Kreutzer J, Meyer EP, Hahnen E, Ganslandt O, Dörfler A, Nimsky C, Buchfelder M, Eyüpoglu IY (2009) Cellular characterization of the peritumoral edema zone in malignant brain tumors. Cancer Sci, 100: 1856-62

Kleindienst A, Brabant G, Bock C, Maser-Gluth C, Buchfelder M (2009) Neuroendocrine function following traumatic brain injury and subsequent intensive care treatment: a prospective longitudinal evaluation. J Neurotrauma, 26: 1435-46

Stadlbauer A, Salomonowitz E, van der Riet W, Buchfelder M, Ganslandt O (2010) Insight into the patterns of cerebrospinal fluid flow in the human ventricular system using MR velocity mapping. Neuroimage, 51: 42-52

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

Department of Neurology

Chair of Neurology

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Research Focus
- Intensive care, stroke
- Public health
- Telemedicine and systems of care
- Pain and functional Imaging
- Cognitive Neurology
- Autonomic nervous system
- Epilepsy
- Neuroimmunology
- Neuromuscular diseases

Structure of the Department

The Department of Neurology of the Universitätsklinikum Erlangen is one of the largest neurological centers in Germany treating 4000 in-patients and more than 14,000 outpatients each year. Thereby, the clinic maintains close collaboration with the Department of Neurosurgery and Neuroradiology.
Our Stroke Unit is the largest in the state of Bavaria and one of the largest in whole germany. Furthermore, the department runs a specialized neurologic intensive care unit and coordinates a telemedical network for regional stroke care (STENO).
The Center of Epilepsy Erlangen (ZEE) represents another outstanding facility for diagnosis and treatment of epilepsy. The field of neuroimmunology and neurocognition has been expanding within the last two years.
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
Project managers: J. Bardutzky, H. Huttner, M. Köhrmann, R. Kollmar, P. Schellinger
Clinical and translational research are major columns of neurointensive care research in Erlangen. Examples include quality of life after ICU-treatment, brain edema treatment after ICH, temperature management in ICH and focal cerebral ischemia, weaning strategies, lumbar drainage after IVH, autonomic measurements and multimodal monitoring.
Stoke-unit care and research are the pivotel fields in neurology these days. We treat more than 1000 in-hospital patients on the stroke-unit. A extremely high level of medical care is combinded with state-of-the-art research including thombolysis, MRI-based interventions, growth-factor treatment, neurostimulation, fever treatment, EKG-monitoring, etc. Residents are part of an educational curriculum for stroke-care.

Public health
Project manager: P. Kolominsky-Rabas
The public health research unit focuses on the demographic impact of cerebro-vascular disorders in the aging German population. Its primary objectives encompass outcomes research for national and international public health authorities with regard to the evaluation of institutions and systems of health care, advisory service to parliamentary institutions and preparation of expert options in the field of health services research and descriptive and analytical epidemiology of cerebro-vascular disorders. Since 2000, the public health research unit is the reporting center for stroke for the federal health monitoring system of the German Federal Government. The data source for this reporting system is the Erlangen Stroke Registry. The register is the only epidemiological population-based register in Germany. Its aim is to provide representative long-term information about resource use and health economics of stroke for the health planning authorities in Germany.

Telemedicine and systems of care
Project managers: R. Handschu, M. Köhrmann
The group is active in research on the use of telemedicine and e-health on the care of neurological disease. Besides interdisciplinary work in the area of stroke prevention, a large telemedical network was initiated to improve acute care of 4000 stroke patients each year in the whole region of Northern Bavaria. Research is now focusing on the effects of the network and further improvement of telemedical technology. Other projects deal with rehabilitation of neurological patients or teleconsultation for mental health.

Pain and functional Imaging
Projectmanager: 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 (German Pain Price 2009; poster awards). Main funding sources are the German Federal Ministry for Education and Research ("German Research Network on Neuropathic Pain") and the German Research Foundation (clinical research unit "Determinants and modulators of post- operative pain", KFO 130).

Cognitive Neurology
Projectmanager: T. Schenk
Our focus of research is the treatment of patients with hemiblindness, investigations into the psychosocial impact of stroke and the neuroscientific analysis of sensorimotor control and spatial attention. In our research we use transcranial magnetic stimulation, 3D movement analysis, psychometrical and psychophysical tools. Currently our research is funded by the National Instiute for Health Research (NIHR, UK) and the German Research Foundation (DFG).

Autonomic nervous system
Project manager: M.J. Hilz
The autonomic research laboratory evaluates cardiovascular autonomic complications of cerebral disorders involving the central autonomic network, e.g. in stroke, traumatic brain injury and epilepsy. Moreover, we investigated the influence of enzyme replacement therapy in lysosomal storage disorders, such as Fabry and Pompe disease, on disease progression.
In patients with congenital autonomic diseases, such as familial dysautonomia, we performed polysomnographic sleep recordings in cooperation with the New York University. Furthermore, we evaluated benefits of counter-maneuvers regarding improved cerebral perfusion in patients with orthostatic hypotension.

Epilepsy
Project manager: H. Stefan
The Erlangen Epilepsy Center ranks among the Top 5 Epilepsy Centers in Germany. Scientific hot spots in 2009-2010 included:

1. New imaging techniques: Magnetencephlography studies (Prof. Stefan, Dr. Rampp); GABA-spectroscopy (PD Dr. Hammen), FET-PET (PD Dr. Kasper, Prof. Kuwert). The implementation of the new multichannel MEG system has almost been completed.
2. Pathophysiology of epilepsy: studies correlating parameters and pathology data from hippocampal morhology and stem cell biology (PD Dr. Pauli, Dr. Coras, Prof. Blümcke)
3. Automated seizure detection (Dr. Hopfengärtner)
4. Drug monitoring (Dr. Graf)
5. Neuropsychology/Cogniton (PD Dr. Pauli, Dr. Schwarz, Dipl-Psych Kurzbuch)
6. Neuroscience history (PD Dr. Kasper)

By the end of 2010 Prof. Hermann Stefan, the head of Epilepsy Center for over 20 years, retired, but ist still active within the MEG scientific team.

Neuroimmunology
Project manager: R. Linker
The neuroimmunological research group is involved in clinically relevant research as well as exprimental studies touching basic science. The group participates in a large number of international phase II/III MS trials on new immunmodulatory therapies in MS. Further research activities concentrate on the investigation of new biomarkers and immune cell populations in MS patients as well as studies on neurodegeneration and neuroprotection in experimental MS models. Present studies of significant impact comprise (1) work on neuroprotective effects of the neurotrophin "brain derived neutrophic factor" (BDNF) and (2) work on antioxidative as well as neuroprotective mechanisms of action of fumaric acid esters, which are at present under investigation in phase III trials in relapsing remitting MS. The group is funded by the IZKF Erlangen, the ELAN Fonds and various industry-funded co-projects.

Neuromuscular diseases
Project managers: Prof. D. Heuss, Dr. R. Linker, Prof. R. Schroeder
The Neuromuscular Disease Center provides a specialized outpatient clinic and a neuropathological laboratory for diagnostic biopsies and for the investigation of neuromuscular diseases. The following studies are performed:

1. Pheno- and genotyping in autosomal recessive CMT II in a Costa Rica family
2. CK2-deficient myopathies
3. Vasculitic neuropathies / clinical follow up
4. Intermidiate filament pathology and mitochondrial dysfunction in epidermolysis bullosa simplex with muscular dystrophy and desmin related-myopathies
5. Identification of novel and disease related VCP binding partners and characterization of the skeletal muscle an cardiac
6. Generation and characterization of a R155C-VCP knock-in mouse: a key to the understanding of VCP-related frontotemporal dementia
7. Establishment of a spodoptera frugiperda cell culture model for the generation of recombinant demin protein.

Therapeutical trials:

1. A Study in Early Onset ALS (SIRONA) ONO-2506POE014
2. Deflacort in Dysferlinopathies - doubleblind, placebo-controlled study/BMBF-subproject R19 MD-NET.

Teaching

PD Dr. R. Kollmar, Prof. Dr. C. Lang
Restucturing of the medical education in neurology improved students' and teachers' satisfaction and knowledge. Currently, our one-week course is rank number 2 and 3 within all clinicals courses. This success led to an increased number of final year medical students (internship) and more applications for residency. Within the next years, we will certainly continue to improve the management in medical education and on a scientific level as well.

Selected Publications

Huttner HB, Schwab S (2009) Malignant middle cerebral artery infarction: clinical characteristics, treatment strategies, and future perspectives. Lancet Neurol, 8: 949-58

Seifert F, Kiefer G, DeCol R, Schmelz M, Maihöfner C (2009) Differential endogenous pain modulation in complex-regional pain syndrome. Brain, 132: 788-800

Hilz MJ, Marthol H, Schwab S, Kolodny EH, Brys M, Stemper B (2010) Enzyme replacement therapy improves cardiovascular responses to orthostatic challenge in Fabry patients. J Hypertens, 28: 1438-48

Kasper BS, Taylor DC, Janz D, Kasper EM, Maier M, Williams MR, Crow TJ (2010) Neuropathology of epilepsy and psychosis: the contributions of J.A.N. Corsellis. Brain, 133: 3795-805

Kollmar R, Staykov D, Dörfler A, Schellinger PD, Schwab S, Bardutzky J (2010) Hypothermia reduces perihemorrhagic edema after intracerebral hemorrhage. Stroke, 41: 1684-9

Linker RA, Lee DH, Demir S, Wiese S, Kruse N, Siglienti I, Gerhardt E, Neumann H, Sendtner M, Lühder F, Gold R (2010) Functional role of brain-derived neurotrophic factor in neuroprotective autoimmunity: therapeutic implications in a model of multiple sclerosis. Brain, 133: 2248-63

International Cooperation

Prof. Zong-Zou, University of Chengdu, Chengdu, China

Prof. G. del Valle, University of Costa Rica, San José, Costa Rica

Prof. JJ. van Hilten, Leiden University, Leiden, The Netherlands

Bernard S. Chang, Ekkehard M. Kasper, Havard Medical School, Boston, MA, USA

Prof. Olaf Stüve, Southwestern University Dallas, Dallas, TX, USA

Prof. Wade Kingery, Stanford University, Palo Alto, CA, USA

Michael Collins, Medical College, Milwaukee, WI, USA

Meetings and International Training Courses

19.–20.06.2009: 5 th Epilepsy Colloquium Erlangen: Networks and epilepsies, Erlangen

23.–26.09.2009: 1. Hypothermiesymposium, Erlangen, Deutschland,

04.–05.06.2010: Ehrensymposium Prof. Hermann Stefan, Erlangen

30.09.2010: 2. Erlanger Telemedizin-Symposium, Erlangen

29.10.2010: Weltschlaganfalltag, Erlangen

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Research Focus
- Neurodegenerative Diseases
- Translational Research

Gait impairment in Parkinson's syndrome (PS) can be detected using a sensor based movement detection system attached to a sport shoe. Motion data is classified using pattern recognition technique and provide objective information of gait impairment in PS

Structure of the Division

The Division of Molecular Neurology aims to establish 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 asses movements using embedded biosensor systems. This project is jointly developed with an industry partner and the Department of Pattern Recognition.

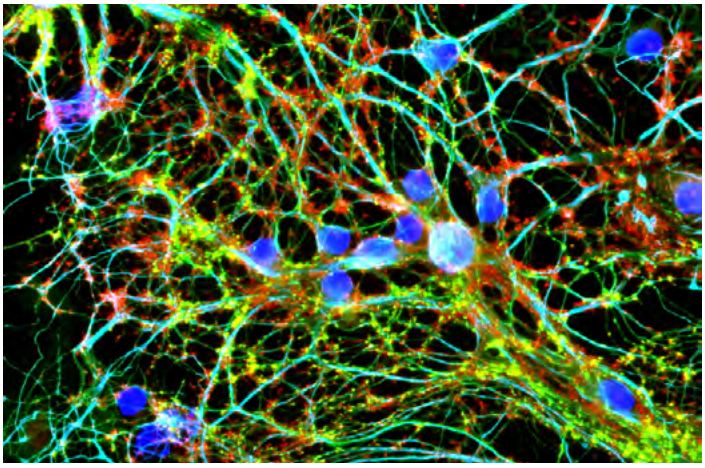
Research

Neurodegenerative Diseases
The scientific focus of the Division of Molecular Neurology emphasizes on adult neurogenesis and neurodegenerative mechanism in Parkinson's disease, Huntington's disease and hereditary spastic paraplegia. Neuroregenerative processes with focus on adult neurogenesis (generation of new neurons in the adult brain) are assessed using cell culture and transgenic models of Parkinson's and Huntington's disease. Complementary to this approach, neurodegenerative mechanisms in synucleinopathies are analyzed in order to understand the underlying molecular processes leading to the neuropathological hallmarks in Parkinson's disease. These efforts are jointly performed with the Institute of Biochemisty.

Translational Research
The scientific focus of the Division of Molecular Neurology is on adult neurogenesis and its interplay with neurodegenerative mechanisms. In this context, 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 newly formed neurons are generated throughout the entire life span. Adult neurogenesis is severely impaired in different neurodegenerative diseases. Accumulating evidence suggests that impaired adult hippocampal and olfactory bulb neurogenesis may be one of the most important underlying pathopyhsiological events in the development of non-motor symptoms in Parkinson's disease like anxiety, depression, cognitive disfunction and olfactory deficits. These symptoms are likely to reflect the compromised ability of the adult brain to generate new neurons in neural circuits. Moreover, cell and molecular techniques have been established to deliniate and modify pathological mechanisms associated with protein aggregation of alpha-synuclein in Parkinson's disease. This strategy may lead to novel and causal therapies for synucleinopathies. In addition, in conjunction with the new Junior Group of the Interdisciplinary Center of Clinical Research (PD Dr. B. Winner) a new technology was established, the generation of inducible pluripotent stem cells from skin fibroblasts. This technical platform will allow us to generate neurons of patients affected with different neurogenerative diseases.

Teaching

The Division participates in the regular courses Neurology for medical students including main lecture and practical courses. The Division is responsible for the section Clinical Neurosciences in the Bc/Master Program Molecular Medicine (main lecture, Bc/Master/Doctorate theses). Doctorates in medicine and basic sciences (PhD) are supervised.



Cultured primary neurons from transgenic Parkinson-mice develop typical processes and neuronal connections.

Selected Publications

Regensburger M, Kohl Z, Grundmann K, Winner B, Riess O, Winkler J (2009) Adult neural precursor cells unaffected in animal models of DYT1 dystonia. Neuroreport, 20: 1529-33

Winner B, Desplats P, Hagl C, Klucken J, Aigner R, Ploetz S, Laemke J, Karl A, Aigner L, Masliah E, Buerger E, Winkler J (2009) Dopamine receptor activation promotes adult neurogenesis in an acute Parkinson model. Exp Neurol, 219: 543-52

Winner B, Vogt-Weisenhorn DM, Lie CD, Blümcke I, Winkler J (2009) Cellular repair strategies in Parkinson's disease. Ther Adv Neurol Disord, 2: 51-60

Kohl Z, Regensburger M, Aigner R, Kandasamy M, Winner B, Aigner L, Winkler J (2010) Impaired adult olfactory bulb neurogenesis in the R6/2 mouse model of Huntington's disease. BMC Neurosci, 11: 114

Moessnang C, Frank G, Bogdahn U, Winkler J, Greenlee MW, Klucken J (2010) Altered Activation Patterns within the Olfactory Network in Parkinson's Disease. Cereb Cortex, :

Schlachetzki JC, Fiebich BL, Haake E, de Oliveira AC, Candelario-Jalil E, Heneka MT, Hüll M (2010) Norepinephrine enhances the LPS-induced expression of COX-2 and secretion of PGE2 in primary rat microglia. J Neuroinflammation, 7: 2

International Cooperation

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

Dr. M. Ingelsson, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden

Prof. Dr. E. Masliah, Department of Neurosciences, University of California San Diego, San Diego, CA, USA

Prof. Dr. B.T. Hyman, Massachusetts General Hospital - MIND, Harvard University, Boston, USA

Prof. Dr. F. Gage, Laboratory of Genetics, The Salk Institute for Biological Studies, La Jolla, CA, USA

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Research Focus
- Molecular Myopathology
- Focal human epilepsies and animal models
- Adult stem cells of the human brain
- Neuro-oncology

Structure of the Institute

Our academic staff and technicians are engaged in studies addressing molecular pathomechanisms of CNS and skeletal muscle disorders. Particular focus is paid to epilepsy surgery, neuro-oncology and myopathies. We have established the neuropathological reference center for epilepsy surgery and the European Epilepsy Brain Bank (supported by the EU).

Research

Molecular Myopathology

Project manager: 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) and the desmin myopathy and cardiomyopathy. 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 German Research Foundation (research unit FOR118), and the Federal Ministry of Education and Research (Muscular Dystrophy Network).

Focal human epilepsies and animal models

Project manager: 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 post surgical follow-up data. During this research period, major advances result in the publication of a first international consensus classification system for Focal Cortical Dysplasias.

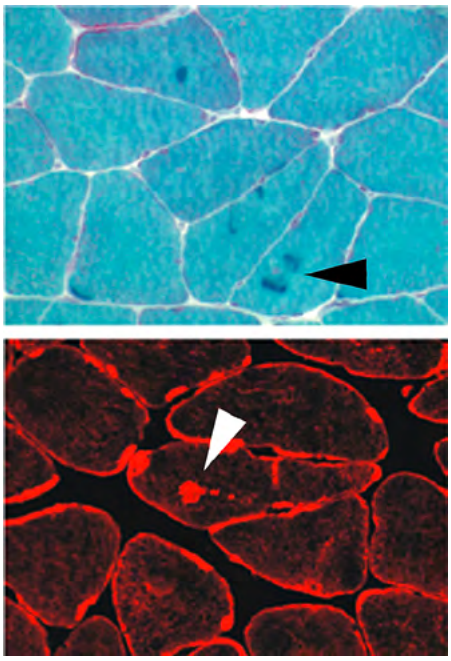
Our group further studies molecular pathomechanism of epileptogenesis. We characterize epigenetic chromatin modifications within human surgical specimens as well as using an experimental animal model which can be monitored and quantitatively examined using a 24h video-EEG monitoring.

Research of human epilepsies and histopathologically well-characterized surgical specimens obtained from patients with temporal lobe epilepsy opens also new avenues to study higher brain function in humans, i.e., the hippocampus serves 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.

Adult stem cells of the human brain

Project manager: R. Coras

Numerous regions of the adult brain maintain neural progenitor cells ("adult stem cells"), which are able to generate new neurons under physiological as well as pathophysiological conditions (neurogenesis). These intriguing precursor cells may gain outstanding importance in regenerative neurobiological treatment modalities and constitute an alternative approach to embryonic stem cells. Basic mechanisms of recruitment, proliferation and differentiation of adult stem cells remain, however, unknown. A fascinating topic is also related to hippocampal neurogenesis and learning, which was shown to be directly linked in animal models. Notwithstanding, experimental evidence is difficult to obtain in humans. We were able to isolate adult stem cells from surgically resected human hippocampus and proliferated them clonally. Our results suggest that encoding new memories is indeed related to the regenerative capacity of the hippocampus also in the human brain (supported by the Bavarian Research Consortium ForNeuroCell2).



Intracellular protein aggregates (arrowheads) present a characteristic finding in desmin myopathies. Upper image: Gomori staining. Lower image: Fluorescence microscopic analysis of desmin immunoreactivity.

Neuro-oncology

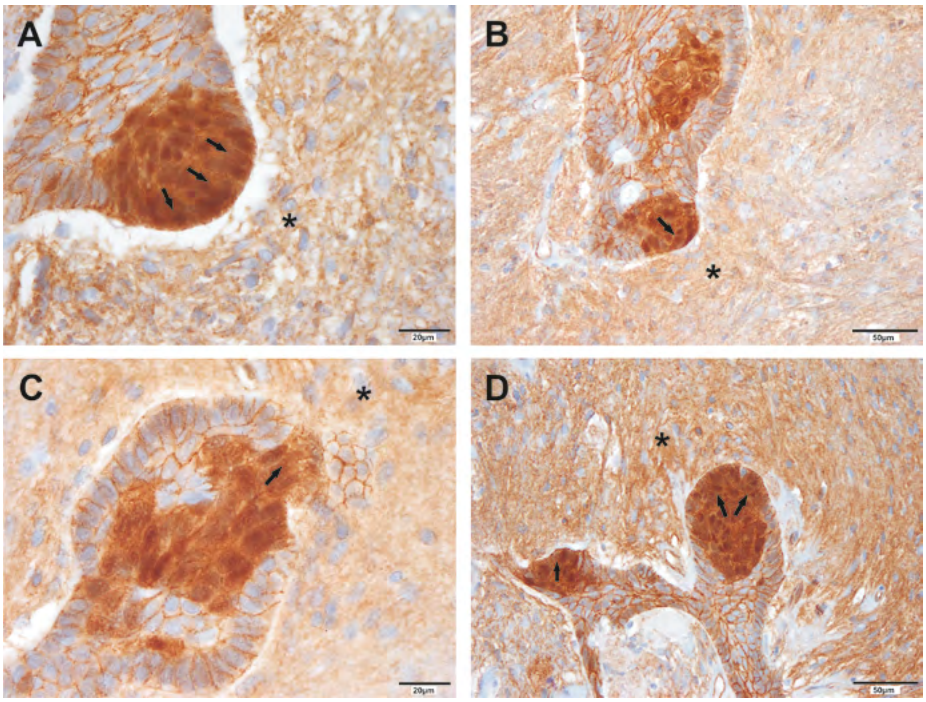
Project manager: R. Buslei

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 invasiveness (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 craniopharyngeomas. Major improvements result from the analysis of beta-catenin mutations in craniopharyngiomas and its impact for 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 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.

Teaching

Our Department is enrolled in pathology training and lectures.



Immunohistochemical beta-catenin staining of FFPE specimens revealed cell clusters within finger-like tumor protrusions into adjacent brain tissue (asterisk), displaying distinct nuclear and cytoplasmic beta-catenin accumulations (arrows). Intriguingly, the cells are often located at the tumor–brain interface compatible with brain invasion.

Axonal reorganization in the hippocampus of chronic epileptic rats. TIMM staining reveales 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).

Selected Publications

Hübbers CU, Clemen CS, Kesper K, Böddrich A, Hofmann A, Kämäräinen O, Tolksdorf K, Stumpf M, Reichelt J, Roth U, Krause S, Watts G, Kimonis V, Wattjes MP, Reimann J, Thal DR, Biermann K, Evert BO, Lochmüller H, Wanker EE, Schoser BG, Noegel AA, Schröder R (2007) Pathological consequences of VCP mutations on human striated muscle. Brain, 130: 381-93

Kobow K, Jeske I, Hildebrandt M, Hauke J, Hahnen E, Buslei R, Buchfelder M, Weigel D, Stefan H, Kasper B, Pauli E, Blümcke I (2009) Increased reelin promoter methylation is associated with granule cell dispersion in human temporal lobe epilepsy. J Neuropathol Exp Neurol, 68: 356-64

Clemen CS, Tangavelou K, Strucksberg KH, Just S, Gaertner L, Regus-Leidig H, Stumpf M, Reimann J, Coras R, Morgan RO, Fernandez MP, Hofmann A, Müller S, Schoser B, Hanisch FG, Rottbauer W, Blümcke I, von Hörsten S, Eichinger L, Schröder R (2010) Strumpellin is a novel valosin-containing protein binding partner linking hereditary spastic paraplegia to protein aggregation diseases. Brain, 133: 2920-41

Coras R, Siebzehnrubl FA, Pauli E, Huttner HB, Njunting M, Kobow K, Villmann C, Hahnen E, Neuhuber W, Weigel D, Buchfelder M, Stefan H, Beck H, Steindler DA, Blümcke I (2010) Low proliferation and differentiation capacities of adult hippocampal stem cells correlate with memory dysfunction in humans. Brain, 133: 3359-72

Hölsken A, Buchfelder M, Fahlbusch R, Blümcke I, Buslei R (2010) Tumor cell migration in adamantinomatous craniopharyngiomas is promoted by activated Wnt-signalling. Acta Neuropathol (Berl), 119: 631-9

Blümcke I, Spreafico R (2011) An international consensus classification for focal cortical dysplasias. Lancet Neurol, 10: 26-7

International Cooperation

Dr. Assam El-Osta, Baker IDI Heart & Diabetes Institute, Melbourne, Australia

Prof. Gerhard Wiche, Max F. Perutz Laboratories, University of Vienna, Vienna, Austria

Dr. Angelika Mühlebner und Prof. Martha Feucht, Department of Pediatrics, Medical University of Vienna, Vienna, Austria

Dr. Fabrice Bartolomei und Prof. Christophe Bernard, Université de la Méditerranée, Marseille, France

Prof. Dr. Roberto Spreafico, Department of Epilepsy Clinic and Experimental Neurophysiology, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milan, Italy

Dr. Eleonora Aronica, Department of (Neuro)Pathology, Academic Medical Center (AMC) University of Amsterdam and Stichting Epilepsie Instellingen Nederland (SEIN), Heemstede, The Netherlands

Dr. Maria Thom und Prof. Sanjay Sisodiya, Institute of Neurology, University College London, London, UK

Prof. Dr. Dennis Steindler, McKnight Brain Institute, University of Florida, Gainsville, FL, USA

Department of Nuclear Medicine

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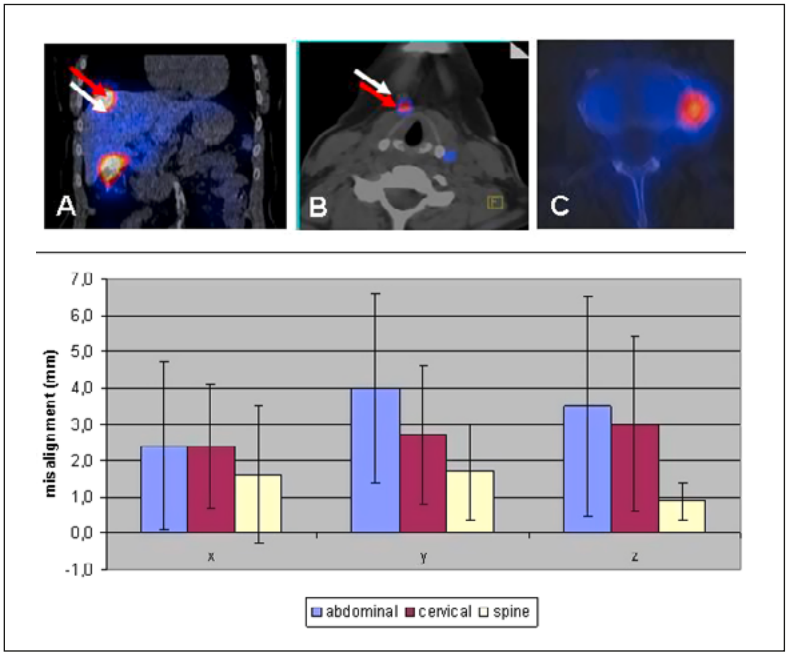
Research Focus
- Correlative Imaging
- Molecular Imaging and Radiochemistry

Structure of the Department

At the Clinic 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 Clinic 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 Clinic is equipped with synthesis modules for synthesising radiotherapeutics and by a further module for producing PET tracers, which is operated under good-manufacturing-practice (GMP) conditions in cooperation with the PET-NET GmbH. In the laboratory of molecular imaging of the Clinic new radiopharmaceuticals are being developed and evaluated. The for this purpose implemented methodology includes chemical, radiochemical, and cell biological facilities. In addition, the laboratory operates a highly resolving autoradiographic detector system and a micro-PET.



Examples of abdominal (A), cervical (B) and bone (C) SPECT/CT fusion images from hybrid scanners with a different extend of misregistration of lesions. The diagram shows the misregistration in the X-, Y- and Z-directions for the different regions.

Research

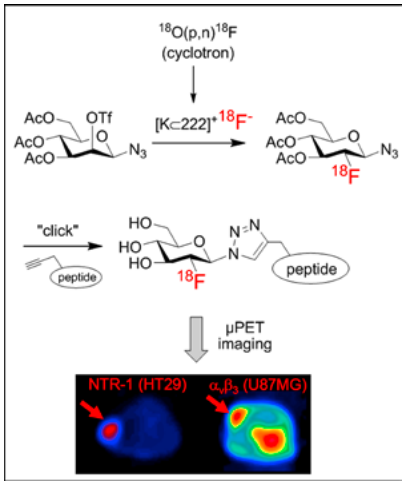
Correlative Imaging

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 much facilitated. In cooperation with the Chair of Pattern Recognition of the Friedrich-Alexander-Universität Erlangen-Nürnberg and Siemens Medical Solutions the Clinic of Nuclear Medicine develops 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; therefore, by visualizing this interaction and thus the expression and activity of proteins, nuclear medicine can bridge the gap between molecular biology and clinical imaging and can correlate imaging results with the molecular pathogenesis of diseases. Following this idea the term molecular imaging has recently been created.
The main research area of the professorship of molecular imaging and radiochemistry is the development of new radiochemical label-

ing 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. In a series of studies, the regulation of uptake of F-18-deoxyglucose (FDG) and the influence of an oncogene expression in thyroid carcinoma cells was studied in detail. The evidence thus gathered is relevant to the interpretation of clinical PET (Prante et al., 2009). Another research focus is the development of highly effective radiochemical labeling methods that are compatible with to the short half life of the positron emitters (Maschauer et al., 2009). The research group succeeded in the development of a highly efficient glycosylation method for the synthesis of F-18-labeled radiopharmaceuticals (Maschauer et al., 2010). In cooperation with the Chair of Pharmaceutical Chemistry of the Friedrich-Alexander-Universität Erlangen-Nürnberg 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 (Hocke et al., 2010). As yet, radiopharmaceuticals suited to study these receptor subtypes, which are 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 2009 and 2010, this project was supported by the German Research Foundation (DFG). In 2009, a part of this project was honored with the Georg-von-Hevesy-Prize of the German Society for Nuclear Medicine. A further research aim of the laboratory of Molecular Imaging and Radiochemistry is 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 Erlangen-Nürnberg (Director: Prof. Hornegger) with a special interest in small-animal PET imaging and was supported by the Federal Ministry of Education and Research (BMBF). 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 2009 and 2010, this research was supported by the German Research Foundation (DFG, clinical research unit FOR 661).



A highly efficient chemical strategy toward ^{18}F-labeling with concomitant glycosylation fpr the synthesis of radiopharmaceuticals for PET has been developed. The mild conditions and general applicability of this reliable reaction gave access to a new class of ^{18}F-glycopeptide radiopharmaceuticals that were successfully subjected to small-animal PET studies in the preclinical setup (Maschauer et al., 2010).

Teaching

The Chair teaches nuclear medicine to students of medicine. Furthermore, the Chair organizes the course on radiation safety for students of molecular medicine. We also participate in teaching physiology, pharmacology and computer sciences. In a broad fashion, the Chair performs postgraduate teaching for physicians in Middle and Upper Franconia. The Professor for Molecular Imaging and Radiochemistry offers practical training for students of molecular medicine and provides lectures for students of molecular sciences in the scientific faculty.

Selected Publications

Maschauer S, Prante O (2009) A series of 2-O-trifluoromethylsulfonyl-D-mannopyranosides as precursors for concomitant 18F-labeling and glycosylation by click chemistry. Carbohydr Res, 344: 753-61

Prante O, Maschauer S, Fremont V, Reinfelder J, Stoehr R, Szkudlinski M, Weintraub B, Hartmann A, Kuwert T (2009) Regulation of uptake of 18F-FDG by a follicular human thyroid cancer cell line with mutation-activated K-ras. J Nucl Med, 50: 1364-70

Schmidt D, Szikszai A, Linke R, Bautz W, Kuwert T (2009) Impact of 131I SPECT/Spiral CT on Nodal Staging of Differentiated Thyroid Carcinoma at the First Radioablation. J Nucl Med, 50: 18-23

Hocke C, Maschauer S, Hübner H, Löber S, Utz W, Kuwert T, Gmeiner P, Prante O (2010) A series of 18F-labelled pyridinylphenyl amides as subtype-selective radioligands for the dopamine D3 receptor. ChemMedChem, 5: 941-8

Maschauer S, Einsiedel J, Haubner R, Hocke C, Ocker M, Hübner H, Kuwert T, Gmeiner P, Prante O (2010) Labeling and glycosylation of peptides using click chemistry: a general approach to (18)F-glycopeptides as effective imaging probes for positron emission tomography. Angew Chem Int Ed Engl, 49: 976-9

Zeintl J, Vija AH, Yahil A, Hornegger J, Kuwert T (2010) Quantitative accuracy of clinical 99mTc SPECT/CT using ordered-subset expectation maximization with 3-dimensional resolution recovery, attenuation, and scatter correction. J Nucl Med, 51: 921-8

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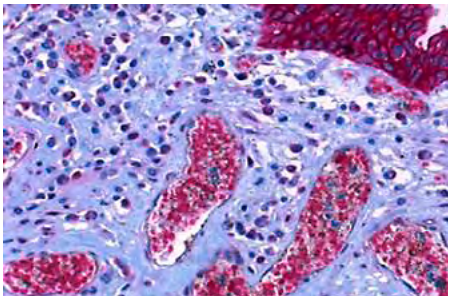
Research Focus
- Experimental Tumor Pathology
- Clinical and Predictive Molecular Pathology
- Molecular Pathology of Urological Tumors
- Pathology of Immune and Inflammatory reactions

Structure of the Institute

The Institute of Pathology includes also the Division of Nephropathology. A total of 85 members of staff work in the Institute of Pathology, 30 are medical professionals or scientists. Of these, 13 are currently financed by third-party funding.
The Institute of Pathology is responsible for all pathology diagnostics within the Universitätsklinikum 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 approx. 40.000 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

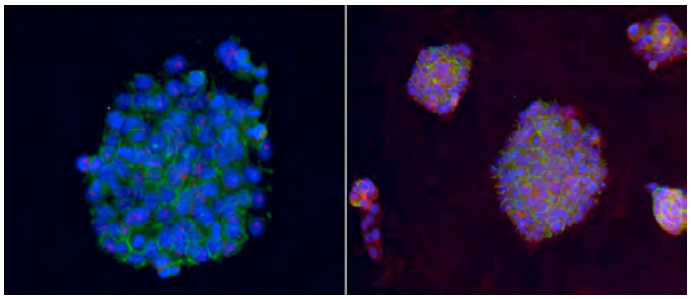
Experimental Tumor Pathology
Project managers: R. Schneider-Stock, A. Agaimy, A. Hartmann, R. Rieker, T. Rau, C. Geppert, D. Wachter, J. Strehl, K. Brunner
A major focus is the molecular and biochemical characterization of genetic and epigenetic induced changes in tumors and preneoplasias of the gastrointestinal 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 of malignant tumors (Dr. T. Rau, Dr. C. Geppert) as well as on the functional consequences of early epigenetic changes in the intestinal epithelium in colitis ulcerosa (Prof. Dr. R. Schneider-Stock, Prof. Dr. A. Hartmann).
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 (PD Dr. A. Agaimy, Prof. Dr. R. Schneider-Stock).
The second main focus is in cooperation with the Department of Obstetrics and Gynecology (Prof. Dr. M. Beckmann, Prof. Dr. P. Fasching) and with 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) on the discovery of genetic and epigenetic changes in breast cancer and ovarian carcinomas (Prof. Dr. A. Hartmann, Dr. D. Wachter, Dr. J. Strehl). 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 (Prof.Dr. R. Schneider-Stock, PD Dr. A. Agaimy, Dr. K. Brunner), in cooperation with the Department of Ear, Nose and Throat, Head and Neck Surgery, (Prof. Dr. H. Iro) and the Department of Oral and Maxillofacial Surgery, (Prof. Dr. Neukam, Prof. Dr. 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, and the second one 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 (Prof. Dr. R. Rieker).



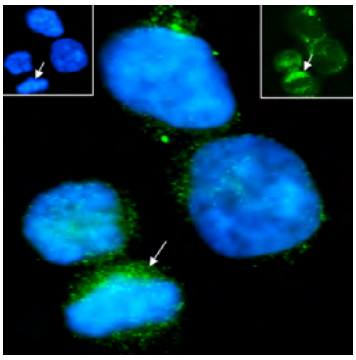
Immunohistochemical analysis of E-Cadherin expression of highly aggressive plasmacytoid urothelial carcinoma of the bladder. Membranous E-Cadherin staining (red colour) in the normal urothelium (right side) and complete E-Cadherin loss in the invasive tumor.

Clinical and Predictive Molecular Pathology
Project managers: R. Stöhr, A. Hartmann, R. Wirtz
The objective of this research topic, involving molecular examination of numerous tumor types, is the identification of molecular markers that can predict the response of malignant tumors to traditional radio- or chemotherapies or to new targeted molecular therapies. The Department of Molecular Pathology (Head Dr. R. Stöhr) examines genetic changes (e.g. through specific mutation analysis) and epigenetic modifications in the tumor (e.g. specific promoter-hypermethylation analysis). A further focus is on the diagnosis of hereditary tumors.

Molecular Pathology of Urological Tumors
Project managers: A. Hartmann, R. Stöhr, C. Stöhr, J. Giedl, 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 Friedrich-Alexander-Universität Erlangen-Nürnberg at the Waldkrankenhaus St. Marien gGmbH and also with numerous national and international cooperation partners.



Papillary bladder cancer cell line BFTC 905: Loss of expresssion of the tumor supressor gene sFRP1 (left side) and re-expression after stable transfection with sFRP1 (right side) (Green colur: E-Cadherin, red colour: sFRP1)



TNF-induced overexpression of the pro-apoptotic death-associated protein kinase in tumor cells with condensed chromatin (immunofluorescence: blue (DAPI), green (DAPK)

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: Dr. M. Büttner

This topic 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 " has 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

Bajbouj K, Poehlmann A, Kuester D, Drewes T, Haase K, Hartig R, Teller A, Kliche S, Walluscheck D, Ivanovska J, Chakilam S, Ulitzsch A, Bommhardt U, Leverkus M, Roessner A, Schneider-Stock R (2009) Identification of phosphorylated p38 as a novel DAPK-interacting partner during TNFalpha-induced apoptosis in colorectal tumor cells. Am J Pathol, 175: 557-70

Ruemmele P, Dietmaier W, Terracciano L, Tornillo L, Bataille F, Kaiser A, Wuensch PH, Heinmoeller E, Homayounfar K, Luettges J, Kloeppel G, Sessa F, Edmonston TB, Schneider-Stock R, Klinkhammer-Schalke M, Pauer A, Schick S, Hofstaedter F, Baumhoer D, Hartmann A (2009) Histopathologic features and microsatellite instability of cancers of the papilla of vater and their precursor lesions. Am J Surg Pathol, 33: 691-704

Hafner C, Toll A, Fernández-Casado A, Earl J, Marqués M, Acquadro F, Méndez-Pertuz M, Urioste M, Malats N, Burns JE, Knowles MA, Cigudosa JC, Hartmann A, Vogt T, Landthaler M, Pujol RM, Real FX (2010) Multiple oncogenic mutations and clonal relationship in spatially distinct benign human epidermal tumors. Proc Natl Acad Sci U S A, 107: 20780-5

Herrmann E, Trojan L, Becker F, Wülfing C, Schrader AJ, Barth P, Stöckle M, Hammerschmied CG, Staehler M, Stief C, Haferkamp A, Hohenfellner M, Legal W, Wullich B, Bolenz C, Klein T, Noldus J, Bierer S, Hertle L, Brenner W, Roos F, Michel MS, Walter B, Wieland W, Gerss J, Otto W, Hartmann A (2010) Prognostic factors of papillary renal cell carcinoma: results from a multi-institutional series after pathological review. J Urol, 183: 460-6

Hoffmann AC, Wild P, Leicht C, Bertz S, Danenberg KD, Danenberg PV, Stöhr R, Stöckle M, Lehmann J, Schuler M, Hartmann A (2010) MDR1 and ERCC1 expression predict outcome of patients with locally advanced bladder cancer receiving adjuvant chemotherapy. Neoplasia, 12: 628-36

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

International Cooperation

Torben Ornthoft, MOMA Aarhus, Denmark

Paco Real und Nuria Malats CNIO, Madrid, Spanien

Ellen Zwarthoff, Erasmus MC Rotterdam, The Netherlands

D. Theodorescu, University of Colorado Cancer Center, Denver, CO, USA

W. EL-Rifai, Vanderbilt University, Memphis, TN, USA

Meetings and International Training Courses

03.–07.06.2009: 93. Jahrestagung der Deutschen Gesellschaft für Pathologie, Freiburg/Breisgau

Research Equipment

PALM Laser-Microdissection Microscope

Zeiss Laser Scanning Microscope

Stratifyer Automated DNA-RNA-Isolation Robot

Decon Science Tec GmbH Microscope Life-cell-Migration

BD Biosciences Flow-cytometer

Institute of Pathology

Division of Nephropathology

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Research Focus
- Clinical research (IZKF)
- Clinical and experimental Nephropathology
- SFB 423 Kidney damage

Structure of the Division

The Division of Nephropathology together with the Chair of General Pathology constitutes the Institute of Pathology. The Department employs a total of 12 members of staff of which six are financed by third-party funds. Research is carried out by one postdoc, two Ph.D. students and four technical staff.
The Department of Nephropathology is responsible for the kidney biopsy diagnosis of the Universitätsklinikum Erlangen (Department of Medicine 4 and Pediatric nephrology of the Department of Pediatrics) 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 research (IZKF)
Project manager: K. Amann

1. Cardiovascular changes in experimental systemic Lupus erythematodes.

Here, in cooperation with Prof. Thomas Winkler (Chair of Genetics) and Prof. Dr. Reinhardt Voll (Department of Immunology, Univ. Freiburg), the hypothesis is explored that in the case of systemic Lupus erythematodes, independent carciovascular changes develop that are independent of the degree of the kidney participation in the disease and which are a considerable clinical problem in particular in younger patients. This hypothesis is evaluated in different animal models of systemic Lupus erythematodes using morphological and molecular methods.

2. Proteasome inhibition as a new therapeutic intervention in inflammatory kidney diseases.

In cooperation with Prof. Dr. Reinhard Voll (Department of Immunology, Univ. Freiburg) and Prof. Dr. Michael Wiesner (Department of Medicine 4) 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 (Figure) and other inflammatory kidney diseases are investigated.

3. Causes and effects of a reduced nephron number.

In cooperation with Ms. PD Dr. Benz (Department of Pediatrics) we are especially interested in whether using an animal model of low nephron number a structural malformation of the kidney is pre-conditional for the formation of hypertension and kidney diseases.

4. The role of CD26 in the manifestation of ischemia/reperfusion injury and acute rejection in kidney transplantation.

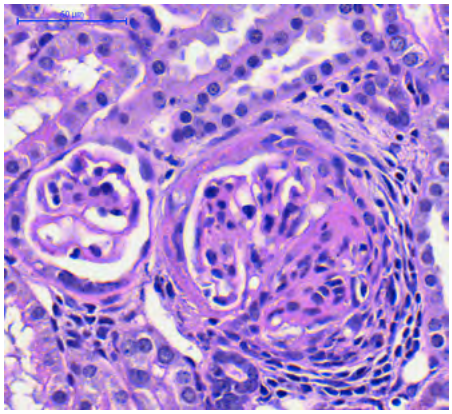
In cooperation with Prof. Dr. Stephan von Hörsten (Experimental Biomedicine) we examine wether the lack or inhibition of dipeptidyl-peptidase IV (DPP4) reduce ischemia/reperfusion injury and acute rejection. In a rat model for kidney transplantation changes in DPP4 expression and localization as well as alterations in kidney function were investigated by using DPP4 deficient and wildtype rats. Hereby, we try to identify how DPP4 influences pathological changes in ischemia/reperfusion injury.

5. The role of Coronin 1 in glomerular injury and repair

Together with Prof. Christian Hugo (Department of Medicine 4) in this project the expression of coronin during kidney development in different glomerulonephritis-models and human glomerulonephritis was initially examined. The isolation of mesangial cells from coronin 1 deficient and wildtype mice allowed us to examine the role of coronin 1a in these cells via migration-assays and proliferation-assays. In the T-cell induced nephrotoxic-serum-nephritis-model (NTN) the role of coronin 1a for the pathogenesis of the disease was evaluated using coronin 1a deficient mice.

Clinical and experimental Nephropathology
Project manager: K. Amann
Clinical and experimental co-operations are well established with clinical partners (Department of Medicine 4 and Pediatric Nephrology) as well as several research groups of the Universitätsklinikum respectively of the Friedrich-Alexander-Universität Erlangen-Nürnberg working in the field of nephrology. Main focus of the Department of Nephropathology is to test molecular hypotheses on experimental and human kidney biopsy material. Furthermore, methods for the quantitative tissue analysis, i.e. for renal phenotyping of transgene and knock-out-animal models are available.

SFB 423 Kidney damage
Project manager: K. Amann
Within research the framework of the Collaborative research center (SFB) 423 renal injury: "Pathogenesis and regeneration" established at the Medical Faculty of the FAU Erlangen-Nürnberg in 1999, the Department of Nephropathology support other projects in the central Project Z2 "Quantitative morphology". Morphometric and stereologic methods as well as laser-assisted micro dissection were used for the investigation of pathophysiologic effects in different renal diseases and experimental animal models. In addition, an intensive assistence and support is given in respect to the above mentioned techniques.



Histologic evaluation of kidneys in the lupus erythomatodes model (Mrl/lpr model) shows progressed glomerular alterations with crescent formation

Teaching

The Department of Nephropathology participates in the teaching of the Institute of Pathology. In addition, nephropathological conferences with the clinical departments of the Universitätsklinikum Erlangen and external biopsy senders are regularly held. Furthermore, twice a year a kidney pathology course takes place for both staff of the Universitätsklinikum Erlangen and staff of external hospitals.

Selected Publications

Benz K, Amann K (2009) Pathological aspects of membranoproliferative glomerulonephritis (MPGN) and haemolytic uraemic syndrome (HUS) / thrombocytic thrombopenic purpura (TTP). Thromb Haemost, 101: 265-70

Haas E, Bhattacharya I, Brailoiu E, Damjanovic M, Brailoiu GC, Gao X, Mueller-Guerre L, Marjon NA, Gut A, Minotti R, Meyer MR, Amann K, Ammann E, Perez-Dominguez A, Genoni M, Clegg DJ, Dun NJ, Resta TC, Prossnitz ER, Barton M (2009) Regulatory role of G protein-coupled estrogen receptor for vascular function and obesity. Circ Res, 104: 288-91

von Eynatten M, Liu D, Hock C, Oikonomou D, Baumann M, Allolio B, Korosoglou G, Morcos M, Campean V, Amann K, Lutz J, Heemann U, Nawroth PP, Bierhaus A, Humpert PM (2009) Urinary adiponectin excretion: a novel marker for vascular damage in type 2 diabetes. Diabetes, 58: 2093-9

Hakkim A, Fürnrohr BG, Amann K, Laube B, Abed UA, Brinkmann V, Herrmann M, Voll RE, Zychlinsky A (2010) Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis. Proc Natl Acad Sci U S A, 107: 9813-8

Jellusova J, Wellmann U, Amann K, Winkler TH, Nitschke L (2010) CD22 x Siglec-G double-deficient mice have massively increased B1 cell numbers and develop systemic autoimmunity. J Immunol, 184: 3618-27

Schietke RE, Warnecke C, Wacker I, Schodel J, Mole DR, Campean V, Amann K, Goppelt-Struebe M, Behrens J, Eckardt KU, Wiesener MS (2010) The lysyl oxidases LOX and LOXL2 are necessary and sufficient to repress E-cadherin in hypoxia: insights into cellular transformation processes mediated by HIF-1. J Biol Chem, 285: 6658-69

International Cooperation

Dr. Ingeborg Beijema, Institute of Pathology, Leiden University, Leiden, The Netherlands

Prof. Dr. Even Rostand, Nephrology, University of Birmingham, Birmingham, UK

Prof. Dr. J. Canvar, Institute of Pathology, North Western University, Chicago, IL, USA

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Research Focus

- Assessment of Avalox Levels in wounds treated with vacuum therapy
- Artificial dermis for coverage of silicon implants to prevent capsular fibrosis
- Influence of Gap junction channels, Angiogenetic Modulators and Irradiation on de novo vascularisation of a bioartificial construct
- Modulation of neovascularisation and the impact of tissue hypoxia in an axially vascularized *in vivo* model of angiogenesis
- Clinical and experimental analyses of ischemia and reperfusion in free tissue transfer
- Tissue Engineering: Bone
- Tissue Engineering: Skeletal Muscle
- Tissue Engineering: generation of axially vascularized bone tissue in a large animal model
- Perfusion of Human Tissue under VAC Therapy
- Clinical evaluation of wound healing in surgical wound closure with titanium-coated suture material (Seratan®)

Structure of the Department

Under the auspices of the head of the department, Prof. Horch and 4 attending plastic surgeons, 8 residents, 2 lab technicians, 2 veterinarian doctors, 2 scientists and 16 medical students are working in different groups on various projects including basic science research 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

Assessment of Avalox Levels in wounds treated with vacuum therapy
Project manager: Dr. M. Schmitz
Since a large number of wounds treated with VAC therapy are contaminated with bacteria, antibiotic treatment is necessary and often initiated before the result of the microbiological resistance testing is available. An efficient antimicrobial therapy should thus be carried out using an antibiotic, which covers a wide spectrum of bacteria typically causing infections of these wounds, has little side effects as well as good tissue penetration and high oral bioavailability. Moxifloxacin meets these requirements and, therefore, after iv injection, its concentration in the wound fluid and granulation tissue will be quantified in wounds and correlated with serum levels of the patient.

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 thus 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, and clinical observation as well as histochemistry and immunohistochemistry will be used for evaluation over a period of 12 weeks.

Influence of Gap junction channels, Angiogenetic Modulators and Irradiation on de novo vascularisation of a bioartificial construct
Projcet manager: Dr. V. Schmidt
Inhibition of Vascular endothelial growth factor (VEGF) has been shown to result in vascular normalization of the chaotic tumor blood vessel system, enabling more efficient delivery of chemotherapeutic agents and resulting in increased radiosensitivity due to superior oxygen supply. Gap junction channels within the cardiovascular system not only guarantee sufficient organ perfusion but also appear to play an important role in angiogenesis and flow-induced angiogenesis. Based on this background knowledge we investigate angiogenetic processes in an *in vivo* model of neovascularisation with emphasis on vascular connexin-mediated gap junction communication, the therapeutic potential of biomodulators of angiogenesis and the influence of ionising radiation.

Modulation of neovascularisation and the impact of tissue hypoxia in an axially vascularized *in vivo* model of angiogenesis
Project manager: O. Bleiziffer
The experimental microsurgical model of intrinsic vascularization by a blood vessel loop in a separation chamber represents the prototype of an organoid and is readily accessible to monitoring and manipulation due to its highly standardized environment. We stipulate that formation of a vascular network is stimulated by tissue hypoxia inside this chamber. The current project investigates the oxygen gradients inside this organoid by detection and localization of the hypoxia-sensitive transcription factor (HIF-) 1alpha in correlation with the vascularization patterns and morphology of the novel blood vessel network. Hypoxic pre-treatment of rats as well as the use of pharmacological HIF stabilizers may modulate de novo angiogenesis in bioartificial constructs and open new therapeutic options towards stimulation and inhibition of blood vessel formation.

Clinical and experimental analyses of ischemia and reperfusion in free tissue transfer
Project manager: Dr. A. Dragu
Microsurgical Free flap transfer represents an established procedure in Plastic and Reconstructive Surgery for successful closure of defects of the human body. However, postoperative monitoring of viability and perfusion of the transplanted tissue (e.g. buried flaps) as well as the limited time of free flap ischemia represent clinical problems. Innovative imaging tools in nuclear medicine are used in an interdisciplinary approach to evaluate viability and perfusion of the free flap. Additionally gene expression analyses are performed to gain further insight in the pathophysiology of ischemia and reperfusion in free flaps. In this context, a new experimental "*ex vivo* free flap perfusion tool" named MOPS (miniaturized oxygenation and perfusion system) was established using the M. rectus abdominis muscle in a domestic pig model.

Tissue Engineering: Bone
Project managers: PD Dr. U.Kneser / Dr. A. Arkudas
The goal of this study is to generate vascularized bioartifical tissue-engineered bone.
In vitro and *in vivo* studies for different approaches towards induction of a directed vascularization in a clinically applicable biomatrix and the time course of vascularization will be investigated. Autologous osteoblasts will be implanted in these prevascularized hard matrices. Bone formation in osteoblasts-containing constructs will be compared to cell-free constructs. Additional studies will include innovative biomaterials which will be provided by the Institute for Glass and Ceramics (Prof. Greil) and the Institute for Biomaterials (Prof. Boccacini).
In cooperation with the Chair for Material Science and Metal Technology (Prof. Singer, PD Körner), the combination of extrinsic and intrinsic vascularization in AV loops with porous titanium chamber has been evaluated. Using these chambers, we will investigate bone formation in a femur defect model in the rat with defect coverage using a pedicled prevascularized tissue-engineered bone construct.

Tissue Engineering: Skeletal Muscle
Project manager: PD Dr. J. Beier
Tissue Engineering of skeletal muscle represents a promising approach towards replacement of congenital or acquired muscle defects. In this research project, we aim to use a selection of differentiation-inducing agents such as myogenic growth factors and, or by co-cultivation with mesenchymal stem cells to induce the formation of mature differentiated muscle cells *in vitro*. For *in vivo* application functional 3D matrices based on electrospun nanofibers will be employed. The *in vivo* application by transplantation of myoblasts and mesenchymal stem cells into functional 3D matrices is carried out in a newly developed AV loop rat model where not only axial vascularization is possible but also the additional insertion of an adjacent motor nerve branch. Hence, the goal of this combined approach is the de novo formation of axially vascularized innervated skeletal muscle tissue.

Tissue Engineering: generation of axially vascularized bone tissue in a large animal model
Project managers: PD Dr. J. Beier / Dr. A. Boos
The goal of this research project is to generate axially vascularized bone in a large animal sheep model in order to pave the way towards application in the human body. In the model of the arterio-venous microsurgically created AV loop in the sheep we aim for the generation of axially vascularized and thereby transplantable bone. Using a selection of clinically approved bone replacement materials in combination with osteoinductive growth factors as well as autologous mesenchymal stem cells, we already demonstrated de novo formation of axially vascularized bone. In cooperation with Dr. A. Hess, Institute of Pharmacology and Toxicology, the process and the time course of axial blood vessel sprouting will be investigated *in vivo* using state of the art 3D imaging techniques.

Perfusion of Human Tissue under VAC Therapy
Project manager: Dr. A Dragu
The Vacuum therapy, (VAC®) as initially described by Morykwas and Argenta in 1997, represented a crucial advancement in the treatment of problem wounds. Despite extensive research, however, the underlying mechanisms and the resulting impact on tissue perfusion on a molecular level have not been elucidated yet. The goal of the current study is to investigate the effects of Vacuum therapy on human tissue. A particular emphasis is placed on parameters of tissue perfusion including oxygen saturation, postcapilllary hemoglobin content, blood flow velocity and blood flow in different areas of the body and under different vacuum settings.

Clinical evaluation of wound healing in surgical wound closure with titanium-coated suture material (Seratan®)
Project manager: Dr. A. Saalabian
All currently used surgical sutures induce significant granulation tissue formation, i.e. a foreign body reaction. Titanium has been shown to heal with very little granulation tissue formation when used as an implant, hence the use of a titanium-coated suture appears very promising in this regard. *In vitro* experiments addressing the question have shown encouraging results so far. The goal of this project is to investigate the ease of handling as well as the quality of the scar formation after wound closure using a monofile titanium-coated polyamide suture.

Teaching

According to the German "Statutes of the medical act (AeAppO)", a lecture series of 25 academic hours per semester (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

Arkudas A, Pryymachuk G, Hoereth T, Beier JP, Polykandriotis E, Bleiziffer O, Horch RE, Kneser U (2009) Dose-Finding Study of Fibrin Gel-Immobilized Vascular Endothelial Growth Factor 165 and Basic Fibroblast Growth Factor in the Arteriovenous Loop Rat Model. Tissue Eng Part A, 15: 2501-2511

Arkudas A, Tjiawi J, Saumweber A, Beier JP, Polykandriotis E, Bleiziffer O, Horch RE, Kneser U (2009) Evaluation of blood vessel ingrowth in fibrin gel subject to type and concentration of growth factors. J Cell Mol Med, 13: 2864-74

Beier JP, Horch RE, Arkudas A, Polykandriotis E, Bleiziffer O, Adamek E, Hess A, Kneser U (2009) De novo generation of axially vascularized tissue in a large animal model. Microsurgery, 29: 42-51

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, Horch RE, Hammon M, Arkudas A, Naschberger E, Rath S, Pryymachuk G, Beier JP, Hatzopoulos AK, Stürzl M, Kneser U (2009) T17b murine embryonal endothelial progenitor cells can be induced towards both proliferation and differentiation in a fibrin matrix. J Cell Mol Med, 13: 926-35

Arkudas A, Beier JP, Pryymachuk G, Hoereth T, Bleiziffer O, Polykandriotis E, Hess A, Gulle H, Horch RE, Kneser U (2010) Automatic quantitative micro-computed tomography evaluation of angiogenesis in an axially vascularized tissue-engineered bone construct. Tissue Eng Part C Methods, 16: 1503-14

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Research Focus
- Dementia
- Schizophrenia
- Addictive Behaviour
- Clinical Neurochemistry and Neurochemical Dementia Diagnostics
- Neurophotonics
- Needs Assessments for Psychiatric Care

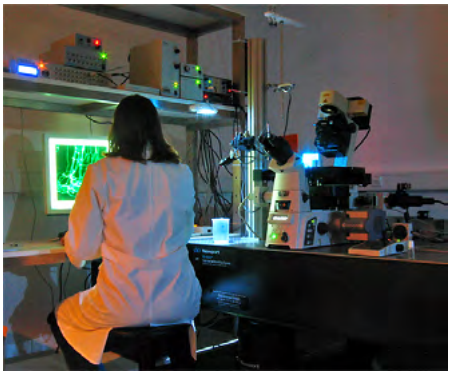
Structure of the Department

All the psychosocial professions are organized under the umbrella of the Department of Psychiatry and Psychotherapy including the independent Division of Psychosomatics and Psychotherapy and the Division of Child and Adolescent Psychiatry and Psychotherapy, as well as the area of medicinal psychology and medicinal sociology. The content network is supported via the common quality management system, as certified according to DIN EN ISO 9001:2008.
We provide a qualified, interdisciplinary team, which is involved in engagement and competence in the patients' convalescence, for treatment in our department. The collaboration of doctors, nursing staff, psychologists, social pedagogues, occupational therapists and physiotherapists ensures a sure and complete diagnostic and concerted treatment. Patient treatment is conducted on an in-patient, day patient, as well as ambulatory basis. The various stimulation methods present a special clinical offer for the treatment of patients with depression.
The research activities of the clinic are multifaceted with a broad diversity. Particularly visible research projects have been developed in the disease areas depression, addiction and dementia. The Clinic is a member of the Competence Network for Dementia Society and plays a leading role with its diagnostic center focusing on early and differential diagnoses. Other european and national projects investigating neurodegenerative diseases are indicative of our particular research expertise in this area. Regarding research in addiction, our work in the field of nicotine and alcohol dependence is to be emphasized. In the FARS (Franconian Alcoholism Research Studies), different neurobiological problems were investigated on a large patient population. The results are promptly implemented in treatment, as is the case with nicotine research, demonstrated in the offered courses to give up smoking. The laboratory for Clinical Neurochemistry and Neurochemical Dementia Diagnostic, the national reference center for the neurochemical dementia diagnostic in the frame work of the competence network dementia, is a part of Psychiatric core clinic. In addition, the laboratories for molecular neurobiology and sensorics are part of the Clinic.

Research

Dementia

Our research focus is on the improvement of early detection and the diagnosis of disease progression in dementia. In the area of psychometrics, we have been able to develop a new version of the Resource Utilization in Dementia (RUD) tool for application in care facilities. This instrument collects data on patients' utilization of support time in regard to activities of daily living, essential activities of daily living and supervision and is suitable for application in needs assessments. The contribution of the immune system to psychiatric illness, with a focus on Alzheimer's disease, is being investigated in cooperation with the Department of Clinical Immunology. PD Dr. Manuel Maler received the Cerebrospinal Fluid (CSF) Research Award 2009 from the German Association for CSF Diagnostics and Clinical Neurochemistry (DLGN) for his work on the detection of complex A-beta peptide sequences in human plasma. The occurrence of affective and cognitive disorders in immunosuppressed kidney transplant recipients and their relationship to soluble and cellular immunological biomarkers is investigated in an additional project conducted in cooperation with the Departments of Nephrology and Clinical Hypertension.



Study on nerve cells using a partly automated fluorescence microscope

Schizophrenia

Prof. Sibylle Schwab commencing as the new W2 Professor for Molecular Psychiatry offers the opportunity for a new research focus on the genetics of schizophrenia. Prof. Schwab has established large subject cohorts for investigating the genetic basis of schizophrenia in Germany, as well as in collaboration with colleagues in Perth, Australia and in Jakarta, Indonesia. The Indonesian sample will be used for the description of gene locations as well as for the investigation of transcultural and population-specific effects. With an overall sample size of more than 1247 patients and more than 1148 controls, this cohort is currently one of the biggest case-control samples from a non-European background and within a defined geographic region that has been able to be assembled.

Addictive Behaviour

Having Prof. Christian Müller commence as W2 professor for addiction medicine leads to an expansion of experimental addiction research. New insights into the biomarkers of and molecular changes in alcohol and nicotine addiction were gained. In the area of alcohol addiction, the focus has been on the investigation of functional adaptations in alcohol detoxification. Here, it could be shown how mRNA-expression and the plasma concentration of various peptide transmitters, neural growth factors and classical receptors change during detoxification. For some of these changes, an epigenetic control via gene-methylation could be proven. A multitude of the changes in gene expression was associated with the severity of detoxification symptoms and the degree of alcohol dependence. Various polymorphisms in genes on the sex hormone axis were identified that are associated with the severity of crav-

ing. Supported through third party funding (ERAB) and in cooperation with the Hannover Medical School (MHH) and the KfN Hannover, a publication was put together on the epidemiology of binge drinking among young people with respect to migration background and city/rural differences.

Research in the area of nicotine dependence was able to show that nicotine consumption leads to an increased activation of intracellular signalling cascades. These cascades contribute fundamentally to the establishment of addictive behaviours. In addition, the effects of nicotine consumption on EEG activity, a significant marker of cognitive performance, have been investigated. Here, a significant decrease of event-related brain activity (P300) could be proven. This research has been supported by funds from the Deutsche Forschungsgemeinschaft (DFG) and the Interdisciplinary Center of Clinical Research (IZKF).

Clinical Neurochemistry and Neurochemical Dementia Diagnostics

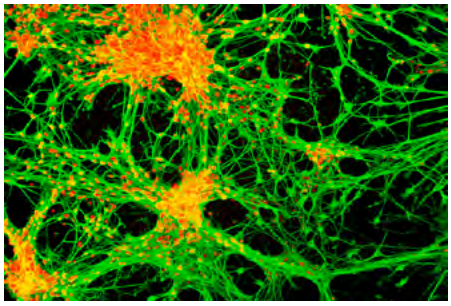
The ISO 9001:2008 certified laboratory is an internationally recognized center for neurochemical dementia diagnostics. Together with four others around the world (Goteborg, Amsterdam, Ghent and Philadelphia), this is the reference laboratory of an Alzheimer Association-funded project on quality control in cerebrospinal fluid (CSF) biomarker diagnostics. CSF analysis provides excellent diagnostic possibilities in relation to a multitude of neurological and psychiatric illnesses (multiple sclerosis and other neuroinflammatory conditions, acute and chronic neural infections, stroke etc.). Neural degeneration and Alzheimer's disease are the focus in this context.

Neurophotonics

The new research focus on biophotonic imaging in neuroscience is devoted to the examination of neurons using light. In this newly built laboratory, researchers from diverse disciplines, namely medicine, engineering, mathematics and physics as well as molecular medicine, work together to gain new insights into the effect of therapeutic drugs on synapses. This research aims to create the foundations for innovative therapeutic approaches. Already, significant structural differences between individual synapses could be shown using modern microscopes and special dyeing processes. During the reporting period, his work has been supported financially by the ELAN Fonds, the IZKF, the German National Academic Foundation and by the Dr. Ernst and Anita Bauer Foundation.

Needs Assessments for Psychiatric Care

Needs assessments for psychiatric care are becoming increasingly meaningful because research into the effectiveness and efficiency of patient-centered diagnostic, therapeutic and care services is gaining importance. The Dementia Care in General Practice (IDA) project, with a total budget of € 3.2 mio, is currently one of the largest intervention studies internationally on outpatient services for dementia patients. The "MAKS aktiv!" longitudinal randomized controlled trial on everyday mobility, cognitive and spiritual training is currently supported by the German Federal Ministry for Health's "Lighthouse Dementia" initiative with around € 550,000.00. In this study, an intensive, drug-free, multi-mode group intervention proved effective for dementia patients living in care facilities. In addition, the research award of the German Alzheimer's Association makes the "BeWiTa" project possible, which investigates the effects of various forms of mobility training and sports games for people with cognitive impairments and their relatives under everyday living conditions, using Wii game consoles.



Confocal immunofluorescent analysis of chicken neurons using anti-tau antibody Primary chicken telencephalic neurons were prepared from 8-day old chick embryos and cultured for 5 days in vitro until fixation. Cells were labeled with a primary anti-tau antibody and a secondary goat anti–mouse antibody labeled with AlexaFluor 488. DNA was stained with DRAQ5. Images were acquired using a 20x oil immersion objective.

Teaching

The clinic offers a broad spectrum of medical education activities in the clinical section, from lectures and seminars, electives, work experience and intern education to blended e-learning. In teaching evaluations, the psychiatric department has regularly scored in the top range among the clinical subjects. Examination planning and assessment is conducted according to scientific principles and high professional standards. Teaching is always accompanied side-by-side by teaching research conducted through the academic teaching workgroup and is organized according to quality management principles. Communication skills are built using new and innovative teaching methods: medical consult situations and communication skills are practiced using facilitated role-play. Performance is evaluated using competency-based assessments. For these, students complete portfolios documenting and reflecting on two actual doctor-patient conversations as well as their care internship. Preparations for the first part of the medical students' examination in the subject of Medical Psychology and Sociology have also been very successful. In 2010, the students from the Friedrich-Alexander-Universität Erlangen-Nürnberg came first in the national comparison of written examination results in this subject, as they had done in the two previous years.

Selected Publications

Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Williams A, Jones N, Thomas C, Stretton A, Morgan AR, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Morgan K, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Love S, Kehoe PG, Hardy J, Mead S, Fox N, Rossor M, Collinge J, Maier W, Jessen F, Schürmann B, van den Bussche H, Heuser I, Kornhuber J, Wiltfang J, Dichgans M, Frölich L, Hampel H, Hüll M, Rujescu D, 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, Carrasquillo MM, Pankratz VS, Younkin SG, Holmans PA, O'Donovan M, Owen MJ, Williams J (2009) Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet, 41: 1088-93

Kornhuber J, Schmidtke K, Frolich L, Perneczky R, Wolf S, Hampel H, Jessen F, Heuser I, Peters O, Weih M, Jahn H, Luckhaus C, Hüll M, Gertz HJ, Schröder J, Pantel J, Rienhoff O, Seuchter SA, Rüther E, Henn F, Maier W, Wiltfang J (2009) Early and differential diagnosis of dementia and mild cognitive impairment: design and cohort baseline characteristics of the German Dementia Competence Network. Dement Geriatr Cogn Disord, 27: 404-17

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Lewczuk P, Kamrowski-Kruck H, Peters O, Heuser I, Jessen F, Popp J, Bürger K, Hampel H, Frölich L, Wolf S, Prinz B, Jahn H, Luckhaus C, Perneczky R, Hüll M, Schröder J, Kessler H, Pantel J, Gertz HJ, Klafki HW, Kölsch H, Reulbach U, Esselmann H, Maler JM, Bibl M, Kornhuber J, Wiltfang J (2010) Soluble amyloid precursor proteins in the cerebrospinal fluid as novel potential biomarkers of Alzheimer's disease: a multicenter study. Mol Psychiatry, 15: 138-45

Luttenberger K, Graessel E (2010) Recording care time in nursing homes: development and validation of the "RUD-FOCA" (Resource Utilization in Dementia-Formal Care). Int Psychogeriatr, 22: 1291-300

Wilhelm BG, Groemer TW, Rizzoli SO (2010) The same synaptic vesicles drive active and spontaneous release. Nat Neurosci, 13: 1454-6

International Cooperation

Prof. Dr. med. J. Leszek and Dr. M. Zboch, Alzheimer's Disease Diagnostic and Therapy Center, University of Wroclaw, Scinawa, Wroclaw, Poland

Prof. Dr. Dr. Klaus R. Liedl, Center for Molecular Biosciences, Leopold-Franzens-University Innsbruck, Innsbruck, Austria

Dr. med. Trine Brogaard, Forschungsbereich Allgemeinmedizin, Aarhus University, Aarhus, Denmark

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Research Focus
- Neurophysiology in child and adolescent psychiatry
- Neurobiology in child and adolescent psychiatry

Structure of the Division

The Division of Child and Adolescent Mental Health at the Department of Psychiatry and Psychotherapy is a self-contained division of the Universitätsklinikum. 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 the head of the department. Research is structured into two working groups (neurophysiology and neurobiology in child and adolescent psychiatry) that investigate the pathophysiological background as well as the neurobiological basis of child and adolescent psychiatric disorders. Clinical focus lies on: attention deficit/hyperactivity disorder, eating disorders, obsessive-compulsive disorders, tic disorders, autistic disorders, anxiety disorders, and reduced intelligence with psychiatric comorbidity.

Research

Neurophysiology in child and adolescent psychiatry

Head of the working group: Dr. sc. hum. H. Heinrich

The working group neurophysiology conducts neurophysiological studies addressing the interaction of brain functions, experience and behaviour. These studies aim at a better understanding of developmental processes and the neurobiological basis of emotional and behavioural disorders as well as the mechanisms underlying therapeutic interventions. The main research topics are neurofeedback, inhibitory processes in children with attention deficit/hyperactivity disorder, and the interaction of cognition and emotion.

1. Neurofeedback - training effects on the behavioural and neurophysiological level: In a neurofeedback training participants learn to gain self-control over certain brain activity patterns. In this way, children with attention deficit/hyperactivity disorder (ADHD) are trained to develop strategies that enable them to improve their attention abilities as well as to better regulate their behaviour. In a randomized controlled trial that was conducted in cooperation with the Child and Adolescent Psychiatry at the University Clinic of Göttingen and the Heckscher-Klinik in Munich, the clinical effectiveness of a neurofeedback training in children with ADHD could be demonstrated. On the clinical level the neurofeedback training led to a larger reduction of the ADHD symptomatology (medium effect size), compared to a conventional computerized attention training. These positive effects proved to be stable at a 6-month follow-up after the end of training. Examinations on the neurophysiological level contributed to a better understanding of the mechanisms underlying a successful neurofeedback training. A further study in students examined the effects of different variants of neurofeedback training on attentional processes, the motor system and well-being. On the behavioural and neurophysiological level only small and medium effects were observed in favour of the neurofeedback groups, for which also differential effects could be described.

2. Inhibitory processes in children with ADHD: Children with ADHD show an inhibitory deficit in the motor system. In order to examine this deficit of inhibition on the neuronal level in more detail, we developed a methodological approach combining transcranial magnetic stimulation and event-related potentials to study inhibitory processes in a differentiated manner. In a pilot study in healthy adults using this methodological approach the interplay of neuronal processes that are involved in inhibiting a motor response could be highlighted. In addition, this study was able to disclose that the methylphenidate medication, which is applied in the therapy of children with ADHD, led to a finetuning of the motor system. This work was awarded the second poster prize at the Conference of Biological Child and Adolescent Psychiatry 2009 in Würzburg. A study comparing children with and without ADHD has recently been finished. First results (transcranial magnetic stimulation) show deviant inhibitory patterns in children with ADHD. Further, this inhibitory pattern is modulated by the degree of hyperactivity / impulsivity.

A boy performs a neurofeedback training. He controls a computer game (goalkeeper at a penalty kick) by modulating his brain electrical activity. The training can help children with ADHD to improve self-control

3. Interaction of cognition and emotion: In adolescents with eating disorders (anorexia nervosa, bulimia nervosa) and a healthy control group, behaviour and emotional reactions e. g. when viewing body scheme pictures of underweight, normal weight, and overweight women were examined on multiple levels (eye movements, central and autonomic nervous system). Patients showed longer fixation times for unclothed body regions (visual attentional bias towards body shape-related information). At the physiological level for anorectic patients strongest reactions for pictures of underweight women were observed at various processing steps. A possible practical implication of this multilevel approach could lie in the field of early recognition of eating disorders (screening for predisposing factors / patterns of behaviour).

Neurobiology in child and adolescent psychiatry

Head of the working group: Prof. Dr. rer. nat. R. Dawirs

1. Behavioural and neural consequences of prenatal trauma. The focus of our research is to study neural mechanisms of prenatal stress

and investigate its consequences on the brain development and behaviour in mice. We investigate learning and memory processes, fear and anxiety as well as depression-like symptoms in the mice that have experienced prenatal trauma. Changes in the neural activity of brain structures that are involved in these processes, as well as changes in the activity of the hypothalamic-pituitary-adrenal axis (HPA) are investigated. By comparing behaviour and neurophysiological functions of the traumatized mothers and their offspring, we explore genetic, epigenetic and environmental factors involved in emergence of resilience and vulnerability to develop psychiatric disorders following prenatal trauma exposure.

2. Development, maintenance and reduction of fear and anxiety in the animal models. We investigated behavioural and neuroanatomical correlates of non-associative and associative fear memory as well as the development of the generalized fear in a mouse model of PTSD. Our results demonstrate the independence of associative and non-associative trauma-related fear and show involvement of several subregions of hippocampus and amygdala in both memory components. Furthermore, we deliver evidence that generalized contextual fear and avoidance after fear incubation depend on associative rather than non-associative memory components.

3. The role of stress responsive neurohormones in anxiety disorders of children and adolescents. We investigate basal and stress-induced activity (Trier Social Stress Test) of HPA- axis in children and adolescents with anxiety disorders. Our goal is to study the impact of psychotherapeutic treatment on the function of the adrenocortical system and correlate the activity of this system with the symptoms reduction. We are interested in investigating a question, how far stress system activity predicts the severity of the disorder and monitors therapy success and relapse probability.

At this psychophysiological working station a subject is looking at an emotion inducing picture on the monitor. Her brain electrical activity, heart rate, skin conductance, speech and eye movements are measured. This multilevel approach can be used to examine the interaction of cognition and emotion.

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 unfortunately not been included in the curriculum of the Medical Faculty 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 since the winter term 2009/2010 as a compulsory optional subject for students of medicine as well as since the winter term 2010/2011 as an optional lecture with accompanying seminar within the course of studies in Psychology (Bachelor/Master). Beyond the scope of lectures, it is continuously possible for students to do an internship in all subdivisions of our department.

Selected Publications

Gevensleben H, Holl B, Albrecht B, Schlamp D, Kratz O, Studer P, Wangler S, Rothenberger A, Moll GH, Heinrich H (2009) Distinct EEG effects related to neurofeedback training in children with ADHD: a randomized controlled trial. Int J Psychophysiol, 74: 149-57

Gevensleben H, Holl B, Albrecht B, Vogel C, Schlamp D, Kratz O, Studer P, Rothenberger A, Moll GH, Heinrich H (2009) Is neurofeedback an efficacious treatment for ADHD? A randomized controlled clinical trial. J Child Psychol Psychiatry, 50: 780-9

Heinrich H, Kolev V, Rothenberger A, Yordanova J (2009) Event-Related Oscillations and Cognitive Processes in Children A Review of Methodical Aspects and Empirical Findings. J Psychophysiol, 23: 199-207

Kratz O, Diruf MS, Studer P, Gierow W, Buchmann J, Moll GH, Heinrich H (2009) Effects of methylphenidate on motor system excitability in a response inhibition task. Behav Brain Funct, 5: 12

Studer P, Wangler S, Diruf MS, Kratz O, Moll GH, Heinrich H (2010) ERP effects of methylphenidate and working memory load in healthy adults during a serial visual working memory task. Neurosci Lett, 482: 172-6

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

International Cooperation

EU Projekt COST Action B27, Brussels, Belgium

Prof. J. Yordanova, Prof. V. Kolev, Institute of Physiology, Bulgarian Academy of Sciences, Sofia, Bulgaria

Prof. Dr. D. Brandeis, Dr. R. Drechsler, Kinder- und Jugendpsychiatrie, University of Zurich, Zurich, Switzerland

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Research Focus
- Eating disorders
- Obesity
- Excessive behaviors / behavioral addictions
- Somatoform disorders
- Body dysmorphic disorder
- Psycho-oncology

Structure of the Division

The independent department 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 University Hospital with a major focus on psycho-oncology. The main clinical focus of the department surrounds eating disorders. Other areas of activity include obesity, excessive behaviors with a special emphasis on pathological buying, somatoform disorders, pain treatment, and psycho-oncology. The treatment focuses on multimodal and multidisciplinary evidence-based psychotherapy. Prof. Dr. Alexandra Martin, who fills a faculty professorship in "Psychotherapy Research", strengthens the field of behavioral medicine and collaborates successfully with the other Departments of the Universitätsklinikum Erlangen. With her work she underlines the importance and impact of psychosomatic medicine as an interdisciplinary medical field.

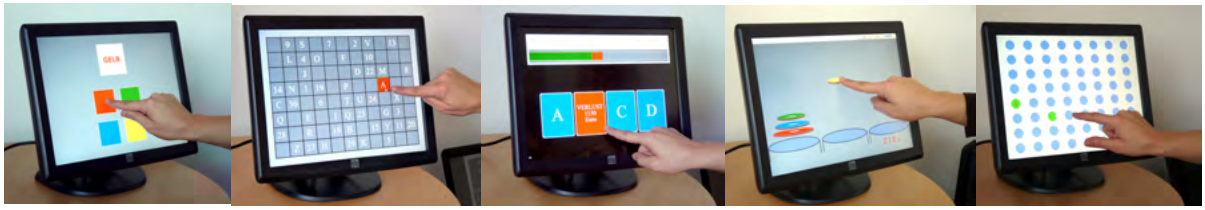
Research

Eating disorders
Project manager: M. de Zwaan
The PI coordinates the "Research consortium on psychotherapy of eating disorders (EDNET)" funded by the German Federal Ministry of Education and Research (BMBF). The funding period runs from 2007 to 2013. Within the consortium 5 large randomized multi-center psychotherapy trials are conducted, all of which represent international milestone studies. The Psychosomatic Department is the coordinating center of a trial for the treatment of Binge-Eating-Disorder which was started 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 have initiated studies covering different areas in the field of eating disorders These include an intervention to support the carers of patients with eating disorders, the specific eating-related psychopathology and structural neuroimaging in patients with anorexia nervosa focusing on DTI tractography conducted in collaboration with the Department of Neuroradiology in Erlangen and the Departments of Psychiatry in Erlangen and Hannover.

Obesity
Project manager: M. de Zwaan
The PI coordinates the consortium on "Weight loss maintenance" within the Competence Network Obesity, which has been funded since August 2008 by the German Federal Ministry of Education and Research (BMBF). In addition, she is deputy speaker of the entire Competence Network. The Psychosomatic Department 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 will lay the foundation 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 1 year. All participants are subsequently followed 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) systems to cover for such aspects will be produced by Prof. Prokosch and his team from the Chair of Medical Informatics at the Friedrich-Alexander-Universität Erlangen-Nürnberg.
A prospective long-term follow-up investigation of 150 consecutive patients with obesity grade 3 prior and 2 years after bariatric surgery was completed in 2009. The goal of the study was to examine of the long-term course of psychosocial parameters after bariatric surgery (psychopathology, eating behavior, quality of life) and to assess psychosocial predictors of post-surgery weight loss.
Newer projects focus on executive functions in grade 3 obesity and their development after weight loss. The goal of an ongoing study is to examine the proposed link between impaired executive function/reduced self-control and dysfunctional eating behavior in morbidly obese individuals before and after substantial weight loss due to bariatric surgery.

Excessive behaviors / behavioral addictions
Project manager: A. Müller
Since 2003 several research projects aimed to investigate compulsive buying disorder. Besides the advancement of cognitive-behavioural therapy concepts for compulsive buying, several ongoing research projects are conducted concerning the validation of screening instruments for compulsive buying and associated psychopathology. Another study examines the extent to which patterns of mood and daily stress experienced by patients with compulsive buying are associated with compulsive buying episodes by using Ecological Momentary Assessment. Additional projects investigate psychiatric co-morbidity (e.g., compulsive hoarding), gender differences, materialistic values endorsement and the role of reactive and regulative temperament as well as executive function in compulsive buying.

Somatoform disorders
Project manager: 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 to Rief, Brähler, & Martin) a longitudinal survey aiming at clarifying predictors of symptom persistence in somatoform disorders was completed.
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



A computerized neurocognitive testing to assess executive functions

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 is currently being evaluated in terms of pain characteristics, cognitive and physiological parameters in patients with non-cardiac chest pain. In addition, relevant cognitive factors are examined in an experimental design to expand existing study results. The study has received a grant by ELAN-Fonds and is conducted in cooperation with the Department of Cardiology.

Body dysmorphic disorder

Project manager: 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. The preoccupation with appearance is excessive and causes significant distress or impairment in functioning. BDD is frequently accompanied by strong 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). Dysfunctional cognitions are assumed to be important in maintaining the disorder; therefore we aim to identify disorder-specific characteristics of BDD in comparison with a clinical control group (eating disorders) and healthy controls. Furthermore, we examine body image variables in individuals with BDD in comparison to clinical and non-clinical controls.

Psycho-oncology

Project manager: H. Sinzinger

The establishment of the University Cancer Center Erlangen-Nürnberg (UCC), which is 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 in a multi-center design.

Teaching

The Division is significantly involved in the curriculum of the Medical Faculty. We test new methods of instruction and teaching formats within the practical course the Division offers, 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 Medical Faculty 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 Psychosomatic Division 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 the practical courses based on the evaluation of the medical students and the Division Head has repeatedly received a Lecturer's Award of the Medical Faculty.

Selected Publications

de Zwaan M, Petersen I, Kaerber M, Burgmer R, Nolting B, Legenbauer T, Benecke A, Herpertz S (2009) Obesity and quality of life: a controlled study of normal-weight and obese individuals. Psychosomatics, 50: 474-82

Glombiewski JA, Rief W, Bösner S, Keller H, Martin A, Donner-Banzhoff N (2010) The course of nonspecific chest pain in primary care: symptom persistence and health care usage. Arch Intern Med, 170: 251-5

Mueller A, Claes L, Mitchell JE, Wonderlich SA, Crosby RD, de Zwaan M (2010) Personality prototypes in individuals with compulsive buying based on the Big Five Model. Behav Res Ther, 48: 930-5

Mueller A, Mitchell JE, Crosby RD, Gefeller O, Faber RJ, Martin A, Bleich S, Glaesmer H, Exner C, de Zwaan M (2010) Estimated prevalence of compulsive buying in Germany and its association with sociodemographic characteristics and depressive symptoms. Psychiatry Res, 180: 137-42

Rief W, Mewes R, Martin A, Glaesmer H, Braehler E (2010) Are psychological features useful in classifying patients with somatic symptoms? Psychosom Med, 72: 648-55

de Zwaan M, Hilbert A, Swan-Kremeier L, Simonich H, Lancaster K, Howell LM, Monson T, Crosby RD, Mitchell JE (2010) Comprehensive interview assessment of eating behavior 18-35 months after gastric bypass surgery for morbid obesity. Surg Obes Relat Dis, 6: 79-85

International Cooperation

Prof. Laurence Claes, Department of Psychology, Katholieke Universiteit Leuven, Leuven, Belgium

PD Dr. Jens Gaab, KlinicalPsychology and Psychotherapy, University of Zurich, Zurich, Switzerland

Prof. Dr. James E. Mitchell, Neuropsychiatric Research Institute and University of North Dakota School of Medicine and Health Sciences, University of North Dakota, Fargo, ND, USA

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Research Focus
- Imaging of the Head and Neck:
- X-ray induced DNA damages in radiology
- Functional and metabolic MRI
- Interventional Radiology
- Cardiovascular Imaging
- Breast Imaging

Structure of the Department

The Department 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 department consists of three professors, eight assistant professors, 35 medical doctors, two experimental scientists and 77 radiographers.
The Department of Radiology provides the full range of radiological imaging modalities. Furthermore, a variety of interventional procedures like imaging guided biopsies or angiographic therapies are performed.
In cooperation with Siemens Medical Solutions the Imaging Science Institute integrates new developments in diagnostic imaging and novel IT-solutions into the clinical routine and into the academic research.
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.

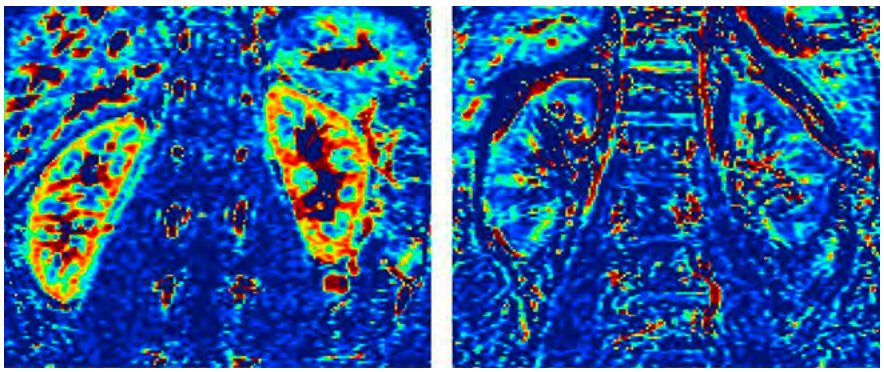
Research

Imaging of the Head and Neck:
PD. Dr. M. Lell; Dr. S. Alibek, Dr. M. Kramer, M. May; Dr. A. Eller, 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 Maxillofacial Surgery (Prof. Dr. Dr. F.W. Neukam) and the Department of Radiotherapy (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 Maxillofacial Surgery (Prof. Dr. med. Dr. dent. F.W. Neukam). Methodological and clinical studies in dose reduction techniques in CT in cooperation with Siemens Healthcare, CT-Division.

X-ray induced DNA damages in radiology
PD Dr. M. Küfner, Dr. Michael Brand, M. May, Dr. S. Schwab, C. Engert, Prof. Dr. M. Uder
Established dose parameters 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. DSBs can be detected by using an immunofluorescence microscopic technique (established in collaboration with Prof. Dr. M. Löbrich, TU Darmstadt). 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 or angiography. Within 24 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, Flat-panel CT) and of dose reducing approaches (e.g. risk organ based current modulation) 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 is assessed *in-vitro* and *in-vivo*.

Functional and metabolic MRI
Prof. Dr. M. Uder, PD. Dr. R. Janka, Dr. M. Hammon, Dr. S. Alibek
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 become 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.

Interventional Radiology
Prof. M. Uder, Dr. A. Schmid, Dr. M. Küfner, PD Dr. M. Lell, PD Dr. R. Janka
Cooperations with the Department of Surgery (Prof. Hohenberger), the Department of Vascular Surgery (Prof. Lang), the Department of Nephrology (Prof. Eckardt), the Division of Nephropathology (Prof. Amann), the Department of Gastroenterology (Prof. Neurath) and the Department of Nuclear Medicine (Prof. 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. In patients with intermediate stage hepatocellular carcinoma the combination of medical therapy and transarterial chemoambolization is explored. Selective internal radiotherapy in patients with liver malignancies and endovascular brachytherapy of recurrent stenosis in the femoropoliteal arteries are initiated. New software tools in ct-guided interventions are evaluated.



Colour coded image of the renal perfusion of a healthy volunteer (left) and a patient suffering from renal insufficiency (right). With the so called Arterial Spin Labeling (ASL) technique no intravenous injection of contrast media is needed For ASL no intravenous injection of contrast media is needed because the patient's blood is non-invasively magnetically marked.

Cardiovascular Imaging

Dr. Anders, PD Dr. Janka, PD Dr. Lell, Dr. Scharf, M. May, Dr. Schmid, Dr. Wüst

Pre-clinical and clinical studies in cooperation with the Department of Cardiology/Medicine 2 (Prof. Dr. W. 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 Cardiology/Medicine 2 (Prof. Dr. W. Daniel, Prof. Dr. S. Achenbach) in line with the "Excellenzclusteriniative", project no. 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 Cardiology/Medizinische Klinik II (Prof. Dr. W. Daniel, Prof. Dr. S. Achenbach) and the Department of Trauma Surgery (Prof. Dr. F. F. Henning) using cardiac MRI (cMRI) to assess physiological myocardial adaptation in professional athletes.

Pre-clinical and clinical trials in cooperation with the Division of Pediatric Cardiology (Prof. Dr. S. Dittrich) and 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

Prof. Dr. R. Schulz-Wendtland, PD Dr. E. Wenkel, PD Dr. Janka, Dr. S. Schwab, Dr. M. Meier-Meitinger, Dr. B. Adamietz

Breast imaging is an important research domain of the Radiological Institute. Professor Schulz-Wendltand and his research team address 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 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. Special radiological "crash-courses" help the students to prepare effectively for the state examination. Furthermore, we always offer the possibility to perform clinical electives or internships in our department. Students who want to do a doctor's degree are supervised for writing their experimental or clinical thesis.

Selected Publications

Achenbach S, Marwan M, Ropers D, Schepis T, Pflederer T, Anders K, Kuettner A, Daniel WG, Uder M, Lell MM (2010) Coronary computed tomography angiography with a consistent dose below 1 mSv using prospectively electrocardiogram-triggered high-pitch spiral acquisition. Eur Heart J, 31: 340-6

Kramer M, Nkenke E, Kikuchi K, Schwab S, Janka R, Uder M, Lell M (2010) Whole-body magnetic resonance angiography for presurgical planning of free-flap head and neck reconstruction. Eur J Radiol, :

Kuefner MA, Grudzenski S, Hamann J, Achenbach S, Lell M, Anders K, Schwab SA, Häberle L, Löbrich M, Uder M (2010) Effect of CT scan protocols on x-ray-induced DNA double-strand breaks in blood lymphocytes of patients undergoing coronary CT angiography. Eur Radiol, 20: 2917-24

Kuefner MA, Hinkmann FM, Alibek S, Azoulay S, Anders K, Kalender WA, Achenbach S, Grudzenski S, Löbrich M, Uder M (2010) Reduction of X-ray induced DNA double-strand breaks in blood lymphocytes during coronary CT angiography using high-pitch spiral data acquisition with prospective ECG-triggering. Invest Radiol, 45: 182-7

Ritt M, Janka R, Schneider MP, Martirosian P, Hornegger J, Bautz W, Uder M, Schmieder RE (2010) Measurement of kidney perfusion by magnetic resonance imaging: comparison of MRI with arterial spin labeling to para-aminohippuric acid plasma clearance in male subjects with metabolic syndrome. Nephrol Dial Transplant, 25: 1126-33

Adamietz BR, Meier-Meitinger M, Fasching P, Beckmann M, Hartmann A, Uder M, Häberle L, Schulz-Wendtland R, Schwab SA (2011) New Diagnostic Criteria in Real-Time Elastography for the Assessment of Breast Lesions. Ultraschall Med, 32: 67-73

International Cooperation

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, CA, USA

Meetings and International Training Courses

27.–29.03.2009: Moderne Mammadiagnostik, Erlangen

18.–20.06.2009: MR Compact, Bamberg

02.–04.07.2009: Cardio MRT, Erlangen

22.–23.07.2009: Angiographiekurs, Erlangen

18.–19.09.2009: CT Compact, Bamberg

26.–27.09.2009: Mammasonokurs, Erlangen

23.–25.04.2010: Moderne Mammadiagnostik, Erlangen

10.–12.06.2010: MR Compact, Bamberg

26.06.2010: Mamma MRT, Erlangen

01.–03.07.2010: Cardio MRT, Erlangen

21.–22.07.2010: Angiographiekurs, Erlangen

06.–07.08.2010: MR Angiographie, Erlangen

25.–26.09.2010: Mammasonokurs, Erlangen

Research Equipment

Siemens Magnetom Verio

Siemens Magnetom Aera

Siemens Somatom Definiton AS+

Siemens Somatom Definition Flash

Siemens Artis mit Flachdetektor

Siemens Mammomat Inspiration

Institute of Radiology

Division of Neuroradiology

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Research Focus

- Clinical and experimental validation of flat-panel volume CT
- Preoperative comprehensive imaging of epilepsy
- Multimodal CT and MR imaging in of cerebrovascular disease
- Functional MR-Imaging
- Quantitative and qualitative assessment of optical fiber tracts in glaucoma patients using diffusion tensor imaging and high-field MRI
- Simulation of hemodynamics and fluid dynamics in cerebral aneurysms
- Experimental research on multimodal imaging in a glioma model and validation and development of new interventional therapies in an aneurysm model

Structure of the Division

In the Division of Neuroradiology a total of 35 staff members are employed. Research is performed by 11 medical doctors, 5 postgraduates, and externally funded by a biologist, a computer scientist, a study nurse and a veterinarian, respectively.
The Division of Neuroradiology performs the neuroradiological work-up for patients of the Universitätsklinikum 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
In cooperation with the Department of Medical Physics, Siemens Medical Solutions and the Department of Computer Science/Institute of Pattern Recognition we evaluate and further develop 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 new perfusion techniques and 3D visualizations in stroke patients.

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 here put on high-resolution morphologic and functional MR imaging, i.e. MR spectroscopy, DTI, functional MRI, perfusion- and diffusion-weighted MRI and MR volumetry. Additionally, a dedicated GABA-specific MR spectroscopy sequence is used to evaluate different antiepileptic therapies.

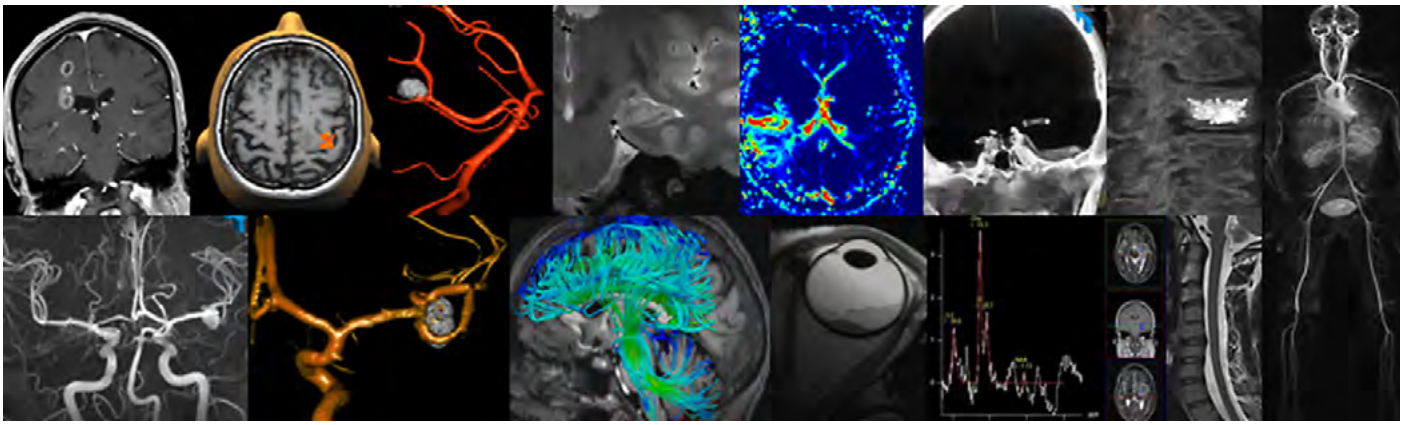
Multimodal CT and MR imaging in of cerebrovascular disease
In cooperation with the Department of Neurology we participate in several acute stroke studies. Using multimodal imaging algorithms including perfusion-, diffusion- and angiographic imaging by CT and mainly MRI we evaluate the individual indication for acute stroke therapies such as thrombolysis and/or other neuroprotective therapies. Another clinical and scientific focus is the evaluation and validation of mechanical devices for revascularization stategies in acute cerebral stroke.
For the follow-up of patients with intracranial microstents we evaluate the potential of flat-panel DynaCT (intravenous contrast media application and rotational angiography) to replace conventional angiography. An additional focus is set on the improvement of non-invasive imaging in the work-up of cerebrovascular disease using different MRA techniques and various contrast agents.

Functional MR-Imaging
There are several ongoing research projects in cooperation with different departments and facilities (e.i. Dep. of Psychiatry and Psychotherapy, Div. of Child and Adolescent Mental Health, Div. of Psychosomatic and Psychotherapy, Dep. of Medicine 3, Dept. of Neurology, Dept. of Neurophysiology, Dept. of Pharmacology) involving functional MR-Imaging (e.g. patients with major depressive disorders, anxiety- and eating disorders, chronic pain syndromes and rheumatoid arthritis). In addition, within a DFG-funded project we investigated functional MR-Imaging of the olfactory system.

Quantitative and qualitative assessment of optical fiber tracts in glaucoma patients using diffusion tensor imaging and high-field MRI
In cooperation with the Department of Ophthalmology (Prof. Michelson) 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 staging and to evaluate therapeutical strategies in glaucoma.

Simulation of hemodynamics and fluid dynamics in cerebral aneurysms
In cooperation with the Department of Computer Science/Institute of Pattern Recognition, Siemens Medical Solutions 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

Experimental research on multimodal imaging in a glioma model and validation and development of new interventional therapies in an aneurysm model
Funded by the DFG (preclinical research group 661) we evaluate multimodal imaging strategies to assess brain gliomas using micro-CT, high-field MRI and micro-PET. We closely cooperate with the Department of Medical Physics, the Pharmacological Institute, Core Unit Small Animal Imaging, and the Department of



The main focus of the Department of Neuroradiology is state-of-the-art imaging of cerebrovascular disease, tumors and epilepsy and interventional neuroradiology

Nuclear Medicine. Additionally, using an elastase-induced aneurysm model, we evaluate different imaging techniques and new materials and techniques for endovascular treatment.

Teaching

The Division of Neuroradiology is involved in training medical students. We offer a variety of lectures and practical courses partially in cooperation with the Neurological and Neurosurgical Department, Ophthalmology, Psychiatry and General Radiology. In addition, we train residents in neuroradiology and general radiology and radiological technicians.

Selected Publications

Engelhorn T, Eyupoglu IY, Schwarz MA, Karolczak M, Bruenner H, Struffert T, Kalender W, Doerfler A (2009) In vivo micro-CT imaging of rat brain glioma: a comparison with 3T MRI and histology. Neurosci Lett, 458: 28-31

Struffert T, Köhrmann M, Engelhorn T, Nowe T, Richter G, Schellinger PD, Schwab S, Doerfler A (2009) Penumbra Stroke System as an "add-on" for the treatment of large vessel occlusive disease following thrombolysis: first results. Eur Radiol, 19: 2286-93

Doelken MT, Mennecke A, Stadlbauer A, Kecskeméti L, Kasper BS, Struffert T, Doerfler A, Stefan H, Hammen T (2010) Multi-voxel magnetic resonance spectroscopy at 3 T in patients with idiopathic generalized epilepsy. Seizure, 19: 485-92

Engelhorn T, Haider S, Michelson G, Doerfler A (2010) A new semi-quantitative approach for analysing 3T diffusion tensor imaging of optic fibres and its clinical evaluation in glaucoma. Acad Radiol, 17: 1313-6

Goericke SL, Engelhorn T, Forsting M, Speck U, Maderwald S, Ladd ME, Doerfler A (2010) Intrathecal corticoids in permanent focal cerebral ischemia in rats. Part I: a new therapeutic approach in the acute phase. J Cereb Blood Flow Metab, 30: 801-7

Struffert T, Deuerling-Zheng Y, Kloska S, Engelhorn T, Strother CM, Kalender WA, Köhrmann M, Schwab S, Doerfler A (2010) Flat detector CT in the evaluation of brain parenchyma, intracranial vasculature, and cerebral blood volume: a pilot study in patients with acute symptoms of cerebral ischemia. AJNR Am J Neuroradiol, 31: 1462-9

Meetings and International Training Courses

07.02.2009: Workshop „Hands-on Stroke-MRT", Linz, Österreich

21.03.2009: Workshop „Neuroradiologie für die Praxis", Linz, Österreich

13.06.2009: Workshop „Hands-on Stroke-MRT", Erlangen

17.10.2009: Workshop „Hands-on Stroke-MRT", Erlangen

20.11.2009: Update neue bildgebende Verfahren. MEDICA, Düsseldorf

04.12.2009: Kursus „Neuroradiologie", Update Neurologie, Düsseldorf

27.03.2010: Workshop „Hands-on Stroke-MRT", Erlangen

17.04.2010: Workshop „Neuroradiologie für die Praxis", Linz, Österreich

26.06.2010: Workshop „Advanced Neuro-MRI", Erlangen

03.12.2010: Kursus „Neuroradiologie", Update Neurologie, Düsseldorf

Research Equipment

Siemens 1.5 Tesla Magnetom Sonata MRT

Siemens 3 Tesla Magnetom TimTrio MRT

Siemens Axiom Artis dBA; Biplanare Flachdetektor-Angiographieanlage mit integrierter CT-Option

Siemens Siemens Axiom Artis zeego; Robotergestützte Flachdetektor-Angiographieanlage mit integrierter CT-Option (OP-Standard)

Siemens Somatom Definition AS+; 128-Zeilen-CT

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Research Focus
- Clinical trials
- Radiation Biology
- Pysical Aspects of Radiation Oncology
- Radiation Immunobiology

Structure of the Department

The Department of Radiotherapy offers the entire spectrum of modern Radiotherapy at the highest level. Clinical, biological and physical aspects of radiation oncology are scientifically analyzed. A multi modal 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 multi modal 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 the hyperthermia unit. A total of 5 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 two scientific employees, two assistant study nurses as well as a secretary involved in documentation are responsible for this work. Radiotherapy treatments are carried at one of four linear accelerators and in the department of interventional radiation therapy. The latter is one of 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, three postdoctoral fellows, three technicians as well as three PhD students and several medical doctoral candidates. The "Medical Radiation Physics" group consist of 5 doctorate holding coworkers, 7 doctoral candidates and graduands and is headed by an assistant professor of physics. Three technicians are also part of the team. Physical benefits are provided in all areas of clinical radiotherapy and research focuses are set within this area.

Research

Clinical trials

1. Phase-III multicenter trial: Preoperative radiochemotherapy and adjuvant chemotherapy with 5-fluorouracil vs preoperative radiochemotherapy and adjuvant chemotherapy with 5-fluorouracil combined with oxaliplatin in patients with locally advanced UICC stage II and III rectal cancer. Project managers: R. Sauer; 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. Investigators: V. Strnad, Erlangen and 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 (PacCis trial). Investigators: R. Fietkau and H. Iro; funded by: Deutsche Krebshilfe.
4. Phase-III multicenter trial: Nutritional therapy of patients with head and neck tumors (Supportan trial). Project manager: R. Fietkau; funded by: Fresenius Kabi AG.
5. Phase-III trial: Assessing the influence of an adjuvant chemotherapy following a simultaneous radiochemotherapy in patients with inoperable lung tumors (GILT-CRT-1). Investigators: R. Huber, München, M. Flentje, Würzburg and R. Fietkau, Erlangen; funded by: Pierre Fabre Pharma GmbH.

The department further participates in the following externally led phase-III trials:

1. Phase-III multicenter trial: radiation dose intensity study in breast cancer of young women: Randomized phase-III trial of additional dose to the tumor bed. Project manager: H. Barteling, Amsterdam, Netherlands.
2. Phase-III trial: hyperfractionated accelerated radiotherapy (HART) with mitomycin C/5-fluorouracil versus Cisplatin / 5-fluorouracil in locally advanced head and neck tumors. Investigators: V. Budach, Berlin, J. A. Werner, Marburg.
3. 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

1. Individual sensitivity to radiation (PD Distel). 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 (Dr. Djuzenova) the usefulness of a bed-side test in determining the beta-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 (PD Distel). 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 University of Erlangen (Dr. Buettner) the role of CD4, CD8, B-cells, macrophages and the influence of regulatory T-cells was studied in patients with head and neck tumors, gastric cancer and carcinoma of the rectum.

Pysical Aspects of Radiation Oncology

1. Development and constitution of a tomotherapy treatment system (PenataRay), Patents: D, EU, US; partner: Forster Ingenieurgesellschaft, Ingolstadt.
2. Simulation, development and construction of a ring-shaped electron beam CT, (EBT, TOM-AGE), Patents: D, EU, US; partner: Fraunhofergesellschaft IIS, Fürth.
3. Development and prototyping of an optical patient-positioning-system (TOPOS), Patents: D, EU, US; partner: cybertechnologies GmbH, Ingolstadt.

4. Monte Carlo algorithm to plan treatments with carbon ions or protons with voxel based biological evaluation of the dose distribution. Development of an "optimizer" for the calculation of treatment parameters in the planning and realization of treatments.
5. Development of new algorithms to evaluate the dose distribution in patients. This contributes to an optimized treatment of the patients with X-rays. Partner: Philips AG.
6. Development of algorithms for the dosimetry with a flat-detector during the concurrent radiation treatment of patients (EPID).
7. Development of phantoms and auxiliary equipment for brachytherapy; partner: Nucleotron.
8. Measuring absolute temperature in hyperthermia using MR-spectroscopy; ZIM-sponsoring; partner: Dr. Sennewald GmbH, München.
9. Monte Carlo Algorithm addressing geometrical problems concerning structural radiation protection. Funded by: EU, SPIRAL2 FP7; partner: GSI, Darmstadt; GANIL, Caen.

Radiation Immunobiology

1. Determination of immune and tumor markers in sera of tumor patients (PD Gaipl). Funded by: BMBF. This project is part of the m4 leading-edge cluster personalized medicine.
2. Role of interaction of therapy induced dead tumor cells with dendritic cells for the induction of tumor immunity (PD Gaipl). Funded by: DFG, GK1660. This project is part of the DFG Graduate School 1660, entitled "key signals of adaptive immunity".
3. Induction of anti-tumor immunity by ionising radiation and the adjuvant AnnexinA5 (PD Gaipl). Funded by: DFG. Clinically relevant combination of ionising radiation alone and in combination with AnnexinA5 will be analyzed applying *in vitro* and *in vivo* mouse models in regard to the induction of long lasting anti-tumor immunity.
4. Cell death and immunogenicity of colorectal tumor cells after treatment with ionising radiation in combination with hyperthermia (PD Gaipl). Funded by: ELAN-FONDS of the Universitätsklinikum Erlangen.
5. Non-targeted effects of ionising irradiation (PD Gaipl). Funded by: European Union (FP6).
6. Analyses of surface changes of cells after low dose radiation that are relevant for phagocytosis within inflammatory reactions (PD Gaipl and Prof. Keilholz). Funded by: Doktor Robert-Pfleger foundation.
7. Manipulation of inflammatory changes by low dose radiotherapy (PD Gaipl and Prof. Keilholz). Funded by: Thomas-Wildey Institute e.V..

Teaching

Apart from the traditional radiotherapy teaching sessions embedded in the course covering the related fields of medical imaging, radiotherapy treatment and radiation protection, the department organizes an interdisciplinary lecture series in collaboration with the University Cancer Center (UCC). 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 Medical Council of Bavaria is held semi-annual. 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 (of all life science studies) takes place within the basic training "Infection Immunology" and the specialization module "Immunobiology". Lab rotations are offered for fast track students of the graduate school GK 1660.

Selected Publications

Distel LV, Fickenscher R, Dietel K, Hung A, Iro H, Zenk J, Nkenke E, Büttner M, Niedobitek G, Grabenbauer GG (2009) Tumor infiltrating lymphocytes in squamous cell carcinoma of the oro- and hypopharynx: prognostic impact may depend on type of treatment and stage of disease. Oral Oncol, 45: e167-74

Frey B, Schildkopf P, Rödel F, Weiss EM, Munoz LE, Herrmann M, Fietkau R, Gaipl US (2009) AnnexinA5 renders dead tumor cells immunogenic--implications for multimodal cancer therapies. J Immunotoxicol, 6: 209-16

Ott OJ, Lotter M, Fietkau R, Strnad V (2009) Accelerated partial-breast irradiation with interstitial implants. Analysis of factors affecting cosmetic outcome. Strahlenther Onkol, 185: 170-6

Wittlinger M, Rödel CM, Weiss C, Krause SF, Kühn R, Fietkau R, Sauer R, Ott OJ (2009) Quadrimodal treatment of high-risk T1 and T2 bladder cancer: transurethral tumor resection followed by concurrent radiochemotherapy and regional deep hyperthermia. Radiother Oncol, 93: 358-63

Karg J, Speer S, Schmidt M, Mueller R (2010) The Monte Carlo code MCPTV--Monte Carlo dose calculation in radiation therapy with carbon ions. Phys Med Biol, 55: 3917-36

International Cooperation

Dr. C.N. Sprung, Monash University, Clayton, Australia

Dr. Michael Lacniel, GANIL, Caen, France

Prof. Dr. Rosanna Nano, Dipartimento di Biologia Animale, Università di Pavia, Pavia, Italy

Meetings and International Training Courses

17.–19.09.2009: 13. Interdisziplinäres Symposium - Interdisziplinäre Radioonkologie 2009, Rothenburg o.d.T., Deutschland, DEGRO

27.–28.11.2009: Grundlagen der Brachytherapie - Interventionelle Radioonkologie, Erlangen, Deutschland, DEGRO

12.–13.03.2010: Radioonkologie bei Tumoren des Zentralen Nervensystems, Erlangen, Deutschland, DEGRO

16.–17.04.2010: Basics of Image Guided Brachytherapy, Erlangen, Deutschland, DEGRO

24.–25.09.2010: Simultane Radiochemotherapie, Erlangen, Deutschland, DEGRO

26.–27.11.2010: Grundlagen der Brachytherapie - Interventionelle Radioonkologie, Erlangen, Deutschland, DEGRO

Research Equipment

Beckman Coulter GmbH Flow Cytometer GALLIOS

General Electrics, Ahrensburg, Deutschland Industrieröntgenröhre

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Chair of Urology

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Research Focus
- Systemic tumor therapy, clinical trials
- Establishment of an annotated tumor tissue repository containing urologic tumors
- Tumor genetic research with focus on identification of biomarkers
- The role of hypoxia and hypoxia-associated signal transduction pathways in solid tumors
- MRT-guided needle biopsy for the diagnosis of prostate carcinoma

Structure of the Department

Universitätsklinikum Erlangen:
- Outpatients' Clinic and pediatric urology.
- Adult renal transplantation unit in cooperation with the Department of Medicine 4 (Prof. Eckardt)
- Pediatric renal transplantation unit in cooperation with the Department of Pediatrics (Prof. Rascher)
- Uro-oncological outpatients' unit for systemic drug therapy (AURONTE) in cooperation with the Department of Medicine 5 (Prof. Mackensen)

Waldkrankenhaus St. Marien gGmbH:
- Adult urology (inpatients' department), private insurance patients (outpatients' department)
- Trial documentation center

Research

Systemic tumor therapy, clinical trials
Project manager: PD Dr. med. P. J. Goebell
The medical care and treatment of patients with uro-oncologic diseases represent an integral part of the urologic specialty. Systemic therapy forms, besides the provision of surgical treatment is one of 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.
With this, it is 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 vs. sorafenib/sunitinib in metastatic renal cell cancer,
Avastin ML24519,
CHANGE study,
HAROW-Study,
Axitinib-Study,
Everolimus-Study,
Dasatinib CA180-227,
DIREG_R_04571 (MATuRITY),
QoLiTax.
Information about open or closed clinical trials can be found at the homepage of the urological trial registry (http://www.urologie.uk-erlangen.de/informationen_fuer_aerzte/studienzentrale/index_ger.html).

Establishment of an annotated tumor tissue repository containing urologic tumors
Project manager: Prof. Dr. med. 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 nontumor 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 a close cooperation with the local Institute of Pathology a repository of urologic tissue samples is established, in which tissue samples of all surgically treated malignant urologic tumors are introduced. This tissue repository is part of the University Cancer Center Biobank. For the establishment of the required 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 organisatory regulations of tissue repositories and Databases (patients informed consent, data security, standard operating procedures 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.

Tumor genetic research with focus on identification of biomarkers
Project manager: Dr. rer. nat. 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 (Fig.1) are a vital component of our research.
The complete spectrum of molecular cytogenetic techniques including fluorescence in situ DNA and RNA hybridization (Fig.2) 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 is a central part of the experimental methods.

The role of hypoxia and hypoxia-associated signal transduction pathways in solid tumors
Project manager: Prof. Dr. rer. nat. Helge Taubert
The lack of oxygen (hypoxia) is a situation seen in many solid tumors. Especially locally advanced malignancies rapidly outgrow the

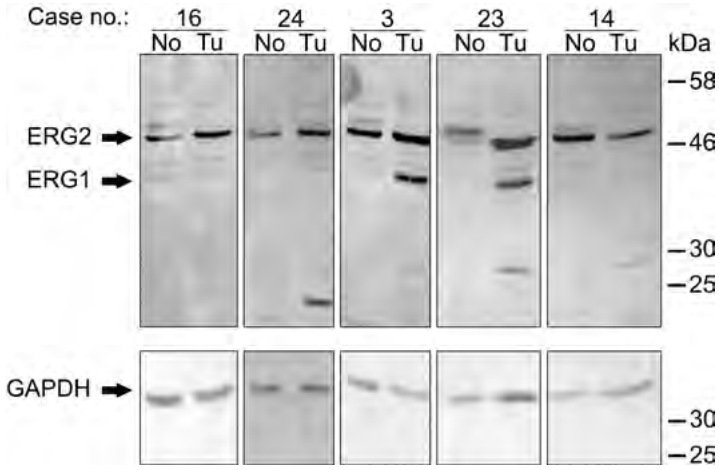

Fig. 1: Western blot analysis of protein expression in prostate carcinoma tissue samples

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.

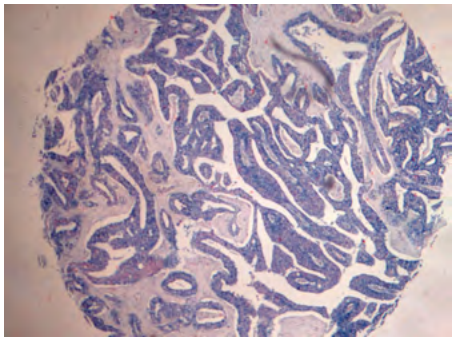

Fig. 2: Visualization of miRNA expression (blue staining) in prostate carcinoma tissue samples.

MRT-guided needle biopsy for the diagnosis of prostate carcinoma

Project manager: PD Dr. med. D. Engehausen

The magnetic resonance tomograpy (MRT)-guided biopsy procedure is a novel procedure for the generation of diagnostic evidence in the case of a suspected prostate carcinoma. This procedure unites the sophisticated MRT 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 60%. This procedure is available in only a few centers worldwide (at this time 4, including Erlangen), requiring the interdisciplinary cooperation between urologists and radiologists and it is constantly improved. Before conducting this type of examination, the modalities of payment should be clarified. The total cost of about 1350 € are at this time not approved by the health insurance GOÄ.

Teaching

Medical students are taught in the lecture series of emergency medicine and specialized urological lectures. Students also conduct a practical course in the urological clinic or one of the associated teaching hospitals. The clinic 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 urologic clinic uses patient simulators. These include models for practicing sterile placement of catheters or laparoscopic methods for minimally invasive surgery.

Selected Publications

Bache M, Kappler M, Wichmann H, Rot S, Hahnel A, Greither T, Said HM, Kotzsch M, Würl P, Taubert H, Vordermark D (2010) Elevated tumor and serum levels of the hypoxia-associated protein osteopontin are associated with prognosis for soft tissue sarcoma patients. BMC Cancer, 10: 132

Keck B, Stoehr R, Wach S, Rogler A, Hofstaedter F, Lehmann J, Montironi R, Sibonye M, Fritsche HM, Lopez-Beltran A, Epstein JI, Wullich B, Hartmann A (2010) The plasmacytoid carcinoma of the bladder-rare variant of aggressive urothelial carcinoma. Int J Cancer, 129: 346-54

Szczyrba J, Löprich E, Wach S, Jung V, Unteregger G, Barth S, Grobholz R, Wieland W, Stöhr R, Hartmann A, Wullich B, Grässer F (2010) The microRNA profile of prostate carcinoma obtained by deep sequencing. Mol Cancer Res, 8: 529-38

Taubert H, Würl P, Greither T, Kappler M, Bache M, Lautenschläger C, Füssel S, Meye A, Eckert AW, Holzhausen HJ, Magdolen V, Kotzsch M (2010) Co-detection of members of the urokinase plasminogen activator system in tumor tissue and serum correlates with a poor prognosis for soft-tissue sarcoma patients. Br J Cancer, 102: 731-7

Weikert E, Kraske S, Schott GE, Wullich B, Hirsch K (2010) Umbilical rotation: A new technique for the cutaneous fixation of continent catheterizable vesicostomies. J Pediatr Urol, epub ahead of print

Wach S, Nolte E, Szczyrba J, Stöhr R, Hartmann A, Orntoft T, Dyrskjøt L, Eltze E, Wieland W, Keck B, Ekici AB, Grässer F, Wullich B (2011) MiRNA profiles of prostate carcinoma detected by multi-platform miRNA screening. Int J Cancer, epub ahead of print, doi: 10.1002/ijc.26064

International Cooperation

Prof. Dr. med. Torben Ørntoft, Department of Molecular Medicine, Århus University Hospital, Århus, Denmark

OA Dr. Peter J. Goebell, Secretary General, International Bladder Cancer Network (IBCN), Barcelona, Spain

Prof. Colin Dinney, MD Anderson Comprehensive Cancer Center, SPORE Bladder Cancer (funded by the National Cancer Institute), Houston, TX, USA

Prof. Pierre Hainaut, IARC, International Consortium of Biological Resource Centers for Cancer, Lyon, France

Peter J. Geary, Marble Arch Working Group on Global Biorepositories, Montreal, Canada

Meetings and International Training Courses

24.04.2009: Astellas Hospitation, Urologie Waldkrankenhaus

06.05.2009: Neues aus der urologischen Onkologie, Waldkrankenhaus St. Marien Pater Natili-Hörsaal

17.06.2009: Interaktiver Workshop Nierenzellkarzinom, Nägelhof Erlangen

15.07.2009: Astellas-Seminar Streßinkontinenz des Mannes, Urologie WKH Erlangen

02.12.2009: Kinderurologische Gespräche, Erlangen, Urologie

10.02.2010: Aktuelle Onkologie Gemeinsame Veranstaltung des BBU und der Urologischen Klinik des UK Erlangen, Urologie WKH Erlangen

21.04.2010: Prostata-Karzinom Schmerztherapie / Psychosomatische Therapie, Erlangen, Urologie

16.–17.07.2010: 16. Bayerische Expertengespräche - Urologie, Nürnberg, Deutschland, Urologie

Institute of Clinical and Molecular Virology

Chair of Clinical Virology

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Head of Department
Prof. Dr. med. Bernhard Fleckenstein

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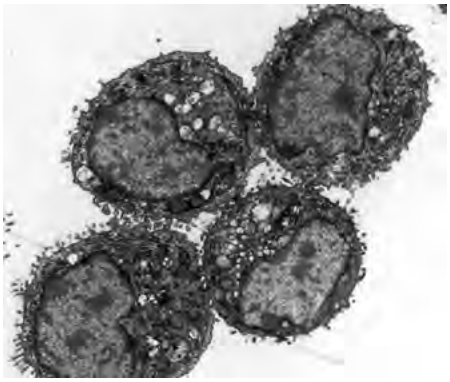
Research Focus
- Retroviruses
- Beta-Herpesviruses
- DNA-Tumor Viruses



Electron microscope image of HIV-exposed plasmacytoid dendritic cells (Barbara Schmidt, Institute of Virology, Erlangen, and Elke Bogner, Charité Berlin)

Structure of the Department

Including graduate students and student assistants, the Institute of Virology has about 130 staff members, the majority of whom are employed through third-party funding. 12 research groups investigate issues of infection biology, tumor virology, vector development, therapy research, immunology, signaling and epigenetics within the institute's research foci Retroviruses, Beta-Herpesviruses and DNA Tumor Viruses, thereby applying a broad range of virological, biochemical, molecular and cell biological as well as immunological methods. The majority of the staff members are students of biology, molecular medicine, biochemistry, and medicine, who are working on their doctoral or master thesis in one of the research groups under the supervision of full, associate, and assistant professors and junior scientists. The research groups are supported by 15 technical assistants.

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 HIV-1 and HBV. As a National Reference Center for Retroviruses (NRC), the institute provides HIV reference material, continuously expands the antiviral drug resistance testing for HIV by new substance classes and develops and optimizes diagnostic methods.

Research

Retroviruses

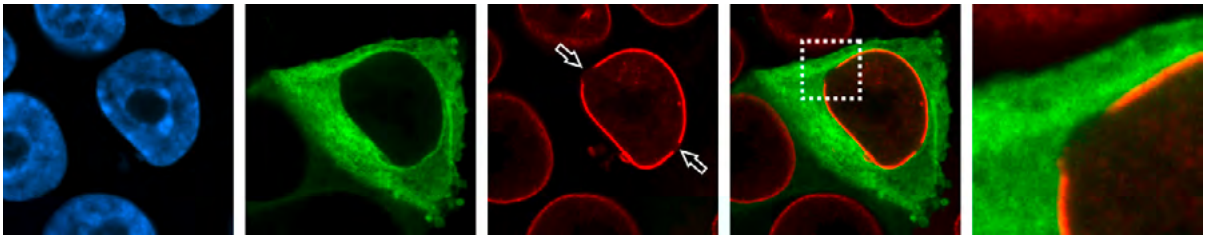
Several HIV research groups and one HTLV research group, which are closely connected to the NRC, are working at the institute. The group of Prof. Ulrich Schubert is studying the interaction of host and virus proteins on the molecular level in order to define interface regions of binding partners that 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 laboratory of Prof. Thomas Gramberg investigates mechanisms of innate and intrinsic immunity in retroviral infection. The innate immune defense of plasmacytoid dendritic cells in HIV-1 and HSV-1 infections is addressed by the group of Priv.-Doz. Barbara Schmidt. Dr. Dr. Heide Reil 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 group of Dr. Andrea Kreß/Prof. Bernhard Fleckenstein investigates molecular mechanisms which lead to the development of ATLL (adult T cell leukemia/lymphoma) caused by the retrovirus HTLV-1 (human T cell lymphotropic virus type 1). In particular, molecular functions of the viral Tax oncoprotein are analyzed.

Beta-Herpesviruses

The characterization of molecular mechanisms of human cytomegalovirus (HCMV) replication and the immune defense against HCMV is another key focus of the institute. The research group of Prof. Michael Mach defines in collaboration with Prof. Thomas Winkler, Chair of Genetics, School 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. The research group of Prof. Thomas Stamminger 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. Stephan Ensminger, Department of Cardiac Surgery, on a mouse xenotransplantation model on the mechanism of CMV induced transplant arteriosclerosis. The research group of Prof. Manfred Marschall investigates the role of protein kinases 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 his research aims to develop novel antiviral drugs on the basis of protein kinase inhibitors. In a translational project, the group of Prof. Armin Ensser develops chimeric immunoreceptors for anti-viral adoptive immunotherapy of CMV infection.

DNA Tumor Viruses

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 B cell lymphoproliferation. The growth promoting and immunoregulatory properties of different HHV-8 proteins are studied by the group of Priv.-Doz. Frank Neipel. They identified novel ligands for two viral glycoproteins. The binding of the viral glycoproteins to the new receptor induces signal transduction pathways known to be involved



Induction of depletions of the nuclear lamina by protein kinases which are activated during the infection with the human cytomegalovirus. (This research was originally published in the Journal of Biological Chemistry. Milbradt J, Webel R, Auerochs S, Sticht H, and Marschall M. Novel Mode of Phosphorylation-triggered Reorganization of the Nuclear Lamina during Nuclear Egress of Human Cytomegalovirus. The Journal of Biological Chemistry. 2010; 285:13979–13989. © the American Society for Biochemistry and Molecular Biology.)

in the tumorigenic process by vascularization. Thus, HHV-8 encounters and activates cellular genes contributing to oncogenesis at the earliest stages of infection. The group of Priv.-Doz. Brigitte Biesinger 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 group of Prof. Armin Ensser within the SFB796. Furthermore, they investigate the chromatin structure and replication of latent herpesvirus genomes in T and B cells. In 2009/2010, Prof. Ensser was a visiting professor in the laboratory of Prof. Jae U. Jung, University of Southern California, Los Angeles, where he started new 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. Prof. Walter Doerfler's laboratory characterizes different aspects of DNA-methylation in transgenic cells and in the human genome.

Teaching

In cooperation with the colleagues from the Instiute of Microbiology, the Institute of Virology offers curricular lectures and practical courses in infectiology and immunology. These general infectiology courses have been expanded to pharmaceutical and dental students, and students of Life Science Engineering and Medical Process Management. Furthermore, our institute is involved in the Molecular Medicine programs. The lectures impart basics of general virology. In the advanced seminar, the students are introduced to original scientific publications. The fundament of our viral education is a four-week F1 practical course, where groups of two to three medical students and students of the Bachelor's degree programs of Molecular Medicine or Biology work under the direct instruction of the team leaders on current research projects in the lab. In the Master's degree programs of Molecular Medicine and Cellular and Molecular Biology, our institute offers a four-week F2 practical course, where the students improve their knowledge of laboratory techniques and learn how to design scientific projects. In the six-week F3 practical course and the eight-week specialization module, respectively, the students work on their own project under the supervision of a group leader. For the students of Biology, the Institute of Virology provides a basic lecture of virology as well as the above-mentioned F-practical courses and special lectures. Moreover, the members of the institute are essentially involved in the weekly seminars, periodic workshops and biannual retreats of the graduate training program 1071 "Viruses of the Immune System".

Selected Publications

Wies E, Mori Y, Hahn A, Kremmer E, Sturzl M, Fleckenstein B, Neipel F (2008) The viral interferon-regulatory factor-3 is required for the survival of KSHV-infected primary effusion lymphoma cells. Blood, 111: 320-7

Mitzner D, Dudek SE, Studtrucker N, Anhlan D, Mazur I, Wissing J, Jänsch L, Wixler L, Bruns K, Sharma A, Wray V, Henklein P, Ludwig S, Schubert U (2009) Phosphorylation of the influenza A virus protein PB1-F2 by PKC is crucial for apoptosis promoting functions in monocytes. Cell Microbiol, 11: 1502-16

Naumann A, Hochstein N, Weber S, Fanning E, Doerfler W (2009) A distinct DNA-methylation boundary in the 5'-upstream sequence of the FMR1 promoter binds nuclear proteins and is lost in fragile X syndrome. Am J Hum Genet, 85: 606-16

Full F, Lehner M, Thonn V, Goetz G, Scholz B, Kaufmann KB, Mach M, Abken H, Holter W, Ensser A (2010) T cells engineered with a cytomegalovirus-specific chimeric immunoreceptor. J Virol, 84: 4083-8

de Jong SJ, Albrecht JC, Schmidt M, Müller-Fleckenstein I, Biesinger B (2010) Activation of noncanonical NF-kappaB signaling by the oncoprotein Tio. J Biol Chem, 285: 16495-503

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-{kappa}B signals. Blood, 117: 3609-12

International Cooperation

Dr. Aileen Rowan/Prof. Charles Bangham, Wright-Fleming Institute, Department of Immunology, Imperial College, London, UK

Prof. William Rawlinson/Dr. Gillian Scott, University of New South Wales, Sydney, Australia

Prof. Sunwen Chou, Oregon Health and Science University, Portland, OR, USA

Prof. Dana Wolf, Hadassah Hebrew-University Hospital, Jerusalem, Israel

Prof. Bimalendu Ray, University of Burdwan, Bardhaman, WB, India

Prof. Edward Gershburg, Southern Illinois University School of Medicine, Springfield, IL, USA

Prof. Jae Ung Jung, Department of Molecular Microbiology and Immunology, University of Southern California, Keck School of Medicine, Los Angeles, CA, USA

Meetings and International Training Courses

15.–17.10.2010: 3rd International GK Symposium Regulators of Adaptive Immunity of the Doctoral Research Training Programs GK 592, FOR832, GK1071, GK/SFB643 & GK1660, Erlangen, Germany

Research Equipment

ABI Prism 3100 Genetic Analyzer u. Datenbank

BD Biosciences Durchflusscytophometer LSR II

Leica konfokales Mikroskop TCS SP5

Institute of Clinical and Molecular Virology

Division of Experimental Therapy

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Head of Division
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Andrea Becher
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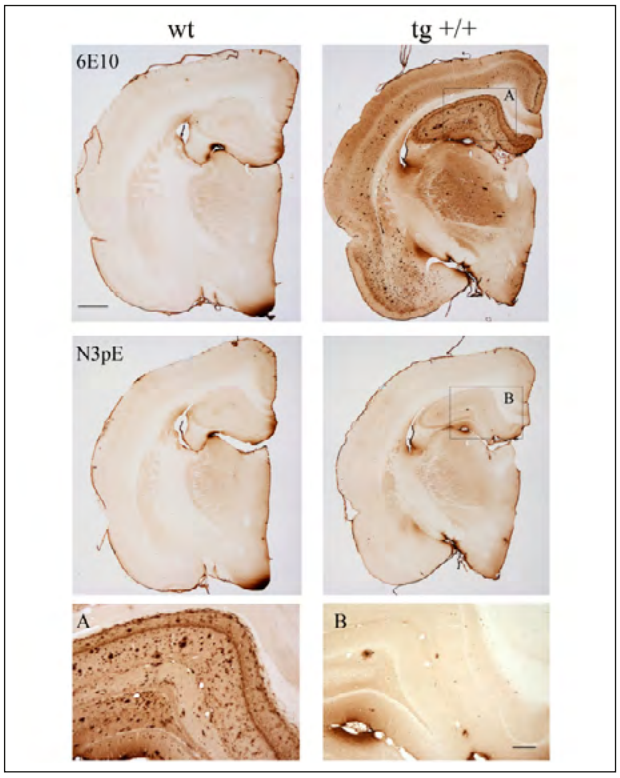
Research Focus

- Comprehenisve phenotyping and therapy in animal models of human neurodegenerative disorders



Immuno-histochemical staining of human Amyloid β and pyroglutamate dependent changes of Aβ in tissue of trangenic rat models for Alzheimer disease.

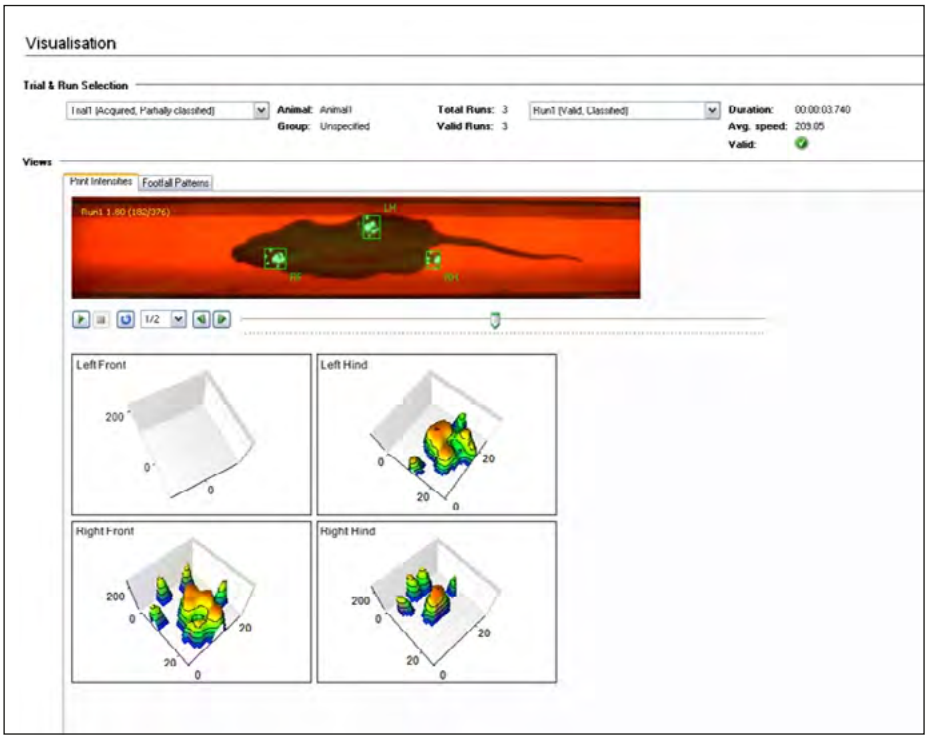
Structure of the Division

The Division of Experimental Therapy is located within the Franz-Penzoldt-Center, a state-of-the-art animal facility, including lab space and small animal imaging facilities. The Division of Experimental Therapy provides comprehensive approaches to characterize phenotypes and corresponding gene functions in transgenic and other animal models of human neurodegenerative disorders.

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.



Video based test of the behavior (catwalk) for the detection of locomotic deficiencies

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 Friedrich-Alexander-Universität Erlangen-Nürnberg and integrated in postgraduate research programs.

Selected Publications

Miller BR, Walker AG, Fowler SC, von Hörsten S, Riess O, Johnson MA, Rebec GV (2010) Dysregulation of coordinated neuronal firing patterns in striatum of freely behaving transgenic rats that model Huntington's disease. Neurobiol Dis, 37: 106-13

Nguyen HP, Björkqvist M, Bode FJ, Stephan M, von Hörsten S (2010) Serum levels of a subset of cytokines show high interindividual variability and are not altered in rats transgenic for Huntington´s disease. PLoS Curr, 2: RRN1190

Skripuletz T, Kruschinski C, Pabst R, von Hörsten S, Stephan M (2010) Postnatal experiences influence the behavior in adult male and female Fischer and Lewis rats. Int J Dev Neurosci, 28: 561-71

Urbach YK, Bode FJ, Nguyen HP, Riess O, von Hörsten S (2010) Neurobehavioral tests in rat models of degenerative brain diseases. Methods Mol Biol, 597: 333-56

International Cooperation

Prof. Asa Petersen, Translational Neuroendocrine Research Unit, University of Lund, Lund, Sweden

Prof. Hans-Peter Lipp, Institute of Anatomy, ETH Zurich, Zurich, Switzerland

Alexander P. Osmand, Ph.D., Research Center - Graduate School of Medicine, University of Tennessee, Knoxville, TE, USA

Research Equipment

TSE Systems GmbH PhenoMaster

New Behavior AG IntelliCage

Dental Department 1 – Operative Dentistry and Periodontology

Chair of Dental, Oral and Maxillofacial Medicine - especially Operative Dentistry, Periodontology and Pediatric Dentistry

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Prof. Dr. med. dent. Anselm Petschelt

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Research Focus

- Development of peptide-based bioadhesives
- Strategies avoiding chipping fractures on zirconia-based frameworks
- Prospective clinical study on glassionomer-cements using the A.R.T. – technique
- Wear analysis of prophylaxis tools on tooth and filling surfaces
- Novel polymer composites for the semipermanent dental application
- Studies on treatment of dentoalveolar traumata
- Antimicrobial dental products with silver technology
- Effects of aging on one-step self-etch adhesives

Structure of the Department

The Dental Clinic 1 – Operative Dentistry and Periodontology employs 56 staff members, thereof 6 professors and associate professors, 14 assistant professors, 21 dental nurses and 4 dental technicians. The Dental Clinic 1 further hosts a Research Laboratory with 11 Research Associates (4 by external funding).
The research is generally conducted by 3 clinically oriented and 1 dental materials, pre-clinically oriented work groups. Eight post-doctoral researchers, 55 dental post-graduate and graduate students and 5 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

Development of peptide-based bio-adhesives
Project manager: PD Dr. U. Lohbauer
The aim of this joint research project with the University of Jena and the IFAM in Bremen is focused on the development of novel bio-inspired nanohybrid adhesives for medical and dental applications based on decapeptide structures derived from the Mytilus edulis foot protein 1 (Mefp-1). Polymer spacers link the Mefp-1 decapeptides to functionalized hydroxyapatite nanoparticles, which in turn serve as centers of cohesion. Thus, chemical binding in addition to micromechanical anchorage should be responsible for stronger adhesion to dentine. Insensibility to wetness is one big advantage of this kind of adhesives for extended dental indications.
Central targets are the preparation and variation of peptide structures by solid phase peptide synthesis, the coupling of the peptides to polymer spacers and onto functionalized nanoparticles. Fundamental insight is expected by investigating the process of synthesis, the surface modifications of oxidic dental ceramics, developing the functionalization of nanoparticles and controlling adhesive mechanisms on collagen scaffolds. (funded by Deutsche Forschungsgemeinschaft (DFG): Lo 1493/2-2)

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))

Prospective clinical study on glassionomer-cements 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 co-operation with our partner university in Joinville / Brazil this innovative glass ionomer cement is to be 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 of 2009. Evaluations were undertaken after 6 months, 1 year and 2 years. The clinical data are verified by an *ex vivo* model analysis.

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 (APDs) 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 later plaque accumulation.

Novel polymer composites for the semipermanent dental application

Project manager: Dr. W. Dasch

Aim of this project is to prolong the lifetime of temporary polymer-based crown- and bridge materials to achieve a permanent, cost-effective and time saving fixed partial denture based on polymer composites instead of materials based on ceramic or metal-ceramic. The polymer based crown- and bridge materials developed by the University of Tübingen in cooperation with Kettenbach corp. are tested by the Dental Clinic 1/University of Erlangen. The suitability of the material intended for permanent dental application will be assessed by the determined material properties - e.g. abrasion behavior, impact strength, flexural strength and fatigue behavior. This cooperation project is sponsored by ZIM (Zentrale Innovationsprogramm Mittelstand) of the AiF- Association (Arbeitsgemeinschaft industrieller Forschungsvereinigungen "Otto von Guericke" e. V).

Studies on treatment of dentoalveolar traumata

Project manager: Dr. C. Berthold

Since 2002, in vitro and *in vivo* investigations focusing on diagnostics and therapy of dentoalveolar trauma have been performed. The research investigates the mechanical properties of dental trauma splints (Fig. 1). For evaluating

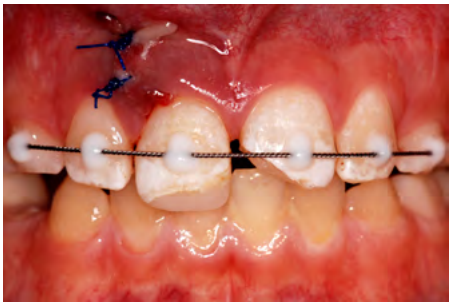

Fig. 1 Status after dental trauma. The crown fractures of the central incisors were temporarily covered using an adhesive technique. A flexible wire-composite splint was inserted for functional immobilization of the traumatically loosened lateral and central incisors. The gingival lesion was adapted with a suture

splint rigidity, a universal in vitro model was developed. Utilizing this model, various influencing factors as i.e. splint materials or splint extension were tested. (Postdoctoral Stipendia from University of Erlangen "Förderung der Chancengleichheit für Frauen in Forschung und Lehre")

Antimicrobial dental products with silver technology

Project manager: Prof. Dr. A. Petschelt

On dental restorative materials adhering bacterial biofilms can cause secondary caries and inflammation of oral mucosa. The objective of this cooperative project of the Dental Clinic 1 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 antimicrobial properties. The subproject at the Dental Clinic 1 focuses on the production, exploration of the impact and effectiveness of antimicrobial dental adhesives and composite resin based filling materials. It is funded by the Bayerisches Staatsministerium für Wirtschaft, Infrastruktur, Verkehr und Technologie, support program "Leitprojekte Medizintechnik"

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 was evaluated by tensile tests (bond strength) and optical evaluation (nanoleakage).

Teaching

The main lectures of the Dental Clinic 1 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. This of course, highly corresponding on own measured data and scientific outcome of the dental materials lab.

Next to the conventional lectures, the dental education is highly practically oriented. Therefore, the Dental Clinic 1 has established practical blockseminars in the graduate courses teaching endodontic treatment strategies (7. Semester) and indirect inlay manufacturing skills (10. Semester). Students as well as doctoral students are required to report in special seminars on recent scientific trends in restorative dentistry.

Selected Publications

Lohbauer U, Zinelis S, Rahiotis C, Petschelt A, Eliades G (2009) The effect of resin composite pre-heating on monomer conversion and polymerization shrinkage. Dent Mater, 25: 514-9

Lohbauer U, Amberger G, Quinn GD, Scherrer SS (2010) Fractographic analysis of a dental zirconia framework: a case study on design issues. J Mech Behav Biomed Mater, 3: 623-9

Lohbauer U, Pelka M, Belli R, Schmitt J, Mocker E, Jandt KD, Müller FA (2010) Degree of conversion of luting resins around ceramic inlays in natural deep cavities: a micro-Raman spectroscopy analysis. Oper Dent, 35: 579-86

Lohbauer U, Wagner A, Belli R, Stoetzel C, Hilpert A, Kurland HD, Grabow J, Müller FA (2010) Zirconia nanoparticles prepared by laser vaporization as fillers for dental adhesives. Acta Biomater, 6: 4539-46

Pelka MA, Altmaier K, Petschelt A, Lohbauer U (2010) The effect of air-polishing abrasives on wear of direct restoration materials and sealants. J Am Dent Assoc, 141: 63-70

Taschner M, Nato F, Mazzoni A, Frankenberger R, Krämer N, Di Lenarda R, Petschelt A, Breschi L (2010) Role of preliminary etching for one-step self-etch adhesives. Eur J Oral Sci, 118: 517-24

International Cooperation

Prof. Dr. F. A. Müller, University of Jena, Jena, Germany

Dr. K. Rischka, IFAM - Frauenhofer Institute, Bremen, Germany

Prof. G. Eliades, University of Athens (UOA), Athen, Greece

Dr. S. Scherrer, University of Geneva, Geneva, Switzerland

Prof. R. Braga, University of Sao Paulo (USP), Sao Paulo, Brazil

Prof. Baratieri, University of Santa Catarina, Florianopolis, Brazil

Prof. E. W. Schubert, University of Joinville (Univille), Joinville, Brazil

Prof. J. Powers, University of Texas, Houston, TX, USA

Dental Department 2 – Prosthetic Dentistry

Chair of Dental, Oral and Maxillofacial Medicine – especially Prosthetic Dentistry

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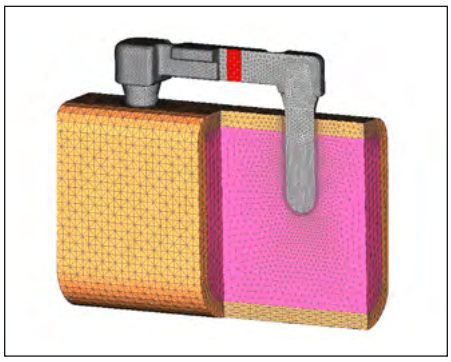
Research Focus

- Biomechanical factors of implant retained superstructures
- CAD/CAM research laboratories
- Assessment of psychogenic influence on dental health and alternative treatment methods
- Evaluation of full-field three-dimensional optical inspection systems in dentistry

Structure of the Department

The Dental Department 2 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 21 full-time faculties 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 is 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 takes the aging population and the resulting demographic changes into consideration and investigates the relation between oral and general health.



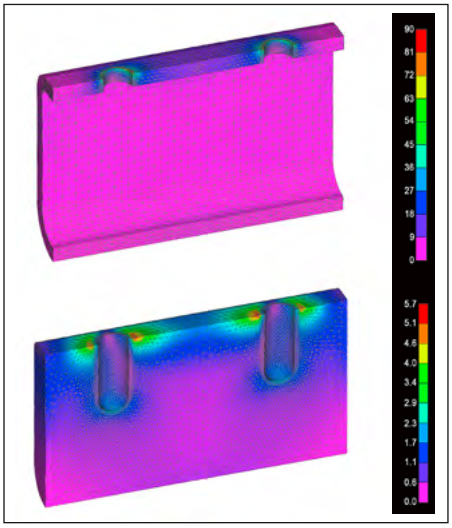
Three-dimensional finite element model representing an implant-supported overdenture bar which can be used for analyzing the stress situation at the implant bone interface under specific loading conditions

Research

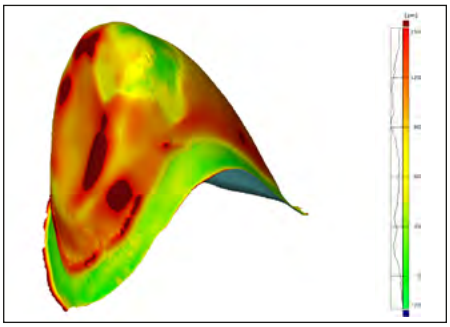
Biomechanical factors of implant retained superstructures
Project manager: M. Karl
Biomechanical factors greatly affect the long term prognosis of implant supported restorations. Possible effects of non-passively fitting superstructures on restorations and peri-implant bone are poorly understood. During the report period, the structural integrity of ceramic-veneered implant restorations has been analyzed showing substantial predamage as a result of static loading caused by superstructure fixation. Strain gauge measurements on CAD/CAM fabricated fixed dental prostheses revealed that computer aided manufacturing may lead to significant improvements in the accuracy of fit as compared to conventionally fabricated restorations. The obtained values are now being used for finite element analyses on the effect of different dimensional error types on strain development. A randomized clinical trial has been set up to study the effects of static implant loading on bone adaptation.

CAD/CAM research laboratories
Project managers: S. Holst, R.E. Matta, 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.

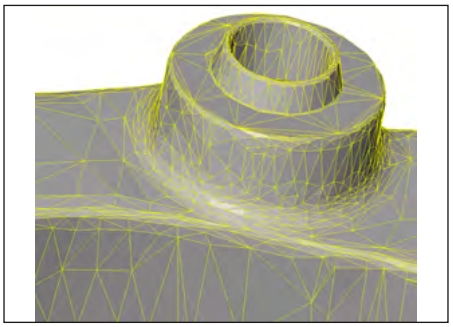
Assessment of psychogenic influence on dental health and alternative treatment methods
Project manager: S. Eitner
Patients requests for so called "alternative treatment methods" are ever increasing. However, there is very little sound research available at the moment. No statistical data can be found on the effectiveness of such methods. The area of research is divided in two main focal points. One evaluates psychogenic influence, one treatment planning and outcome of dental disease patterns with a psychogenic background. Amongst other factors is a subject's



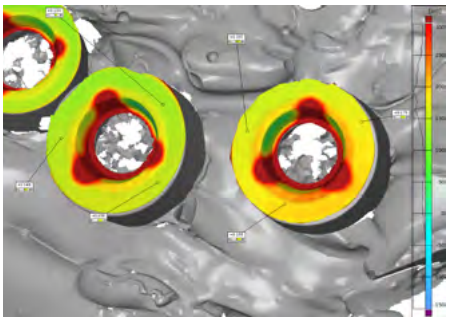
Loading situation of cortical and trabecular bone occurring as a consequence of superstructure fixation



Display and measurement of cement space thickness between abutment tooth and crown restoration



Digitized CAD/CAM implant superstructure prepared for further assessment



Display of gap between implant and restoration

appraisal of his own body, or the etiologic correlation of gag reflexes during dental treatment. Another focal point regards the therapeutic intervention via acupuncture and hypnosis in dental treatment and the influence of external stress factors on the anxiety and depressive behaviour, as well as sociological factors of dental patients.

Evaluation of full-field three-dimensional optical inspection systems in dentistry
Project managers: M. Goellner, S. Holst
The main focus of this research area is the development and application of optical non-contact measurement techniques for quantification of biomechanical influences on oral tissues for *in vivo* investigations. Using photogrammetric measurement systems, different experimental *in vitro* set-ups were investigated and validated. Based on findings the optical system was adapted for application in human subjects and initial clinical pilot studies were arranged. Long-term objectives are the implementation of the optical technique for clinical queries and to provide a validated alternative to existing measurement techniques in biomechanical research. First statements could be taken concerning dimensional stability and quantification of deformation of dental materials during force application.
In interdisciplinary clinical investigations the quantitative measurements of tooth movements following various load application protocols were performed. It was not only shown that the technology allows for capturing three-dimensional displacements in the low micrometer range in a reproducible manner, but compared well to other measurement systems.

Teaching

The main focus of traditional prosthodontic education will shift from a technically oriented towards an interdisciplinary treatment approach in the future. Prophylaxis and biology will be in the focus as well as minimally invasive treatment concepts. Clinically relevant topics will be introduced into the preclinical curriculum focusing on biologic interactions and material properties. While theoretical knowledge remains integral part of dental education, manual manufacture of dental restoration will be taught exemplarily.
A unique opportunity for all dental students at the Dental School of the Friedrich-Alexander-Universität Erlangen-Nürnberg is the opportunity to participate in a 3-year extra-curricular implant program. The "iLect" program is funded by third parties and provides – in cooperation with the Department for Oral and Maxillofacial Surgery – for participating students a structured and in-depth training, focusing on dental implants from basic material and biologic knowledge to advanced treatment concepts and protocols.

Selected Publications

Eitner S, Stingl K, Schlegel AK, Wichmann M, Nickenig A (2009) Biopsychosocial correlations in patients with chronic oro-facial pain. Part II. Experiences of pain and dramatic events before the 16th year of life. J Oral Rehabil, 36: 408-14

Karl M, Kelly JR (2009) Influence of loading frequency on implant failure under cyclic fatigue conditions. Dent Mater, 25: 1426-32

Schmitt J, Holst S, Wichmann M, Reich S, Gollner M, Hamel J (2009) Zirconia Posterior Fixed Partial Dentures: A Prospective Clinical 3-year Follow-up. Int J Prosthodont, 22: 597-603

Göllner M, Holst A, Berthold C, Schmitt J, Wichmann M, Holst S (2010) Noncontact intraoral measurement of force-related tooth mobility. Clin Oral Investig, 14: 551-7

Nickenig HJ, Wichmann M, Hamel J, Schlegel KA, Eitner S (2010) Evaluation of the difference in accuracy between implant placement by virtual planning data and surgical guide templates versus the conventional free-hand method - a combined in vivo - in vitro technique using cone-beam CT (Part II). J Craniomaxillofac Surg, 38: 488-93

Winter W, Mohrle S, Holst S, Karl M (2010) Bone loading caused by different types of misfits of implant-supported fixed dental prostheses: a three-dimensional finite element analysis based on experimental results. Int J Oral Maxillofac Implants, 25: 947-52

International Cooperation

Blatz, MB, University of Pennsylvania, Philadelphia, PA, USA

Weber, HP, Harvard University, Boston, MA, USA

Taylor, TD; Kelley JR, University of Connecticut, Farmington, CT, USA

Dental Department 3 – Orthodontics and Orofacial Orthopedics

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Research Focus

- Investigation of the reproducibility of skeletal maxillary landmarks in CT scans
- 3D-CT Evaluation of the asymmetry index by Katsumata/Maeda
- The applicability of the Frankfurt horizontal as reference plane in CT scans
- 3D CT based ratings of unilateral impacted canines
- CT- assisted determination of mesio-distal width of maxillary impacted canines
- Impression trays for cleft-lip and palate newborns: sterilized, individual KS- impression trays
- Erlangen 3D- model analysis for cleft-lip and palate newborn- long term documentation
- Face Scan - Stereophotogrammetry
- Pilot study about accuracy and dimensional stability
- Three dimensional efficiency evaluation of aligner treatment
- Material scientific investigations

Structure of the Department

The Chair of Dental Department 3 is integrated in the Department of Dentistry with regular rotation of the head of department every second year.
Altogether, 25 employees are working in the Dental Department 3. The research is carried out by ten scientists and 19 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. Referring to this, there are internal and external university cooperation's.
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 "Dental Department 3 - Orthodintics and Orofacial Orthopedics" is authoritatively involved in the Interdisciplinary Center of Cleft Lip and Palate of the Friedrich-Alexander-Universität Erlangen-Nürnberg. In this interdisciplinary center, therapy concepts are continuously updated and initiated by the team.

Research

Investigation of the reproducibility of skeletal maxillary landmarks in CT scans
The skeletal landmarks anterior and posterior nasal spine are showing a higher morphological variability.
Aim of the study was to verify the reproducibility of these and other cephalometric maxillary landmarkds in CT scans in the x-y-z- axis (transverse, sagittal and vertical). For this study the CT- examination software Voxim® was applied.

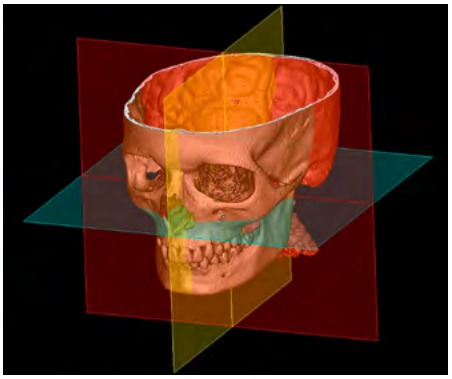
3D-CT Evaluation of the asymmetry index by Katsumata/Maeda
So far, skeletal and facial asymmetries were difficult to locate in the orthodontic diagnosis by using cephalograms (lateral and frontal)because of structural superimpositions.
With CT-scans and the use of the CT-software Voxim® the significance of the asymmetry index by Katsumata et al. and Maeda et al. 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 should be evaluated.

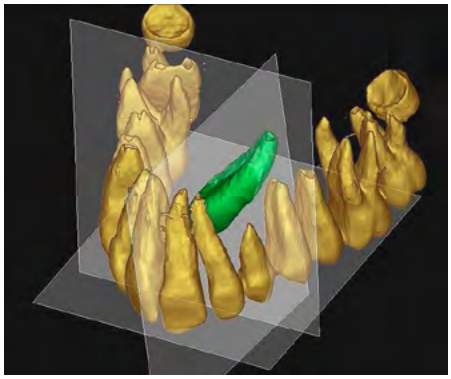
3D CT based ratings of unilateral impacted canines
In context of a current project a reference system for the tree-dimensional evaluation of CT scans was developed to facilitate the exact metric analysis of the displacement of permanent upper canines in this system. The tooth length and axis within this reference system should be described and compared for displaced and non-displaced canine axis. The analysis was performed on present CT data of patients with unilateral displaced upper canines.

CT- assisted determination of mesio-distal width of maxillary impacted canines
3D CT-images from patients with impacted maxillary canines were taken to obtain the largest mesio-distal diameter by use of the mesial and distal contact point. All existing maxillary canines were included in this study. In addition to that the mesio-distal tooth width was determined via calliper on a plaster model after the orthodontic treatment was completed.

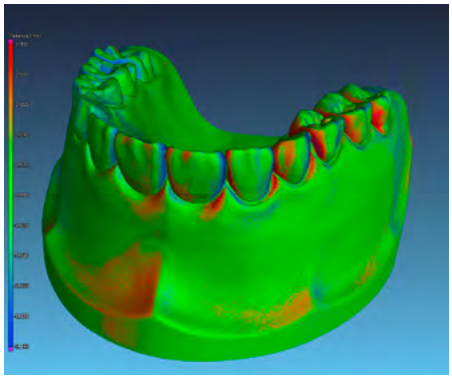
Impression trays for cleft-lip and palate newborns: sterilized, individual KS- impression trays
The maxillary impression of a newborn with cleft-lip and palate requires the use of individual impression trays. So far, these were fabricated with polymethylmethacrylate (e.g. Orthocryl®). The increasing incidences of infectional diseases explain the need for sterilization to protect the patient. The fabricated polymethylmethacrylate impression trays deformed and changed consistency after sterilization and had to be renewed at regular intervals.
The 10 sizes of individual KS- impression trays® made of chrome-cobalt-molybdenum-alloy for newborn with unilateral, bilateral or median cleft- lip and palate conform to the hygienic standards and can be sterilized. The durability in comparison to the acrylic trays is improved and allows a routinely and easy use for maxillary impressions of cleft-lip and palate newborns.



Definition of a three-dimensional reference system based on CT data sets with regard to 3D-cephalometry



3D-aspect of a palatinally impacted green colour-coded canine on the left hand side



With high resolution micro-CT-research scanner "Mikrofocus 3D-CT" digitalized impressions of a reference model in order to generate virtual models of the jaws

Erlangen 3D- model analysis for cleft-lip and palate newborn- long term documentation

During treatment of CLP patients it is the goal, because of long term and interdisciplinary treatment, to establish a consistent and well-arranged documentation. The treatment with presurgical orthopedic appliances in Erlangen takes place in 4 week intervals until surgical palate closure. During this time plaster models are made at four defined dates within the first year and later on every year.

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 (Fa.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, Firma 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.

Pilot study about accuracy and dimensional stability

The study was performed in cooperation with the Fraunhofer Entwicklungszentrum Röntgentechnik EZRT in Fürth and financed by the reasearch fund of DGKFO.

With computertomography scans orthodontic impressions can be saved and worked with as virtual data. Aim of the study was to evaluate the influencing parameters of different impression materials (different alginates and polyether) and impression trays with industrial CT-measurements according to accuracy and dimensional stability of the tested materials.

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 (Firma 3D shape, GmbH).

Material scientific investigations

In order to minimize bracket failure rates during orthodontic treatment, in this study the bond strength of orthodontic brackets on enamel (n= 500 extracted teeth) was investigated using different bonding materials. The influence of different polymerization devices (LED light-emitting diode, QTH quartz-tungsten-halogen) and polymerization times was tested.

Teaching

E-learning platform: Seminar on orthodontic technique.

Development and integration of an e-learning platform, supported by the virtuelle Hochschule Bayern (vhb), for the support of teaching students of dentistry.

The e-learning platform will be used in combination with the technical orthodontic course to repeat and explain theoretical knowledge from the course. It also simplifies the process for the students to make orthodontic appliances with the support of film material.

E-learning platform: Interactive virtual orthodontic case studies.

Development and integration of an e-learning platform, supported by the virtuelle Hochschule Bayern (vhb), for the support of teaching students of dentistry.

With interactive virtual orthodontic case studies the students of dentistry or for example postgraduate orthodontic students get an insight in orthodontic analysis, diagnosis and treatment planning and the resulting therapeutic consequences. Important aspects of orthodontic diagnostics can be applied in several case studies. Through independent and interactive step by step evaluation of patient cases the student will be prepared intensively for exams and can improve the knowledge of solving orthodontic cases.

Selected Publications

Boldt F, Weinzierl C, Hertrich K, Hirschfelder U (2009) Comparison of the spatial landmark scatter of various 3D digitalization methods. J Orofac Orthop, 70: 247-63

Holst AI, Hirschfelder U, Holst S (2009) Diagnostic Potential of 3D-Data-Based Reconstruction Software: An Analysis of The Rare Disease Pattern of Cherubism. Cleft Palate Craniofac J, 46: 215-9

Holst AI, Holst S, Nkenke E, Fenner M, Hirschfelder U (2009) Vertical and sagittal growth in patients with unilateral and bilateral cleft lip and palate-a retrospective cephalometric evaluation. Cleft Palate Craniofac J, 46: 512-20

Holst AI, Karl M, Karolczak M, Goellner M, Holst S (2010) Quantitative assessment of orthodontic mini-implant displacement: The effect of initial force application. Quintessence Int, 41: 59-66

Meetings and International Training Courses

01.01.2009–31.12.2010: Curriculare Weiterbildung zum Fachzahnarzt für Kieferorthopädie - 10 Veranstaltungen á 2 Tage im Jahr, Erlangen

15.–16.05.2009: Kinderzahnheilkunde : Überwachung der Gebissentwicklung, Erlangen, Akademie Praxis und Wissenschaft der DGZMK

19.–21.11.2009: Alles über Extraktionen - Prof. Dr. A. Hasund, Erlangen

18.–20.11.2010: Offener Biss und offene Konfiguration - Prof. Dr. A. Hasund, Erlangen

Collaborative Research Center (SFB) 423: Kidney injury: Pathogenesis and Regenerative Mechanisms

Speaker
Prof. Dr. med. Kai-Uwe Eckardt

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Aims and Structure

Acute and chronic kidney diseases play an increasing medical and health economic role in all parts of the world. In Germany approximately 85.000 patients require chronic renal replacement therapy in the form of dialysis or kidney transplantation. In addition, approximately 10 million people in Germany suffer from less severe chronic kidney disease. In view of the relevance of kidney disease and the insufficient knowledge about the pathophysiologic basis, the Collaborative Research Center (SFB 423) was founded in 1999 under the leadership of Prof. R. B. Sterzel. In 2004, his successor Prof. Dr. K.-U. Eckardt became coordinator of the center grant. Scientists from nine clinics and institutes have collaborated in this research center at the Friedrich-Alexander-Universität Erlangen-Nürnberg. The aim was to identify mechanisms of tissue injury and regeneration of renal tissue with the long term goal to develop novel diagnostic and therapeutic strategies. The SFB 423 is the first and single collaborative research center founded by the German Research Foundation (DFG) and one of the few research consortia in Europe, focusing on kidney disease. Funding period: 1999 – 2010 (12 years).

Research

Section A: Pathophysiology of renal cells and initial mechanisms of renal injury
Section A encompassed 8 projects that focus on the pathophysiology and mechanisms of initial injury of glomerular and tubular cells. The first project (A1) analyzed mechanisms of the initiation of lupus nephritis, in particular the role of anti-DNA autoantibodies and how they bind in the glomerulum and induce subsequent inflammation and damage. The second project (A2) dealt with cell matrix interactions in the mesangium and in the renal tubular interstitium focusing on the special role of alpha8 integrin. Project A12 focused on the regulation of the epithelial sodium channel (ENaC) in distal tubular cells and addressed mechanisms which are potentially relevant for the pathogenesis of secondary hypertension in patients with kidney disease.
Two projects (A14, A16) dealt with the regulation and pathophysiological relevance of hypoxia inducible gene expression mediated by HIF transcription factors. Project A14 focused on the expression, regulation and functional relevance of HIF prolylhydroxylases, enzymes that are of the critical importance for oxygen-dependent destabilization of HIF transcription factors. While one of the long term aims of this project is to validate the HIF pathway as a potential novel target for nephroprotection, project A16 dealt with the adverse consequences of HIF overexpression in renal cancer. Two genes that have been identified as being constitutively upregulated due to VHL loss of function in clear cell renal carcinoma and which may play important roles in cancer progression, are characterized in detail. Project A15 analyzed the functional relevance of the antiapoptotic protein Survivin in the kidney. A marked accumulation of this protein in the brush border of proximal tubular epithelial cells has first been described during the preceding funding period.
Project A17 dealt with the role of p38MAPK during the development of rapid progressive glomerulonephritis and thereby attempted to identify a novel, drugable therapeutic target for this serious disease, which can so far only be treated with unspecific immunosuppression. Another project within this area (A18) dealt with the analysis of syndromal diseases characterized by congenital or infantile nephrosis. Using complex genetic approaches, this project identified critical, pathogenetically relevant molecules that may also play an important role in noninheritable nephrotic diseases.

Section B: Mechanisms of progressive renal disease
Section B focused on complex mechanisms that influence the progression of renal disease. These studies also aim to identify novel targets for intervention. Project B5 used experiments in transgenic animals and studies in humans to assess endothelial dysfunction in the renal circulation and to determine the role of oxidative stress for the progression of diabetic nephropathy. Project B6 dealt with the functional relevance of Thrombospondin 1 and 2 in the regulation of chronic kidney disease and during this funding period focused on the impact of these molecules on chronic allograft nephropathy. Two additional projects in this project area studied different modulators of inflammatory processes. Project B12 dealt with the functional relevance of renal afferent neurons for mechanisms of inflammation and sclerosis within the kidney. This project combined complex neurophysiological investigations with the application of pharmacological modulators of neurotransmitter release and function. Project B13 dealt with effects of intrauterine growth restriction and perinatal programming and reprogramming on the susceptibility towards renal injury during subsequent development.

The two Sections A and B were complemented by a third area, which included an administrative project and two core units that focused on methodological aspects. The goal of these core units was to rationalize and structure the cooperation between different projects in two important areas. Prof. Dr. K. Amann led a core unit for quantitative structural analysis of kidney injury and Prof. Dr. T. Winkler coordinated the development of genetically modified mice.

Collaborative Research Center (SFB) 473: Switch Processes of Transcription

Speaker
Prof. Dr. rer. nat. Wolfgang Hillen
deceased on October 17th, 2010

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Aims and Structure

Transcription factors are the central regulators of gene expression and play essential roles in the biology of all organisms including humans and, thus, are also relevant for human disease. Transcription factors represent the main topic of the SFB 473 "Mechanisms of Transcriptional Regulation", which was funded between 1997 and 2009 and represents a scientific conglomerate of 13 groups from the Faculty of Natural Science and the Medical Faculty.
In the SFB 473, structural, biochemical and theoretical approaches are used to characterize regulatory proteins in transcription, as well as their effectors, mechanisms of regulation and their integration into signaling chains. The regulatory proteins of interest are derived from bacteria, plants and mammals, and are either transcription factors or sensors of proteins processing information to be passed on to transcription factors in response to the physiological state of the cell, the presence or absence of hormones or nutrients outside the cell or communication with other cells.
Funding period: 1997 – 2009

Research

The interdisciplinary SFB integrates a wide range of biological and medical problems in various organisms. The study of different organisms has proven to be very fruitful, because the regulatory mechanisms themselves are quite similar, while their cell specificity mainly results from their participation in individual communication patterns operating in the respective organisms. The individual projects profit from the exchange of mechanistic principles and the large variety of methods in integrating similar regulatory mechanisms into their particular cellular activities. This has led to many new insights for each project. The SFB is subdivided into three research topics.

Section B: Modulation and interaction of transcriptional regulators
This section combines research strategies dealing with the molecular analysis of transcriptional switch proteins. The switches can either be triggered by covalent modification or changes of localization of viral transcription factors, or an allosterical conformational change in case of the Tet repressor. The combination of bacterial and human regulators is reasonable because Tet repressor is widely used to regulate genes in nearly all organisms. Tetracycline dependent gene regulation is one of the most intensely studied and best understood transcriptional regulatory systems. Therefore, it has paradigmatic character for transcriptional switches. In addition, the results may also contribute to the understanding of more fundamental properties of proteins in general, like the plasticity of effector binding sites, the dynamics and conformational changes of allosterical proteins and protein-protein recognition. We address this problem in a collaborative effort, combining applied and theoretical chemistry with molecular genetics.

Section C: Signaling pathways to transcriptional regulatory proteins
The transcription factors studied in these projects have their coupling to signaling pathways in common, so that their switching reaction is dependent on a number of signaling proteins. Molecular genetic and theoretical aspects of signaling are cooperatively studied to elucidate catabolite repression in Gram-positive bacteria, nitrogen metabolism in Corynebacteria and the role of beta-catenin in tumorigenesis, lending substantial medical importance to this transcriptional switch. These projects have in common that more or less complicated signaling pathways, related to the physiological state of the cell or the cell cycle, transfer their signals to transcription factors. The molecular details of these events are the subject of this research area.

Section D: Transcription factors in differentiation
The projects grouped in this section have the goal to molecularly understand transcription factors involved in cell differentiation. The projects deal with differentiation in mammalian systems and study the MLL/ENL oncoprotein in hematopoiesis and leukemia, the GCM protein in embryonic development and human disease and the Sox-8 transcription factor in mesodermal differentiation. Additional emphasis is placed on changes of DNA topology as a means of transcription factor function and transcriptional control, and on snoRNA-dependent alternative splicing as a further regulatory mechanism of gene expression with important implications for human disease.

Teaching

All groups of the SFB participate in curricular teaching activities. Over the years they have provided an attractive environment for Diploma, Master, MD and PhD theses and continue to do so. Joint teaching efforts include a weekly seminar series, a guest scientist program and biannual international symposia with leading scientists in transcriptional research.

Collaborative Research Center (SFB) 539: Glaucomas including Pseudoexfoliation Syndrome

Speaker
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Aims and Structure

Glaucomas are chronic neurodegenerative diseases which, if untreated, lead to blindness by a progressive irreversible loss of retinal ganglion cells and optic nerve axons. The Research Center, which has been funded by the German Research Foundation (DFG) from August 1997 until June 2009, integrated clinical and basic scientists of one clinical department (Department of Ophthalmology) and five clinical-theoretical institutions (Anatomical Institute II, Institute of Biochemistry, Institute of Human Genetics, Institute of Experimental and Clinical Pharmacology and Toxicology, Institute of Medical Informatics, Biometry and Epidemiology) of the Medical Faculty, the Institute of Animal Physiology of the Faculty of Natural Science, and the Chair of Computer Science 5 of the Technical Faculty. The interdisciplinary networking between the Faculties of Medicine, Natural Science and Technics represented a particular strength of this Research Center. The focus of the SFB 539 was on the methodological improvement of early diagnosis and follow-up monitoring of chronic glaucomas as well as on the analysis of etiologic and pathogenetic factors contributing to the multifactorial causes and structural damage in order to identify targets for novel therapeutic approaches. These thematic contents lead to the division into three sections, which dealt with the structural and functional glaucomatous damage of the sensory retina and optic nerve head (section A), the multifactorial pathogenetic factors contributing to glaucoma development, particularly regarding the ocular outflow pathways and ocular microcirculation (section B), and the analysis of genetic factors for glaucoma as well as the medical-bioinformatic integration, processing and analysis of clinical data (section C). An integral part of the Research Center were the clinical data collected from more than 1500 patients since 1991, which were adjusted and coordinated into a unique glaucoma registry by creation of networked and integrated IT systems in order to improve both health care and research activities.
Funding period: 1997 – 2009.

Research

During the funding period, the Research Center has gained fundamental insights into glaucomas and produced new developments of seminal importance. Novel diagnostic tools for the detection of early structural changes and functional deficits were developed and evaluated. The most specific and sensitive imaging methods and physiological tests have been implemented in clinical practice or have even been developed into commercially available instruments (e.g. flicker test Erlangen). The combination of telemedicine and methods of automated pattern recognition have enabled the systematic screening of a large number of individuals for a population-based early glaucoma detection. Basic research projects have analyzed the molecular pathomechanisms of intraocular pressure rise, vascular dysfunction, and retinal ganglion cell death. The identification of novel glaucoma genes by means of genetic linkage and genome-wide association studies allowed new insights into the etiology and pathogenesis of glaucomas. Together, the studies identified various disease-related target molecules providing the basis for further translational research projects, preclinical and clinical trials, and novel therapeutic approaches.

With the help of the SFB 539, glaucoma-related research has developed into a core area of university research of international reputation and worldwide networking. In their concluding report, the reviewers assessed the research activities of the Center, which significantly advanced the body of knowledge on the multifactorial glaucomas and the management of patients, as very successful and internationally well received. The Research Center was attested a remarkable combination of clinical and basic science integrating biochemical analyses, genetic principles, morphological characterization, and clinical diagnostics in an exemplary manner.

Teaching

The study groups of the SFB 539 were involved in the training of doctoral students in medicine, molecular medicine, natural science and technical science. Supervision of doctoral theses was in part integrated into the graduate school "Advanced Optical Technologies". In addition, the principal investigators participated in lectures for students of different fields of study (medicine, biology, engineering), in the research-oriented study course of molecular medicine, and in the mentoring program ARIADNEmed for young female scientists. 73 completed doctoral theses and ten postdoctoral lecture qualifications confirm the successful promotion of young academics.

Collaborative Research Center (SFB) 643: Strategies of Cellular Immune Intervention

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Aims and Structure

The SFB 643 "Strategies of cellular immune intervention" exists since July 2004 and is currently in its second 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. The research program is conceptually structured in three closely interconnected project areas: A) basic immunology B) immune intervention in animal models and C) therapeutic applications.
Funding period: since 2004.

Research

Several representative projects will be described briefly: The project of Prof. 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 Dr. U. Schleicher and Prof. 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. D. Dudziak will translate the strategy concept of *in vivo* "antigen targeting" of Dendritic Cells (DC) into the human system. Thereby, the work will focus on the production of antigen-conjugated antibodies to analyze T cell responses in tissue culture. These data will be important for an eventual implementation into the clinic.

Prof. F. Nimmerjahn will focus 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 from Prof. Herrmann focuses on the immune modulation by apoptotic cells, necrotic cells and annexins. 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. T. Winkler and Prof. M. Mach is concentrating on the adoptive transfer of memory B cells as a new cell based therapy for infection with Cytomegalovirus after transplantation. 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.

The project of Prof. 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 in trans 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. 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 Sklerosis and in skin- and heart-transplant studies in murine models. This represents the basis for further preclinical and clinical developments.

The project of Dr. Siebler and Prof. 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, Dr. N. Schaft and Prof. G. Schuler is the development of new and innovative immunotherapies based on DCs 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 using DCs which have been electroporated with defined RNAs encoding the tumor associated antigens MAGE-3, MelanA and Survivin has been initiated. In addition new and advanced antigen loading strategies have been developed using RNA electroporation.

The ability to adoptively transfer T cells to treat cancer is in the focus of the project of Prof. 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.

The project of Prof. G. Fey and Prof. W. Hillen deals 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 will be generated.

Collaborative Research Center (SFB) 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 bases 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 initiated by the Faculty of Science has an interfacultary structure. Groups of the Medical Faculty 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.

To reach the long-term goal, the SFB incorporates closely cooperating scientists with complementary expertise, as well as a core unit to study structure-function relationships. Presently, the SFB harbors 17 different projects that can be divided into three sub-areas:
A) Structural basis of molecular interactions,
B) Reprogramming of cellular processes and
C) Replication structures and transport processes.

Research

Sub-area 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 project area A. Linear sequence motifs mediating protein-protein interactions are widely used by pathogenic organisms to reprogram cellular processes. The elucidation of the structural requirments for the promicuity is the focus of several projects of this sub-area.

Sub-area B: Reprogramming of cellular processes
The focus of project area 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.

Sub-area C: Replication structures and transport processes
The focus of project area 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 Sub-area.

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. The Z project is divided into four interconnected modules: protein crystallography, bioinformatics, protein interaction networks and live cell imaging.

Program of Emphasis (SPP) 1468 "Osteoimmunologie - IMMUNOBONE – A Program to Unravel the Mutual Interactions between the Immune System and Bone"

Speaker

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Aims and Structure

The interdisciplinary project IMMUNOBONE is a program to unravel the mutual interaction 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 € 7.3 million. The consortium includes 27 subprojects and aims to strengthen the new research field of Osteoimmunology through the collaboration of scientists from the fields immunology, bone and cartilage biology, rheumatology, orthopaedic surgery, hematology and molecular genetic. The different research groups are located in 23 different German research facilities.

Micro-CT imaging of tibia for determining the structure of trabecular bone

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 10 years ago by the discovery of a protein termed Receptor Activator of NF-kappa 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 incompletely 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 the immune system so 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.

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 January 26, 2010 as one of five winners in the Leading Edge Cluster Competition sponsored by the German Federal Ministry of Education and Research (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.

The Medical Valley EMN is one of the world’s most scientifically active, financially stable medical engineering clusters. Its leading position national is due to the close links between science, industry, hospitals, and nursing facilities, as well as their innovation strength. The cluster includes more than 500 companies with over 45,000 employees working exclusively or partially in medical engineering join the cluster. More than 60 academic chairs and professorships at the university and universities of applied science that focus on medical engineering and more than 20 non–university research facilities closely linked to medical engineering participate in the cluster. More than 500,000 people treated annually on an inpatient basis benefit from the high-quality care environment of the cluster.

MEDICAL VALLEY
Europäische Metropolregion Nürnberg

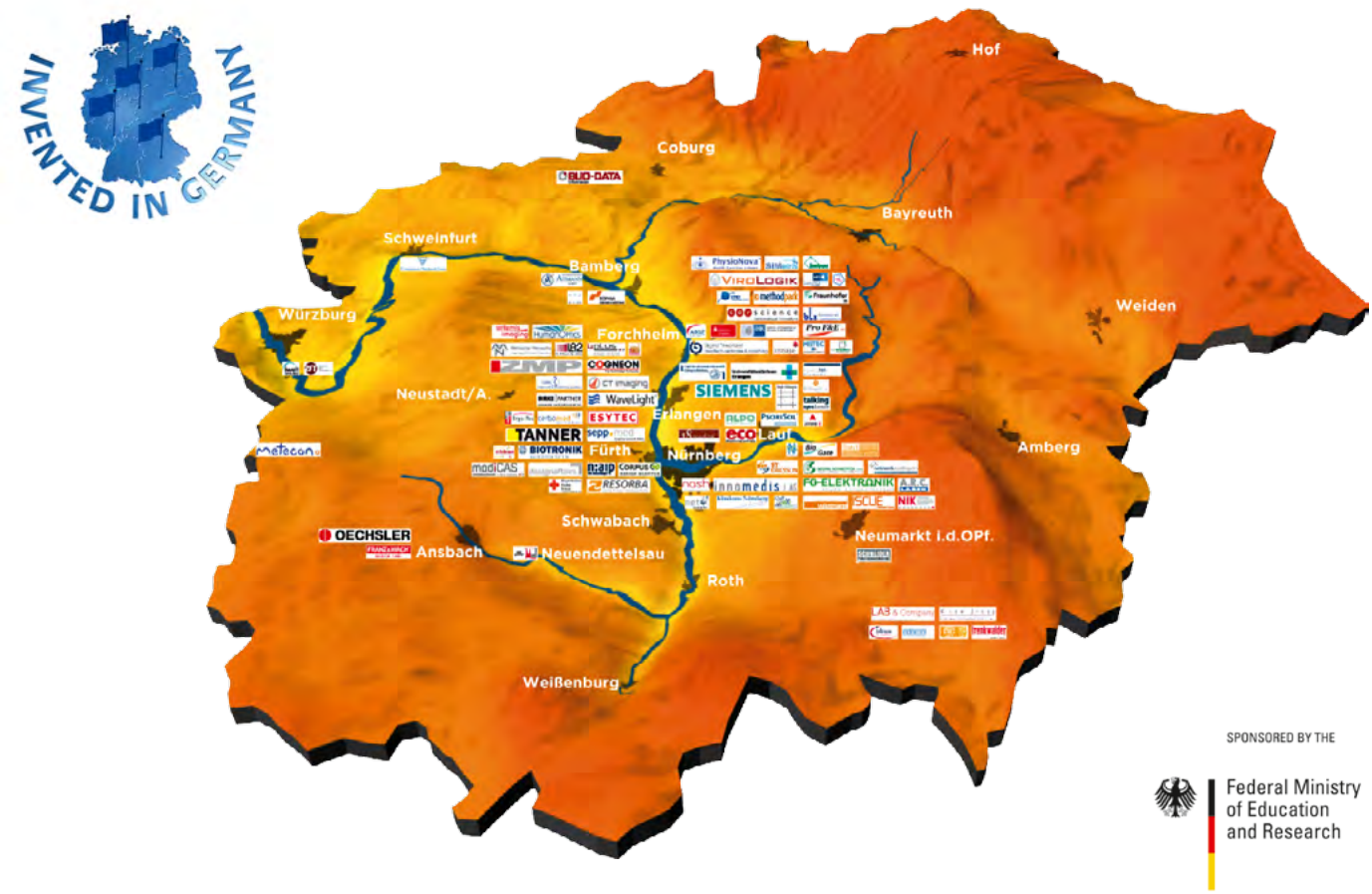
Research

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 (BD)
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 the following projects, many of which were performed in cooperation with the Women’s Clinic, the Radiological Institute, the ENT Clinic and Medical Clinic 1:
BD-01: Development of a dedicated CT scanner for the female breast (breast CT)
BD-02: CT angiography for early detection of coronary heart disease
BD-03: High-performance X-ray tube system for breast CT
BD-04: Integrated breast care: early detection and breast diagnosis
BD-05: 3D-catheter localization for ablation of the heart using bi-plane fluoroscopy
BD-06: Local tumor treatment using magnetic nanoparticles
BD-07: Open, quiet MR tomography system using new coils and gradient technology
BD-08: Automated, image-supported, magnet-controlled capsule endoscopy
BD-09: Development of a procedure for the production of superconductive contacts for new types of superconductors in MR scanners
BD-10: Improving the absolute precision of medical positioning devices through the use of optical measurement systems
BD-12: Human-machine interface and intelligent control concept for magnet-controlled capsule endoscopy

Intelligent sensors (IS)
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 chronic obstructive pulmonary disease (COPD), heart insufficiency, and chronic kidney failure. The following projects, some with the participation of Medical Clinics 2 and 4, are associated with this core research area:
IS-01: SmartSensors-C: Development of a standardized communication platform suitable for mass marketing
IS-02: SmartSensors-D: Seamless internal and external localization with UMTS, WLAN, aGPS, Galileo
IS-03: SmartSensors-A: Integration of close body sensors into textiles
IS-04: Remote care for patients with chronic obstructive pulmonary disease (COPD) and at-home ventilation
IS-05: SmartSensors-B: Development of a microwave-based sensor for non-invasive acquisition of blood gas values
IS-06: Support for dialysis patient autonomy through telematics methods
IS-07: Barrier-free health assistance
IS-08: Home monitoring of patients with cardiac insufficiency to avoid decompensation and reduce hospitalization rates
IS-09: Early detection of falling risk
IS-10: SmartSensors-E: Infrastructure, data maintenance, and integrated demonstrator

Treatment systems (T)
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 Chair of Medical Informatics Technology, the Chair for Technical Thermodynamics, Medical Clinic 1 and the Chair of Anatomy I. The projects are designed to increase personalization and safety in drug the-



rapy, make treatment with anti-infective drugs more efficient and economical, and to develop innovative procedures for early diagnosis and safe treatment. The treatment systems core research area is divided into the following projects:

T-01: Personalized, effect-controlled drug application

T-03: Chemoinformatics-based optimization of drug therapy safety and pharmacotherapy individualized for the patient

T-04: Development of a transcutaneous vagus nerve stimulator for treating medically refractory epilepsy

T-06: Revision and individualized implants in orthopedics – cost-lowering solutions for infections and osteoporosis - Acronym: „Osteofit 2030“

T-07: Production of ceramic-metallic implants for dental surgery using powder injection molding (“complete implants”)

T-08: Clinical on-site and online anesthesia gas analysis and monitoring

T-09: Development of an *in vivo* sensor for detecting infections with Helicobacter pylori

T-10: Development of a “magnetic hand” for minimally-invasive surgical interventions using endoscopy and laparoscopy

Ophthalmology (A)

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. Together with the Ophthalmic Clinic, 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. The following projects are part of the Ophthalmology core research area:

A-01: Integrated femtosecond laser technology for therapeutic application in corneal surgery

A-02: E.ATLAS – Platform-independent, barrier-free publication of medical images and creation of suspected diagnosis

A-03: Formulation of technological principles for the subsequent development and production of optimized phakic intraocular lenses

A-04: Low-cost fundus camera system for the Third World

A-05: Laser therapy for treating age-related macular degeneration (AMD)

A-06: Semi-synthetic corneal substrate for reconstruction and regeneration of the eye surface

Horizontal innovations for product and process optimization (H)

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. The horizontal innovations core research area includes the following projects:

H-01: ProHTA – Prospective Health Technology Assessment Medical Valley EMN

H-02: Real-time ERP system for medical care centers and medical practices (mVZs)

H-04: Data quality and integration capabilities of medical products

H-05: Certified training program: “Certified Professional for Medical Software” (CPMS)

Bavarian Research Cooperation for Adult Neuronal Stem Cells (ForNeuroCell II)

Speaker
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Co-Speaker
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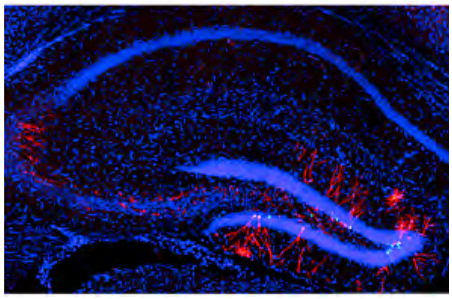
Aims and structure

The research network ForNeuroCell focuses on adult 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, Munich, Regensburg, Würzburg and the Helmholtz Center Munich. 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 stem cell based regenerative approaches for the clinic.

Research

The projects from Erlangen are headed by Prof. Dr. M. Wegner (Chair of Biochemistry and Pathobiochemistry, Emil-Fischer-Zentrum), Prof. Dr. I. Blümcke (Chair of Neuropathology, Department Kopfkliniken) and PD Dr. J. Klucken/ Prof. Dr. J. Winkler (Division of Molecular Neurology, Department Kopfkliniken). The project of Prof. 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. 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 to show 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. Klucken and Prof. Dr. 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 toward 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 Munich and at the Helmholtz-Zentrum in Munich and imaging projects at the University of Regensburg and the Technical University of Munich 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.



Newly generated hippocampal neurons

Teaching

The administrative core of ForNeuroCell, headed by Dr. R. Lederer together with Mrs. 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 two doctoral seminars with the topics „Biostatistic" and „Grant Writing for Scientists" were organized. In April 2011, an outstanding symposium was held at the Carl-Friedrich-von-Siemens-Foundation (Munich) with international speakers from the USA, Canada, Japan, Israel, Switzerland, and Italy.

German Chronic Kidney Disease (GCKD- Study): National Cohort Study on Chronical 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 the progression to end stage renal disease with requirement of dialysis and from a disproportionate risk of cardiovascular diseases including myocardial infarction and stroke. However, the course of progression of kidney disease 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 Friedrich-Alexander-Universität (FAU) Erlangen-Nürnberg is coordinating a large prospective observational cohort study in Germany including the cooperation with the Universities of Aachen, Berlin, Freiburg, Hannover, Heidelberg, Innsbruck, Jena, Munich, Regensburg and Wuerzburg.
The study aims to gain 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 Federal Ministry of Education and Research.

Research

Up to 5000 patients with impaired kidney function 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 to establish valid associations between biomarkers affecting the disease progression and to open 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 the onset of dialysis.
GCKD enrols patients with moderate kidney impairment under the care of a specialized nephrologist in Germany.

Regional Teams

BMBF Core Program "Molecular Diagnostics"

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www.polyprobe-bmbf.de/Seiten/Default.aspx

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 are expected to significantly foster the development and validation of novel markers. The Federal Ministry for Education and Research (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 € 2 Mio. Within the frame of this project, different institutes and clinics of the clinical centers in Erlangen and Frankfurt 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 (PD Dr. R.S. Croner, Universitätsklinikum Erlangen) and predict angiogenesis-related survival (Prof. Dr. M. Stürzl, Universitätsklinikum Erlangen), as well as responses to chemotherapy (PD Dr. W. Brückl, Universitätsklinikum Erlangen) and radiochemotherapy (Prof. Dr. C. Rödel, PD Dr. F. Rödel, Clinical Center Frankfurt).

(2) The industrial partner of the consortium has established a technology for the isolation of RNA from formalin-fixed, paraffin-embedded tissues, which are acquired from routine pathological procedures. In this process, the RNA is isolated by silicate-coated magnetic beads, which bind nucleic acids with high affinity. Based on this simple but efficient purification principle, the extraction of RNA from tissue sections could be fully automated. The process has been optimized so that from only one thin section of a tumor tissue RNA amounts, which are sufficiently high enough for quantitative RT-PCR analyses of the expression of more than 1000 different genes (Polyprobe-test), can be extracted. Siemens Healthcare Diagnostic Products GmbH has established this key technology at the Universitätsklinikum 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. Up to the end of the funding period (36 months) 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. The study is carried out in a non-randomized prospective manner. It is aimed to recruit 650 patients. Accordingly, this study will be one of the largest studies on this subject worldwide.

BMBF-Network on Clinics and Pathophysiology of Osteophytes and Ankylosis (ANCYLOSS)

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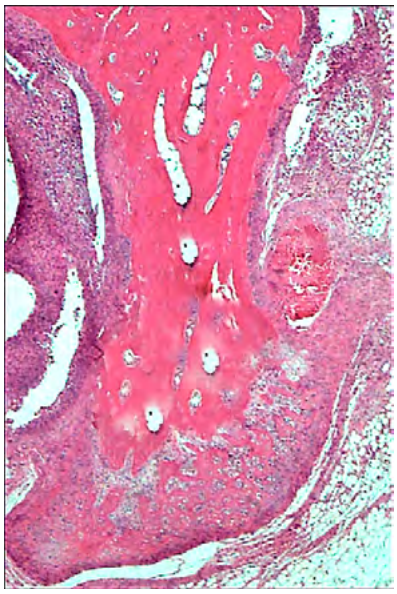

Osteophytes surrounding calcaneus bone HE staining

Aims and Structure

The aim of the interdisciplinary project ANCYLOSS is to define the pathophysiology and clinical impact of osteophyte formation. This program is intended to develop new concepts for a better understanding of joint diseases such as osteoarthritis (OA), psoriasis arthritis (PsA) and ankylosing spondylitis (AS). The project is funded by the Deutsches Zentrum fuer Luft- und Raumfahrt (DLR) with a total amount of 1.5 Mio. Euro for the first period of three years. The interdisciplinary consortium includes six different work packages, which investigate different aspects of osteophyte formation in degenerative and inflammatory rheumatic disease. 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. Different research fields and research techniques such as bone biology, lipid metabolism, molecular biology, genetics, animal models, imaging and clinical research are interlinked within ANCYLOSS and represent an example of interdisciplinary research.

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. The formation of bone spurs is characteristic for degenerative (osteoarthritis) and inflammatory rheumatic diseases (psoriatic arthritis and spondylarthritis). Research within ANCYLOSS will thus help to obtain a better understanding of rheumatic diseases including their management. ANCYLOSS is the first consortium, which pursues research on osteophytes by using an interdisciplinary approach.

Current scientific concepts in rheumatic diseases focus on disease aspects such as inflammation, pain and functional impairment, but do not sufficiently target the structural aspects of rheumatic diseases. In the last years we could gain first mechanical insights in the molecular regulation of osteophyte formation. ANCYLOSS aims to close this gap in knowledge and concentrates on defining the mechanism of osteophyte formation. Research will focus on key pathways of bone formation such as Wnt and hedgehog proteins and their interaction with the adipose tissue, which represents a major link between obesity and joint diseases such as osteoarthritis.

Knowledge is gained from investigating experimental arthritis models, including the genetic modulation of molecules that are relevant for bone and fat metabolism, as well as human data on the genetics, biomarkers and imaging of osteophyte formation. Thereby, the consortium contributes to strengthen research in the field of musculoskeletal disease. The interdisciplinary structure of the project also facilitates to translate 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.

Teaching

The interdisciplinary research is particularly suitable for the education of young scientists. The research group leaders supervise basic as well as clinically oriented thesis works 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.

Euratom, 7. Research Framework Program, "BREAST CT"

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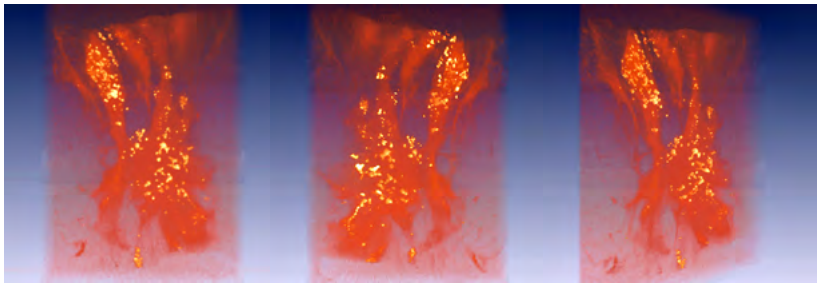

Fig. 1: High-resolution µCT acquisition of a surgical breast specimen. The three different perspectives indicate the 3D nature of the data.

Aims and Structure

Between the 1st of January 2008 and the 30th of June 2010 the European Union (EU) funded within their 7th frame work program the project on feasibility and optimization of a dedicated breast CT with an amount of 2.05 Mio €. In addition to the team at the Institute of Medical Physics (IMP) under the leadership of Prof. Willi Kalender, two leading European medical imaging institutions, the Universities of Leuven (KUL) in Belgium and Rotterdam (EMC) in the Netherlands and one industrial partner, CT Imaging GmbH (CTI) from Erlangen, were involved in this trend-setting work.
The following tasks were executed in nine work packages structured by topic:
(The institution in charge of the topic is put in parentheses)

WP1 Management (IMP)
WP2 Simulation studies for breast CT image quality optimization (IMP)
WP3 Dose determination by simulation and measurements (IMP)
WP4 Image quality measurements for breast CT (IMP)
WP5 Evaluation and optimization of tomosynthesis (KUL)
WP6 Quality assurance for 2D and 3D breast imaging (KUL)
WP7 Assessment of alternative diagnostic approaches (EMC)
WP8 Software design and development (CTI)
WP9 Patient setup and mechanical design (CTI)

Research

Based on the tasks defined above a feasibility study on breast CT was performed. Step by step the concept was ameliorated and refined taking into account the outcome of simulation and the results achieved by experimental studies. An experimental µCT setup was used to simulate a dedicated breast CT with high spatial resolution. Acquisitions of a breast surgical specimen at about 80 µm isotropic spatial resolution indicate the 3-dimensional structure of calcifications at an image quality level not achievable in clinical imaging so far (Figure 1).

The principal requirements for an ideal breast imaging setup for early detection of breast cancer are

- the full three-dimensional acquisition of the whole breast,
- a good soft tissue display and differentiation,
- dynamic imaging capabilities at a temporal resolution of less than a minute,
- high isotropic resolution of about 100 µm,
- low dose of X-rays and contrast medium to the patient
- as well as patient comfort without breast compression.

Using the latest technologies in the field of x-ray sources and detectors and an innovative mechanical design (see Figure 2), the breast CT concept developed during the project fulfills the given requirements and is therefore a promising candidate to improve breast imaging.

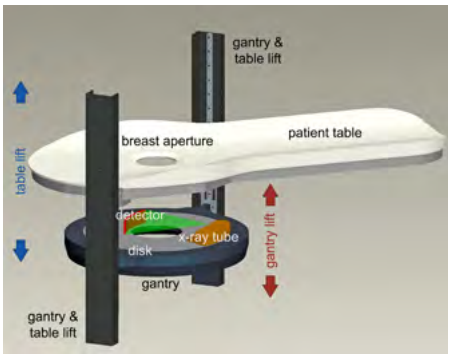

Fig. 2: Mechanical design of the dedicated breast CT scanner for the examination of the female breast with x-ray computed tomography.

Eating Disorders Diagnostic and Treatment Network (EDNET)

EDNET Forschungsverbund zu Essstörungen

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The online program for the treatment of Binge Eating disorder (INTERBED) is based on the Salut BED program developed by the University Hospital of Geneva (HUG) and NetUnion (copyright 2006 - 2011 NetUnion)

Aims and Structure

The German Federal Ministry of Education and Research (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 and which are located all over Germany (Aachen, Bochum, Dresden, Essen, Erlangen, Heidelberg, Marburg, Munich, Tuebingen). The central coordination is located in Erlangen. 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 is coordinated in Erlangen.

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 with 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, 1100 patients will be included into the five psychotherapy trials. The long-term success will be investigated in follow-up assessments conducted 6 months to 1.5 years after the end of the acute treatment phase. Overall 35 clinical centers are recruiting and treating patients within the five psychotherapy trials. The treatment phase has already been completed in three of the five studies. 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 4000 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 what conditions the treatment works. 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 (www.awmf.org)
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.

National Genome Research Network – Mental Retardation Network (MRNET)

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(Left) locations of universities and research centers involved, (right) poster of the MRNET-conference

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 has become 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. Identification and characterization of molecular networks involved will eventually allow identification of targets for therapeutic intervention.

MRNET is funded within the medical genome research program (National Genome Research Network, NGFNplus) of the Federal Ministry of Education and Research with a total budget of 5.8 Mio. €. The central coordination located in Erlangen brings together the efforts of ten centers distributed throughout Germany and the Netherlands. The network combines the clinical and scientific expertise of researchers and physicians from seven German universities (Bonn, Dresden, Erlangen, Essen, Heidelberg, Münster, Tübingen), one institute of the Max-Planck-Society, a research center of the Helmholtz-Society and the University of Nijmegen (The Netherlands). An internet webpage (www.german-mrnet.de) informs physicians as well as patients and families about aims and achievements of the project.

Research

The project combines a medical genetic approach with systematic genome analysis. To date, more than 2,500 patients were recruited and receive a standardized clinical evaluation based on international phenotype ontology. Patients' data are collected in a specially developed, pseudonymized database. Sporadic as well as familial cases are included. Sporadic ones are subsequently investigated for submicroscopic aberrations (copy number variants, CNVs) using state of the art micro-array based technologies. In about 15% of cases de novo CNVs were detected. Patients with similar phenotype to those with the CNV were screened for point mutations in candidate genes from the respective genomic region. This way we could describe several new genes for ID. In familial cases we studied cosegregation of genetic markers with the disease (linkage analysis) to likewise reveal candidate genes from linked regions. To date, we performed linkage analysis in over 100 families with consanguineous parents and identified numerous linked regions as well as several new genes for ID. Furthermore, some patients are subject to comprehensive sequencing of large genomic intervals with next-generation sequencing technologies. First successes have been achieved by sequencing the X chromosomes in families with X-linked inherited ID. As a result, it is already possible to determine the genetic cause in about 60% of patients with sex-linked inherited ID. Furthermore, candidate genes and their respective signaling pathways are currently functionally investigated using cellular assays and animal models. Three genes have already been characterized in more detail in the nervous system of the fruit fly drosophila melanogaster.
Finally, the results of the study substantially extend the diagnostic options in affected patients and contribute to a better understanding of disease etiology as well as the underlying pathomechanism. An important finding is that the majority of mutations found in the patients represent new (de novo) mutations. Therefore, the corresponding parents have only a slightly increased recurrence risk. These and other results were discussed at the international MRNET conference "Genetics and Neurobiology of Mental Retardation" in Erlangen. This conference was also the Biennial Conference of the German National Academy of Sciences Leopoldina, demonstrating the high attractiveness and visibility of the field and the research association. About 200 participants from 11 European countries, the USA and Canada attended the conference held from September 29th to October 1st 2010.

National Reference Center for Retroviruses

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Aims and Structure

In 1996, the Robert Koch Institute (RKI) established the National Reference Center (NRC) for Retroviruses at the Institute of Clinical and Molecular Virology, Friedrich-Alexander-Universität Erlangen-Nürnberg, headed by Prof. Bernhard Fleckenstein. The NRC was reevaluated and confirmed in 2010. The main tasks of the NRC focus on the development, standardization and improvement of diagnostic and therapeutic procedures, distribution of reference materials, epidemiological surveillance, support in cases of unclear laboratory results and other diagnostic issues as well as advisory service and public relations.

Diagnostic

The NRC for Retroviruses offers a broad diagnostic service consisting of 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 NRC has extensive experience in testing antiretroviral drug susceptibility. Within the last years, the repertoire of methods was expanded to test the two most recently approved antiretroviral drug classes, the CCR5-coreceptor antagonists and the integrase inhibitors. The continuous development and permanent improvement of diagnostic procedures are additional topics of the NRC to meet the requirements within clarification of infections and confirmation of diagnoses. In 2010, major activities of the NRC targeted on establishment of reliable protocols for real-time PCR analyses of XMRV, a retrovirus whose pathogenic relevance for humans is still unknown, as well as of HIV-2.

Additionally, the NRC was engaged in the initiation and realization of quality control trials again. This included for the first time a QC trial for HTLV serology with participants from Germany, Austria, and Switzerland. Furthermore, a standardized operational protocol for analyzing a quality control trial based on sequence analyses in order to detect HIV-1 drug susceptibilities was developed in cooperation with the German Society for Virology. In the last years, the NRC has performed quality control trials for genotypic HIV-1 resistance testing. In order to extend the number of participating laboratories and to improve logistics it was decided in 2009 to offer this round-robin test by INSTAND e.V.. In 2010, the NRC provided the required samples for such an extended interlaboratory test for the first time.
A further topic of the NRC is the identification and characterization of HIV-1 drug resistance associated mutations. Besides the continuous updates of the bioinformatically supported resistance interpretation system geno2pheno, the NRC coordinates a team of clinical virologists generating the German HIV-1 resis tance interpretation system HIV-GRADE. Both interpretation tools are freely available online (www.geno2pheno.org and www.hiv-grade.de, respectively).
Since 1998, the Retrovirus-Bulletin is an essential part of public relations. The NRC quarterly publishes this bulletin to provide scientific and clinical information on HIV, AIDS and other retroviral infections like HTLV-1/2 (in German). The Bulletin is freely distributed by mail to a broad readership like specialized clinicians, members of the public health system and of the HIV community. All published articles can be downloaded from the institute's homepage.

Research

With regard to epidemiological analysis and evaluation of HIV-1 resistance, there is a close cooperation between the NRC and the RKI. Important aspects are the epidemiological surveillance of transmitted HIV-1 drug resistance in untreated patients, the investigation of the appearance of new drug resistance mutations and the analysis of cross-resistance for newly approved drugs. Additionally, the NRC takes part in a nationwide HIV incidence study, which was initiated by the RKI to determine the proportion of recently acquired (incident) infections among newly diagnosed HIV infections. Finally, the efforts of the NRC are broadened by a huge 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 German Research Foundation (DFG), the German Ministry of Education and Research (BMBF), the European Union (EU) and by several companies.

Teaching

The members of the NRC offer 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, a HIV seminar addressing recent scientific results performed by members of the institute, and experimental training courses in the laboratories.

Research Unit (FOR) 661: Multimodal Imaging in Pre-clinical Research

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Aims and Structure

A team of scientists from different faculties and research areas was supported by the German Research Foundation (DFG) from October 2006 to September 2009 with about 3.5 million € 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 3 years from October 2009 to September 2012 with a funding of about 3 million € was therefore approved by the DFG. In total, 6 subprojects were prolonged directly from phase 1; another subproject with the topic small animal positron emission tomography was added and integrated into phase 2.

Subprojects:

TP1: Contrast, dose, spatial and temporal resolution in computed tomography focusing on micro CT and small animal imaging (W.A. Kalender, Institute of Medical Physics)

TP2: 3D and 4D statistical CT image reconstruction (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 (A. Dörfler, T. Engelhorn, Division of Neuroradiology)

TP4: Optimized multimodal imaging of the cerebral vessel to improve functional imaging of pain induced activity (A. Hess, K. Brune, Institute of Pharmacology and Toxicology)

TP5: Development and evaluation of ultrasound imaging modalities for small animal imaging (H. Ermert, Research group of High Frequency Technology, Ruhr-University Bochum; R. Lerch, Chair of Sensor Technology, FAU Erlangen-Nürnberg)

TP6: Combination of optical fluorescence imaging with Micro CT procedures for fusion imaging on small animals (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 (G. Schett, Department of Medicine 3 – Rheumatology and Immunology; 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 (O. Prante, T. Kuwert, Department of Nuclear Medicine)

Research

Using the field of small animal imaging, a multi-disciplinary team endeavors 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 shall improve the possibilities for early non-invasive diagnosis and can finally lead to improved and often more cost-efficient patient care.

It is the central goal of the Research Unit 661 to enhance and transfer the recent developments in the field of X-ray computed tomography (CT) and to augment them with further efforts in basic CT research and the combination of 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 institutions offers 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, focus 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 aim 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 of High Frequency Engineering at the Ruhr University Bochum and the researchers of Sensor Technology at the Friedrich-Alexander-Universität Erlangen-Nürnberg work 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 is 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 Universitätsklinikum Erlangen the work focus is on the field of medical biological basic research and clinical application. 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 is one topic. The intention is to deploy CT to encircle ischemic tissue that is not yet irreversibly damaged and still treatable.

At the Institute of Pharmacology and Toxicology the researchers focus on the improvement of functional MRI (fMRI) respectively angioplasty by recording and merging data of vascular trees of rodents and optimizing modeling. This work enhances 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 is working on the high resolution imaging of bone damages due to arthritis with micro CT and micro MR in small animals. The research focus is 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 is now also available for functional imaging of arthritis and tumor models on small animals by using new peptide-based PET tracer.

Research Unit (FOR) 832: Regulators of Humoral Immunity

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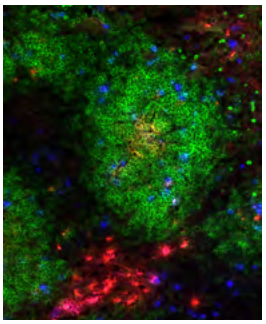

Fig. 1: Histology of a B-cell folicule in the spleen

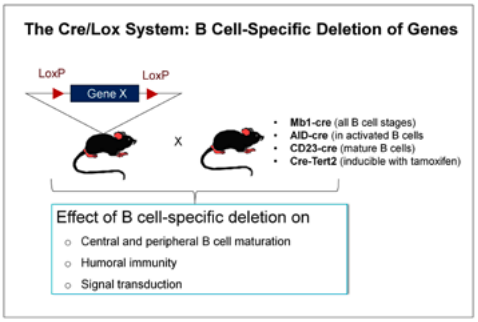

Fig. 2: Gene Deletion by the Cre/Lox System

Aims and Structure

Since 2008, the German Research Foundation (DFG) has sponsored a new interdepartmental research unit with the main topic of "Regulators of the Humoral Immune Response" and granted a total volume of 2 million Euros for it. Eight scientists from the Institute for Biology (three projects) of the Faculty of Natural Science and the Universitätsklinikum Erlangen (five projects) are participating in the research unit. Five of the eight participating project leaders, which include both biologists and clinicians, are residing at the Nikolaus-Fiebiger-Center for Molecular Medicine. In close cooperation, the eight 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 DFG Research Training Group 592, the participation in supervisory commissions for doctoral students, as well as scientific colloquia (B-cell retreat), additionally promote the mutual scientific objective.
The educational concept for the doctoral students can be seen as a special feature of the DFG research unit. The structured education of doctoral students occurs in cooperation with the Research Training Group 592 on "Lymphocytes: Differentiation, Activation and Deviation." The doctoral students of the research unit participate in all of the events and courses of the Research Training Group. This is, also in the context of international networking, intended to ensure an excellent education for the new generation of scientists.

Research

The B-cell is at the center of attention for the unit 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, which allows it 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. The research unit 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 the research unit 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 in humans. The possibility of using and also establishing "genetically tailored" mouse models here in Erlangen will be employed by the research unit (Fig. 2: The cre/lox system), 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 Night of Science and supervision of seminar thesis for high school students).

Research Unit (FOR) 894: Fundamentals on Fluid and Physical Dynamics in Human Voice Production

Speaker
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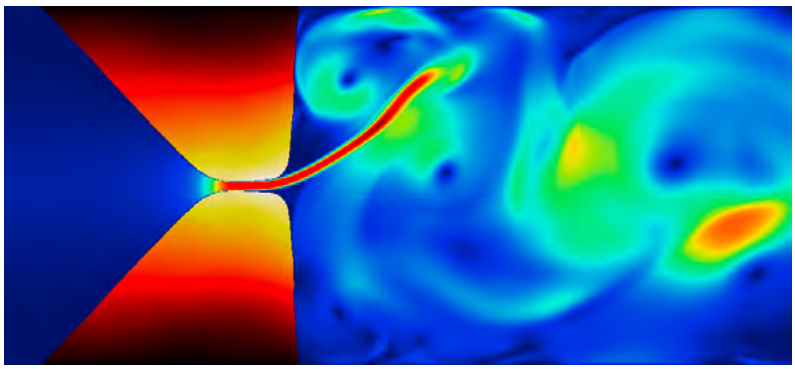

Simulation of vocal fold oscillations by a numerical 2D-FEM model. The airflow (left to right) keeps the vocal folds oscillating. Above the vocal folds, the airflow exhibits a Coanda effect (tilts to one side of the folds, here upper side). Also visible are the air vortexes contributing to the acoustical signal.

Aims and Structure

Participating Institutions: Division of Phoniatrics and Pediatric Audiology, Chair of Applied Mathematics II, Chair of Sensorics, Institute of Processmachinery and Systems Engineering, Chair of Flow Mechanics; Institute of Mechanics and Fluid Dynamics, (TU Bergakademie Freiberg); Applied Mechatronics (Alpen-Adria University Klagenfurt). Funding period since 2008.

Voice production within the larynx is still not entirely understood, neither in normal nor in pathological voice. The goal of the interdisciplinary group Research Unit (FOR) 894 is to get substantiated 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 modelling 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, the research unit FOR 894 is performing pioneer research. To coordinate and lead the interdisciplinary group, the German Research Foundation (DFG) established a W2-professorship. Prof. Dr. Ing. Michael Döllinger is the scientific manager.

Research

The strategy of the group is the application of different experimental and numerical models, yielding a comprehensive description of voice production. The basis for the models are endoscopic high speed digital video recordings from both healthy and pathological subjects. At the Division for Phoniatrics and Pediatric Audiology biomechanical models are fitted to the recorded dynamics for receiving quantitative information on the severity of diseases.
For analysing fluid mechanical causalities an air driven physical model has been developed presenting a realistic model of human voice production. Vocal folds consisting of a silicon mixture are set into vibration and enable 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. 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 observable 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 (Fig.) and a 3d-finite volume model. Hereby 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 future, conclusions based on the cause-and-effect chain, for medical conservative as well as surgical treatments will be driven.

Teaching

The participating groups in FOR 894 supervise mathematical, technical and medical thesis, as well as interdisciplinary master thesis and student research projects. The principal investigators of the different projects are involved in lectures in three different faculties: medical, engineering sciences and natural sciences.

Research Unit (FOR) 1228: Molecular Pathogenesis of Myofibrillar Myopathies

Speaker
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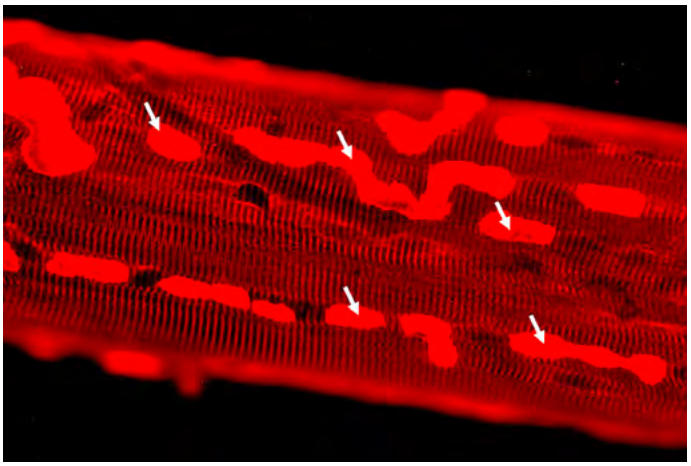

Microscopic illustation of pathological protein aggregates (arrows) in an isolated muscle fiber from a patient suffering from myofibrillar myopathy

Aims and Structure

The multilocation research unit FOR 1228, which has been funded by the German Research Foundation (DFG) since the first of November 2009, focuses on the molecular pathogenesis of myofibrillar myopathies. The position of the speaker of this consortium is held by Prof. Dr. Rolf Schröder at the Institute of Neuropathology, Universitätsklinikum Erlangen. The work of FOR 1228, which aims to clarify the molecular processes that lead to progressive skeletal muscle damage and loss of muscle function in myofibrillar myopathies, is laid out for a period of six years and will be supported by the DFG with € 1.8 million in its first 3-year term of funding. The research unit, which combines the scientific expertise of physicians, biologists and biochemists, is composed of eight distinguished groups from the Universities of Erlangen, Munich, Wuerzburg, Bonn, Bochum, Cologne, Heidelberg and Vienna.

Research

Myofibrillar myopathies (MFM) comprise a specific group of hereditary diseases affecting skeletal and cardiac muscle. These myopathies, which manifest in child- or adulthood, lead to progressive muscle weakness and muscle depletion and are often associated with a high degree of disability in late stages of the disease. Their clinical presentations resemble those encountered in various forms of limb girdle muscular dystrophies or distal myopathies. To date, no specific or even ameliorating therapy is available. The genetic basis of MFM is complex. 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 alphaB-crystallin, BAG3), the other half of these diseases is due to still unresolved gene defects. The microscopic pathology of MFM is characterized by a partial or complete destruction of myofibrils (structural components, which exert the contraction of individual muscle cells) as well as the presence of pathological protein aggregates. The precise molecular and sequential pathways leading from an individual MFM gene defect to a mutually shared myopathological disease manifestation are currently not clear. The work of Research Unit FOR 1228 focuses on the characterization of individual and shared disease mechanisms in myofibrillar myopathies due to pathogenic desmin-, plectin-, filamin C, ZASP-, VCP-, FHL1-, and alphaB-crystallin mutations. Special emphasis is put on the generation and characterization of MFM specific cell and animal models as well as the identification of novel genes and proteins, which are involved in the pathogenesis of MFM. The long term goal of the Research Unit FOR 1228 is to clarify the molecular pathogenesis of various forms of MFM and to provide the basis for the validation of novel treatment concepts.

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.

Clinical Reserach Unit 130: Determinants and Modulators of Postoperative Pain

Speaker
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Aims and Structure

The clinical research unit KFO 130 has been established at the Department of Anesthesiology in August 2005. In July 2008, the KFO has been successfully re-evaluated and funded until May 2012. Contributing Departments are: Anesthesiology, Pharmacology, Physiology, Neurology, Human Genetics (all Erlangen), Physiological Psychology (University Bamberg) and Pharmacology (University Zurich).

Research

The focus of the interdisciplinary research team is 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 accidental or hazarded 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 is the influence of intra- and postoperative applied anesthetics and analgesic drugs, genetic factors, and psychological susceptibility.

In an interdisciplinary and translational approach, various methods of basic and clinical research are combined to identify neurobiological, pharmacological, genetic, and psychosocial factors of postoperative pain and to characterize clinical and pathophysiological situations that may facilitate the development of persistent pain.

The methods used by the interdisciplinary research unit comprise not only biomedical, genetic, and psychological techniques, but also functional magnetic resonance imaging (fMRI) in rodents and man. Probands and patients for clinical studies are recruited by the acute pain service as well as by the interdisciplinary pain center within the Department of Anesthesiology. The acute pain service is in charge of all patients that are part of the clinical study and use a drug delivery system for a patient-controlled analgesia (PCA). The Department of Anesthesiology provides physicians, clinical scientists, and study nurses to check the criteria for in- resp. exclusion, coordinate patient consent, and process clinical trials. Prof. Dr. med. Carla Nau is in charge of the scientific management of the group.

The following scientific objectives are pursued by the KFO:
- How do anesthetics and analgesics influence mechanisms of pain sensitization within the peripheral and central nervous system?
- Are there any unknown molecular entities which contribute to postoperative pain sensitization?
- Are there ways to selectively influence mechanisms of pain sensitization within the peripheral nervous system on a molecular level?
- How do inflammatory or activity-dependant mechanisms of spinal pain sensitization contribute to postoperative hyperalgesia?
- Which cortical and subcortical regions represent postoperative pain sensitization?
- Are polymorphisms in genes which code for key elements of inflammatory central hyperalgesia responsible for individual differences in postoperative hyperalgesia?
- Which genetic factors determine an increased postoperative pain perception?
- Can hypervigilance generally predict acute and persisting postoperative pain?
- Can acute and persisting postoperative pain be influenced favorably by a psychological prophylaxis program?
- Which clinical and biological data can help to set up a risk profile for persisting postoperative pain?

Teaching

The clinical research unit provides rotational positions which enable physicians and junior scientists to be discharged from patient care, thus enabling dedication to research projects of the KFO.
The clinical research unit has hosted an international Winter School “Methods in Pain Research” and several “Pain Days”. These events aimed at offering interdisciplinary training in methods of pain research as well as inspiration for a more effective translation of preclinical knowledge into clinical practice to students and young scientists. The clinical research unit also regularly hosts research colloquia and Journal Clubs for scientists and guests. A final international symposium is planned for January 2012.

Bavarian Immunotherapy Network (BayImmuNet): Adoptive Immunotherapy

Speaker
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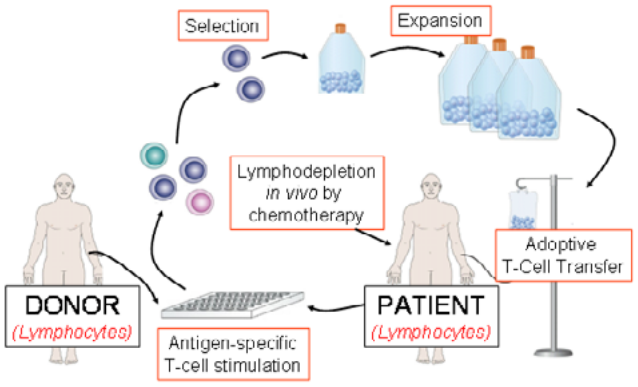

Schematic description of the goals of the Clinical Research Group "Adoptive Immuntherapy"

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 due to the Medical Preparations Act 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 10 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, Wuerzburg and Munich.

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 "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 to develop 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 Center for Internal Medicine (INZ) building provides two clean-rooms within the hematology department for the GMP conform production of cellular products. Currently, a quality management handbook for the manufacturing of T-cells is in the making in order to prepare a clinical study for adoptive T-cell therapy of CMV and EBV specific –cells after allogeneic stem cell transplantation.

Teaching

The head of the clinical research group is 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.

Project Group of the Academy of Science and Literature, Mainz

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Aims and Structure

Persistence of pathogens is one of the requirements for the development of AIDS and virus induced tumors. The Academy of Sciences and Literature in Mainz supports a research program together with the State of Bavaria, which is devoted to the investigation of persistent and oncogenic viruses of the hematopoetic system.

Research

Section A: Mechanism of the viral interference between GB Virus C and HIV-1
The research group of Dr. rer. nat. Dr. med. Heide Reil is studying the phenomenon of viral interference. Persistent HIV can be suppressed by a human non-pathogenic virus, the GB virus C (GBV-C), which delays the progress to AIDS. The clarification of the underlying mechanisms can lead to new perspectives for the development of alternative HIV therapies. It could be demonstrated that the glycoprotein E2 is able to inhibit specifically very early replication steps of HIV. The group could identify the E2 region from amino acid 37 to 64 as the responsible domain. E2-derived peptides that represent this region bind directly to the HIV glycoproteins (gp160) and suppress after the binding to the cellular CD4 receptor the subsequent fusion between the virus and cell membrane. The IC50 values are between 0,1 und 2 µM. Therefore, these peptides can be considered as new HIV fusion inhibitors. Furthermore, other findings of the research group indicate that a structural mimicry between GBV-C and HIV exists. Indeed, a variety of lab adapted or primary HIV strains can be potently neutralized by anti-GBV-C E2 positive sera as well as by some specific monoclonal anti-GBV-C E2 antibodies. Interestingly, the cross reactivity goes in both directions. Some broad neutralizing HIV antibodies bind to the GBV-C E2 protein, which is a promising observation that may lead to new HIV vaccine strategies.

Section B: Oncogenesis induced by the Kaposi sarcoma associated human herpesvirus 8
The research group of PD Dr. med. Frank Neipel is analyzing the role of herpes viruses like the Kaposi sarcoma associated human herpesvirus 8 in carcinogenesis and AIDS. Using RNA interference, it could be demonstrated that the viral Interferon regulatory factor 3 (vIRF-3) is involved in HHV-8 induced oncogenesis. The group could identify the Interferon regulatory factor 5 (IRF-5) as the cellular binding partner. Hereby a domain of 40 amino acids could be determined in vIRF-3 that binds to IRF-5, and prevents the binding of IRF-5 to some responsive promoters. Using this strategy, HHV-8 circumvents some aspects of the cellular immune response and prevents the programmed cell death. The group could identify novel ligands for two HHV-8 glycoproteins. The high-affinity interaction of the glycoprotein H/L complex with a tyrosin-kinase receptor is particularly noteworthy. This new receptor is not only relevant for attachment and entry into target cells. Binding of viral glycoproteins does also induce signal transduction pathways known to be involved in the pathogenesis of Kaposi's sarcoma. Thus, HHV-8 encounters and activates cellular genes contributing to oncogenesis at the earliest stages of the infection.

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
The scientific focus of the research group of PD Dr. med. Barbara Schmidt is the innate immune response of plasmacytoid dendritic cells (PDC) in infections with HIV-1 and HSV-1. In HIV-infected patients, a functional PDC deficit was detected which impaired the induction of interferon production and the migratory capacity of these cells. Notably, stimulation with a new class of CpG oligodeoxynucleotides improved this deficit, which may support the impaired innate immunity in HIV-1 infection. Furthermore, the group succeeded in characterizing the surface receptor repertoire of PDC in response to HSV-1 stimulation. Using a modern chip-based approach, four new receptors were characterized which may play an important role in cell-cell interactions. The regulation of surface receptors provides a detailed picture on the PDC "life cycle" in the innate immune defense against herpes virus infections: PDC are obviously attracted to the site of infection to interact with effector cells, emigrate into the blood and migrate to secondary lymphatic tissue, where they interact with cells of the adaptive immune system. Altogether, these data support important functions of PDC in the immune defense.

Section D: Transformation mediated by human T-cell lymphotropic virus type 1 (HTLV-1)
The research group of Dr. rer. nat. Andrea Kreß deals with an oncogenic retrovirus, human T-cell lymphotropic virus type 1 (HTLV-1). HTLV-1 transforms CD4+ T-cells via the viral transactivator protein Tax to permanent growth and is the causative agent of adult T cell leukemia/lymphoma (ATLL). The research group mainly focuses on identifying new functions of Tax, which may be relevant to viral persistence, transformation and pathogenicity. The tumor marker Fascin could be identified as a novel Tax target gene. Moreover, a novel mode of transcriptional regulation of Fascin was discovered, as the group demonstrated that Tax-mediated induction of Fascin requires NF-kappaB signals in T-cells. Using RNA interference, it could be shown that Fascin is important for the invasive capacity of ATLL-derived T-cells into extracellular matrix. Thus, Fascin may play a role in HTLV-1-mediated pathogenesis.

Emil Fischer Graduate School of Pharmaceutical Sciences and Molecular Medicine (EFS)

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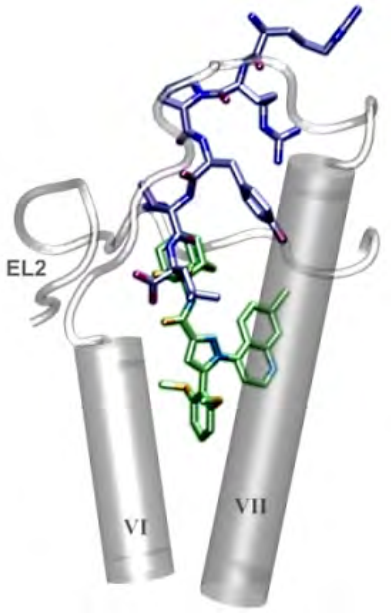
Aims and Structure

It is the aim of the Emil Fischer graduate program to provide young researchers pursuing their doctoral thesis in an interdisciplinary environment with key qualifications required for a successful career in drug target research and drug development. Main areas of interest are the identification and characterization of target proteins, signal cascades, drugs and mechanisms of action and related bioanalytical techniques.
The program is supported by members of the following chairs of the faculties of 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 and the Chair of Pharmaceutical Technology.

Research and Teaching

The graduate school 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 43 PhD students enrolled in the program. Already four candidates successfully completed the program with a PhD and a program certificate.



Erlangen Graduate School in Advanced Optical Technologies (SAOT)

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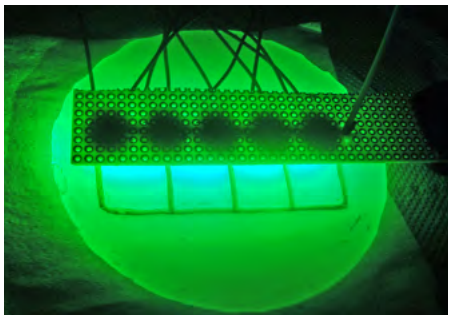
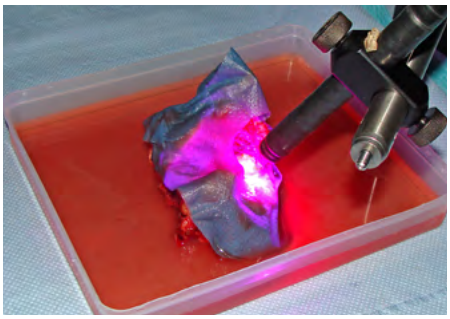


Measurements on biotissue phantom: proof of principle phase of the Epithelium Capillary Grid Real Time Monitoring project



Development of surgery navigation technology for laser ablation cancer resection

Aims and Structure

In November 2006, the SAOT was established at the Friedrich-Alexander-Universität (FAU) within the framework of the excellence initiative of the German federal and state governments to promote science and research at German universities. SAOT offers doctoral candidates a structured, internationally oriented (working language English) and interdisciplinary education program. 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 SAOT topics 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 partly overlap with other fields. In particular this is true for the topic "Optics in Medicine", which could be considered to be an application field of the other subjects, e.g., by 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 intensities of light. These detailed investigations of the interaction between 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), which is headed by Dr. Sasha Douplik, 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 all over the world and inside FAU with vaious medical and clinics research institutes. To intensify the interdisciplinary and international collaborations, SAOT organizes international workshops routinely. Within the topic "Optics in Medicine" two workshops have been organized so far, "Retina image processing" and "Advanced Optical Methods for Diagnostics, Assessment and Monitoring of Clinical Therapy and Surgery".

Teaching

During the semester 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 internationally leading institutions are invited to give a one hour talk on specialized themes at the SAOT seminar. Workshops with several speakers of leading international research institutions, contributing a talk to a major subject, usually last up to three days. This has already been done within the mentioned workshops on "Retina image processing" and "Advanced Optical Methods for Diagnostics, Assessment and Monitoring of Clinical Therapy and Surgery". During the one week lasting academies, which take place outside Erlangen once in the winter and once in the summer, the doctoral candidates are in charge to contribute 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. In the end of this academy they have to pass the entrance examination which comprises problems covering all scientific topics of SAOT.

Research Training Group 592: Lymphocytes – Differentiation, Activation and Deviation

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www.lymphozyten.de

Aims and Structure

From May 1, 2000, to May 2010, the German Research Foundation (DFG) and the State of Bavaria have sponsored the first Research Training Group GK592 on Lymphocytes: Differentiation, Activation & Deviation at the Universitätsklinikum Erlangen. Sixteen university lecturers from the Medical Faculty and the Faculty of Natural Sciences participate in the program as mentors. In order for both the doctoral students and the project leaders to participate in the important decision-making processes of the Research Training Group (GK), a Research Training Group commission consisting of four elected project leaders and three representatives of the doctoral students has been formed. The Research Training Group commission decides on the acceptance of scholarship recipients and associated students to the Research Training Group and the annual sponsorship of scholarship recipients, as well as the annual budget. The research focus of the Research Training Group is concentrated on the study of the development and activation of lymphocytes, their derailment in autoimmune diseases and chronic processes of inflammation, as well as the development of tumors of the immune system (next chapter). Within this research field, doctoral students and university lecturers are offered an interactive and professionally oriented training program. The core elements are a supervisory commission for each doctoral candidate, a trainee program at European and North American institutions that has been established and financed by the Research Training Group, as well as one- to two-day workshops at which topics such as the "Requirements of the Industry," "Elements of the Rhetoric" and the "Writing of Scientific Manuscripts and Proposals" are taught. Highlights of the current period were the joint network meetings with our partner Research Training Groups from Wuerzburg (speaker: Professor Hünig) and Tuebingen (speaker: Professor H-G. Rammensee) that take place in an annual rhythm, as well as the 1st and 2nd International GK Symposium on Regulators of Adaptive Immunity initiated by GK592 doctoral students. Twenty prestigieous immunologists from around the world were involved as speakers in the 2nd GK Symposium, which also had more than 400 registered participants. (See http://www.lymphozyten.de/symposium2008; Kroczek, C., Thiele, S. and Winkelmann, R. (2009). Doctoral Students in the Limelight at the 2nd Erlangen International Immunology Symposium. Eur J Immunol. 39, 339-341).

Research

As in the first two funding periods, the topics of the research projects concentrated on the cellular, molecular and functional aspects of the differentiation, activation and deviation of lymphocytes and their role in autoimmunity, allergy and leukemia. This also includes immunotherapeutic approaches for the treatment of tumors. The research program of the GK592 has set the goal of clarifying the molecular and cellular processes and signal cascades that are involved in the development of both physiologically desired and pathological lymphocyte populations in autoimmune, allergic and leukemic diseases. Research-oriented and clinical aspects of lymphocyte biology are integrated within this research program. The intention is for students to be trained as highly qualified immunologists who are capable of independently developing scientific hypotheses, verifying them through experiments, critically interpreting the experiment findings and discussing them under consideration of published data. This means that the GK592 is designed in an interdisciplinary approach with regard to the expertise of the project leaders; and it concentrates on the biology and pathophysiology of lymphocytes in relation to the research topics.

Teaching

In addition to the classic lectures (such as concepts of immunology, literature seminars, etc.) and practical courses within the scope of the Bachelor's Degree (Biology and Molecular Medicine), Master's Degree (Cell and Molecular Biology in the Department of Biology) and the graduate degree program for Molecular Medicine (Medical Faculty), all of the project leaders also participate in a methods seminar organized by one of the doctoral students. Furthermore, the project leaders are directly and actively integrated into the supervision of the respective doctoral students as members of the doctoral supervisory commissions. All of the members of the Research Training Group

Fig. 1 Poster of the 3rd International GK Symposium

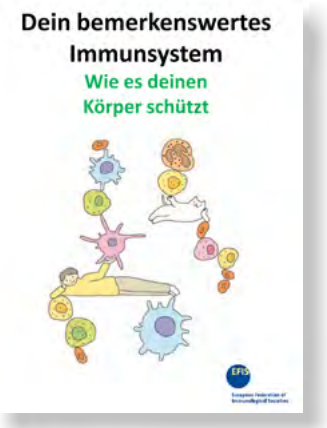

Fig. 2 The Amazing Immune System, an extraction of the joint project of the Marie-Therese-Gymnasium, GK 592, FOR 832 and GK1660.

are also actively participating in the public relations work of the Research Training Group (such as the 2008 International Day of Immunology, see Ill. 2) and projects conducted with the Erlangen grammar schools (Gymnasium). A definite highlight of this was the cooperation of the GK592 with pupils from the Marie-Therese High School in Erlangen. In this W-seminar the pupils got in contact with the field of immunology in seminars and practical courses. Furthermore the pupils translated the book: "Your Amazing Immune System" under mentoring of the doctoral students into German. This book was initiated by the Japanese society of Immunology with the aim of being translated into several languages. It was translated into English in 2009 and the German version will be printed in summer 2011.

Research Training Group 1071: Viruses of the Immune System

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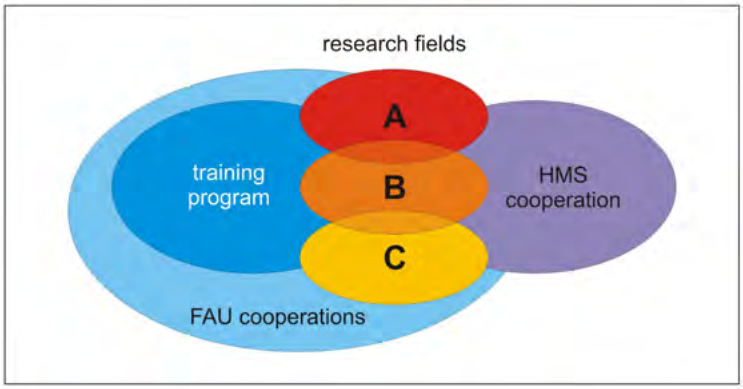

Aims and Structure

The Research Training Group "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 Medical Faculty and the Faculty of Natural Sciences at the Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU). The special feature of the Research Training Group 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 research training group 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. Thereby, this network contributes to the research focus on infectiology/immunology at the Medical Faculty.

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 public-oriented and scientific events. Particularly, the International GK Symposium in Erlangen (www.lymphozyten.de/symposium.html), realized for the third time in October 2010 together with students of the Research Training Group 592 and the Research Unit 832, was again a great success.

Research Training Group 1660: Key Signals of Adpative Immunity

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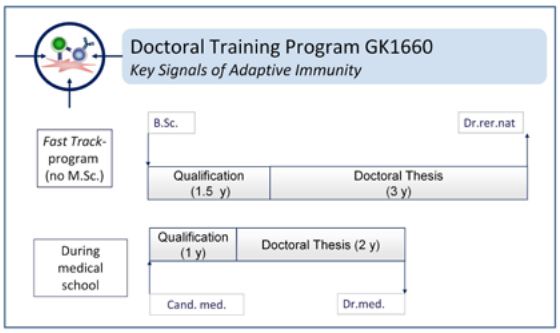

Fig. 1: Structure of the training program of the GK 1660

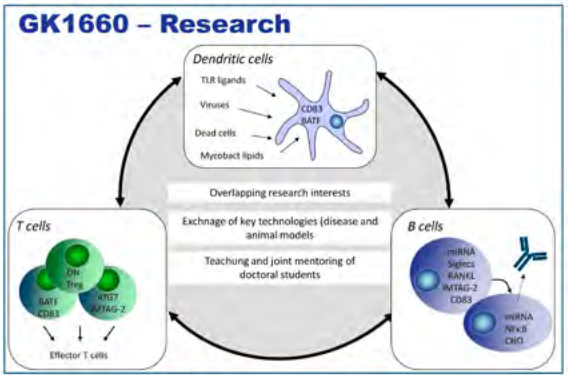

Fig. 2: Research focus of the GK 1660

Aims and Structure

Since October 1, 2010, the German Research Foundation (DFG) and the Free State of Bavaria have been supporting the fist 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 10 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 (Fig. 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 (Fig. 2). The main research interest is on the intra- and the 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 10 institutes and clinical departments at the Friedrich-Alexander-Universität Erlangen-Nürnberg. All supervisors have external funding and are experienced in graduate training.

Teaching

During their thesis the doctoral graduate and medical students will participate in the successfully tested core events and activities of the finished training grant GK592:

(1) An bi-weekly doctoral „jour fixe" 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 3-member thesis advisory committee. To internationally position our doctoral students, they will organize the 3rd International GK Symposium on "Regulators of Adaptive Immunity" (www.lymphozyten.de/symposia).
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.

Integrated Graduate School SFB 643: Strategies of Cellular Immune Intervention

Speaker
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Aims and Structure

The graduate school is integrated in the Collaborative Research Center (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 Jour-Fixe, workshops in 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" exists since July 2004 and is currently in its second 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 develop them into independent scientist 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 Jour-Fixe the candidates discuss literature, methodical problems and their own research-data. Internal Report-Symposiums and Network-Meetings with other topically relevant and external Graduate Schools, 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.

Intergrated Reasearch Training Group 796: Erlangen School of Molecular Communication

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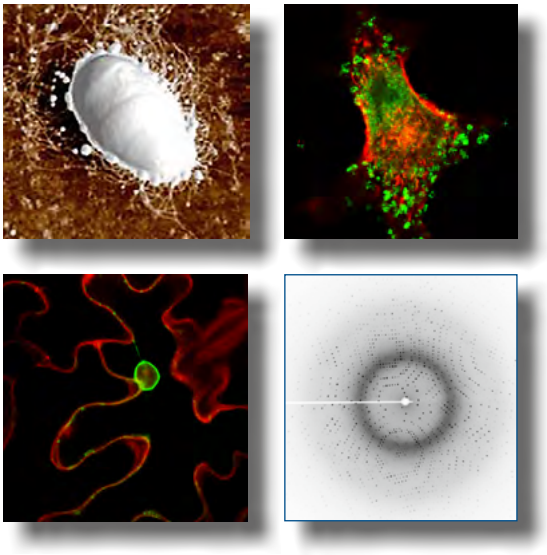

Selected examples of projects within the integrated graduate school of the SFB 796. (Left upper panel) Pili of Corynebacterium diphtheria *are necessary for the adhesion to human cells. (Right upper panel) Adhesion of* C. diphtheriae *to a human macrophage. (Left lower panel) The attachment of the MP17 protein (shown as GFP fluorescence in the red-labelled cell wall) of the potato leaf roll virus in the plasmodesmata of a plant cell allows the spreading of virus particles within the plant. (Right lower panel) X-ray diffraction pattern of a protein crystal.*

Aims and Structure

The Graduate School "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 Medical Faculty and the Faculty of Natural Sciences of the FAU as well as the Universitätsklinikum Erlangen and the Fraunhofer Institute of Integrated Circuits. The school 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 Graduate School offers now a fast track program beginning in October 2011. Outstanding students will be given the opportunity to replace the two-year masters degree with a one-year curricular phase, and thus to start with their doctoral studies more quickly.
First funding period: 2009-2012

Research

The strong focus on interdisciplinary research at the Graduate School "Erlangen School of Molecular Communication" is both attractive and challenging. The Research within the SFB 796 aims to investigate 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 of 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 graduate school 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 graduate school seminars according to their own requirements and are 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, have also been provided on student request.

BioMedTec International Graduate School of Science (BIGSS): Lead Structures and Cell Function

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Announcement poster of the Bayreuther Strukturtage 2009 and 2010

Aims and Structure

Involved universities are Bayreuth, Erlangen-Nürnberg and Würzburg.
Participants from the Medical Faculty Erlangen-Nürnberg: Prof. Dr. Cord-Michael Becker, Chair of Biochemistry and Molecular Medicine, Prof. Dr. Bernhard Fleckenstein, Institute of Clinical and Molecular Virology, Prof. Dr. Peter Gmeiner, Institute for Medicinal Chemistry, Prof. Dr. Christoph Korbmacher, Institute of Cellular and Molecular Physiology, Prof. Dr. Ulrich Schubert, Institute of Clinical and Molecular Virology, Prof. Dr. Thomas Stamminger, Institute of Clinical and Molecular Virology, Prof. Dr. Heinrich Sticht, Institute of Biochemistry, Prof. Dr. Michael Wegner, Chair of Biochemistry and Pathobiochemistry.
Funding period: since 2004.

Research

The International Graduate School BIGSS (BioMedTec International Graduate School of Science) is themed "Lead Structures of Cell Function", indicating that the focus of interest is in the area of biological macromolecular structures. The graduate school applies 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 is limited to three years and offers optimal conditions for currently 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, Wuerzburg and Erlangen. It constitutes 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 is 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 is necessary. Consequently, the PhD students are supported by thesis advisory committees consisting of three supervisors. The privileges of the PhD students include numerous offers to acquire soft skills and a generous travel budget that ensures the possibility to participate at international scientific congresses and workshops. There are, however, also several obligatory yearly events like written yearly progress report, summer school, seminars and evaluation by independent international reviewers.
The annual summer school is 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 guarantee a high degree of interdisciplinarity, a vivid scientific exchange and high quality dissertations. The success of the graduate school is reflected by 33 publications in important journals within the last two years. In the years 2009 and 2010 eight more students finished their PhD and meanwhile have taken up continuative research and industry projects.

Interdisciplinary Center for Clinical Research (IZKF)

Speaker
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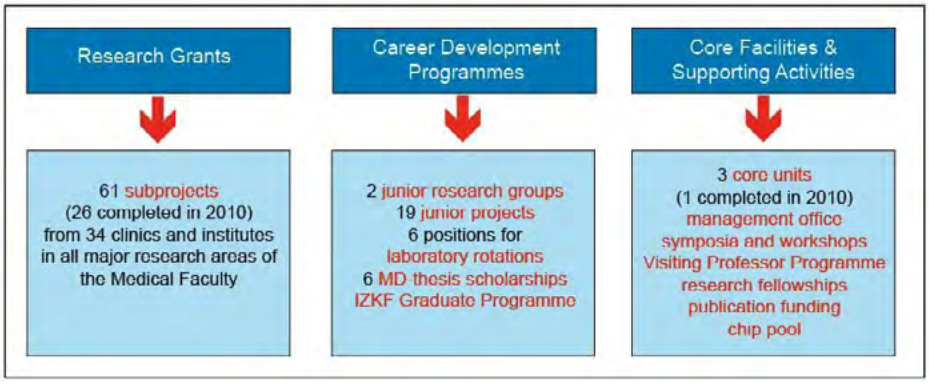
interdisziplinäres Zentrum für Klinische Forschung

Aims and Structure

The Interdisciplinary Center for Clinical Research (IZKF) is a central structure of research development of the Medical Faculty. Its mission is to improve the overall quality of clinical research at the Medical Faculty, 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 Federal Ministry of Education and Research within the program "Health related research 2000". Since 2004 it has been fully funded by the Universitätsklinikum Erlangen and the Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU). The initial scientific focus on inflammation research could be developed further also accommodating other research areas, without sacrificing this distinctive topic, thus allowing more institutions of the Medical Faculty to participate. IZKF activities can be subdivided into three major areas:

Research Grants
The IZKF offers research grants in all major research areas of the Medical Faculty. Grants cover a 3-year period and include one graduate student and one technician as well as consumables. Project leaders must have an active publication record and 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 as well as ensuring that students are directly exposed to these modern developments.



Overview about the activities of the IZKF

Supporting activities include the "Visiting Professor Program" and a triennial international scientific meeting.
Various parameters are used to evaluate the performance of the IZKF in advancing clinically oriented research at the Medical Faculty. Scientific publications and academic success of young scientists are the most obvious and straightforward ones. Furthermore, patents, scientific prizes and offers of professorships are relevant parameters. In 2010, the 53 funded projects altogether published 80 original articles (excluding reviews) with a cumulative impact factor (IF) of 510.173. The high quality of many of these publications is reflected in 62 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.

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 Nikolaus-Fiebiger-Center for Molecular Medicine offer an attractive career development opportunity for outstanding young scientists with a training in medicine or natural sciences and a strong background and reputation in one of the faculties' main research fields. Over a period of up to six years each junior research group receives funding for the group leader, one postdoctoral and one postgraduate scientist, one technical assistant and consumables. The group of Jens Titze works on „Immune system as regulator of volume and blood pressure" and the group of Beate Winner on "Modeling neurodegenerative diseases using stem cells".
In addition the IZKF supports six positions for a laboratory rotation and six MD-thesis scholarships. Since 2009 the IZKF offers in collaboration with the ELAN-Fonds starting grants to young postdoctoral physicians and scientists up to 34 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.

University Cancer Center Erlangen (UCC)

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Aims and Structure

Erlangen University Cancer Center (UCC) is an interdisciplinary center of excellence established to coordinate medical care, research and teaching. For patients, physicians, and scientific researchers, the UCC is the central contact for all questions connected to cancer diseases. Nationwide, there are currently only ten institutions of this type, sponsored by German Cancer Aid as leading centers for cancer research and treatment.
The UCC works in close collaboration with specialist physicians and hospitals in the European Metropolitan Region of Nuremberg and is supported by the Universitätsklinikum Erlangen and the Department of Medicine at the Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU). A merger with experts at Nuremberg Hospital to form a joint Erlangen-Nuremberg CCC is scheduled for mid-2011. The highly qualified staff at the UCC ensure individual interdisciplinary and cross-professional diagnosis and treatment for cancer patients, based on the very latest guidelines and research results. They also advise physicians in private practice and in hospitals in difficult decision-making processes. The center organizes further education and training courses on topics in oncology and coordinates research projects. In addition, the UCC runs a free tumor consultancy service for patients and their relatives.

Interdisciplinary treatment based on a clear plan
The founding of the UCC at the Universitätsklinikum Erlangen has provided an interdisciplinary and interprofessional focus for competence in tumor treatment. This strong grouping at the level of an internationally networked university hospital offers patients the assurance that they are being treated in an individualized way with the very latest methods.

At the UCC'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.
The advantage for patients is that they are treated with multiple skills in an interdisciplinary way in what are known as "organ cancer centers."
All treatment decisions are taken jointly by the experts in each specialty, at meetings known as "tumor conferences".

Interdisciplinary and inter-organizational regional networking
The aims of the UCC in Erlangen are:
- 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.

Assured quality
In collaboration with certified oncology centers, the affected patients receive optimal care and support in an integrated way during every phase of their disease.
Under the aegis of certified organ cancer centers, a total of 14 interdisciplinary treatment units at the UCC are responsible for the development of clinical treatment pathways and the establishment of tumor conferences.

Research

Treatment standard based on research and clinical studies
If possible, patients are treated in the framework of clinical studies. Links with the Center for Clinical Studies (CCS) at the Universitätsklinikum Erlangen and with the medical faculty at the FAU are available for this purpose.
UCC patients are the first to benefit from medical advances and can be treated in accordance with the highest safety standards in the context of clinical studies. The patients are registered with the "Soarian" electronic documentation system and the data are sent on to the Clinical Cancer Registry and Erlangen-Nuremberg Tumor Center. This enables cancer researchers at the university hospital to assess disease courses and to investigate and develop improved treatments.
Research on biomaterials forms the basis for new discoveries. For this purpose, a biomaterials bank has been set up both for tumor tissue and also normal tissue, DNA from tumor patients and control individuals, and also for other types of body fluid (e.g., pleural effusions, ascites, feces, urine, etc.). With the consent of the patients involved, these biomaterials can be used to pursue major research goals using investigational methods at the highest scientific standards, leading to medical advances, with new discoveries and the development of new forms of treatment.

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.

Interdisciplinary Center: Medical Immunology Campus Erlangen (MICE)

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Aims and Structure

The Medical Immunology Campus Erlangen (MICE), interdisciplinary center of the Friedrich-Alexander-Universität Erlangen-Nürnberg, 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, hospitals, departments and research groups of the Medical Faculty, the Biology Department of the School of Sciences, the Fraunhofer Institute for Integrated Circuits (IIS) and the Max Planck Institute for the Science of Light have been integrated into the campus. The MICE 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 concerted participation in funding initiatives. By bundling the available scientific resources in the field of immunology, the MICE is dedicated to strengthen the research focus Immunology and Infection Research of the Medical School and, in the long run, to enable the founding of a Leibniz Institute for the Function and Deficiency of the Immune System.

Research

The MICE researchers investigate the basic mechanisms of the development, composition, function, and of 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.
Projects of the Research Area **Target Identification and Imaging** focus on the identification of new biological factors that can be used as indicators for predispositions and for the progress of diseases of the immune system, and the response to immunological therapies. For example, genetic susceptibility factors for inflammatory diseases have been identified by genome-wide association studies, the role of microRNAS during the maturation and activation of B cells is analyzed, and key factors of the humoral immune response are investigated using classical, transgenic, and humanized mouse models. Furthermore, the characterization of individual immune cell subsets opens up new channels for the identification of targets for future therapies. To visualize disease and therapy progress of autoimmune and inflammatory diseases and to detect infections, new methods based on imaging technologies such as positron emission tomography, computer tomography, and magnetic resonance tomography as well as laser spectroscopy, single molecule detection, and nanoscopy, are developed. Molecular mechanisms of host defense, signaling pathways and the regulation of the immune system are addressed by the Research Area **Mechanisms and Processes**. The projects range from elucidating the mechanisms involved in the maturation, activation and regulation of different immune cells and their role in pathogen recognition and defense, analyzing deficiencies of the immune system and the development of autoimmune and inflammatory diseases, to characterizing the role of the immune system in neuropathic pain or in interstitial volume and blood pressure regulation. In addition, the impact of viral oncoproteins on immunological signaling is analyzed.
Projects of the Research Area **Immunotherapy** translate the results from preclinical research into new therapeutic strategies which are adjusted to the individual disease and patient and therefore promise high efficiency. Research topics include approaches for antiinfectives that enhance intrinsic pathogen defense mechanisms or for therapies based on antibodies and immunologically relevant receptors. The development and evaluation of new approaches for cell based immunotherapy such as cellular vaccines for the treatment of tumors and Colitis ulcerosa and the adoptive transfer of antigenspecific T cells is another key focus of this research area.

Teaching

The MICE members are involved in teaching medical students and students of the Bachelor's and Master's degree programs of Molecular Medicine at the Medical School, and students of the life science programs at the School of Sciences. Furthermore, the campus promotes scientific exchange by hosting national and international speakers of a broad, interdisciplinary range of topics at the weekly MICE Immunological Colloquium. The yearly Joachim Kalden Lecture was initiated by the Medical Immunology Campus Erlangen in order to honor outstanding researchers who have supplied a substantial impact to immunological research such as nobel laureate and tumor virologist Prof. Harald zur Hausen in 2009, and the cytokine researcher Prof. Charles Dinarello in 2010.

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 Friedrich-Alexander-Universität (FAU) Erlangen-Nürnberg on July 28, 2010. The ECI is a consortium of more than 30 professors and lecturers and their research groups, which belong to the Medical Faculty, 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 Erlangen-Nürnberg and the Universitätsklinikum 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 to provide 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 expertises 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 ECI comprises an executive board of four scientists (Prof. Dr. med. Christian Bogdan, speaker; Prof. Dr. rer. nat. Jutta Eichler, Prof. Dr. med. Thomas Harrer, Prof. Dr. med. Thomas Stamminger), a steering committee - consisting of the members of the executive board and five additional faculty members (Prof. Dr. med. Andreas Baur, Prof. Dr. rer. nat. Andreas Burkovski, Prof. Dr. med. Bernhard Fleckenstein, Prof. Dr. rer. nat. Ivana Ivanovic-Burmazovic and Prof. Dr. med. Roland 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 Federal Ministry of Education and Research (BMBF) research competition for the foundation of the German Center for Infection Research (DZI). The ECI 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, so that the ECI was not selected as one of the final seven sites of the DZI. Nevertheless, the ECI researchers will continue with their concept to set up new collaborative research grant applications.

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. The first international research symposium of the ECI is planned for spring 2011 and will focus on the intracellular lifestyle of infectious pathogens.

Interdisciplinary Center of Gerontology (ICG)

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Aims and Structure

Since its foundation in 2003 the Interdisciplinary Center of Gerontology (ICG) is active in the fields of biological, medical, psychiatric, psychological, behavioral, humanistic, economical and technological aging research. The ICG initiates and supports interdisciplinary collaboration on aging research at the Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU). The ICG is also actively collaborating with communal institutions of medical care and with nursing homes of the region. Currently the ICG has 29 members coming from four different faculties and five associated institutions.

Research

Research of the members of the ICG 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
Within the framework of the Teo and Friedl Schöller foundation professorship for clinical nutrition in old age previous research attempts could be intensified. In the context of ongoing frailty research could be shown, that in a sample of community dwelling seniors mediterranean diet reduces the risk of becoming frail. An intervention study proved the benefit of nutritional supplement beverages on malnutrition in rest home residents. A study on the development of rest homes residents´ body weight showed that about two thirds of the population is suffering from unintentional weight loss after being referred to a hospital.

ICG
Interdisciplinary Centre of Gerontology

Furthermore, the degree of weight loss correlates highly with the mean residence time at the hospital.

Field of Research: Physical activity
Targeted activation of physical activity can improve physical function and thus help to maintain the independence of older persons. The project „Fitness im Alter durch professionelles Training" (F.i.A.T.) analyses the dose-response relationship of different physical activity programs (e.g. power vs. resistance training) with regard to subjective and objective measures of health. Common understanding is that multifactorial physical exercises help to prevent falls and increases physical resources like strength and balance. A multilevel intervention program dealing with different risk factors of falls is therefore recommended (Project: prevention of falls in old age). Another focus of research is on the effects of physical activity on pain in chronic diseases (e.g. chronic back pain; project PASTOR) and on symptom relief and improvement of functional performance in patients with multiple sclerosis.

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 (GesA-Projekt, Maks-Aktiv Projekt) is also of great importance. Additional projects analyse the situation of family caregivers, particularly with respect to the potentials of psychoeducation of family caregivers (GesA project). 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 (z.B. HL-PDL-Project; GEMIT; EduKation TANDEM).

Interdisciplinary and comprehensive research approaches focus on questions of prevention and interventions strategies with regard to dementia and age-related frailty (e.g. projekt F.I.A.T). Additional non clinical research is centered around the possibilities of assistive technology for supporting mobility and independent living in later life (e.g. Fit4Age).

Teaching

The majority of the ICG-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 ICG, especially those related to gerontological practice. A series of lectures (Q7 – medical science of aging) focussing geriatric and ethical topics are organized by numerous members of the ICG at the medical school of the FAU.
Furthermore, the ICG 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.

Interdisciplinary Center for Ophthalmic Preventive Medicine and Imaging (IZPI)

Speakers
Prof. Dr. med. Georg Michelson &
Prof. Dr.-Ing. Bernhard Schmauss

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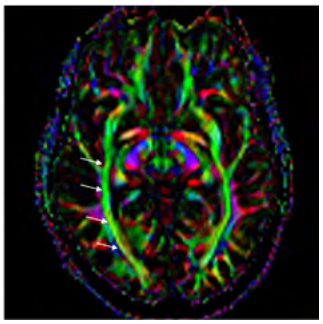
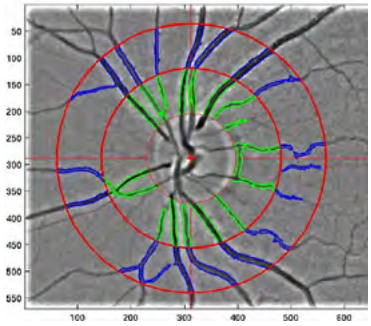


3-Tesla-MR, Diffusion Tensor Imaging, Tractography of 4. Neuron of Visual Tract: Regular visual tract (from Project A02-Medical Valley Spitzencluster)



Automated definition of diameter of retinal arteries and venoles (from Project A04-Medical Valley Spitzencluster)

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 Medical and Technical Faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg 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 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 to elute relevant information from a given image.

Research

IZPI researchers from 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 and therapy of diabetic retinopathy, hypertensive retinopathy and glaucoma.
(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. This data base will allow platform-independent (a) download of images, and (b) upload of images with an automated comparison of the submitted image with pre-diagnosed images of the database to give a tentative diagnosis. In cooperation with the Atlas of Ophthalmology www.atlasophthalmology.com there are 6000 available reference images.

(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 Ph.D.-projects a gesture-controlled, interactive system is developed, enabling the measurement and training of the stereo vision capacity.
(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.
(3) Computer Aided Diagnosis: An automated analysis of retinal colour images allows a fast tentative-diagnosis of glaucomatous optic nerve atrophy. Especially in broad population-based "glaucoma-trials" this system enables to examine a huge number of patients, keeping the costs low.

(III) Other third party-funded cooperations
Researchers from the IZPI cooperate with the University of Muenster in respect to telemedical evaluation of retinal images. A scientific cooperation with the University of Portland (David Huang, USA) focuses on methods of the Optical Coherence Technology to analyse the morphology and function of retinal vessels.

Teaching

IZPI researchers give lectures within several interdisciplinary frameworks of Medical and Technical Faculty. On the Medical Faculty the lecture "retinal microangiopathy as early marker of cardio-vascular diseases" and lectures for students are given of the degree program "Medizintechnik". 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.
In addition, a weekly colloquium "Biological and Technical Vision" is offered to the students.

Interdisciplinary Center for Public Health (IZPH)

Speaker
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Chairman and Member of Board of the IZPH

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Dr. Kolominsky-Rabas, Managing Director of the IZPH with representatives of the Center of Excellence for Medical Technology – "Medical Valley EMN e.V." at the anniversary celebration 2010.

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 Friedrich-Alexander-Universität Erlangen-Nürnberg (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 Nuremberg Metropolitan Region the IZPH bundles all relevant stakeholders of the health care management industry i.e. medical professionals (doctors, hospitals trusts, outpatient sectors); the payers (statutory health insurances); 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 Promotion/ Preventive Medicine, Health Technology Assessment/Health Economics 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 chronic ill patients (dementia, cancer and stroke) as well as assessment of health care services funded externally with 3.6 million Euros.
With its emphasis on Health Promotion/ Preventive Medicine, Health Economics/ Health Technology Assessment 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.).

Center for Clinical Studies (CCS)

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Aims and Structure

In 2008, the CCS Erlangen was created as a common service unit of the Medical Faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg and the Universitätsklinikum Erlangen. From an organizational point of view, it belongs to the hospital as one of its central units. Its tasks include:
1) Providing counseling and services to members of the Medical Faculty and employees of the Universitätsklinikum Erlangen regarding the design, planning, conduct and evaluation of clinical studies, taking into account the relevant legal and regulatory requirements.
2) Organizing educational events on all aspects of clinical studies.
3) Designing and running the clinical studies database of the Medical Faculty.
Since its inception, the CCS Erlangen was involved in more than 100 clinical research projects of members of the Medical Faculty and employees of the Universitätsklinikum Erlangen.
The CCS Erlangen consists of the departments of study management and clinical monitoring, quality management, pharmacovigilance and data management.

Counseling and Services for Clinical Studies

Counseling:
Each year, the CCS Erlangen provides a broad range of counseling services, especially during the preparatory phase of clinical studies. The main focus is on so-called investigator-initiated trials (IITs), planned and conducted by members of the Medical Faculty and employees of the Universitätsklinikum Erlangen. During counseling, the CCS Erlangen concentrates mainly on the feasibility of the research project from an economic and organizational perspective as well as on adherence to the relevant legal and regulatory requirements. Furthermore, the CCS Erlangen establishes the contact to potential partners and providers of financial support and clarifies legal issues with the regulatory authorities. All counseling services are provided for free.

Study Management and Clinical Monitoring:
Prior to clinical study start, the CCS Erlangen offers various services, ranging from the generation of the study protocol and the Investigational Medicinal Product Dossier to obtaining approval from federal regulatory authorities and votes from the Ethics Commissions. The CCS Erlangen covers also multicenter and multinational clinical research projects.
During the conduct of the clinical study the CCS Erlangen provides the clinical monitoring, if requested by the sponsor or the project leader.

Quality Management:
Institutions which in the framework of clinical studies take over sponsor tasks and duties are requested to work along standard operating procedures (SOPs). The department Quality Management of the CCS Erlangen helps identify and create the SOPs necessary for the performance of sponsor activities.
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 the compliance with the regulatory requirements. Furthermore, the CCS Erlangen provides advice and guidance for inspections by the regulatory authorities and audits by the sponsor, as requested by the sponsor or the project leader.

Pharmacovigilance:
For clinical studies sponsored by the Universitätsklinikum Erlangen and falling under the laws AMG or MPG, the CCS Erlangen ensures the follow-up and timely notification of serious adverse events according to legal and regulatory requirements. To cover 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 offers the generation of study-specific electronic case report forms. Additional services such as the generation of the data management plan or data cleaning prior to database lock may be ordered by the sponsor or the project leader.

Research

Clinical Study Database:
The planned study database serves as basis for the presentation of the clinical research efforts of the Medical Faculty. It will contain prospective interventional clinical studies which may be listed according to predefined criteria, thus allowing an overview of the clinical research activities.

Teaching

At the request of the Medical Faculty, the CCS Erlangen has organized six educational events for investigators and coordinating investigators of clinical studies over the last two years. Apart from discussion of the relevant legal and regulatory requirements, the focus is set on real-life aspects and advice which often have a big influence on the feasibility and timely recruitment of study participants. For the time being more than 200 study physicians from the Universitätsklinikum Erlangen and the associated Academic Teaching Hospitals attended the courses.

Emil Fischer Center (EFC)

Speaker
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Aims and Structure

Members of the Faculty of Science and the Medical Faculty within the Friedrich-Alexander-Universität Erlangen-Nürnberg combine into the Emil Fisher Center (EFC). The organization includes full and associate professors at the Chairs of Bioinorganic Chemistry, Biochemistry and Molecular Medicine, Biochemistry and Patho-Biochemistry, Clinical Pharmacology and Clinical Toxicology, Pharmacology and Toxicology, Food Chemistry, Pharmaceutical Biology, Pharmaceutical Chemistry and Pharmaceutical Technology.
The objective of the interdisciplinary center is to promote and conduct joint projects between pharmaceutical sciences, food chemistry, chemistry and molecular medicine in the fields of research and education. The members' scientific work is interlinked by the EFC, which operates a core unit "Bioanalytics" and several collective basic technical facilities. The EFC represents the members in respect to external contacts, coordinates interdisciplinary fund-raising activities and serves as a platform for the cooperation with partners from the pharmaceutical and food industry. Research and education at the Emil Fischer Center is supported by several organizations and research collaborations, such as the Collaborative Research Centers SFB 423, SFB 583, SFB 796, KFO 130, FOR 661, the German Research Foundation (DFG) graduate program 1071, the Federal Ministry of Education and Research (BMBF), the European Union (EU), the Elite Network of Bavaria and the Bayerische Forschungsstiftung.
Interdisciplinary post-graduate training is accomplished at the Emil Fischer Graduate School (EFS).

Research and Teaching

Main research topics at the Emil Fischer Center concentrate on agents, drug targets and bioanalytics. The core unit "Bioanalytics" focuses the members' scientific and technical competence on protein and proteome analysis and the analysis of low molecular agents. The bioanalytical expertise further covers 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 interaction of new bioactive small molecules with their target proteins and in their physiological function and to 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 micro injection and electroporation, real-time PCR devices, various electro-physiological setups as well as a computer cluster.

Nikolaus-Fiebiger-Center of Molecular Medicine (NFZ)

Speaker
Prof. Dr. rer. nat. Jürgen Behrens

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Aims and Structure

The Nikolaus-Fiebiger-Center of Molecular Medicine (NFZ) is a research institution of the Medical Faculty. 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 Science Faculty, as well as two junior research groups of the Interdisciplinary Clinical Research Center (IZKF) of the Medical Faculty. Additionally, lab space is provided to rotating clinical research groups. The intention of the research center is to strengthen biomedical research in the Medical Faculty by stimulating cooperations between basic and clinical researchers and by giving young clinicians the opportunity to carry 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 recent appointment of Prof. Dominik Müller as new head of the Chair of Experimental Medicine I, research is extended to cardiovascular diseases.
The Nikolaus-Fiebiger-Center 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.

Franz Penzoldt Center (FPZ)

Speaker
Prof. Dr. med. Stephan von Hörsten

Executive Board
Prof. Dr. M. Wegner (Chair)
Prof. Dr. C. Bogdan (Deputy Chair)
Prof. Dr. J. H. Brandstätter
Prof. Dr. S. von Hörsten
Prof. Dr. R. Horch (since 2010/11)
Prof. Dr. Nimmerjahn (since 2010/11)
Prof. Dr. T. Winkler (until 2009/10)

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Aims and Structure

The Franz Penzoldt Center (FPZ) is a center of the Friedrich-Alexander-Universität Erlangen-Nürnberg that serves faculty and staff as a state-of-the-art animal testing facility. Two buildings, one located in the city center at the campus of the Universitätsklinikum Erlangen (Palmsanlage) the other at the science campus in the south of Erlangen as part of the Biotechnological Development Laboratories (BTE) are dedicated to the highest care of small and large animals. The FPZ offers modern, standardized housing, operating theaters and biocontainment levels (up to safety level 3) to support basic, translational and clinical research.

The FPZ is a research-oriented animal facility that provides its customers a modern infrastructure and specific-pathogen-free conditions for preclinical animal tests. The center offers various research related services, e.g. importation of transgenetic mouse strains via embryonic transfer as well as veterinary advice or supervision for surgical or toxicological studies on large or small animals. An integrated transgenetic unit also offers pronucleus and blastocyte injection techniques for the design, development, and production of new transgenetic rodents.

Researchers from universities and clinics working on life sciences, medical engineering and novel therapies as well as partners from research institutes and industry find a reliable partner in the FPZ. With its infrastructure, the FPZ supports and effective research and makes translation of results possible to benefit patients in a controlled, standardized environment appropriate to the species.

Research

The overriding goal of the FPZ is the continuous implementation of the principles of reduction, replacement or refinement (3R's) of animal tests as well as responsibility, which includes the constant optimization of the keeping conditions that will benefit both, the animals' well being and the quality of the scientific results.

Central tasks of the FPZ in research, development, and management are:
- Achieving responsible and ethical animal husbandry and handling
- Optimizing and standardizing processes in animal keeping
- Implementing a modern quality assurance
- Assuring continual professional development of the scientific and technical personnel.

The FPZ provides statutorily regulated areas of operation such as e.g. housing and experimental rooms that meet the safety levels for genetically modified organisms S1 to S3, and the biological safety levels (BSL) for infectious agents from BSL I to BSL III. Work in the experimental rooms is possible in accordance with the statutory regulations of the German Infection Protection Act, Pharmacy Law, and the Chemicals Act.

Currently, the FPZ houses 35 academic chairs and 20 independent units of the university, of which 49 are members of the Medical Faculty. Intramural funding for the running and upkeep of the FPZ are provided by the university and the university hospital. Additional project related costs are provided by users through intra- and extramural funding.

Teaching

The FPZ organizes qualifying professional development courses in laboratory animal science (e.g., FELASA courses), offers the opportunity to learn animal testing techniques and functions as a training company (Ausbildungsbetrieb) for the recognized trade of laboratory animal technician that is certified by the chamber of commerce. The center places a priority on being a family friendly institution and implements the principles of gender mainstreaming in its processes and management to help its staff achieve a work-life-balance.

Medical Technology Test and Application Center (METEAN) of the Fraunhofer Institute for Integrated Circuits IIS

Speaker
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Aims and Structure

Intention and main focus of the METEAN is to combine the research competence in biomedical engineering of the Fraunhofer Institute for Integrated Circuits (IIS) with clinical expertise of regional partners from industry, reimbursement agencies and specifically the Universitätsklinikum 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 within the Universitätsklinikum 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 Collaborative Research Center (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,

Interdisciplinary workshop in the METEAN seminary room

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 Chair of Diagnostic 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 we developed 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 Chair of Internal Medicine IV, the Chair 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 Federal Ministry of Education and Research (BMBF), is a continuous monitoring of patients with cardiac risk constellations for both stationary and home care monitoring. After optimization towards a microsystem, the portable vital-sensor system (developed earlier within the project SOMATEK) will be certified as medical class II product. Based on this sensor system, two observer studies will be conducted in cooperation with the Department of Internal Medicine of the Heidelberg University Hospital and the local Chair of Anesthesiology. While in Heidelberg the "KARDIKOM Wireless" system will be tested with respect to clinical use and its integration into a patient data management system, the focus of investigation in Erlangen will be the user acceptance and suitability for home care monitoring.

Teaching

Within METEAN, students of medical und applied informatics, biomedical technology and electronic devices, physics and mathematics of the Friedrich-Alexander-Universität Erlangen-Nürnberg as well as of Universities of Applied Science are educated through assignments and supervision of internships, bachelor- und master thesis. Additionally, scientists from METEAN are involved in various lecture units of the Medical and Technical Faculty.

Imaging Science Institute (ISI)

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Aims and Structure

The Imaging Science Institute (ISI) was founded in 2005 as a joint venture between Siemens Healthcare and the Institute of Radiology of the Friedrich-Alexander-Universität Erlangen-Nürnberg. Its location within the Universitätsklinikum Erlangen makes it possible to study the contribution of modern imaging systems to successful 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.

Research

A wide variety of studies are 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 Federal Ministry of Research and Education.

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 guarantee 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 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 soon came to enjoy 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 5,000 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 five years since its establishment roughly 15,000 people from all over the world have visited the ISI Erlangen, among them about 5,000 course participants (doctors, radiographers, medical technicians), but also decision-makers of other clinics as well as representatives of public healthcare systems and politicians.

Central Institute of Medical Engineering (ZiMT)

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Aims and Structure

Medical technology is one of the main focuses of the Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU). About 50 professors and university lecturers are working in this sector linked together in the Central Institute of Medical Engineering (ZiMT) which was founded in December 2009. The coordination of responsibilities of numerous cooperation partners is an important core area of this institute. Therewith, the biggest university of northern Bavaria has established a new organizational unit which sharpens its biomedical engineering profile and improves the general conditions for interdisciplinary collaboration in diversified research areas in medical technology.

Head of the ZiMT is an interdisciplinary cooperative direction consisting of Prof. Dr.-Ing. Joachim Hornegger (Faculty of Technology), Prof. Dr. med. Dr. h.c. Jürgen Schüttler (Medical Faculty) and Prof. Dr. Ben Fabry (Faculty of Science). Operatively, the ZiMT is managed by an agency directed by the executive director Dr.-Ing. Kurt Höller.

Research

The scientific focus on "healthcare engineering" is of greatest social relevance considering the demographic development. At the FAU it is perfectly embedded in an excellent research environment. In January 2010, the staff responsible for the ZiMT was approved by the positive decision concerning a competition of the federal research department for clusters of excellence. During the period of application of the Center of Excellence for Medical Technology "Medical Valley EMN e.V." for the BMBF grant, the ZiMT supported the applying staff of the university and sorted single applications by main topics. In addition the ZiMT represented the university as a formal applicant in front of the project agency.
The aim of the Center of Excellence for Medical Technology "Medical Valley EMN e.V.", and therefore of the ZiMT, is the development of technologies which increase life expectancy, improve quality of life and reduce costs in the public health sector. Scientists at the FAU contributed fundamentally to progress in areas of medical imaging, telemedicine, bio-materials, and therapeutical systems. The close collaboration with Siemens Healthcare, Fraunhofer IIS and about 50 medical technology enterprises of the metropolitan area fulfill the excellent research environment at the FAU.

The ZiMT concentrates all activities within the university together with representatives of the university clinic. Its mission is to expand the research network in the priority area of healthcare engineering within and around the university. In addition, the institute provides a more transparent public image of the highly dynamic area of healthcare engineering at the Friedrich-Alexander-Universität.

Many chairs of the FAU, especially the faculties of Technology, Natural Sciences and Medicine and the Department of Economics deal with research questions about healthcare engineering such as medical biotechnology, biomaterials, medical imaging, molecular imaging, MR imaging, image processing, computational medicine, medical computer science, medical process management, bioinformatics, physics and healthcare management, etc.

Teaching

At the FAU, the relevance of "healthcare engineering" as the focus of science is not only shown in research but also in the educational sector.

The newly established bachelor course healthcare engineering started as second largest study program at the Faculty of Technology in the winter term 2009/2010 with great motivation and satisfaction of the students. In the second year, it turned into the largest program with 300 registered students. In particular, courses such as informatics, electrical engineering, electronic engineering, information technology, mechanical engineering, material engineering as well as chemical and biological engineering are embedded in the degree course healthcare engineering. Right from the start in the first terms, the basics for mathematics, physics, and medical subjects are set. Beyond the obvious cooperation of the faculties of technology, medicine and natural science, there are also specific references to arts, humanities and economics.

In the upcoming winter term 2011/2012, the master program in healthcare engineering will be initiated 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 production engineering, instrument engineering, and prosthetics (mechanical and material engineering).
In order to assure the high quality of these study programs, the bachelor as well as the master program is expected to be internationally certified in 2011. This will allow further conclusions to the feasibility of the program. The definition and the validation of aims as well as organizational and resource requirements will be monitored and compared to existing concepts.

ELAN Program for Supporting Clinical Research and Teaching

Speaker
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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 are devoted to funding projects for limited periods of time, taking also into consideration 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 financial support for research projects, promotion of innovative didactic models and internationalization of clinical teaching as well as its evaluation.

Funding

First of all, funding is provided for projects of highly qualified young investigators and newly established groups. Besides this, pilot projects and bridging of financial gaps in ongoing investigations are also supported. The project specific funding for highly qualified young investigators is primarily supported by a co-initiated and cofinanced "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 6 to 12 months appeared best suited for this purpose in the standard program, whereas an extension up to 24 month for the "first-application-program" is possible. From mid 1998 until the end of 2010, a total of 724 grant applications have been submitted (2009: 57, 2010: 51), coming from virtually all clinical departments. The numbers of grant proposals from the respective departments reflected both their sizes and research activities, though to different extents. The average funding was about € 34,000 in 2009 and increased in 2010 to 38,000 in standard program and about € 100,000 in the "first-application-program". The total amount of funding requested was 1.9 million euro in 2009 and remained the same in 2010. 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. 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 483 out of 544 projects were completed, representing a total funding of €11 million. From these projects, 258 papers (20 in 2009, 15 in 2010) were published mostly in high ranking or well respected journals. Additionally 88 (8 in 2009, 4 in 2010) grants were acquired from external funding sources (1.3 million euro in 2009, 0.35 million euro in 2010) amounting since 1998 to a total of about 15 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 for dynamically improving clinical research in our faculty.

Johannes and Frieda Marohn-Foundation

Speaker
Prof. Dr. med. Dr. med. dent.
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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 Medical Faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg, serving diagnosis, prevention and therapy of diseases in general. Projects dealing with diseases in the field of gastroenterology including all liver and pancreatic diseases with 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 Medical Faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg.

According to the rules of the foundation, five members of the faculty have to be elected for a three years period to serve on 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 costs of cooperation between scientific and clinical departments.

Grant applications should be sent to the president of the scientific committee. The rules of the foundation itself can be provided by the secretary of the Johannes and Frieda Marohn-Foundation.

Accepted projects (Time of funding 2009 – 2010)

Financial year	Budget	Number of accepted applications
2009	402.172,99 €	5 = 88.962,00 €
2010	529.565,99 €	15 = 428.000,00 €

Finalized projects (Time of funding 2007 - 2009)

Number of projects	Number of publications	Continued funding by other foundations *
17	25 (from 16 projects)	6 projects

* German Research Foundation DFG = 4 projects; other foundations = 2 projects
12 projects could not obtain further financial support

Advancement of Women and Gender Research Promotion

Speaker
Prof. Dr. med. Kerstin Amann

Deputies
Prof. Dr. med. Carla Nau
Prof. Dr. rer. nat. Ursula Schlötzer-Schrehardt

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Aims and Structure

The women's representative of the medical faculty was placed at the disposal of academic staff of the Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU) and of the Universitätsklinikum Erlangen. In October 2007, the Executive Board of the FAU and the Medical Faculty concluded a target agreement to support women in science. The targets for 2012 are:

To increase in the number of habilitated women from 17 % (2004/2006) to 25 % (2012).
To 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.

Several programs were particularly initiated to support women in achieving the requirements of a scientist eligible for the appointment as a professor.

Mentoring program - ARIADNEmed

Project coordinator: Dr. phil. Micaela Zirngibl
Part of the target agreement is the installation of a mentoring program called ARIADNEmed. ARIADNE is already successfully running in other faculties. The first pass of ARIADNEmed started in October 2008 and ended in December 2009. The program interconnects highly talented young female scientists (postdoctoral students) and experienced male and female mentors. The mentor gives advice and supports in the matter of career planning and finding. Regular network events and workshops, e. g. working towards professorship, research promotion and third-party funds and management and leadership training are offered during the project phase. The second pass of the program, serves 16 Mentees and 14 male and female mentors. For quality assurance, the program is evaluated externally.

Winter semester 2010/11	
Elementary Students	152 (67 %)
Female Students in total	1868 (64 %)
Females graduated	186 (55 %)
Females habilitated	6 (17 %)
Female professors in total	9 %
W1	1
C3 / W2	10
C4 / W3	1

Headhunting

Headhunting was first started in 2008. We try to raise the number of applicants for professor calls. Furthermore the medical faculty involves one mentee of the ARIADNEmed Mentoring program subject-specific in appointment procedures as advisory member.
In order to make appointment procedures more transparent, the women's representative who is entitled to vote, is participating in every appeal committee as well as two additional female experts.

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 2010 we received 26 applications – 24 female PostDocs received financial support. In 2010 the total funding amounted to € 11,103, an increase of € 4,455 compared to 2009.
As part of the ELAN-Program seven scholarships were granted to especially talented young female scientist of the medical faculty within the reporting period. The scholarships allow for early and independent research work as it enables the recipients to be exempt from clinical duties to do research.

Gender Research

The women's representative of the Medical Faculty endeavors to acquire experienced female scientists, who serve as role models for our so-called "Gender Lectures". We want to positively influence the decision of young talented females for a scientific career.
Per semester we invite three to five female guest lecturers, who motivate young female scientists with their interesting lectures. The lectures are becoming more and more popular and, depending on the lecturer and topic, are well attended.
€ 40,000 were one-time available to support females, who do research in gender-specific areas. Two female scientists, who have done research on gender aspects could be funded.

Research Foundation of Medicine

Speaker
Prof. Dr. med. Werner G. Daniel

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Aims and Structure

In December 2007, the Research Foundation of Medicine at the Universitätsklinikum Erlangen was founded at the initiative of the professors of the Universitätsklinikum Erlangen and the Medical Faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg. The foundation aims at creating a governing body for patients, patrons and donors based on the American model, where the practice of founding has a long tradition, so that research at the Universitätsklinikum Erlangen but also at single hospitals and specific projects can be fostered centrally. The Research Foundation is intended to be a means of financing independent from public funds that grants an enduring support for the medicine in Erlangen. There were 36 primal founders, mainly hospital directors, heads of the departments and institutes, but also the mayor of Erlangen that facilitated the development of the foundation through their personal assets. Already shortly after the foundation was established, numerous former patients, who had been treated at the Universitätsklinikum Erlangen, offered donation. During the period under report the capital stock of the foundation has increased continuously, particularly due to the support by some very generous donors who became honored by personal named chapters within the Research Foundation, and first research projects received financial support. Following the "Matching Funds" concept, all financial supports given by the Research Foundation are increased by the same amount by the Universitätsklinikum Erlangen out of its income that is subject to income tax. Everyone is able to foster the foundation by choosing e.g. a clinic he wants to support at the Universitätsklinikum Erlangen. The head of the clinic then decides which concrete area is fostered by the donation. In addition to the tax concessions, after a certain fostering sum, it is possible to establish an own self-named foundation within the Research Foundation. This was the case, when in 2009 the auditorium "Medizinische Klinik und Frauenklinik" was renamed as "Rudolf-Wöhrl-Hörsaal". The recently deceased 95-year-old entrepreneur from Nuremberg, who has founded the Wöhrl's fashion boutiques, donated a sum of € 250,000 for research projects (see figure).
Foundation Account: account number: 62 000, Sparkasse Erlangen, bank code: 763 500 00

From the right: Hans Rudolf Wöhrl, founder Rudolf Wöhrl with his wife Mizzi; Prof. Dr. med. Werner G. Daniel, speaker of the Research Foundation of Medicine; Prof. Dr. Bernhard Fleckenstein, chairman of the foundation
Source: Dean Office of the Medical Faculty

Advancement

Four main goals have been set for the emerging Research Foundation of Medicine. The advancement of science and research in all fields of basic and clinical medicine, the advancement of training and further education of students, physicians and scientists, the fostering of the Public Healthcare, especially in the fields of prevention and early diagnostics of disease, and, last but not least, benevolence within the medical care of patients in need.
Furthermore, every two years the Research Foundation together with the Medical Faculty gives the Jakob-Herz-Prize to an outstanding researcher in the field of Medicine. In 2009, this newly established prize was first given to Prof. Robert A. Weinberg, Whitehead Institute for Biomedical Research, Cambridge, USA. In addition, a series of 12 to 14 lectures on up-to-date medical issues, initiated in 2007 and addressed each semester to interested citizens is also supported by the Research Foundation.

Jakob-Herz-Prize

Speaker
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Fig. 1: Medal with the portrait of Jakob Herz.
Source: Dean Office of the Faculty of Medicine

Fig. 2: Prof. Fleckenstein congratulates Prof. Weinberg, next to him Prof. Schüttler
Source: Dean Office of the Faculty of Medicine

Aims and Structure

Since 2009 the Medical Faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg has been offering the Jakob-Herz-Prize. This Award was named after Jakob Herz, the famous doctor from Erlangen and the first Jewish professor in Bavaria. The decoration is given for outstanding scientific success in the whole field of theoretical and clinical medicine. Individual achievements in research as well as scientifical lifework can be honored. The prize will be awarded biennial in the course of a ceremony arranged by the Medical Faculty. This event includes a talk given by the laureate. The committee of the Jakob-Herz-Prize consists of the professors of the commission for research and young academics of the Medical Faculty, who evaluate the documents of nomination. Adequate candidates can be recommended by all professors of the faculty. The final decision is made by the faculty council. The prize comprises an amount of € 10,000 donated by the professors of the medical faculty as well as a certificate and a medal with the portrait of Jakob Herz (Fig. 1).

History and Funding

The prominent doctor and researcher from Erlangen, Jakob Herz, shall be honored with the designation of this prize. Jakob Herz (1819-1871) was in due course the leading instructor of pathological anatomy and surgery and is considered as the founder of surgical anatomy. In 1869 Jakob Herz was nominated as the first Jewish professor in the kingdom of Bayreuth. At this time he has already been honorary citizen of Erlangen for two years. Jakob Herz died in 1871 during an effort for his patients. A larger than life monument of him at the Erlanger market place was destroyed by the Nazis. His native town Bayreuth removed a memorial tablet of him and redefined streets named in honor to him during the National Socialism. The Jewish physician, scientist and philanthropist was therefore also after his death persecuted for his religion. Only many years after the Second World War, at 1983, the citizens of Erlangen repented and installed a new memorial at the corner Universitaetsstrasse/Krankenhausstrasse. On this memorial, which shall be a compensation of the destroyed one, the sentence "We remember Jakob Herz, a citizen whom our town raised and destroyed a monument" is inscribed. In 2000, the principal of the university disclosed a memorial tablet in honor of Jakob Herz at the Hugenottenplatz.

The Medical Faculty elected the most famous scientist Prof. Robert Weinberg from Cambridge, Massachusetts the first laureate (Fig. 2). The important contributions of Prof. Weinberg in cancer research are the discovery of the oncogenes and tumor suppressor genes. In the last years, Prof. Weinberg studied with his group the genetics of metastasis and started to investigate how tumor stem cells affect carcinogenesis. One of his main achievements is to employ his scientific finding to improve the clinical diagnostics and therapy of breast cancer. He is an internationally accepted authority in the field of tumor genetics.

Further Foundations for Research Support

In addition to the ELAN program and the Johannes and Frieda Marohn Foundation, more than 20 different foundations and endowments are established at the Medical Faculty, which support research projects at different levels. Furthermore, there are donations to the Medical Faculty (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 university and closely connected to the Medical Faculty are mentioned in detail:

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 2009 the prize was given to Prof. Dr. Hendrik Kehlet, University of Copenhagen, Denmark for his outstanding contributions to pain research and the implementation of Fast-Track-Concept in surgery. The Dr. Fritz Erler junior prize was given to PD Dr. Ulrich Kneser, Department of Plastic and Hand Surgery, FAU, to appreciate his results in Tissue-Engineering.

The Gottfried and Lieselotte Naumann Fund supports ophthalmology, especially clinical ophthalmo-pathology and contribution to microsurgery of the eye. (Contact: Mrs. Penschuck, Ref. F3, FAU) In a four-year rhythm the prize is given to an extraordinary researcher. 2009 the award of $50,000 was donated to Prof. Dr. Ursula Schlötzer-Schrehardt, Department of Ophthalmology at the Universitätsklinikum Erlangen.

The Dr. Norbert Henning Foundation gives a prize for research in the field of gastroenterology every two years. 2009 Prof. Dr. Karl Lenhard Rudolph director of the Institute of Molecular Medicine, University of Ulm was awarded for his scientific achievements in the field of cirrhosis of the liver tumor development in the gastrointestinal tract.

At the end of 2007 the professors of the Universitätsklinikum Erlangen and the Medical Faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg initiated the founding of the Research Foundation of Medicine at the Universitätsklinikum Erlangen. The foundation purposes to supports scientific progress in all areas of basic and clinical medicine. The foundation also intends to support teaching and advanced training of medical students, physicians and young scientists, to advance the public health system (particularly with regard to prevention and early diagnosis of disease) and to assist benevolence within the medical care of patients in need. Besides, it is planned that prizes for outstanding achievements of scientists as well as scholarships and education allowances for gifted students will be awarded.

The Dr. Kurt and Margarete Groß Donation support specific achievements in the field of cardiology, cardiac-physiology or cardiac surgery.

The Ria Freifrau von Fritsch Foundation (Contact: Mrs. Penschuck, Ref. F3, FAU) was established to support cancer research and to finance the Ria Freifrau von Fritsch Prize for an outstanding research achievement.

The Sofie Wallner Foundation (contact: Mrs. Penschuck, Ref. F3, FAU) 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.

Research projects in environmental medicine can be supported by the Adolf Rohrschneider Foundation (contact: Mr. J. Hubert Ref. F3, FAU).

The Wilhelm and Helene Dörfler Foundation (contact: Prof. Dr. G. Schett, Department Medicine 3) 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: Mrs. Penschuck, Ref. 3, FAU).

The Dr. Ernst and Anita Bauer Foundation is an unaffiliated donation with base in Nuremberg. Its aim is to support gifted young physicians who come 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 decorates as well as the Fritz and Maria Hofmann foundation outstanding master´s and diploma theses.

The best and most concise postdoctoral qualification (Habilitation) is awarded annually by the Thiersch Prize.

Most outstanding doctoral theses are awarded by the Staedtler Prize.

The Novartis foundation supports especially young investigators at our Medical Faculty.

The Foundation for Teaching was founded to support and improve the education of young clinicians. (contact: Mrs. Penschuck, Ref. F3, FAU)

Detailed information to the different foundations mentioned above can be found on the Homepage:
www.uni-erlangen.de/universitaet/stifter-foerderer/stiftungen/

Physico-Medical Society Erlangen

Council
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. Dr. h.c. Karl-Heinz Plattig (Treasurer)

Contact
Prof. Dr. med. Christian Bogdan
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www.physicomedica-erlangen.de

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 Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU). In the year of the 200th birthday of the PMSE the Medical Society, which had segregated from the PMSE in 1958 after the 150th birthday celebration of the Societas physico-medica Erlangensis, united again with the PMSE.

As of December 31st, 2010 the society has 408 members inside and outside Germany, with five of them being honorary and 46 being corresponding members. Once per year the society holds a members´ assembly upon invitation by the council.

Every semester the society holds three regular meetings with lectures given by members or invited guests. From 1984 to 2010 ten volumes of reports were published, each of them consisting of four single issues (ISSN 0371-2117).

Figure from the talk of Prof. Quick, at February 4th, 2010: Magnetic resonance imaging (MRI) provides imaging of the entire human body from head to toe with high soft tissue contrast and in every oblique image orientation while not using X-rays.
Source Prof. Quick

Beside scientific papers the reports contain recent outstanding academic speeches, for example inaugural or farewell speeches, addresses on the occasion of honorary promotions and of the annual graduation ceremony of the Medical Faculty of the FAU.

Lectures in the Years 2009 and 2010

February 4th, 2009
Prof. Dr. rer. nat. Ulrich Kalinke
Director of the Center for Experimental and Clinical Infectious Disease Research (TWINCORE), Hanover Medical School, Germany
"Type I Interferon in Virus Infection, Tumor Disease and Autoimmunity"

June 3rd, 2009
Prof. Dr. med. Heiko Braak
Clinical Neuroanatomy, Center for Clinical Research, University of Ulm
"The Systemic Spread of Parkinson-associated Pathological Changes in the Human Nervous System"

June 17th, 2009
Prof. Dr.-Ing. Gerd Hirzinger
The German Aerospace Center (DLR) in the Helmholtz Society
Institute for Robotics and Mechatronics, Oberpfaffenhofen
"Perspectives of the Use of Robots in Surgery"

October 28th, 2009
Prof. Dr. med. Josef Martin Penninger
Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA)
Vienna, Austria
"RANKL - From Mice to Human Medicine"

February 4th, 2010
Prof. Dr. Harald H. Quick, Ph.D.
MR Imaging, Institute for Medical Physics, Friedrich-Alexander-Universität Erlangen-Nürnberg
"MR Imaging: Soft Tissue Contrast without Radiation"

June 2nd, 2010
Prof. Luigina Romani, M.D. Ph.D.
Microbiology Section, Department of Experimental Medicine and Biochemical Science, University of Perugia, Perugia, Italy
"Distinct modules of immunity provide resistance and tolerance to fungi"

June 30th, 2010
Prof. Dr. Bernd J. Pichler, PhD
Labor für Präklinische Bildgebung und Bildgebungstechnologie der Werner Siemens-Stiftung, Department Radiologie, Universität Tübingen
"PET/MRI – a new hybrid technology for preclinic research and clinical diagnostic"

Degree Program in Medicine

Speaker
Prof. Dr. med. Hans Drexler
Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, Clinical study section

Prof. Dr. med. Winfried Neuhuber
Institute of Anatomy, Chair of Anatomy I

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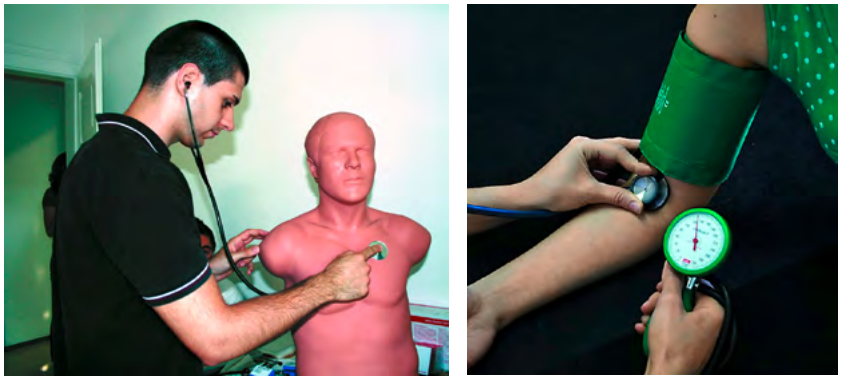

Training to practice the medical checkup in the Skills Lab

Aims and Structure

In the 2009/2010 winter term, 2,008 students were enrolled in the study program Medicine (173 in the 1st semester) and in the 2010 summer term the number was 2005 (159 in the 1st semester). The percentage of women studying Medicine increased compared to the 2007/2008 winter term. In the 2009/2010 winter term 63.6% of the enrolled students were female and in the 2010 summer term there were 64.4% female students.
According to statistics of the Friedrich-Alexander-Universität Erlangen-Nürnberg, for the 2009/2010 winter term and the 2010 summer term, 7.7% of the students enrolled in the study program Medicine were foreigners.

Applicants for the study program Medicine are chosen according to the criteria of the German Foundation for University Placement ("Stiftung für Hochschulzulassung") through hochschulstart.de (the successor of ZVS). In the 2011/2012 winter term applicants will for the first time be able to improve their chances of receiving a place in the study program Medicine in Erlangen by taking the so-called "Test für medizinische Studiengänge" (test for medical study programs). Taking the test is, however, optional. Applicants who decide to take the test can, for the selection process in Erlangen, improve their grade in the final secondary school examination (Abitur). Applicants who pass the test among the best 10% can improve their grade by 0.8, the best 20% by 0.6, the best 30% by 0.4 and the best 40% by 0.2. For example, an applicant with the grade 2.1 in the final secondary school examination can improve his grade to 1.3 if he belongs to the best 10% of the test participants in the "Test für medizinische Studiengänge".

Online-Evaluation

Each semester, all courses are evaluated online by the students with the help of the online evaluation system EVALuna (Dr. Ganslandt, Institute of Medical Informatics). The results of the online evaluation are presented and discussed in the central faculty meeting once per semester by the Dean of Student Affairs. A major part of the state funds in the university clinics is distributed according to the results of the online evaluation. Each semester the students vote for the best lecturers and monetary sums are awarded to the clinic or institute that the winners are employed by. 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 study program (semesters 5 – 10) for Medicine receive grants of 30,000, 20,000 and 10,000 euro respectively. Since fewer professorships in the study program for Dentistry participate in the instruction of students, only one grant (10,000 euro) is awarded to an instructor in the clinical part of the study program for Dentistry. The awarded instructor receives a certificate for good teaching; the grants go to the instructor's clinic or institution and add to their respective budgets. Instructors in the pre-clinical or theoretical part of the medical study program (semester 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 receive a grant if it has been evaluated by at least 20% of the students in the particular semester.

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, among other things, practice auscultation, catheterization, or taking blood with the help of artificial arm-models.

Skills Lab PERLE is fully funded by student fees and a visible enrichment of the medical education in Erlangen. Courses can be attended by all students during the semester. Additionally, the Skills Lab offers special courses during the lecture free time.

Traditionally, the courses offered in Skills Lab PERLE give students the opportunity to prepa-

re themselves for their clinical electives (Famulaturen) and also their practical year (Praktisches Jahr).

Since the 2010 summer term the Skills Lab has also been offering courses for students in their preclinical studies (semester 1-4) in order to prepare them for their first clinical traineeship (Pflegepraktikum). Very popular amongst the students are the new so-called "Bettenprüfungskurse", small training groups guided by two experienced doctors who prepare the students for the oral part of their second state examination (2. Staatsexamen).

Medical State Examination

In 2009 and 2010 students in Erlangen achieved very good results in the Medical State Examination, especially in part one after the fourth semester. All medical students in Germany take the same examination. Therefore, results are objective and comparable. According to the students' State Examination results (1. Abschnitt der Ärztlichen Prüfung), the Medical Department in Erlangen belongs to the top group of Medical Departments in Germany, in the winter term 2010/2011 the students from Erlangen came forth in the national ranking. In order to improve the results of the second part of the Medical State Examination (2. Abschnitt der Ärztlichen Prüfung), a revision course was introduced for students who have completed their practical year and are preparing for their second Medical State Examination. In three weeks of intensive teaching doctors from all clinics repeat the most important aspects of the medical curriculum and point out what is important for the students to know for the second part of the Medical State Examination (2. Abschnitt der Ärztlichen Prüfung).

Degree Program in Dentistry

Speaker
Prof. Dr. med. dent. Anselm Petschelt

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Aims and Structure

The school of dentistry at the Friedrich-Alexander-Universität Erlangen-Nürnberg (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 subjects taught at medical school. 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 we provide in dentistry from the training we provide in medicine.

As in the first phase of medical school, 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 6 students per academic staff member in dentistry school as opposed to somewhere between 3 and 6 students per academic staff member in medical school; 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 is constant in 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 to achieving steady improvement in the quality of teaching.

Our dental clinic 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. The Erlangen School of Dentistry continues to maintain the first position in German university rankings published by the CHE (Center for University Development) since 2006.

Degree Program in Molecular Medicine

Speaker
Prof. Dr. rer. nat. Michael Wegner

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Analysis of a cloning, bacterial colonies
Source: Andreas Brunner

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 has created a future-oriented program for medical scientists interested in research careers in industry, administration and academics. Nationwide, this program in Molecular Medicine has been met by an extraordinary interest. Each academic year 38 students are admitted from more than 700 applicants. Starting from the winter term 2007/2008, students have been admitted to the new B.Sc./M.Sc program, which was established according to the guide lines of the Bologna declaration. With graduation of the first B. Sc. students in summer 2010, 30 students started with the consecutive master program in the winter term 2010/11.

Objectives of the degree program in Molecular Medicine

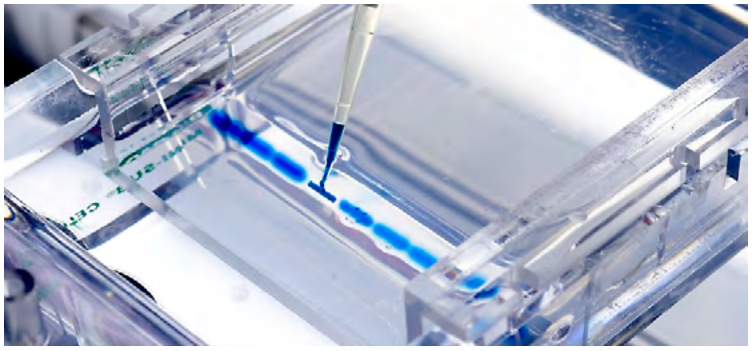
The advances in biomedical research continually change our knowledge and understanding of basic biological mechanisms and disease-induced alterations, reflected in new and improved therapies. The consecutive B. Sc. / M. Sc. program in Molecular Medicine addresses the necessity to teach both medical and 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 6 semesters, 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 Nikolaus-Fiebiger-Center. During the first academic year the focus is 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. focuses on functional aspects, the M.Sc. program mediates interdisciplinary topics, which are taught jointly by different institutes. This profile is already put to work in the courses 'Molecular Pathomechanisms' and 'Neurosciences' that are taught by the biochemistry, pathology and physiology institutes and the biochemistry, physiology, neurology and psychiatry, respectively. The Master Program ends with a thesis of 6 month.

Due to the financial support of the Innovation Initiative at the Friedrich-Alexander-Universität Erlangen-Nürnberg, a new professorship was established that further broadens the M. Sc. curriculum by introducing the module "Molecular Imaging" to the program. This module will reflect another scientific strength of Erlangen, as it will bridge the gap between the degree program and industrial applications.
The first year students in Molecular Medicine are welcomed by an annual symposium, introducing them to the program and the Medical Faculty of the Friedrich-Alexander-Universität Erlangen-Nürnberg. 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 at meetings of the module representatives and 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 Medical Faculty, the central advisory service of the Friedrich-Alexander-Universität, as well as by brochures and the internet homepage www.molmed.eu. At present, half of the students enrolled in Molecular Me-



DNA-Analysis, Agarose gel electrophoresis
Source: Andreas Brunner

dicine 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. When asking 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 21 applicants compete for one admission slot in Molecular Medicine. For the winter term of 2010/2011, admission requirements for the program had reached the highly selective grade point average of 1.4, representing extremely strict criteria. 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. This examination system has led to higher performance pressure and less flexible time schedules particularly during the B. Sc. phase. Starting with the master program, this pressure is somewhat reduced due to a higher portion of practical courses that allows a more flexible schedule. The first two months of the third M. Sc. are a "mobility slot" 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 Friedrich-Alexander-Universität of Erlangen-Nürnberg. 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 quality 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). One of the most successful graduates recently applied for a W3 professorship.

Medical Process Management

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

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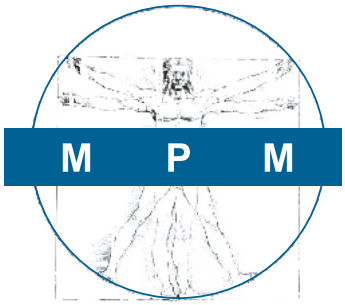

Aims and Structure

The degree program in Medical Process Management is a non-consecutive Master of Science (M.Sc.) program. Lectures are taking place at the Friedrich-Alexander-Universität Erlangen-Nürnberg (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 and 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, it is dealt with fundamental questions concerning quality and risk management, financial management, medical information technology and psychology of communication.

All in all, the degree program in Medical Process Management 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 the degree program's 30 different courses, but also two other faculties. With reference to the number of 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.

Medical Process Management 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 semesters plus the time needed for writing the master's thesis. Generally, students graduate after four semesters. A total of 120 ECTS-credits is necessary to successfully complete the degree program. Students graduate as soon as they fulfil the following conditions: firstly, they must have passed all exams, which are written in the course of the first three semesters. 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 Medical Process Management has been existing for three years now. While it was taken up by 20 students in 2008, already 30 students enrolled one year later, and in 2010, the number amounted to 33 respectively.

Medical Process Management 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 to 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 gain ground on the labor market immediately, having found very good jobs in the healthcare sector.

Honorary Doctorate

Honorary Doctorate 2009

Prof. Dr. h.c. Ronald C. Desrosiers Ph. D.
New England Primate Research Center, Harvard Medical School, Southborough, MA, USA

Honorary Doctorate 2010

Dr. med. h.c. Wolfgang Schaffer
President (ret.) of the Higher Regional Court Nuremberg, Germany

A Selection of Awards 2009 – 2010

2009

Auszeichnung: „Eminent Scientist of the Year 2009"
Prof. Dr. med. Rolf Schröder
Chair of Neuropathology

Bundesverdienstkreuz am Bande
Prof. Dr. med. Helmut Legal, i. R.
Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH

Duchenne-Erb-Preis 2009
Prof. Dr. med. Bernhard Neundörfer
Emeritus of the Chair of Neurology

Ehrendoktorwürde im Fach Medizin der Med. Fakultät der RWTH Aachen
Prof. Dr. Dr. med. h.c. Willi A. Kalender PhD
Chair of Medical Physics

Ehrenmitgliedschaft bei der Kalbresischen Chirurgenvereinigung
Prof. Dr. med. Dr. h. c. Werner Hohenberger
Chair of Surgery

Ehrenurkunde des Bayerischen Staatsministeriums f. Wirtschaft, Infrastruktur, Verkehr und Technologie für seine Verdienste in der Ausbildung
Prof. Dr. Dr. med. h.c. Willi A. Kalender PhD
Chair of Medical Physics

Erler-Juniorpreis 2009
PD Dr. med. Ulrich Kneser
Department of Plastic and Hand Surgery

Ernennung zum Professor h.c. des China-Japan Friendship-hospitals Beijing
Prof. Dr. med. Dr. h. c. Werner Hohenberger
Chair of Surgery

Förderpreis der Stiftung Versorgungsforschung der Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte e.V. 2009
Prof. Dr. med. Renke Maas
Chair of Clinical Pharmacology and Clinical Toxicology

Förderpreis der Wyeth Pharma 2009
Prof. Dr. med. Michael Sticherling
Chair of Skin and Venereal Diseases

Förderpreis für Schmerzforschung der Deutschen Gesellschaft zum Studium des Schmerzes (DGSS) 2009
Dr. med. Frank Seifert
Chair of Neurology

Förderstipendium: „For Women in Science"
Prof. Dr. med. Mareike Leffler
Until august 2010 Department of Plastic and Hand Surgery

Forschungspreis der Gustav Adolf und Erika Dornberger-Stiftung 2009
Dr. rer. nat. Annick Seithel
Chair of Clinical Pharmacology and Clinical Toxicology

Forschungsstipendium der Tom-Wahlig-Stiftung
PD Dr. med. Beate Winner
IZKF – Interdisciplinary Center for Clinical Research
Prof. Dr. Jürgen Winkler
Division of Molecular Neurology, Chair of Neurology
Dr. Zacharias Kohl
Division of Molecular Neurology, Chair of Neurology

Franz-Koelsch-Medaille 2009
Dipl.-Ing. Karl-Heinz Schaller
Chair of Occupational and Social Medicine

Ria Freifrau von Fritsch-Preis 2009
Prof. Dr. rer. nat. Diana Dudziak
Chair of Skin and Venereal Diseases

Georg-von-Hevesy-Preis 2009
PD Dr. rer. nat. Olaf Prante
Chair of Clinical Nuclear Medicine

GlaxoSmithKline-Wissenschaftspreis für Klinische Forschung 2009
PD Dr. med. Reinhard Voll
IZKF / Chair of Internal Medicine III

Helen-Keller Prize for Vision Research 2009
Prof. Dr. med. Elke Lütjen-Drecoll
Chair of Anatomy II

Innovationspreis der deutschen Hochschulmedizin 2009
Prof. Dr. med. Christoph Alexiou
Chair of Otorhinolaryngology

Liquorpreis 2009
PD Dr. med. Juan Maler
Chair of Psychiatry and Psychotherapy

Nachwuchsförderpreis der Deutschen Gesellschaft für Thrombose und Hämostase
Dr. rer. nat. Christiane Mühle
Chair of Psychiatry and Psychotherapy

Paul Ehrlich- und Ludwig Darmstaedter-Nachwuchspreis 2009
Prof. Dr. rer. nat. Falk Nimmerjahn
Until march 2010 Chair of Internal Medicine III

PRO-SCIENTIA-Förderpreis 2009
Prof. Dr. rer. nat. Falk Nimmerjahn
Until march 2010 Chair of Internal Medicine III

Renate Wittern-Sterzel Preis 2009
Prof. Dr. med Michael Uder
Chair of Diagnostic Radiology

Simon Dack Award for Outstanding Scholarship 2009
Prof. Dr. med. Stephan Achenbach
Chair of Internal Medicine II

Staatsmedaille für die Verdienste um die Gesundheit in Bayern
Prof Dr. med. Hans Drexler
Chair of Occupational and Social Medicine

Unterberger-Preis 2009
PD Dr. med. Abbas Agaimy
Chair of General Pathology and Pathological Anatomy

Verfassungsmedaille des Freistaats Bayern in Silber
Prof. Dr. med. Elke Lütjen-Drecoll
Chair of Anatomy II

Wahl zu Mitglied in die Deutsche Akademie der Naturforscher Leopoldina - Nationale Akademie der Wissenschaften, Halle (Saale)
Prof. Dr. Dr. med. h.c. Willi A. Kalender PhD
Chair of Medical Physics

Wilhelm-Vaillant-Preis
Prof. Dr. med. Anita Rauch
Until january 2009 Chair of Human Genetics

William D. Coolidge Award
Prof. Dr. Dr. med. h.c. Willi A. Kalender PhD
Chair of Medical Physics

World SIVA Achievement Award 2009
Prof. Dr. med. Dr. h.c. Jürgen Schüttler
Chair of Anesthesiology
Prof. Dr. med. Dr. rer. nat. Helmut Schwilden
Chair of Anesthesiology

2010

August-Bier-Preis 2010
PD Dr. med. Andreas Leffler
Until september 2010 Chair of Anesthesiology

Award Zukunft und Ernährung
Dr. med. Pascal Burger
Chair of Psychiatry and Psychotherapy
PD Dr. med. Teresa Biermann
Chair of Psychiatry and Psychotherapy

Carl-Ludwig-Schleich-Preis 2010
Dr. med. Andreas Wehrfritz
Chair of Anesthesiology

Cotterman Award der Amerikanischen Gesellschaft für Humangenetik (ASHG)
Dr. med. Christiane Zweier
Chair of Human Genetics

Dieter-Klaus Förderpreis für die Hochdruckforschung 2010
PD Dr. med. Kerstin Benz
Chair of Pediatrics
Dr. med. Ulrike Raff
Chair of Internal Medicine IV

Ehrenmitgliedschaft bei der Europäischen Gesellschaft der Radiologie (ESR)
Prof. Dr. Dr. med. h.c. Willi A. Kalender PhD
Chair of Medical Physics

Erster Wissenschaftspreis 2010 der Deutschen Gesellschaft für Senologie e.V.
Prof. Dr. med. Peter Andreas Fasching
Chair of Obstetrics and Gynecology

Forschungsförderpreis der Dt. Alzheimer Gesellschaft e.V.
Dipl. Psychologin Birgit Eichenseer
Chair of Psychiatry and Psychotherapy
Dipl. Soziologin Gudrun Ulbrecht
Chair of Psychiatry and Psychotherapy

Gunther Bastert Innovationspreis
Prof. Dr. med. Peter Andreas Fasching
Chair of Obstetrics and Gynecology

Helmut-Bauer Nachwuchspreis für Multiple Sklerose Forschung 2010
Dr. med. De-Hyung Lee
Chair of Neurology

Innovationspreis 2010 für Krankenhausapotheker im Bereich Klinische Pharmazie
Dr. phil. nat. Frank Dörje
Pharmacy of the Universitätsklinikum Erlangen
Dr. Sonja Koch
Pharmacy of the Universitätsklinikum Erlangen
PD Dr. med. Richard Feyrer
Chair of Cardiac Surgery
Prof. Dr. med. Michael Weyand
Chair of Cardiac Surgery

INSTAND-Förderpreis der Gesellschaft zur Förderung der Qualitätssicherung in med. Laboratorien e.V., Düsseldorf
Dr. med. Rüdiger Zimmermann
Chair of Psychiatry and Psychotherapy

Junior Investigator Award 2010
Dr. med. Jacobus Bosch
Chair of Hematology and Oncology

Konrad BIESALSKI-Preis 2010
PD Dr. med. Lutz Müller
Chair of Orthopedics and Orthopedic Surgery

Ophthalmic Pathology Award 2010
Prof. Dr. rer. nat. Ursula Schlötzer-Schrehardt
Chair of Ophthalmology

Walter-Clawiter-Preis
PD Dr. med. Jens Titze
IZKF / Chair of Internal Medicine IV

Werner-Rosenthal-Preis
Dr. Roland Coras
Chair of Neuropathology

Ziedses des Plantes-Medaille der Physikalisch-Medizinischen Gesellschaft zu Würzburg und der Deutschen Gesellschaft für Neuroradiologie
Prof. Dr. Dr. med. h.c. Willi A. Kalender PhD
Chair of Medical Physics

Doctorate Theses, Board Qualifications, Additional Qualifications, Habilitations

Institute of Anatomy
Chair of Anatomy I

Doctorate Theses

Dietrich, Stefan, Dr. med. dent. (2009): *Transkutane nicht-invasive Vagusnervstimulation: Darstellung aktivierter Gehirnareale und ihrer Verbindungen mittels diffusionsgewichteter und funktioneller MR-Bildgebung*

Lindig, Tobias Maximilian, Dr. med. (2009): *Stachel- versus Stummelneuronen: 3D Rekonstruktion myenterischer (Typ I) Nervenzellen des Menschen*

Weidmann, Simone Birgit, Dr. med. dent. (2009): *Quantifizierung des Anteils der mutmaßlichen primär-afferenten Neuronen im Plexus myentericus des menschlichen Dünndarms*

Wolf, Matthias Friedrich Maximilian, Dr. med. (2009): *Calcitonin gene-related Peptide: Ein Marker für mutmaßliche primär-afferente Neuronen im Plexus myentericus des Schweinedünndarms?*

Kestler, Christine Vera, Dr. med. (2010): *Immunreaktivivtät des ATP-Rezeptors P2X3 in myenterischen Ganglien des Mäuseösophagus*

Schöffl, Isabelle, Dr. rer. biol. hum. (2010): *Biomechanik des Ringbandsystems der Finger*

Institute of Anatomy
Chair of Anatomy II

Doctorate Theses

Wasielewski, Rainer-Christian, Dr. med. (2009): *Surgical intervention and accommodative reponses II. Forward ciliary body accommodative movement is facilitated by zonular attachment to the lens capsule*

Wüst, Wolfgang, Dr. med. (2009): *Morphologische Untersuchungen zum Einfluss von Bimatoprost auf den Haarzyklus*

Board Qualification

Scholz, Michael, Dr.rer.nat. (2010): *Anatomy*

Habilitations

Birke, Marco, Dr. rer. nat. (2010): *In vitro Studien zur Rolle von Kammerwasserfaktoren bei der Induktion glaukomatöser Effekte in Zellen des Kammerwasserabflusswegs und Astrozyten des N. opticus*

Scholz, Michael, Dr. rer. nat. (2010): *Morphologische und physiologische Analysen von Tiermodellen mit glaukomatöser Opticusneuropathie und Retinadegeneration*

Institute of Biochemistry – Emil-Fischer-Center
Chair of Biochemistry and Molecular Medicine

Doctorate Theses

Kreisler, Annelen Andreas, Dr. rer. nat. (2009): *NRSF-Expression in Zelllinien des Bronchialkarzinoms: Regulation und Einfluss auf den Zellphänotyp*

Melzer, Nima, Dr. rer. nat. (2009): *Strukturelle und funktionelle Untersuchung der intrazellulären Domäne des Glycinrezeptors Motive für strukturelle Stabilität und Proteininteraktion*

Völkl, Thomas Michael Karl, Dr. med. (2009): *Untersuchungen zum Zelltod von Krebszellen ausgelöst durch extrazelluläres ATP und UTP*

Müller, Katharina Maria, Dr. rer. nat. (2010): *Entwicklung einer mehrstufigen Analysemethode zur Identifizierung potentieller Biomarker für die Alzheimer Demenz im Blut*

Seebahn, Angela, Dr. rer. biol. hum. (2010): *Characterization of Group III Metabotropic Glutamate Receptor C-Terminal regions*

Habilitation

Villmann, Carmen, PD Dr. rer. nat. (2009): *Pathologische Kanalerkrankungen und Bedeutung von Rezeptordomänen für die Ionenkanalfunktion auf dem Weg zu molekularen Therapieansätzen.*

Institute of Biochemistry – Emil-Fischer-Center
Chair of Biochemistry and Pathobiochemistry

Doctorate Theses

Hoser, Melanie, Dr. rer. nat. (2009): *Die Rolle der SoxC-Proteinein der Mausembryogenese*

Wolf, Friedrich Michael, Dr. rer. nat. (2009): *Klasse III POU-Transkriptionsfaktoren als wichtige Regulatoren der frühen Gehirnentwicklung*

Cossais, Francois Gilles Olivier, Dr. rer. nat. (2010): *Struktur-Funktionsanalyse des Transkriptionsfaktors Sox10 und Aspekte der Evolution*

Finzsch, Markus, Dr. rer. nat. (2010): *Einfluss von SoxE-Proteinen auf die Entwicklung glialer Vorläuferzellen im zentralen und peripheren Nervensystem*

Guth, Sabine Irmgard Erika, Dr. rer. nat. (2010): *Das Sox8-Gen: Bestimmung seiner genregulatorischen Elemente und Bedeutung für die Adipogenese*

Hammer, Alexander Andreas, Dr. med. (2010): *Die Rolle der evolutionär konservierten Region U2 für die Expression von Sox10 in Oligodendrozytenvorläuferzellen*

Potzner, Michaela Roswitha, Dr. rer. nat. (2010): *Die Rolle der SoxC-Proteine im sich entwickelnden zentralen und sympathischen Säuger-Nervensystem*

Reiprich, Simone Barbara, Dr. rer. nat. (2010): *The impact of SoxE transcription factors on the development of neural crest derivatives*

Institute of Physiology and Pathophysiology
Chair of Physiology

Doctorate Theses

Barta, Birgit Michaela, Dr. med. (2009): *Altersabhängige Veränderungen von C-Nervenfasern beim Menschen. Eine mikroneurographische Untersuchung*

Hager, Ulrich Alexander, Dr. med. (2009): *Morphological characterization of rat Mas-related G-protein-coupled receptor C and functional analysis of agonists*

Herde, Lina, Dr. med. (2009): *Die zentrale Verarbeitung des Juckreizes im Vergleich zum Schmerz*

Hoffmann, Tal, Dr. rer. biol. hum. (2009): *Inherent sensory capacities of unmyelinated peripheral nerves*

Jacob, André Klaus Ronald, Dr. med. dent. (2009): *Wirkungen des Somatostatin-Agonisten Octreotid auf den meningealen Blutfluss und die Neuropeptidfreisetzung in der Dura mater encephali der Ratte*

Langhammer, Andreas Josef, Dr. med. (2009): *Forward And Backward Enhancement bei ballistischer Stoßreizung der Haut - eine taktile Sinnestäuschung?*

Roch, Michael, Dr. med. (2009): *Ongoing activity in trigeminal wide-dynamic range neurons is driven from the periphery*

Schlechtweg, Philipp Martin, Dr. med. (2009): *Increase in NADPH-diaphorase positive and neuronal NO synthase immunoreactive neurons in the rat spinal trigeminal nucleus following infusion of a nitric oxide donor - evidence for a feed-forward process in nitric oxide production involved in trigeminal nociception*

Auer, Jürgen Wilhelm, Dr. med. (2010): *Die protektive Säure-induziert CGRP-Freisetzung des Magens ist unabhänigig von TRPV1- und ASIC3-Rezeptoren*

Eberhardt, Mirjam Jeannette, Dr. med. (2010): *Einfluss von Stickstoffmonoxid auf Freisetzung und Genexpression von Calcitonin gene-related peptide im trigeminalen Ganglion der Ratte*

Forster, Alexander Benedikt, Dr. med. (2010): *Morphin in hohen Konzentrationen sensibilisiert und aktiviert Spinalganglienzellen der Maus mittels TRPV1- und TRPA1-Rezeptoren*

Hein, Alexander, Dr. med. (2010): *Phänotypisierung sensorischer Nervenendigungen in vitro in transgenen Mäusen*

Karasek, Johannes Dieter, Dr. med. (2010): *Diacylglycerol-aktivierte Calciumsignale und TRPC-Kanäle in Spinalganglienneuronen der Ratte*

Rohé, Hanna, Dr. med. (2010): *Abhängigkeit der Schwitzrate im Sudomotoren-Axonreflex von der Stimulationsfrequenz beim Menschen*

Röder, Juliane, Dr. med. dent. (2010): *Hochregulation der Stickstoffoxid (NO) produzierenden Neurone im spinalen Trigeminuskern der Ratte nach Infusion eines NO-Donators. Increase in NADPH-diaphorase positive and neuronal NO synthase immunoreactive neurons in the rat spinal trigeminal nucleus following infusion of a nitric oxide donor - evidence for a feed-forward process in nitric oxide production involved in trigeminal nociception*

Habilitations

Namer, Barbara, Dr. med. habil. (2010): *Sensorische und axonale Eigenschaften menschlicher peripherer C-Fasern unter physiologischen und pathophysiologischen Bedingungen*

Zimmermann, Katharina, Dr. med. habil. (2010): *Transduktion und Erregung in Nervenendigungen der Haut bei schmerzhaften Reiztemperaturen*

Institute of Cellular and Molecular Physiology
Chair of Physiology (Vegetative Physiology)

Doctorate Theses

Wielpütz, Mark Oliver, Dr. med. (2009): *N-Myc downstream-regulated gene 2 stimuliert amiloridsensitive Na+-Ströme in Xenopus laevis-Oozyten und Fisher Rat Thyroid-Zellen*

Härteis, Silke, Dr. rer. nat. (2010): *Effects of the d- subunit andd of proteolyytic channel cleavage on the function of the epithelial sodium channel (ENaC)*

Schätzle, Christine Ulrike, Dr. med. (2010): *Konventionelle und laparoskopische Chirurgie bei entzündlichen Darmerkrankungen - Eine vergleichende Untersuchtung*

Habilitation

Rauh, Robert, PD Dr. med. (2009): *Molekulare Mechanismen der Regulation des epithelialen Natriumkanals (ENaC)*

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

Doctorate Theses

Bertz, Michaela, Dr. med. (2009): *Evaluation präventiver Angebote im Gesundheitsdienst. Gesundheitscheck bei Beschäftigten eines Universitätsklinikums*

Bräu-Dümler, Christine Mathilde, Dr. med. (2009): *Gefährdungsanalyse und Untersuchung des Zusammenhangs zwischen äußerer und innerer Selen-Belastung von Beschäftigten der Selen-verarbeitenden Industrie*

Hafizovi´c, Kamber, Dr. med. dent. (2009): *Identifikation von Risikofaktoren für die Genese von Adenokarzinomen der Nasenhaupt- und Nasennebenhöhlen unter besonderer Berücksichtigung von beruflichen und außerberuflichen Faktoren - Eine Fall-Kontroll-Studie an einem Kollektiv der HNO-Klinik der Universität Erlangen-Nürnberg im Zeitraum von 1979-2007*

Merkl, Kerstin Barbara, Dr. med. dent. (2009): *Welchen Nutzen hat eine erste arbeitsmedizinsche Vorsorgeuntersuchng bei Medizinstudenten im vorklinischen Studienabschnitt?*

Gundelfinger, Martina Carolin, Dr. med. (2010): *Exposition gegenüber polycyclischen aromatischen Kohlenwasserstoffen in der Bitumen-verarbeitenden Industrie in einem Niedrig-Expositionsbereich*

Hager, Meta Cornelia Johanna, Dr. med. dent. (2010): *Prävalenz und Verlauf von allergischen Erkrankungen bei Beschäftigten in Tierversuchsanlagen*

Lücking, Hannes Martin, Dr. med. (2010): *Enzephalopathie und Polyneuropathie durch organische Lösungsmittel - Review aktueller Literatur und Patientenuntersuchung am Institut für Arbeitsmedizin der Universität Erlangen*

Board Qualification

Straube, Sabine, Dr. med. (2009): *Internal Medicine*

Institute of Experimental and Clinical Pharmacology and Toxicology
Chair of Clinical Pharmacology and Clinical Toxicology

Doctorate Theses

Dreier, Jürgen, Dr. med. (2010): *Retrogrades Riechen - Ein Riechtest für Kinder*

Werner-Mathienz, Thomas, Dr. med. (2010): *Untersuchung zur Differenzierung von pharmakologischen und sensorischen Wirkungen des Niktoins an gesunden Probanden. Teil II - Pharyngeale Applikation*

Habilitation

Gläser, Hartmut, Dr. rer. nat. (2010): *In vitro- und in-vivo-Studien zur Bedeutung humaner intestinaler Cytochrom P450 Enzyme und gastrointestinaler Aufnahmetransporter für Arzneimittel*

Institute of Experimental and Clinical Pharmacology and Toxicology
Chair of Pharmacology and Toxicology

Doctorate Theses

Chremina, Olga, Dr. rer. nat. (2009): *Pharmakokinetische und phamakodynamische Untersuchungen zu selektiven und nicht selektiven Cyclooxygenasehemmern*

Hösl, Evelyn Elisabeth Brigitte, Dr. rer. nat. (2009): *Konditionelle Gendeletion im Reizleitungssystem der Maus*

Klinger, Nina Kerstin, Dr. med. (2009): *Wirkungen der pharmakologischen oder molekularbiologischen Inhibition der Proteinkinase CK2 auf das hepatozelluläre Karzinom*

Kröger, Irena, Dr. rer. nat. (2009): *The Role of Sensory Neuropeptides during Experimental Hepatitis*

Reinold, Heiko, Dr. med. (2009): *Verhaltenspharmakologische Untersuchungen zum zellulären Wirkmechanismus der Prostaglandinvermittelten spinalen Schmerzensibilisierung in Mäusen*

Hösl, Katharina Maria, Dr. med. (2010): *Die Rolle spinaler Prostaglandin E-Rezeptoren vom EP2-Subtyp und der Glycinrezeptor a3-Untereinheit bei neuropathischer und chemisch induzierter Schmerzsensibilisierung*

Schädle, Mirjam Franziska, Dr. med. (2010): *Die Bedeutung der Hämoxygenase-1 für Proliferation und Suppressionsaktivivtät humaner CD4+CD25+ regulatorischer T-Lymphozyten*

Institute of Experimental and Clinical Pharmacology and Toxicology
Doerenkamp-Chair of Innovations in Animal and Consumer Protection

Doctorate Thesis

Angerer, Florian Johannes Rainer, Dr. med. (2009): *Untersuchung zur dosisabhängigen Irritation der Rachenschleimhaut nach Stimulation mit Nikotin und Teer*

Institute of the History of Medicine and Medical Ethics
Chair of the History of Medicine

Doctorate Theses

Büttner, Winfried Otto, Dr. med. (2009): *Vom Arzt des Leibes zum Arzt der Seele. Heilige christliche Ärzte und Ärztinnen aus Spätantike und Frühmittelalter*

Thurner, Annette Petra, Dr. med. (2009): *Johann Georg Hasenest (1689-1771) und sein Werk. Der Medicinische Richter*

Habilitation

Dross, Fritz, PD Dr. phil. (2010): *Das Nürnberger Sondersiechenalmosen, 1394-1664. Eine ex-*

emplarische Studie zur Institutionengeschichte der Fürsorge für Arme, Fremde und Kranke

Institute of the History of Medicine and Medical Ethics
Professorship for Medical Ethics

Doctorate Thesis

Weinfurtner, Nadine, Dr. med. (2009): *Rechtsmedizin, Politik und Ethik. Gerichtliche Medizin in Göttingen in der ersten Halfte des 20.Jahrhunderts*

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

Doctorate Thesis

Steffan, Sabine, Dr. rer. biol. hum. (2010): *Empirische Struktur- und Prozessanalyse zum informationstechnologischen Unterricht innerhalb der schulischen Pflegeausbildung*

Institute of Medical Informatics, Biometry and Epidemiology
Endowed Chair of Medical Informatics

Doctorate Theses

Heinrich, Patrick, Dr. rer. biol. hum. (2009): *Entwicklung und Bewertung IT- gestützter Klinischer Behandlungspfade*

Jantsch, Stefan Christoph, Dr. med. (2009): *Evaluation von Pathifier. Ein zeitstrahlbasiertes Präsentationsprogramm integrierter Patientendaten als Basis für vielseitige klinische Anwendung*

Beyaz, Serkan, Dr. rer. biol. hum. (2010): *Konzeption, Einführung und Integration eines Monitoringsystems in bestehende Netzwerkdienste in einer Krankenhausumgebung*

Kammerer, Ferdinand Josef, Dr. med. (2010): *Entwicklung eines Webportals zur interdisziplinären Recherche in medizinischen Online-Bilddatenbanken*

Kraska, Detlef, Dr. rer. biol. hum. (2010): *Patientendatenkommunikation - Wege zur Interoperabilität*

Oschem, Martin Udo, Dr. rer. biol. hum. (2010): *Evaluation und Schaffung eines objektivierbaren Vergleichs von Methoden zur Optimierung der Arztbriefschreibung in der Hautklinik des Universitätsklinikums Erlangen*

Pflüger, Christian, Dr. rer. biol. hum. (2010): *Workflowgestützte medizinische Qualitätssicherung am Beispiel der ambulanten Basisdokumentation psychiatrischer Institutsambulanzen*

Suc, Jasmina, Dr. rer. biol. hum. (2010): *Change Management im Krankenhaus vor dem Hintergrund der Einführung der Kostenträgerrechnung am Universitätsklinikum Erlangen*

Institute of Medical Physics
Chair of Medical Physics

Doctorate Theses

Henke, Maria, Dr. rer. biol. hum. (2009): *Multidimensionale adaptive Filterung zur Rauschreduktion in der Computertomographie: Vergleich und Kombination faltungs- und splinebasierter Verfahren*

Konerth, Laura Cristina, Dr. rer. biol. hum. (2009): *Entwicklung eines Perfusionsmodells für quantitative und qualitative Messungen mit Perfusions-CT*

Tovar-Arriaga, Saúl, Dr. rer. biol. hum. (2009): *Investigations on a navigated CT-guided robotic system for needle placement interventions*

Wilharm, Sylvia, Dr. rer. biol. hum. (2009): *Interaktive Variation von Ortsauflösung und Rauschen für Anwendungen in der Flachdetektor-CT*

Bergner, Frank, Dr. rer. biol. hum. (2010): *4D Rekonstruktion für Flachdetektor Computertomographie*

Grimmer, Rainer Peter, Dr. rer. biol. hum. (2010): *Verbesserung und Evaluation der Bildqualität bei Flachdetektor Computertomographie*

Hillebrand, Lars, Dr. rer. biol. hum. (2010): *Echtzeitfähige Rekonstruktion für die Flachdetektor-Computertomographie auf Grafikhardware*

Karg, Jürgen Rainer, Dr. rer. biol. hum. (2010): *MCPTV -Ein Monte Carlo Algorithmus für die Dosisberechnung in der Strahlentherapie mit Kohlenstoffionen*

Kirschstein, Uwe, Dr. rer. biol. hum. (2010): *Assistenzsystem für die Zervikale Spondylodese*

Meyer, Friedrich Michael, Dr. rer. biol. hum. (2010): *Neuartige Ansätze zur Streustrahlungskorrektur in der Flachdetektor-Computertomographie*

Prell, Daniel, Dr. rer. biol. hum. (2010): *Metallartefaktreduktion in der Flachdetektor-Computertomographie*

Speer, Stefan Paul, Dr. rer. biol. hum. (2010): *OptiC - Ein Programm zur Dosisoptimierung und Bestrahlungsplanung in der Ionentherapie*

Steckmann, Sven, Dr. rer. biol. hum. (2010): *Hochperformante Spiral-CT Bildrekonstruktion auf Many-Core Prozessoren mit Vektorrechenheit*

Stenner, Philip Paul, Dr. rer. biol. hum. (2010): *Quantitative Methoden in der Dual-Source-Computertomographie*

Zerfass, Peter, Dr. rer. biol. hum. (2010): *Quantitative CT des Kniegelenks zur Arthrosediagnostik*

Habilitation

Kyriakou, Yiannis, Dr. rer. biol. hum. (2009): *Image quality and dose issues in cone-beam CT*

Institute of Forensic Medicine
Chair of Forensic Medicine

Doctorate Theses

Eckardt, Gerlinde, Dr. rer. biol. hum. (2009): *Quantifizierung von Betäubungsmitteln in Haaren. Praktische Untersuchungen zur Aufnahme von Betäubungsmitteln in Haare bei beruflich exponierten Personen im Vergleich zu Drogenkonsumenten*

Meier, Maria Ilona, Dr. med. (2009): *Entwicklung und Validierung eines Short Tandem Repeat Multiplex Systems für die Typisierung degradierter DNA-Proben*

Watzinger, Anne-Katrin, Dr. med. (2009): *Zeitlicher Verlauf der PCNA-Expression im Zentralnervensystem nach gedecktem Schädel-Hirn-Trauma des Menschen*

Nikolaus-Fiebiger-Center of Molecular Medicine
Chair of Experimental Medicine I (Connective Tissue Research)

Doctorate Thesis

Pacho, Frederic, Dr. rer. nat. (2010): *Novel determinants of spontaneous readthrough of nonsense mutations*

Nikolaus-Fiebiger-Center of Molecular Medicine
Chair of Experimental Medicine II (Molecular Oncology)

Doctorate Thesis

Mattauch, Sandra, Dr. rer. nat. (2010): *Identifizierung und funktionelle Charakterisierung von Liprin-a 4 als neues Zielgen des hypoxia-inducible factors HIF*

Institute of Biomedicine of Aging
Chair of Internal Medicine (Geriatrics)

Doctorate Theses

Tomaschautzki, Jürgen Andreas Bruno Josef Richard, Dr. med. dent. (2009): *Akute Vergiftungen mit Sedativa und Hypnotika: Häufigere und mit Verspätung auftretende Komplikationen im höheren Lebensalter. Ergebnisse einer prospektiven Studie an der Giftinformationszentrale Nürnberg*

Willschrei, Heinz Peter, Dr. med. (2009): *PEG-Sonden in der stationären Altenpflege - Ergebnisse einer bundesweiten Umfrage*

Cupic, Dragica, Dr. med. (2010): *Zytokinmuster und Funktionalität bei Patienten einer geriatrischen Tagesklinik*

Hinkelthein, Johannes, Dr. med. (2010): *Primäres, sekundäres und Langzeitüberleben betagter Patienten nach kardiopulmonaler*

Reanimation an einer Intensivstation mit dem Schwerpunkt Akutgeriatrie

Onay, Esra, Dr. med. (2010): *Veränderungen der Medikation durch Hausärzte bei älteren und hochbetagten Patienten nach der Entlassung aus dem Krankenhaus*

Board Qualifications "Internal Medicine"

Gor, Irina, Dr. med. (2010)
Schlee, Steffen, Dr. med. (2010)
Wicklein, Susanne, Dr. med. (2010)

Additional Qualifications "Geriatrics"

Cramer-Ebner, Ralf, Dr. med. (2009)
Schindler, Tobias, Dr. med. (2009)

Habilitation

Gassmann, Karl-Günther, PD Dr. med. (2009): *Geriatrische Prävention als interdisziplinäre Aufgabe*

Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH
Chair of Orthopedics and Orthopedic Surgery

Doctorate Theses

Birk, Kerstin Julia, Dr. med. (2009): *Nachbehandlungskonzepte nach Implantation von Hüfttotalendoprothesen - derzeitiger Stand an deutschen Rehabilitationskliniken*

Demmelmeyer, Uwe, Dr. med. (2009): *Langzeitergebnisse der Standardpfanne nach Wagner*

Lange-Riess, Dorothee, Dr. med. (2009): *Lanzeitergebnisse der operativen Behandlung des schnellenden Fingers im Erwachsenenalter*

Pflugfelder, Miriam, Dr. med. (2009): *Der endoprothetische Kniegelenkersatz bei Patienten mit rheumatoider Arthritis*

Remmel, Edgar, Dr. med. (2009): *Langzeitergebnisse der zweizeitigen operativen Behandlung der spät erkannten angeborenen Hüftluxation*

Riedel, Frank Achim, Dr. med. (2009): *Atomemissionsspektralanalyse mit induktiv gekoppeltem Plasma (ICP-OES) von Granulomen zementierter und zementfreier Hüftendoprothesen*

Scheller, Alexander, Dr. med. (2009): *Langzeitergebnisse der operativen Behandlung der Tendovaginitis stenosans de Quervain*

Schilasky, Ingo, Dr. med. (2009): *Die ossäre Transplantatintegration nach vorderer Kreuzbandersatzplastik mit dem Ligamentum patellae - eine klinische, radiologische und MR-tomografische Evaluation*

Al-Assaf, Mushtaq, Dr. med. (2010): *Ist Übergewicht ein perioperativer Risikfaktor in der Hüftendoprothetik?*

Drummer, Sandra, Dr. med. (2010): *10 Jahre Erfahrungen mit dem zementfreien Vektor-Titanschaft*

Estelmann, Alexandra, Dr. med. (2010): *CRPS I der Hand: Langzeitergebnisse*

Gold, Andreas Josef, Dr. med. (2010): *Axiale Steifigkeitsermittlung von regeneriertem Knochen nach Segmenttransport mit Ilizarov-Ringfisyteur*

Graser, Wolfgang, Dr. med. (2010): *Akzeptanz von Trainingstherapie und Eigentraining in der Weiterbehandlung von Patienten nach orthopädischer Rehabilitation*

Kopschina, Carsten, Dr. med. (2010): *Entwicklung, klinische Verläufe, Auswirkungen und Behandlung von Funktionseinschränkungen und Deformitäten der Extremintäten bei Patienten mit proximalen spinalen Muskelatrophien*

Krutsch, Hans Werner, Dr. med. (2010): *Differentialstrategien zum Weichteil-Balancing bei der knieendoprothetik in Abhängigkeit von der präoperativen Deformität*

Thomas, Dietmar Josef, Dr. med. (2010): *Der Krankheitsverlauf der Gelenkzerstörung bei der rapide destruierenden Coxarthrose im Vergleich zur Hypertroph sklerosierenden Coxarthrose*

Zeller, Philip, Dr. med. dent. (2010): *Expression der Interleukine -1ß, -6, -10, -18 und Tumornekrosefaktor-a bei asepitscher Lockerung von Hüfttatalendoprothesen*

Zweifel, Jochen Nicol, Dr. med. (2010): *Langzeitergebnisse der varisierenden intertrochanteren Korrekturosteotomie bei der Dysplasiecoxarthrose*

Department of Orthopedics in the Waldkrankenhaus St. Marien gGmbH
Division of Orthopedic Rheumatology

Doctorate Thesis

Plötzner, Jan, Dr. med. (2010): *Zementfreie Hüftendoprothesenimplantation bei Patienten mit rheumatoider Arthritis - Minimum 10-Jahres Ergebnisse-*

Board Qualification

Gelse, Kolja, PD Dr. med. (2009): *Orthopedics and Accident Surgery*

Habilitation

Gelse, Kolja, PD Dr. med. (2009): *Zelluläre und molekulare Therapieansätze bei Knorpeldefekten und Arthrose*

Department of Anesthesiology
Chair of Anesthesiology

Doctorate Theses

Feuchter, Sonja, Dr. med. (2009): *Wirksamkeit und Verträglichkeit von transdermalem Buprenorphin bei einer Applikationsdauer von 4 Tagen im Vergleich zu 3 Tagen*

Heinl, Kathrin Anna-Christina, Dr. med. (2009): *Einfluss einer multimodalen Gruppentherapie auf Medikamentenverhalten und Symptomatik bei chronischen Kopfschmerzpatienten.*

Kusnik, Stefan Martin, Dr. med. (2009): *Einfluss von erhöhter Hauttemperatur auf die Plasmaspiegel von transdermal appliziertem Buprenorphin (Transtec®)*

Leimeister, Ines Verena, Dr. med. (2009): *Einfluss des Geschlechts auf die Pharmakodynamik von Cisatracurium*

Leuthold, Christian Dietrich, Dr. med. (2009): *Entwicklung eines neuen Tiermodells für Reanimation bei akutem Myocardinfarkt und Evaluation der Hämodynamik nach Wiederkehr des Spontankreislaufes am Hausschwein*

Puthawala, Martin, Dr. med. (2009): *Die Wirkung von intravenös verabreichten Adenosin auf elektrisch induzierten Schmerz beim Menschen*

Rohmer, Stefan Werner, Dr. med. (2009): *Veränderungen der Selen-Vollblutspiegel nach koronarchirurgischen Eingriffen mit, bzw. ohne Einsatz der Herz-Lungen-Maschine*

Schulte, Ralph Georg, Dr. med. (2009): *Identifikation geeigneter EEG-Parameter für das Narkosemonitoring durch Approximation ihres Rausch-Signal-Verhätnisses mittels kubischer Splines*

Zapke, Tobias Gerhard, Dr. med. (2009): *Alcuronium und Atracurium im Vergleich hinsichtlich ihrer lytischen Wirkung auf Succinylcholin-induzierte Muskelfaszikulationen*

Ammon, Carolin Susanne, Dr. med. (2010): *Untersuchung zur Eignung von prozessierten EEG-Parametern als Überwachungsparameter der Narkosetiefe bei Kindern*

Bornhof, Manuel, Dr. med. (2010): *Der orofaziale Formalintest an der Maus zur Quantifizierung trigeminaler Nozizeption*

Gunreben-Stempfle, Birgit Margit, Dr. rer. biol. hum. (2010): *Effektivität eines multimodalen Intensivbehandlungsprogramms bei chronischen Kopfschmerzen*

Hunsicker, Alexander Erwin, Dr. med. (2010): *Einfluss der Opioide Remifentanil, Alfentanil und Sufentanil auf die hämodynamische und humorale Streßreaktion bei transsphenoidalen Hypophysenoperationen.*

Peter, Jochen Marc, Dr. med. (2010): *Qualität notärztlicher Diagnosen: Ein Vergleich von Fachärzten und Weiterbildungsassistenten der Anästhesie*

Saalfrank-Schardt, Christina, Dr. med. (2010): *Untersuchung zur Qualitätssicherung des intraoperativen Recurrensmonitorings bei operativen Eingriffen an der Schilddrüse*

Schmidt, Stephanie Therese Veronika, Dr. med. (2010): *Die Interaktion von Physostigmin und Alfentanil in einem experimentellen Schmerzmodell am Menschen*

Tröster, Andreas Kostantin Paul, Dr. med. (2010): *Quantifizierung analgetischer und antihyperalgetischer Effekte von Buprenorphin und Fentanyl am Menschen*

Weiss, Michael Paulo, Dr. med. (2010): *Klinische Evaluierung einer Methode zur kontinuierlichen nichtinvasiven Messung des arteriellen Blutdrucks im Rahmen kardiochirurgischer Eingriffe*

Board Qualifications "Anesthesiology"

Frank, Paul, Dr. med. (2009)
Kroeber, Stefanie, Dr. med. (2009)
Boeswald, Yvonne, Dr. med. (2010)
Dausch, Sabine, Dr. med. (2010)
Fischer, Mathias (2010)
Gerke, Tobias, Dr. med. (2010)
Hunsicker, Alexander, Dr. med. (2010)
Irouschek, Andrea, Dr. med. (2010)
Ludwig, Stefanie, Dr. med. (2010)
Schmitt, Christopher, Dr. med. (2010)

Additional Qualifications

Dausch, Sabine Margitta, Dr. med. (2009): *Emergency Medicine*
Eckermann, Thomas, Dr. (2009): *Intensive Care*
Fechner, Jörg, PD Dr. med. (2009): *Emergency Medicine*
Lang, Anne-Katharina, Dr. (2009): *Intensive Care*
Reinhardt, Melanie (2009): *Emergency Medicine*
Schoen, Christoph, Dr. med. (2009): *Special Pain Therapy*
Suchodolski, Klaudiusz, Dr. (2009): *Intensive Care*
Troester, Andreas, Dr. med. (2009): *Emergency Medicine*
Wehrfritz, Andreas Peter, Dr. med. (2009): *Emergency Medicine*
Wilhelm, Ilka, Dr. med. (2009): *Special Pain Therapy*
Bokern, Jens, Dr. (2010): *Intensive Care*
Krajinovic, Ljubica, Dr. med. (2010): *Emergency Medicine*
Kränzlein, Diana, Dr. med. (2010): *Emergency Medicine*
Nowak, Katharina (2010): *Emergency Medicine*
Weiss, Marina Elvira Lucia (2010): *Emergency Medicine*
Wintzheimer, Simone Christine, Dr. med. (2010): *Emergency Medicine*

Habilitations

Leffler, Andreas, PD Dr. med. (2010): *Function and pharmacology of transduction proteins in nociceptive sensory neurons*
Tzabazis, Alexander, PD Dr. med. (2010): *Experimental pain in rodents: Establishing new models and evaluating new therapeutic approaches*

Department of Anesthesiology
Division of Palliative Medicine

Additional Qualification

Klein, Carsten, Dr. med. (2009): Palliative Medicine

Department of Ophthalmology
Chair of Ophthalmology

Doctorate Theses

Baleanu, Delia, Dr. med. (2009): *Wall to lumen ratio of retinal arterioles and arteriole to venule ratio of retinal vessels in patients with cerebrovascular damage*
Eppig, Timo Michael, Dr. rer. biol. hum. (2009): *Untersuchungen zur Abbildungsqualität asphärischer Intraokularlinsen*
Gieck, Björn Lars, Dr. med. dent. (2009): *Besonderheiten der phototherapeutischen Keratektomie bei der makulären Hornhautdystrophie*
Kapsreiter, Markus Johannes, Dr. med. (2009): *Über die Innervation der Arteria centralis retinae des Menschen*
Rössler, Christopher Wolfgang, Dr. med. (2009): *Homocystein bei primären Offenwinkelglaukomen ohne erhöhten Augeninnendruck (Normaldruckglaukomen)*
Arnold, Stefan Michael, Dr. rer. biol. hum. (2010): *Automatisiertes Messsystem zur Quantifizierung und Charakterisierung des menschlichen Tränenfilms in-vivo*
Düz, Melek, Dr. med. (2010): *Evaluation der parapapilliären Autofluoreszenz bei Normaldruckglaukom und primärem Offenwinkelglaukom mit einem semi-automatischem Mustererkennungssystem (SAFAS)*
Fiermann, Thomas, Dr. med. (2010): *Pulskurvenanalyse in der Arteria ophthalmica als Funktion von Alter, Geschlecht, kardio-vaskulärer Risikofaktoren, Glaukom, Verdacht auf Glaukom und okulärer Hypertension*
Gärtner, Christian Gerhard Ulrich, Dr. med. dent. (2010): *Ergebnisse nach Augenmuskeloperationen bei sekundärem sensorischen Strabismus*
Janunts, Edgar, Dr. rer. biol. hum. (2010): *Optical Fluorescence Tomography: Light Transport and Image Reconstruction*
Kozich, Christian Peter, Dr. med. (2010): *Perimetrie mit dem Octopus 500 und dem Octopus 900 - ein Gerätevergleich*
Preclik, Anne Christina, Dr. med. (2010): *Langzeitverlauf nach perforierender Keratoplastik bei Keratokonus - Auswirkungen von präoperativem Visus und Astigmatismus auf die funktionellen Ergebnisse*
Pöschinger, Thomas, Dr. rer. biol. hum. (2010): *Non-Contact Optical Fluorescence Tomography for Small Animal Imaging: System Development and Multispectral Applications*
Schürer, Michael, Dr. rer. biol. hum. (2010): *Einfluss von farbigen Filtermedien und Farbsinnstörungen auf das Farbunterscheidungsvermögen*
Walter, Annette, Dr. rer. biol. hum. (2010): *Konstruktion eines Messplatzes zur Analyse humaner Farbunterscheigunsschwellen unter Beeinflussung gefärbter Filtermedien*
Zhu, Zhongxia, Dr. rer. biol. hum. (2010): *Mathematical Study for Customized Intraocular Lens Design*
Zimmermann, Paul, Dr. med. (2010): *Tumor-associated lymphangiogenesis in conjunctival malignant melanoma*

Department of Surgery
Chair of Surgery

Doctorate Theses

Bahr, Tobias, Dr. med. (2009): *Vergleichende Studie über die Behandlungsergebnisse der Dorsalen Kapsulodese nach Berger und der STT-Arthrodese nach Watson bei der Skapholunären Dissoziation*
Bialecki, Diana, Dr. med. (2009): *Prä- und posttherapeutische Schätzung der Prognose bei Resektion kolorektaler Lebermetastasen am Krankengut der Chirurgischen Klinik am Universitätsklinikum Erlangen im Zeitraum 1995-2006*
Ditterich, Daniel Martin, Dr. med. (2009): *Intrathorakale Vakuumversiegelung - eine neuartige Wundbehandlungsmethode bei septischen Pleuraprozessen*
Godzik, Mirko, Dr. med. (2009): *Chirurgische Therapie von Fernmetastasen maligner Melanome*
Jochmann, Ramona Paula, Dr. rer. nat. (2009): *O-linked N-Actetylglucosaminylation of Sp1 Inhibits the Human Immunodeficiency Virus Type-1 Promoter*
Konrad, Carsten Andreas, Dr. rer. nat. (2009): *Systematische Untersuchung von Kombinationswirkungen HHV-8-kodierter Gene auf die NF-?B-Aktivierung*
Kümmet, Christina Anneliese, Dr. med. (2009): *Die operative Behandlung des Hämorrhoidalleidens durch die Methode von A. Longo*
Laukert, Anna, Dr. med. dent. (2009): *Klinische Ergebnisse laparoskopischer Therapie bei Endometriose mit intestinalem Befall*
Lippmann, Marion Elisabeth Manuela, Dr. med. (2009): *Descending Perineum Syndrome. DPS.- Langzeitergebnisse nach operativer Sanierung*
Marquardt, Gaby, Dr. rer. nat. (2009): *Systematic analysis of the intracellular localization of human herpesvirus 8-encoded proteins*
Rix, Ronald Jürgen, Dr. med. (2009): *Komplikationsraten und Letalität bei der Chirurgie des Kolorektalen Karzinoms in Abhängigkeit von chirurgisch-technischen und klinischen Parametern*

Rungweber, Thomas, Dr. med. (2009): *Klinische Ergebnisse der PTA bei chronisch-kritischer Ischämie*

Spiegel, Astrid Frederike, Dr. med. (2009): *Bedeutung der Lymphangiogenese bei der Lymphknotenmetastasierung des Kolonkarzinoms*

Wanninger, Sebastian Johannes, Dr. med. dent. (2009): *Evaluation des postoperativen Verlaufs bei parastomalen Hernien - eine Analayse des Patientenguts der Chirurgischen Klinik des Universitätsklinikums Erlangen*

Weinländer, Kristina, Dr. rer. nat. (2009): *Charakterisierung molekularer Mechanismen der antiangiogenen Aktivitäten GBP-1 in Endothelzellen*

Wesemann, Alena Isabel, Dr. med. (2009): *Moje-Prothese im proximalen Interphalangealgelenk*

Wolf, Maximilian Karl Gerhard, Dr. med. dent. (2009): *Große Hiatushernien mit Thoraxmagen. Ergebnisse minimal invasiver Operationsverfahren*

Wolter, Inken Eva, Dr. med. (2009): *Der Einsatz biodegradierbarer Implantate in der Extremitätenchirurgie unter besonderer Berücksichtigung der Komplikationen: Ergebnisse einer Literaturanalyse von 6752 Fällen der Jahre 1987 - 2007*

Zimmermann, Patrick Guenter, Dr. med. (2009): *Risikoabschätzung für septische Komplikationen nach großen abdominalchirurgischen Eingriffen anhand der Zytokine IL-6 und TNF-a*

Hoffmann, Marlen, Dr. med. (2010): *Sigmadivertikulitis Stand der Therapie an der Frankenwaldklinik Kronach*

Kiessling, Elke, Dr. med. (2010): *Laparoskopischer Bruchpfortenverschluß von Narben-, Nabel- und Bauchdeckenhernien mittels ePTFE-Netz (DualMesh) - Ergebnisse der ersten Nachuntersuchung-*

Kleine, Michael, Dr. med. (2010): *Ergebnisse kompletter operativer Handgelenksversteifungen nach posttraumatischer oder degenerativer Arthrose. Retrospektive Studie (1989-1999) aus dem Friederikenstift Hannover*

Klossek, Daniela Margareta Maria, Dr. med. (2010): *Analyse von Qualitätsindikatoren im Rahmen eines Projekts zur Implementierung von Leitlinien beim kolorektalen Karzinom an der Chirurgischen Klinik im Universitätsklinikum Erlangen*

Lamberti, Julia Annette, Dr. med. (2010): *Kolektomie bei Colitis ulcerosa. Komplikationsraten und Lebensqualität in Abhängigkeit von verschiedenen Operationstechniken und Operationszeitpunkten*

Meyer, Alexander, Dr. med. (2010): *Cdc2 as prognostic marker in stage UICC II colon carcinomas*

Sagkob, Jan Rudolf, Dr. med. (2010): *-Die periostale und kortikale Durchblutung des Knochens - Eine intravitalmikroskopische Untersuchung zur mikrozirkulation des Knochens im hypovolämischen Schock*

Tinkl, Dominik, Dr. med. (2010): *Downtaging des Pankreaskarzinoms nach Neoadjuvanter Radiochemotherapie*

Weiger, Alexander Ludwig, Dr. med. (2010): *Chirurgische Therapie des Morbus Crohn - Entwicklung und Ergebnisse der letzten drei Jahrzehnte*

Witzenrath, Andrea Christine, Dr. med. (2010): *Risikofaktoren für abdominelle Komplikationen nach kardiopulmonalem Bypass*

Board Qualifications

Besendörfer, Manuel, Dr. med. (2009): *General Surgery*

Croner, Roland, PD Dr. med. (2009): *Visceral Surgery*

Golcher, Henriette, Dr. med. (2009): *General Surgery*

Schellerer, Vera, Dr. med. (2009): *General Surgery*

Zhang, Wei, Dr. med. (2009): *General Surgery*

Demir, Resit, Dr. med. (2010): *Visceral Surgery*

Müller, Volker, PD Dr. med. (2010): *Visceral Surgery*

Habilitations

Schönleben, Frank, PD Dr. med. (2009): *Mutational Analyses of Multiple Oncogenic Pathways in Intraductal Papillary Mucinous Neoplasms of the Pancreas.*

Siassi, Michael, PD Dr. med. (2009): *Lebensqualität in der kolorektalen Chirurgie*

Department of Surgery
Division of Thoracic Surgery

Board Qualification

Schreiner, Waldemar, Dr. (2010): *Thoracic Surgery*

Department of Surgery
Division of Transfusion Medicine and Hemostaseology

Doctorate Theses

Bumiller, Nadja, Dr. med. dent. (2009): *Untersuchungen zur Anzüchtung von Dendritischen Zellen aus Monozyten in zwei unterschiedlichen Beutelsystemen*

Büttner, Stephanie, Dr. med. (2009): *TAFI - Thrombin-aktivierbarer Fibrinolyseinhibitor- und Faktor XIIA-Konzentration bei Patienten mit Systemischem Lupus Erythematodes*

Frank, Maximilian Alberto, Dr. med. dent. (2009): *Transfusionsindikation für Gefrorenes Frischplasma aus Eigenblutspenden*

Krex, Daniel Mirco, Dr. med. dent. (2009): *Der Einfluss unterschiedlicher Verdünnungsmedien auf die Hypotone Schock und die Extent of Shape Change Reaktion von in additiver Lösung gelagerten Thromobzyten*

König, Julia, Dr. med. dent. (2009): *Die Wirkung der Antikoagulation von Proben auf die Messung von zirkulierenden Wachstumsfaktoren, die aus Thrombozyten freigesetzt werden*

Lange, Nikolaus Maximilian, Dr. med. (2009): *Warum spenden manche Apherespender nur ein einziges Mal?*

Ruppel, Renate, Dr. med. (2009): *Marburg-I-Variante der Faktor-VII-aktivierenden Protease und ihre Rolle bei der Entstehung von venösen Thromboembolien*

Schaffer, Sonja, Dr. med. (2009): *In-vitro-Untersuchung des Einflusses von Ringer-Lösung und Hydroxyethylstärke-Lösung auf Gerinnungstestverfahren*

Wintzheimer, Simone Christine, Dr. med. (2009): *In-vitro-Qualitätskontrollen von mit verschiedenen Methoden Leukozytendepletierten und teilweise mit 30 Gray bestrahlten Erythrozytenkonzentraten*

Zapf, Ingo, Dr. med. (2009): *Vergleichsuntersuchung zum Screening auf erythrozytäre Alloantikörper mit Hilfe von Röhrchen Test, Mikrosäulenmethoden und Festphasensystemen*

Brügel, Janina Christine, Dr. med. (2010): *Untersuchung der Effizienz der Herstellung CD14- und CD16- positiver Monozyten mit den Zellseparatoren Cobe Spectra und COM.TEC*

Friedhoff, Helena Sarah, Dr. med. dent. (2010): *Der Einfluß von vier verschiedenen Probenverdünnungsmitteln (Diluents) auf die gemessene Thrombozytenkonzentration in Thrombozytenkonzentraten*

Hofmann, Petra Rosemarie, Dr. med. (2010): *Infektionsserologische Testbefunde bei Spendern verschiedener autologer Blutbestandteile*

Huzurudin, Nilofar, Dr. med. (2010): *Die Wirkung von Paracetamol und Parecoxib auf die in vitro Thrombozytenfunktion*

Klaus, Julia, Dr. med. (2010): *Optimierung von Techniken zur apparativen Präparation von Stammzellen aus Plazentarestblut*

Krätzer, Moritz Stephan, Dr. med. (2010): *Vergleich verschiedener Techniken zur Anreicherung hämatopoetischer Stammzellen aus Plazentarestblut*

Department of Surgery
Division of Trauma Surgery

Doctorate Theses

Bauer, Susanne Franziska Ingeborg, Dr. med. (2009): *Einfluss der Rekonstruktion der Gelenkkapsel auf die Entstehung von Heterotoper Ossifikation nach Totalendoprothese des Hüftgelenks mit posterolateralem Zugang*

Bauer, Svenja-Yvonne Pamela Marianne, Dr. med. (2009): *Rotatorenmanschettenruptur und deren Therapie beim alten Menschen über dem 60. Lebensjahr*

Dobre, Cristinel Ionut, Dr. med. (2009): *Optimierung der Versorgungs- und Betreuungssituation von Patienten mit einem längerfristigen stationären Aufenthalt: Eine empirische Untersuchung unter besonderer Berücksichtigung der Behanslungsschwerpunkte Psychiatrie und Unfallchirurgie*

Grötecke, Telse, Dr. med. (2009): *Komplementäre Kirschnerdrahtosteosynthese im Vergleich zur Stand-alone-Fixateur-externe-Versorgung der distalen Radiusfraktur*

Allmendinger, Jörg, Dr. med. (2010): *Mikroradiografische Untersuchung zur Osseointegration von laserstrukturierten Titanimplantaten im intramedullären Kaninchenmodell*

Baierl, Franziska, Dr. med. (2010): *Postoperative Untersuchungsergebnisse betagter Patienten nach Implantation einer Humeruskopfprothese bei Humeruskopffraktur*

Obier, Simon, Dr. med. (2010): *Die Rolle des Transkriptionsfaktors HIF-1a für die Integrität murinen Gelenkknorpels*

Reindl, Tobias Michael, Dr. med. (2010): *Periprothetische Frakturen bei liegender Hüfttotalendoprothese*

Schulz-Drost, Stefan, Dr. med. (2010): *Einfluß von kognitiver Leitungsfähigkeit auf die Rehabilitation nach Hüft-Totalendoprothesen-Implantation*

Schönrock, Helge Lars, Dr. med. (2010): *Auswirkungen von unterschiedlichem Mobilisationsbeginn auf langfristige Stabilität und Bewegungsumfang bei unidirektionaler Schulterinstabilität nach operatier Versorgung einer klassischen Bankart-Läsion. Retrospektive Analyse mit Nachuntersuchung von 27 Patienten nach Versorgung durch offene arthroskopische Bankart Operation*

Spethmann, Anja, Dr. med. (2010): *Untersuchung von Veränderungen des Körperwachstums und des Körpergewichts und einer möglichen Korrelation dieser Veränderungen mit dem Schulabschluss sowie Wirbelsäulenerkankungen anhand von Musterungsuntersuchungen von Wehrpflichtigen der Geburtsjahrgänge 1965 bis 1982*

Board Qualifications

Mauerer, Andreas, Dr. med. (2009): *Orthopedics and Accident Surgery*

Brem, Matthias, Dr. med. (2010): *Orthopedics and Accident Surgery*

Gelse, Kolja, Dr. med. (2010): *Orthopedics and Accident Surgery*

Hornung, Dominik, Dr. med. (2010): *Surgery*

Habilitations

Welsch, Goetz, PD Dr. med. (2009): *Morphologische und Biochemische Analyse von Knorpelersatzgewebe mittels fortschrittlicher Magnetresonanztomographie*

Brem, Matthias, Priv.Doz.Dr.med. (2010): *MRT basierte Darstellung der Arthrose*

Gelse, Kolja, Priv.Doz.Dr.med. (2010): *Molekulare und Zelluläre Therapiestrategie bei Knorpeldefekten und Arthrose*

Department of Obstetrics and Gynecology

Chair of Obstetrics and Gynecology

Doctorate Theses

Altmann, Harald-Hans, Dr. med. (2009): *Übelkeit und Erbrechen in der Schwangerschaft und die Assoziation mit Polymorphismen des HTR3-Gens und des NK1-Gens*

Egger, Nathalie, Dr. med. (2009): *Fetale Gewichtsschätzung im Ultraschall: Einfluss des Untersuchers und Vergleich elf verschiedener Regressionsformeln*

Ernst, Veronika Christine, Dr. med. (2009): *Neurovaskuläre Kompression und hypertensive Erkrankungen in der Schwangerschaft*

Fritsche, Anja Stefanie, Dr. med. (2009): *Immunhistochemische Prädiktoren des Ansprechens auf eine neoadjuvante anthrazyklinhaltige Chemotherapie beim Mammakarzinom und deren Bedeutung als prognostische Faktoren*

Fromm, Ellen, Dr. med. (2009): *Ergebnisse der Wertheim-Meigs-Operation im Klinikum Neumarkt*

Hager, Ina-Maria, Dr. med. (2009): *Assoziation verschiedener Polymorphismen mit einer gestörten Fertilität bei in-vitro Fertilisationspatientinnen mit oder ohne ovariellem Hyperstimulationssyndrom*

Heusinger, Katharina, Dr. med. (2009): *Genauigkeit der Tumorgrößenbestimmung im Rahmen des klinischen Stagings von Brustkrebspatientinnen - eine vergleichende, prospektive klinische Studie*

Hildebrandt, Thomas Hans Gerhard, Dr. med. (2009): *Kenntnisstand über zertifizierte Zentren und Einfluss der Zentrumsbildung auf deren Wahl durch Patientinnen am Beispiel von Brust- und Perinatalzentren*

Knörr, Jutta Maria, Dr. med. (2009): *Der Einfluss der Inanspruchnahme von Pränataldiagnostik und des Geburtsmodus auf die Entstehung postpartaler Depressivität*

Körber, Frauke Insa Anna, Dr. med. (2009): *Höchsensitives C-reaktives Protein im Vergleich zu C-reaktivem Protein als löslicher Serummarker zur Diagnostik bei Endometriose*

Kösztner, Heike, Dr. med. (2009): *Die Kryokonservierung von Geweben und Organen am Beispiel des Schweineuterus*

Leipold, Susanne Julia, Dr. med. dent. (2009): *Die Intrauterininsemination (IUI): Gegenüberstellung der Untersuchungszeiträume 2001-2002 und 2004-2005 und Vergleich verschiedener einflussnehmender Parameter auf den Erfolg einer IUI*

Paulsen, Mareike Stephanie, Dr. med. (2009): *Kongenitale uterine Malformationen, Formen, Symptome, Ursachen: Die äthiologische Rolle des Gens HOX-A11*

Rauh, Claudia, Dr. med. (2009): *Einfluss von hormonellen und reproduktiven Faktoren auf die Entstehung und Prognose eines Mammakarzinoms*

Schälike, Michael, Dr. med. (2009): *Analyse der Ergebnisse der kombinierten Erst-Trimester-Diagnostik*

Sindhuwinata, Clivia, Dr. med. (2009): *Vergleich der Wirkung verschiedener kontraktionsauslösender Pharmaka auf den intrauterinen Druck und Perfusionsdruck im extrakorporal perfundierten nichtschwangeren Schweineuterus*

Strahl, Olga, Dr. med. (2009): *Wirkung unterschiedlicher Progesterone (natürliche, pflanzliche, synthetische) auf die Kontraktion der glatten Muskulatur anhand des extrakorporalen Uterusperfusionsmodels*

Widjaja, Widya Kusuma, Dr. med. dent. (2009): *Etablierung eines Mikrochip-Präzisionsdruckkatheters zur Messung intrauteriner Druckverläufen sowie Einführung der Perfusionsdruckmessung mit einem digitalen Transducer im ex vivo Schweineuterusperfusionsmodell*

Wiesner, Folkward Godehard Christoph, Dr. med. (2009): *Evaluation des Proliferationsmarkers Ki-67 als Prognosefaktor für Patientinnen mit einem Mammakarzinom*

Allali, Faouz, Dr. med. (2010): *Einfluss von Lebensqualität, Angst und Depression sowie klinisch-demographischen Daten auf den psychoonkologischen Bedarf bei Mammakarzinom-Patientinnen*

Backhaus, Kathrin Christa Inge, Dr. med. (2010): *Qualitätsbeeinflussende Faktoren der Nabelschnurblutspende. Untersuchungen von 1500 Nabelschnurblutpräparaten der Erlanger Nabelschnurblutbank*

Boosz, Alexander Stephan, Dr. med. (2010): *Präoperativer Schmerz als Prädiktor des Rezidivrisikos bei Patientinnen mit Endometriose*

Claassen, Monika Tomma, Dr. med. (2010): *Veränderung der Knochendichte und Body Composition bei transsexuellen Patienten nach zweijähriger gegengeschlechtlicher Hormonbehandlung*

Esper, Jürgen Friedrich, Dr. med. (2010): *Selektive Behandlung von Hitzewallungen mit 17 alpha-Östradiol, einem Östradiol-Epimer ohne klassische Östrogenwirkung*

Festl, Cornelia, Dr. med. dent. (2010): *Volumen, Vaskularisation und Perfusion der Plazenta im frühen zweiten Trimenon und Outcome der Schwangerschaft*

Hilbert, Antonia Valerie Maria, Dr. med. (2010): *Neue Methoden zur fetalen Gewichtsschätzung mittels Ultraschalls*

Künzel, Julian, Dr. med. (2010): *Rolle neurotroper und muskulotroper Spasmolytika in der*

In-vitro Fertilisation (IVF): Untersuchungen am perfundierten Schweineuterus

Müller, Lena-Katharina, Dr. med. (2010): *Einfluss von Seminalplasma auf die Kontraktionen des Östrogen- und Tamoxifen-behandelten Schweineuterus - Eine experimentelle Arbeit -*

Naton-Schötz, Susanne, Dr. med. (2010): *Die Häufigkeit des Syndroms der polycystischen Ovarien bei Frau - zu - Mann - Transsexuellen*

Pau, Susan, Dr. med. (2010): *Postpartale Sexualität - Korrelation zwischen dem Zeitpunkt des ersten Postpartalen Coitus, dessen subjektiver Beurteilung durch die Frau und der Coitusfrequenz, mit prä-, peri- und postpartalen Faktoren.*

Rabenbauer, Bernhard, Dr. med. (2010): *Der Einfluss von Flutamid auf die Gonadotropinsektretion und Insulinempfindlichkeit bei Hyperandrogenämischer Ovarialinsuffizienz*

Rackl, Nadja Petra, Dr. med. (2010): *In-vitro Untersuchungen zum Einfluss von Progesteron und verschiedener Prostaglandine auf die Kontraktion extracorporal perfundierter, nichtschwangerer Schweine-Uteri*

Rauber, Diana Alexandra, Dr. med. (2010): *Die prognostische Bedeutung des Nachweises des L1-Proteins von humanen Papillomviren bei milden bis mäßigen zervikalen intraepithelialen Läsionen*

Scheuerer, Annette, Dr. med. (2010): *Schwangerschaftsbezogene Veränderungen auf den weiblichen Körper als Prognosefaktoren bei Patientinnen mit Mammakarzinom*

Zaherdoust, Olga, Dr. med. (2010): *Mutationssuche im FSH-Rezeptor-Gen bei Frauen mit herabgesetzter ovarieller Stimulierbarkeit im Rahmen der künstlichen Befruchtung*

Board Qualifications "Gynecology and Obstetrics"

Beckmann, Kai, Dr. med. (2009)

Löhberg, Christian, Dr. med. (2010)

Habilitations

Lux, Michael Patrick, PD Dr. med. (2009): *Einflussfaktoren der Therapieentscheidung bei der Patientin mit einem Mammakarzinom*

Strick, Reiner, PD Dr. rer. nat. (2009): *Differentielle Genregulationen in der Karzinogenese am Beispiel von Steroidhormon- und Wachstumsfaktor-abhängigen gynäkologischen Tumoren*

Bani, Mayada Rita, PD Dr. med. (2010): *Die Behandlung der Patientin mit Mammakarzinom - Einflussfaktoren auf Langzeitfolgen und die persönliche Zufriedenheit*

Frobenius, Wolfgang, MME, PD Dr. med. (2010): *Lernzielorientierte messbare Verbesserungen der Lehre in der Gynäkologie und Geburtshilfe*

Renner, Stefan, PD Dr. med. (2010): *Genetische und klinische Risikofaktoren bei Endometriose*

Strissel, Pamela, PhD, PD Dr. (2010): *The role of steroid hormone receptor signalling and the human papilloma virus in benign gynecological diseases*

Department of Ear, Nose and Throat - Head and Neck Surgery

Chair of Otorhinolaryngology

Doctorate Theses

Burger, Pascal Heinrich Maria, Dr. med. (2009): *Untersuchung der Speichelchemie, sonographische Speicheldrüsenbiometrie und Serologie bei Patientinnen mit Adipositas und Essstörungen*

Diesner, Hartmut, Dr. med. (2009): *Die prognostische Relevanz des R-Status bei Kopf-Hals-Karzinomen*

Gürlek, Ercan, Dr. med. (2009): *Prognostische Bedeutung des Befalls der vorderen Kommissur bei glottischen Larynxkarzinomen*

Havla, Johannes Georg Dieter, Dr. med. (2009): *Reproduzierbarkeit und Reliabilität des Phonovibrogramms (PVG) Quantifizierung gesunder Stimmlippenschwingungen*

Psychogios, Georgios, Dr. med. (2009): *Evaluation of the revised TNM classification in advanced laryngeal cancer*

Schmitt, Christian Michael, Dr. med. dent. (2009): *Untersuchungen zur statischen und dynamischen Genauigkeit von chirurgischen Navigationssystemen an Phantom*

Schnotz, Alexander, Dr. med. dent. (2009): *Speech With Gaps: Effects of Periodic Interruptions on Speech Intelligibility*

Weidinger, Cornelia Sabine, Dr. med. (2009): *Die Halslymphknotenmetastasierung des Zungengrundkarzinoms. Eine retrospektive Auswertung von 217 Patienten*

Becker, Swetlana, Dr. med. (2010): *Cholesteatome im Kindesalter. Erfahrungen mit offener und geschlossener Technik - eine retrospektive Analyse*

Bucher, Sebastian Georg, Dr. med. (2010): *Radiofrequenzablation als palliative Therapieoption bei HNO Tumoren In vivo und in vitro Versuche*

Danilkina, Galina, Dr. med. (2010): *Late auditory evoked potentials in Cochlear Implant Listeners during the first days of hearing rehabilitation (Auditorische Hirnrindenpotentiale bei Cochlear Implantat Patienten während der Erstanpassung des Sprachprozessors*

Digeser, Frank Michael, Dr. rer. biol. hum. (2010): *Contribution of Spectrotemporal Features on Auditory Event-Related Potentials Elicited by Consonant-Vowel Syllables. Einfluss der spektralen und temporalen Eigenschaften von Konsonant-Vokal Silben auf die auditorischen Hirnrindenpotentiale*

Forster, Stefan Winfried, Dr. med. dent. (2010): *Funktionelle Ergebnisse nach transtemporaler und translabyrinthärer Vestibularisschwannomoperation*

Gill, Simone, Dr. med. (2010): *Kernpintomographische und neuropsychologische Analyse des Temporallappens nach transtemporaler Vestibularisschwannomchirurgie*

Richter, Catja, Dr. med. (2010): *Prognostische Relevanz des Gradings von Kopf-Hals-Tumoren Eine retrospektive Krankengutanalyse von Patienten der Jahre 1970-1990*

Schapher, Mirco Lothar, Dr. med. (2010): *Salivary Leptin as a Candidate Dignostic Marker in Salivary Gland Tumors*

Schernick, Caroline Sophie, Dr. med. (2010): *Chronische Otitis media. Eine retrospektive Studie zum Vergleich der verschiedenen Defektdeckungstechniken und der Auswirkungen der Tympanoplastik auf das Innenohr.*

Werth, Katrin Christine, Dr. med. (2010): *Clinical value of acoustic voice measures - a retrospective study*

Board Qualification

Psychogios, Georgios, Dr. med. (2010): *Ear, Nose and Throat Medicine*

Habilitations

Bozzato, Alessandro, PD Dr. med. (2009): *Hochauflösende sonographische Diagnostik der Kopf-Hals Region*

Bumm, Klaus, PD Dr. med. (2009): *Entwicklung der endoskopischen Nasennebenhöhlenchirurgie unter Berücksichtigung stereotaktischer Verfahren*

Wurm, Jochen, PD Dr. med. (2009): *Entwicklung eines navigierten robotischen Assistenzsystems für die Chirurgie der Nasennebenhöhlen und der vorderen Schädelbasis*

Hornung, Joachim Albert, PD Dr. med. (2010): *Evaluation selbstcrimpender Prothesen in der Steigbügelchirurgie*

Koch, Johannes Michael, PD Dr. med. (2010): *Die Rolle der Speicheldrüsenendoskopie in der Diagnostik und Therapie von obstruktiven Speicheldrüsen-Erkrankungen*

Department of Ear, Nose and Throat - Head and Neck Surgery

Division of Phoniatrics and Pediatric Audiology

Doctorate Theses

Bauer, Patricia Britta, Dr. med. (2009): *Analysis of relations between psychometric tests and mismatch negativity in pre-school children*

Glas, Katharina Marianne, Dr. med. (2009): *Klagsamkeit bei Dysphonien*

Kohler, Regina Dagmar, Dr. med. dent. (2009): *Quantitative Bewertung der Verständlichkeit nach der Behandlung kleiner Mundhöhlenkarzinome*

Petermann, Miriam, Dr. med. (2009): *Statistical detection and analysis of mismatch negativity*

derived by a multi-deviant design from normal hearing children

Preclik, Markus Christian, Dr. med. (2009): *Anamnesebogen für Auditive Verarbeitungs- und Wahrnehmungsstörungen - Psychometrische Korrelate bei Vorschulkindern*

Schmitt, Claudia Maria, Dr. med. dent. (2009): *Screening der kognitiven Entwicklung von Vorschulkindern - Bewertung der essentiellen Grenzsteine der kindlichen Entwicklung nach Michaelis*

Schumacher, Carola, Dr. med. (2009): *Zum Nutzen der stationären Therapie von Stimmstörungen*

Schwanfelder, Carla Margareta, Dr. med. (2009): *Stimmbezogene Lebensqualität: Struktur, Gültigkeit und Bedingungsfaktoren des deutschen Fragebogens*

Windrich, Martin, Dr. med. dent. (2009): *Automatic Quantification of Speech Intelligibility of Adults with Oral squamous Cell Carcinoma*

Colmant, Anne Clarissa Lena, Dr. med. (2010): *Diagnostik der taktil-kinästhetischen Wahrnehmung bei Vorschulkindern Ein Methodenvergleich*

Dames, Franziska, Dr. med. dent. (2010): *Sprachverständlichkeit von Kindern mit bilateralen und unilateralen Lippen-Kiefer-Gaumen-Spalten*

Kutzner, Klaus Eugen, Dr. med. (2010): *Stationäre Untersuchung und Behandlung von Patienten mit Dysphagien in der Erlanger Abteilung für Phoniatrie und Pädaudiologie - eine sozialmedizinische Bewertung*

Pröls, Renate Eva Hildegard, Dr. med. (2010): *Diagnostik visueller Wahrnehmung bei Vorschulkindern zur Früherkennung von Lese-Rechtschreibschwierigkeiten - ein Methodenvergleich zur Ökonomisierung des klinischen Untersuchungsaufenthalts in der Phoniatrie und Pädaudiologie*

Tutsch, Ariane Dominique Fleur Melanie, Dr. med. (2010): *Heidelberger Lautdifferenzierungstest H-LAD und Basiskompetenzen für Lese-Rechtschreibleistungen BAKO 1-4 bei jugendlichen Sprachheilschülern*

Voigt, Daniel, Dr.-Ing. (2010): *Datamining und Klassifizierungsansätze der Stimmlippenschwingung mittels Phonovibrogrammen*

Department of Dermatology
Chair of Skin and Venereal Diseases

Doctorate Theses

Bauer, Nicolas Felix, Dr. med. (2009): *Untersuchung der spontanen antitumoralen T-Zell-Antworten bei Melanompatienten mit progressivem vs. stabilem Krankheitsverlauf*

Löhberg, Lisa, Dr. med. (2009): *Aktivierung und Reifung dendritischer Zellen durch Toll-like-Rezeptor Ligand S-27609*

Vogel, Bianca Claudia Monika, Dr. med. (2009): *Untersuchungen zur Generierung und Funktion humaner immunsuppressiver dendritischer Zellen in vitro*

Greifenberg, Verena, Dr. med. (2010): *Myeloid-derived suppressor cell activation by combined lipopolysaccharide plus interferon-γ treatment impairs dendritic cell development*

Humrich, Jens Henner Peter Yorck, Dr. med. (2010): *Interaktion von Vaccinia Virus mit dem Chemokin-System der dendritischen Zelle*

Department of Cardiac Surgery
Chair of Cardiac Surgery

Doctorate Theses

Rubio López, Álvaro, Dr. med. (2009): *Nichtinvasive Zerebralprotektion mittels Nahinfrarotspektroskopie während Rekonstruktionschirurgie des Aortenbogens bei Erwachsenen und Kindern*

Zielezinski, Thorsten, Dr. med. (2009): *12 Jahre kardiale Tumoren am Herzzentrum Erlangen-Nürnberg Ein Follow-Up von 1994 bis 2006*

Koch, Sonja, Dr. rer. biol. hum. (2010): *Pharmazeutische Betreuung von Patienten mit koronarer Herzkrankheit nach aortokoronarer Bypassoperation - eine Pilotstudie*

Krätzer, Victoria Elsbeth Maria, Dr. med. (2010): *Immunologische Veränderungen in der Reperfusionsphase nach Aortenbogenoperationen mit hypothermen Kreislaufstillstand im Vergleich zu kontinuierlichem Low-Flow-Bypass - eine tierexperimentelle in vivo Studie*

Schlude, Ina-Kristin, Dr. med. (2010): *Akute Funktionelle und histologische cerebrale Schäden nach Aortenbogenoperationen in Hypothermie abhängig von verschiedenen Perfusionsmethoden unter besonderer Berücksichtigung des pH-Managements - eine tierexperimentelle in vivo Studie an 26 männlichen Jungferkeln-*

Board Qualification

Strecker, Thomas, PD Dr. med (2009): *Heart Surgery*

Habilitation

Strecker, Thomas, PD Dr. med (2009): *Neuropeptidfreisetzung nozizeptiver Afferenzen am Herzen - Bedeutung von Calcitonin Gene-Related Peptide*

Institute of Human Genetics
Chair of Human Genetics

Doctorate Theses

Bördlein, Annegret, Dr. rer. nat. (2009): *Untersuchungen zur Funktion von SPOCI: Molekulare und funktionelle Analyse einer Mausmutante*

Dietrich, Andreas Fabian, Dr. med. (2009): *Analyse von Kandidatengenen für Erkrankungen mit kongenitaler Nephrose und Mikrozephalie (Galloway-Mowat-Syndrom)*

Lascorz-Puértolas, Jesús, Dr. rer. biol. hum. (2009): *Systematic association studies and functional characterization of positional and functional candidate genes for psoriatic arthritis and psoriasis vulgaris*

Fernández Martínez, Lorena, Dr. rer. biol. hum. (2010): *Systematic mutation analysis and functional characterization of candidate genes for primary open angle glaucoma*

Department of Pediatrics
Chair of Pediatrics

Doctorate Theses

Abendroth, Franziska, Dr. med. (2009): *Der Einfluss von Hochfrequenzoszillationsventilation und Perfluorcarbonbeatmung auf die frühe Entzündungsreaktion beim neonatalen Atemnotsyndrom*

Albert, Christian Franz, Dr. med. (2009): *Untersuchungen zur intrakapillären Hämoglobinoxygenierung bei Kindern mit Wachstumshormonmangel unter Wachstumshormontherapie mit dem Erlanger-Mikrolichtleiter-Spektrophotometer (EMPHO)*

Berzl, Gabriele Maria, Dr. med. (2009): *Veränderungen endokriner Parameter in der Plazenta bei hypotrophen Früh- und Neugeborenen*

Bosch, Stephanie Elisabeth, Dr. med. (2009): *Pollen- und Sporenflug in Erlangen - Beobachtung über 18 Jahre*

Brehm, Hans Ulrich, Dr. med. (2009): *Nachweis der leukämiespezifischen Translokation t(4;11) in chromosomaler D N A aus Guthrie-Karten*

Busch, Henriette Martha Erika, Dr. med. (2009): *Frühe Störungen der weiblichen Pubertät - Erfahrungen der endokrinologischen Ambulanz der Kinder- und Jugendklinik*

Drexel, Linda Sigrid, Dr. med. (2009): *Die Rolle von Leptin und IGFBP-1 in der Plazenta hypotropher Neugeborener*

Hablawetz, Birgit Susanne, Dr. med. (2009): *Frühe Einflussfaktoren auf das Körpergewicht und die Prävalenz von Übergewicht zum Zeitpunkt der Schuleingangsuntersuchung bei 4610 Kindern im Raum Erlangen/Nordbayern*

Hauck, Barbara Luise, Dr. med. (2009): *Regulation von plazentarem Tachykinin 3 und Monoaminooxidase B in der humanen Plazenta in Abhängigkeit vom Geburtsgewicht*

Hollweg, Claudia Ingrid, Dr. med. (2009): *Einfluss der intrauterinen Wachstumsretardierung auf den Mechanismus und das Ausmaß glomerulärer Nierenschädigung - Morphologische und stereologische Untersuchungen bei mesangioproliferativer Glomerulonephritis der Ratte nach intrauteriner Malnutrition*

Kitzsteiner, Tobias Claus, Dr. med. (2009): *Relevante Faktoren für die Erhöhung der Plasmakonzentration des natriuretischen Peptids vom B-Typ (BNP) bei Kindern nach kardiochirurgischen Eingriffen.*

Kohler, Eva Maria, Dr. rer. nat. (2009): *A general model that explainsthe complex pattern of biallelic APC mutations in colorectal carcinoma, duodenal and desmoid tumours*

Meierkord, Lars, Dr. med. (2009): *Sequenzierung der Bruchpunktregion innerhalb des TEL-Gens (ETV6) bei der leukämiespezifischen chromosomalen Translokation t(12;21)*

Peeters, Joanna Maria, Dr. med. (2009): *Gesundheitsbezogene Lebensqualität bei chemotherapeutisch behandelten Patienten mit akuter lymphoblastischer Leukämie - ein Bericht des Late Effects Surveillance Systems in Deutschland*

Raake, Michael, Dr. med. (2009): *Expression und Regulation des humanen Leptinrezeptors unter dem Einfluss von Hypoxie*

Scheuerer, Katrin, Dr. med. (2009): *Aerosolisierte Perfluorcarbone im Vergleich: Verbesserung von Gasaustausch und Lungenmechanik beim surfactantdepletierten Ferkel*

Schuster, Sonja, Dr. med. (2009): *Die Genexpression von Adrenomedullin, Leptin, ihrer Rezeptoren und Neuropeptid Y in Tumoren des zentralen Nervensystems beim Menschen*

Weidinger, Martina Maria, Dr. med. (2009): *Die plazentare Regulation von 11ßHydroxysteroiddehydrogenase Typ2 und Corticotropin bei intrauteriner Wachstumsrestriktion*

Wich, Christina Edda, Dr. med. (2009): *Genexpression des plazentaren Fusionsproteins Syncytin und dessen Transkriptionsfaktors GCMa, des Syncytin-Rezeptors ASCT2 und des Effektormoleküls Connexin43 unter Normoxie und Hypoxie in humanen trophoblastären Zellen*

Franz, Andreas Tobias, Dr. med. (2010): *Die Bedeutung von Adrenomedullin und Endothelin an der Entstehung der angeborenen Aortenisthmusstenose*

Krenleitner, Brigitte, Dr. med. dent. (2010): *Untersuchung zur Entwicklung des Asthmas ehemaliger Patienten der Kinderklinik Erlangen nach der Pubertät*

Mühle, Anja, Dr. med. (2010): *Juvenile arterielle Hypertonie als Folge intrauteriner Wachstumsrestriktion bei Mehrlingsschwangerschaft? Eine prospektive Studie am Schafmodell*

Mueller, Verena Rabea, Dr. med. (2010): *Einfluss von akuter Hypoxie auf die Adipokinsynthese bei diabetischen und nicht-diabetischen Mäusen*

Petrasch, Maurice, Dr. med. (2010): *Aktives Visfatin zeigt erhöhte Serumkonzentrationen bei Hämodialysepatienten und korreliert invers mit zirkulierendem HDL-Cholesterin*

Requadt, Christoph, Dr. med. (2010): *Neurokognitive Spätfolgen bei Kindern und Jugendlichen mit akuter lymphoblastischer Leukämie und Hirntumor*

Schöw, Katrin, Dr. med. (2010): *Aktivierung des Leptinpromotors durch Hypoxie und Insulin führt nicht in allen Zelllinien zu erhöhter Leptinsynthese*

Seidel, Julia Gabriele, Dr. med. (2010): *Einfluss von Dexamethason auf endokrine Regulatoren der Fetalen Programmierung in humanen Trophoblastenzellen*

Sprenger, Ina Helga, Dr. med. (2010): *Endogene Rhythmizität und ihre pathologischen Veränderungen als Grundlage zur Entwicklung eines Screeningverfahrens für das Aufmerksamkeitsdefizitsyndrom bei Kindern*

Board Qualifications "Child and Adolescent Medicine"

Benz, Kerstin, Dr. med. (2009)
Fecker, Gisela, Dr. med. (2009)
Frank, Susi, Dr. med. (2009)
Herrmann, Kathrin, Dr. med. (2009)
Jung, Ronny, Dr. med. (2009)
Metzler, Markus, Dr. med. (2009)
Nüsken, Kai-Dietrich, Dr. med. (2009)
Palberg, Andreas, Dr. med. (2009)
Plattig, Bernhard, Dr. med. (2009)
Topf, Hans-Georg, Dr. med. (2009)
Völkl, Thomas, Dr. med. (2009)
Weise, Anja, Dr. med. (2009)
Blessing, Holger, Dr. med. (2010)
Breuer, Christian, Dr. med. (2010)
Gravou-Apostolatou, Chara, Dr. med. (2010)
Nögel, Stephanie, Dr. med. (2010)
Rüth, Eva-Maria, Dr. med. (2010)
Tzschoppe, Anja, Dr. med. (2010)

Habilitations

Metzler, Markus, PD Dr. med. (2009): *Characterization of fusion genes in childhood leukaemia – clinical applications and biological conclusions from breakpoint analysis*

Plank, Christian, PD Dr. med. (2010): *Renale Folgen der intrauterinen Wachstumsrestriktion*

Department of Pediatrics
Division of Pediatric Cardiology

Doctorate Thesis

Schuster, Cornelia, Dr. med. (2010): *Aortenisthmusstenosen bei Kindern. Untersuchung des mittelfristigen postoperativen Verlaufs in Abhängigkeit von morphologischer Ausgangslage, Operationsalter und Operationstechnik*

Department of Medicine 1 – Gastroenterology, Lung Diseases and Endocrinology
Chair of Internal Medicine I

Doctorate Theses

Abel, Reinhard Ernst, Dr. med. (2009): *Prävalenz des obstruktiven Schlafapnoesyndroms bei Patienten mit Normaldruckglaukom*

Aljukic, Emgijada, Dr. med. (2009): *Lebensqualitätserfassung von Intensivpatienten: Psychometrischer Vergleich eines spezifischen mit einem generischem Fragebogen*

Baumann, Anne, Dr. med. (2009): *Retrospektive Analyse zur Prävalenz viralen Genoms bei Patienten mit CED und deren klinische Relevanz auf den Verlauf der chronischen Darmentzündung*

Brehm, Barbara, Dr. med. (2009): *Beeinflussung verschiedener Fibrosescores durch eine Langzeittherapie von normaldosiertem beziehungsweise niedrigdosiertem Interferon in Kombination mit Silymarin bei Patienten mit chronischer Hepatitis C nach erfolgloser Vortherapie*

Bruckmoser, Tim Oliver, Dr. med. (2009): *Retrospektive Erfassung von Risikofaktoren für fehlerhafte Anlage und Komplikationen (kurz- und langfristig) sowie der Gesamtüberlebensrate nach PEJ-Anlage (Direkte PEJ und sog. Jet-PEG)*

Dorlaque, Laure Odile, Dr. med. dent. (2009): *Die Bedeutung der Genexpression von Matrix-Metalloproteinasen bei metastasierten kolorektalen Karzinomen*

Gaca, Piotr Jakub, Dr. med. (2009): *Ghrelin ameliorates colonic inflammation: role of nitric oxide and sensory nerves*

Gümüs, Buket, Dr. med. (2009): *Einführung eines klinischen Behandlungspfades Ambulant erworbene Pneumonie: Einfluss des Schweregrades*

Hammer, Robert Heiner, Dr. med. (2009): *Untersuchung der Unbedenklichkeit von gliadin- und alkoholfreiem Bier bei Sprue - Patienten*

Herbst, Alexandra Larissa, Dr. med. (2009): *Analyse der prädiktiven und prognostischen Faktoren beim kleinzelligen Bronichalkarzinom unter palliativer Erstlinien-Therapie mit ACE - eine retrospektive Analyse über einen Zeitraum von 16 Jahren*

Hinkmann, Carolin, Dr. med. (2009): *Untersuchung quantitativer Besonderheiten peripherer dendritischer Zellen und ihrer Subpopulationen bei Patienten mit Diabetes mellitus Typ 1*

Kandler, Lukas Johannes, Dr. med. (2009): *Molekularbiologisches Genexpressions-Profil humaner hochgradig stenosierter und verkalkter Aortenklappen unter dem Einfluss von Statinen*

Kirchner-Brüggemann, Astrid Ingeborg, Dr. med. (2009): *Alkoholismusprävalenz und alkoholassoziierte Erkrankungen in einem norddeutschen Krankenhaus der Regelversorgung*

Kleinecke, Diane Grete Christina, Dr. med. (2009): *Kontrastmittelkinetik hepatozellulärer Kerzinome in der dynamischen Kontrastmittel-*

sonographie in Korrelation zum Goldstandard Histologie

Klintworth, Nils, Dr. med. (2009): *Rezeptor- und Substratselektivität kardialer RGS-Proteine am Beispiel der G-Protein-abhängigen Aktivierung der Proteinkinasen ERK1/2 und Akt: Ein neuer Ansatz für die Therapie der kardialen Hypertrophie?*

Kollmann, Sylvia Maria, Dr. med. (2009): *Untersuchung von Geschmack und Ernährung bei Patienten mit Morbus Crohn*

Kränzlein, Diana, Dr. med. (2009): *Auswirkungen einer Langzeit-enteralen Ernährung mit Formula-Diäten per Perkutaner Endoskopischer Gastrostomie (PEG)*

Lampel, Emilia, Dr. med. (2009): *Biochemische Evaluation des Effektes von Pankreasenzymen auf die Allergenstruktur von wichtigen Nahrungsmittellallergenen*

Lindner, Annette Simone, Dr. med. (2009): *Spektrum und Komplikationen sonographisch gesteuerter Interventionen an der Medizinischen Klinik 1 Erlangen in den Jahren 2001-2002*

Meyer, Stefanie Sigrid, Dr. med. (2009): *Spektrum und Komplikationen sonographisch gesteuerter Interventionen im Abdomen an der Medizinischen Klinik 1 Erlangen von 2003 - 2004*

Münch, Sabine, Dr. med. (2009): *Aktivierung und gesteigerte Zytotoxizität tumorspezifischer T-Lymphozyten nach laserinduzierter Thermotherapie von Patienten mit hepatischen Metastasen eines kolorektalen Karzinoms*

Quint, Karl, Dr. med. (2009): *Das Expressionsmuster von PDX-1, SHH, Patched und Gli-1 im humanen Pankreaskarzinom ist mit pathologischen und klinischen Eigenschaften assoziiert*

Richter, Elisabeth Susanne, Dr. med. (2009): *Evaluation der TNFa Konzentrationen in der endoskopischen Spülflüssigkeit bei chronisch entzündlichen Darmerkrankungen und Kontrollpersonen*

Rienecker, Helmut Jürgen, Dr. med. (2009): *Protektiver Effekt von H.pylori auf die Entstehung einer gastro-intestinalen vermittelten Allergie*

Schaller, Tina Gerhilde, Dr. med. (2009): *Reduktion der Zahl im Blut zirkulierender Dendritischer Prekursorzellen bei der stabilen koronaren Herzerkrankung*

Schuller, Andrea Elisabeth, Dr. med. (2009): *Schulungsbedarf von Patienten unter Cortisonersatztherapie*

Siebert, Stefan, Dr. med. (2009): *Analyse von Risikofaktoren für das Auftreten von Pankreatitiden, Blutungen und Gesamtkomplikationen nach endoskopischer retrograder Cholangiopankreatikographie*

Simon, Kerstin, Dr. med. (2009): *Bestimmung des eosinophilen kationischen Proteins aus der Darmlavage bei chronisch entzündlichen Darmerkrankungen, mikroskopischen Colitiden und gastrointestinal vermittelten Allergien*

Stegemann, Tanja, Dr. med. (2009): *Die Auswirkungen von Alkohol- und Nikotinabusus auf die Rate von unerwünschten Arzneimittelwirkungen während der stationären Behandlung*

Stengel, Christiane Dorothea, Dr. med. (2009): *Evaluation des klinischen effektes des Antihistaminikums Loratadin auf den Verlauf des Morbus Crohn und der Colitis ulcerosa*

Stöcklein, Daniela Renate, Dr. med. (2009): *Die Wirksamkeit von normal- bzw. niedrigdosiertem Interferon in Kombination mit Silymarin zur Beeinflussung der Fibroseentwicklung und des entzündlichen Infiltrats der Leber bei Patienten mit chronischer Hepatitis C nach erfolgloser Vortherapie*

Tasi, Atingwa MacDonald, Dr. med. (2009): *Ghrelin- und Obestatinspiegel bei Typ-2-Diabetikern mit und ohne Gastroparese*

Tietz, Volker Christian, Dr. med. (2009): *Perkutane ultraschallgesteuerte Radiofrequenzablation mit perfundierten Nadelapplikatoren - Langzeitbeobachtungen bei Lebermetastasen*

Uhlke, Daniel, Dr. med. (2009): *Perkutane ultraschallgesteuerte Radiofrequenzablation mit perfundierten Nadelapplikatoren - Langzeitbeobachtungen an Patienten mit Hepatozellulärem Karzinom*

Wagner, Jannis Mathias, Dr. med. (2009): *Diagnostische Wertigkeit der Kontrastmittelsonographie und Kontrastmittelendosonographie in der Differentialdiagnose von Pankreasraumforderungen*

Weng, Alexander Tobias Manuel, Dr. med. (2009): *Die Wirkung von HMG-CoA Reduktase Inhibitoren (Statinen) auf humane kultivierte Dendritische Zellen*

Wolff, Kerstin Maria Anne, Dr. med. (2009): *Wöchentliche Hochdosisbehandlung mit 5-FU als 24h-Infusion und Natriumfolinat (AIO Regime) plus Irinotecan bei Patienten mit fortgeschrittenen, inoperablen und metastasierten Adeno- oder Plattenepithelcarcinomen des Ösophagus: Endauswertung einer Phase II-Studie*

Berner, Larissa, Dr. med. (2010): *Einfluss der Extrakorporalen Stoßwellenlithotripsie (ESWL) auf die Durchgängigkeit okkludierter Pankreasgangendoprothesen*

Burgeth, Ulrike Monika, Dr. med. dent. (2010): *Das Hepatozelluläre Karzinom und der Vergleich verschiedener HDAC-Hemmer in vitro / in vivo*

Dittel, Christian Andreas Max, Dr. med. (2010): *Insulinresistenz, energiehomöostatische Hormone und subklinisch inflammatorische Parameter unter nCPAP Therapie beim obstruktiven Schlafapnoesyndrom im Langzeitverlauf*

Frank, Thomas Gregor, Dr. med. (2010): *Systemische Inflammationsmarker und Koronarkalzifizierungen im Mehrzeilenspiral-Computertomographen bei Patienten mit Verdacht auf koronare Herzkrankheit*

Fröber, Kathrin Barbara, Dr. med. (2010): *Eine prospektive Erfassung der Lebensqualität von Patienten einer internistischen Intersivstation im zeitlichen Verlauf nach 5 Monaten und r Jahren sowie der Zusammenhang präexistenter Einflussfaktoren*

Fuchs, Tanja Helga, Dr. med. (2010): *Bedeutung der Reduktion im Blut zirkulierender Dendritischer Prekursorzellen bei der akuten zerebralen Ischämie*

Gabriel, Sarah, Dr. med. (2010): *Ex-Vivo Messung der Stickstoffmonoxid-Freisetzung von humanen Colonbiopsien bei gastrointestinalvermittelten Allergien, chronisch entzündlichen Darmerkrankungen und kontrollen.*

Hagel, Doris Freya, Dr. med. (2010): *Ernährungs-, Trink- und Kochgewohnheiten sowie Kontakt zu Detergenzien bei Patienten mit chronisch-entzündlichen Darmerkrankungen im Vergleich zu einem gesunden Normalkollektiv*

Hahne, Rebekka Ruth Dorothea, Dr. med. (2010): *Fibroseprogression bei chronischer Hepatitis C-Infektion. Charakterisierung einzelner Hepatitis C Virus Gene exprimierender Zelllinien.*

Jabari, Samir, Dr. med. (2010): *Zelluläre Plastizität von Trans- und Dedifferenzierung in humanen Hepatomzellen in vitro und in vivo*

Jukic, Jelena, Dr. med. (2010): *Inflammatorische Mechanismen in der Pathogenese der essentiellen arteriellen Hypertonie*

Karl, Martina Natascha, Dr. med. (2010): *Die Atherosklerose als chronische Entzündungskrankheit: Die Bedeutung des CD40-CD 154-Systems bei Patienten mit moderater Hypercolesterinämie*

Kufer, Verena Luise Angelika, Dr. med. (2010): *Zur anatomischen Verteilung von adulten kardialen Stammzellen in humanen Myokard*

Legal, Wolfgang Matthias, Dr. med. (2010): *Zeigen Nierenzellkarzinome typische Vaskularisationsmuster in der Kontrastmittelsonographie?*

Leistner, Christane, Dr. med. dent. (2010): *Klinische Evaluation der Behandlung des obstruktiven Schlafapnoesyndroms mit einer Protrusionsschiene*

Ludwig, Christine Annett, Dr. med. (2010): *Nationale Erhebung zur endoskopischen und medikamentösen Terapie der Ulkusblutung in Deutschland*

Müller, Michael Thomas Goetz, Dr. med. (2010): *Obstruktives Schlafapnoesyndrom bai diabetischen Patienten ohne übermäßige Tagesschläfrigkeit im Patientengut einer niedergelassenen Praxis*

Nabe, Andrea, Dr. med. (2010): *Bestimmung von Tumornekrosefaktor alpha, totalem und spezifischem IgE bei Nahrungsmittelallergikern und chronisch entzündlichen Darmerkrankungen am unteren Gastrointestinaltrakt mittels endoskopisch gesteuerter segmentaler Darmlavage*

Plogsties, Elivra, Dr. med. (2010): *Klinische und genetische Prognosefaktoren bei Adenokarzinomen des Dünndarms*

Sailer, Anja Katrin, Dr. med. (2010): *Art und Häufigkeit von Komplikationen der flexiblen diagnostischen Bronchoskopie an einem universitären Zentrum unter besonderer Berücksichtigung von Tumorpatienten*

Schinhammer, Silke Gabriele, Dr. med. (2010): *Untersuchung möglicher Zusammenhänge zwischen Hashimoto-Thyreoiditis, psychischen Störungen und genetischen Varianten des Adenosinsystems*

Schwab, Angelika, Dr. med. (2010): *Untersuchung möglicher Zusammenhänge zwischen Hashimoto-Thyreoiditis, psychischen Störungen und genetischen Varianten des Katecholamin-, Serotonin- und Folat- bzw. Homocystein-Stoffwechsels*

Schütz, Annette Luitgard, Dr. med. (2010): *Immunhistologische Untersuchungen zum Einfluss demographischer Daten und kardialer Pathologien auf die Verteilung adulter kardialer Stammzellen in humanem Myokard*

Seelig, Sebastian Justus, Dr. med. (2010): *Prospektive einarmige Studie zur Endoskopischen Mukosaresektion (EMR) als Therapie prämaligner und früher maligner Läsionen im oberen Gastrointestinaltrakt und Dünndarm unter besonderer Berücksichtigung von Adenomen und Adenokarzinomen des Magens*

Stelzer, Nadine, Dr. med. (2010): *Die Rolle von endothelialem RGS4 bei der ERK 1/2-Aktivierung in der arteriosklerotischen Inflammation*

Trummer, Katrin Sabine, Dr. med. (2010): *Einfluss von Somatostatinanaloga auf die Proliferation von Tumorzellen des Gastrointestinaltraktes unter besonderer Berücksichtigung von neuroendokrinen Tumoren*

Ullmann, Sophie, Dr. med. (2010): *Art und Häufigkeit von Komplikationen der flexiblen diagnostischen Bronchoskopie an einem universitären Zentrum unter besonderer Berücksichtigung von pulmonal und kardial erkrankten Patienten*

Özcan, Rahman, Dr. med. (2010): *Prognosesysteme für das Hepatozelluläre Karzinom. Ergebnisse einer retrospektiven Studie*

Board Qualifications "Internal Medicine"

Bergmann, Tanja, Dr. med. (2009)
Zirlik, Sabine, Dr. med. (2009)
Gahr, Susanne, Dr. med. (2010)
Heide, Roland, Dr. med. (2010)
Hess, Thomas, Dr. med. (2010)
Hübner, Inka, Dr. med. (2010)
Muskoski, Dane, Dr. med. (2010)
Nägel, Andreas, Dr. med. (2010)
Zopf, Yurdaguel, Dr. med. (2010)
de Rossi, Thomas, Dr. med. (2010)

Additional Qualifications

Boxberger, Frank, Dr. med. (2009): *Gastroenterology*

Pour-Schahin, Simin, Dr. med. (2009): *Pneumology*

Bergmann, Tanja, Dr. med. (2010): *Edocrinology*

Zirlik, Sabine, Dr. med. (2010): *Pneumology*

Department of Medicine 2 – Cardiology and Angiology

Chair of Internal Medicine II

Doctorate Theses

Dietz, Stefanie, Dr. med. (2009): *Erfassung hochgradiger Koronararterienstenosen mittels der kontrastverstärkten nicht-invasiven Mehrzeilen-Spiral-Computertomographie mit Sub-Millimeter-Kollimation*

Graf, Sabine, Dr. med. (2009): *Diagnostik von Abstoßungsreaktionen nach Herztransplantation mittels Magentokardiographie*

Nowak, Kathrin Johanna, Dr. med. (2009): *Interventionelle Therapie und klinischer Langzeitverlauf bei Patienten mit akutem ST-Streckenelevations-Myokardinfarkt im Alter = 75 Jahre - Ergebnisse im Vergleich mit jüngeren Patienten -*

Schineis, Nicolai, Dr. med. (2009): *Power-Doppler-Myokardkontrastechokardiographie zur Messung der linksventrikulären Funktion und myokardialen Perfusion bei Wistar-Ratten, vor und nach RIVA-Ligatur als auch nach Implantation von künstlich erzeugtem Herzmuskelgewebe*

Ehrenreich, Sonja, Dr. med. (2010): *Nachweis von koronaren Stenosen mittels Multi-Detektor-Computertomographie mit 16 c 0,75 mm Kollimation und 375ms Rotation*

Graf, Verena Maria, Dr. med. (2010): *Interobserver-Variabilität bei der Detektion von Koronarstenosen mittels Mehrzeilen-CT*

Layritz, Christian Michael, Dr. med. (2010): *Quantitative Echo- und Gewebe-Doppler-Echokardiographie: Prädiktion systolischer und diastolischer Funktionsstörungen mittels natriuretischer Peptide verschiedener Radioimmunassays in einem ambulanten Patientenkolletiv*

Raum, Philipp Gerhard, Dr. med. (2010): *Erfassung der Transplantatvaskulopathie nach orthotoper Herztransplantation mittels kontrastmittelverstärkter Dual Source Computertomographie im Vergleich zum intravaskulären Ultraschall*

Schneider, Thomas-Michael, Dr. med. (2010): *Die Auswirkungen von Erregungsleitungsstörungen auf die regionale Myokardfunktion des linken und rechten Ventrikels Eine Studie mittels Gewebedoppler-Echokardiografie*

Seltmann, Martin Reinhard, Dr. med. (2010): *Volumetrische Quantifizierung koronarer atherosklerotischer Plaques mittels Mehrzeilen-Computertomographie: Vergleich zum intravaskulären Ultraschall*

Board Qualifications "Internal Medicine"

Rost, Heinz Christian, Dr. med. (2009)
Schmid, Michael, Dr. med. (2009)

Habilitations

Stumpf, Christian, PD Dr. med. (2009): *Inflammatorische Mechanismen in der Pathogenese und Progression der chronischen Herzinsuffizienz*

Yilmaz, Attila, Dr. med. habil. (2009): *Bedeutung von Dendritischen Zellen für die Atherosklerose und entzündliche Gefäßerkrankungen*

Pohle, Falk Karsten, PD Dr. med. (2010): *Nichtinvasive Analyse von Kalzifikationen der Aortenklappe und der Koronargefäße mit der Elektronenstrahltomographie*

Department of Medicine 3 – Rheumatology and Immunology

Chair of Internal Medicine III

Doctorate Theses

Akel, Samer, Dr. med. (2009): *Optimierung von Zellaufbereitung und Immunfärbung für die diagnostische Durchflusszytometrie von Blutproben*

Brandl, Andreas Bernhard, Dr. rer. nat. (2010): *MicroRNA-vermittelte Kontrolle der Antigen-induzierten B-Zell-Differenzierung und deren Rolle in der B-Zell-Entwicklung*

Dütting, Sebastian Michael, Dr. rer. nat. (2010): *Charakterisierung von Swiprosin-2/EFHD1 und dessen Funktion während der frühen B-Zellentwicklung.*

Lutz, Gabriele Claudia, Dr. med. (2010): *Klinische Studie über die Wirksamkeit und Verträglichkeit von Leflunomid in Kombionation mit TNF-a-Inhibitoren in der Therapie der rheumatioiden Arthritis verglichen mit Methotrexat und TNF-a-Inhibitoren*

Metzner, Mirjam Franziska, Dr. rer. nat. (2010): *Complex Formation of AID and ist Function in Innate Immunity*

Ramming, Andreas Guenter, Dr. med. (2010): *Homotypische T-Zell-T-Zell-Interaktionen induzieren T-Zell-Aktivierung, Proliferation und Differenzierung*

Schreiber, Sandra, Dr. rer. nat. (2010): *Die Rolle von micro RNAs in der frühen B-Zellentwicklung.*

Stadler, Kathrin, Dr. med. (2010): *Photopheresis with UV-A light and 8-methoxypsoralen leads to cell death and to release of blebs with anti-inflammatory phenotype ind activated and non-activated lymphocytes*

Wacker, Jochen, Dr. med. (2010): *Untersuchungen zur Rolle des intrazellulären Kalziums in einem Modell der Kostimulation durch CD 28 Bei Jurkat-Zellen*

Wagner, Sabine, Dr. med. (2010): *Klinische und immunologische Untersuchung an Patienten mit Borreliose*

Board Qualification

Rech, Jürgen, Dr. med. (2010): *Internal Medicine and Rheumatology*

Habilitations

Distler, Jörg, PD Dr. med. (2009): *Die Rolle von Fibroblasten in der Pathogenese der systemischen Sklerose und der rheumatoiden Arthritis*

Zwerina, Jochen, PD Dr. med. univ. (2009): *Die Rolle von Zytokinen in der Pathogenese der arthritischen Gelenkdestruktion*

Biburger, Markus, PD Dr. rer. nat. (2010): *Mechanismen und Modulation der zellulären Immunantwort – Die Balance zwischen Aktivierung und Toleranz*

Department of Medicine 4 - Nephrology and Hypertensiology

Chair of Internal Medicine IV

Doctorate Theses

Haas, Alexander Georg, Dr. med. (2009): *Die Bedeutung von NO-Synthase-Isoformen für die frühe diabetische Hyperfiltration am Modell der Streptozotocin-Diabetesratte*

Lechler, Philipp, Dr. med. (2009): *Expression des Tumorgens Survivin in adulten renalen Tubuluszellen - Eine Rolle in der renalen (Patho) Physiologie*

Opgenoorth, Mirian Julia, Dr. med. (2009): *Verbesserte Abschätzung der Qualität postmortaler Spendernieren mittels Proteinurieddifferenzierung und Quantifizierung*

Ott, Christian, Dr. med. (2009): *Die Bedeutung der Rho-Proteine und des Actincytoskeletts für die Synthese von CTGF*

Renk, Sindy, Dr. med. (2009): *Der Einfluss der Rezeptoren P2Y1 und P2Y12 auf den Krankheitsverlauf der passiven nephrotoxischen Halbmondnephritis in der Maus*

Schafflhuber, Markus, Dr. med. (2009): *Mechanismen der osmotisch inaktiven Na+ - Speicherung*

Schneider, Andreas, Dr. med. (2009): *Kardiale Effekte der Mineralkortikoidrezeptor-Blockade bei Patienten mit arterieller Hypertonie*

Baenkler, Marc Adi, Dr. med. (2010): *Functional Analysis of Eicosanoids from White Blood Cells in Sepsis and SIRS*

Bauer, Katharina Kristine, Dr. med. (2010): *Extrarenale Regulation des Natriumhaushalts bei Ratten mit Mineralokortikoidexzess*

Cura, Holger, Dr. med. (2010): *Der apo(a)-Polymorphismus und Lipoprotein(a)- Spezifitäten beim terminal Niereninsuffizienten Experimentelle Identifizierung neuer Phänotypen Analyse der 5-Jahres-Mortalität zur Bewertung der klinischen Relevanz*

Höfer, Martina Juliane, Dr. med. (2010): *Endogenes CGRP - Untersuchung zur renalen Freisetzung aus renalen Afferenzen in vitro*

Ilies, Christoph Sven Viktor, Dr. med. (2010): *Ovariektomie als Modell einer erworbenen, verminderten osmotisch inaktiven Natriumspeicherfähigkeit bei Ratten*

Nagel, Andrea Angela, Dr. med. (2010): *Einfluss von Thrombospondin-1 auf den Verlauf des Desoxy-Cortico-Steron-Acetat-induzierten Hypertonie Schadens in der Niere unter Verwendung von Throbospondin-1 Knockout Mäusen*

Ritt, Martin, Dr. med. (2010): *Analyse der Struktur retinaler Arteriolen bei unbehandelten Patienten mit essentieller Hypertonie*

Samarin, Jana, Dr. rer. nat. (2010): *Molekulare Regulationsmechanismen der connective tissue growth factor (CTGF) Expression in Endothelzellen unter Hypoxie*

Schaub, Katrin Susanne, Dr. med. (2010): *Einfluss von Thrombospondin 1 (TSP1) auf das Krankheitsbild der Streptozotozin-induzierten diabetischen Nephropathie unter Verwendung von TSP1-knock-out-Mäusen*

Stix, Jana Nora Lisa, Dr. med. (2010): *Untersuchungen zur Migration von humanen renalen tubulären Epithelzellen*

Wessel, Julia Marina, Dr. med. (2010): *Zelltypspezifische Regulation des Connective Tissue Growth Factor (CTGF) in renalen Zellen durch Hypoxie*

Board Qualifications

Bernhardt, Wanja, Dr. med. (2009): *Internal Medicine*

Böhm, Brigitte, Dr. med. (2009): *Internal Medicine and Nephrology*

Poliak, Roudolf, Dr. med. (2009): *Internal Medicine and Nephrology*

Schrauzer, Thomas, Dr. med. (2009): *Internal Medicine and Nephrology*

Wiesener, Michael, Dr. med (2009): *Internal Medicine und Nephrologie*

Wöhl, Stefan, Dr. med. (2009): *Internal Medicine*

Bock, Dieter, Dr. med. (2010): *Internal Medicine*

Börner, Carola, Dr. med. (2010): *Internal Medicine and Nephrology*

Forster, Christian, Dr. med. (2010): *Internal Medicine*

Kim, Jae-Sun, Dr. med. (2010): *Internal Medicine*

Kueri, Nadja, Dr. med. (2010): *Internal Medicine and Nephrology*

Röseler, Tilman, Dr. med. (2010): *Internal Medicine*

Türk, Tobias, Dr. med. (2010): *Internal Medicine*

Additional Qualification

Hübner, Silvia, Dr. med. (2009): *Emergency Medicine*

Habilitations

Wiesener, Michael, PD Dr. med. (2009): *Sauerstoffabhängige Genregulation als wichtiger Adaptationsmechanismus gesunder und tumoröser Gewebe*

Daniel, Christoph, Dr. rer. nat. (2010): *Thrombospondine bei renalen Erkrankungen Angriffspunkt für eine anti-fibroitsche Therapie in der Niere*

Schneider, Markus, PD Dr. med. (2010): *Role of nitric oxide and entothelin for renal haemodynamics*

Department of Medicine 5 - Hematology and Oncology

Chair of Hematology and Oncology

Doctorate Thesis

Rech, Dorit, Dr. med. (2010): *Korrelation von monoklonalem und polyklonalem Ciclosporinspiegel bei Patienten nach allogener Stammzelltransplantation*

Board Qualifications "Internal Medicine and Hematology and Oncology"

Ferstl, Barbara, Dr. (2010)

Winkler, Julia, Dr. (2010)

Institute of Microbiology – Clinical Microbiology, Immunology and Hygiene

Chair of Microbiology and Immunology of Infection

Doctorate Theses

Braun, Joachim Manfred, Dr. med. (2009): *Regulation von Effektormolekülen Natürlicher Killerzellen bei der Tuberkulose des Menschen*

Braun, Tobias Walter, Dr. med. (2009): *Hydrophobe mykobakterielle Antigene als Bestandteil eines Impfstoffes gegen die Tuberkulose*

Traxdorf, Maximilian Thomas, Dr. med. (2009): *Entzündungsgenese und bakterielle Elimination im experimentellen murinen Modell der Lyme-Borreliose*

Wetzel, Gabriel Andreas, Dr. med. (2009): *Produktion und Wirkung von Bactericidal/Permeability Increasing Protein (BPI) bei Infektionen mit Gram-prositiven Keimen*

Becker, Sebastian, Dr. med. (2010): *Modulation der CD83-Expression auf humanen B-Zellen während anti-TNF-Therapie von Patienten mit Autoimmunerkrankungen*

Henning, Dorothee Natascha Irmgard, Dr. med. (2010): *Die entzündungshemmende Wirkung einer niedrigdosierten Strahlentherapie beinhaltet eine verminderte CCL20-Chemokin-Expression und Adhäsion von Granulozyten an Endothelzellen*

Hölzer, Stefanie Ute, Dr. rer. nat. (2010): *Functional analysis of type III secretion systems in Salmonella enterica*

Müller, Petra, Dr. rer. nat. (2010): *Characterization of SseF, a Salmonella pathogenicity island 2-encoded type three secretion system effector involved in the formation of Salmonella-induced filaments*

Otte, Manuel, Dr. rer. nat. (2010): *Funktionen des alternativen Interleukin-4-Rezeptor-Signalosoms in vitro und in vivo.*

Rajashekar, Roopa, Dr. rer. nat. (2010): *Novel approaches to understand the intracellular lifestyle of Salmonella enterica by live cell imaging and ultrastructural studies.*

Sitte, Selina, Dr. rer. nat. (2010): *Die Rolle von Jun activation domain-binding protein 1 (JAB1) in B-Zellen, Makrophagen und der Interleukin-4-Rezeptor-Signaltransduktion*

Department of Oral and Maxillofacial Surgery

Chair of Dental, Oral and Maxillofacial Medicine - especially Oral and Maxillofacial Surgery

Doctorate Theses

Bauersachs, Anne Franziska, Dr. med. dent. (2009): *Prognostische Relevanz perioperativer Bluttransfusionen nach R0-Resektion von Plattenepithelkarzinomen der Mundhöhle und mikrovaskulärer Rekonstruktion*

Fischer, Kathrin, Dr. med. dent. (2009): *Bedeutung der Restknochenhöhe bei der Einlagerungsosteoplastik im Oberkiefer und simultaner Implantatinsertion: eine Tierexperimentelle Analyse*

Meisel, Ulf, Dr. med. dent. (2009): *Poly-Ether-Ether-Ketone (PEEK) mit modulierter Oberfläche - eine tierexperimentelle Analyse*

Moll, Christine Sabine, Dr. med. dent. (2009): *Tierexperimentelle Untersuchung zur knöchernen Regeneration enossaler Implantate mit Vakuum-Titanplasma-Spray- und Calciumphosphat-Beschichtung*

Schwarz, Christin-Sophie, Dr. med. dent. (2009): *Rekonstruktion knöcherner Defekte durch extrakorporal autoklavierte Autotransplantate mit Hilfe von Tissue Engineering - eine tierexperimentelle Pilotstudie*

Seiß, Martin, Dr. med. (2009): *Kosten-Erlös-Kalkulation auf Grundlage eines klinischen Behandlungspfades am Beispiel der bignathen Umstellungsosteotomie*

Stauber, Irene Maria, Dr. med. dent. (2009): *Dreidimensionale Analyse der Gesichtssymmetrie von Patienten mit einseitiger Lippen-Kiefer-Gaumenspalte anhand optischer Oberflächendaten*

Thews, Bettina, Dr. med. dent. (2009): *Klinische Evaluation von Knochendefekten des Unterkiefers nach Behandlung von Pseudoarthrosen mit osteoinduktivem Kollagen (Targobone®)*

Behzad, Ali, Dr. med. (2010): *Einfluss von Thrombin auf den neuronalen Aß-Peptid-Stoffwechsel in vitro*

Brandner, Sebastian, Dr. med. (2010): *Einfluss proinflammatorischer Zytokine auf die Aß-Sekretion mononukleärer Phagozyten*

Bumiller, Lars Theodor, Dr. med. (2010): *Rekonstruktion knöcherner Defekte durch extrakorporal autoklavierte Autotransplantate und Tissue Engineering*

Dehner, Jan-Friedrich Hans Rudolf, Dr. med. dent. (2010): *Vergleichende In-vivo-Untersuchung der Knochenneubildung mit konvertierten osteogenen Effektorzellen aus Stammzellen des Fettgewebes*

Fruck, Monika Christine, Dr. med. dent. (2010): *Ossäre Regeneration eines experimentellen critical size-Defektes der Schweinekalotte mit einem biphasischen Knochenersatzmaterial und biodegradierbarer Polyethylenglycol-Membran - Einfluss auf die Wnt-vermittelte, osteogene Rekrutierung und Maturation mesenchymaler Osteoblast- und Osteoklastprogenitoren*

Häussinger, Philipp Michael, Dr. med. dent. (2010): *Prognoserelevante Bedeutung der Expression von Repp86 bei Plattenepithelkarzinomen der Mundhöhle*

Jehle, Marc Adolf, Dr. med. (2010): *Vergleich der klinischen Anwendung vo Hydroxylapatitkeramik als Knochenersatzmaterialien beim Sinuslift*

Knoll, Nadine, Dr. med. dent. (2010): *Ossäre Regeneration eines experimentellen critical-size Defektes der Schweinekalotte mit einem biphasischen Knochenersatzmaterial (HA / TCP) und lokalem Gentransfer (BMP-2) - Einfluss einer biodegradierbaren PEG-Membran auf Ossifikation und Mineralisation*

Kölpin, Felix, Dr. med. dent. (2010): *Ossäre Regeneration eines experimentellen critical-size Defektes der Schweinekalotte durch ein biphasisches Knochenersatzmaterial mit lokalem Gentransfer. Einfluss einer biodegradierbaren PEG-Membran auf Ossifikation und Mineralisation*

Meisel, Mark, Dr. med. dent. (2010): *Lichtmikroskopische und immunhistologische Untersuchung oberflächenmodifizierter Titanimplantate - eine tierexperimentelle Analyse*

Schmitt, Christian Martin, Dr. med. dent. (2010): *Untersuchungen zur Knochenregeneration unter Verwendung von konvertierten osteogenen Effektorzellen aus mesenchymalen Stammzellen des Knochenmarks und Periostes - Eine vergleichende tierexperimentelle Studie*

Seiß, Martin, Dr. med. dent. (2010): *Osteotomie und primärer Wundverschluss bei der bisphosphonat-assoziierten Kieferknochennekrose eine prospektive klinische Studie von 12 Monaten*

Stelzle, Florian, Dr. med. dent. (2010): *Evaluation of different methods of indirect sinus floor elevation for elevation heigths of 10 mm - An experimental ex vivo study*

Trabert, Susanne, Dr. med. dent. (2010): *Vergleichende Untersuchung zur Expression antimikrobieller Peptide (humanerß-Defensine 1-3) bei der bisphosphonat-assoziierten Knochennekrose und der Osteoradionekrose*

Widenmayer, Martin, Dr. med. dent. (2010): *Elektronenstrahlgesinterte Titanwerkstoffe -eine tierexperimentelle Studie-*

Board Qualifications "Oral and Maxillofacial Surgery"

Bumiller, Lars, Dr. (2010)
Stockmann, Philipp, Dr. Dr. (2010)
Tudor, Christian, Dr. (2010)

Additional Qualification

Schlegel, Karl Andreas, PD Dr. Dr. (2010): *Plastic Surgery*

Habilitation

Fenner, Matthias, PD Dr. Dr. (2009): *Fragen der Rekonstruktion des Kieferknochens nach Resektion von Plattenepithelkarzinomen der Mundhöhle*

Department of Neurosurgery

Chair of Neurosurgery

Doctorate Theses

Filis, Andreas, Dr. med. (2010): *Der trigeminokardiale Reflex bei transsphenoidalen Operationen von Hypophysenadenomen - Eine prospektive Studie von 40 Patienten*

Sirtl-Dodenhöft, Natalie, Dr. med. (2010): *Verbesserte Darstellung von Hirnnerven und Gefäßen durch Registrierung und Fusion*

Wolf, Marcel Nikolaj, Dr. med. (2010): *Nukleärer Transport von ß-Catenin in Kraniopharyngeomen: Mutationsanalyse des ß-Catenin-Gens und immunhistochemische Untersuchung der Verteilung des Adenomatosis polyposis coli-Proteins*

Board Qualification

Bischoff, Barbara, Dr. med. (2010): *Neurosurgery*

Habilitation

Eyuepoglu, Ilker, PD Dr. med. (2009): *Molekulare Mechanismen der Ödementwicklung und Neurodegeneration bei malignen Gliomen*

Department of Neurology

Chair of Neurology

Doctorate Theses

Anderer, Saskia Christina Ulrike, Dr. med. (2009): *Stationäre neurologische Rehabilitation: Entwicklungen von Patientenzahlen, Ver-*

weildauern und funktionalen Defiziten nach Einführung der DRGs in der Akutbehandlung

Dörfler, Carolina, Dr. med. dent. (2009): *Verstärkte sympathische kardiovaskuläre Aktivierung bei Patienten mit linkshemisphärischem lakunären Hirninfarkt während des Eiswassertests*

Jungfer, Isabella Margarete, Dr. med. (2009): *Repräsentation UV-B induzierter thermischer und mechanischer Hyperalgesie im menschlichen Gehirn - eine Studie mittels funktioneller Magnetresonanztomografie*

Raschick, Marlitt, Dr. med. (2009): *Versorgung von Patienten nach akutem Schlaganfall auf einer Stroke Unit: Prognostische Wertigkeit intensivmedinischer Scores bezüglich des Outcome von Schlaganfallpatienten*

Schäfer, Iris, Dr. med. (2009): *Lateralisation von Sprach- und Gedächtnisfunktionen mittels funktioneller Magnetresonanztomographie in der prä-operativen Diagnostik von Temporallappenepilepsien*

Steigleder, Tobias, Dr. med. (2009): *Neuroprotektive und neurorestaurative Effekte von Granulocyte-Colony Stimulating Factor (G-CSF) und Brain-derived neurotrophic factor (BDNF) nach akuter fokaler zerebraler ischämischer Läsion im Tiermodell*

Wolf, Nursel, Dr. med. (2009): *Pathologische Barorezeptorreflex - vermittelte Reaktionen der Herzfrequenz und des Blutdruckes auf Stimulation der Barorezeptoren bei Patienten mit Multipler Sklerose*

Akhundova, Aynur, Dr. med. (2010): *Assoziation zwischen hohen Werten auf der National Institutes of Health Stroke Scale (NIHSS) und Störungen der kardiovaskulären autonomen Kontrolle*

Blinzler, Christian Hans-Joachim, Dr. med. (2010): *Prävalenz und Prädiktoren von neu diagnostizierter gestörter Glucosetoleranz und Diabetes mellitus bei Patienten mit akutem ischämischen Schlaganfall*

Greim, Verena, Dr. med. (2010): *Validierung und Optimierung eines Algorithmus zur Detektion epileptischer Anfälle im Oberflächen-EEG*

Krause, Martin Friedrich, Dr. med. (2010): *Untersuchung des Geschmacksinns bei verschiedenen Formen des Parkinsonsyndroms*

Mauer, Christoph, Dr. med. (2010): *Prävalenz der peripheren arteriellen Verschlusskrankheit bei Patienten mit akutem Schlaganfall*

Rauch, Christophe Josef, Dr. med. (2010): *EEG-, Verhaltens- und Perfusionsänderungen nach Gabe von Etomidat bei Patienten mit Epilepsie und zerebral gesunden Patienten*

Stammler, Tanja Marianne, Dr. med. (2010): *Funktionelle Bildgebung von Hyperalgesie und sensiblen Ausfallserscheinungen*

Staykov, Dimitre Stefampv, Dr. med. (2010): *Intraventricular Fibrinolysis and Lumbar Drainage for Ventricular Hemorrhage*

Board Qualifications "Neurology"

Köhrmann, Martin, Dr. med. (2009)
Huttner, Hagen, Dr. med. (2010)

Habilitations

Köhrmann, Martin, PD Dr. med. (2009): *Neue Ansätze in der Diagnostik und Therapie des akuten ischämischen Schlaganfalls*

Huttner, Hagen, PD Dr. med. (2010): *Behandlung intraventrikulärer Blutungen*

Kasper, Burkhard, PD Dr. med. (2010): *Differentialtypologie epileptogener Läsionen*

Pauli, Elisabeth, PD Dr. med. (2010): *Gedächtnisfunktionen bei Temporallappenepilepsien, Implikationen für die Behandlung und Beiträge zur Aufklärung der neurobiologischen Grundlagen des menschlichen Gedächtnisses*

Institute of Neuropathology
Chair of Neuropathology

Doctorate Theses

Kistner, Iris, Dr. med. (2009): *Spektrum der neuropathologischen Veränderungen im Gyrus dentatus bei Patienten mit Temporallappen-Epilepsien*

Meißner, Stephan Guether, Dr. med. (2009): *Mutationsanalyse von axin1 und immunhistochemische Untersuchung der Verteilung von ß-Catenin in Hypophysenadenomen und Kraniopharyngeomen*

Burghaus, Stefanie Helga, Dr. med. (2010): *A tumor-specific cellular environment at the brain invasion border of adamantinomatous craniopharyngiomas*

Kobow, Katja, Dr. rer. nat. (2010): *Epigenetc gene regulation in focal epilepsies*

Habilitation

Buslei, Rolf, PD Dr. med. (2009): *Die molekulare Pathogenese adamantinöser Kraniopharyngeome - Charakterisierung aktivierender beta-catenin Mutationen und neue diagnostische Marker für die Differentialdiagnose sellärer Tumoren*

Department of Nuclear Medicine
Chair of Clinical Nuclear Medicine

Doctorate Theses

Schulz, Valentine Katharina, Dr. med. (2009): *Der Effekt der CT-basierten Schwächungskorrektur auf die Visualisierung und Quantifizierung des Knochenstoffwechsels mit SPECT*

Spörl, Markus, Dr. med. dent. (2009): *PEDBONE: Online-Referenzdatenbank für Standardröntgenaufnahmen in der Pädiatrie*

Wolz, Gabriele, Dr. med. (2009): *Vergleich der anatomischen Genauigkeit interaktiver manueller und automatischer, Software-basierter starrer und nicht-starrer Registrierung von Röntgencomputertomographie (CT) und F-18-Deoxyglukose-Positronenemissionsstomographie (FDG-PET)*

Board Qualifications "Nuclear Medicine"

Fritscher, Torsten, Dr. med. (2009)
Kühn, Christine, Dr. med. (2009)
Grunewald, Markus, Dr. med. (2010)

Institute of Pathology
Chair of General Pathology and Pathological Anatomy

Doctorate Theses

Balandat, Jan Erik, Dr. med. (2009): *Beeinflussende Faktoren der Genauigkeit der Prostatastanzbiopsie*

Casper, Sandra Rita, Dr. med. (2009): *Systemische Wirkung von Tabak- und Asbestexposition auf Niere und Gefäßsystem im Tierversuch*

Friebel, Daniela Lydia, Dr. med. (2009): *Prognostische Bedeutung tumorinfiltrierender T-Zellen beim klassischen Hodgkin Lymphom*

Hübner, Silvia, Dr. med. (2009): *Effekte einer antioxidativen Therapie mit Tempol auf Atherosklerose und Entzündungsmediatoren bei experimenteller Niereninsuffizienz im Modell der ApoE(-/-)Maus*

Koutra, Marisa, Dr. med. (2009): *Strukturveränderungen am Herzen unter Salzbelastung bei Metabolischem Syndrom am Modell der ZDF-Ratte*

Polak, Artur Jakub, Dr. med. (2009): *Morphologische Charakterisierung der Mesangiolyse bei experimentellen Hypertonie- und Diabetes Modellen*

Sesselmann, Stefan Manfred, Dr. med. (2009): *DNA methylation is not responsible for p21 WAF1/CIP1 down-regulation in osteoarthritic chondrocytes*

Wassermann, Stella, Dr. med. (2009): *Beta-Catenin reguliert die Expression des Zellzyklus-Inhibitors p16 ink4a in humanen kolorektalen Karzinomen*

Arend, Nicole, Dr. med. (2010): *Effekte einer Therapie mit Darbepoetin alpha auf Atherosklerose und Entzüngunsmediatoren bei experimenteller Niereninsuffizienz im Modell der Apo E-Knockout-Maus*

Bezold, Mareile Arntrudis, Dr. med. (2010): *Vergleich der Auswirkung einer oralen Therapie mit Metformin und EMD 387008 auf renale Schäden im Tiermodell der diabetogenen ZDF-Ratte*

Diezemann, Christoph, Dr. med. dent. (2010): *Einfluss einer antioxidativen Therapie mit Tempol auf Nierenveränderungen bei ApoE (-/-) Mäusen mit experimenteller Niereninsuffizienz*

Dornauer, Kerstin Helga, Dr. med. dent. (2010): *Zellbiologie und Matrixbiochemie der dedifferenzierten Chondrosarkome*

Götze, Ulrike, Dr. med. (2010): *Untersuchung des Einflusses von Metformin und EMD 387008*

auf kardiovaskuläre Strukturen sowie laborchemische und physiologische Parameter im tierexperimentellen Modell der diabetogenen ZDF-Ratte

Tegtmeier, Stefanie, Dr. med. dent. (2010): *Prognostische Bedeutung von Lymphfollikeln und tumorinfiltrierenden B-Lymphozyten beim Hodgkin Lymphom*

Teichmann, Martina, Dr. med. (2010): *Expression des Interferon-induzierbaren Protein 10 (IP-10) in Epstein-Barr-Virus-assoziierten Tumoren*

Habilitation

Riener, Marc-Oliver, PD Dr. med. (2010): *Gewebs- und Serummarker zur Frühdiagnose von Tumoren der Leber- und Gallenwege*

Department of Plastic and Hand Surgery

Doctorate Theses

Kontzi, Melanie Isabelle, Dr. med. (2009): *Evaluation von Wirkung und Effizienz verschiedener Transplantationstechniken autolog und allogen gewonnener Keratinozyten bei chronischen, therapierefraktären Wunden unterschiedlicher Genese: Eine Metaanalyse*

Lanczak, Johanna Elisabeth, Dr. med. (2009): *Aktivierung des Jak1-Stat1-Cross-Talks zur Blockade des profibrotischen TGFß1-Signalweges. Adenoviral codiertes IFN? agiert Via Überexpression von Smad7*

Messingschlager, Katrin Julia, Dr. med. (2010): *In vivo Blockade der TGF-ß1-assoziierten akuten hypertrophen Narbenbildung mittels Smad7 codierender adenoviraler Vektoren am Kaninchenohr*

Habilitations

Beier, Justus, PD Dr. med. (2010): *Tissue Engineering von vaskularisiertem muskulo - skelettalem Gewebe*

Unglaub, Frank, PD Dr. med. (2010): *Experimental and clinical investigations of triangular fibrocartilage disc lesions in the wrist*

Department of Psychiatry and Psychotherapy

Chair of Psychiatry and Psychotherapy

Doctorate Theses

Beutler, Sonja, Dr. med. (2009): *In-vitro-Einfluss von Nikotin und Nikotinentzug auf D N A-Methylierung und mRNA-Expression suchtassoziierter Gene in neuronalen SH-SY5Y-Zellen*

Cimmino, Natalie, Dr. med. (2009): *Einfluss moderner Antidepressiva auf Körperzusammensetzung, Körpergewicht, Tumor-Nektrose-Faktor, Leptin und Psychopathologie*

Höfer, Anna-Maria, Dr. med. (2009): *Expression suchtassoziierter Gene in peripheren Leukozyten bei Rauchern*

Jung, Pius Hermann, Dr. med. (2009): *Einfluss des Lebensstils auf die Serumhomocysteinkonzentration unter besonderer Berücksichtigung von Ernährungsfaktoren*

Krauß, Katharina Andrea, Dr. med. dent. (2009): *Circadianer Rhythmus der Reaktionszeit bei Depressiven verglichen mit gesunden Kontrollpersonen*

Mittelbach, Franziska Hildegard, Dr. med. (2009): *Epigenetische Dysregulation des dopaminergen Systems - ein Beitrag zur Neurobiologie psychogener Essstörungen*

Nehmer, Christina Maria, Dr. med. (2009): *Der Serum-Homocysteinspiegel im Tagesverlauf und seine Korrelation mit der psychischen Befindlichkeit bei gesunden Probanden*

Ott, Sabine, Dr. med. (2009): *Effekte von Aß-Peptiden auf Phosphorylierung, subzelluläre Lokalisation und Löslichkeit von Tau in Neuroblastoma-Zellen der Linie SH-SY5Y*

Polster, Kerstin Brigitta, Dr. med. dent. (2009): *Tetracain-Liposome (Oberflächenanästhetikum) - Eine Untersuchung der schmerzreduzierenden Wirkung bei Behandlung im Frontzahnbereich*

Rauh, Johannes Fritz Heinz, Dr. med. (2009): *Genetische Variationen des Serotonin-Transporter-Gens im Zusammenhang mit Craving bei Patienten mit Alkoholabhängigkeit*

Reichardt, Cornelia, Dr. med. (2009): *Transkranielle Magnetstimulation in der Therapie der Depression - Untersuchung der Beeinflussung von Sekretion und Transkription verschiedener Zytokine in neuronenähnlichen Zellmodellen*

Reinhold, Angelika Maria, Dr. med. (2009): *Lesbarkeit von Informationsbroschüren zum Thema Demenz: Ein internationaler Vergleich*

Rogler, Katrin Julia, Dr. med. (2009): *Einfluss von Phosphatase- und Kinase- Inhibitoren auf die Phosphorylierung und Aggregation von Tau in Zellkulturzellen*

Scholz, Sarah Simone, Dr. med. (2009): *Die Rolle epigenetischer Faktoren bei der Kontrolle des dopaminergen Systems bei Essstörungen*

Sieling, Swantje, Dr. med. dent. (2009): *Früherkennung qualitativ hoch stehender Forscher der deutschen Neurologie durch global zugängliche bibliometrische Indikatoren*

Spannenberger, Rita, Dr. rer. biol. hum. (2009): *Untersuchung der Geruchs- und Geschmackswahrnehmung in Abhängigkeit von Nationalität, Alter, Geschlecht, BMI und Aktivität der Nervus vagus*

Warbruck, Ingo, Dr. med. (2009): *Demenzscreeing am Krankenbett? Vergleich zwischen einem traditionellen psychometrischen Test und einem computergetützten Verfahren zur Messung kognitiver Beeinträchtigung*

Weiss, Julian Peter, Dr. med. (2009): *Leptinserumkonzentrationen im Zusammenhang mit Craving bei Untergruppen alkoholabhängiger Patienten*

Zajc, Dorothea, Dr. med. dent. (2009): *Veränderungen kognitiver Funktionen im höheren Lebensalter und derer Determinanten*

Bergner, Matthias, Dr. med. (2010): *Zirkadiane Rhythmik der Gewalt*

Bohmann, Julia Lisa, Dr. med. (2010): *Aktivität der Sauren Sphingomyelinase bei Kontrollpersonen*

Brunner, Susanne, Dr. med. (2010): *Einfluss eines akustischen Vigilanztests auf den Pupillographischen Schläfrigkeitstest*

Clepce, Marion Brigitte, Dr. rer. biol. hum. (2010): *Anhedonie als psychopathologisches Symptom - Eine Untersuchung zur hedonischen Bewertung von Geruchsstoffen bei psychiatrischen Patienten*

Dietl, Markus Leonhard Wolfgang Maximilian, Dr. rer. biol. hum. (2010): *Kosteneffektivitätsmodell eines ambulanten Hilfeangebotes für pflegende Angehörige von Demenzkranken*

Dimpfl, Doris Christine Michaela, Dr. med. (2010): *Die Bedeutung individueller Sinnkonstruktion für die psychische Gesundheit am Beispiel depressiver Patienten*

Gruß, Barbara Brigitte, Dr. rer. biol. hum. (2010): *Die Erlanger Therapieskala (TERLA) - Entwicklung einer Skala zur Abbildung des Therapieverlaufs im Rahmen des Qualitätsmanagements eines psychiatrischen Universitätsklinikum*

Günther, Florian Dierk, Dr. med. (2010): *Homocystein, Liquorparameter und Apolipoprotein E bei Demenzerkrankungen und leichter kognitiver Störung*

Hartl, Thomas Richard, Dr. med. (2010): *Alkoholabhängigkeit und die spezifische Methylierung des Dopamin-Transporter-Gens*

Jagiello, Adrianna Stefania, Dr. med. (2010): *Veränderung der Proteinexpression in SH-SY5Y-Zellen und der Analyse der a-Synuclein-Expression im humanen Blut und SH-SY5Y-Zellen unter Alkoholapplikation*

Jank, Jeanette Margit, Dr. med. (2010): *Die Rolle epigenetischer Faktoren bei der Kontrolle des volumenregulierenden Systems bei Essstörungen mit Schwerpunkt auf ANF und Vasopressin*

Knöpfler, Felix, Dr. med. (2010): *Langzeiterfolg nach geriatrischer Rehabilitation: Einfluss medizinischer und psychologischer Faktoren*

Kothe, Alexander Robert, Dr. med. (2010): *Transkutane Vagusnervstimulation - Veränderung psychometrischer Parameter in Abhängigkeit von verschiedenen Stimulationsorten*

Kraska, Peter Markus, Dr. med. (2010): *Effekte einer computergestützten Ernährungsberatung auf das vaskuläre Risikoprofil einer gesundheitsorientierten Bevölkerungsstichprobe - eine präventivmedizinische Pilotstudie aus der Psychiatrie*

Kumpf, Sonja, Dr. med. (2010): *Psychophysische und neurophysiologische, sensorische Charakterisierung der Stereoisomere des Nikotins in einem experimentellen, humanen Suchtmodell*

Limpert, Petra Maria, Dr. med. (2010): *Adaptation und Habituation bei repetetiver Geschmacksreizung mittels objektiver Gustometrie*
Lindner, Babett Ute, Dr. med. (2010): *Differenzierung von Gewaltverbrechen unter der Berücksichtigung der Alkohol-Klassifikation nach Lesch*
Luber, Katja Maria Christina, Dr. med. (2010): *Epigenetische Regulation und mRNA-Expression von Vasopressin während des Alkoholentzug*
Luttenberger, Katharina Ruth, Dr. rer. biol. hum. (2010): *Erfassung der Pflegezeit bei Demenzpatienten im Heim - Entwicklung und Validierung des RUD-FOCA (Resource Utilization in Dementia - Formal Care)*
Löwe, Alexander, Dr. med. (2010): *Soziodemographische Multivarianzanalyse bei Frühberentung aufgrund psychiatrischer Erkrankungen*
Meintker, Lisa Marie, Dr. med. (2010): *Psychopharmaka und Antibiotika beeinflussen die genomische DNA-Methylierung von SH-SY5Y Neuroblastomzellen*
Naumann, Sandy, Dr. med. (2010): *Gen-Umweltinteraktion bei alkoholabhängigen Patienten am Beispiel von ApoE und Homoxystein*
Pechmann, Georg Franz, Dr. med. (2010): *Objektive Testung der Geruchperzeption bei Morbus Crohn*
Plodeck, Verena, Dr. med. (2010): *Cytochrom P450 2D6-Genotypisierung in der klnischen Praxis: Der Einfluss des Genotyps auf die Serumkonzentrationen psychiatrisch relevanter Cytochrom P450 2D6-Substrate*
Poersch, Christian Claus, Dr. med. dent. (2010): *Aufgaben-, geschlechts- und medikamentenspezifische Auswirkungen von Antidepressiva auf die Veränderungen der Reaktionszeiten depressiver Patienten*
Reichard, Heidi, Dr. med. (2010): *Cannabinoid-Rezeptor 1 und Essstörungen*
Rost, Juliane Roswitha, Dr. med. (2010): *Der Einfluss des Antipsychotikums Quetiapin auf die D N A-Methylierung in neuronalen Zellmodell*
Sankowski, Natalia, Dr. med. (2010): *Die Wirksamkeit von Antipsychotika der zweiten Generation in der Behandung der Negativ-Symptomatik der Schizophrenie*
Schanze, Anja Silvina, Dr. med. (2010): *Zusammenhang zwischen Craving und Serumghrelinspiegeln bei Patienten während de Alkoholentzugsbehandlung*
Schuh, Sebastian, Dr. med. (2010): *Reliabilität geschmackssevoierter Potentiale und psychophysischer Parameter unter Verwendung des neu entwickelten Gustometers Gu001*
Stöhr, Christian Benjamin, Dr. med. (2010): *Exekutive Funktionen bei Patienten mit obstruktivem Schlafapnoesyndrom (OSAS) vor und nach CPAP-Therapie*
Sulimma, Anne-Kathrin Christine Hildegard, Dr. med. (2010): *Vergleich der Therapietreue von zwei regional benachbarten Gedächtnissprechstunden mit unterschiedlicher Struktur*
Toncar, Sebastian Frank, Dr. med. (2010): *Der verfolgungsbedingte Grad der Erwerbsminderung von Holocaustopfern. Eine langzeitkatamnestische Betrachtung somatischer und psychiatrischer Diagnosen unter Berücksichtigung des Gesamtschauaspektes*
Triebner, Sascha, Dr. med. (2010): *Randomisierte Studie zum Vergleich von zwei E-Learningformaten mit einer Präsenzveranstaltung*

Habilitations

Frieling, Helge, Dr. med. habil. (2009): *Zur Neurobiologie psychogener Essstörungen*
Maler, Juan Manuel, PD Dr. med. (2009): *Periphere Zellpopulationen bei Morbus Alzheimer – regenerative und immunologische Aspekte*
Biermann, Anna Teresa, PD Dr. med. (2010): *Neurobiologische Veränderungen im Rahmen des Alkoholentzuges bei Patienten mit Alkoholabhängigkeit*
Wilhelm, Julia, Dr. med. habil. (2010): *Apolipoprotein E und Homocystein als modulierende Faktoren in der Pathophysiologie von stoffgebundenen und nicht-stoffgebundenen Suchterkrankungen*

Department of Psychiatry and Psychotherapy
Division of Child and Adolescent Mental Health

Doctorate Thesis

Parchmann, Caroline, Dr. rer. biol. hum. (2009): *Chancen und Grenzen von computergestützer Diagnostik bei Kindern mit Lesestörung*

Additional Qualifications "Child and Adolescent Psychotherapist"

Grimm, Jennifer (2009)
Stubenrauch, Christa (2009)
Yasar, Bettina (2010)

Department of Psychiatry and Psychotherapy
Division of Psychosomatics and Psychotherapy

Doctorate Theses

Arold, Michaela Karin Franca, Dr. med. (2009): *Die Auswirkungen von Koffein auf Herzratenvariabilität und autonome Gefäßantworten*
Mertens, Christian, Dr. med. (2009): *Persönlichkeitsstörungen bei pathologischen Käuferinnen im Vergleich zu zwei Kontrollgruppen*
Oumard, Daniela Gabriela, Dr. med. (2009): *Geschlechtsspezifische Unterschiede in Psychopathologie, Lebensqualität und Essverhalten vor chirurgischer Adipositastherapie*
Postler, Peter Karl, Dr. med. (2009): *Beschreibung und Prä-Post-Vergleich der vollstationären und tagesklinischen Behandlung der Psychosomatischen und Psychotherapeutischen Abteilung des Universitätsklinikums Erlangen*
Schönlebe, Jana, Dr. med. (2009): *Einflüsse von BMI, Cannabis-Konsum und psychischer Gestimmtheit auf Blutdruck und neurokardiale Steuerung*
Silbermann, Andrea, Dr. rer. biol. hum. (2009): *Der Einsatz von Ecological Momentary Assessment bei Patienten mit pathologischem Kaufverhalten*
Celik, Seda, Dr. med. (2010): *Beschreibung und Therapieverlauf von Patientinnen mit einer Essstörung und der Vergleich mit einer Normstichprobe*
Herbst, Florian, Dr. med. (2010): *Angehörige anorektischer und bulimischer Patientinnen: ihre Probleme, ihr Bedarf und ihre Bedürfnisse an Unterstützung*
Olbrich, Katharina, Dr. med. (2010): *Night Eating, Binge Eating and Related Features in Patients with Obstructive Sleep Apnea Syndrome*

Habilitation

Müller, Astrid, PD Dr. med. Dr. phil (2010): *Behandlung und psychische Komorbidität unter besonderer Berücksichtigung des zwanghaften Hortens*

Institute of Radiology
Chair of Diagnostic Radiology

Doctorate Theses

Kerl, Josef Matthias, Dr. med. (2009): *Split-Bolus Contrast Medium Injection with Diluted Contrast Material for Visualization of The Right Heart at Coronary CT Angiography*
Klemm, Christine, Dr. med. (2009): *Stereotaktische Vakuumbiopsie - Erfolg, Korrelation von Histologie und BI-RADS TM-Klassifikation, Patientenakzeptanz*
Runck, Frank, Dr. med. (2009): *Magnetic resonance imaging: Influence of imaging modality and post processing on measurement of internal carotid artery stenosis*
Baloglu, Sabine Selin, Dr. med. (2010): *Kontrastmittelverstärkte Magnetresonanz-Angiographie vor Nierenlebendspende: Korrelation präoperativer Bildgebung mit intraoperativen Befunden*
Klenner, Friederike, Dr. med. (2010): *Mehrzeilen-Spiral-CT (MSCT) des Abdomens: Dosisoptimierung unter Berücksichtigung der Bildqualität*
Mager, Simone, Dr. med. (2010): *Quantitative Bestimmung des Liquorraumes bei Patienten mit Spinalkanalstenose mittels Magnetresonanztomographie (MRT) und Computertomographie (CT)*

Board Qualifications "Diagnostic Radiology"

Adamietz, Boris, Dr. (2009)
Alibek, Sedat, Dr. (2009)
McKenna-Küttner, Axel, PD Dr. (2009)
Heckmann, Martina, Dr. (2010)
Schwab, Siegfried, Dr. (2010)

Habilitations

Wenkel, Evelyn, PD Dr. med (2009): *Moderne Bildgebung in der Mammadiagnostik*
Küfner, Michael Andreas, PD Dr. med. (2010): *Biologische Dosimetrie in der diagnostischen und interventionellen Radiologie*
McKenna-Küttner, Axel, Dr. med. habil. (2010): *Computertomographische Entwicklung der kardialen Bildgebung vom 4-Zeilen-CT bis zum Dual-Source-CT*

Institute of Radiology
Division of Neuroradiology

Board Qualification

Dölken, Marc, Dr. med. (2009): *Diagnostic Radiology*

Additional Qualification

Gölitz, Philipp, Dr. med. (2010): *Neuroradiology*

Habilitation

Struffert, Tobias, PD Dr. med. (2010): *Moderne Ansätze in der Diagnostik und Therapie zerebrovaskulärer Erkrankungen mit Flachdetektor-Bildgebung*

Department of Radiotherapy
Chair of Radiotherapy

Doctorate Theses

Albrecht, Christine, Dr. med. (2009): *Expression und Modulation von p53 und Mdm2 in Kopf-Hals-Tumoren*
Brandl, Isabella, Dr. med. (2009): *Die Bedeutung von p53-Mutationen für die Wirksamkeit einer adjuvanten Radiotherapie bei Plattenepithelkarzinomen des Oropharynx*
Bär, Daniel Alexander, Dr. med. (2009): *Nachweis von strahleninduzierten D N A-Schäden in Rattenhirnen durch ATMpSer1981*
Fickenscher, Rainer Christian, Dr. med. dent. (2009): *Der prognostische Einfluss von tumorinfiltrierenden Lymphozyten im Plattenepithelkarzinom des Oropharynx ist abhängig von der Art der Behandlung*
Förtsch, Claudia Barbara, Dr. med. (2009): *Posttranslationale Modifikation am PML-Protein*
Horner, Alexandra Maria, Dr. med. (2009): *Präzisionsuntersuchung am Novalis*
Müllner, Johannes Peter, Dr. med. (2009): *Neoadjuvante Radiochemotherapie von Weichteilsarkomen - Optimierung der lokalen Tumorkontrolle unter dem Aspekt von Funktionalität und Extremitätenerhalt. Eine retrospektive Studie*
Posch, Florian, Dr. med. (2009): *Qualität und Effektivität der stereotaktischen Radiochirurgie und fraktionierten stereotatischen Radiotherapie bei der Behandlung des Meningeoms*
Schultes, Dominik Karl-Heinz, Dr. med. (2009): *Qualität und Effektivität der stereotaktischen Radiochirurgie und fraktionierten stereotaktischen Radiotherapie bei der Behandlung des Hypophysenadenoms*
Ullmann, Christian, Dr. med. (2009): *Ergebnisse der multidisziplinären Behandlung lokalisierter Ewing-Sarkome bei Kindern und Jugendliche*
Bermeiser, Nina Natalie, Dr. med. (2010): *Nachweis von Phosphorylierung der Reparaturproteine Nbs1 und Pml nach strahleninduzierten D N A-Schäden*
Beyer, Christian, Dr. med. (2010): *Tumor-infiltrierende Lymphozyten beim Glioblastoma multiforme*
Brunner, Maria, Dr. med. dent. (2010): *Vergleich der Reparaturfähigkeit von yH2AX zu immunologischen Eigenschaften bei Patienten mit Mamma- und Rektumkarzinom*
Bäumler, Judith, Dr. med. dent. (2010): *Vergleich der Strahlensensitivität von Zellen aus oralen Plattenepithelkarzinomen und gesunder Mundschleimhaut*
Drescher, Christina Helene Kunigunde, Dr. med. (2010): *Unterschiede in der Reparatur von D N A-Doppelstrangbrüchen zwischen einer normalen menschlichen Zelllinie und einer Zelllinie mit Nijmegen Breakage Syndrom in den unterschiedlichen Phasen des Zellzyklus*
Engemann, Timo Michael, Dr. med. (2010): *Beteiligung von DNA -PK an der durch Gemcitabine induzierten Phosphorylierung von H2AX*
Hung, Alexander D e i, Dr. med. (2010): *Der prognostische Einfluss von tumorinfiltrierenden Lymphozyten in oropharyngealen Plattenepithelkarzinomen*
Höhne, Brit-Ragna, Dr. med. (2010): *Multivariate Analyse prognostischer Faktoren beim malignen Gliom*
Meier, Iris, Dr. med. (2010): *Adenokarzinome mit Lokalisation am gastroösophagealen Übergang: Lymphatisches Metastasierungsmuster als Grundlage für die Definition des Planungszielvolumens bei neoadjuvanter Radiochemotherapie*
Noisternig, Timmo Manfred, Dr. med. (2010): *Prädiktive Relevanz des Apoptoseinhibitors Survivin für das Gesamtüberleben nach organerhaltender Radiochemotherapie des Harnblasenkarzinoms*
Pretscher, Dominik, Dr. med. (2010): *Distribution of immune cells in head and neck cancer: CD8+ T-cells and cD20+ B-cells in metastatic lymph nodes are associated with favourable outcome in patients with oro- and hypopharyngeal carcinoma*
Schmidtner, Johannes Julian, Dr. med. (2010): *Einfluss von Hyperthermie und Bestrahlung von Tumorzellen der Kopf-Hals-Region auf das Migrationsverhalten tumorinfiltrierender Lypmhozyten*

Habilitations

Distel, Luitpold, PD Dr. med. (2009): *Untersuchungen zur individuellen Strahlenempfindlichkeit*
Ott, Oliver, PD Dr. med. (2010): *Akzelerierte Teilbrustbestrahlung beim Mammakarzinom mit interstitieller Brachytherapie*

Department of Urology
Chair of Urology

Doctorate Theses

Landsmann, Susanne Brigitte, Dr. med. (2009): *Die Behandlung des fortgeschrittenen Harnblasenkarzinoms mit Irinotecan im Tiermodell - Eine sinnvolle Alternative zur üblichen Medikation?*
Manke, Christina Elisabeth, Dr. med. (2009): *Permanente interstitielle Brachytherapie mit Iod-125 Seeds bei lokal begrenztem Prostatakarzinom - Einfluss des postoperativen Schwellungsverlaufs auf die Dosisverteilung im Vergleich zur prospektiv durchgeführten Bestrahlungsplanung*
Seltmann, Claudia, Dr. med. (2009): *Funktionelle Rekonstruktion der Blasenekstrophie - Auswertung der einaktigen Erlanger Technik*
Engelhardt, Nina Heike, Dr. med. (2010): *Serotonin als Marker in der Diagnostik und Prognostik urologischer Tumore Serotonin Used As Prognostic Marker of Urological Tumors*
Kisch, Thomas Michael, Dr. med. (2010): *Magnetresonanztomographisch gesteuerte Prostatastanzbiopsie in der Diagnostik des Prostatakarzinoms*

Board Qualifications "Urology"

Kraske, Susanne, Dr. med. (2009)
Krot, Dimitrij, Dr. med. (2009)
Legal, Wolfgang, Dr. med. (2009)

Additional Qualifications

Engehausen, Dirk G., PD. Dr. med. (2009): *Medical quality management*
Krause, F. Steffen, PD Dr. med. (2009): *Medicinal tumor therapy*
Legal, Wolfgang, Dr. med. (2009): *Medicinal tumor therapy*
Strasser, Hans, Dr. med. (2009): *Medicinal tumor therapy*
Walter, Bernhard, Dr. med. (2009): *Medicinal tumor therapy*

Habilitation

Goebell, Peter J., PD Dr. med. (2010): *Wissenschaftliche Netzwerke – wichtiger Baustein translationaler Forschung Eine Darstellung am Beispiel des Harnblasenkarzinoms*

Institute of Virology – Clinical and Molecular Virology

Chair of Clinical Virology

Doctorate Theses

Bals, Tanja Maria, Dr. med. (2009): *Charakterisierung des nukleozytoplasmatischen Transports adenoviraler Proteine*

Klink, Nicole Simone, Dr. med. (2009): *Molekularbiologische und Immunologische Analyse von sequenziellen Isolaten des Humanen Cytomegalovierus in AIDS-Patienten*

Meythaler, Mareike Andrea, Dr. rer. nat. (2009): *Basis for differential immune activation and apoptosis in pathogenic and ninpathogenic SIV infection*

Mitzner, David George, Dr. rer. nat. (2009): *Biochemische und molekularbiologische Charakterisierung des neuartigen Influenza-A-Virus Proteins PBI-F2*

Pichler, Klemens, Dr. rer. nat. (2009): *Survival functions of HTLV-1-infected T cells during the leukemogenic process*

Schellhorn, Tim Albert, Dr. med. (2009): *Funktionelle Domänen und Wechselwirkungen des K10.5-Gens des humanen Herpesvirus 8*

Votteler, Jörg Philip, Dr. rer. nat. (2009): *Characterization of virus host-interactions thet regulate HIV-1 replication*

Wies, Effi, Dr. rer. nat. (2009): *Funktionelle Analyse des KSHV-kodierten vIRF-3: Interferonantogonismus und Onkogenese*

Hahn, Alexander Siegfried, Dr. rer. nat. (2010): *Zelluläre Rezeptoren des Kaposi-Sarkom assoziierten Herpesvirus*

Urbach, Yvonne Kristin, Dr. rer. nat. (2010): *Automated phenotyping and molecular characterization of rat models transgenic for the human Huntington´s disease and Spinocerebellar ataxia type 17 mutations*

Board Qualifications "Microbiology, Virology and Infection Epidemiology"

Ensser, Armin, Prof. Dr. med. (2010)
Schmidt, Barbara, Priv.-Doz. Dr. med. (2010)
Stamminger, Thomas, Prof. Dr. med. (2010)

Dental Department 1 – Operative Dentistry and Periodontology

Chair of Dental, Oral and Maxillofacial Medicine - especially Operative Dentistry, Periodontology and Pediatric Dentistry

Doctorate Theses

Beck, Philipp Alexander, Dr. med. dent. (2009): *Einfluss der Schmelzabschrägung auf das Dentinrandverhalten zervikaler Kompositfüllungen*

Bertz, Claus, Dr. med. dent. (2009): *Ein automatisiertes Kariesmodell zur Erzeugung sekundärkariöser Läsionen*

Bienert, Karin, Dr. med. dent. (2009): *Einfluss des Sauerstoffgehalts der Umgebungsluft auf die Festigkeit des Komposit-Dentinverbunds im Microtensile-Verfahren*

Deines, Irene, Dr. med. dent. (2009): *Der Einfluss verschiedener Wurzelkanalsealer auf das Wachstum unterschiedlicher Bakterien*

Dennerlein, Michael Wolfgang, Dr. med. dent. (2009): *Untersuchung der apikalen und koronalen Undichtigkeit von adhäsiven und nichtadhäsiven Wurzelkanalsealern*

El Aryan, Mirco Christian Abraham, Dr. med. dent. (2009): *Dichtigkeitsuntersuchung fünf verschiedener Wurzelstiftzementierungen in Verbindung mit Quarzfaserstiften. Eine In-vitro-Studie*

Flassig, Thomas Horst, Dr. med. dent. (2009): *Detailerkennbarkeit von Lufteinschlüssen im Wurzelkanalfüllmaterial AH Plus™ bei Zahnfilmaufnahmen*

Herga, Barbara, Dr. med. dent. (2009): *Einfluss der Sealerapplikationstechnik auf apikal überpresstes Material und die Dichtigkeit von Wurzelkanalfüllungen mit GuttaFlow und RelyX Unicem*

Härting, Julia, Dr. med. dent. (2009): *Gründe und Häufigkeit der Extraktion von Zähnen an der Zahnklinik-1 im Vergleich mit einer Kassenpraxis*

Leupold, Tobias Michael, Dr. med. dent. (2009): *Der Einfluss der Schallaktivierung auf den Komposit-Dentin-Verbund*

Malekpour, Nasrollah, Dr. med. dent. (2009): *Einfluss von Füllungs- und Belichtungstechnik auf die Polymerisationsspannung von Komposit*

Mark, Carmen Tina, Dr. med. dent. (2009): *Zum Einfluss der Sauerstoffinhibitionsschicht auf die marginale Adaptation von Kompositfüllungen*

Schab, Stefan, Dr. med. dent. (2009): *In vivo Abrasion und quantitative Randspaltanalyse von Cergogold-Inlays nach 2 Jahren*

Schneider, Harald, Dr. med. dent. (2009): *Zwei-Körper-Abrasion von Füllungsmaterialien - eine in-vitro-Studie-*

Schneider, Katja, Dr. med. dent. (2009): *Vergleich verschiedener Präparationsmethoden zur erweiterten Fissurenversiegelung: rotierend - kinetisch - sono abrasiv*

Schultes, Camilla, Dr. med. dent. (2009): *Haftverbund zweier adhäsiver Sealer am Wurzelkanaldentin unter dem Einfluss unterschiedlicher Spüllösungen*

Trautmann, Sandra Hildegard, Dr. med. dent. (2009): *Über die Effizienz vier verschiedener Pulver und Pulverstrahlgeräte*

Welz-Reitinger, Fabian, Dr. med. dent. (2009): *Einfluss unterschiedlicher Verarbeitungsmodi moderner Adhäsivsysteme auf die Dentinhaftung*

Wirth, Elmar Jochen, Dr. med. dent. (2009): *Der Einfluss des Rauchens auf die Parodontalbehandlung und die Prognose des Behandlungserfolges*

Altmaier, Katharina Maria, Dr. med. dent. (2010): *Materialabrasion auf direkten zahnärtzlichen Restaurationsmaterialien und Fissurenversieglern durch verschiedene Prophylaxepulver*

Beck, Nina, Dr. med. dent. (2010): *Sind Self - etch - Adhäsive zur Fissurenversiegelung geeignet?*

Friedemann, Isabell, Dr. med. dent. (2010): *Koronale Dichtigkeit adhäsiv Zementierter Glasfaserstifte bei unterschiedlichen Placementtechniken - Eine In-vitro-Untersuchung*

Gerstbrein, Oliver, Dr. med. dent. (2010): *Dichtigkeitsuntersuchung von Wurzelkanalfüllungen nach verschiedenen medikamentösen Einlagen*

Grohmann, Claudia Alexandra, Dr. med. dent. (2010): *Zum Einfluss unterschiedlicher Sealerapplikationstechniken auf die apikale Dichtigkeit von Wurzelkanalfüllungen mit AH Plus und Maxcem*

Hopp, Imke, Dr. med. dent. (2010): *Zeitabhängige Putzeffektivität unterschiedlich großer Putzaufsätze für die Sonicare Schallzahnbürste*

Höfer, Margarita, Dr. med. dent. (2010): *Einfluss von Flüssigkeitskontamination auf die Verbundfestigkeit von Wurzelkanalsealern (Adseal und RelyX Unicem)*

Kaiser, Nadja Helga, Dr. med. dent. (2010): *Koronale Dichtigkeit verschiedener Obturationstechniken nach Präparation einer Wurzelkanalstiftkavität*

Kaulfuß, Yvonne, Dr. med. dent. (2010): *Marginale Füllungsrandqualität in Klasse-V-Kavitäten unter Verwendung vorgewärmter Komposite in Kombination mit einem Etch-and-Rinse Adhäsiv*

Millian, Matthias Hans, Dr. med. dent. (2010): *Dichtigkeitsuntersuchung von adhäsiv eingesetzten Glasfaserstiften*

Muhr, Christian, Dr. med. dent. (2010): *Drei elektronische Wurzelkanallängenmessgeräte im klinischen Vergleich. Eine In-vivo-Untersuchung*

Neumann, Tobias Stefan, Dr. med. dent. (2010): *Vergleich verschiedener Methoden zur Darstellung von gefüllten Dentinkanälchen*

Nikolova, Iglika Naskova, Dr. med. dent. (2010): *Einfluss Flüssigkeitskontamination auf*

die Verbundfestigkeit von Wurzelkanalsealern (AH Plus und FibreFill™

Pelka, Anna-Kristina, Dr. med. dent. (2010): *Zeitabhängige Putzeffektivität einer Schallzahnbürste im Vergleich mit einer ADA-Referenz - Handzahnbürste*

Pourmaafi, Perham, Dr. med. dent. (2010): *Dichtigkeit von Wurzelkanalfüllungen und Sealerextrusion in verschieden konischen Wurzelkanälen unter Verwendung von AH Plus und GuttaFlow*

Schwertner, Katharina Elisabeth, Dr. med. dent. (2010): *Vergleich verschiedener Methoden zur Haftkraftmessung von Dentinadhäsiven*

Simkowski, Nadja, Dr. med. dent. (2010): *Marginale Füllungsrandqualität in Klasse-V-Kavitäten unter Verwendung vorgewärmter Komposite in Kombination mit einem Self-Etch-Adhäsiv*

Steinmüller, Stefan, Dr. med. dent. (2010): *In-vitro-Untersuchung dreier Wurzelkanallängenmessgeräte*

Täuber, Holger, Dr. med. dent. (2010): *Randspaltverhalten neuer ästhetischer Komposite mit unterschiedlichen Haftvermittlern in Klasse-V-Kavitäten*

Ursu, Stefan, Dr. med. dent. (2010): *Ermüdung des Dentin-Komposit-Komplexes im Zugversuch*

Dental Department 2 – Prosthetic Dentistry

Chair of Dental, Oral and Maxillofacial Medicine - especially Prosthetic Dentistry

Doctorate Theses

Bendkowski, Johanna Maria Lina, Dr. med. dent. (2009): *Die Passgenauigkeit von gegossenen und im CAD/CAM-Verfahren hergestellten Titankronen in vitro: Ein Vergleich verschiedener Systeme und Hersteller*

Kirchner, Elena, Dr. med. dent. (2009): *Lexikalische Analyse des implantologischen Wortschatzes der russischen Sprache*

Kollmannsberger, Judith Elisabeth, Dr. med. dent. (2009): *Klinische Studie zur Evaluation des Verlaufs der mundgesundheitsbezogenen Lebensqualität mit dem Oral Health Impact Profile (OHIP) beim impantologischen Versorgungen*

Titiz, Irem, Dr. med. dent. (2009): *Vergleichende klinische Studie zur Beurteilung oraler Augmentationsmassnahmen mit Hilfe der Guided Bone Regeneration*

Abels, Fränzi, Dr. med. dent. (2010): *Die klinische Bewertung von Vollkeramischen drei- und viergliedrigen Brücken nach 36 Monaten*

Bittner, Christian, Dr. med. dent. (2010): *Vergleich unterschiedlicher Behandlungsmethoden bei Dentinhypersensibilität unter Berücksichtigung medizinischer Hypnose*

Ebert, Thomas, Dr. med. dent. (2010): *Zum Einfluss verschiedener Mechanorezeptoren auf die bisssperrungsabhängige relative Aktivierung der Kieferelevatoren bei isometrischem Beißen*

Götz, Alexander Michael, Dr. med. dent. (2010): *Keramikfrakturen verschraubter Implantatbrücken unter zyklischer Belastung*

Habermann, Ingeborg, Dr. med. dent. (2010): *Untersuchung zur Festigkeit verklebter Brückenkonstruktionen*

Kiefer, Julia Claudia, Dr. med. (2010): *Studie zum Kenntnisstand über Wirkungen und Nebenwirkungen von Bisphosphonaten*

Korb, Kristina, Dr. med. dent. (2010): *Die Wirksamkeit von Clonacepam bei Patienten mit Burning Mouth Syndrom*

Oeßelmann, Nina, Dr. med. dent. (2010): *Untersuchung zur Bestimmung der Knochendichte in der zahnärztlichen Implantologie*

Rösch, Silke Monika, Dr. med. dent. (2010): *Statische Implantatbelastung bei keramisch verblendeten Suprakonstruktionen*

Schomburg, Svenja, Dr. med. dent. (2010): *Nachsorgebedarf bei gebräuchlichen Attachmentsystemen zur Verankerung von implantatgetragenem Zahnersatz*

Habilitation

Nickenig, Hans-Joachim, Dr. med. dent. (2010): *Dreidimensionale Diagnostik in der Zahnärztlichen Implantologie*

Dental Department 3 – Orthodontics and Orofacial Orthopedics

Chair of Dental, Oral and Maxillofacial Medicine - especially Orofacial Orthopedics

Doctorate Theses

Zimmermann, Anja, Dr. med. dent. (2009): *Ergebnisbewertung kieferorthopädischer Behandlungen anhand des Jahrganges 2001*

van der Heyd, Sabine, Dr. med. dent. (2009): *Untersuchungen zur Korrosion von Brackets mittels Elektronenstrahl-Mikrosonde - eine klinische Studie*

Boldt, Florian Johannes Gottfried, Dr. med. dent. (2010): *Gegenüberstellung der räumlichen Messpunktstreuung verschiedener 3D-Digitalisierungsverfahren*

Gerner, Carolin Barbara, Dr. med. dent. (2010): *Untersuchung zur Symmetrie von Ober- und Unterkiefer bei Patienten mit Lippen-Kiefer-Gaumenspalten - Eine Untersuchung anhand von Computertomogrammen*

Habilitation

Holst, Alexandra Joana, PD Dr. med. dent. (2009): *Einbeziehung optischer Messtechniken zur Darstellung biodynamischen Verhaltens kieferorthopädischer Verankerungselemente*

In Memoriam

2009 – Deceased Persons

Prof. Dr. med. Dr. med. h.c. Jacques Bourguet
Honorary doctor of the Medical Faculty

Prof. Dr. med. Dr. med. dent. Walter Gräf
Professor emeritus of the Chair of Hygiene and Medical Microbiology II

Prof. Dr. med. Walter Hilmer
Associate professor of the Department of Medicine 2

Prof. Dr. med. dent. Adolf Kröncke
Professor emeritus of the Chair of Operative Dentistry and Periodontology
(1968/69 Dean of the Medical Faculty)

Prof. Dr. med. Udo Merkle
Associate professor at the Institute of Anatomy

2010 – Deceased Persons

Prof. Dr. med. Karl Brand
Professor emeritus of the Chair of Physiological Chemistry II

Prof. Dr. phil. Hellmut Erzigkeit
Head of the Division of Clinical Psychology at the Department of Psychiatry and Psychotherapy

Prof. Dr. med. Hermann Gutheil
Associate professor of the Department of Pediatrics

Prof. Dr. med. Dr. med. h.c. Gerhard Lehnert
Professor emeritus of the Chair of Occupational and Social Medicine
(1991 – 1997 Dean of the Medical Faculty)

Prof. Dr. rer. biol. hum. Dr. med. Michael E. W. Mück-Weymann, M.A.
Scientist in the Department of Psychiatry and Psychotherapy and at the Institute of Cellular and Molecular Physiology

Prof. Dr. med. Hans-Jürgen Pesch
Associate professor at the Institute of Pathology

Personnel Index

Chairpersons, Directors and Speakers of the Institutions

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Cover
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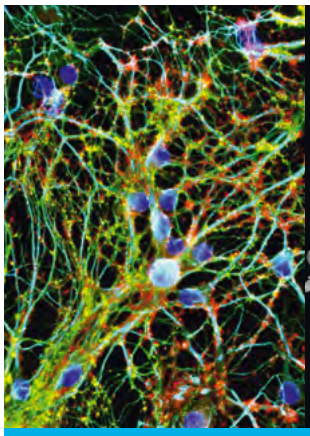
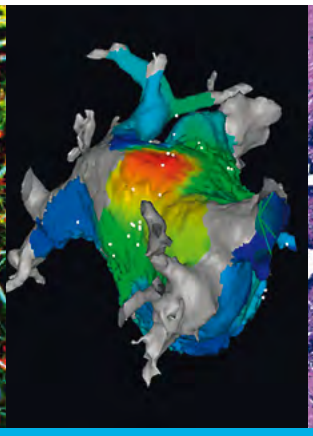
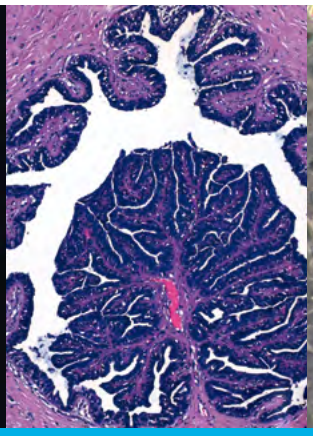
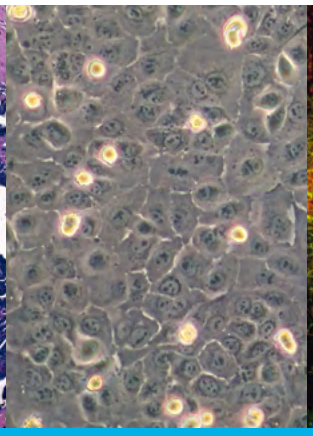
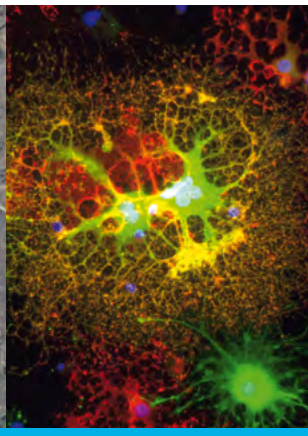

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