Research Report 2009
Faculty of Medicine

Friedrich-Alexander-University
Erlangen-Nürnberg

Table of Contents

Preface 6

PRECLINICAL INSTITUTES

Anatomical Institute
Chair of Anatomy I 10
Chair of Anatomy II 12

Institute of Physiology and Pathophysiology
Chair of Physiology 14

Institute of Cellular and Molecular Physiology
Chair of Physiology
(Vegetative Physiology) 16

Institute of Biochemistry – Emil-Fischer-Centre
Chair of Biochemistry and Molecular Medicine 18
Chair of Biochemistry and Pathobiochemistry 20

CLINICAL THEORETICAL INSTITUTES

Institute of Medical Informatics, Biometry and Epidemiology
Chair of Biometry and Epidemiology 22
Endowed Chair of Medical Informatics 24

Institute of the History of Medicine and Medical Ethics
Chair of the History of Medicine 26
Professorship for Medical Ethics 28

Institute of Pathology
Chair of General Pathology and
Pathological Anatomy 30
Division of Nephropathology 32

Institute of Neuropathology
Chair of Neuropathology 34

Institute of Microbiology – Clinical Microbiology, Immunology and Hygiene
Chair of Microbiology and Immunology of Infection 36

Institute of Virology – Clinical and Molecular Virology
Chair of Clinical Virology 38
Franz-Penzoldt-Centre of Experimental Biomedicine 40

Institute of Experimental and Clinical Pharmacology and Toxicology
Chair of Pharmacology and Toxicology 42
Chair of Clinical Pharmacology and
Clinical Toxicology 44
Doerenkamp-Chair of Innovations in Animal and
Consumer Protection 46

Institute of Human Genetics
Chair of Human Genetics 48

Institute of Forensic Medicine
Chair of Forensic Medicine 50

Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine
Chair of Occupational and Social Medicine 52

Institute of Medical Physics
Chair of Medical Physics 54

Nikolaus-Fiebiger-Centre of Molecular Medicine
Chair of Experimental Medicine I
(Connective Tissue Research) 56
Chair of Experimental Medicine II
(Molecular Oncology) 58

CLINICAL CHAIRS ADDITIONALLY TO THE UNIVERSITY HOSPITAL

Institute of Biomedicine of Aging
Chair of Internal Medicine - Geriatrics 60

Department of Orthopaedics in the Waldkrankenhaus
Chair of Orthopaedics and Orthopaedic Surgery 62
Division of Orthopaedic Rheumatology 64

UNIVERSITY HOSPITAL

Department of Medicine 1 – Gastroenterology, Lung Diseases and Endocrinology
Chair of Internal Medicine I 66

Department of Medicine 2 – Cardiology and Angiology
Chair of Internal Medicine II 68

Department of Medicine 3 – Rheumatology and Immunology
Chair of Internal Medicine III 70
Division of Molecular Immunology 72

Department of Medicine 4 – Nephrology and Hypertensiology
Chair of Internal Medicine IV 74

Department of Medicine 5 – Haematology and Oncology
Chair of Haematology and Oncology 76

Department of Nuclear Medicine
Chair of Clinical Nuclear Medicine 78

Institute of Radiology
Chair of Diagnostic Radiology 80
Division of Neuroradiology 82

Department of Surgery
Chair of Surgery 84
Division of Pediatric Surgery 86
Division of Trauma Surgery 88
Division of Transfusion Medicine and Haemostaseology 90

Department of Plastic and Hand Surgery 92

Department of Cardiac Surgery
Chair of Cardiac Surgery 94

Department of Urology
Chair of Urology 96

Department of Anaesthesiology
Chair of Anaesthesiology 98

Department of Obstetrics and Gynaecology
Chair of Obstetrics and Gynaecology 100

Department of Radiation
Chair of Radiation Therapy 102

Department of Pediatrics
Chair of Pediatrics 104
Division of Pediatric Cardiology 106

Department of Dermatology
Chair of Skin and Venereal Diseases 108

Department of Ear, Nose and Throat – Head and Neck Surgery
Chair of Otorhinolaryngology 110
Division of Phoniatrics and Pediatric Audiology 112

Department of Ophthalmology
Chair of Ophthalmology 114

Department of Neurology
Chair of Neurology 116
Division of Molecular Neurology 118

Department of Neurosurgery
Chair of Neurosurgery 120

Department of Psychiatry and Psychotherapy
Chair of Psychiatry and Psychotherapy 122
Division of Child and Adolescent Mental Health 124
Division of Psychosomatics and Psychotherapy 126

Department of Oral and Maxillofacial Surgery
Chair of Dental, Oral and Maxillofacial Medicine – especially Oral and Maxillofacial Surgery 128

Dental Department 1 – Operative Dentistry and Periodontology
Chair of Dental, Oral and Maxillofacial Medicine – especially Operative Dentistry, Periodontology and Pediatric Dentistry 130

Dental Department 2 – Prosthetic Dentistry
Chair of Dental, Oral and Maxillofacial Medicine – especially Prosthetic Dentistry 132

Dental Department 3 – Orthodontics and Orofacial Orthopedics
Chair of Dental, Oral and Maxillofacial Medicine – especially Orofacial Orthopedics 134

DFG COLLABORATIVE RESEARCH CENTRES AND RESEARCH GROUPS

Collaborative Research Centre (SFB) 423: Kidney injury: pathogenesis and regenerative mechanisms 136

Collaborative Research Centre (SFB) 466: Lymphoproliferation and Viral Immunodeficiency 137

Collaborative Research Centre (SFB) 473: Switch Processes of Transcription 138

Collaborative Research Centre (SFB) 539: Glaucomas including Pseudoexfoliation Syndrome 139

Collaborative Research Centre (SFB) 603: Model-Based Analysis and Visualization of Complex Scenes and Sensor Data 140

Collaborative Research Centre (SFB) 643: Strategies of Cellular Immune Intervention 141

Clinical Research Unit (KFO) 106: Target Organ Damage in Hypertension 142

Clinical Reserach Unit 130: Determinants and Modulators of postoperative pain 143

Clinical Research Unit Bavarian Immunotherapy Network (BayImmuNet): Adoptive Immunotherapy 144

Research Unit (FOR) 661: Multimodal Imaging in Pre-clinical Research 145

Research Unit (FOR) 832: Regulators of humoral immunity 146

Research Unit (FOR) 894: Fundamentals on Fluid and Physical Dynamics in Human Voice Production 147

National Reference Centre for Retroviruses 148

National Genome Research Network – Infection and Inflammation – Work package "Viral Infections", Erlangen 149

National Genome Research Network – Mental Retardation Network (MRNET), Erlangen 150

Project group of the Academy of Science and Literature, Mainz 151

DFG RESEARCH TRAINING GROUPS

Research Training Group 516: Cultural Transfer in the European Middle Ages 152

Research Training Group 592: Lymphocytes – Differentiation, Activation and Deviation 153

Research Training Group 1071: Viruses of the Immune System 154

BioMedTec International Graduate School of Science (BIGSS): Lead structures of Cell Function 155

Erlangen Graduate School in Advanced Optical Technologies (SAOT) 156

INTERDISCIPLINARY CENTRES

Interdisciplinary Centre for Clinical Research (IZKF) 157

Interdisciplinary Centre for Public Health (IZPH) 158

Interdisciplinary Centre for Gerontology (ICG) 159

Interdisciplinary Centre for Functional Genomics (FUGE) 160

PROGRAMMES AND FOUNDATIONS FOR RESEARCH SUPPORT

ELAN programme for supporting clinical research and teaching 161

Johannes and Frieda Marohn-Foundation 162

Further foundations for research support 163

ACADEMIC SOCIETY

Society for Physics and Medicine Erlangen 164

DEGREE PROGRAMMES

Degree Program in Medicine 165

Degree Program in Dentistry 167

Degree Program in Molecular Medicine 168

Medical Process Management 170

APPENDIX

Honorary Doctorate 171

A Selection of Awards 2007 – 2008 172

Doctorate Theses, Board Qualifications, Additional Qualifications, Habilitations 174

In Memoriam 191

Imprint 192

Medical Research in Erlangen

This report for the years 2007-2008 marks the fifth time we have presented an overview of the research areas concentrated on and projects carried out by the various institutes and clinics at the University of Erlangen-Nürnberg Medical School. The aim is to provide an account of the work done 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 sphere. It is intended to serve as a source of information both for internal and interdisciplinary use and to encourage suggestions for future cooperative projects.

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

The University of Erlangen-Nürnberg Medical School 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 (incl. Glaucoma), Pain
4. Tumor Research.

These research focuses are networked 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 University of Erlangen-Nürnberg Medical School. 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.

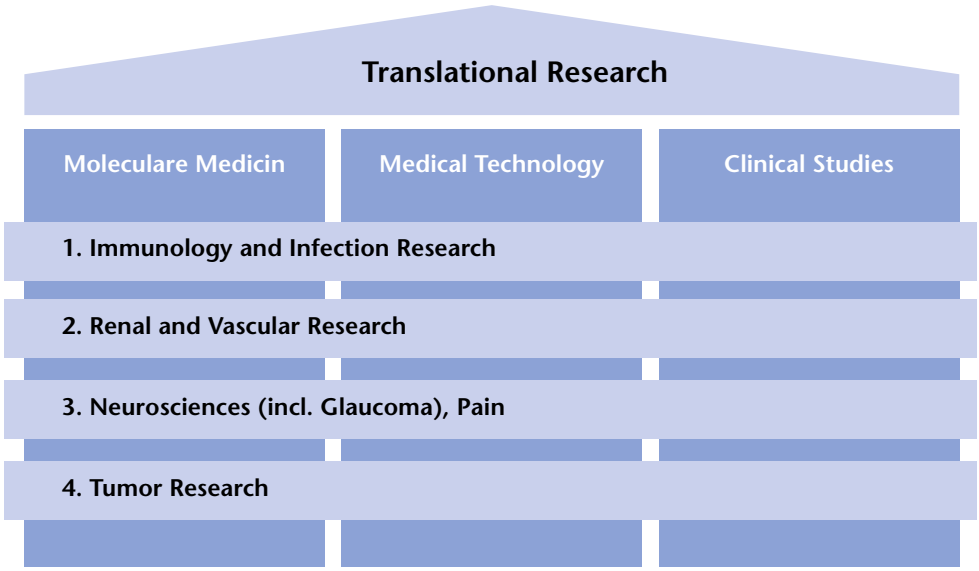
These focal research areas are characterized by interdisciplinary networks supported by third-party funding provided in the framework of collaborative research centers, graduate research centers, DFG research training groups, as well as network projects funded by the Federal Ministry of Education and Research (BMBF) and the EU. A more detailed account is given on page 136 ff. of this report. In recent years there has been a steady rise in levels of third-party funding. In 2008 the Medical School applied for and obtained more than 32 million euros in third-party funding.

Our Medical School plays an important part in the University of Erlangen's scientific research focuses: "Molecular Life Sciences and Medicine" as well as "Medical Technology". There is close cooperation between the Medical School and the relevant science and engineering departments in the various research networks. Collaborative Research Center 796, Control Mechanisms of Microbial Effectors in Host Cells, was given a positive assessment by the DFG Senate and approved for funding in late 2008. How do viruses and bacteria cause diseases? Collaborative Research Center 796 aims to acquire new knowledge on this pivotal medical problem. Also involved, in addition to the Medical School, are the various science and engineering departments at the University of Erlangen-Nürnberg, as well as the Fraunhofer Institute for Integrated Circuits (IIS) in Erlangen.

In the course of the report period 2007-2008 a wide range of activities were carried out aimed 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 School is reflected by the existence of the Interdisciplinary Center for Clinical Research (IZKF, p. 157), the Franz Penzoldt Center (p. 40), as well as the newly established Center for Clinical Studies (CCS). The latter will be responsible, among other things, for coordinating the legal aspects of bench-to-bedside research projects.

In 2007, inventory was taken of the amount of floor space in Medical School 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 floor space dedicated to research 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 School is currently formulating 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. Consideration is also being given to the development of a system for renting additional rooms to be used for research purposes.

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 Medical Center to individual clinics or institutes to use at their own discretion for research-related purposes. This money has been used, for example, to create a position for a research coordinator who advises researchers and assists them in submitting national and international applications for project funding. The same person initiates and coordinates network projects. However, the distribution of funds from the newly introduced 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 School administration of Medical Center budgets from those of non-clinical institutes. A university working group on medical facility structures is endeavoring to find a solution to this problem.



Research focuses at the University of Erlangen-Nürnberg Medical School.

In 2007 a new organization plan was introduced for the Medical School with a view to promoting its strategic development and to professionalizing the Office of the Dean. The plan provides for the introduction of additional assistant deans, including an Assistant Dean for Research as well as two Assistant Deans of Students.

In 2008, after a report by an international commission of experts on the status of research in Bavaria („Wissenschaftsland Bayern 2020") attested to the fact that our Medical School had assumed a leading role in the establishment of clinical research in Germany over the past twenty years, we succeeded in getting the Translational Research Center (TRC) in the framework of a program for the construction of research facilities of national and international importance in accordance with Article 91b of the German constitution. The construction of this facility as part of the University Medical Center will provide an innovative interdisciplinary infrastructure for clinical research of a kind never before seen at a university location in Germany. The TRC will bring together in exemplary manner all those areas from which there is a need to translate research results into diagnostic and therapeutic procedures. By this means our Medical School will be able to counteract a much lamented lack of development in clinical research and to create new research focuses on the basis of a planned strategy.

With a view to further strengthening our research focuses and to supporting the establishment of a Leibniz Institute for Immunology, preparations were made in 2008 for the founding of the Medical Immunology Campus Erlangen (MICE), an interdisciplinary center at the University of Erlangen-Nürnberg, with the objective of establishing the nucleus of an institute in the course of the next five years.

Another unique facility, the Medical Technology Testing and Applications Center (METEAN), was opened in October 2007. It received a presidential award in 2008 in the framework of the competition „Deutschland – Land der Ideen" (Germany – Land of Ideas). The University of Erlangen-Nürnberg, the Fraunhofer Institute for Integrated Circuits, and the University Medical Center have agreed to work together to transfer innovative medical technology as rapidly and effectively as possible to patient care applications.

In June 2007 an agreement was concluded between the administration of the University of Erlangen-Nürnberg and the Medical School 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, p. 161, Johannes and Frieda Marohn Foundation, p. 162, IZKF Funding for Young Academic Talent, p. 157, as well as other foundations, p. 163).

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 School. 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 School 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 University of Erlangen-Nürnberg Medical School currently has degree programs in Medicine (p. 165), Dentistry (S. 167), Molecular Medicine (p. 168), and a new master's degree program in Medical Process Management (p. 170) offered since winter semester 2008/2009.

Since 2007 the students at the University of Erlangen-Nürnberg Medical School have regularly ranked among the best three out of 36 medical schools 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 School 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 School 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.

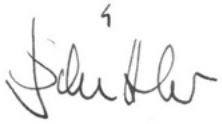
In summer semester 2007 a skills lab, PERLE (Practice, Experience and Learning), was created with money taken from tuition fees. Here students are able to improve their skills and prepare for practical examinations with the support of medical specialists and trained student tutors. Funds from this source 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 schools 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 University of Erlangen-Nürnberg Medical School 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 School 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. Annette Pfeiffer, and the Administrative Director, Dr. Esther Schnetz, for their active involvement in formulating the text. The report can be downloaded from the website of the Office of the Dean of the Medical School (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 School. The scientists involved will be happy to respond to questions sent in by mail or asked in person about their projects.

Erlangen, November 2009



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

Anatomical Institute

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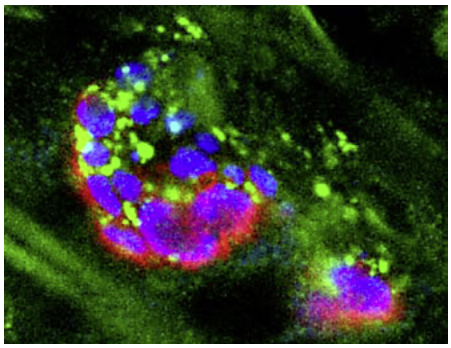
Research Focus
- Innervation of the gastrointestinal tract
- Autonomic innervation of the eye
- Nervous system, inflammation and pain
- Cell biology of neurofibromatosis type 2 tumor suppressor proteins

Structure of the Institution

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 manager: 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. It appears that TRPV1 expressing sensory neurons and neurokinins are also involved in this mechanism.

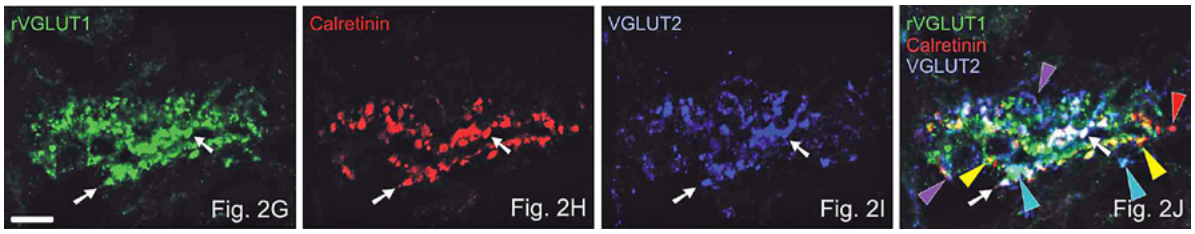


A motor endplate in striated muscle of human esopahgus. Cholinergic vagal (VAChT, blue) and peptidergic enteric (VIP, green) terminals co-innervate the alpha-bungarotoxin labeled motor endplate (red). (from Kallmuenzer et al. 2008)

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, glutamate receptors, e.g., GLUR2/3 were demonstrated in myenteric neurons suggesting local effects of glutamatergic IGLEs onto enteric neurons.
Morpho-chemical phenotyping of myenteric neurons in the human and porcine intestines was continued (collaboration with Departments of Pathology and Surgery in Erlangen, Fuerth and Bamberg). Meanwhile, intrinsic sensory neurons and other hitherto poorly discernible neuron types could be characterized using combined morphological and chemical features. Thus, we made an important step ahead towards neuropathological diagnostics of so-called functional gastrointestinal disorders.

Autonomic innervation of the eye
Project manager: F. Schroedl
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 human and birds using immunohistochemistry, electron microscopy, neuronal tracing and electrophysiology. Based on development of novel techniques for complete autonomic denervation of the chicken eye, extensive ongoing studies on the function of ICN were performed. Furthermore, putative lymphatic vessels in the human choroid were studied in collaboration with the Erlangen Department of Ophthalmology.

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 focussed 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. Likewise, the influence of the autonomic innervation was also studied in kidney inflammation. In collaboration with the Departments of Nephrology and Pharmacology, we were able to show alleviation of experimental glomerulonephritis by renal denervation.
In collaboration with the institute of Physiology and experimental Pathophysiology, we studied nociceptive innervation of the esophagus through the vagus nerve and the distribution of CGRP receptors in meninges and trigeminal system. Both projects yielded basic data for understanding the pathogenesis of gastro-esophageal reflux and migraine, respectively.
In collaboration with the Institutes of Pharmacy, University of Tuebingen, and Pharmacology, University of Frankfurt, we studied the role of CRP2, a molecule of the nitrergic signaling cascade, in an animal model of chronic inflammatory pain.

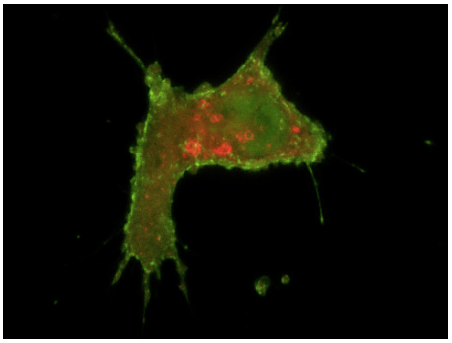


Intraganglionic laminar endings (IGLEs) in a myenteric ganglion of the rat esophagus identified by calretinin immunocytochenmistry (red) contain either the vesicular glutamate transporter 1 (green) or 2 (blue) or both (white in the merge on the right). (from Ewald et al. 2006)

Cell biology of neurofibromatosis type 2 tumor suppressor proteins

Project manager: M. Kressel

Neurofibromatosis type 2 (NF2) gene is a tumor suppressor gene whose deletion typically results in schwannomas of the VIIIth cranial nerve, so-called acoustic neurinomas. Cell biological investigations aimed at elucidating the function of merlin, the protein coded by the NF2 gene, were continued. It turned out that one isoform of this protein functions as a nucleo-cytoplasmic shuttle protein. This extends the classical view of merlin as a pure linker protein between plasma membrane and cytoskeleton and suggests a nuclear mechanism regulating cell proliferation. Thus, we focussed on



A NIH3T3 fibroblast transfected with a phospholipid biosensor (green) and a NF2 fusion construct with mCherry (red), which labels vesicles of the late endosomal compartment. (M. Kressel)

elucidating transport mechanisms of merlin to the nucleus. We found binding of merlin to membrane lipids to be crucial. A repertoire of molecular biological and morphological methods is applied for studying mechanisms that determine its cytoplasmic and nuclear localizations, respectively. In particular, artificial NF2 fusion proteins with green fluorescent protein are used. This resulted already in confining specific protein domains which regulate transport into the nucleus.

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 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

Kraus T, Neuhuber WL, Raab M (2007) Distribution of vesicular glutamate transporter 1 (VGLUT1) in the mouse esophagus. Cell Tissue Res, 329: 205-19

Weidmann S, Schroedl F, Neuhuber W, Brehmer A (2007) Quantitative estimation of putative primary afferent neurons in the myenteric plexus of human small intestine. Histochem Cell Biol, 128: 399-407

Kallmuenzer B, Soerensen B, Neuhuber WL, Woerl J (2008) Enteric co-innervation of striated muscle fibres in human oesophagus. Neurogastroenterol Motil, 20: 597-610

Lennerz JK, Ruehle V, Ceppa EP, Neuhuber WL, Bunnett NW, Grady EF, Messlinger K (2008) Calcitonin receptor-like receptor (CLR), receptor activity-modifying protein 1 (RAMP1), and calcitonin gene-related peptide (CGRP) immunoreactivity in the rat trigeminovascular system: differences between peripheral and central CGRP receptor distribution. J Comp Neurol, 507: 1277-99

Schroedl F, Brehmer A, Neuhuber WL, Kruse FE, May CA, Cursiefen C (2008) The normal human choroid is endowed with a significant number of lymphatic vessel endothelial hyaluronate receptor 1 (LYVE-1)-positive macrophages. Invest Ophthalmol Vis Sci, 49: 5222-9

Veelken R, Vogel EM, Hilgers K, Amann K, Hartner A, Sass G, Neuhuber W, Tiegs G (2008) Autonomic renal denervation ameliorates experimental glomerulonephritis. J Am Soc Nephrol, 19: 1371-8

International Cooperation

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

Prof. C. Chiang, Department of Cell and Developmental Bilogiy, Vanderbilt University Medical Centre, Nashville, USA

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

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

Prof. T. Takewaki, Department of Basic Veterinary Science, Gifu University, Japan

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

Dr. M.E. De Stefano, Dipt. di Biologia Celluara e di Sviluppo, Università "La Sapienza", Roma, Italy

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

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

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

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

Meetings and International Training Courses

25.–28.04.2007: Plastisch-rekonstruktive und aesthetische Nasen- und Ohrmuschelchirurgie, Blepharoplastik und Face Lift, Erlangen

20.10.2007: Anatomie fuer Anaesthesisten, Erlangen

18.10.2008: Anatomie fuer Anaesthesisten, Erlangen

Anatomical Institute

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Research Focus
- Morphological changes in glaucomatous eyes
- Retrospective 3-D-microscopy
- Role of aqueous humor factors in glaucoma pathogensis
- Mouse model for glaucomatous changes in retina and optic nerve
- Detection of hyaluronan acid by dynamic light scattering
- APC guidance in the anterior eye segment
- Accommodation and presbyopia
- Influence of Prostaglandin F2α on hair growth

Structure of the Institution

The Department of Anatomy consists of Chair I and Chair II. Chair II has 30 members of staff. 7 positions are financed by grant money. 8 doctoral researchers (from the field of medical, natural and 1 of computer science) contribute to the scientific research. The curriculum of the Anatomical Institute II comprises the functional anatomy of the human body including embryology, microscopic anatomy and neuroanatomy. The scientific focus of the Institute lies 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 are performed by the use of immuno-histochemistry, transmission- and scanning -electron-microscopy, cell cultures, molecular biology and physiological methods. There are close collaborations with the other projects of the Collaborative Research Centre (SFB) 539 and long-term international cooperations.

Research

Morphological changes in glaucomatous eyes
Project manager: E. Luetjen-Drecoll, O. Tektas
In the last years we received a number of entire globes derived from patients with POAG, so that for the first time changes in the optic nerve head could be studied qualitatively and quantitatively. We found that in contrast to the postlaminar region the capillary density in the nerve head was not reduced. There were, however, significant changes in the vessel walls. There was a thickened connective tissue sheath containing type IV and type VI collagen, so that the diffusion distance between vessel lumen and Astroglia is increased. This could result in underperfusion.

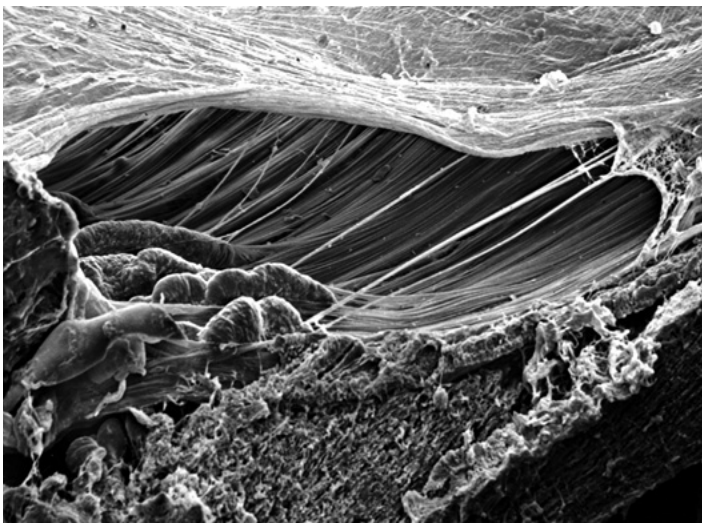
Retrospective 3-D-microscopy
Project manager: M. Eichhorn, E. Luetjen-Drecoll, J. Hornegger
Glaucoma research suffers from the lack of an adequate animal model or an experimental glaucoma model comparable to open angle glaucoma (POAG) in humans. As a consequence morphological investigations are limited to human post mortem eyes. We have started a program to correlate vascular changes with axon damage in the optic nerve head applying serial sectioning. However, detecting vessels in a tissue requires 3-D reconstruction. In collaboration with the Institute of pattern recognition (Prof. Hornegger) we try to develop algorithms enabling us to visualize the morphological structures and their changes in 3-D.

Role of aqueous humor factors in glaucoma pathogensis
Project manager: M. Birke, E. Luetjen-Drecoll
TGF-β2 is increased in the AH of app. 50% of the POAG patients, being the factor with the highest incidence thereby. We demonstrated that TGF-β2 in-vitro strongly activated the de-novo synthesis of various ECM components frequently found to be accumulated in POAG. Concurrently TGF-β2 induced the inhibitory molecule PAI-1, thereby repressing MMP-dependent ECM degradation and additionally favouring ECM accumulation. These findings applied both in TM cells and astrocyts of the optic nerve. In a cooperative study with Prof. Welge-Luessen, we demonstrated that hypoxia followed by a subsequent reoxygenation phase lead to an elevated secretion of TGF-β2 by astrocytes, presenting a first mechanistical explanation for the local increase of TGF-β2 observed in POAG. By perfusion of anterior human eye segments we demonstrated that TGF-β2 physiologically increases IOP. In an ongoing study using porcine eyes, we found that IL1a counteracts this effect and moreover induces expression of ELAM-1, a designated marker molecule for the glaucomatous TM.

Mouse model for glaucomatous changes in retina and optic nerve
Project manager: M. Scholz, E. Luetjen-Drecoll
The DBA/2J mouse is a commonly used model for glaucoma. The purpose of our studies focused on qualitative and quantitative analyses of morphological investigations of DBA/2J eyes in correlation with physiological data. In addition, we searched for differences in protein composition of the aqueous humor of DBA/2J and control mice. Individual data analysis showed no general dependency between elevated IOP and ON in DBA/2J mice. In cooperation with the Department of Ophthalmology (Prof. Kremers), ERG data of DBA/2J and B6 controls were compared with corresponding IOP measurements. In both strains a decrease in ERG responses with age was observed. In DBA2/J, however, this decrease was considerably higher than in B6. A significant correlation with elevated IOP values in DBA2/J was not found.

Detection of hyaluronan acid by dynamic light scattering
Project manager: M. Eichhorn, E. Luetjen-Drecoll, A. Leipertz, A. Froeba
The transparency of cornea and lens has to be maintained all life long, although proteins and pigment granules set free from the iris and anterior ciliary body permanently circulate in the humor aqueous (AqH) and are in contact with the surfaces of the transparent tissues. In collaboration with the Institute for Technical Thermodynamics (Prof. Leipertz, Prof. Froeba) a program was started to detect an inert anti-adhaesive surface molecule by “dynamic light scattering”. First results suggest that hyluronan is an interesting candidate.

APC guidance in the anterior eye segment
Project manager: M. Birke, E. Luetjen-Drecoll
Absence of completely endothelial lined lymphatic capillaries is considered to be one of the basic principles for ocular immunprivilege. However, the anterior eye segment underlies immunological surveillance and moreoever, the route chosen by APCs to leave this has significant relevance for immune privilege. We



Scanning electronmicrograph of a newly described complex zonular fiber system connecting the zonular plexus with the vitreous membrane (in "Morphology and accommodative function of the vitreous zonule in human and monkey eyes", Lütjen-Drecoll et al., IOVS, accepted)

demonstrated that the entry sites into AH outflow, the trabecular meshwork and the trabeculum ciliare, were positive for the lymphatic marker podoplanin (Pdpn), as well as the anterior iris surface, where APCs enter the anterior eye chamber. Pdpn was shown to bind Ccl21 *in vitro*, a ligand for CCR7 expressed on migrating APCs. By immunofluorescens staining we detected Ccl21 expression at the iris surface, partially colocalizing with Pdpn and CCR7 positive cells exiting the iris there. *In vitro* cultured human TM cells also co-expressed Pdpn and Ccl21. Taken together, our data suggest the existence of a migration mechanism based on the constitution of a Ccl21 gradient directed out of the iris towards the AH outflow tissues via binding to Pdpn.

Accommodation and presbyopia

Project manager: E. Luetjen-Drecoll

Flexible intraocular lenses can only be sufficient to reestablish accommodation if the remaining accommodative apparatus is still working. In the present studies we have investigated 1) whether the opened and ageing lens capsule still has enough elasticity; 2) morphology and ageing of the vitreous zonule; 2) afferent innervation of the ciliary muscle. The studies were performed in collaboration with P. Kaufman, Madison, Wisconsin. He performed the experiments and investigated shape changes of the accommodation apparatus in presbyopic Rhesus monkeys. Their UBM data were compared with our morphological ones. We found that 1) the opened lens capsule still has enough elasticity to allow accommodation; 2) that there is a complex vitreous zonule which in ageing animals restricts muscle movement. Lysis of this zonule restored muscle contraction; 3) that there is a complex afferent innervation at all muscle tendon regions and overlying the circular muscle portion. Intrinsic ganglion cells seem to allow an intrinsic circuit to fine modulate ciliary muscle contraction.

Influence of Prostaglandin F2α on hair growth

Project manager: M. Tauchi, E. Luetjen-Drecoll

Our research focus is to understand the mechanism of trichomegaly induced by a Prostaglandin F2α (PGF2α). We use mice as a model (eyelashes and dorsal skin hairs) and investigate the effect of PGF2α on activation of hair follicle stem cells and hair growth cycle regulation. We characterized mouse eyelashes and found that PGF2α activates hair follicle stem cells to enter anagen phase, extends anagen period, and in eye lashes increases bulb thickness resulting in longer and thicker eyelashes. The molecular mechanisms of these events are under investigation.

Teaching

Chair II of the Anatomical Institute organizes the lectures "functional anatomy" and "functional histology", the accompanying courses "anatomical demonstration" and "microscopic anatomy" as well as the "neuroanatomical seminar". The lectures and courses are attended by the students of human medicine, dentistry and molecular medicine. Prof. Eichhorn is part of the teaching stuff in the MAOT and SAOT graduate schools.

Selected Publications

Neumann C, Yu A, Welge-Luessen U, Luetjen-Drecoll E, Birke M (2008) The Effect of TGF-{beta}2 on Elastin, Type VI Collagen, and Components of the Proteolytic Degradation System in Human Optic Nerve Astrocytes. Invest Ophthalmol Vis Sci, 49: 1464-72

Scholz M, Buder T, Seeber S, Adamek E, Becker CM, Luetjen-Drecoll E (2008) Dependency of Intraocular Pressure Elevation and Glaucomatous Changes in DBA/2J and DBA/2J-Rj Mice. Invest Ophthalmol Vis Sci, 49: 613-21

Yu AL, Fuchshofer R, Birke M, Kampik A, Bloemendal H, Welge-Lussen U (2008) Oxidative stress and TGF-beta2 increase heat shock protein 27 expression in human optic nerve head astrocytes. Invest Ophthalmol Vis Sci, 49: 5403-11

Tektas OY, Lütjen-Drecoll E (2009) Structural changes of the trabecular meshwork in different kinds of glaucoma. Exp Eye Res, 88:769-75

International Cooperation

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Majo Klinik Rochester, USA

Prof. D. Kerjaschki, Wien, Austria

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Research Focus
- Neurophysiologic principles of higher brain functions
- Transduction, integration, plasticity in primary nociceptive neurons
- Trigeminal nociception and headaches
- Microneurography of nociceptive axons in human
- Functional imaging of brain activity by fMRI

Structure of the Institution

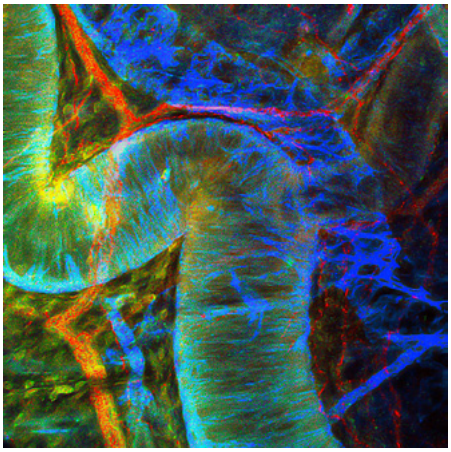
The institute comprises one reoccupied chair and two professorships for physiology with their work groups, two further groups are associated to an Academic Directorate and a professor emeritus. In addition, the institute houses collaborating work groups of the Nephrological, Anesthesiological, and Neurological Hospitals, guest researchers of the Medical and Gynaecological Hospitals as well as from Japan and Spain.
Altogether 55 persons work in the institute, 14 of them funded by grants. The research is done by 22 PhD/MD scientists, 21 doctoral students and 12 technical assistants.
The institute is just integrating 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

Neurophysiologic principles of higher brain functions
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^+ channels.

Transduction, integration, plasticity in primary nociceptive neurons
Project manager: P. 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 and release of substance P and calcitonin gene-related peptide. Aim is to elucidate nociceptive transduction and integration of stimuli as well as possible pharmacological interventions. 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) recently 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.

Trigeminal nociception and headaches
Project manager: K. Messlinger
The group is working on nociceptive processes in the cranial dura mater, trigeminal ganglion and spinal trigeminal nucleus as basis of headaches. Single-fibres are recorded from dura nerves *in vitro* to study sensitivity and responses to CGRP, prostaglandins or histamine, probably involved in generation of headaches. Release of these mediators and actions on dural blood vessels are analyzed as well. Intracellular signal transduction is studied using immunohistochemical and molecular biological methods. Central nervous mechanisms of headache are examined by recording from secondary neurons in the spinal trigeminal nucleus and testing potential headache drugs.



CGRP meets its receptor in the rat dura mater
CGRP (red) is expressed in perivascular nerve fibers. The CGRP receptor protein CLR (green) appears in smooth muscle cells (blue) of arteries (left) but not veins (right upper half).

Microneurography of nociceptive axons in human

Project manager: H.O. Handwerker, B. Namer

Microneurography, recording of single unit action potentials, is applied to awake human subjects or patients. Three major projects:

1) Mechano-insensitive "sleeping" unmyelinated nociceptors had been found particularly sensitive to histamine which plays a major role in mediating itch sensations. Another very similar itch sensation is evoked by a protease isolated from mucuna pruriens, which surprisingly excites a different subpopulation of unmyelinated nociceptors. The properties of these separate peripheral pathways of pruritus are studied with psychophysiological and electrophysiological methods.
2) Aging of nociceptors occurs throughout the long life span of humans which is not comparable to that of laboratory animals. It is shown that characteristic functional changes such as spontaneous activity and lowering of stimulation thresholds, but also loss of excitability in a subgroup of C-fibers, reflect a normal aging process, though previously regarded as pathologic.
3) Recording of nerve fibers in patients with chronic polyneuropathies allows characterizing pathologic discharge patterns and altered conductile properties in particular in diabetic polyneuropathy.

Functional imaging of brain activity by fMRI

Project manager: C. Forster

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

Teaching

In the context of preclinical training of students of medicine, dentistry and molecular medicine the institute mainly teaches neurophysiology. Besides 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 block which is positively evaluated by the students. This appreciation is further supported by upgrading of the experimental setups that were funded by the students' fees. Colleagues from the hospitals are regularly invited to complement actual topics from a clinical point of view which they often do with presenting a patient. Furthermore, interdisciplinary lectures are given to students of natural and technical sciences and of psychology who selected medicine as subsidiary subject or main focus. To them not only neurophysiology but all topics of physiology are presented.

Selected Publications

Zimmermann K, Leffler A, Babes A, Cendan CM, Carr RW, Kobayashi J, Nau C, Wood JN, Reeh PW (2007) Sensory neuron sodium channel Nav1.8 is essential for pain at low temperatures. Nature, 447: 855-8

Leffler A, Fischer MJ, Rehner D, Kienel S, Kistner K, Sauer SK, Gavva NR, Reeh PW, Nau C (2008) The vanilloid receptor TRPV1 is activated and sensitized by local anesthetics in rodent sensory neurons. J Clin Invest, 118: 763-76

Lennerz JK, Ruehle V, Ceppa EP, Neuhuber WL, Bunnett NW, Grady EF, Messlinger K (2008) Calcitonin receptor-like receptor (CLR), receptor activity-modifying protein 1 (RAMP1), and calcitonin gene-related peptide (CGRP) immunoreactivity in the rat trigeminovascular system: differences between peripheral and central CGRP receptor distribution. J Comp Neurol, 507: 1277-99

Schoedel AL, Zimmermann K, Handwerker HO, Forster C (2008) The influence of simultaneous ratings on cortical BOLD effects during painful and non-painful stimulation. Pain, 135: 131-41

Namer B, Carr R, Johanek LM, Schmelz M, Handwerker HO, Ringkamp M (2008) Separate peripheral pathways for pruritus in man. J Neurophysiol, 100: 2062-9

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

International Cooperation

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G. Pethoe, Univ. of Pecs, Hungary

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Research Focus
- Renal epithelial ion channels
- Cardiac ion channels

Structure of the Institution

The Department of Cellular and Molecular Physiology (Chair of Systems Physiology) is housed in a teaching and research building in central location. In addition to modern research laboratories the building offers a lecture hall with a capacity of 200 seats and 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 at 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 at Erlangen known to have a strong renal and cardiovascular research focus as evidenced e.g. by the DFG funded centre research grant Collaborative Research Centre (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 interaction between transport proteins 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, cell physiological and molecular 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 renal 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 Deutsche Forschungsgemeinschaft in the context of the centre research grant Collaborative Research Centre (SFB) 423 ('Kidney pathology: Pathogenesis and regenerative mechanisms') and from the IZKF (interdisciplinary centre of 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 repolarisa-

tion. Within the left ventricular free wall, for example, APD is much longer in endocardial than in epicardial myocytes with the consequence, that endocardial myocytes repolarise last although they become depolarised first. Hence, the wave of excitation travels from endocardial to epicardial regions, while the wave of repolarisation travels in the opposite direction.
Under pathological conditions such as cardiac hypertrophy or failure, this well organised 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 lead 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 investigates the consequences of cardiac hypertrophy in animal models. Using the patch-clamp technique on isolated myocytes from different regions of the left ventricular free wall of rats with ascending aortic stenosis, a decrease in the transient outward potassium current (Ito) was identified as the primary cause underlying the increase in APD in epicardial regions. The specific importance of Ito for an altered organisation of repolarisation in cardiac hypertrophy is underlined by the observation that other ionic currents, such as the L-type Ca2+ current, are largely unaffected by hypertrophy.
Apart from affecting the regional organisation of repolarisation, alterations in the magnitude of Ito indirectly influence the intracellular Ca2+ homeostasis of ventricular myocytes. A reduction of Ito leads to an increase in transmembranous Ca2+ 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 repolarisation and will help to develop therapeutic strategies to influence the organisation of repolarisation and hence to prevent the development of malignant arrhythmia.

Analysis in the research laboratory
Source: University Hospital Erlangen

Teaching

The Chair of Physiology (Department of Physiology and Pathophysiology) and the Chair of Systems Physiology (Department of Cellular and Molecular Physiology) jointly organise 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 fuer Pruefungen in der Medizin – Baden-Wuerttemberg'.

Selected Publications

Goltz D, Schultz JH, Stucke C, Wagner M, Bassalaý P, Schwoerer AP, Ehmke H, Volk T (2007) Diminished Kv4.2/3 but not KChIP2 levels reduce the cardiac transient outward K+ current in spontaneously hypertensive rats. Cardiovasc Res, 74: 85-95

Wielpuetz MO, Lee IH, Dinudom A, Boulkroun S, Farman N, Cook DI, Korbmacher C, Rauh R (2007) (NDRG2) stimulates amiloride-sensitive Na+ currents in Xenopus laevis oocytes and fisher rat thyroid cells. J Biol Chem, 282: 28264-73

Bertog M, Cuffe JE, Pradervand S, Hummler E, Hartner A, Porst M, Hilgers KF, Rossier BC, Korbmacher C (2008) Aldosterone responsiveness of the epithelial sodium channel (ENaC) in colon is increased in a mouse model for Liddle's syndrome. J Physiol, 586: 459-75

Diakov A, Bera K, Mokrushina M, Krueger B, Korbmacher C (2008) Cleavage in the {gamma}-subunit of the epithelial sodium channel (ENaC) plays an important role in the proteolytic activation of near-silent channels. J Physiol, 586: 4587-608

Nesterov V, Dahlmann A, Bertog M, Korbmacher C (2008) Trypsin can activate the epithelial sodium channel (ENaC) in microdissected mouse distal nephron. Am J Physiol Renal Physiol, 295: F1052-62

Wagner M, Rudakova E, Volk T (2008) Aldosterone-induced changes in the cardiac L-type Ca(2+) current can be prevented by antioxidants in vitro and are absent in rats on low salt diet. Pflugers Arch, 457: 339-49

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Research Focus

- Receptors and receptor associated diseases of the nervous system
- Synaptic signal complexes in the retina
- Mass spectrometry: Analysis of molecular heterogeneities
- Bioinformatics of biomolecular interactions

Structure of the Institution

The Institute of Biochemistry comprises the Chair of Biochemistry and Molecular Medicine and the Chair of Biochemistry and Pathobiochemistry, in addition to the professorship of Bioinformatics. The Institute of Biochemistry constitutes the interdisciplinary Emil-Fischer-Centre 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 12 scientists, 13 postgraduate students and 8 technicians.

Research

Receptors and receptor associated diseases of the nervous system

Project manager: C.-M. Becker, K. Becker, C. Kluck, C. Villmann
The strychnine sensitive glycine receptor is an inhibitory neurotransmitter receptor of the postsynaptic membrane predominantly expressed in spinal cord and brain stem participating in neuronal regulation of the muscle tone. The toxic alkaloid strychnine inhibits glycine binding and leads to death. Symptoms following a sublethal strychnine poisoning are similar to those observed in the glycine receptor-associated neurological motor disorder, hyperekplexia (startle disease, stiff-baby syndrome) that is characterized by increased startle reaction and episodic muscle stiffness. Indeed, defects within the glycine receptor gene are found in hereditary hyperekplexia.
The glycine receptor is a ligand-gated ion channel, composed of 2 α- and 3 β-subunits, each comprising four transmembrane domains connected by intra- and extracellular loops of varying length.
The main focus of the group is the characterization of structure-function relationships of the glycine receptor and its disease associated mutations. Upon recombinant expression, the secondary structure of the N-terminal domain of the glycine receptor resembles the immunoglobulin-like structure of the acetylcholine binding protein of the mollusc Lymnaea stagnalis. This isolated N-terminal domain binds the antagonist strychnine with high affinity.
Besides different subunits, allelic and splice variants contribute to the heterogeneity of the receptor. A splice variant of the GlyRβ-subunit lacking exon 7 (βΔ7) is highly expressed in glial cells, and was also found in extra-neuronal tissues (heart, liver). The expression of this βΔ7-subunit in tissues lacking the ligand-binding α1-subunit indicates alternative glycinergic signal transmission pathways.
The localization of a mutation in the glycine receptor gene influences the biogenesis and function of the receptor channel. A full inactivation of the glycine receptor gene was found in patients with recessive hyperekplexia where homozygosity for a large deletion leads to the complete loss of the α1-subunit. Besides these genetic forms, an autoimmune variant of a glycine receptor disease was characterized with autoantibodies directed against the α1-subunit. Even in several tumor cell lines transcripts of the glycine receptor genes were detectable.
Glycine receptor defects of the mouse mutants spastic, spasmodic and oscillator serve as genetic models for hypertonic motor disorders and serve as therapeutic test systems for neuron-specific gene transfer. The spastic mouse has an insertion mutation in the Glrb gene by an intronic LINE-1 element resulting in missplicing and a dramatic numerical loss of functional receptors. Studies with different mouse strains revealed that the spastic phenotype varies considerably between strains despite an identical mutant allele probably due to splice differences.
The molecular pathomechanism of an additional mouse mutant entla characterized by a hyperexcitatory syndrome was elucidated. This syndrome is caused by an exon duplication in the Cacna2d2 gene which modulates the electrophysiological properties of voltage-gated calcium channels.

Synaptic signal complexes in the retina

Project manager: R. Enz
The central nervous system (CNS) is regulated by neurotransmitter receptors and ion channels that coassemble with enzymes and scaffold proteins into synaptic signaling complexes. Malfunction of these protein complexes can lead to impaired signal transduction and may ultimately cause diseases such as epilepsy, schizophrenia and autism. The retina as part of the CNS is ideally suited to study basic principles of synaptic signaling mechanisms. Therefore, structure and function of synaptic signaling complexes of glutamate and γ-aminobutyric acid (GABA) receptors are investigated in the healthy and diseased retina.
Metabotropic glutamate receptors interact with protein phosphatase-1, RanBPM, Filamin-A and band 4.1-proteins. $GABA_C$ receptors bind PNUTS and Tax1BP1. Furthermore, ZIP proteins interact with $GABA_C$ receptors, voltage-gated potassium channels and protein kinase C. These protein complexes regulate intracellular signal cascades and control the sub-cellular targeting of neurotransmitter receptors. Mapping of interacting protein regions and modeling of their 3D-structure led to the definition of a new consensus sequence for proteins binding to protein phosphatase-1.
To analyze retinal gene expression in glaucoma, we used the DBA/2J mouse model. These animals suffer from an elevated intraocular pressure leading to degeneration of the optic nerve and deregulation of epithelial sodium channel expression.
A detailed knowledge of the structure, expression and function of synaptically localized signal complexes is fundamental to understand the function of the retina and the CNS. The description of new players contributing to this mechanism has the potential to identify key proteins that can be targeted, e.g. by specific drugs.

High-tech molecular basic research
Source: University Hospital Erlangen

Mass spectrometry: Analysis of molecular heterogeneities

Project manager: K. Schiebel, N. Vogel, W. Xiang, E. Schachmann

Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) is a method to determine the molecular mass of biomolecules such as DNA, proteins and lipids.

Genetic polymorphisms may alter the predisposition for diseases and are therefore used as molecular markers. Our group has developed methods for the MALDI-TOF-MS based diagnosis of molecular heterogeneities in hyperekplexia, thrombosis, cancer and other diseases. An association of polymorphisms of the prion protein gene promoter to a prolonged incubation time in BSE infected cattle was demonstrated.

On protein level, our group focuses on the identification and characterization of proteins by MALDI-TOF-MS. After separation of complex protein mixtures, the proteins of interest are analyzed by comparison of mass fingerprints of specific proteins to fingerprints stored in data bases. In addition, posttranslational modifications (PTM, like phosphorylation, glycosylation, glycation) of specific proteins are characterized and quantified. During neurodegeneration, free radical attack leads to oxidation of methionine and cysteine residues, nitrosative stress-induced modifications of tyrosine and cysteine residues as well as oxidative deimination of arginine residues. All these PTMs are detectable by MALDI-TOF-MS.

The neuronal cell death is investigated in glaucoma of DBA/2J mice and β-bungarotoxin-induced neuronal cell death in cell culture.

In neurodegeneration, lipid composition of membranes changes as shown by MALDI-TOF-MS. Currently, an HPLC coupled electrospray iontrap MS (ESI-IT-MS) is being established that allows even further characterization of biomolecules.

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 identification of the underlying principles of molecular recognition is important for the understanding of regulatory mechanisms and for the prediction of novel, physiologically relevant protein interactions. The bioinformatics group is primarily interested in investigating molecular interactions by a variety of computational tools (e.g. sequence data analysis, molecular modeling, and molecular dynamics).

Molecular dynamics simulations are used to study the dynamics of viral proteins (e.g. HIV protease), the conformational transitions of human proteins (e.g. Alzheimer Aβ-Amyloid), or the effect of covalent modifications on molecular recognition processes. Molecular modeling is used to generate the structure of isolated proteins or biomolecular complexes, which provides the basis for a molecular understanding of the effects of mutations on protein stability and binding properties. In addition, sequence based methods are developed that allow an improved detection of functional linear interaction motifs. Such motifs play an important role for the interactions of numerous pathogens with the target molecules of their host.

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

Dinkel H, Sticht H (2007) A computational strategy for the prediction of functional linear peptide motifs in proteins. Bioinformatics, 23: 3297-303

Kashkevich K, Humeny A, Ziegler U, Groschup MH, Nicken P, Leeb T, Fischer C, Becker CM, Schiebel K (2007) Functional relevance of DNA polymorphisms within the promoter region of the prion protein gene and their association to BSE infection. FASEB J, 21: 1547-55

Oertel J, Villmann C, Kettenmann H, Kirchhoff F, Becker CM (2007) A novel glycine receptor beta subunit splice variant predicts an unorthodox transmembrane topology. Assembly into heteromeric receptor complexes. J Biol Chem, 282: 2798-807

Hutchinson M, Waters P, McHugh J, Gorman G, O'Riordan S, Connolly S, Hager H, Yu P, Becker CM, Vincent A (2008) Progressive encephalomyelitis, rigidity, and myoclonus: a novel glycine receptor antibody. Neurology, 71: 1291-2

Rose M, Duetting E, Schroeder N, Sticht H, Brandstaetter JH, Enz R (2008) PNUTS forms a trimeric protein complex with GABA(C) receptors and protein phosphatase 1. Mol Cell Neurosci, 37: 808-19

International Cooperation

Dr. A. Pickford, University of Portsmouth, UK

A. Vincent, St Vincent's University Hospital, Dublin, Irland

A. Triller, INSERM, Paris, France

Institute of Biochemistry – Emil-Fischer-Centre

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Research Focus

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

Structure of the Institution

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

Research

Transcription factors as regulators of neural development

Several groups are interested in the characterization of transcriptional regulators that participate during development of the mammalian nervous system in determination and differentiation of neural stem cells to glia and neurons. Work is mainly focused on transcription factors of the Sox protein family and their interacting partners. Analysis of these transcription factors will lead to a better understanding of developmental defects, tumor formation and regenerative processes in the nervous system.

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.

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.

SoxC Proteins

Project manager: E. Sock
All SoxC proteins occur according to 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 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.

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.

Signal transduction processes at the forming neuromuscular synapse

Project manager: S. Hashemolhosseini

Muscle-specific MuSK is the main switch for synaptogenesis at the postsynaptic apparatus of the neuromuscular junction. Own work identified Erbin and CK2 as binding partners of MuSK. Protein kinase CK2 furthermore bound MuSK via its β subunit, phosphorylates MuSK and thereby regulates the stability of acetylcholine (AChR) clusters. Muscle-specific CK2β-deficient mice are myasthenic. To identify the cause for the destabilization of AChR aggregates in CK2β-deficient muscles, their phenotype is compared with the one of CK2α/CK2α'-deficient muscles. Behavioural tests and electrophysiological studies 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.

β-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 β4 is now regarded as the main intracellular G-actin sequestering peptide in most mammalian cells. Domains of thymosin β4 were identified which are important for the interaction with G- and F-actin. Apart from this intracellular function of thymosin β4, this peptide seems to be a player in wound healing and inflammation. β-thymosins are substrates of transglutaminases. Glutaminyl residues of β-thymosins can be cross-linked to amino groups of other molecules. Surprisingly, these derivatives are still able to sequester G-actin. Blood platelets contain a high concentration of thymosin β4. During aggregation of blood platelets, thymosin β4 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.

β-Thymosins can be labelled by fluorescent derivatives of cadaverine. The fluorescent β-thymosins are comparable to the natural β-thymosins with respect to their G-actin sequestering ability. Therefore, these fluorescent peptides are novel tools to study the interaction of β-thymosins with other proteins as well as their intracellular distribution in living cells. Surprisingly, thymosin β4 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 β4 was expected to freely diffuse through the nuclear pore complex into the nucleus. However, when thymosin β4 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 β4 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, Hillgaertner 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

Hoser M, Baader SL, Boesl MR, Ihmer A, Wegner M, Sock E (2007) Prolonged glial expression of Sox4 in the CNS leads to architectural cerebellar defects and ataxia. J Neurosci, 27: 5495-505

Zoubek RE, Hannappel E (2007) Influence of the N terminus and the actin-binding motif of thymosin beta4 on its interaction with G-actin. Ann N Y Acad Sci, 1112: 435-41

Finzsch M, Stolt CC, Lommes P, Wegner M (2008) Sox9 and Sox10 influence survival and migration of oligodendrocyte precursors in the spinal cord by regulating PDGF receptor alpha expression. Development, 135: 637-46

Schubert SW, Lamoureux N, Kilian K, Klein-Hitpass L, Hashemolhosseini S (2008) Identification of integrin-alpha4, Rb1, and syncytin a as murine placental target genes of the transcription factor GCMa/Gcm1. J Biol Chem, 283: 5460-5

Stolt CC, Lommes P, Hillgaertner S, Wegner M (2008) The transcription factor Sox5 modulates Sox10 function during melanocyte development. Nucleic Acids Res, 36: 5427-40

International Cooperation

Prof. Jean-Paul Borg, Inserm-Institut, Paoli-Calmettes-Université de la Méditerranée, Marseille, France

Prof. Hans-Rudolph Brenner, Pharmazentrum/Biozentrum, Basel, Switzerland

Prof. Patrik Ernfors, Karolinska Institutet, Stockholm, Schweden

Prof. Allen Goldstein, George-Washington-University, Washington, USA

Prof. Veronique Lefebvre, Lerner Institute, Cleveland, USA

Prof. James Lupski, Baylor College, Houston,Texas, USA

Prof. Lin Mei, Medical College of Georgia, Augusta, USA

Prof. Mengsheng Qiu, University of Louisville, Louisville, USA

Prof. Clarke Slater, University NewCastle, NewCastle, England

Prof. Xin Yuan, Harvard Medical School, Boston, USA

Meetings and International Training Courses

10.–11.10.2008: Third International Symposium of the Collaborative Research Centre (SFB) 473: "Transcriptional Control of Development and Disease", Erlangen, Deutschland

Research Equipment

Molecular Devices, Zeiss Fluoreszenz-Mikroskop

Institute of Medical Informatics, Biometry and Epidemiology

Chair of Biometry and Epidemiology

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Research Focus
- Dermatoepidemiology
- Epidemiological Concepts of Population Risk
- Participation in Collaborative Research Centre 539
- Prognosis modeling for censored and high-dimensional data
- Co-operative epidemiological and clinical studies

Structure of the Institution

The institute comprises the Endowed Chair of Medical Informatics (Prof. H.-U. Prokosch) and the Chair of Biometry and Epidemiology. Staff of the Chair of Biometry and Epidemiology includes 16 scientists (9 post-docs, 7 doctoral students) and 3 further employees. 50% of staff is financed by external funds.
Different working groups address biostatistical methods and epidemiological research. Moreover, the Chair cooperates with various clinical researchers. A MPI-PC-Cluster with 15 nodes is available as infrastructure for computer-intensive biostatistical simulation studies.

Research

Dermatoepidemiology

Project manager: 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 analysed 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 in a pharmaco-epidemiological project for assessment of contact allergy risk following application of topical therapeutics, or the impact of meteorological conditions on patch test reactivity. Moreover, the network "ESSCA" (www.essca-dc.org) is collecting and analysing such data on a European level since 2002, with the data centre at the Chair of Medical Biometry and Epidemiology.
The epidemiology of malignant melanoma and acquired melanocytic nevi is a further research interest: acquired melanocytic nevi, surrogate or potential precursor of malignant melanoma, are addressed as outcome in a bi-centric cross sectional study NAEVAC (impact of vaccination and infections on nevus density in schoolchildren) in Salzgitter and Erlangen including 2086 children. With a similar aim the current MONA-study includes an standardised assessment of student cohorts. In cooperation with Lower Saxonian health authorities the cmonde-study attempts to monitor childhood UV exposure via nevus density.

Epidemiological Concepts of Population Risk

Project manager: O. Gefeller
The methodological project addresses statistical methods for multifactorial risk attribution in epidemiology. Partitioning methods such as the partial attributable risk and its hierarchical and grouped variants divide the combined attributable risk of all risk factors into components that can be attributed to single risk factors. The specification of rules for the partitioning process is inspired by methods of mathematical game theory. In addition to conceptual aspects of defining the methods, the construction of point and interval estimators for their practical application is of central interest. Software tools for epidemiologic researchers are also developed.

Participation in Collaborative Research Centre 539

Project manager: B. Lausen, 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 multidisciplinary project with the Department of Ophthalmology and the Instiute of Informatics a computer based system for the diagnosis "suspected glaucoma", based on image analysis and other data, is being developed.

Prognosis modeling for censored and high-dimensional data

Project manager: T. Hothorn, O. Gefeller
The modeling of a censored outcome based on several, possibly many explanatory variables is of fundamental importance for the analysis of clinical and experimental studies with time-to-event primary outcomes. The application of new methods (for instance, ensemble methods for regression problems with continuous and censored outcomes) and optimisation methods can solve difficult problems. The aim of this project is the evaluation of tree-based methods, such as survival trees or so-called Random Forests, and boosting algorithms for the fitting of various models for censored outcomes. The estimation of models with empirical risk minimisation employing gradient boosting makes it possible to formulate in a uniform theory, adapt and compare both classical linear models as well as additive and flexible nonparametric variants. The possibility in particular to estimate classical models in a high dimensional setting exploiting the variable selection properties of these algorithms renders these methods very interesting for application in biostatistics and motivates their evaluation.

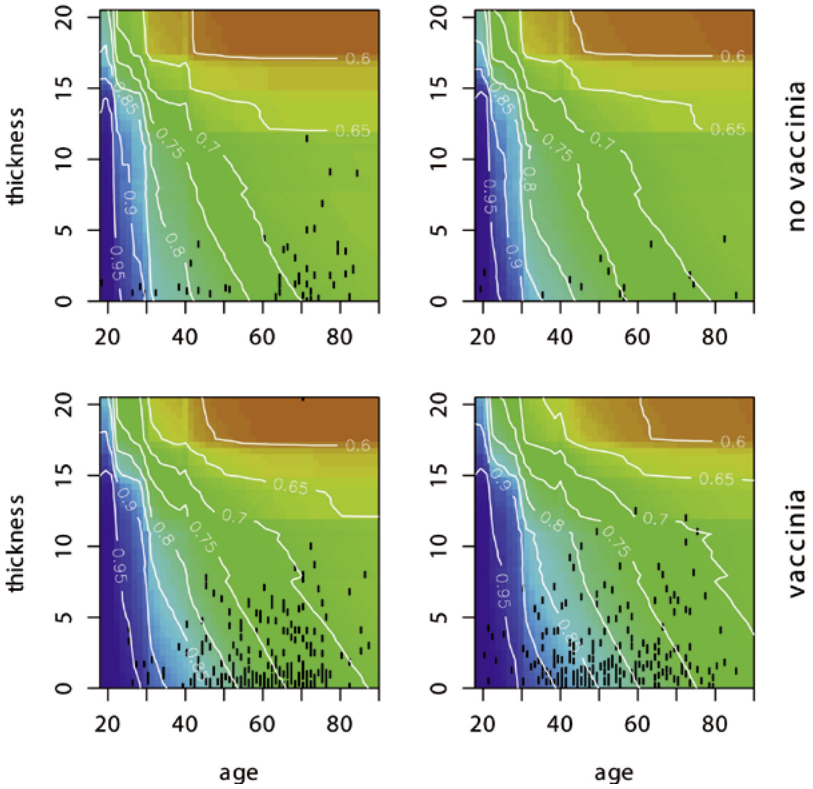
Co-operative epidemiological and clinical studies

Project manager: 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 provided by the Chair of Medical Biometry and Epidemiology in these cooperative projects. The most important projects in the reporting period include:
- a cross-sectional study in the field of environmental medicine addressing the internal burden with acrylamide and monoarylamines
- implementation of a remote database for electronic data capturing in a number of phase II studies on vaccination therapy in patients with progressive malignant melanoma along with development of statistical methods

- identification of prognostically relevant factors in a cohort of patients with moderate to severe atopic eczema
- an intervention study with the "Department of Medicine 2" on acupuncture treatment of hypertension
- multi-centric European studying on "Accelerated Partial Breast Irradiation" (www.apbi.uni-erlangen.de) Chaired by the Department of Radiation Therapy and a controlled clinical trial on the multimodal therapy of rectal cancer (CAO/ARO/AIO-04)
- biostatistical support of the ENT department in studies on the therapy of nasal polyps, diagnostic value of perfusion imaging in tumours 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 fuer Heimdialyse".

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). Moreover, this introduction to biometry and epidemiology (lecture and seminars in small groups) is part of the bachelor phase of the course on "molecular medicine" together with a seminar on the practice of data analysis which teaches basic programming skills in the statistical programme "R". Regarding the new master course "medical process management" the Chair is responsible for the part of "health care management II / public health and evidence-based medicine" (seminar). For students of medicine and dental medicine a seminar on "design and data analysis in clinical and experimental studies" is 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.



Visualisation of the Model Fit of a "Random Forest" Model based on Epidemiological Data on the Prognosis of Malignant Melanoma

Selected Publications

Hothorn T, Buehlmann P, Dudoit S, Molinaro A, van der Laan MJ (2006) Survival ensembles. Biostatistics, 7: 355-73

Gefeller O, Tarantino J, Lederer P, Uter W, Pfahlberg AB (2007) The relation between patterns of vacation sun exposure and the development of acquired melanocytic nevi in German children 6-7 years of age. Am J Epidemiol, 165: 1162-9

Rabe C, Lehnert-Batar A, Gefeller O (2007) Generalized approaches to partitioning the attributable risk of interacting risk factors can remedy existing pitfalls. J Clin Epidemiol, 60: 461-8

Uter W, Hegewald J, Kraenke B, Schnuch A, Gefeller O, Pfahlberg A (2008) The impact of meteorological conditions on patch test results with 12 standard series allergens (fragrances, biocides, topical ingredients). Br J Dermatol, 158: 734-9

de Pádua CA, Schnuch A, Nink K, Pfahlberg A, Uter W (2008) Allergic contact dermatitis to topical drugs--epidemiological risk assessment. Pharmacoepidemiol Drug Saf, 17: 813-21

Brenning A, Lausen B (2008) Estimating error rates in the classification of paired organs. Stat Med, 27: 4515-31

International Cooperation

Prof. J. D. Johansen, National Allergy Research Centre, Gentofte Hospital, Univ. Kopenhagen, Denmark

Prof. Geir E. Eide, Haukeland Hospital, Universitaet Bergen, Norwegen

Prof. Sandrine Dudoit, School of Public Health, UCLA Berkeley, USA

Meetings and International Training Courses

12.12.2008: Workshop "Parallel Computing", IMBE, Erlangen, Deutschland, AG Statistical Computing (GMDS/IBS-DR), der AG Klassifikation und Datenanalyse in den Biowissenschaften (GfKl), Collaborative Research Centre (SFB) 539

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Research Focus
- Architecture of health information systems
- Evaluation of health information systems
- Inference, assessment and visualization of medical facts out of medical databases
- Process analysis, process modelling and process optimization
- Medical ontologies and medical knowledge processing
- IT-infrastructure applications for medical research

Structure of the Institution

Together with the Chair for Biometry and Epidemiology, the Chair for Medical Informatics makes up the Institute for Medical Informatics, Biometry and Epidemiology. The Chair for Medical Informatics is, at the same time, member of the Technical Faculty, in the latter case in form of the research group M.
The Chair for Medical Informatics has 14 scientific employees, 7 of them are paid by projects. Research work is done by 6 scientics with doctoral degrees, 10 doctoral candidates and one medical documentalist.
The design and introduction of electronic health files, the integration of knowledge-processing fuctions into hospital information systems, the modelling and optimization of clincial workflows, data-warehouse- and data-mining-applications, the design of image management systems, the development of methods and procedures for multi-sector-networks as well as electronic health files for citizens, the evaluation of the effects of IT-measures and electronic information systems on all participants in the health system, usage of mobile technologies in medicine and the design of IT-infrastructures in research and development are evaluated by various scientific teams.
The head of the Chair for Medical Informatics, Professor Hans-Ulrich Prokosch, is at the same time responsible, as Chief Information Officer (CIO), for operative design and strategic development of information processing in the Erlangen University Hospital.

Research

Architecture of health information systems
Project manager: H.-U. Prokosch
Research around the design, implementation and management of Hospital Information Systems (HIS) is currently in a transition phase. For many years optimization of communication processes as well as the integration of heterogeneous departmental systems into a consistent and comprehensive HIS was the major task in this context. Today however, we are faced with new challenges. The integration efforts need to be extended across the borders of the hospital, to establish telematic networks across institutional borders. Parallel to this, requirements within a hospital also have changed. The main focus is no longer only on functions for order entry/results review or medical documentation. The questions of how to optimize process support, to integrate clinical pathways and to establish integrated electronic decision support functions have gained major importance. Integration of clinical guidelines or clinical pathways and electronic communication between hospitals and doctors are part of the topics adressed in this context, as well as transferring functionalities to modern electronic input media and mobile appliances. Hospital-wide image data management has to be supported by processes that nowadays include the radiological background and its connection to the IT-infrastructure as well as the peculiarities of image generating, image processing and image distribution in the departments of cardiology, radiology, nuclear medicine, dermatology, pathology and other image-generating departments. The Chair of Medical Informatics of Erlangen-Nürnberg University is concerned with the abovementioned questions in the contexts of piloting the clinical workplace system SOARIAN, of the OPAL-health-project (supported by the German Federal Research Ministry) directed at the analysis of the potential for RFID-technologies in hospitals, and of various health telematics projects.

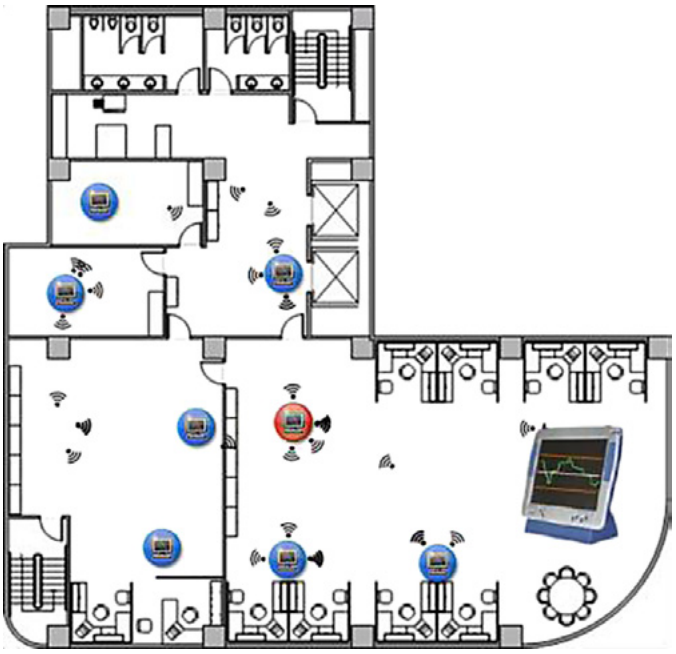
Evaluation of health information systems
Project manager: T. Buerkle
Cost-benefit-analyses aiming at the assessment of profitability often precede the introduction of new medical information systems. After system implementation, however, evaluation of the effects of new information technologies on user satisfaction, work processes, process costs or even on medical care, are rarely performed. Other preconditions for an efficient use of new technologies in the health system are the evaluation of user attitudes towards such new technologies/systems, the user-friendliness of the interface and of the acceptance of new technologies. Within all these health technology assessment analyses, issues of health economics as well as socio-technological issues have to be taken into account. In this context, the Chair for Medical Informatics investigates new evaluation methods and applies them in practical evaluation studies. The European research project “eHealth Consumer Trends Survey”, was an analysis citizens‘/patients‘ attitudes, wishes and real usage of Internet technologies for questions of health.

Inference, assessment and visualization of medical facts out of medical databases
Project manager: T. Ganslandt
Both in-patient and out-patient treatment routinely involve digital recording and documentation of numerous data elements. In view of this ever-increasing flood of information, a purposeful editing and visualization of these data is of the utmost importance for clinical users. By the means hitherto available, metaphors and tools for evaluation or presentation, demonstration of clinical treatment procedures is only insufficiently possible. The “Pathifier”-project of the Chair for Medical Informatics is aimed at the design, implementation and customization of a software tool for the visualization of patient data by means of the timeline-paradigm. This paradigm allows for a multitude of data elements to be presented both intuitively and graphically. Pathifier is currently being used in its pilot phase and evaluated at the University Hospital. The systems permits a flexible adaptation to the existing data sources and can therefore be transferred to other IT-contexts easily. This could be demonstrated within the frame of international cooperations by further pilot phase installations at the hospital Innsbruck, Austria, and the Hôpital Européen George Pompidou, Paris, France.

Process analysis, process modelling and process optimization
Project manager: T. Buerkle
We are currently facing an explosion of health care costs due to longer average life spans, an increasingly over-aging population, multimorbidity in old age and increased diagnostical and therapeutical possibilities. Potential for cost saving in medical treatment results from an optimized process management of treatment workflows, together with a better run-to-capacity of expensive diagnostic and therapeutical apparatuses. Clinical pathways, which have hitherto been used for that purpose, can be augmented by modern software tools. In this context, analysis of clinical workflows and modelling of clinical processes are indispensable prerequisites for an IT-based optimization of clinical workflows.

Medical ontologies and medical knowledge processing
Project manager: R. Sojer
The use of knowledge processing systems in medicine is aimed at optimizing the quality of medical care by prospective measures (decision support and decision monitoring). Numerous studies (e.g. the publications of the American Institute of Medicine "To err is human.") have revealed a considerable potential for improvements. In this context, the research projects of the Chair for Medical Informatics primarily concentrate on knowledge modeling for drug therapy and the implementation of standardized knowledge modules to be used within the context of drug prescription, e.g. to reduce adverse side effects.

IT-infrastructure applications for medical research
Project manager: H.-U. Prokosch, T. Ganslandt
Medical research is increasing based on closely connected multicentric structures, which require a productive, efficient and safe IT-infrastructure. Internet portals for secured communcation and collaboration as well as for web-based recording of patient-related research data at various workstations have been designed and provided by the Chair for Medical Informatics for the Research Network Epidermolysis Bullosa and for the Competence Network Adipositas. Similar platforms have been developed e.g. for the exchange of image data in clinical studies for the Department of Ophthalmology of the Erlangen University Hospital. The Chair for Medical Informatics is currently providing IT-support for bio-databases and processing data from electronic health files for clinical research, being member of various workgroups and participant in projects of the German Platform for Telematics for Medical Research Networks.



Smart Objects Technology
Use of Smart Objects (RFID) Technology for localizing of medical equipment

Teaching

The Chair for Medical Informatics is committed to the study of Medicine (Medical Informatics, Biometry and Epidemiology), Informatics (subsidiary subject Medical Informatics) and the new main subject Medical Process Management (Master-Degree). In this context, 10 final theses and 6 preparatory theses were written in 2007 and 2008.
All lectures are based on the concept of blended learning. The Chair for Medical Informatics introduced and evaluated the study management system Moodle in the winter semester 2008/2009, paving the way for the rest of the Faculty of Medicine. The system is currently being administered by the office of the Dean for Academic and Student Affairsof the Faculty of Medicine. The design, implementation and procurement of a web-based portal for searching and navigating medical image data bases was another point of emphasis of the Chair for Medical Informatics.

Selected Publications

Andreassen HK, Bujnowska-Fedak MM, Chronaki CE, Dumitru RC, Pudule I, Santana S, Voss H, Wynn R (2007) European citizens' use of E-health services: a study of seven countries. BMC Public Health, 7: 53

Klein A, Prokosch HU, Mueller M, Ganslandt T (2007) Experiences with an interoperable data acquisition platform for multi-centric research networks based on HL7 CDA. Methods Inf Med, 46: 580-5

Lang M, Kirpekar N, Buerkle T, Laumann S, Prokosch HU (2007) Results from data mining in a radiology department: the relevance of data quality. Medinfo, 12: 576-80

Buerkle T, Beisig A, Ganslmayer M, Prokosch HU (2008) A randomized controlled trial to evaluate an electronic scoring tool in the ICU. Stud Health Technol Inform, 136: 279-84

Kummervold PE, Chronaki CE, Lausen B, Prokosch HU, Rasmussen J, Santana S, Staniszewski A, Wangberg SC (2008) eHealth trends in Europe 2005-2007: a population-based survey. J Med Internet Res, 10: e42

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

International Cooperation

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

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

Prof. Dr. Elske Ammenwerth, Private Universitaet fuer Medizinische Informatik und Technik (UMIT), Hall near Innsbruck, Austria

Institute of the History of Medicine and Medical Ethics

Chair of the History of Medicine

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Research Focus
- History of Scientific Collection
- The social history of the hospital and the sanatorium

Structure of the Institution

The Institute of the History of Medicine and Medical Ethics consists of a Chair for the History of Medicine and a Professorship for Medical Ethics. The institute also houses the "Forum for Medicine and Human Rights," established in 2006 and the office of the Clinical Ethics Committee. In addition it is charged with the care for the Medical Collection in the city of Erlangen. Fourteen associates are in the institute's employ. Research is conducted by 12 scholars, seven of which are part-time. Currently 18 dissertations on the history and ethics of medicine are being supervised under the auspices of the institute. Six scientific book series are overseen by members of the institute.
The Chair of the History of Medicine researches questions associated with ancient medicine and its reception in the Renaissance and the Enlightenment (R. Wittern-Sterzel), the social history of medicine in early modernity with a focus on the history of anatomy and surgery, as well as patient history (M. M. Ruisinger). Further research examines networks of medical correspondence (also the subject matter of several dissertations) as well as the pre-history and early history of the health and hospital systems (F. Dross). Finally, projects on the history of medicine and health in the region (homeopathy in Franconia by M. M. Ruisinger and F. Dross) and in particular on the history of the medical faculty of the Friedrich-Alexander University Erlangen-Nürnberg are also underway.
A larger joint project combining history and ethics, commissioned by the governing body of the university and the medical faculty, researched and documented, e.g., the issue of doctor's titles being revoked during the "Third Reich" (R. Wittern-Sterzel, A. Frewer).
The Professorship for Medical Ethics is particularly active in the areas of clinical ethics and ethics counseling. It also has a research focus in medicine and human rights. The research program "clinical ethics" deals with the basic moral questions surrounding proper care for patients, with the justification of actions undertaken by physicians in everyday medicine, and with conflict situations in the hospital and private practice. Core questions concern clinical problem cases from the beginning of life (prenatal diagnostics, pregnancy conflicts, neonatology, etc.) ethical questions in crisis situations (oncology, genetic counseling, psychiatry, transplantation) to controversies about the end of life (euthanasia, care for the dying). Important instruments of clinical ethics are argumentation analyses of the counseling given by committees in applied medical and bioethics as well as empirical research studies.
The research area "medicine and human rights" deals with the various levels and aspects of human rights questions in the fields of medicine and biological sciences. This research focus is the only one of its kind in German medical faculties; its institutional anchor is the "Forum for Medicine and Human Rights."

Research

History of Scientific Collection
Project manager: U. Andraschke, M. M. Ruisinger
Collecting, ordering, and systematizing the world of objects has numbered among the central practices in the production of knowledge since the Renaissance. Collections were assembled at universities and were a core element of research and instruction in many disciplines. The history of these collections therefore reflects the history of academic disciplines in terms of their founding and their internal differentiation. The collections that still exist today are an important resource for inquiries into the history of science and the universities. They also offer the possibility of communicating research findings to a larger public in an appealing and immediately comprehensible manner. One result of the research project, sponsored by the Staedtler-foundation and the commission of universities, and accomplished in part with the aid of the study group of university collections in Erlangen's Metropolitan Museum, was the special exhibition "Unpacked. The Collections of the Erlangen-Nürnberg University," along with the publication "U. Andraschke, M. M. Ruisinger (eds.): Die Sammlungen der Universität Erlangen-Nürnberg. Nürnberg 2007."

The social history of the hospital and the sanatorium
Project manager: F. Dross
Ever since the leprosaria of the High Middle Ages, specialized care and isolation facilities have existed in Europe. Since the beginning of the modern period, intensive scrutiny has been paid to the close connection between poverty and illness. At the beginning, for instance in the case of sanatoria for plague victims, the concern was to isolate the ill, but by 1800 the notion had arisen that the hospital could become a publicly funded facility for the care of the indigent that could prevent poverty by curing illness. Nevertheless, quick and efficient medical treatment in the specialized surroundings known as the "hospital" was only available after the revolution of modern surgery in the late 19th century. The concept of the modern hospital is thus far older than the medicine that could breathe life into the concept. The research project investigates the social, political and regulatory debates, as well as the medical debates in history since the Late Middle Ages. At the point where these debates converged there emerged a specialized sanatorium for the prevention of poverty by means of medical services as a hospital avant la lettre. (The Invention of a Medical Institution? The Discussion on Hospitals Around 1800. In: M. Dinges (ed.), Health and Health Care between Self-Help, Intermediary Organizations and Formal Poor Relief (1500-2005), Lisbon 2007, S. 133-144).

Teaching

The Institute of the History of Medicine and Medical Ethics is responsible for instruction in medical terminology, as well as the history, theory and ethics of medicine. In the HTE seminars students learn the foundations of medical history, the theory of medicine and medical ethics by examining specific topics such as the history of the plague, the concept of health or

questions of medical ethics. Teaching methods include the interpretation of texts, cases discussion, roll-playing, short presentations, multimedia presentations and class excursions.
The topical seminar "medicine and aging" is the institutes' contribution to the module "dealing with age in the past and present." Moreover, the institute is responsible for the area of ethics as a part of the introduction to clinical medicine. As an elective, the course "skills in ethical communication," is offered as a subdivision of the modules "breaking bad news," "speaking about death and dying," and "intercultural communication." Innovative techniques in instruction are utilized such as working with simulated patients.
As a part of the major in molecular medicine students also study the subject "history of science and ethics." In cooperation with the philosophy faculty courses are offered to deepen the students' knowledge in the subjects of medical and bioethics.
Beyond this, a survey lecture course is offered on questions of the history and ethics of medicine and six series of scientific books are edited by members of the institute.

Wittern, R./Frewer, A. (2008):
Erlanger Forschungen, Sonderreihe Band 12.
Verlag: Universitätsbund Erlangen-Nürnberg e. V.

Selected Publications

Ruisinger M M (2007) Surgery in letters. The example of Lorenz Heister's epistolary consultation. Med Ges Gesch, 29: 131-42, 266

Dross F (2008) "Battlefield of love": the Fronberg-Hospital of the Deaconry Motherhouse Kaiserswerth. Medizinhist J, 43: 149-82

International Cooperation

Prof. Dr. Laurinda Abreu, PhoenixTN European Thematic Network on Health and Social Welfare Policy, Universidade de Évora, Portugal

Deutsch-Polnische Gesellschaft fuer Geschichte der Medizin e.V., TU Dresden, Germany/Poland

Meetings and International Training Courses

11.–13.07.2008: Medizintechnik – Sammeln, Forschen, Ausstellen: Symposium Medizinhistorische Museologie, Erlangen

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

Structure of the Institution

The Institute of the History of Medicine and Medical Ethics consists of a Chair for the History of Medicine and a Professorship for Medical Ethics. The institute also houses the "Forum for Medicine and Human Rights," established in 2006, and the office of the Clinical Ethics Committee. In addition it is charged with the care for the Medical Collection in the city of Erlangen. Fourteen associates are in the institute's employ. Research is conducted by 12 scholars, seven of which are part-time. Currently 18 dissertations on the history and ethics of medicine are being supervised under the auspices of the institute. Six scientific book series are edited by members of the institute.

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The Professorship for Ethics in Medicine is particularly active in the areas of clinical ethics and ethics counseling. It also has a research focus in medicine and human rights. The research program "clinical ethics" deals with the basic moral questions surrounding proper care for patients, with the justification of actions undertaken by physicians in everyday medicine, and with conflict situations in the hospital and private practice. Core questions concern clinical problem cases from the beginning of life (prenatal diagnostics, pregnancy conflicts, neonatology, etc.), ethical questions in crisis situations (oncology, genetic counseling, psychiatry, transplantation) to controversies about the end of life (euthanasia, care for the dying). Important instruments of clinical ethics are argumentation analyses of the counseling given by committees in applied medical and bioethics as well as empirical research studies.

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Research

Clinical Ethics and Ethics Counseling
Project manager: A. Frewer, U. Fahr

Particular emphasis is placed on the investigation of clinical ethical counseling, which is conducted by the Professorship of Ethics in Medicine in close association with the Clinical Ethics Committee. Topics of research include the theoretical foundations of ethical counseling, the evaluation of ethics counseling in hospitals, questions of narrative theory and the documentation of ethics counseling (U. Fahr, T. Ramsauer, L. Kovács, A. Frewer). The framework afforded by this research includes the "Day of Ethics" conference and "Yearbook Ethics in the Clinic" (YEC) [Jahrbuch Ethik in der Klinik].

Medicine and Human Rights
Project manager: A. Frewer

This branch 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 and bioethics are considered and the dimensions of the concept of human rights are investigated in this context (M. Rothhaar). In a practical vein this area of research involves questions of medical investigation and the documentation of human rights violations (translation and edition of the Istanbul Protocol of the United Nations for the Documentation of Torture), 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 (K. Krása). In connection with this area of research the reference book series "Medicine and Human Rights" appears. On the occasion of the 60th anniversary of the Universal Declaration of Human Rights the Professorship for Ethics in Medicine has organized in 2008 a special issue of the Human Rights Magazine (Potsdam University) on the topic of "Medicine and Human Rights."

Teaching

The Institute of the History of Medicine and Medical Ethics is responsible for instruction in medical terminology, as well as the history, theory and ethics of medicine. In the HTE seminars students learn the foundations of medical history, the theory of medicine and medical ethics by examining specific topics such as the history of the plague, the concept of health or questions of medical ethics. Teaching methods include the interpretation of texts, cases discussion, roll-playing, short presentations, multimedia presentations and class excursions.

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ence and ethics." In cooperation with the Faculty of Philosophy courses are offered to deepen the students' knowledge in the subjects of medical and bioethics.
Beyond this, a survey lecture course is offered on questions of the history and ethics of medicine and six series of scientific books are edited by members of the institute.

Selected Publications

Frewer A, Fahr U (2007) Clinical Ethics and Confidentiality: Opinions of Experts and Ethics Committees. HEC Forum, 19: 277-291

Saefken C, Frewer A (2007) The Duty to Warn and Clinical Ethics: Legal and Ethical Aspects of Confidentiality and HIV/AIDS. HEC Forum, 19: 313-326

International Cooperation

Prof. J. D. Moreno, Ph.D., Centre of Medical Ethics and the History and Sociology of Science, University of Pennsylvania, USA

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

Meetings and International Training Courses

24.11.2007: 7. Ethiktag des Klinischen Ethikkomitees und der Professur fuer Ethik in der Medizin: Patientenverfuegung und Ethikberatung in der Praxis, Erlangen

22.11.2008: 8. Ethiktag des Klinischen Ethikkomitees und der Professur fuer Ethik in der Medizin: Ethik im klinischen Alltag, Erlangen

Series of lectures on "Medicine, Ethics and Human Rights"
Source: Prof. Dr. A. Frewer

Institute of Pathology

Chair of General Pathology and Pathological Anatomy

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Research Focus
- Molecular pathology of urological tumors
- Experimental tumor pathology
- Pathology of immune and inflammatory reactions
- Clinical and predictive molecular pathology

Structure of the Institution

The Institute of Pathology includes also the Division of Nephropathology. A total of 75 members of staff work in the Institute of Pathology, 22 are medical professionals or scientists. Of these 8 are currently financed by third-party funding.
The Institute of Pathology is responsible for all pathology diagnostics within the University Hospital 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 histological evaluations of approx. 35,000 samples more than 1,500 molecular pathology investigations are carried out.
The diagnostics specialities 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 Pathologie" and "Diagnostic Molecular Pathology".

Research

Molecular Pathology of Urological Tumors
Project manager: A. Hartmann, R. Stoehr, C. Hammerschmied
The research group investigates the basic molecular principles of the development of urothelial carcinoma of the urinary bladder and renal cell carcinoma. There is a close cooperation with the Department of Urology of the University Erlangen-Nürnberg at the hospital Waldkrankenhaus and also with numerous national and international cooperating partners. The objective is the identification of genomic and epigenetic changes in urothelial carcinomas of the urinary bladder and kidney tumors to identify new markers for early diagnosis and new therapeutic target molecules. In addition one of the priorities of the work is the correlation of clinical-pathological findings with the molecular changes.

Experimental tumor pathology
Project manager: R. Schneider-Stock, A. Hartmann, S. Schwarz, A. Agaimy
The first focus is the molecular characterization of maligant gastrointestinal tumors. Research projects for the molecular regulation of apoptosis in colorectal carcinomas and adeno-carcinomas of the lower oesophagus (Barrett-carcinoma) are an important topic of the research work. Other areas deal with the basic molecular principles of chronic gastritis and Barrett metaplasia and the significance of epigenetic changes in the genesis of malignant tumors (Dr. T. Rau) and with molecular genetics and prognosis assessment in gastrointestinal stromal tumors (PD Dr. A. Agaimy, Prof. Dr. R. Schneider-Stock). Another research project investigates the basic molecular principles of tumorigenesis in patients with Colitis ulcerosa.
The second main focus is in cooperation with the Department of Obstetrics and Gynaecology (Prof. Dr. M. Beckmann, PD Dr. P. Fasching) and with the West German Study Group (Prof. Dr. U. Nitz, Dr. O. Gluz) and the Institute of Pathology of RWTH Aachen (Prof. Dr. E. Dahl) in the discovery of genetic and epigenetic changes in breast cancer and ovarian carcinomas (Prof. Dr. A. Hartmann, Dr. D. Wachter). The objective of the research here is to discover prognostic markers and to identify molecular markers that could be used in the clinical-pathological differential diagnosis and therapeutic stratification of breast cancer.
The subject of a further research project are the molecular changes in tumors in the head and neck region (Dr. S. Schwarz, 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 detect early molecular markers to identify dysplastic changes as tumor precursors in the mucosa of the head and neck region.

Pathology of immune and inflammatory reactions
Project manager: M. Buettner
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 tumors (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.

Clinical and predictive molecular pathology
Project manager: R. Stoehr, A. Hartmann
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 Diagnostic (Head Dr. R. Stoehr) 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 the diagnosis of hereditary tumors.

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 for-

mats (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

Agaimy A, Wuensch PH, Hofstaedter F, Blaszyk H, Ruemmele P, Gaumann A, Dietmaier W, Hartmann A (2007) Minute gastric sclerosing stromal tumors (GIST tumorlets) are common in adults and frequently show c-KIT mutations. Am J Surg Pathol, 31: 113-20

Dahl E, Wiesmann F, Woenckhaus M, Stoehr R, Wild PJ, Veeck J, Knuechel R, Klopocki E, Sauter G, Simon R, Wieland WF, Walter B, Denzinger S, Hartmann A, Hammerschmied CG (2007) Frequent loss of SFRP1 expression in multiple human solid tumours: association with aberrant promoter methylation in renal cell carcinoma. Oncogene, 26: 5680-91

Hafner C, López-Knowles E, Luis NM, Toll A, Baselga E, Fernández-Casado A, Hernández S, Ribé A, Mentzel T, Stoehr R, Hofstaedter F, Landthaler M, Vogt T, Pujol RM, Hartmann A, Real FX (2007) Oncogenic PIK3CA mutations occur in epidermal nevi and seborrheic keratoses with a characteristic mutation pattern. Proc Natl Acad Sci U S A, 104: 13450-4

Wild PJ, Giedl J, Stoehr R, Junker K, Boehm S, van Oers JM, Zwarthoff EC, Blaszyk H, Fine SW, Humphrey PA, Dehner LP, Amin MB, Epstein JI, Hartmann A (2007) Genomic aberrations are rare in urothelial neoplasms of patients 19 years or younger. J Pathol, 211: 18-25

Gluz O, Wild P, Meiler R, Diallo-Danebrock R, Ting E, Mohrmann S, Schuett G, Dahl E, Fuchs T, Herr A, Gaumann A, Frick M, Poremba C, Nitz UA, Hartmann A (2008) Nuclear karyopherin alpha2 expression predicts poor survival in patients with advanced breast cancer irrespective of treatment intensity. Int J Cancer, 123: 1433-8

Wassermann S, Scheel SK, Hiendlmeyer E, Palmqvist R, Horst D, Hlubek F, Haynl A, Kriegl L, Reu S, Merkel S, Brabletz T, Kirchner T, Jung A (2009) p16(INK4a) Is a beta-Catenin Target Gene and Indicates Low Survival in Human Colorectal Tumors. Gastroenterology, 136: 196-205.e2

International Cooperation

Ellen Zwarthoff, Erasmus MC Rotterdam, Netherlands

Torben Ornthoft, MOMA Aarhus, Denmark

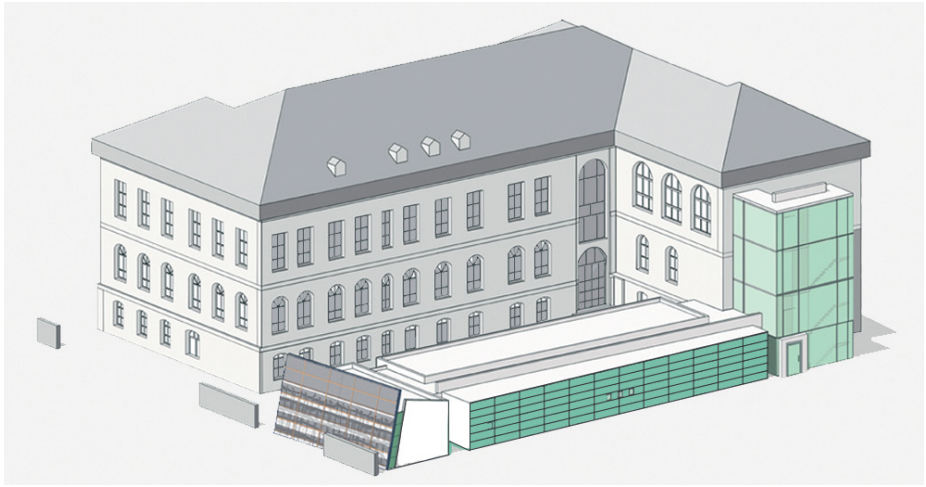
Paco Real und Nuria Malats CNIO, Madrid, Spain

W. EL-Rifai, Vanderbilt University, Memphis, USA

Research Equipment

PALM Laser-Mikrodissektions-Mikroskop

General renovation of the historic building of the Institute of Pathology
Source: University Hospital Erlangen



Version Pathology - Finished in 2010
Source: State Building Authority Erlangen-Nürnberg

Institute of Pathology

Division of Nephropathology

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Prof. Dr. med. Kerstin Amann

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Research Focus
- Clinical and experimental nephropathology
- Collaborative Research Centre (SFB) 423 kidney damage
- Interdisciplinary Centre for Clinical Research

Structure of the Institution

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 two Ph.D. students and four technical staff.
The Department of Nephropathology is responsible for the kidney biopsy diagnosis of the University Hospital Erlangen (Department of Medicine 4 and Pediatric nephrology of the Department of Pediatrics) and of further 42 external biopsy senders. The kidney biopsy diagnosis is carried out using the latest light-microscopic, immunohistological, electron microscopic and molecular methods. In this field there are close links with the corresponding structures of the Institute of Pathology.

Research

Clinical and experimental nephropathology
Project manager: K. Amann
There is extensive clinical and experimental cooperation with clinical partners (Department of Medicine 4 and pediatric nephrology of the Department of Pediatrics) as well as numerous task groups of the University Hospital and the University Erlangen-Nürnberg which are active in the area of kidney research. The task of the Division of Nephropathology is predominantly the testing of molecular hypotheses on material of animal experiments and human kidneys. In addition, equipment is available to carry out methods of quantitative tissue analysis for renal phenotyping of transgenic and knock-out animal models.

Collaborative Research Centre (SFB) 423 kidney damage
Project manager: K. Amann
Within the framework of the Collaborative Research Centre (SFB) 423 renal injury: "Pathogenesis and regeneration" established in 1999 at the Medical Faculty of the University Erlangen-Nürnberg, the Division of Nephropathology makes the central project Z2 "Quantitative morphology" available by putting at the disposal of the other projects of the Collaborative Research Centre (SFB) morphometric and sterologie methods of tissue analysis and in particular the laser-assisted micro dissection. In respect of the mentioned technologies an intensive induction does take place and surrance.

Interdisciplinary Centre for Clinical Research
Project manager: K. Amann
1. Cardiovascular changes in experimental systemic Lupus erythematodes. Here in cooperation with Prof. Thomas Winkler (Chair of Genetics) and PD Dr. Reinhardt Voll (Department of Medicine 3) 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. Proteases inhibition as a new therapeutic intervention in inflammatory kidney diseases.
In cooperation with PD Dr. Reinhardt Voll (Department of Medicine 3) and PD Dr.Michael Wiesner (Department of Medicine 4) it is explored whether proteases 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, medicational interventions for proteases inhibition in standard models of systemic Lupus erythematodes and other inflammatory kidney diseases are investigated.

Teaching

The Department of Nephropathology participates in the teaching of the Institute of Pathology. In addition, nephropathological conferences with the clinical departments of the University Hospital and external biopsy senders are regularly held. Furthermore, twice a year a kidney pathology course takes place for both staff of the University Hospital and staff of external hospitals.

Selected Publications

Aigner T, Neureiter D, Câmpean V, Soder S, Amann K (2008) Expression of cartilage-specific markers in calcified and non-calcified atherosclerotic lesions. Atherosclerosis, 196: 37-41

Boor P, Casper S, Celec P, Hurbánková M, Beno M, Heidland A, Amann K, Sebeková K (2008) Renal, vascular and cardiac fibrosis in rats exposed to passive smoking and industrial dust fiber amosite. 2008 Oct 6. [Epub ahead of print]

Câmpean V, Karpe B, Haas C, Atalla A, Peters H, Rupprecht H, Liebner S, Acker T, Plate K, Amann K (2008) Angiopoietin 1 and 2 gene and protein expression is differentially regulated in acute anti-Thy1.1 glomerulonephritis. Am J Physiol Renal Physiol, 294: F1174-84

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

Amann K, Haas CS, Zeiler GA, Benz K, Bader BL, Hartner A, Hilgers KF (2009) Lack of nidogen-2 increases blood pressure, glomerular and tubulointerstitial damage in DOCA-salt hypertension. Eur J Clin Invest, 39: 116-25

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

International Cooperation

Prof. Dr. J. Kanwar, Pathologisches Institut, North Western University, Chicago, USA

Prof. Dr. S. Rostand, Nephrologie, University of Birmingham, Alabama, England

Dr. Ingeborg Bajema, Pathologisches Institut, Universitaet Leiden, Netherlands

Research Equipment

PALM Laser-Mikrodissektions-Mikroskop

Institute of Neuropathology

Chair of Neuropathology

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Research Focus
- Molecular myopathology
- Focal human epilepsies / european epilepsy brain bank
- Neuro-oncology
- Adult stem cells of the human brain

Structure of the Institution

The Institute has become part of the University Hospital in 2007. A total of 20 collaborators were employed (7 paid from external grants): 5 academic staff, 8 post-graduate students and 6 technicians. Different research units address the molecular pathomechanisms of CNS and skeletal muscle disorders. Particular focus is paid to epilepsy surgery, neuro-oncology and neuromuscular disorders. We have established the neuropathological reference centre for epilepsy surgery and the European Epilepsy Brain Bank (supported by EU).

Research

Molecular myopathology

Project manager: R. Schroeder

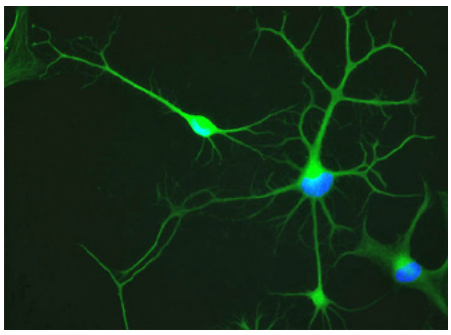
A central research topic is the molecular characterisation of progressive skeletal muscle and cardiac diseases, which are morphologically characterized by pathological protein aggregation. These adult onset protein aggregate myopathies are clinically characterized by a progressive course leading to severe disability and premature death. To date, no causative treatment is available for these disorders. The main focus of our current research work (funded by the German Research Foundation, the Federal Ministry of Education and Research; Fritz-Thyssen Foundation) 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.

Focal human epilepsies / european epilepsy brain bank

Project manager: I. Bluemcke

This research topic focuses on therapy-refractory focal epilepsies in humans. To unravel the molecular pathogenesis of major entities associated with chronic epilepsies, e.g. hippocampal sclerosis, glio-neuronal tumours 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 from improved classification systems for mesial temporal sclerosis.

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 human brain stem cells
Induced neuronal differentiation in a stem cell obtained from the adult human hippocampus (epilepsy surgery). Fluorescence microscopy of MAP2 immunoreactivity (in green). Hoechst nuclear staining in blue.

The European EpiCure Consortium (funded by EC) has established an Epilepsy Brain Bank (www.epicure-bank.org), which is associated to our institution, to achieve the following goals: (1) To standardize histopathological diagnosis among European countries. (2) To standardize sampling and long-term storage of surgical tissue specimens for research purpose. (3) Colleagues with rare expertise in examining epilepsy-surgical specimens can request for a consultant opinion (free of charge). (4) Regular workshops are organized to achieve common diagnosis and classification schemes within European countries.

Neuro-oncology

Project manager: R. Buslei

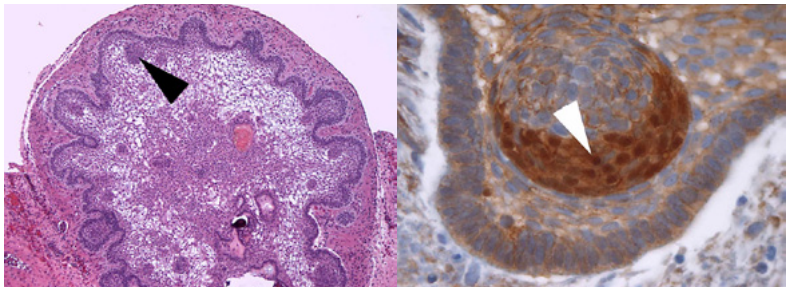
Neuro-oncology plays an important role in our clinico-neuropathological surveillance. With the international reputation of the Department of Neurosurgery in Erlangen and its emphasis on the treatment of neuroendocrine tumors (e. g. pituitary adenomas, craniopharyngeomas) an unique collection of surgical 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 molecular-biological and genetical 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 β-catenin mutations in craniopharyngiomas and its impact for the differential diagnosis of cystic tumours of the sellar region. Future work will address the development of novel animal models and *in vitro* cultures to unravel the molecular pathogenesis of this peculiar tumour entity.

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, un-

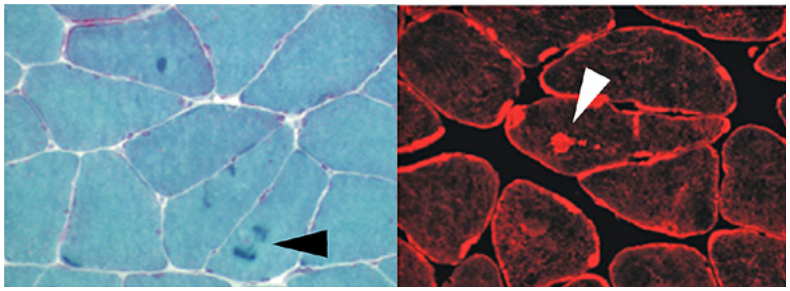
known. The identification of these mechanisms is a major topic of our project. To address this question, we have access to unique models: organotypic slice cultures of rat and mice hippocampus, but also from epilepsy surgical specimens are available resources. Furthermore, we are able to isolate adult stem cells from acute brain slices and proliferate them clonally. The possibility to generate high numbers of differentiated neurons or glia cells from autologues stem cells of the brain may unravel novel treatment strategies in apoplexia, Parkinson's disease but also epilepsies or multiple sclerosis (supported by the Bavarian Research Consortium ForNeuroCell).



Craniopharyngioma
Left Image: H&E staining in a craniopharyngeoma reveals the characteristic epithelial architecture with enamel dots and wet ceratin deposits. Right image: the majority of craniopharyngeomas carry mutations in the β-catenin gene, which lead to nuclear β-catenin protein accumulation and activation of the wnt signalling pathway.

Teaching

Our Department in enroled in pathology training and lectures.



Desminopathy
Intracellular protein aggregates (arrowheads) present a characteristic finding in desmin myopathies. Upper image: Gomori staining. Lower image: Fluorescence microscopic analysis of desmin immunoreactivity.

Selected Publications

Blumcke I, Pauli E, Clusmann H, Schramm J, Becker A, Elger C, Merschhemke M, Meencke HJ, Lehmann T, von Deimling A, Scheiwe C, Zentner J, Volk B, Romstock J, Stefan H, Hildebrandt M (2007) A new clinico-pathological classification system for mesial temporal sclerosis. Acta Neuropathol (Berl), 113: 235-44

Kley RA, Hellenbroich Y, van der Ven PF, Fuerst DO, Huebner A, Bruchertseifer V, Peters SA, Heyer CM, Kirschner J, Schroeder R, Fischer D, Mueller K, Tolksdorf K, Eger K, Germing A, Brodherr T, Reum C, Walter MC, Lochmueller H, Ketelsen UP, Vorgerd M (2007) Clinical and morphological phenotype of the filamin myopathy: a study of 31 German patients. Brain, 130: 3250-64

Hoelsken A, Kreutzer J, Hofmann BM, Hans V, Oppel F, Buchfelder M, Fahlbusch R, Bluemcke I, Buslei R (2008) Target Gene Activation of the Wnt Signaling Pathway in Nuclear beta-Catenin Accumulating Cells of Adamantinomatous Craniopharyngiomas. Brain Pathol Epub 2008 May 29.

Huttner HB, Janich P, Koehrmann M, Jászai J, Siebzehnrubl F, Bluemcke I, Suttorp M, Gahr M, Kuhnt D, Nimsky C, Krex D, Schackert G, Loewenbrueck K, Reichmann H, Juettler E, Hacke W, Schellinger PD, Schwab S, Wilsch-Braeuninger M, Marzesco AM, Corbeil D (2008) The stem cell marker prominin-1/CD133 on membrane particles in human cerebrospinal fluid offers novel approaches for studying central nervous system disease. Stem Cells, 26: 698-705

Konieczny P, Fuchs P, Reipert S, Kunz WS, Zeoeld A, Fischer I, Paulin D, Schroeder R, Wiche G (2008) Myofiber integrity depends on desmin network targeting to Z-disks and costameres via distinct plectin isoforms. J Cell Biol, 181: 667-81

Siebzehnrubl FA, Jeske I, Mueller D, Buslei R, Coras R, Hahnen E, Huttner HB, Corbeil D, Kaesbauer J, Appl T, von Hoersten S, Bluemcke I (2008) Spontaneous In Vitro Transformation of Adult Neural Precursors into Stem-Like Cancer Cells. Brain Pathol Epub 2008 Jul 10

International Cooperation

Prof. Gerhard Wiche, Max F. Perutz Laboratories, Universitaet Wien, Austria

Prof. Dr. Roberto Spreafico, Department of Epilepsy Clinic and Experimental Neurophysiology, Fondazione IRCCS Istituto Neurologico "Carlo Besta", Milano, Italy

Prof. Dr. Dennis Steindler, McKnight Brain Institute, University of Florida, Gainsville, USA

Institute of Microbiology – Clinical Microbiology, Immunology and Hygiene

Chair of Microbiology and Immunology of Infection

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Research Focus

- Innate immunity and myeloid cells
- Innate immunity and natural killer cells
- Signal transduction of interleukin-4 receptor signaling
- Bacterial virulence factors
- Innate immunity and antimicrobial proteins
- New methods of diagnostic microbiology

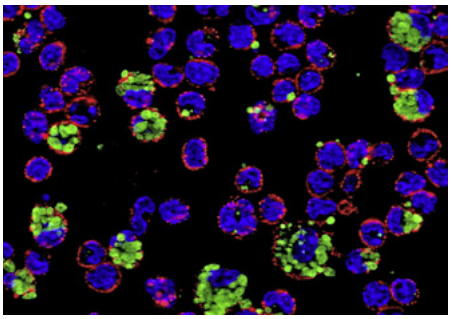
Structure of the Institution

The Institute of Microbiology – Clinical Microbiology, Immunology and Hygiene houses the Chair of Microbiology and Immunology of Infectious Diseases (Head: Prof. Dr. med. C. Bogdan), the Diagnostic Laboratories for Clinical Microbiology and Hospital Hygiene (Head: OA Dr. med. Dipl. Chem. C. Schoerner) and, since November 1, 2008, the newly installed Division of Infection Biology. The institute employs 84 coworkers, of which 29 are payed by extramural funding sources. The research is carried out by 14 scientists with a M.D. or Ph.D. degree, 16 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 analyse the regulation of basic inflammatory processes, using immunological, cell-biological and molecular techniques. Various infectious disease models are studied, which include Lyme arthritis (Borrelia burgdorferi), gastrointestinal infections (Salmonella typhimurium, Yersinia enterocolitica), pulmonary infections (Pseudomonas aeruginosa), cutaneous (Leishmania major) and visceral leishmaniasis (Leishmania infantum). 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 focussed 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 institute functions as reference centre for the country-wide quality control and proficiency tests.

Research

Innate immunity and myeloid cells

Project manager: H.U. Beuscher
In cooperation with the Department of Medicine 3 and a Junior Research Group of the IZKF the survival strategies, the immunoregulatory functions and the production of inflammatory mediators by neutrophils from patients with rheumatoid arthritis will be investigated. The study aims to characterize an anti-apoptotic factor and its mechanism of action as well as possible therapeutic applications. A second project analyses, how mast cells interact with B lymphocytes, modulate the antibody synthesis and thereby optimize the specific immune defense of the host organism.
Project manager: C. Bogdan
The interferon (IFN)-γ inducible nitric oxide synthase (iNOS), which generates nitric oxide from the amino acid L-arginine, is essential for several functions of the immune system and the defense against intracellular microorganisms (e.g. Leishmania spp.). In macrophages, the mechanism underlying the suppression of iNOS protein synthesis by L-arginine-deficiency, which occurs following induction of the arginine-metabolizing enzyme arginase, will be studied. Another area of research is the autoactivation of macrophages via endogenously produced IFN-β and the effect of hypoxic conditions in inflamed tissues on the antimicrobial function of myeloid cells.
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.



Leishmania infantum (green) is endocytosed by myeloid dendritic cells (red surface with blue nucleus) (Schleicher et al. J Exp Med 2007)

Innate immunity and natural killer cells

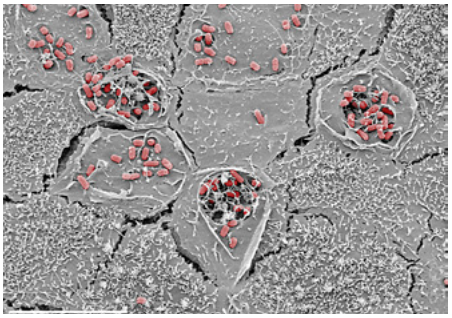
Project manager: U. Schleicher
The early phase of Leishmania infections is characterized by the rapid activation of natural killer (NK) cells. The group investigates, which receptors (e.g. toll-like receptors, TLR), cytokines and cell-types (macrophages, myeloid and plasmacytoid dendritic cells) are required for NK cell activation. As activated NK cells contribute to the control of pathogens, experiments are carried out to unravel the underlying direct or indirect effector mechanisms. For the functional analysis of NK cells *in vivo* during cutaneous (L. major) and visceral leishmaniasis (L. infantum) a transgenic mouse model, which allows for the selective deletion of NK cells, and novel NK cell activators will be applied.

Signal transduction of interleukin-4 receptor signaling

Project manager: A. Gessner
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 major, Borrelia burgdorferi, Pseuodomonas aeruginosa).

Bacterial virulence factors
Project manager: M. Hensel
The ability of bacterial pathogens to evade the immune system and to cause disease are a consequence of the expression of virulence factors, some of which are encoded by pathogenicity islands. Using the gastrointestinal pathogen Salmonella typhimurium, the group investigates the molecular mechanisms of adhesion, invasion and intracellular replication of the bacteria, the genetic basis for the adaptation of the bacterial metabolism to the intracellular life and the (immuno)modulatory impact of the bacterial effector molecules on the host cells. Further projects aim to optimize the use of Salmonella as recombinant carriers for prophylactic and therapeutic vaccines and to develop new methods for the efficient genetic manipulation of bacterial pathogens.



Salmonella (red) adhere to the apical side of polarized epithelial cells (using a SPI4-encoded adhesin), induce the elimination of microvilli and invade the host cells (image provided by Dr. Manfred Rohde, HZI, Braunschweig).

Innate immunity and antimicrobial proteins
Project manager: M. Schnare
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. In cooperation with the group of A. Gessner 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.

New methods of diagnostic microbiology
Project manager: W. Geißdoerfer, F. Albert, B. Kunz, C. Schoerner
Aim of the project is the development and evaluation of new microbiological diagnostic procedures that are highly specific, sensitive, fast and cost-efficient. The group focuses on the establishment of novel real-time polymerase-chain-reactions, the utilization of mass spectrometry (MALDI-TOF) for direct identification of bacterial and fungal species, the routine application of rapid screening procedures for multi-resistant pathogens and the implementation of a new electronic data processing system that offers online accessibility for placing orders and viewing results. The spectrum of infectious pathogens, for which the diagnostic procedures have been improved, range from bacteria (e.g. MRSA, C. trachomatis, L. pneumophila, T. whipplei) to fungi and protozoa (T. gondii, Leishmania spp.).

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

Auer J, Blaess M, Schulze-Koops H, Russwurm S, Nagel T, Kalden JR, Roellinghoff M, Beuscher HU (2007) Expression and regulation of CCL18 in synovial fluid neutrophils of patients with rheumatoid arthritis. Arthritis Res Ther, 9: R94

Gerlach RG, Jaeckel D, Stecher B, Wagner C, Lupas A, Hardt WD, Hensel M (2007) Salmonella Pathogenicity Island 4 encodes a giant non-fimbrial adhesin and the cognate type 1 secretion system. Cell Microbiol, 9: 1834-50

Schleicher U, Liese J, Knippertz I, Kurzmann C, Hesse A, Heit A, Fischer JA, Weiss S, Kalinke U, Kunz S, Bogdan C (2007) NK cell activation in visceral leishmaniasis requires TLR9, myeloid DCs, and IL-12, but is independent of plasmacytoid DCs. J Exp Med, 204: 893-906

Groer GJ, Haslbeck M, Roessle M, Gessner A (2008) Structural characterization of soluble E-Syt2. FEBS Lett, 582: 3941-7

Wittmann I, Schoenefeld M, Aichele D, Groer G, Gessner A, Schnare M (2008) Murine bactericidal/permeability-increasing protein inhibits the endotoxic activity of lipopolysaccharide and gram-negative bacteria. J Immunol, 180: 7546-52

Werninghaus K, Babiak A, Gross O, Hoelscher C, Dietrich H, Agger EM, Mages J, Mocsai A, Schoenen H, Finger K, Nimmerjahn F, Brown GD, Kirschning C, Heit A, Andersen P, Wagner H, Ruland J, Lang R (2009) Adjuvanticity of a synthetic cord factor analogue for subunit Mycobacterium tuberculosis vaccination requires FcRgamma-Syk-Card9-dependent innate immune activation. J Exp Med, 206: 89-97

International Cooperation

Larry Keefer, National Cancer Institute, Bethesda, USA

Peter Murray, St. Jude Children's Research Hospital, Memphis, USA

Dipshikha Chakravortty, Indian Institute of Science, Bangalore, India

Pavel Kovarik, Max F. Perutz Laboratories, University of Vienna, Austria

Research Equipment

Applied Biosystems DNA-Sequenzierautomat

Applied Biosystems ABI Prism 7900 Taqman sequence detector

BD Biosciences FACS Canto II

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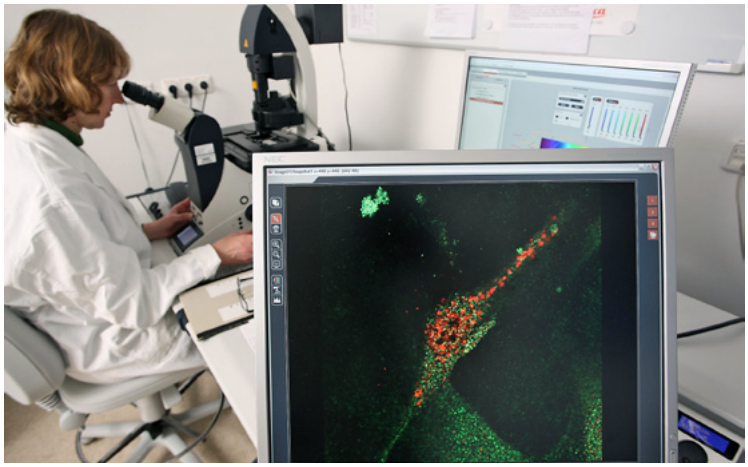
Research Focus
- HIV and other retroviruses
- Expert Laboratory for Beta-Herpesviruses
- Research Network on DNA tumor viruses



Confocal Laser Scanning Microscopy for determination of intracellular localization of viral proteins in infected cells.
Source: Foto Fuchs Design, Erlangen

Structure of the Institution

The research focuses of the institute are pathogenic Retroviruses, Human Cytomegalovirus and Oncogenetic Herpesviruses. The research fields range from infection biology, tumor virology, vector development, therapy research, immunology to clinical diagnostics. Altogether the institute has about 130 staff members. The majority are students of biology, medicine, biochemistry and molecular medicine who are working on their dissertation or master thesis in one of the 14 research groups. Head of the project groups are full, associate and assistant professors and junior scientists. 15 technical assistants support the research groups. The majority of the research staff is supplied by research supporting organizations.

The renovations and extension of the north wing of our institute was completed in mid-2008. This construction measure provided adequate security standards for the majority of the scientific laboratories. Furthermore, the institute has five security labs of security level three. The diagnostic labs offer a modern spectrum of diagnostic tests for all relevant viral infections. The focus lies on retrovirus diagnostic for HIV/AIDS and Human T-cell-Leukemia virus. Very important in this field is the resistance test for HIV to determine the susceptibility to antiretroviral drugs. In addition, the institute offers HIV reference material in its role as National Reference Centre for Retroviruses.

Research

HIV and other retroviruses

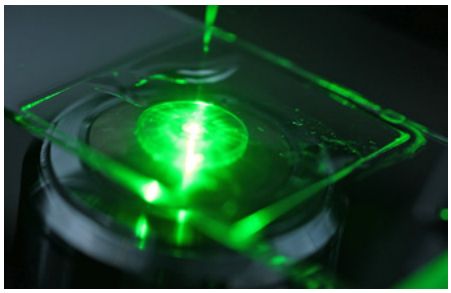
Several basic research projects in the institute have a close connection to the task of the National Reference Centre for Retroviruses. The group of Prof. Dr. U. Schubert is studying the interaction of host and virus proteins on the molecular level in order to define interface regions of binding partners 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 (UPS) in late processes of the HIV replication cycle. The group of PD B. Schmidt surveys the role of plasmacytoid dendritic cells in innate immune defenses against HIV. Dr. Dr. H. Reil is engaged in the interference of flavivirus GB Virus C (GBV-C) and immunodeficiency viruses. Dr. H. Walter and Dr. K. Korn are working on the development of methods for the detection of HIV resistance against new drug classes. In close connection, PD Dr. K. Metzner investigates the pathology of the development of drug resistance in immunodeficiency viruses under the aspect of appearance of HIV viral quasispecies. Prof. R. Grassmann was the head of the HTLV group until July 2008, when he suddenly died. His group studied the molecular biology of the development of ATLL (adult T cell Leukemia/Lymphoma) caused by the retrovirus HTLV-1 (human T cell leukemia virus). They investigate the molecular function of the Tax oncoprotein of the virus.

Expert Laboratory for Beta-Herpesviruses

The broad research activity of the institute focuses on the immune defense and on the molecular mechanisms of replication of the clinically relevant human cytomegalovirus (HCMV). The research group of Prof. Dr. M. Mach defines in collaboration with Prof. Th. Winkler, Chair of Genetics (Faculty of Natural Science), the key factors providing protective humoral immunity following HCMV infection using a mouse model. They disprove the still ongoing opinion that antibodies are irrelevant for protection from CMV infection in risk groups. The group of Prof. T. Stamminger characterizes 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. Prof. Stamminger's research 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. Ensminger (cardiac surgery) on a mouse xenotransplantation model on the mechanism of CMV induced transplant arteriosclerosis. The research group of Prof. Dr. M. Marschall investigates the roles of viral and cellular protein kinases in herpesviral replication and herpes virus pathogenicity. This area of his work serves the

purpose to develop novel antiviral drugs of protein kinase inhibitors (including inhibitors of cellular signal transduction).

Research Network on DNA tumor viruses
This network is coordinated by Prof. Dr. B. Fleckenstein and is focused on the mechanism of cellular growth transformation by DNA tumor viruses. The Kaposi´s sarcoma-associated human herpesvirus type 8 (HHV-8) is also associated with B-cell lymphoproliferation. The growth promoting and immunoregulatory properties of different HHV-8 proteins are studied by the group of PD Dr. F. Neipel. In 2008, 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 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 Prof. A. Ensser narrowed down transformation-relevant domains and the function of the herpesviral effector oncoprotein Tip of Herpesvirus saimiri (H. Saimiri). H. Saimiri induces tumors in non-human primates and, like HHV-8, belongs to the family of rhadinoviruses. The second focus is the analysis of viral episomal replication and chromatin structure in eukaryotic cells, particularly in human T-cells. The group of PD B. Biesinger studied T-cellular signaling pathways regulated by the viral oncoproteins StpC and Tip from Herpesvirus saimiri C488 as well as Tio from Herpesvirus ateles. Via the regulation of gene expression, DNA methylation and/or histone modification have been documented to affect many biomedical processes. Prof. W. Doerfler's laboratory characterizes different aspects of DNA-methylation in transgenic cells and in the human genome.



Living cells on a slide during confocal laser scanning microscopy.
Source: Foto Fuchs Design, Erlangen

Teaching

In cooperation with the microbiology colleagues, the Institute of Virology offers curricular lectures and practical courses in infectiology and immunology. These general infectiology courses have been expanded to students of pharmaceutics, dentistry and life science engineering. Furthermore, our institute is involved in the four-year full-time degree program in molecular medicine. The lectures for the students mediate basics of general virology like clinical aspects and pathogenetis of viruses, viral replication and gene regulation, viral transformation, viral vectors, immune defense and antiviral therapy. In the advanced seminar for students of molecular medicine, the students are introduced to original scientific publications. The fundament of our viral education is a F1 practical course that lasts four weeks. Groups of two to three students of medicine, molecular medicine or biology work under direct instruction of the team leaders on current research projects in the lab. Insight into the actual research project of the institute is provided in the weekly seminar on methods in molecular virology. A seminar on current topics in clinical virology is also offered weekly. For the scientific education of biology students, the Institute for Virology provides a basic lecture of virology, as well as the above-mentioned F1 practical course and method seminars. Beside this the biology students should attend a couple of the special lectures like molecular and immunopathogenicity, viral and cellular signal transduction, strategies of viral replication, development of antiviral therapy, innate immune defense against viruses and bioinformatics. Courses for the recently introduced Master of Science (M.Sc.) degree program for biology students are currently established. Furthermore 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

Gack MU, Shin YC, Joo CH, Urano T, Liang C, Sun L, Takeuchi O, Akira S, Chen Z, Inoue S, Jung JU (2007) TRIM25 RING-finger E3 ubiquitin ligase is essential for RIG-I-mediated antiviral activity. Nature, 446: 916-920

Klenovsek K, Weisel F, Schneider A, Appelt U, Jonjic S, Messerle M, Bradel-Tretheway B, Winkler TH, Mach M (2007) Protection from CMV infection in immunodeficient hosts by adoptive transfer of memory B cells. Blood, 110: 3472-9

Goldwich A, Hahn SS, Schreiber S, Meier S, Kaempgen E, Wagner R, Lutz MB, Schubert U (2008) Targeting HIV-1 Gag into the defective ribosomal product pathway enhances MHC class I antigen presentation and CD8+ T cell activation. J Immunol, 180: 372-82

Pichler K, Kattan T, Gentzsch J, Kress AK, Taylor GP, Bangham CR, Grassmann R (2008) Strong induction of 4-1BB, a growth and survival promoting costimulatory receptor, in HTLV-1-infected cultured and patients' T cells by the viral Tax oncoprotein. Blood, 111: 4741-51

Tavalai N, Papior P, Rechter S, Stamminger T (2008) Nuclear domain 10 components promyelocytic leukemia protein and hDaxx independently contribute to an intrinsic antiviral defense against human cytomegalovirus infection. J Virol, 82: 126-37

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

International Cooperation

Prof. Dr. J. Sinclair, Addenbrooke's Hospital, Cambridge, UK

Dr. Jeffery Kopp, Kidney Disease Section, NIDDK, NIH, Bethesda, MD, USA

Dr. Ashok Balasubramanyam, Baylor College of Medicine, Houston, TX, USA

Dr. David Ott, SAIC Frederick, NCI FCRDC, NIH, Frederick, MD, USA

Prof. Jae Ung Jung, Molecular Microbiology & Immunology, University of Southern California, Los Angeles, CA, USA

Meetings and International Training Courses

01.–05.09.2007: Third European Congress of Virology, Nürnberg, Germany

17.–19.10.2008: Second International Symposium, Erlangen, Germany, GRK 592, GRK 1071, Forschergruppe FOR 832

Research Equipment

BD Biosciences Durchflusscytophometer LSR II

Leica konfokales Mikroskop TCS SP5

ABI Prism 3100 Genetic Analyzer u. Datenbank

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Research Focus
Comprehensive Phenotyping of transgenic mice and rats

Structure of the Institution

The lab occupies dedicated space within the newly build Franz-Penzoldt-Centre (FPZ) in Erlangen, which compromises in a central animal facility and corresponding lab space. Presently a small animal-imaging centre is additional build and small animal PET is already running. In the lab we have established molecular biology equipment including quantitative real time PCR machine, histology lab, cell culture lab, various microscopes including centrifuges, incubators etc; a dedicated rat and mouse behaviour floor combining space for automated and classical behavioural equipment is available. Automated home-cage-phenotyping systems (TSE-Phenomaster, NewBehavior-IntelliCage) run since very recently.

Research

Comprehensive Phenotyping of transgenic mice and rats

The use of transgenic animal models is central for modern biomedical research. Advances in transgenic technology nowadays more readily allow bridging the gap from genes to physiology and behaviour. The human, rat and mouse genome projects, coupled with an impressive array of molecular genetic technologies to manipulate expression of individual genes within an organism, have provided unprecedented opportunities for investigating the influence of genes on all systems within an organism. Consequently, the field of comprehensive phenotyping rapidly evolves and bridges a "post-genomic-gap" between genomics and phenomics. Due to these developments in the field, scientists are frequently challenged by the task of detecting discrete differences in mice and rats. The Franz-Penzoldt-Centre provides all prerequisites not only for genetic manipulations but also for comprehensive phenotyping of transgenic models for human diseases.
Within several European projects and collaborations, the research group at the Section for Experimental Therapy characterizes and use transgenic models of neurological diseases, which are world wide unique.
Neurodegenerative disorders including Alzheimer´s disease, Parkinson´s disease, as well as the polyglutamine disease such Huntington´s disease and Spinocerebellar ataxias can neither be cured nor treated in a satisfactory way. Transgenic rodent models are needed to more rapidly study pathogenesis and therapeutic approach. Our group presently characterizes rat and mouse models of HD, SCA, PD, and AD.

Teaching

Seminars contribute to the curricula in clinical and experimental biomedicine including anatomy, pharmacology, reproductive biology, and laboratory animals sciences. We employe modern educational technologies in several seminars and practical courses, which also have repeatedly been evaluated. The seminars are part of the B.Sc./M.Sc. of Molecular Medicine at Friedrich-Alexander University Erlangen-Nürnberg and integrated in postgraduate research programs.

Selected Publications

von Hoersten S, Schmitt I, Nguyen HP, Holzmann C, Schmidt T, Walther T, Bader M, Pabst R, Kobbe P, Krotova J, Stiller D, Kask A, Vaarmann A, Rathke-Hartlieb S, Schulz JB, Grasshoff U, Bauer I, Vieira-Saecker AM, Paul M, Jones L, Lindenberg KS, Landwehrmeyer B, Bauer A, Li XJ, Riess O (2003) Transgenic rat model of Huntington's disease. Hum Mol Genet, 12: 617-24

Nguyen HP, Kobbe P, Rahne H, Woerpel T, Jaeger B, Stephan M, Pabst R, Holzmann C, Riess O, Korr H, Kántor O, Petrasch-Parwez E, Wetzel R, Osmand A, von Hoersten S (2006) Behavioral abnormalities precede neuropathological markers in rats transgenic for Huntington's disease. Hum Mol Genet, 15: 3177-94

Bode FJ, Stephan M, Suhling H, Pabst R, Straub RH, Raber KA, Bonin M, Nguyen HP, Riess O, Bauer A, Sjoberg C, Petersén A, von Hoersten S (2008) Sex differences in a transgenic rat model of Huntington's disease: decreased 17beta-estradiol levels correlate with reduced numbers of DARPP32+ neurons in males. Hum Mol Genet, 17: 2595-609

Forssmann U, Stoetzer C, Stephan M, Kruschinski C, Skripuletz T, Schade J, Schmiedl A, Pabst R, Wagner L, Hoffmann T, Kehlen A, Escher SE, Forssmann WG, Elsner J, von Hoersten S (2008) Inhibition of CD26/dipeptidyl peptidase IV enhances CCL11/eotaxin-mediated recruitment of eosinophils *in vivo*. J Immunol, 181: 1120-7

Kruschinski C, Skripuletz T, Bedoui S, Raber K, Straub RH, Hoffmann T, Grote K, Jacobs R, Stephan M, Pabst R, von Hoersten S (2008) Postnatal life events affect the severity of asthmatic airway inflammation in the adult rat. J Immunol, 180: 3919-25

Frerker N, Raber K, Bode F, Skripuletz T, Nave H, Klemann C, Pabst R, Stephan M, Schade J, Brabant G, Wedekind D, Jacobs R, Joerns A, Forssmann U, Straub RH, Johannes S, Hoffmann T, Wagner L, Demuth HU, von Hoersten S (2009) Phenotyping of congenic dipeptidyl peptidase 4 (DP4) deficient Dark Agouti (DA) rats suggests involvement of DP4 in neuro-, endocrine, and immune functions. Clin Chem Lab Med, 47: 275-87

International Cooperation

Bertrand Tavitian, EU-Projekt "RatStream", Orsay, France

Prof. A. van der Linden, Bio Imaging Lab, Universitaet Antwerpen, Belgium

Prof. Hans-Peter Lipp, Anatomisches Institut, ETH Zuerich, Switzerland

Alexander P. Osmand, Ph.D., Research Centre – Graduate School of Medicine, Universitaet Tennessee, Knoxville, USA

Takashi Yamamura MD, PhD, Department of Immunology, National Institute of Neuroscience, Tokio, Japan

Research Equipment

TSE Systems GmbH PhenoMaster

New Behavior AG IntelliCage

Franz-Penzoldt-Centre entrance

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Chair of Pharmacology and Toxicology

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Research Focus
- Rhythm generation in the sinoatrial node
- HCN-channels in nociceptors and other neurons
- Immunological mechanisms in inflammatory liver and kidney injury
- Pharmacological imaging and image analysis

Structure of the Institution

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 form together 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 heart, brain and dorsal root ganglions, immunological mechanisms in liver injury and functional MR-Imaging. These areas are explored by combining methods from molecular biology, mouse genetics, electrophysiology, immunology and whole-animal studies. Research is supported by various grants from the DFG, EU and BMBF. In 2008 Prof. Gisa Tiegs left the institute to take over a position as director of the unit for experimental immunology and hepatology at the University Medical Centre Hamburg-Eppendorf.

Research

Rhythm generation in the sinoatrial node
Project manager: J. Stieber, S. Herrmann, A. Ludwig
The role of various ion channels for the generation of rhythmic cardiac activity is studied. One focus is the function of HCN pacemaker channels. These channels underly the If current and are thought to be essential for the generation of action potentials in the sinoatrial node. Since global deletion of HCN4-channels turned out to be embryonic lethal, we now deleted HCN4 selectively in the heart. If was severly reduced leading to the disturbed generation of action potenials and sinus pauses (Fig.). In contrast to earlier assumptions we found that HCN4 is not required for the sympathetic upregulation of heart rate. We currently attempt the complete deletion of sinoatrial If by generating double (HCN2/4) and triple (HCN1/2/4) knockout mice.
In addition, we generated the mouse line HCN4-KiT by "knock-in" of a Cre recombinase into the HCN4 locus. By using this line we are able to delete any gene selectively in the sinoatrial and atrioventricular node in a temporally controlled manner (Fig.). The line is currently used to analyse the exact mechanisms of action potenial generation in the cardiac conduction system. We focus on the physiological role of voltage-gated calcium channels and ryanodine-receptors.
Another project deals with the generation of arrhythmias in the hypertrophied heart. It was proposed that increased activtity and upregulation of ventricular HCN channels contributes to arrhythmogenesis. We study this hypothesis by induction of cardiac hypertrophy in HCN deficient mice.

HCN-channels in nociceptors and other neurons
Project manager: S. Herrmann, A. Ludwig
Various ion channels are involved in the generation and transmission of painful stimuli. Several reports suggest that HCN channels may play an important role in neuropathic and inflammatory pain. We found in earlier work that HCN1 and HCN2 are strongly expressed in dorsal root ganglions. We now study the exact role of these isoforms by generation of nociceptor-specific deletion mutants of HCN1 and HCN2. We also generated a brain-specific deletion of HCN4. In thalamocortical neurons of these mice, Ih was reduced by about 50 %. Contrary to expectations, brain specific HCN4-KOs do not show absence epilepsy, but a resistance towards seizures provoked by GABAA antagonists. In addition we could show that HCN4 is involved in the control of motor function during demanding motor tasks.

Immunological mechanisms in inflammatory liver and kidney injury
Project manager: G. Tiegs, G. Sass
The group addresses immunological mechanisms and signal transduction pathways in inflammatory liver and kidney disease. Based on TNFα- and TNFα-receptor signals which induce apoptosis but also cell proliferation, liver regeneration and the expression of "survival factors", the group worked on the identification of cytoprotective liver proteins. These proteins including heme oxygenase-1 exert mostly anti-apoptotic effects and are important for the protection of organ function but can also promote tumor growth. The RNAi-technology for the knockdown of genes *in vitro* and *in vivo* was established and used to downregulate the expression of pro- and antiapoptotic proteins.
Another research area focused on the mechanisms guiding the differentiation of adaptive tolerogenic T cells (Tregs and NKT cells) which can induce immune tolerance in the liver.
The group also studied interactions between immune and nervous system in animal models of hepatitis and nephritis. Based on the immunological mechanisms involved and the modulation of these mechanisms by neuropeptides and neurotransmitters new approaches for immunotherapy were developed.

Pharmacological imaging and image analysis
Project manager: A. Hess
The group uses non-invasive magnetic resonance tomography to study plastic nociceptive processes in the central nervous system of rodents. Further details can be found in the report of the Doerenkamp-Foundation professorship. In addition, various topics ranging from cardiology to lipid metabolism, imaging of vessels and in- vivo-tracing of marked cells are analysed in different cooperations (IZKF, DFG FG 661 Praeklinische Bildgebung, DFG KFG Postoperativer Schmerz). The combination of non-invasive MR imaging with the delineation of soft-tissue contrasts and state-of-the art image analysis proves to be highly effective and minimizes animal stress.

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, seminars and laboratory internships.

Selected Publications

Erhardt A, Biburger M, Papadopoulos T, Tiegs G (2007) IL-10, regulatory T cells, and Kupffer cells mediate tolerance in concanavalin A-induced liver injury in mice. Hepatology, 45: 475-85

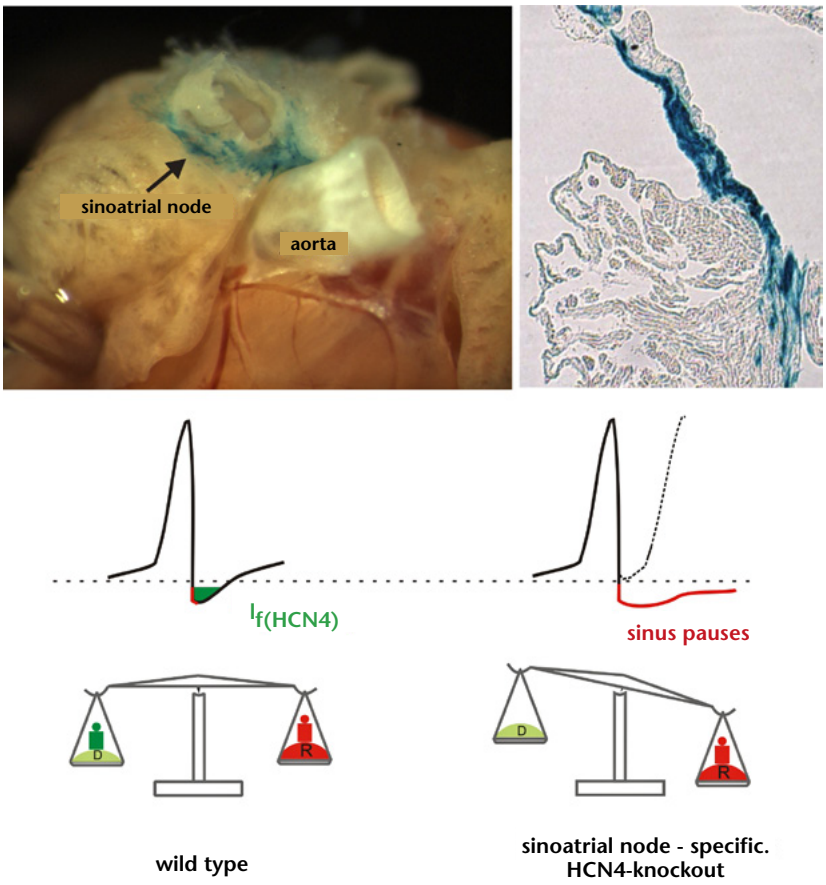
Herrmann S, Stieber J, Stoeckl G, Hofmann F, Ludwig A (2007) HCN4 provides a ‚depolarization reserve' and is not required for heart rate acceleration in mice. EMBO J, 26: 4423-32

David R, Brenner C, Stieber J, Schwarz F, Brunner S, Vollmer M, Mentele E, Mueller-Hoecker J, Kitajima S, Lickert H, Rupp R, Franz WM (2008) MesP1 drives vertebrate cardiovascular differentiation through Dkk-1-mediated blockade of Wnt-signalling. Nat Cell Biol, 10: 338-45

Hoesl E, Stieber J, Herrmann S, Feil S, Tybl E, Hofmann F, Feil R, Ludwig A (2008) Tamoxifen-inducible gene deletion in the cardiac conduction system. J Mol Cell Cardiol, 45: 62-9

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

Ludwig A, Herrmann S, Hoesl E, Stieber J (2008) Mouse models for studying pacemaker channel function and sinus node arrhythmia. Prog Biophys Mol Biol, 98: 179-85



Temporally controlled gene deletion in the sinoatrial node
Top, A target gene is deleted selectively in the sinoatrial node after administration of tamoxifen to HCN4-KiT mice. Blue staining indicates successful recombination (left, whole-mount; right, section). Middle, Lack of HCN4 channels in the sinoatrial node results in disturbed action potential generation and sinus pauses. Bottom, Diagram of proposed mechanism. HCN4-deficient animals have difficulties counter-balancing hyperpolarizing currents.

International Cooperation

Prof. Kenneth Chien, Harvard Medical School, Boston, USA

Prof. L. Cervetto, Dipartimento di Scienze Fisiologiche, Università di Pisa, Italy

Dr. Ming Lei, Cardiovascular Research Group, University of Manchester, Great Britain

G. Fishman, MD, Division of Cardiology, NYU Department of Medicine, New York, USA

Prof. Jeffrey Holt, Department of Neuroscience, University of Virginia, Charlottesville, USA

Meetings and International Training Courses

01.08.2008: DFG Forschergruppe 923 – Molecular Dissection of Cardiovascular Functions, Erlangen

Research Equipment

Bruker 4,7 Tesla Kleintier-MRT

Zeiss Konfokales Laserscanning-Mikroskop LSM 5

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Research Focus

- Molecular characterization of drug transporters
- Expression and function of uptake transporters in gastrointestinal tract
- Pharmacogenetics of cardiovascular drugs
- Molecular and clinical characterisation of therapeutic targets in the L-arginine-NO-nitrate pathway

Structure of the Institution

The Chair of Clinical Pharmacology and Clinical Toxicology forms 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.
35 persons are working at the Chair with 10 of them being funded by extramural sources. In July 2008 a Professor of Clinical Pharmacology (W2) was appointed. Research is conducted by 6 scientists with 4 of them being specialists in clinical pharmacology, 10 MD or PhD students and 10 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 University Hospital and for external physicians.

The following topics, which are funded e.g. by the German Research Council (DFG) and the German Cancer Aid, are in the focus of our studies: uptake and efflux transporters for drugs, genetic determinants of drug effects (pharmacogenomics), drug metabolism (cytochrome P450 enzymes), drug uptake in tumors, cardiovascular pharmacology and risk factors, alterations of the L-arginine-NO-metabolism.

Research

Molecular characterization of drug transporters

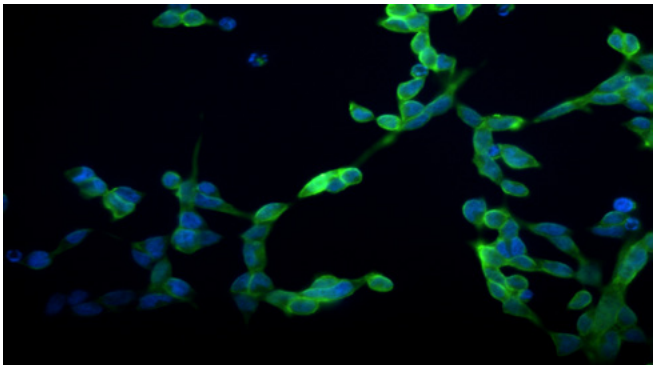
Project manager: J. Koenig, M. F. Fromm
Transporter proteins located in distinct plasma membrane domains are important for uptake, distribution and excretion of drugs and drug metabolites. Therefore, modulation of transport function may result in adverse drug reactions (ADR). Two molecular mechanisms can account for such modulations of transport function. First, variations in transporter genes (polymorphisms) may result in mutated transporter proteins with altered transport kinetics. Second, 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 are in the focus of our studies.
Organic Anion Transporting Polypeptide 1B1 (OATP1B1) is an important uptake transporter located in the basolateral hepatocyte membrane mediating the uptake of several endogenous compounds and drugs from the portal venous blood into the liver. In a cooperation with the University of Greifswald we could demonstrate that the cholesterol-lowering drug ezetimibe inhibited OATP1B1-mediated uptake and that the metabolite ezetimibe-glucuronide is a substrate of this transporter. Furthermore, we have demonstrated that a frequent polymorphism of the OATP1B1 protein (variant OATP1B1*5) is associated with reduced uptake rates for ezetimibe-glucuronide compared to the wild type protein. These results are in agreement with results from a clinical study conducted in parallel.
OATP1B1, together with the OATP family members OATP1B3 and OATP2B1 that are also expressed in human hepatocytes were in the focus of studies investigating transporter-mediated drug-drug interactions. First, we could demonstrate that macrolides inhibit OATP1B1- and OATP1B3-mediated pravastatin uptake. *In vivo*, this reduced hepatic uptake may lead to elevated pravastatin plasma concentrations with an increased risk of adverse drug reactions. A second study showed that frequently prescribed oral antidiabetic drugs inhibit OATP-mediated pravastatin uptake.

Expression and function of uptake transporters in gastrointestinal tract

Project manager: H. Glaeser, M. F. Fromm
The knowledge on the importance of OATP uptake transporters for drug transport, physiology and pathophysiology in the human gastrointestinal tract is still limited. Therefore, studies regarding the expression and function of OATPs in human stomach and intestine were performed. In collaboration with the University of Kentucky, (Lexington, KN, USA), the University of Western Ontario (London, Ontario, Canada) and the Vanderbilt University (Nashville, TN, USA; Prof. W. Lee und Prof. R. B. Kim) the expression of the OATP1B3 in multiple colon carcinoma samples was detected. Moreover, OATP1B3 mediated apoptosis resistance in several colon carcinoma cell lines after treatment with the antineoplastic agents oxaliplatin and camptothecin.
A further member of the human OATP-family is the prostaglandin transporter OATP2A1. The transport of prostaglandins from the extracellular space to the cytosol by OATP2A1 contributes to the termination of prostaglandin effects. In collaboration with the Institute of Pathology (Prof. K. U. Amann, Dr. T. Rau) it was possible to show the localization of OAT2A1 in parietal cells and deep glands of corpus and antrum of human stomach, respectively. Furthermore, using OATP2A1-overexpressing cell lines we were able to demonstrate that NSAIDs (non steroidal anti-inflammatory drugs) can stimulate or inhibit the function of OATP2A1. Such functional modifications may contribute to NSAID-induced side effects such as ulcerations or bleeding in the human gastric mucosa.

Pharmacogenetics of cardiovascular drugs

Project manager: O. Zolk, M.F. Fromm
Cardiovascular diseases are the most common, and cardiovascular drugs belong to the most frequently prescribed drugs. Their use contributes to reduced mortality from cardiovascular events, for example dual antiplatelet inhibition with ASS and clopidogrel significantly reduces the risk of fatal coronary stent thrombosis after PCI. However, there are marked differences in



Expression of the human uptake transporter OCT2 (green) in HEK293 cells

the treatment effects between individual patients with treatment failure or enhanced toxicity occurring in some patients. In this project genetic variations in genes involved in drug transport or metabolism that cause interindividual differences in response to cardiovascular drugs are investigated. In a collaborative project with the Heart Centre Bad Krozingen the association of polymorphisms in drug transporters and cytochrome P450 enzymes with the inhibitory effect of clopidogrel on platelet aggregation was investigated.

Another study focused on the impact of gender and genetic differences in genes involved in transport and metabolism of drugs on the pharmacokinetics of the diuretic torasemide. Moreover, in a collaborative project with the Department of Medicine 4 – Nephrology and Hypertensiology (University Hospital Erlangen) we investigate a potential association of polymorphisms in catecholamine transporter genes with the diagnosis of essential hypertension.

Molecular and clinical characterisation 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 interventions. Presently we study the regulation of the L-arginine-NO-nitrate pathway by endogenously formed compounds such as ADMA and L-NMMA and the metabolic fate of these compounds. For *in vitro* and *in vivo* investigations new isotope- and mass spectrometry-based methods are developed. In a DFG funded project and in cooperation with colleagues at the Department of Medicine 4 – Nephrology and Hypertensiology (University Hospital Erlangen) we investigate the biologic effects of disturbed methylarginine metabolism on vascular function in animal models and experimental studies. The experimental investigations are complemented by clinical and population-based studies performed in cooperation with the Department of Medicine 2 – Cardiology and Angiology and international partners at the Framingham Heart Study (USA) and at the Institute of Bio-Medicine of the National Research Council (Italy). With these partners we presently investigate causes and long term clinical effects of elevated plasma concentrations of ADMA and related substances.

In further projects we study genetic and biochemical/pharmacological causes of treatment failure in cardiovascular medicine, with a special focus on the prevention of thromboembolic events. Related health services research projects are directed at real life problems in translating knowledge and implementing guidelines into clinical practice.

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

Zolk O, Jacobi J, Pahl A, Fromm MF, Schmieder RE (2007) MDR1 genotype-dependent regulation of the aldosterone system in humans. Pharmacogenet Genomics, 17: 137-44

Bachmakov I, Glaeser H, Fromm MF, Koenig J (2008) Interaction of oral antidiabetic drugs with hepatic uptake transporters: focus on organic anion transporting polypeptides and organic cation transporter 1. Diabetes, 57: 1463-9

Gradhand U, Lang T, Schaeffeler E, Glaeser H, Tegude H, Klein K, Fritz P, Jedlitschky G, Kroemer HK, Bachmakov I, Anwald B, Kerb R, Zanger UM, Eichelbaum M, Schwab M, Fromm MF (2008) Variability in human hepatic MRP4 expression: influence of cholestasis and genotype. Pharmacogenomics J, 8: 42-52

Lee W, Belkhiri A, Lockhart AC, Merchant N, Glaeser H, Harris EI, Washington MK, Brunt EM, Zaika A, Kim RB, El-Rifai W (2008) Overexpression of OATP1B3 confers apoptotic resistance in colon cancer. Cancer Res, 68: 10315-23

Trenk D, Hochholzer W, Fromm MF, Chialda LE, Pahl A, Valina CM, Stratz C, Schmiebusch P, Bestehorn HP, Buettner HJ, Neumann FJ (2008) Cytochrome P450 2C19 681G>A polymorphism and high on-clopidogrel platelet reactivity associated with adverse 1-year clinical outcome of elective percutaneous coronary intervention with drug-eluting or bare-metal stents. J Am Coll Cardiol, 51: 1925-34

Lieb W, Benndorf RA, Benjamin EJ, Sullivan LM, Maas R, Xanthakis V, Schwedhelm E, Aragam J, Schulze F, Boeger RH, Vasan RS (2009) Plasma asymmetric dimethylarginine, L-arginine and left ventricular structure and function in a community-based sample. Atherosclerosis, 204: 282-7

International Cooperation

Prof. Carmine Zoccali, Renal Dialysis Transplantation and Hypertension Unit & Institute of Bio-Medicine of the National Research Council, Reggio Calabria, Italy

Prof. Ramachandran Vasan, Framingham Heart Study, USA

Prof. Jean-Luc Cracowski, INSERM Grenoble, France

Research Equipment

Applied Biosystems API 4000 MS/MS System Package

Zeiss LSM 5 Pascal

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Research Focus
- Analgesics and anti-rheumatics
- Non-invasive functional imaging
- Development of cell culture systems to detect new drugs

Structure of the Institution

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 31 March 2011. 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 4 post-doctoral and 6 doctoral collaborators.
The research goals of the Doerenkamp professorship are persued 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 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

Analgesics and anti-rheumatics

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 analysed 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, analysing concepts for tissue, toxicity sparing doses were developed.
The analysis of older drugs, including (aside of acetaminophen) metamizol (dipyrone), showed that dipyrone is overdosed under clinical conditions.
Recently, COX-inhibitors were shown to cause cardiac infarctions and accelerated artherosclerosis in certain patients. Using 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.

Non-invasive functional imaging

Non-invasive functional imaging employing magnet resonance tomography in rats and mice demonstrated that nociceptive inputs in experimental animals can be detected, localized and quantified despite the fact that the animals are in anaesthesia. Consequently, this approach allows for measuring antinociceptive effects, locating new pathways of pain processing in the brain of mammals and defining new targets for pain therapy, in particular for chronic pain. This approach has been applied successfully to rats and is presently also used in genetically modified strains of mice allowing to define the role of distinct pain mediators and their antagonists in nociception (figure).

Development of cell culture systems to detect new drugs

These projects lead to the funding of two large pieces of equipment, i.e. the total remodelling and modernisation of the existing animal MRT as well as the funding of a modern MRT-improved resolution.
Together with PD Dr. Pahl we tried to develop cell culture systems to detect new drugs, possibly useful in chronic obstructive pulmonary disease (COPD). The work lead to the employment of PD Dr. Pahl as head of a research group with Nycomed, Hamburg. Due to the change of employment of PD Dr. Pahl, this approach will not be persued further within the next years.
Finally, the chairholder was and still is engaged in many research and pharmaco-political activities. Some of the insights gained have resulted in essays related to health politics, science in Europe and animal protection (see also publications).

Teaching

The engagement of Prof. Brune as speaker at international conferences, his membership in several administrative bodies and advisory structures has led to many additional invitations to comment on timely 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 is to be on the homepage of the Department.

Selected Publications

Haeupl T, Burmester GR, Giannitsis E, Rohrlach T, Spanuth E, Parsch H, Brune K (2007) N-terminal prohormone brain natriuretic peptide: a biomarker for detecting cardiovascular risks in patients with rheumatoid arthritis or osteoarthritis? Ann Rheum Dis, 66: 838-9

Hinz B, Cheremina O, Bachmakov J, Renner B, Zolk O, Fromm MF, Brune K (2007) Dipyrone elicits substantial inhibition of peripheral cyclooxygenases in humans: new insights into the pharmacology of an old analgesic. FASEB J, 21: 2343-51

Puljic R, Benediktus E, Plater-Zyberk C, Baeuerle PA, Szelenyi S, Brune K, Pahl A (2007) Lipopolysaccharide-induced lung inflammation is inhibited by neutralization of GM-CSF. Eur J Pharmacol, 557: 230-5

Brune K, Katus HA, Moecks J, Spanuth E, Jaffe AS, Giannitsis E (2008) N-terminal pro-B-type natriuretic peptide concentrations predict the risk of cardiovascular adverse events from antiinflammatory drugs: a pilot trial. Clin Chem, 54: 1149-57

Hinz B, Cheremina O, Brune K (2008) Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. FASEB J, 22: 383-90

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

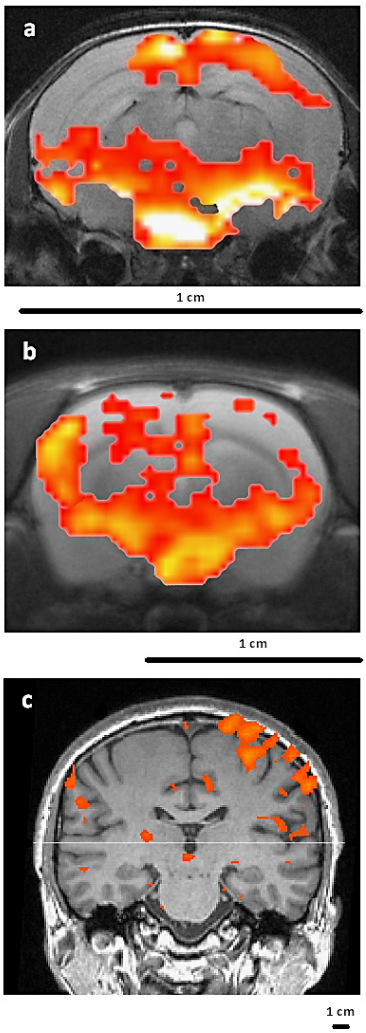

Fig.: Activation of the pain matrix of the mouse, rat and man following the application of a nociceptive stimulus to the skin
Despite the differences in size (comp. 1 cm), it is evident that similar brain structures are activated by the stimulus. The development of highly sensitive fMRI-technology is the basis of non-invasive pain research in rodents. The options of this technology are further enhanced by the use of genetic modifications of the mouse genome. a: mouse, b: rat, c: man

Institute of Human Genetics

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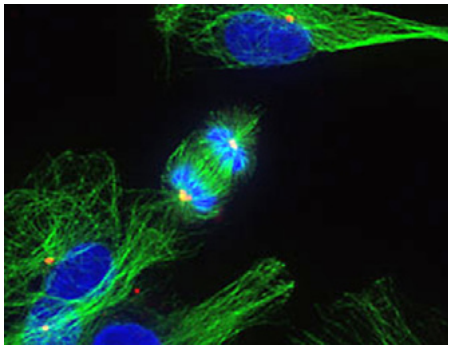
Research Focus
- Molecular basis of monogenic traits and genotype-phenotype correlation
- Genetics of complex diseases
- Developmental genetics

Structure of the Institution

The Institute is active in teaching, research and health care. At the end of 2008 a total of 64 persons were working at the Institute: 19 scientists (natural scientists and physicians), 13 PhD-students, 24 technical and administrative employees and 8 graduate students. 25 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 specialised cytogenetic and molecular genetics investigations. Research activities are organised in 5 research groups. Members of the Institute participate in various collaborative research groups (SFBs and "Forschergruppen"). The head of 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 Interdisciplinary Centre for Clinical Research (IZKF) at the Medical Faculty. In addition, he was elected in 2008 president of the German Society of Human Genetics (GfH). The Institute runs 2 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.

Research

Molecular basis of monogenic traits and genotype-phenotype correlation
Project manager: A. Reis, A. Rauch, M. Zenker
The main scientific focus of the institute is the elucidation of the molecular basis of inherited disease. Major approaches used include positional cloning strategies and the detection of copy number variations using molecular karyotyping. Using the latter strategy the group of Prof. Rauch recently identified the molecular cause of Pitt-Hopkins syndrome, a severe form of mental retardation with characteristic respiratory apnea. In the context of the BMBF project "rare diseases network: skeletal dysplasia (SKELNET)" the group also identified the molecular defect in MOPD II (microcephalic osteodysplastic primordial dwarfism type II). This disease is characterized by the most extreme form of short stature in man. Patients are viable but their final height ranges between 70 and 90 cm. Using linkage studies the group discovered biallelic loss-of-function mutations in the centrosomal pericentrin gene on chromosme 21 (figure) underlying this disorder. In addition, using homozygosity mapping they succeeded in collaboration with the group of Prof. Reis to identify mutations in the STRA6 gene underlying Mathew-Woods syndrome, a pleiotropic malformation syndrome with anophthalmia.
The group of PD Dr. M. Zenker mainly focuses on the molecular basis of the Johanson-Blizzard (JBS) and the Noonan syndromes. Previously the group had identified mutations in the UBR1 gene as the cause of JBS. In the context of a DFG-funded project they now investigated the cellular and systemic effects resulting from a loss of UBR1 enzyme activity. In addition, the group was able to identify SOS1 as the second most common gene affected in Noonan syndrome and was able to publish several findings on a genotype-phenotype correlation for this disease. Dr. Kraus and her group worked on the aetiology and pathogenesis of neuromuscular disorders using the mdf mouse as a model. During the report period the group identified mutations in the Scyl1 gene as the cause of this murine phenotype in collaboration with Prof. Bittner.



Cell division in a healthy human fibroblast cell line: the pericentrin protein, which is missing in MOPDI patients is marked in red, chromosomal material green in blue and spindle fibers, which are formed properly during anaphase, in green.

Genetics of complex diseases
Project manager: A. Reis
Complex and multifactorial diseases are caused by a combination of mostly unknown environmental and genetic factors. The group of Prof. André 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 funded within the Collaborative Research Centre (SFB) 539 (glaucoma and pseudoexfoliation syndrome) and the IZKF. In collaboration with partners from England and the Netherlands the group was able to demonstrate a significant association between an increased copy number of the β-defensin gene cluster on chromosome 8 and the risk to develop psoriasis. Moreover, the group performed several association studies for psoriatic arthrtitis in functional and positional candidate genes. For secondary glaucoma with pseudoexfoliation the group was able to replicate an association of common polymorphism in the LOXL1 gene (originally described in Scandinavian patients) also in German and Italian patients and to recognise it as predisposing to exfoliation syndrome rather than glaucoma. In collaboration with Prof. Schloetzer-Schrehardt (Department of Ophthalmology) the involvement of the LOXL1 gene product in disturbed fibrogenesis, the primary cause of the disease, could be demonstrated.

Developmental genetics
Project manager: A. Winterpacht
The group is interested in the molecular basis of developmental processes and their individual variability. This includes elucidation of regulatory networks of organogenesis and cell differentiation as well as the identification of variants in specific components of these networks. For

most of the projects the group works on mouse or chicken as model organisms. The projects comprise work on: 1. the skeletal system, which aims at the global and systematic identification and molecular characterisation of novel genes and gene networks involved and cartilage/ bone formation. In the context of this project UCMA, a novel secreted factor and highly specific marker of distal chondrocytes, could be identified, which probably plays an important role in early stages of chondrocyte differentiation. 2. the nervous system, where the group focuses on cognitive processes, which were investigated using the example of Wolf-Hirschhorn syndrome. In addition, in collaboration with the Departments of Anaesthesiology and Surgery the group worked on the identification of susceptibility genes for post-operative pain perception. This work is supported by the DFG in the context of the "Klinische Forschergruppe 130 (KFO 130)". 3. tumor development and progression, where the group investigated the novel gene SPOC1 (PHF13). Expression of SPOC1 in tumours is associated with survival time in patients with ovarian cancer. The group was able to show that the gene plays a role in germ cell development.

Teaching

The Institute is involved in curricular teachings at the medical school and in the diploma, bachelor- and master programmes in molecular medicine as well as biology and molecular and cellular biology, respectively. During the report period 17 diploma theses in biology and molecular medicine were finished at the institute. In addition doctoral theses in medical and natural sciences were supervised.

Selected Publications

Pasutto F, Sticht H, Hammersen G, Gillessen-Kaesbach G, Fitzpatrick DR, Nuernberg G, Brasch F, Schirmer-Zimmermann H, Tolmie JL, Chitayat D, Houge G, Fernández-Martínez L, Keating S, Mortier G, Hennekam RC, von der Wense A, Slavotinek A, Meinecke P, Bitoun P, Becker C, Nuernberg P, Reis A, Rauch A (2007) Mutations in STRA6 cause a broad spectrum of malformations including anophthalmia, congenital heart defects, diaphragmatic hernia, alveolar capillary dysplasia, lung hypoplasia, and mental retardation. Am J Hum Genet, 80: 550-60

Schmidt WM, Kraus C, Hoeger H, Hochmeister S, Obersdorfer F, Branka M, Bingemann S, Lassmann H, Mueller M, Macedo-Souza LI, Vainzof M, Zatz M, Reis A, Bittner RE (2007) Mutation in the Scyl1 gene encoding amino-terminal kinase-like protein causes a recessive form of spinocerebellar neurodegeneration. EMBO Rep, 8: 691-7

Zweier C, Peippo MM, Hoyer J, Sousa S, Bottani A, Clayton-Smith J, Reardon W, Saraiva J, Cabral A, Gohring I, Devriendt K, de Ravel T, Bijlsma EK, Hennekam RC, Orrico A, Cohen M, Dreweke A, Reis A, Nurnberg P, Rauch A (2007) Haploinsufficiency of TCF4 causes syndromal mental retardation with intermittent hyperventilation (Pitt-Hopkins syndrome). Am J Hum Genet, 80: 994-1001

Hollox EJ, Huffmeier U, Zeeuwen PL, Palla R, Lascorz J, Rodijk-Olthuis D, van de Kerkhof PC, Traupe H, de Jongh G, den Heijer M, Reis A, Armour JA, Schalkwijk J (2008) Psoriasis is associated with increased beta-defensin genomic copy number. Nat Genet, 40: 23-5

Rauch A, Thiel CT, Schindler D, Wick U, Crow YJ, Ekici AB, van Essen AJ, Goecke TO, Al-Gazali L, Chrzanowska KH, Zweier C, Brunner HG, Becker K, Curry CJ, Dallapiccola B, Devriendt K, Doerfler A, Kinning E, Megarbane A, Meinecke P, Semple RK, Spranger S, Toutain A, Trembath RC, Voss E, Wilson L, Hennekam R, de Zegher F, Doerr HG, Reis A (2008) Mutations in the pericentrin (PCNT) gene cause primordial dwarfism. Science, 319: 816-9

Tagariello A, Luther J, Streiter M, Didt-Koziel L, Wuelling M, Surmann-Schmitt C, Stock M, Adam N, Vortkamp A, Winterpacht A (2008) Ucma--A novel secreted factor represents a highly specific marker for distal chondrocytes. Matrix Biol, 27: 3-11

International Cooperation

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

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

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

Prof. Reginald Bittner, Centre of Anatomy and Cell Biology, Neuromuscular Research Department, Medical University of Vienna, Austria

Prof. Marco Tartaglia, Istituto Superiore di Sanità, Università La Sapienza, Rome, Italy

Meetings and International Training Courses

15.–17.06.2007: "Cardinal symptoms in differential diagnosis of syndromal disorders". 16. Symposium of the Arbeitsgemeinschaft Klinische Genetik in der Paediatrie, (Chairperson Prof. Anita Rauch), Kloster Banz, Arbeitsgemeinschaft Klinische Genetik in der Paediatrie

Research Equipment

Applied Biosystems DNA-Sequenzierautomat

Affymetrix Genomik-Chip-Plattform

Institute of Forensic Medicine

Chair of Forensic Medicine

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Research Focus

- Comparison of laser and mercury-arc lamp for the detection of body fluids on different substrates
- Impairment of driving skills after intravenous administration of propofol
- Study on the incorporation of drugs in hair – comparison between consumers and job-related exposition
- Development and validation of PCR-multiplex systems for forensic DNA analysis

Structure of the Institution

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 University. Beside responsibilities in the field of research and education official expertises are made for other medical facilities and by order of justice, 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 home 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

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.

Impairment of driving skills after intravenous administration of propofol
Project manager: S. Seidl
The severity and duration of cognitive performance capacity deficits after intravenous administration of propofol were determined using the validated psychological test procedure SKT (Syndrome Short Test), a simple reaction test and original driving license exam questions. The test battery was performed before, immediately after as well as 1 and 2 h after propofol administration in 23 persons. Immediately after propofol anaesthesia, 6 individuals had a slight performance loss and 4 subjects showed mild deficits, consistent with medium organic neuropsychologic disorder or dementia. The status of the subjects rapidly changed for the better and 2 h after propofol anaesthesia only one person (4%) showed slight deficits of memory and attention. Therefore it is suggested that patients refrain from any participation in road traffic for at least 2 h after propofol anaesthesia. Driving a car should not be admitted until an interval of 6 h has elapsed.

Study on the incorporation of drugs in hair – comparison between consumers and job-related exposition
Project manager: G. Eckardt
Hair analysis is a well established procedure for a variety of problems, such as retrospective estimation of criminal responsibility, evidence of abstinence but also for the evidence of handling of drugs. However, the significance of hair analysis results, especially for the differentiation between past drug abuse and external contamination remains controversal.
All in all 24 hair samples of persons with job-related contact to drugs were collected and analyzed parallel to hair samples of drug consumers.
All samples were decontaminated and the decontamination solution as well as the crushed hair material were analyzed with gas chromatography/ mass spectroscopy (GC-MS) for residues of cannabinoids, amphetamines, benzoylecgonin and opiates. The ratios between the absolute amount of substance in the hair sample itself and in the decontamination solution were compared. An external contamination leads usually to lower concentrations in the hair, but the applied methods did not allow a definite differentiation between external contamination and drug consume. Although an estimation by trend could be possible.

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 offences.
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 should be expanded by five more STR-loci ("European recommended loci"). Furthermore, population data of the new markers should be surveyed.

Beside autosomal polymorphisms gonosomal localized systems play an upcoming role in the forensic diagnostic. 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. By that reason different analysis-systems for these markers were established.

Teaching

The Institute of Forensic Medicine performs the education given by the 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.

Selective preparation of spermatozoa by laser-catapulting

Selected Publications

Hausmann R, Seidl S, Betz P (2007) Hypoxic changes in Purkinje cells of the human cerebellum. Int J Legal Med, 121: 175-83

Lederer T, Braunschweiger G (2007) Commentary on: Coble MD, Butler JM. Characterization of new miniSTR loci to aid analysis of degraded DNA. J Forensic Sci 2005;50:43-53. J Forensic Sci, 52: 493; author reply 494

Peters AS, Schwarze B, Tomandl B, Probst-Cousin S, Lang CJ, Hilz MJ (2007) Bilateral striatal hyperintensities on diffusion weighted MRI in acute methanol poisoning. Eur J Neurol, 14: e1-2

Seidl S, Hausmann R, Neisser J, Janisch HD, Betz P (2007) Severity and duration of mental deficiency symptoms after intravenous administration of propofol. Int J Legal Med, 121: 281-5

Lederer T, Braunschweiger G, Dunkelmann B, Betz P (2008) Characterization of two unusual allele variants at the STR locus ACTBP2 (SE33). Forensic Sci Med Pathol, 4: 164-6

Seidl S, Hausmann R, Betz P (2008) Comparison of laser and mercury-arc lamp for the detection of body fluids on different substrates. Int J Legal Med, 122: 241-4

Research Equipment

Applied Biosystems DNA Sequencer

Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine

Chair of Occupational and Social Medicine

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Research Focus

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

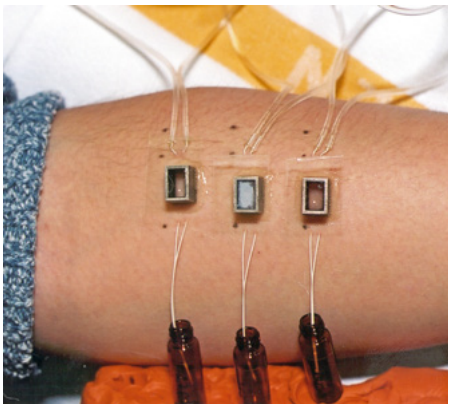
Structure of the Institution

The Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine belongs to the clinical theoretical institutes. The institute has 37 employees (12 of them are financed by third-party funds). Research is carried out by 11 PhD scientist, 6 PhD students and 12 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 pre medical 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", "Analysis in biological materials" and "Skin absorption" 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 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

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 specificy, sensitivity and toxicokinetic behaviour of the different parameters.
An important pre-requisite for sensitive and specific biomonitoring is the use of very sensitive and molecular-structural distinguishing analyzing techniques. The institute therefore possesses very good technical equipment which is modernized on a regular basis. Gas chromatographic techniques as well as high performance liquid chromatographic systems belong to the equipment which are particularly connected to one-dimensional and multiple-dimensional mass spectrometry (GC-MS/MS and LC-MS/MS) and to modern analytical techniques for the determination of metals in body fluids (GF-AAS und ICP/MS).

Dermatoxicology
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 focussing 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 European Union. Furthermore one work group of the institute deals with 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 labelling hazardous substances which can penetrate via skin. The DFG work group headed by Dipl.-Ing. K. H. Schaller is responsible for labelling 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.



In vivo studies of dermal penetration of hazardous substances by microdialysis

Work related health research
Field studies, taking into account the workplace conditions, aiming 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 weld-

ing techniques used in the aluminium processing industry, or the replacement of classical solvents by alternative solvents with a higher risk of skin irritation of the exposed employees are named. Furthermore allergically mediated diseases at the workplace, with clearly improved hygienic conditions, are still a problem. Therefore an important topic for the institute is the assessment of exposure and effect of toxic, mutagenous and sensitizing working materials in Germany and abroad. Many field studies qualitatively assess the uptake which can be absorbed percutaneously by taking into account the workplace conditions. These studies are often carried by the 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, plasticizer in pharmaceuticals or toys, aromatic amines in fabric. These studies are often carried by local authorities, the Bavarian State Ministry of the Environment and Public Health and the German Federal Environment Agency.

Quality assurance of Biomonitoring methods

On behalf of the German Association for Occupational and Environmental Medicine (DGAUM) the institute currently organizes external quality assessment schemes worldwide for the evaluation of occupational and environmental biomarkers. The 42nd round robin test of G-EQUAS was finished within the report period. At the moment G-EQUAS comprises 122 analysis parameters; 150 to 200 laboratories worldwide (2/3 international) take part in G-EQUAS every six months.

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 be preserved after an initiation phase 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.

Teaching

Professor Drexler is the dean of the 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

Broding HC, Schettgen T, Göen T, Angerer J, Drexler H (2007) Development and verification of a toxicokinetic model of polychlorinated biphenyl elimination in persons working in a contaminated building. Chemosphere, 68: 1427-34

Korinth G, Weiss T, Penkert S, Schaller KH, Angerer J, Drexler H (2007) Percutaneous absorption of aromatic amines in rubber industry workers: impact of impaired skin and skin barrier creams. Occup Environ Med, 64: 366-72

Hartmann EC, Boettcher MI, Schettgen T, Fromme H, Drexler H, Angerer J (2008) Hemoglobin adducts and mercapturic acid excretion of acrylamide and glycidamide in one study population. J Agric Food Chem, 56: 6061-8

Kuetting B, Uter W, Drexler H (2008) The association between self-reported acrylamide intake and hemoglobin adducts as biomarkers of exposure. Cancer Causes Control, 19: 273-81

Schmid K, Merkl K, Hiddemann-Koca K, Drexler H (2008) Obligatory occupational health check increases vaccination rates among medical students. J Hosp Infect, 70: 71-5

Wellner T, Lueersen L, Schaller KH, Angerer J, Drexler H, Korinth G (2008) Percutaneous absorption of aromatic amines - A contribution for human health risk assessment. Food Chem Toxicol, 46: 1960-8

International Cooperation

Nadine Fréry, Institut de Veille Sanitaire, Franz. Gesundheitsbehoerde, 94415 St. Maurice, France

ACGIH – American Conference of Governmental Industrial Hygienists, Cincinnati, USA

Patrick J. Parsons, DOH, Department of Health, Albany, New York, USA

Biomonitoring Team, Finnish Institute of Occupational Health, Helsiniki, Finland

Alain LeBlanc, Institut national de santé publique du Québec, Centre de toxicologie, INSPQ, Québec, Canada

Dr. S. Kezic, Coronel Institute of Occupational Health, Universitaet Amsterdam, Academic Medical Centre, Amsterdam, Netherlands

Larry Needham, CDC, Atlanta, USA

Research Equipment

Varian GC-MS/MS-System 2100

Sciex API 2000 LC-MS/MS-System

Institute of Medical Physics

Chair of Medical Physics

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

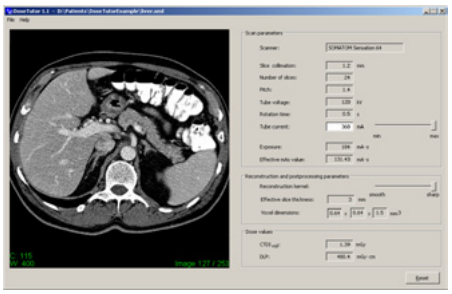
The C-arm system allows almost unlimited freedom of movements. (Picture: Kurt Fuchs, IMP, Erlangen)

Structure of the Institution

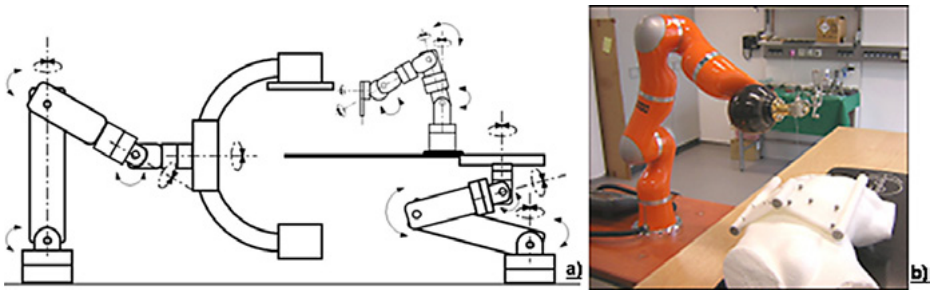
In addition to the chair and full professorship of Medical Physics, the Institute of Medical Physics comprises the professorship of Medical Imaging (held by Prof. Dr. M. Kachelrieß since 07/2005) and the professorship of Medical Optics (held by Prof. Dr. A. Langenbucher until 09/2009).
In all the Institute employs 62 persons, whereof 43 are financed by third-party funds. The researchers, 35 of them are 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: medical imaging, medical image processing, computer assisted surgery, medical optics, radiation therapy, dosimetry and radiation protection, osteoporosis research.
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, the Bavarian Research Foundation and cooperations with industrial partners reach an amount of about one million Euros per year.

Research

Development and application of imaging procedures in medical diagnosis and image-guided therapy
The focus of the 30 ongoing research projects is on 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 leading position here. Four selected research projects are described in the following:
From July 2005 to July 2010 the German Federal Ministry of Research and Technology supports a major project to minimally invasive surgery methods in orthopedics. More than one million patients have to undergo orthopedic surgery every year. The main objective of orthoMIT is to develop an integrated platform for the "gentle" operative 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) participates in the orthoMIT project by working on the implementation of 3D CT imaging in minimally invasive interventions. The aim of this subproject is to provide high image quality with significantly improved spatial resolution and an acceptable radiation exposure in the operating room. The main focus lies on the implementation of artificial joints and surgical procedures at the spine.
In January 2008 the new unit Artis zeego (Siemens Healthcare) was installed, a device equipped with a worldwide unique robot arm that allows with only one device all x-ray examinations from roentgenoscopy to CT-like scanning. The combination of a C-arm with a powerful industrial robot provides the treating physician with almost unlimited freedom of movement, even rotating around the patient. The application of the new system enables working on improvement of image quality in principle and also new developments in the areas of interventional radiology and intra operative medical imaging. The acquisition of the unit was supported with about 1.5 million Euros in the framework of the orthoMIT main project.
From 01/2005 to 12/2007 the European Union supported a major project to investigate the safety and efficacy of computed tomography (CT) in the 6th Research Framework. The technological advances of the previous years have enormously improved the performance of computed tomography and strengthened its role as an important tool for non-invasive diagnostics. All body regions or organs can be scanned three-dimensionally on modern CT scanners in only a few seconds and in exceptional quality. However, many times it is not the high performance that is in the focus of discussions but the assumed high patient dose in CT examinations. The main objective of the whole project in which 10 european institutes participated was to provide recommendations for the use of CT to optimize the examination procedure and, in particular, to reduce dose. At the institute the focus of the research lay on developing methods for optimization and dose efficiency of CT and on validating and providing the results for clinical use in cooperation with the industry. The introduction of an automatic exposure control (AEC) for CT allows to determine the minimal dose automatically. Taking into account that children are more sensitive to higher radiation exposure than adults it is particularly necessary to adapt the scan parameters conscientiously to the relative body size in examinations with children. DoseTutor, a software program, enables the user to demonstrate the relation between scan parameters, image quality and patient dose without having to carry out several CT scans with different scan parameter settings.
In the 7th Research Framework the European Union supports with 2.05 million Euros from 01/2008 to 06/2010 the research on dedicated CT of the female breast (project director and speaker: W. A. Kalender).
Three academic partners representing internationally renowned and well established centres for modern radiological imaging at the universities of Erlangen-Nürnberg, Leuven and Rotterdam and one industrial partner, VAMP GmbH from Erlangen, are working together on the development of a special device for scanning of 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 diag-



Screenshot of DoseTutor (VAMP GmbH, Erlangen). A PC program to simulate CT scans with a lower dose or another reconstruction kernel. When changing one of these parameters, the program interactively shows the effect on the dose and image quality.



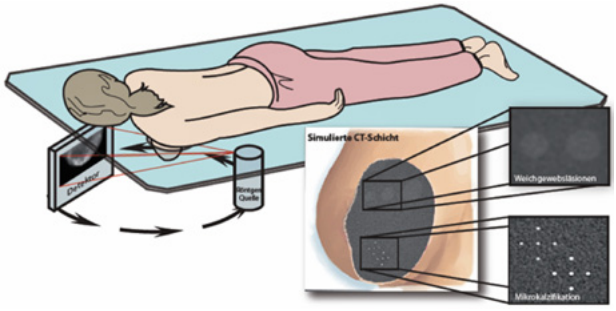
a) Concept of using robots in medical imaging and surgical interventions. [Kalender, Kyriakou 2007]
b) Implementation of a KUKA light robot in experiment in a navigation and robot assisted intervention at the IMP

nosis 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 is called a too small sensitivity – respectively there are findings suspected although there aren't any – in this case this is called a too small specificity. To improve image quality the significant advantages of 3D imaging for the examination of the female breast is generally acknowledged. In eight different subprojects the potential of a dedicated CT scanner for the female breast is to be scrutinized and its performance features are to be characterized. Besides the specification of a dedicated breast CT scanner another aim is to evaluate the role of the different competing methods to diagnose breast cancer. The main objective is above all to make breast tumors detectable as early as possible. From this point of view the different alternative imaging procedures are to be explored and evaluated.

Since 10/2006 the German Research Foundation is 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.

Teaching

The institute participates in the education of the medical students in the area of medical imaging by offering lectures and seminars. The course on the basics of medical physics including a tutorial gives students of natural science 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 thesis of different fields and of doctoral studies to graduate as Dr. rer. biol. hum.



In dedicated breast CT a multitude of projection images from all directions on a circular path are taken with low x-ray dose. Calculations indicate 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 overlaying tissue in mammography. Fig.: Inst. f. Med. Physik

Selected Publications

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

Deak P, van Straten M, Shrimpton PC, Zankl M, Kalender WA (2008) Validation of a Monte Carlo tool for patient-specific dose simulations in multi-slice computed tomography. Eur Radiol, 18: 759-72

Ertel D, Kroeber E, Kyriakou Y, Langner O, Kalender WA (2008) Modulation transfer function-based assessment of temporal resolution: validation for single- and dual-source CT. Radiology, 248: 1013-7

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Lapp RM, Kyriakou Y, Kachelriess M, Wilharm S, Kalender WA (2008) Interactively variable isotropic resolution in computed tomography. Phys Med Biol, 53: 2693-713

Vollmar SV, Kalender WA (2008) Reduction of dose to the female breast in thoracic CT: a comparison of standard-protocol, bismuth-shielded, partial and tube-current-modulated CT examinations. Eur Radiol, 18: 1674-82

International Cooperation

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

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

Prof. J.M. Boone, Dep. of Radiology, UC Davis Medical Centre, Sacramento, CA, USA

Dep. of Ophthalmology, Semmelweis University, Budapest, Ungarn

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

Prof. Gabriel P. Krestin, Erasmus Medical Centre, Rotterdam, Netherlands

Dr. J. Geleijns, Medical Centre, Leiden University, Leiden, Netherlands

Dr. P. Shrimpton, Radiation Protection, Health Protection Agency, Chilton, United Kingdom

Prof. Dr. J. Damilakis, University Of Crete, Iraklion, Crete, Greece

Research Equipment

Siemens SOMATOM Definition Dual Source CT

Siemens MR-Scanner Magnetom Vision

VAMP GmbH In-vivo Mikro-CT-Scanner

Siemens C-Bogen-CT-Scanner Axiom Artis zeego

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Chair of Experimental Medicine I (Connective Tissue Research)

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Research Focus

- Structure, function and gene regulation of extracellular cartilage matrix proteins
- Molecular mechanisms of endochondral ossification in skeletal development
- Cell-matrix interactions in biomimetic titandioxide nanotubes

Structure of the Institution

The Chair of Experimental Medicine I is located in the Nikolaus-Fiebiger Centre of Molecular Medicine and is responsible together with the Chair of Experimental Medicine II for the organisation and administration of the Centre. In 2007-2008 about 15 persons were involved in research and teaching at the department Experimental Medicine I, among them 5 postdoctoral and senior scientists, 3 graduate students, 3 undergraduate students and 4 technicians. Half of the staff was financed through grants. Since October 2008 the department chair is advertised for reneweal.

Research

Cartilage cells (chondrocytes) have two rather adverse properties and functions in the fetal and the adult skeleton: A transient role in 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.

Structure, function and gene regulation of extracellular cartilage matrix proteins

Project manager: M. Stock, C.Surmann-Schmitt
By subtractive suppression hybridization we were able to identify novel genes involved in the regulation of chondrocyte differentiation by subtractive hybridization of mRNA obtained from distinct chondrocyte populations of the growth plate. One of them, twisted gastrulation (TSG), an antagonist of bone morphogenic proteins (BMPs) is expressed predominantly in hypertrophic cartilage and inhibits BMP-1 – induced collagen II-and- X synthesis. Transgenic models in which TSG is overexpressed under a cartilage specific promoter, have been developed to analyse the function of this protein in skeletal development. Two further genes seem to be involved in the regulation of early cartilage and bone development: the Wnt inhibitory factor Wif-1 is expressed exclusively in the upper zone of articular cartilage and seems to control wnt-induced chondrocyte dedifferentiation during joint development (Fig.1). While Wif-1 has so far been only investigated in context of its potential role as tumor supressor, we have shown that its major expression site is in cartilage, and that witf-1 is able to neutralize wnt3a –induced inhibition of chondrogenesis. The putative role of Wif-1 as a stabilizer of articular cartilage and its role in degenerative joint diseases is currently being investigated in collaboration with Prof. Schett, Department of Medicine 3.
A novel cartilage-specific gene was discovered which codes for a small extracellular cartilage protein (UCMA), a secreted protein. It is expressed only in juvenile, distal chondrocytes of fetal epiphyseal and vertebral cartilage. The protein is processed by a furin -like protease, binds to cartilage collagens and contains tyrosine sulphate and γ-carboxyl glutamic acid (Gla), indicating that it maybe involved in matrix assembly and/or calcification. A UCMA knockout mouse was generated and is currently being investigated in order to get insight into the possible function of UCMA in cartilage development and homeostasis.

Molecular mechanisms of endochondral ossification in 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 Sox 9 significantly blocked resorption of hypertropic cartilage, capillary invasion and bone marrow formation in the developing long bones, resulting in impaired skeletal growth and reduced bone length (Fig.2). 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 trabelcular 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 the hypertropic zone using the Col10-Cre deleter mouse.

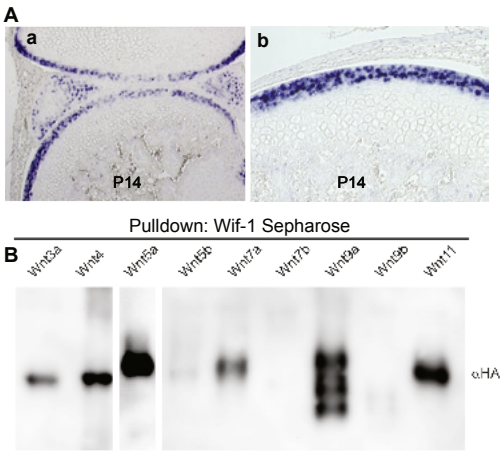

Fig.1: The Wnt-inhibitor Wif-1 is strongly expressed in the upper zone of articular cartilage (14 d mouse knee joint), suggesting a protective function against degenerative actions of Wnt factors.

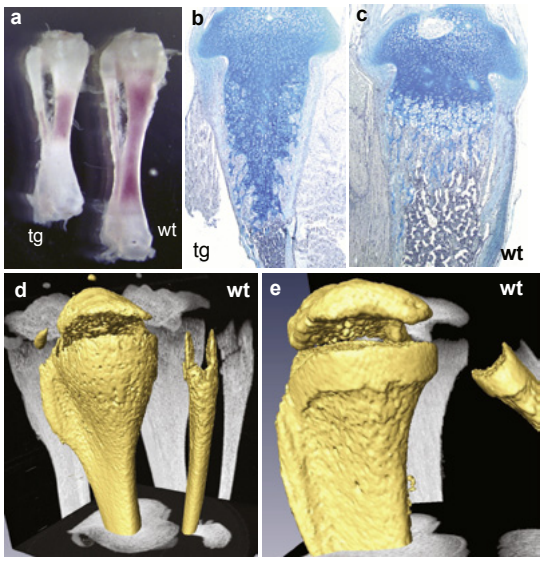

Fig.2: Overexpression of Sox9 in hypertrophic chondrocytes of the growth plate under a BAC Col10promoter causes substantial retardation of bow marrow formation in transgenic (tg) mice (a), impairs resorption of hypertrophic cartilage (b,c) and bone growth (d,e ; MicroCT image: A.Hess, Pharmacology, Friedrich-Alexander-University Erlangen-Nürnberg)

Cell-matrix interactions in biomimetic titandioxide nanotubes

Project manager: J. Park

Critical features of biomimetic materials used for vascular grafts and stents are surface geometry and chemical features of the implant material supporting adhesion, proliferation, and differentiation of endothelial cells and smooth muscle cells, the major cell types of blood vessels. Recently increasing experimental evidence has accumulated showing that nanoscale topography is an important factor for cellular recognition and cell behaviour on biomimetic material used for vascular grafts, stents, or bone implants. Prof. P. Schmuki Dr. Sebastian Bauer at the Department of Material Sciences, Friedrich-Alexander University Erlangen-Nürnberg, developed a procedure to coat titanium surfaces with vertically aligned Titanium dioxide nanotubes by anodizing Ti sheets in a phosphate-fluoride electrolyte with defined lumen diameters ranging between 15nm and 100 nm. In collaboration with this group cell behaviour of various cell type including osteoblasts, bone marrow mesenchymal stem cells (BMSC), and endothelial cells on Ti02 nanotubes was investigated with respect to adhesion, proliferation, migration, differentiation and cell death. Surprisingly, all cell types showed a maximum response to nanotubes with a lumen diameter of 15 nm, whereas on 100nm nanotubes cells tended toward enhanced apoptosis. On 15 nm nanotubes osteoblasts showed a maximum mineralisation tendency, BMSC the highest rate of osteogenic differentiation, and endothelial cells high expression of PECAM (CD31). The size of 15 nm corresponds to the size of the extracellular domain of integrin receptors which are responsible for cell-matrix interactions of all cells. We postulate that the surface geometry of 15 nm allows a maximum of integrin receptor clustering on the cell surface, thus initiating intracellular signalling and cytoskeletal reorganisations. This hypothesis was supported by immunohistological and electronmicroscopical analysis of cells after adhesion to nanotubes of various diameters. These studies were supplemented by experimental animal implantation experiments performed in collaboration with Dr. Schlegel and Prof Neukam, Department of Oral and Maxillofacial Surgery, Friedrich-Alexander University 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 celldifferentiation and development, cell-cell and cell-extracellular matrix interactions are given.

Selected Publications

Brachvogel B, Pausch F, Farlie P, Gaipl U, Etich J, Zhou Z, Cameron T, von der Mark K, Bateman JF, Pöschl E (2007) Isolated Anxa5+/Sca-1+ perivascular cells from mouse meningeal vasculature retain their perivascular phenotype *in vitro* and *in vivo*. Exp Cell Res, 313: 2730-43

Gebhard S, Hattori T, Bauer E, Bösl MR, Schlund B, Pöschl E, Adam N, de Crombrugghe B, von der Mark K (2007) BAC constructs in transgenic reporter mouse lines control efficient and specific LacZ expression in hypertrophic chondrocytes under the complete Col10a1 promoter. Histochem Cell Biol, 127: 183-94

Park J, Bauer S, von der Mark K, Schmuki P (2007) Nanosize and vitality: TiO2 nanotube diameter directs cell fate. Nano Lett, 7: 1686-91

von der Mark H, Pöschl E, Lanig H, Sasaki T, Deutzman R, von der Mark K (2007) Distinct acidic clusters and hydrophobic residues in the alternative splice domains X1 and X2 of alpha7 integrins define specificity for laminin isoforms. J Mol Biol, 371: 1188-203

Gebhard S, Hattori T, Bauer E, Schlund B, Bösl MR, de Crombrugghe B, von der Mark K (2008) Specific expression of Cre recombinase in hypertrophic cartilage under the control of a BAC-Col10a1 promoter. Matrix Biol, 27: 693-9

Surmann-Schmitt C, Dietz U, Kireva T, Adam N, Park J, Tagariello A, Onnerfjord P, Heinegård D, Schlötzer-Schrehardt U, Deutzmann R, von der Mark K, Stock M (2008) Ucma, a Novel Secreted Cartilage-specific Protein with Implications in Osteogenesis. J Biol Chem, 283: 7082-93

International Cooperation

Benoit de Crombrugghe, MD Anderson Cancer Centre, Texas University, Houston, USA

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

Christine Hartmann, Institut of Molecular Pathology, IMP, Wien, Austria

Beate Lanske, Department of Cell Biology, Havard Medical School, Boston, USA

Research Equipment

Leica Konfokales Laserscanning Mikroskop

Biacore Surface Plasmone Resonance

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Research Focus
- Molecular oncology of wnt signalling
- Tumour suppressor APC
- Transcriptional regulation by β-catenin
- Functional genomics of renal cell carcinoma

Structure of the Institution

The Chair of Experimental Medicine II is situated at the Nikolaus-Fiebiger-Centre 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 target is to investigate the molecular mechanisms of tumour development and progression by cell and molecular biological methods to find new ways for diagnosis, prognosis and therapy.

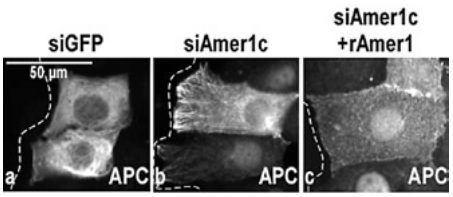
Research

Molecular Oncology of Wnt Signalling

The Wnt signalling pathway regulates various processes during embryonic development and can lead to cancer. Wnts are secreted glycoproteins, which induce the accumulation of β-catenin in cytoplasm and nucleus by binding to frizzled and LRP receptors. β-Catenin interacts with TCF transcription factors and activates target genes. The destruction of β-catenin is induced by phosphorylation in a multi-protein complex, which consists of the scaffold component conductin, the serine/threonine kinase GSK3β, and the tumour suppressor APC (Adenomatous Polyposis Coli). The wnt signal inhibits phosphorylation of β-catenin and thereby leads to its stabilisation. In colorectal tumours, mutations of APC or conductin, or mutations of the serine/threonine phosphorylation sites of β-catenin lead to stabilisation of β-catenin and trigger constitutive signalling to the nucleus. Such β-catenin mutations are also found in a multitude of other tumour types suggesting that aberrant activation of wnt signalling is a key mechanism of oncogenic transformation. During the report period we have investigated the consequences of APC mutations on wnt signalling in tumours, and we have identified a new interaction partner of APC, which recruits APC to the plasma membrane. A further focus of our studies is on the regulation and consequences of β-catenin dependent transcription.

Tumour suppressor APC

Project manager: A. Grohmann, K. Tanneberger, A. Alzner, J. Schneikert, E. Kohler
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 β-catenin . To investigate the functional relevance of truncated APC proteins, we have introduced tumour-associated mutations into the APC cDNA and analyzed the effects on the binding to β-catenin and on β-catenin destruction. We found that in most cases truncated APC retains reduced, but still significant binding to β-catenin as well as the capacity of negative regulation of wnt signalling. β-Catenin binding is mediated by the first of in total seven 20 amino acid repeats. This repeat is always retained in the APC fragments. 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 β-catenin inhibitory domain (CID), results in a complete loss of APC activity. Altogether we have come to a functional definition of the MCR: Mutations in tumours are selected for the presence of the first 20 amino acid repeats, lack of the third repeat and frequent inactivation of the CID domain. Our data also indicate that a certain control of activity of wnt signalling needs to be retained in colon tumours to allow for "just-right-signalling".
Besides its function as a negative regulator of the wnt signalling pathway APC plays also a role in the organization of microtubules and of cell contacts. In a yeast-two-hybrid screen we have identified a novel interaction partner of APC, which we have called Amer1 (APC Membrane Recruitement 1). Amer1 is associated to the plasma membrane through interaction with phosphatidylinositol lipids and recruits APC from the microtubules to the plasma membrane. Conversely, loss of Amer1 by siRNA leads to an increased association of APC to the tips of microtubules (see Figure). In addition we observed a loss of cell-cell contacts in epithelial cells when Amer1 is down regulated. It turned out that Amer1 is identical to the tumour suppressor WTX, which is mutated in Wilms tumours.



The localisation of exogenous AP in MCF-7 cells was analysed by immunofluorescence. APC is localised along microtubules in control cells (A, siGFP). Knock-down of Amer1 leads to a redistribution of APC t othe tips of mictrotubules in cellular protrusions (B, siAmer1c). Expression of Amer1 leads to the recruitment of APC to the plasma membrane (c, siAmer1c+rAmer1).

Transcriptional regulation by β-catenin

Project manager: V. Stemmer, M. Dehner, M. Hadjihannas
Using DNA microarray we have identified genes whose expression is modulated by activation of wnt signalling in cell lines. We found that the expression of SGK1 (serum and glucocorticoid-inducible kinase 1) is induced after knock-down of APC or stimulation with wnt-conditioned medium. Promoter analysis and chromatin immunoprecipitation showed that SGK1 is a direct target gene of β-catenin. SGK1 can inhibit the transcription factor FoxO3a through phosphorylation. We found, that wnt signalling leads to the exclusion of FoxO3a from the nucleus in a SGK1 dependent manner. Furthermore, wnt signalling inhibited FoxO3a transcription and apoptosis. Altogether we have identified a novel negative crosstalk between the oncogenic wnt signalling pathway and the pro-apoptotic action of FoxOs.
We found that the transcriptional repressor snail acts as a positive regulator of β-catenin dependent transcription. Snail can bind to β-catenin and is required for efficient activation of wnt target genes. As snail has been described as a target gene of the wnt pathway,

this could result in positive feedback for stimulation of signalling.

Functional genomics of renal cell carcinoma

Project manager: I. Wacker, M. Sachs

We have established gene expression patterns of renal cell carcinomas using DNA microarrays in order to identify genes relevant for the tumour biology and clinical course of this disease. The von Hippel Lindau tumour 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 TGFβ family, is highly over expressed in kidney tumours 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 tumour cells *in vitro*. Importantly, knockdown of Activin B inhibited tumour growth of kidney tumour cells in nude mice. Collectively, the data show that the loss of Activin B has similar consequences as the reconstitution of wild-type VHL in kidney tumour cells. Our results indicate that Activin B is a major oncogenic factor in kidney tumours.

Teaching

Training of students of molecular medicine in cell biology in cooperation with Chair of Experimental Medicine I.

Selected Publications

Grohmann A, Tanneberger K, Alzner A, Schneikert J, Behrens J (2007) AMER1 regulates the distribution of the tumor suppressor APC between microtubules and the plasma membrane. J Cell Sci, 120: 3738-47

Schneikert J, Behrens J (2007) The canonical Wnt signalling pathway and its APC partner in colon cancer development. Gut, 56: 417-25

Dehner M, Hadjihannas M, Weiske J, Huber O, Behrens J (2008) Wnt signaling inhibits Forkhead box O3a-induced transcription and apoptosis through up-regulation of serum- and glucocorticoid-inducible kinase 1. J Biol Chem, 283: 19201-10

Kohler EM, Derungs A, Daum G, Behrens J, Schneikert J (2008) Functional definition of the mutation cluster region of adenomatous polyposis coli in colorectal tumours. Hum Mol Genet, 17: 1978-87

Stemmer V, de Craene B, Berx G, Behrens J (2008) Snail promotes Wnt target gene expression and interacts with beta-catenin. Oncogene, 27: 5075-80

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

International Cooperation

Dr. Geert Berx, VIB Department for Molecular Biomedical Research, Universitaet Gent, Belgium

Research Equipment

Dako Cytomation MoFlo – Zellsortiergeraet

Applied Biosystems Genetic Analyzer ABI 3130

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Research Focus

- Acute poisoning in old age: most frequent and most dangerous drugs in an analysis of the Poison Control Centre Nürnberg
- Metabolism and nutrition in old age (Sarcopenia – frailty)
- The GerontoNet feasibility study – A descriptive study of older people among a network of European research Centres
- Use of the interRAI emergency department screener to improve hospital and community-based care for frail elderly individuals
- Health economics and medical supply allocation in the elderly

Structure of the Institution

The Institute for Biomedicine of Aging of the Friedrich-Alexander-University is characterized by a close cooperation with the Internal Medical Clinic 2, Clinical Centre Nürnberg, which includes the Acute Geriatric Hospital and the Geriatric Day Hospital. Head of the Chair of Internal Medicine – Geriatrics, of the institute and of the hospital is Professor Cornel C. Sieber. Scientific projects with a medical focus can be realized in close cooperation between experts of the institute and the hospital. 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, molecular and cellular aging, and nutrition in geriatrics. The research on malnutrition is not only focused to inpatients but also to nursing home residents. Therefore a close collaboration with the municipal nursing homes of Nürnberg was established in 2006.

Research

Acute poisoning in old age: most frequent and most dangerous drugs in an analysis of the Poison Control Centre Nürnberg
Project manager: W. Muehlberg, H.-J. Heppner
Although acute poisoning in old age is associated with an increased morbidity and mortality, only few literatures exist to this topic. In a retrospective study of 37,124 poison emergency calls which arrived from 1995 to 2006 at the Poison Control Centre Nürnberg, the age of the patents, kind of poison (i. e. drugs), symptoms of the poisoning at the time of the telephone call, and the "ad hoc" therapy advice were recorded in a data base. Statistical evaluation (comparison between expected and observed frequencies) was done by cross tables using the SPSS for Windows software. Results: Acute poisoning (accidental/suicidal) with drugs ($p < 0.001$) and with commercial chemicals was much more frequent in older patients (age ≥ 65 yrs) as compared to younger patients. Statistically significant less frequent in old age were intoxications with plant or animal poisons, with illegal drugs, and with household chemicals. Severe intoxication needing rapid admission to a hospital were more frequent in the older patients ($p < 0.001$). In addition, symptoms of the central nervous systems, the gastrointestinal tract, and the heart/circulation system occurred earlier and more frequent in the older patients ($p<0.001$). No such age difference could be observed for ventilation symptoms. Looking at single drugs, poisonings with bromazepam ($p<0.05$) and with zopiclon/zolpidem ($p<0.001$) were much more frequent in old patients (≥ 65 yrs) as compared to the young. Statistically significant less poisonings in the elderly patients were observed for acetylic salicylic acid, ibuprofen and paracetamol. Discussion: zolpidem/zopiclon were announced as less dangerous for older patients (as compared to benzodiazepines), but with respect to the risk of poisoning this was apparently not true. Neuroleptics (normal and atypic), antidepressants (TCA and SSRI) showed no increased risk of poisoning in old age. As somehow surprising result, poisonings (not adverse drug effects) with NSAIDS were less frequent in the old patients as compared to the young patients.

Metabolism and nutrition in old age (Sarcopenia – frailty)
Project manager: J. M. Bauer
During the past two years the working group on nutrition, sarcopenia and frailty realized several projects that were supported by research grants from charitable foundations and from the industry. The Else Kroener-Fresenius-Foundation sponsored a one year follow-up study on 200 nursing home residents, which was carried out in cooperation with the Council of Nürnberg. In this study a multitude of parameters has been analysed for their relevance with regard to functionality and mortality in this population. It could be shown that obese residents had a better survival than residents with underweight and than those who were within the normal weight range (BMI 20 – 25 kg/m2). In addition, the obese residents did not differ from the other groups with regard to functionality. In this study the working group also tested the applicability and prognostic validity of several nutritional screening tools. The Mini Nutritional Assessment (MNA) proved to be the best suited instrument for the nursing home setting. Nestlé supported the working group in a project that reevaluated the MNA on the basis of an internationally pooled database. In addition, a modified composition of the MNA short form (MNAsf) was tested. This project was realized with the help of the Institute of Medical Informatics, Biometry and Epidemiology of the University of Erlangen-Nürnberg. The new MNAsf is supposed to facilitate the screening of the nutritional status in older persons without compromising sensitivity and specifity. In cooperation with the Else-Kroener-Fresenius Centre of Nutritional Medicine at the Technical University of Munich the working group analysed the basal and postprandial secretion of appetite regulating hormones ghrelin, leptin and insulin in young and old study participants. Older test persons showed a reduced feeling of hunger and an increased feeling of satiety while postprandial levels of ghrelin did not decrease like in the younger group. This age-associated alteration of ghrelin secretion has to be discussed as a contributing factor in the anorexia of aging.

The GerontoNet feasibility study – A descriptive study of older people among a network of European research Centres
Project manager: W. Swoboda
The Geriatric Minimum Data Set (GMDS) developed by GerontoNet centres, is a consensus assessment tool dedicated to make data comparable across Europe. The GMDS needs to be evaluated in clinical research in terms of duration, relevance and availability of scales in the different countries and languages in a feasibility study. Frailty appears to be a new area of interest for pharmaceutical and biotech companies around the world. The Food and Drug Administration (FDA) and European Medicines Agency (EMEA) have expressed their interest to make an issue out of frailty. However, they underlined the need for better definition and knowledge. Although the frailty syndrome seems easy to recognise in clinical practice there is still no consensus-based definition or an assessment tool to define it. Preliminary results from 37 centres were presented at the 3 rd GerontoNet Meeting in Nürnberg in December 2008.

Use of the interRAI emergency department screener to improve hospital and community-based care for frail elderly individuals
Project manager: K. Singler, W. Swoboda in cooperation with interRAI
The inter RAI ED screener functions as a compatible assessment system in the interRAI family of instruments and it employs the same clinical logic as the interRAI contact assessment for identifying service urgency and need of assessment. Since 2008 a multicenter study is in progress including centres in Canada (John Hirdes), Australia (Len Gray), Iceland (Palmi Jonsson) and Germany. The project has the following primary objectives: 1. to demonstrate the clinical utility of the interRAI ED screener as a tool for identifying elderly persons with complex health needs in the emergency department; 2. to evaluate the ability oft the ED screener to support improved coordination between home care agencies and acute hospitals with respect to frail elderly persons discharged from ED's to the community; 3. to pilot the ED screener as a tool for triggering specialized geriatric assessment and intervention for frail elderly persons admitted to hospital from ED; 4. to track outcomes of care for persons admitted to hospital based on their baseline ED screener assessment.

Health economics and medical supply allocation in the elderly
Project manager: H.-J. Heppner
The demographic development generates new challenges in medical supply and management for older patients. Age-related functional restrictions and multi-morbidity in time of limited resources need cost-effective modern therapies. Economic aspect gets more and more important, so Dr. H.-J. Heppner works with PD Dr. rer. pol. A. S. Esslinger (Department of Management Science, University of Erlangen-Nürnberg) on the problems of ageism and the development of cost effective structures in the health care of older patients. For a long time it was not possible to describe the operating expense for required supply in this patient group and to work out and discuss changes in structure and processing quality in clinical treatment under economic aspects. Age dependent priorisation of medical supply and its implication for the health care system are critically discussed in this research group. Also rationing of necessary medical supply for the ageing society is critically questioned. In this context experts are consulted and relevant data of cross-national evaluations are collected. For their research studies among quality of life in older age against the background of narrow resources in the health care system, the work group was awarded with the Ignatius Nascher Award of Vienna (Austria) to Advance Geriatric Research. Representation of the German Geriatric Society at the AMWF-S-3 guideline "non-invasive ventilation" and the AMWF-S-2 guideline "weaning" enabled the research group to point out the strong medical distinctions of elderly patients. Integration of those patients in innovative treatment shows big chances in optimizing health care systems as to effectiveness in medical supply, resulting in higher quality of life for the elderly.

Teaching

"Instant Aging" is a simulation model of aging. It was integrated in the practical Geriatric of the Medical Clinic 2, Clinical Centre Nürnberg. "Instant Aging" provides tools for medical students to bodily experience different age- and illness-related limitations of activity.

Selected Publications

Bauer JM, Wirth R, Troegner J, Erdmann J, Eberl T, Heppner HJ, Schusdziarra V, Sieber CC (2007) Ghrelin, anthropometry and nutritional assessment in geriatric hospital patients. Z Gerontol Geriatr, 40: 31-36

Brosche T, Brueckmann M, Haase KK, Sieber C, Bertsch T (2007) Decreased plasmalogen concentration as a surrogate marker of oxidative stress in patients presenting with acute coronary syndromes or supraventricular tachycardias. Clin Chem Lab Med, 45: 689-91

Wirth R, Bauer J, Sieber C (2007) Erythrocyte volume is a poor predictor of cobalamin and folate deficiency in geriatric patients. J Am Geriatr Soc, 55: 2100-1

Dragonas C, Wagner JT, Heppner HJ, Bertsch T, Muhlberg W, Wicklein S, Pahl A, Diewald C, Bachmakov I, Sieber CC, Fromm MF (2008) The association of ABCB1 polymorphisms and elevated serum digitoxin concentrations in geriatric patients. Eur J Clin Pharmacol, 64: 367-72

Bauer JM, Kaiser MJ, Sieber CC (2008) Sarcopenia in nursing home residents. J Am Med Dir Assoc, 9: 545-51

Bauer JM, Sieber CC (2008) Sarcopenia and frailty: a clinician's controversial point of view. Exp Gerontol, 43: 674-8

International Cooperation

Prof. Bruno Vellas, GerontoNet, Toulouse, France

Prof. Ian Hastie, United European Medicine Societies – Geriatric Medicine Section (UEMS-GMS), London, Great Britain

Prof. Cornel Sieber, European Academy for Medicine of Ageing (EAMA), Sion, Switzerland

Meetings and International Training Courses

15.–17.11.2008: Alter als gesellschaftliche Herausforderung, Nürnberg, Germany, Deutsche Gesellschaft fuer Geriatrie

12.–13.12.2008: GerontoNet Meeting, Nürnberg, Germany, GerontoNet – europaeisches Konsortium fuer klinische Forschung in der Geriatrie

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

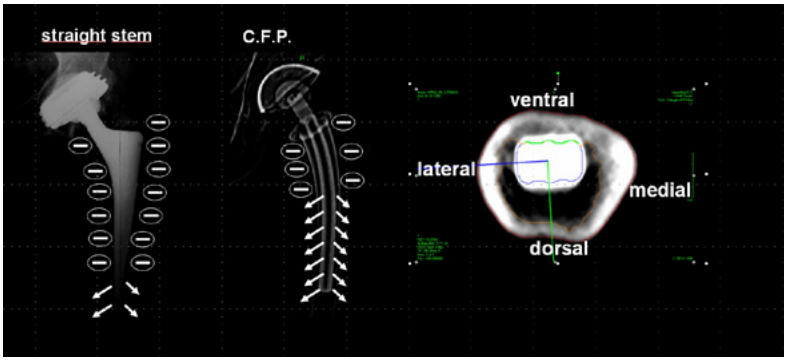
Structure of the Institution

17 medical doctors work in the departement of orthopaedic surgery. The research is accomplished by 5 postdoctorate medical doctors, 14 graduate students and 3 technical assistants.
In the endoprosthesis working group, apart from the standardised clinical and radiological long-term investigations for quality control after navigated and non-navigated total hip and knee surgery, periprosthetic bone density measurements are accomplished by means of computer tomography (CT) – assisted osteodensitometrie and 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 optimising of orthopaedic 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, pedeatric orthopeadics, foot surgery, tumorsurgery, arthroscopic operations.

Research

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 2 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 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 µm and 0.03°-0.6°. Altogether 200 patients are supervised with radiostereometric analysis after total hip replacement in Erlangen since 1998. The following examinations are carried out with this clients in different studies: measuring of migration of polyethelene cups after bone grafting and reinforcement acetabular ring with hook for severe acetabular dysplasia; measuring of initial stability of acetabular components with alumina and polyethylen liner in a comparison essay, measuring of migration of cemented femoral components into dependence of various cementing techniques in a comparison essay, measuring of migration of uncemented femoral components after early load transfer.



CT-Osteodensitometrie: proximal stress-shielding (-) after straight stem versus collum femoris preserving (C.F.P) cementless total hip arthroplasty.

Computertomography-assisted periprosthetic osteodensitometry after total hip arthroplasty
Project manager: R. Forst, L. Mueller
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 mea-

sured. Bone demsity measurements are undertaken to in respect to fixation methods (cemented/uncemented), coating (e.g. hydroxyapatite) and design (collum femoris preserving/ standard).

Neuromuscular disorders

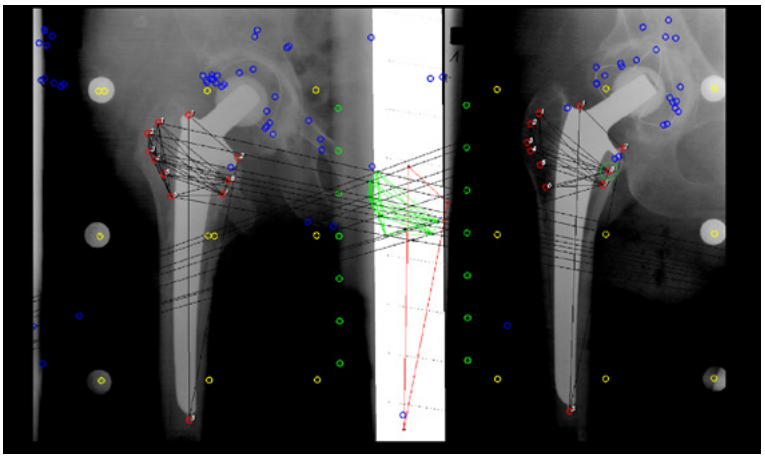
Project manager: J. Forst, A. Fujak, R. Forst

The research group for neuromuscular disorders is engaged in an evaluation of orthopaedic symptoms, conservative and operative treatment in children and adult patients with neuromuscular disorders. The aim of research is the optimising of orthopaedic 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 Anaesthesiology the special features in anaesthesia and pain therapy in patients with the neuromuscular disorders are investigated.

In common projects with the Division of Pediatric Cardiac Surgery and Institute of Radiology the participation of the heart musculature in DMD is examined.



Radiostereoanalysis after total hip arthroplasty is based on the radiographic evaluation of small tantalum markers and calibration cages which permit an accurate (1-250µm and 0.03-0.6°) three-dimensional analysis of the migration pattern of the prosthesis.

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 accuray 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 analysed 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 analysed.

Teaching

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

Selected Publications

Fujak A, Ingenhorst A, Heuser K, Forst R, Forst J (2005) Treatment of scoliosis in intermediate spinal muscular atrophy (SMA type II) in childhood. Ortop Traumatol Rehabil, 7: 175-9

Schmidt R, Pitto RP, Kress A, Ehremann C, Nowak TE, Reulbach U, Forst R, Müller L (2005) Inter- and intraobserver assessment of periacetabular osteodensitometry after cemented and uncemented total hip arthroplasty using computed tomography. Arch Orthop Trauma Surg, 125: 291-7

Fujak A, Wollinsky KH, Forst R (2007) Proximal spinal muscular atrophy (SMA). Z Orthop Unfall, 145: 233-52

Mueller LA, Nowak TE, Mueller LP, Schmidt R, Ehrmann C, Pitto RP, Pfander D, Forst R, Eichinger S (2007) Acetabular cortical and cancellous bone density and radiolucent lines after cemented total hip arthroplasty: a prospective study using computed tomography and plain radiography. Arch Orthop Trauma Surg, 127: 909-17

Mueller LA, Voelk M, Kress A, Pitto RP, Schmidt R (2007) An ABJS Best Paper: Progressive cancellous and cortical bone remodeling after press-fit cup fixation: a 3-year followup. Clin Orthop Relat Res, 463: 213-20

Fujak A, Forst R, Forst J (2008) Outcome after Achilles tendon lengthening with a posterior capsulolysis according to Imhäuser in idiopathic congenital clubfoot. Ortop Traumatol Rehabil, 10: 367-76

International Cooperation

Gaetano Conte Academy, Neapel, Italy

Institute Duchenne de Boulogne, Poitiers, France

Meetings and International Training Courses

Repetitorium Orthopaedie und Unfallchirugie, Banz, Deutschland, Stiftung Akademie Deutscher Orthopaeden

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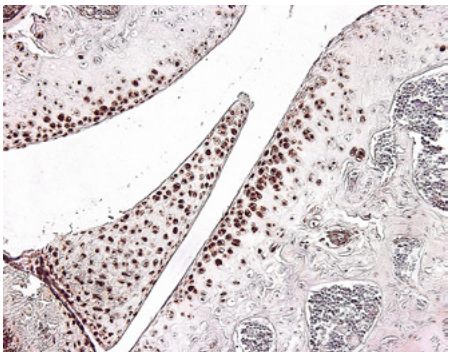
Research Focus
- Cellular and molecular basis of cartilage degeneration and regeneration
- Endoprostheses for degenerative and inflammatory joint diseases
- Arthroscopic synovectomy in rheumatoid patients

Structure of the Institution

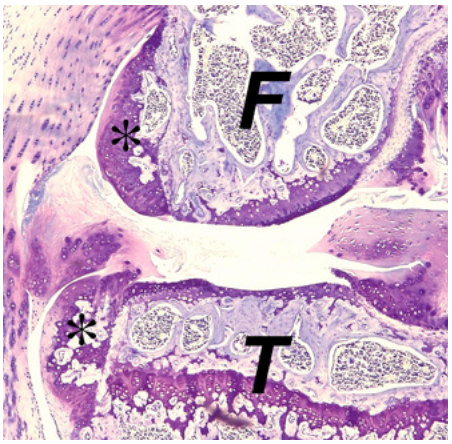
The Division of Orthopaedic Rheumatology is an independent institution of the Friedrich-Alexander University which is associated to the Department of Orthopaedics.
Clinical activities focus on the treatment of patients with degenerative and inflammatory joint diseases. The head of the department is also speaker of the Erlangen Arthritis Centre which is an interdisciplinary association of physicians treating these patients.
Clinical research activities concentrate on the evaluation of surgical treatments. Of interest are preventive procedures like synovectomies. Comparing joint replacements in patients with degenerative and inflammatory joint diseases will help to identify different preoperative findings, different intraoperative challenges as well as long term patients´ satisfaction.
Another focus of basic research are the mechanisms of induction and progression of osteoarthritis. Projects are funded by the DFG and the IZKF. A better understanding of osteoarthritis will help to develop new therapeutic approaches like tissue engineering.
The scientific projects are done 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

Cellular and molecular basis of cartilage degeneration and regeneration
Besides clinical and epidemiological studies on human osteoarthritis, the research work focussed on the pathomechanisms of osteoarthritis and differentiation patterns of chondrocytes. Based on these biomolecular principles, novel strategies for regeneration and repair of articular cartilage were investigated.
1) The role of hypoxia for chondrocyte differentiation and cartilage metabolism
Project manager: K. Gelse
Articular cartilage is an avascular tissue and, thus, characterized by severe hypoxic conditions. Chondrocytes are well adapted to such low oxygen levels. In this respect, the transcription factor Hypoxia inducible factor-1 α (HIF-1α) does not only play an important role for the metabolic adaption of the cells, but also for the differentiation of chondrocytes. We could demonstrate that HIF-1α is essential for the survival and activity of the chondrocytes within the articular cartilage. In an animal model, the chemical inhibition of this factor resulted in significant apoptosis of the chondrocytes coinciding with servere degenerative changes of the articular cartilage. Furthermore, it could be shown that the chondrocyte phenotype is associated with the activity of HIF-1α. In cartilage repair tissues, transplanted mesenchymal stem cells differentiated into chondrocytes exclusively in deeper hypoxic tissue layers, while in more superficial layers with higher oxygen levels, the cells only adopted a fibroblast-like phenotype. In this respect, we could demonstrate that the growth-factor bone morphogenetic protein-2 efficiently induced chondrogenesis even in areas of the repair tissue with higher oxygen levels. Interestingly, this was strongly associated with a striking increase in HIF-1α activity. Current research investigates the role of hypoxia and HIF-1α as a therapeutic tool for the generation of hyaline repair cartilage.
2) Cell- and gene therapy approaches for cartilage regeneration
Project manager: K. Gelse
A number of specific growth- and differentiation factors, such as bone morphogenetic protein-2 (BMP-2) or Insulin-like growth factor-1 (IGF-1) have the capability to induce and support chondrogenic differentiation of mesenchymal cells. Gene transfer of these factors may be suited to provide a more prolonged supply of these proteins. Using adenoviral and AAV-based gene transfer systems, we could achieve the secretion of biologically relevant amounts of IGF-1 and BMP-2 for a period of several weeks. The therapeutical potential of mesenchymal stem cells stimulated by such gene therapy approaches was investigated in an animal model with large cartilage defects within the knee joint. In these experiments, only BMP-2 gene transfer proved to be a sufficient stimulus to efficiently induce chondrogenic differentiation of the cells and to support, at least transiently, the generation of hyaline-like cartilage repair tissue. However, in the long term, with a decline of transgene expression, a recurring dedifferentiation of the mesenchymal cells could be observed which coincided with a deterioration of the repair tissue quality.
As an alternative for cell stimulation by gene therapeutical methods, a further project investigated the endogenous secretory-paracrine potential of autologous chondrocytes. We could show that rib chondrocytes represent an endogenous source for chondrogenic factors (including BMP-2). Chondrocytes, which were applied in form of cell spheroids into the subchondral bone plate of cartilage lesions, exerted a positive paracrine chondrogenic effect on ingrowing mesenchymal stem cells from the bone marrow and supported the formation of secondary repair cartilage. The reservoir of further endogenous factors, which are of therapeutic value for cartilage and bone regeneration, is currently intensively investigated.



Immunohistochemical detection of cellular hypoxia in articular cartilage and meniscus of murine knee joints



Degeneration of articular cartilage of femur (F) and tibia (T) with the formation of osteophytes (*) in the murine knee

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.

Arthroscopic synovectomy in rheumatoid patients

Project manager: H.-D. Carl

We investigated the results following synovectomy in studies comprising patients with juvenile and adult-onset rheumatoid arthritis.

A study on open hip joint synovectomy in JIA patients was performed in collaboration with the Orthopaedic accident clinic 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.

A histologic and immunohistochemical study was carried out in collaboration with Prof. R. Kinne, Experimental Rheumatology Unit, University of Jena, to assess the intraoperative reduction of inflammatory infiltrates achieved by arthroscopic knee joint synovectomy in patients with adult-onset rheumatoid arthritis with special regard to the removal site, using preoperative and postoperative synovial tissue samples. Our results confirmed that arthroscopic synovectomy effectively reduces acute and chronic inflammatory infiltrates in patients with RA who have refractory synovitis of the knee and improves knee function. However, the reduction of inflammatory infiltrates appears to depend on the anatomic region of the joint, so that additional measures such as radiation synovectomy may be applied.

Teaching

Staff of the Division of Orthopaedic Rheumatology is active in the curriculum for general orthopaedics. 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.

Selected Publications

Carl HD, Schraml A, Swoboda B, Hohenberger G (2007) Synovectomy of the hip in patients with juvenile rheumatoid arthritis. J Bone Joint Surg Am, 89: 1986-92

Grimmer C, Pfander D, Swoboda B, Aigner T, Mueller L, Hennig FF, Gelse K (2007) Hypoxia-inducible factor 1alpha is involved in the prostaglandin metabolism of osteoarthritic cartilage through up-regulation of microsomal prostaglandin E synthase 1 in articular chondrocytes. Arthritis Rheum, 56: 4084-94

Pullig O, Tagariello A, Schweizer A, Swoboda B, Schaller P, Winterpacht A (2007) MATN3 (matrilin-3) sequence variation (pT303M) is a risk factor for osteoarthritis of the CMC1 joint of the hand, but not for knee osteoarthritis. Ann Rheum Dis, 66: 279-80

Gelse K, Mühle C, Knaup K, Swoboda B, Wiesener M, Hennig F, Olk A, Schneider H (2008) Chondrogenic differentiation of growth factor-stimulated precursor cells in cartilage repair tissue is associated with increased HIF-1alpha activity. Osteoarthritis Cartilage, 16: 1457-65

Gelse K, Pfander D, Obier S, Knaup KX, Wiesener M, Hennig FF, Swoboda B (2008) Role of hypoxia-inducible factor 1 alpha in the integrity of articular cartilage in murine knee joints. Arthritis Res Ther, 10: R111

International Cooperation

Prof. Dr. T. Kirsch, PhD, Departement of Orthopaedic Surgery, Director of MusculoskeletaL Research Centre, 301 East 17 th Street Suite 1500, New York, NY 1003, USA

Meetings and International Training Courses

23.06.2007: Frueharthritis, Kollegienhaus Friedrich-Alexander University Erlangen-Nürnberg

19.04.2008: Der entzuendliche Rueckenschmerz, Kollegienhaus, Friedrich-Alexander University Erlangen-Nürnberg

Department of Medicine 1 – Gastroenterology, Lung Diseases and Endocrinology

Chair of Internal Medicine I

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Research Focus
- Endocrinology
- Experimental hepatology & oncology
- Intensive Care, Infectious Diseases, Tropical and Travel Diseases
- Clinical and experimental pneumology
- Drug safety and pharmacovigilance
- Gastroenterologic oncology
- Ultrasound
- Inflammatory bowel diseases
- Meetings and continuing education
- International cooperations

Structure of the Institution

The Department of Medicine 1 covers research in the fields of gastroenterology, hepatology, metabolism and nutrition, endocrinology, pneumology, intensive care medicine, infectious diseases, endoscopy and ultrasound.
Several research groups investigate these fields in clinical and experimental approaches. Recently, projects in the area of medical teaching were established.

Research

Endocrinology
Project manager: I. Harsch
Metabolic characteristics and coincidence with obstructive sleep apnea sydrome (OSAS) as well as effects of appetite regulating hormones were investigated in patients with diabetes mellitus. In an experimental setting, we investigated wound healing in diabetic pigs. Psychological factors and expression of adenosin deaminase were investigated in patients with autoimmune thyroiditis. Patients with multiple symmetric lipomatosis (Launois Bensaude syndrome) were characteristic for metabolic and psychologic factors and intervention strategies compared to alimentary adipositas. The knowledge status of patients with primary or secondary adrenal insufficiency regarding hormone substitution was evaluated and teaching concepts were established. We investigated metabolic and inflammatory parameters in patients witgh OSAS.

Experimental hepatology & oncology
Project manager: M. Ocker
The group investigates translational approaches for therapy and pathogenesis of gastroenterologic and hepatologic diseases. The expression of embryonic genes as a prognostic factor in pancreatic cancer was investigated. Mechanisms of epigenetic tumor therapy and identification of alternative pathways of apoptosis by HDAC inhibitors are a focus in hepatocellular carcinoma. This project was continued to a phase I clinical trial. In an animal model of hepatocellular carcinoma (HCC), the technique of transarterial chemoembolisation was established. We also established a model of liver fibrosis in cannabinoid receptor knockout mice.

Intensive care, infectious diseases, tropical and travel diseases
Project manager: R. Strauß
Incidence and extensity of posttraumatic stress syndrome were investigated in intensive care patients. A multicenter study on the influence of dornase alpha on lung function and ventilation time was closed. Dosage of pharmaceuticals, esp. antiinfective drugs, are difficult to calculate in intensive care patients. In a pilot project, we obtained data on therapeutic drug monitoring in intensive care patients. A German-Arabic alumni network was established together with the German Academic Exchange Service (DAAD).

Clinical and experimental pneumology
Project manager: F. Fuchs
Metabolic effects of sleep related breathing disorders are the research focus of the group. Previous results showing an amelirotation of insulince resistance under therapy were confirmed. Currently, the effects of continuous positive airway pressure (CPAP) therapy on plasma levels of obestatin, apelin and visfatin are investigated. We also examined the influence of an optimized diabetes therapy on OSAS. Mechanisms of arousal reactions in OSAS are a further research topic. Here, model of inudec arousals by nCAPA is under development.

Drug safety and pharmacovigilance
Project manager: H. Dormann
A database of unwanted side effects was established. Aspects of epidemiology, risk profiles and predictors of side effects were analysed with a special focus on malnutritioned patients. The KLASSE system was established on collaboration with the department of pharmacology, the Department of Medicine 1 and the Pharmacy of the University Regensburg and the Hadassah University in Jerusalem, Israel. The system was introduced in various hospitals. A further system for optimised prescription of antiinfective drugs was established on the basis of medical logic modules and a stratified drug safety database. The GaID system generates individuale risk profiles and contraindications. In cooperation with BfArM, PEI, the national drug safety commission and the department of psychiatry, hepatic side effects of drugs were analysed.

Gastroenterologic oncology
Project manager: A. Wein
The IVOPAK project was performed together with the department of surgery and gives evidence on the treatment of patients with metastatic colorectal cancer in Northern Bavaria.
The multicenter phase II trial on Irinotecan and 5-FU after progression of platinum-based first-line treatment in patients with colorectal cancer was continued. A prospective multicenter phase II trial (InTACT II-GeMicAn) investigates gene expression profiles in primary colorectal cancers to investigate if risk patterns predicting a disease recurrence could be identified.
A new project on the influence of a palliative second line treatment on life quality in patients with metastatic colorectal cancer was established. A phase II trial on palliative care in patients with gastric cancer was prepared.

Ultrasound
Project manager: D. Strobel
Ultrasound contrast enhancers allow to differentiate solid liver tumors. In collaboration with the German society for ultrasound in medicine, the following multicenter trials were erstablished: 1) characterisation of liver tumors, 2) detection of liver metastases in colorectal cancer, 3) detection of liver metastaes in pancreatic cancer.

View to the Departments of Medicine 1 and Medicine 2
Source: University Hospital Erlangen

Tumor differentiation by ultrasound contrast enhancers was investigated in patients with solid pancreas and kidney tumors. A pilot trial on computer assisted quantification of contrast enhancement in liver tumors was performed. The value of high resolution ultrasound in comparison to MR-Sellink was analysed.
The application of ultrasound-guided percutaneous high frequency thermotherapy was investigated in hepatocellular carcinoma. In addition to local effects on tumor integrity, immunostimulatory effects were obserevd in an animal model and in patients. The spectrum of side effects after ultrasound guided interventions in the abdomen was investigated.

Inflammatory bowel diseases
Project manager: M. Raithel
The following projects were investigated: 1) Differentiation of IgE- and non-IgE-mediated allergies in the gastrointestinal tract. 2) Determination of luminal TNFalpha and of plasma levels of TNF and histamine in IBD. 3) Levels of leukotriene in urine (LTB4, LTC4, D4 and E4) in patients with IBD and mastocytosis. 4) Activity of diaminoxidase in small intestine in correlation with plasma-DAO. 5) Mediator diagnostics from urine and plasma after histamine provocation tests

Teaching

The Department of Medicine 1 contributes to curricular teaching for medical students from 2nd to final year. The necessary skills are tought in practical courses in (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

Angstwurm MW, Engelmann L, Zimmermann T, Lehmann C, Spes CH, Abel P, Strauss R, Meier-Hellmann A, Insel R, Radke J, Schuettler J, Gaertner R (2007) Selenium in Intensive Care (SIC): results of a prospective randomized, placebo-controlled, multiple-center study in patients with severe systemic inflammatory response syndrome, sepsis, and septic shock. Crit Care Med, 35: 118-26

Okamoto K, Ocker M, Neureiter D, Dietze O, Zopf S, Hahn EG, Herold C (2007) bcl-2-specific siRNAs restore gemcitabine sensitivity in human pancreatic cancer cells. J Cell Mol Med, 11: 349-61

Wagner AD, Buechner-Steudel P, Wein A, Schmalenberg H, Lindig U, Moehler M, Behrens R, Kleber G, Kuss O, Fleig WE (2007) Gemcitabine, oxaliplatin and weekly high-dose 5-FU as 24-h infusion in chemonaive patients with advanced or metastatic pancreatic adenocarcinoma: a multicenter phase II trial of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Ann Oncol, 18: 82-7

Boeck S, Hoehler T, Seipelt G, Mahlberg R, Wein A, Hochhaus A, Boeck HP, Schmid B, Kettner E, Stauch M, Lordick F, Ko Y, Geissler M, Schoppmeyer K, Kojouharoff G, Golf A, Neugebauer S, Heinemann V (2008) Capecitabine plus oxaliplatin (CapOx) versus capecitabine plus gemcitabine (CapGem) versus gemcitabine plus oxaliplatin (mGemOx): final results of a multicenter randomized phase II trial in advanced pancreatic cancer. Ann Oncol, 19: 340-7

Gali-Muhtasib H, Kuester D, Mawrin C, Bajbouj K, Diestel A, Ocker M, Habold C, Foltzer-Jourdainne C, Schoenfeld P, Peters B, Diab-Assaf M, Pommrich U, Itani W, Lippert H, Roessner A, Schneider-Stock R (2008) Thymoquinone triggers inactivation of the stress response pathway sensor CHEK1 and contributes to apoptosis in colorectal cancer cells. Cancer Res, 68: 5609-18

Gali-Muhtasib H, Ocker M, Kuester D, Krueger S, El-Hajj Z, Diestel A, Evert M, El-Najjar N, Peters B, Jurjus A, Roessner A, Schneider-Stock R (2008) Thymoquinone reduces mouse colon tumor cell invasion and inhibits tumor growth in murine colon cancer models. J Cell Mol Med, 12: 330-42

International Cooperation

The international collaborations of the department are listed at http://www.medizin1.klinikum.uni-erlangen.de

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: http://www.medizin1.uk-erlangen.de/e114/index_ger.html

Department of Medicine 2 – Cardiology and Angiology

Chair of Internal Medicine II

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Research Focus
- Cardiac computed tomography
- Echocardiography
- Magnetic Resonance Tomography
- Interventional cardiology
- Electrophysiology
- Molecular and experimental cardiology

Structure of the Institution

The department is the internal medicine department focussing 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 Centre of Erlangen. The department is a tertiary referral centre 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 have permanent teaching positions at the Medical Faculty (Habilitation), a biologist, and 109 non-physician nursing or supporting staff. It possesses two large normal care wards, an coronary care unit, three cath lab suites, and an out-patient department with several specialized clinics for heart failure, congenital heart disease, arrhythmias and pacemakers/defibrillators. Furthermore, the department disposes of a large basic-science laboratory.

Research

Cardiac computed tomography
Project manager: S. Achenbach
A major focus of the internationally renowned research group "Cardiac Computed Tomography (CT)" is the development and validation of new techniques for coronary artery visualization by contrast-enhanced CT, as well as the analysis of the accuracy for detection of coronary artery stenoses in various clinical situations (Fig. 1). Similarly, the use of CT techniques to detect, quantify and characterize coronary atherosclerotic plaque especially in the context of acute coronary syndromes is a main area of research. Further topics are efforts to reduce radiation exposure in cardiac CT, analysis of post-processing tools for coronary CT angiography and analysis of myocardial perfusion by contrast-enhanced CT. Researchers and clinicians of the Department of Cardiology collaborate closely with colleagues from the Department of Radiology as well as the Institute of Medical Physics (Prof. Dr. med. W. Kalender). Further national and international cooperations exist for example with the German Heart Centre, Munich, the University Hospital in Zurich and the Massachusetts General Hospital, Boston, MA, USA.

Echocardiography
Project manager: F. A. Flachskampf
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.

Magnetic Resonance Tomography
Project manager: M. Schmid, S. Achenbach
In collaboration with the 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 prognostic importance of T2 weighted and contrast-enhanced imaging after myocardial infarction and the determination of infarct size as an 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 peri-myocarditis, so-called edema-sensitive sequences are evaluated to detect the acute inflammatory process. Additional research topics are the non-invasive quantitation of valvular heart disease, in particular aortic stenosis, with comparison to established standards (echo, catheterization), morphologic and functional MRI imaging in stress cardiomyopathy (tako-tsubo) and characterization and localization of myocardial fibrosis in dilated cardiomyopathy.

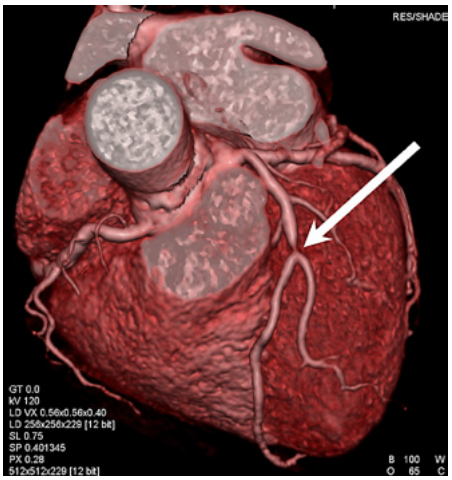

Fig. 1: Cardiac computed tomography. 3D visualization of coronary morphology by "dual source" computed tomography. The arrow indicates a severe narrowing of the left anterior descending artery.

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 cor-

onary 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 is evaluated, with special attention to post-interventional arrhythmias and cerebral ischemia.

Electrophysiology

Project manager: M. Wilhelm

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. Another study examines the clinical value of a lung water sensor in heart failure patients for monitoring therapy (Biotronik Lumax 540 HF-T). All ICD patients are included in a structured, prospective follow-up 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 atrialfibrillation by cryo-balloon, 3-dimensional fusion imaging based on electro-anatomical mapping and cardiac computed tomography is being developed and refined (Fig. 2).

Finally, professional football players are systematically evaluated by ECG and other non-invasive techniques.

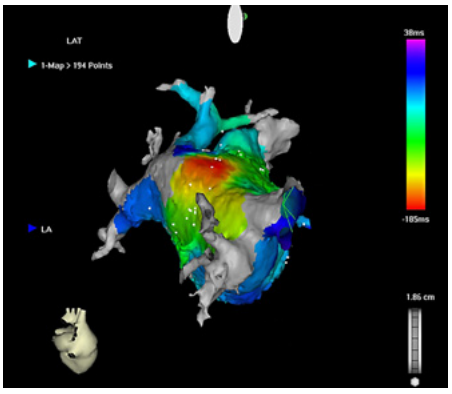

Fig. 2: Fusion imaging of cardiac computed tomography and electro-anatomical mapping to enable detection and percutaneous catheter ablation of tachycardias (arrhythmias with rapid heart beat).

Molecular and experimental cardiology

Project manager: A. Yilmaz, C. Stumpf, C. Garlichs

Atherosclerosis is a chronic inflammatory disease. The research projects of the group therefore focus on new pathomechanisms of this 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 (FcγR) moved into the focus of atherosclerosis research. Collecting a large patient databank enabled us to examine the role of C-reactive protein (CRP) and FcγR 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) DC (dendritic cells) 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 canditates 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.

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 analyze experimentally 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 diseseas 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 25 teaching activities (from lecture to practical exercise) per semester. Members of the department repeatedly won the prize for good teaching of the Medical Faculty. Interdisciplinary teaching events are organized together together with other departments. The department is also involved in the planning, development, and implementation of the newly created curriculum of "medical process management". The cardiac computed tomography group holds regular international courses in this method, and the echocardiography group organizes a yearly workshop on new techniques. Hospitations for guest physicians can be arranged in all laboratories of the department.

Selected Publications

Flachskampf FA, Gallasch J, Gefeller O, Gan J, Mao J, Pfahlberg AB, Wortmann A, Klinghammer L, Pflederer W, Daniel WG (2007) Randomized trial of acupuncture to lower blood pressure. Circulation, 115: 3121-9

Ropers U, Ropers D, Pflederer T, Anders K, Kuettner A, Stilianakis NI, Komatsu S, Kalender W, Bautz W, Daniel WG, Achenbach S (2007) Influence of heart rate on the diagnostic accuracy of dual-source computed tomography coronary angiography. J Am Coll Cardiol, 50: 2393-8

Yilmaz A, Lipfert B, Cicha I, Schubert K, Klein M, Raithel D, Daniel WG, Garlichs CD (2007) Accumulation of immune cells and high expression of chemokines/chemokine receptors in the upstream shoulder of atherosclerotic carotid plaques. Exp Mol Pathol, 82: 245-55

Cicha I, Goppelt-Struebe M, Muehlich S, Yilmaz A, Raaz D, Daniel WG, Garlichs CD (2008) Pharmacological inhibition of RhoA signaling prevents connective tissue growth factor induction in endothelial cells exposed to non-uniform shear stress. Atherosclerosis, 196: 136-45

Schmid M, Pflederer T, Jang IK, Ropers D, Sei K, Daniel WG, Achenbach S (2008) Relationship between degree of remodeling and CT attenuation of plaque in coronary atherosclerotic lesions: an in-vivo analysis by multi-detector computed tomography. Atherosclerosis, 197: 457-64

Stumpf C, Lehner C, Raaz D, Yilmaz A, Anger T, Daniel WG, Garlichs CD (2008) Platelets contribute to enhanced MCP-1 levels in patients with chronic heart failure. Heart, 94: 65-9

International Cooperation

Thomas J.Brady, Massachusetts General Hospital, Harvard University, Boston, USA

Research Equipment

Siemens Healthcare Herzkatheter-Angiographieanlage (3 Labore)

GE Healthcare Vivid 7 (2 Geraete)

Siemens Healthcare Dual Source Computertomograph

Philips Echokardiographiegeraet 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
- Clinical Immunology and Rheumatology
- National and International Clinical Trials
- Immunodeficiencies and Infectious Diseases
- Immunogenetics and Transplant-immunology

Structure of the Institution

Up to September 2007 the Department of Medicine 3 covered the fields of Immunology, Rheumatology, Hematology and Oncology. With the appointment of Prof. Mackensen, the Department got divided into the present Department of Medicine 3 (Rheumatology and Immunology) under the administration of Prof. Dr. med. Georg Schett and the new instituted Department of Medicine 5 under the administration of Prof. Dr. med. Andreas Mackensen.
Different research groups are investigating the inflammatory joint diseases: pathogenesis and development of therapeutic strategies; pathogenesis of autoimmune diseases, systemic vasculitis, therapeutic strategies for immune deficiencies, infectious immunology, immunogenetic, diagnosis and treatment of allergic diseases, clearance of apoptotic cells and pursue clinical trials.
The Department of Medicine 3 got awarded as "EULAR Centre of Excellence", with the DVO Research Unit Award and Dr. Joerg Distler was awarded with the Career Promotion Award.

Research

Clinical Immunology and Rheumatology
- Pathomechanisms of bone destruction in rheumatoid arthritis

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

Project manager: 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 for the development of tumor vaccines.
- Regulation of NF-κB

Project manager: 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-κB-activation induces various anti-apoptotic factors. The latter are able to prevent cell death. Due to the central role of NF-κB for inflammation and immune response a targeted inhibition of NF-κB 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

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 the investigation of premature atherosclerosis and ovarian failure in SLE.
- Analysis of inflammatory mechanisms in adult onset Still´s disease

Project manager: 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 an massive up-regulation of pro-inflammatory cytokines and proliferation leading to the crescent formation in affected glomeruli. Potential candidate molecules responsible for this deregulation are investigated in kidney biopsies of patients with a RPGN as well as experimental RPGN models.
- The role of 12/15-lipoxygenase (12/15-LO) in the regulation of innate and adaptive Immunity

Project manager: G. Kroenke
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).

- Allergology

Project manager: G. Eger

The group of Internistic Allergology is working on the diagnosis and the development of new treatment principles for allergological disease entities. These disease entities include bronchitic asthma, chronic sinusitis, food and drug allergies/hypersensitivities, contact allergies and pollinosis as well as allergies against animal hair and house dust. The group has successfully developed a test procedure to differentiate so called Pseudoallergies within the respiratory tract being induced by different medications, from allergological disorders i.e. pollinosis or allergic asthma.

National and International Clinical Trials

Project manager: M. Baeuerle, M. Ronneberger, J. Wacker, C. Stach

Various national and international studies were conducted, primarily to investigate new treatment approaches in rheumatic diseases. The major focus of the therapeutic trials is on treatment with "biologicals" e.g. therapeutic principles which block the proinflammatory cytokine tumornecrosis factor α. Another focus is the initiation and conduction of a multicenter trial with the TNF-inhibitor infliximab in patients with psoriatic arthritis. 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 centre for patients with primary and secondary immunodeficiencies, with HIV-infection and with a variety of other infectious diseases such as borrelia infections, chronic viral infections and patients with chronic fatigue syndrome. The major interest of research of the group are various aspects of HIV-infection such as immunology of HIV-infection and basic and clinical research on development and evaluation of new therapeutic and diagnostic procedures. The clinic is working on the development of immunotherapies such as therapeutic vaccines and immunomodulators. The clinic participated in national and international clinical studies including studies for the evaluation of new innovative therapeutics of HIV-infection such as preventive and therapeutic vaccines with recombinant MVA-Nef vectors. In addition other projects are investigating further infectious and immunologic diseases such as Borrelia burgdorferi infections, chronic fatigue syndrome and humoral immunodeficiencies.

Immunogenetics and Transplant-immunology

Project manager: B. Spriewald

The laboratory provides service for the Eurotransplant area Northern Bavaria with the transplant centres 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 analyse polymorphisms of several cytokines and T cell regulatory genes and their association with rheumatic, malignant and endocrinological disorders.

Teaching

The education offered by the Department of Medicine 3 is bound with lectures, courses and internships into the master plan of teaching in the internal medicine.

Graduate School

The graduate school is integrated in the Collaborative Research Centre (SFB) 643 and engaged with strategies pf cellular immune intervention. Speaker: Prof M Herrmann.

Selected Publications

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

Bondanza A, Zimmermann VS, Rovere-Querini P, Turnay J, Dumitriu IE, Stach CM, Voll RE, Gaipl US, Bertling W, Pöschl E, Kalden JR, Manfredi AA, Herrmann M (2004) Inhibition of phosphatidylserine recognition heightens the immunogenicity of irradiated lymphoma cells *in vivo*. J Exp Med, 200: 1157-65

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 (2007) Dickkopf-1 is a master regulator of joint remodeling. Nat Med, 13: 156-63

McInnes IB, Schett G (2007) Cytokines in the pathogenesis of rheumatoid arthritis. Nat Rev Immunol, 7: 429-42

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International Cooperation

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

Prof. E. Wagner, Prof J Penninger, Prof K Redlich, Prof J Smolen, Institut fuer Molekulare Biotechnologie, Vienna, Austria

Prof. S. Kiechl, Prof L Wildt, Univ.-Klinik Innsbruck, Austria

Prof. L. Joosten, Radboud University, Nijmegen, Netherlands

Prof. J. B. Imboden, University of California, San Francisco, USA

Prof. J. Savill, Prof I Dransfield, The University of Edinburgh, GB

Prof. D. S Pisetzky, Durham University, Durham, USA

Prof. T. Swaak, Erasmus Universiteit Rotterdam, Netherlands

Prof. J. van de Winkel, University Medical Centre Utrecht, Netherlands

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

Prof. D. Isenberg, Centre for Rheumatology Research, London, GB

Prof. O. P. Rekvig, University of Tromso, Norway

Prof. S. Muller, Institut de Biologie Moléculaire et Cellulaire du CNRS, Strassbourg, France

Prof. Y. Shoenfeld, Sheba Medical Centre, Tel-Hashomer, Israel

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

Prof. B. Walker, Boston Medical Centre, Boston, USA

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

Prof. A. Vandamme, Katholieke Universiteit Leuven, Netherlands

Research Equipment

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

- Nonsense-codon mediated decay (NMD) of non-functional mRNA (mRNA surveillance)
- The role of small, non coding RNAs (miRNAs) in the control of B cell maturation and antigen-induced B cell activation
- Molecular control of early B cell differentiation
- Signaltransduction in B cells

Structure of the Institution

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-Centre and the division is headed by Prof. Dr. Hans-Martin Jaeck together with three senior postdoctoral scientists, who supervise currently eight PhD students, five technicians and various rotation students. The main scientific focus of the division concentrates on the humoral immune response with a special emphasis on B cell biology. In addition, members of the division participate in teaching at the undergraduate, graduate and doctoral levels, which is reflected by a broad offer of lectures, seminars and lab courses.

Research

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 and cell sorting, and mouse immunology. Cell culture systems are being used to identify new, for instance miRNAs, adaptor proteins and transcription factors. 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-Centre and through its leading role in research groups and training grants (e.g., Research Unit (FOR832) and post graduate programme (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 needs to be carefully and tightly controlled to avoid the generation of self-reactive or leukemic B cells. One part of the first critical checkpoint in early B cell development is the expression of the pre-B cell receptor (pre-BCR) in early progenitor B cells. Only cells that express a functional IgH chain can assemble a pre-BCR and subsequently receive signals for survival, proliferation and differentiation. During the next developmental stage, rearrangement takes place at the IgL locus, leading to the synthesis of an IgL chain that is then assembled with the IgH chain to form the B cell receptor (BCR). The BCR is then controlled for binding to self structures in the bone marrow environment. B cells with a non-self BCR leave the bone marrow and differentiate via transitional stages into mature antigen-responsive B cells.

Nonsense-codon mediated decay (NMD) of non-functional mRNA (mRNA surveillance)

Project manager: H.-M. Jaeck, 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.

The role of small, non coding RNAs (miRNAs) in the control of B cell maturation and antigen-induced B cell activation

Project manager: H.-M. Jaeck, J. Wittmann

Another research focus is 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 in 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

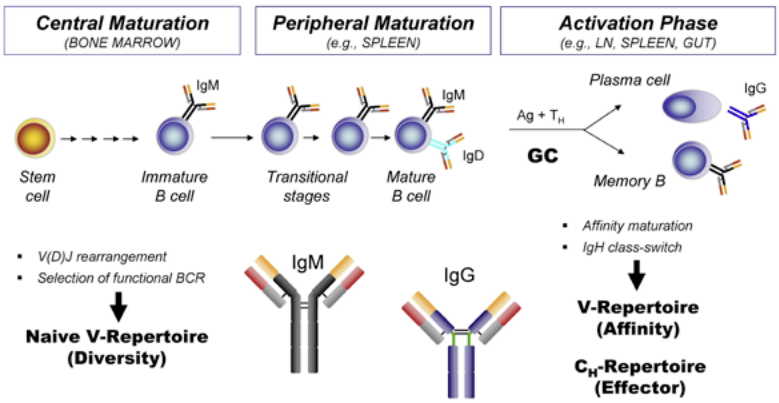

Fig. 1: Overview – humoral immunity

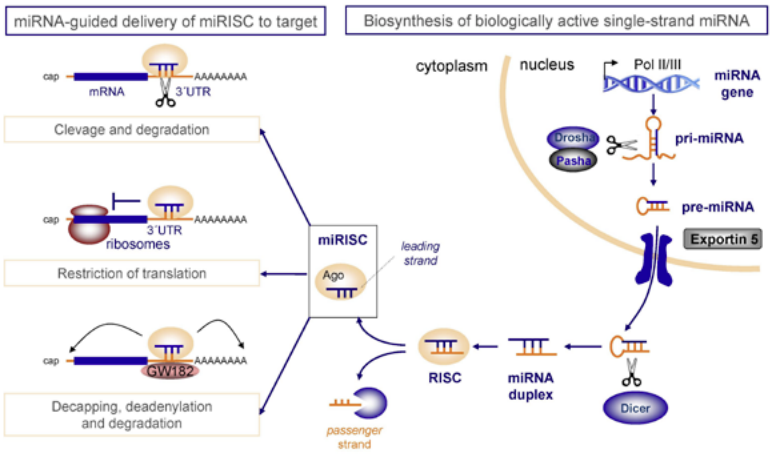

Fig. 2: RNA interference by endogenous microRNA

functional analysis of specific miRNAs involved in the B cell maturation and the generation of multiple myeloma or B cell lymphoma.

Molecular control of early B cell differentiation

Project manager: H.-M. Jaeck, W. Schuh

One major focus is the analysis of mechanisms that control early B cell development and signalling 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 signalling cascade, for example the transcription factor Krueppel-like factor 2 (KLF2) and a number of small non-coding microRNAs (miRNAs). We currently investigate the function of KLF2 in B cell maturation and activation as well as the function of pre-BCR-controlled miRNAs in conditional B cell-specific knockout mouse lines.

Signaltransduction 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 signalling pathways of the BCR and CD40 is currently being investigated in cell culture systems and transgenic mouse lines.

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

Wittmann J, Hol EM, Jaeck HM (2006) hUPF2 silencing identifies physiologic substrates of mammalian nonsense-mediated mRNA decay. Mol Cell Biol, 26: 1272-87

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Wittmann J, Jaeck HM (2008) Chapter 13. Identifying substrates of mRNA decay factors by a combined RNA interference and DNA microarray approach. Methods Enzymol, 449: 263-94

International Cooperation

Prof. Dr. Matthias Wabl, University of California, San Francisco, USA

Prof. Dr. Heinz Jacobs, University of Amsterdam, Netherlands

Meetings and International Training Courses

15.09.2007: International Symposium 10 Years ´Molecular Immunology, Erlangen

15.10.-17.10.2008: 2nd International GK Symposium, Regulators of Adaptive Immunity, Erlangen

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 Institution

The Department of Internal Medicine 4 comprises the Department of Medicine 4 (Nephrology and Hypertension) at the University Hospital Erlangen and the Community Hospital in Nürnberg. Together they represent the largest research and treatment centre for kidney disease and hypertension in Germany.
More than 90 physicians and basic scientists work in the Department of Medicine 4.
Patient related and experimental research aims 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 play a major role in research networks, such as the Clinical Research Unit 106 (End organ damage in arterial hypertension) and the Collaborative Research Centre 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, renal transplantation, diagnosis and therapy of essential and secondary hypertension and treatment of sepsis and multiorgan failure. The transplant centre Erlangen-Nürnberg and the Northbavarian regional centre of the German Sepsis Network are associated with the Department of Medicine 4.

Research

Development and progression of chronic kidney disease
Projects in this research area aim to determine changes of specialized renal cells 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, analyses are being performed in isolated glomerular, endothelial or tubular cells, human kidney tissue and animals. One focus in this area includes the growth and migration pattern of glomerular 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.
In parallel to the experimental studies, clinical studies are performed, which aim to retard the progression of specific kidney disease, including certain types of glomerular diseases and adult polycystic kidney disease.

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 analysed, in particular fibrogenesis, epithelial mesenchial transition and the growth of renal cysts. A junior research group at the Nikolaus-Fiebiger-Centre deals with the role of HIF in kidney cancer (PD Dr. M. Wiesener).
Mechanisms of hypoxia inducible gene expression are of particular relevance also for the regulation of erythropoiesis through the synthesis of erythropoietin (EPO). In addition to animal experiments investigating this regulation, it could be shown for the first time in a Phase I/II study in dialysis patients that therapy with an inhibitor of HIF degradation induces endogenous EPO production within and outside the kidneys.

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 aetiology 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.
Additional 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 are indirectly measured through determination of renal perfusion and sodium excretion. Additional studies in patients are dealing with the regulation of endothelial function and in particular the influence of lipids and hormones. In cooperation with the Department of Ophtalmology, perfusion, structure and endothelial

function of retinal vessels in patients with hypertension are being analysed.
The Clinical Research Unit "Target organ damage in arterial hypertension" (KFO 106), coordinated by Prof. Schmieder, uses a clinical research unit for its investigations, which has been established at the Medical Clinic 4.

Acute and chronic renal allograft failure
In cooperation with the Departments of Urology and Surgery, approximately 80 – 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 participated in several multicenter trials evaluating novel immunosuppressive drugs or their combination and has played an important role in the so called Elite Symphony Study.
An additional aim of this research area is to better characterize donor kidneys. In cooperation with the Deutsche Stiftung Organtransplantation, kidney function of brain dead kidney donors in Bavaria has been systematically investigated to identify parameters, which allow to predict the subsequent success of organ transplantation and will thus be helpful for future decision making about donor acceptance. In addition, during the first month after the transplantation, marker proteins are searched for in serum and urine, which indicate rejection episodes at an early stage. A further prospective trial deals with the influence of kidney transplantation on the course of vascular calcifications. 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
Approximately 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 Department of Medicine 4 in this context deal with epidemiological questions, aspects of public health care, the causes of an increased cardiovascular risk and the optimization of renal replacement therapy. Partly in collaboration with the Department of Medicine 2 mechanisms of atherogenesis are being investigated 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.
A rare complication of anemia management with recombinant human EPO is the development of neutralizing antibodies leading to pure red cell aplasia. A therapeutic trial with a novel EPO-mimetic that does not cross react with the antibodies has been initiated.
The AURORA trial has 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 Centre, located at the Department of Medicine 4 in Erlangen and Nürnberg has participated in observational and treatment trials and has played an important role in the so called "VISEP" study.

Teaching

The Department of Medicine 4 with its clinical units in Erlangen and Nürnberg contributes to the entire spectrum of curricular teaching in internal medicine, including main lectures, different courses and training of final year medical students. In addition, several specialized seminars are being offered and optional courses in Intensive care medicine, transplantation, kidney and vascular system.
There is also the opportunity for clerkships and short term visits. To demonstrate the link between experimental research and clinical pathophysiology, a lecture series has been offered for the first time for advanced medical students.

Selected Publications

Ekberg H, Tedesco-Silva H, Demirbas A, Vítko S, Nashan B, Gürkan A, Margreiter R, Hugo C, Grinyó JM, Frei U, Vanrenterghem Y, Daloze P, Halloran PF, ELITE-Symphony Study (2007) Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med, 357: 2562-75

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Machnik A, Neuhofer W, Jantsch J, Dahlmann A, Tammela T, Machura K, Park JK, Beck FX, Müller DN, Derer W, Goss J, Ziomber A, Dietsch P, Wagner H, van Rooijen N, Kurtz A, Hilgers KF, Alitalo K, Eckardt KU, Luft FC, Kerjaschki D, Titze J (2009) Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. Nat Med, 15: 545-52

International Cooperation

Please find further informations on our website:
www.medizin4.uk-erlangen.de

Meetings and International Training Courses

03.03.2007: Sepsis und Multiorganversagen, Nürnberg

22.–23.02.2008: Target Organ Damage in Arterial Hypertension, Erlangen

17.–19.10.2008: Molecular Targets in Renal Disease, Bamberg

Department of Medicine 5 – Haematology and Oncology

Chair of Haematology and Oncology

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Research Focus
- T cell based immunotherapy
- Tumor immune escape
- Natural killer (NK) cells
- Antibodies
- HLA-laboratory

Structure of the Institution

On October 1st 2007, the Chair of Hematology and Oncology at the University Hospital of the Friedrich-Alexander-University Erlangen-Nürnberg was created. Professor Dr. Andreas Mackensen holds the first Chair of Hematology and Oncology and serves as the chairman of the Department of Medicine 5 – Hematology and Oncology, which was newly established in the internal medicine of the University Hospital Erlangen. The department has a total of 61 employees (15 on extra-departmental funding). The scientific section counts 10 post-doctoral fellows, 12 graduate students and 9 technicians.
The scientific section is constituted of various research subgroups with a common focus on the development of new treatment strategies for cellular and humoral immunotherapy of malignant diseases. In addition, core research projects include studies on tumor immune-escape mechanisms and allogeneic bone marrow transplantation with a special emphasis on the use of regulatory cells (T lymphocytes and NK cells) to modulate the graft-versus-host immune response after allogeneic stem cell transplantation. The Chair of Hematology and Oncology jointly operates the laboratory for immunogenetics and transplantation (HLA-laboratory, head PD Dr. B. Spriewald) together with the Chair of Medicine III. The main activities of this laboratory include HLA class I and class II typing and chimerism analysis after allogeneic stem cell transplantation. Since 1999, this laboratory has been accredited by the European Federation of Immunogenetics (EFI) and provides as one of twelve laboratories of the German Transplantation Foundation (Deutsche Stiftung Organtransplantation, DSO) immunogenetic diagnostics for the area of Northern Bavaria.
The clinical focus is on hematologic and lymphatic malignancies, including but not limited to acute and chronic leukemias, myelodysplasias, myeloproliferative disorders, malignant lymphoma and multiple myeloma. In addition, solid tumors are being treated, including osteosarcoma, gastrointestinal tumors, head and neck cancer, lung cancer, and urological tumors. The full range of treatment modalities, including allogeneic stem cell transplantation, is available at the department. Furthermore, in 2008, the interdisciplinary outpatient urologic-oncologic centre "AURONTE" was established together with the Chair of Urology, realizing an important step towards interdisciplinairy treatment of urogenital tumors.

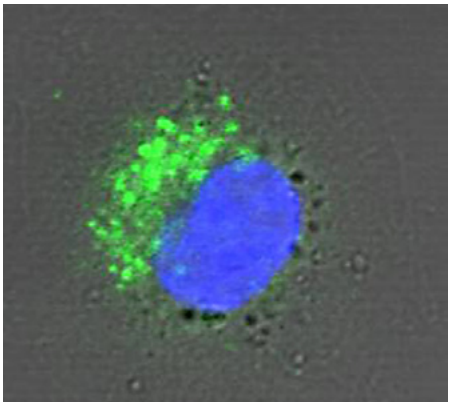
Research

T cell based immunotherapy
Project manager: A. Mackensen, M. Aigner, S. Voelkl
The Collaborative Research Centre (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. In a clinical research group (leader Prof. Mackensen) supported by the Bavarian immune therapy network (BayImmuNet), the isolation and subsequent expansion of patient-derived tumor-specific T-cells under "Good Manufacturing Practice" (GMP) conditions is being established as prerequisite for the application of these cellular products in the context of clinical studies for treatment of malignant diseases. The population of human TCRα/β+ 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.

Tumor immune escape
Project manager: A. Mackensen, M. Aigner, K. Singer, R. Gary
Tumors can evade the recognition by the immune system. One well-known immune escape mechanism is the dysregulation of the antigen processing machinery (APM) in tumors, which consists of all proteins and complexes involved in the processing of antigens either produced intra-cellular or taken up externally. In a project funded by the German José Carreras Leukemia Foundation we try to determine the importance of this particular mechanism for the pathogenesis of acute myeloid leukaemia.
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/ Dipl. Biol. K. Singer in a project funded by the interdisciplinary clinical research centre (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.

Natural killer (NK) cells
Project manager: E. Ullrich
The research group of Prof. Dr. E. Ullrich, Dipl. Biol. K. Meinhardt and A. Abendroth mainly focus on the role of natural killer (NK) cells in cellular immunoregulation, especially in anti-tumor responses and bone marrow transplantation for treatment of malignant hematologic diseases.
Bone marrow transplantation (BMT) and stem cell transplantation (SCT) have gained wide acceptance in the treatment of hematological malignancies. Although BMT provides curative graft-versus-leukemia (GVL) effects, the graft-

versus-host disease (GVHD) is an often lethal complication of allogeneic BMT. A great challenge of current research on allogeneic BMT attempts to separate the undesirable GVHD complications from the desirable GVL effects.
Recently, clinical studies exploiting the impact of innate effector cells such as NK cells have provided promising results, especially in killer inhibitory receptor-ligand-mismatched transplantation. It has been observed that allogeneic donor NK cells mediate GVL effects and



Confocal microscopy of activated NK cells showing perforin expression (green fluorescence). Prof. Ullrich 2008.

support immune reconstitution, while preventing GVHD.
It has now been shown that NK cells represent a highly heterogeneous population of phenotypically and functionally different subsets. Our own previous work focused on the characterization of different subpopulations of murine NK cells, Dendritic Cells (DC) and Killer Dendritic Cells (KDC). Our recent projects aim to analyse the immunoregulatory functions of different NK- and DC-subsets in different tumor models and in a murine GVHD model 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. An international collaboration with the laboratory of Prof. L. Zitvogel, Paris-Villejuif, France, is funded by INCa and German Academic Exchange Service (DAAD).

Antibodies
Project manager: B. Stockmeyer
The team of PD Dr. Bernhard Stockmeyer, Dipl. Biol. Heike Horner and Dipl. Biol. Yvonne Guettinger focuses on the development of recombinant monoclonal antibodies and derivatives for targeted tumor therapy. Therefore we characterize tumor cell antigens, which are suitable for polymorphonuclear granulocyte (PMN)-mediated antibody-dependent cytotoxicity (ADCC). We are particularly interested in the interaction between the intracellular parts of target antigens with the cytoskeleton or signal transduction molecules like phosphokinases to define motives that induce target cell death.
We have identified the receptor for the constant part of immunoglobulin A (FcaRI) as trigger molecule for PMN mediated ADCC. In cooperation with Prof. G. Fey, Department of Genetics, Faculty of Natural Science, we are currently generating multispecific recombinant antibody constructs triggering FcaRI mediated ADCC. Due to the specific requirements of PMN for suitable target antigens we will combine different specifities for tumor antigens (e. g. HLA-class II and CD19) in a single recombinant antibody derived small modular immunopharmaceutical. Thereby we expect to increase tumor selectivity and cytotoxicity in the treatment for B-cell malignancies. This project is funded by the Wilhelm Sander-Stiftung.

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 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. This project is funded by the Interdisciplinary Centre of Clinical Research (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 interdisciplinairy fashion. In the summer semester of 2008, 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

Fischer K, Hoffmann P, Voelkl S, Meidenbauer N, Ammer J, Edinger M, Gottfried E, Schwarz S, Rothe G, Hoves S, Renner K, Timischl B, Mackensen A, Kunz-Schughart L, Andreesen R, Krause SW, Kreutz M (2007) Inhibitory effect of tumor cell-derived lactic acid on human T cells. Blood, 109: 3812-9

Gottfried E, Kreutz M, Mackensen A (2008) Tumor-induced modulation of dendritic cell function. Cytokine Growth Factor Rev, 19: 65-77

Spriewald BM, Ensminger SM, Bushell A, Wood KJ (2008) Neutralizing interleukin-4 prevents transplant arteriosclerosis mediated by indirect pathway T cells under CD40-CD154 costimulation blockade. Transplantation, 86: 1615-21

Terme M, Ullrich E, Delahaye NF, Chaput N, Zitvogel L (2008) Natural killer cell-directed therapies: moving from unexpected results to successful strategies. Nat Immunol, 9: 486-94

International Cooperation

Michael I. Nishimura, Department of Surgery, Medical University of South Carolina, Charleston, USA

J. van de Winkel, University of Utrecht, Netherlands

Laurence Zitvogel, Institut Gustave Roussy, Paris – Villejuif, France

Research Equipment

Becton Dickinson FACS Canto II

Applied Biosystems Sequencer AB Genetic Analyser 3130

Department of Nuclear Medicine

Chair of Clinical Nuclear Medicine

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Research Focus
- Molecular imaging
- Correlative imaging

Structure of the Institution

The Department of Nuclear Medicine covers a broad range of the diagnostic and therapeutic procedures of this specialty. It is equipped by a therapeutic ward, three planar γ cameras, two multidetector SPECT cameras, and one SPECT/spiral-CT hybrid system. In cooperation with the Institute of Radiology, a PET/CT hybrid camera is operated in the Imaging Sciences Institute, a joint venture between Siemens Medical Solutions and the Department. The radiochemical laboratory of the Department is equipped by synthesis modules for synthesising radiotherapeutics and by a further module for producing PET tracers, which is operated under GMP conditions in cooperation with the PETNET GmbH. In the laboratory of molecular imaging of the Department new radiopharmaceuticals are being developed and evaluated. The 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.

Research

Molecular imaging

Molecular medicine interprets disease as disturbed expression or activity of proteins such as enzymes or receptors. Diagnostic nuclear medicine images the distribution of radioactively labelled 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. an important condition to capitalize on this potential of nuclear medicine as an also clinically useful tool of molecular imaging is a scientific infrastructure that unifies elements of chemical, cell biological and molecular biological techniques. therefore, recently, a laboratory of molecular imaging has been established within the Department of Nuclear Medicine. One main research area of the laboratory of molecular imaging is the investigation of the metabolism and uptake of radiopharmaceuticals in cell cultures aimed at elucidating the regulation of the accumulation of F-18-deoxyglucose and radiolabelled amino acids within endothelia, inflammatory cells, and thyrocytes. The evidence thus gathered is relevant to the interpretation of clinical PET. In 2007, one of the publications from this scientific focus was honoured with the Brahms-Prize of the German Society for Nuclear Medicine. The development of new radiopharmaceuticals is the second research focus of the Laboratory of Molecular Imaging: In cooperation with Prof. Gmeiner from the Chair of Pharmaceutical Chemistry of the University of Erlangen-Nürnberg radioligands for the D3- and D4-subtype of the dopamine receptor have been synthesized and validated *in vitro*. As yet, radiopharmaceuticals suited to study these receptor subtypes supposed to be implicated in the pathogenesis of several neuropsychiatric disorders are lacking so that this project may be considered to be truly innovative. In 2007 and 2008, this project was supported by the German Research Foundation (DFG). In 2008, a part of this project was awarded the pharmaceutical science prize "Phoenix". Furthermore, new radiotracers for the imaging of angiogenesis and peptides are being developed. In 2007 and 2008, this research was supported by the German Research Foundation (DFG) and the Federal Ministry of Education and Research (BMBF).

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 socalled 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 University of Erlangen-Nürnberg (Director: Prof. Hornegger) and Siemens Medical Solutions the Clinic of Nuclear Medicine develops new methodology of correlative imaging and investigates its clinical value.

Teaching

The Chair teaches nuclear medicine to students of medicine. Furthermore, the Chair organizes the course on radioprotection for students of molecular medicine. He also participates in teaching physiology, pharmacology and computer sciences. In abroad fashion, the Chair performs postgraduate teaching for physicians in Middle and Upper Franconia.

Selected Publications

Prante O, Einsiedel J, Haubner R, Gmeiner P, Wester HJ, Kuwert T, Maschauer S (2007) 3,4,6-Tri-O-acetyl-2-deoxy-2-[(18)F]fluoroglucopyranosyl Phenylthiosulfonate: A Thiol-Reactive Agent for the Chemoselective (18)F-Glycosylation of Peptides. Bioconjug Chem, 18: 254-262

Salama I, Hocke C, Utz W, Prante O, Boeckler F, Hübner H, Kuwert T, Gmeiner P (2007) Structure-selectivity investigations of D2-like receptor ligands by CoMFA and CoMSIA guiding the discovery of D3 selective PET radioligands. J Med Chem, 50: 489-500

Han J, Köstler H, Bennewitz C, Kuwert T, Hornegger J (2008) Computer-aided evaluation of anatomical accuracy of image fusion between X-ray CT and SPECT. Comput Med Imaging Graph, 32: 388-95

Kollorz EK, Hahn DA, Linke R, Goecke TW, Hornegger J, Kuwert T (2008) Quantification of thyroid volume using 3-d ultrasound imaging. IEEE Trans Med Imaging, 27: 457-66

Prante O, Tietze R, Hocke C, Löber S, Hübner H, Kuwert T, Gmeiner P (2008) Synthesis, Radiofluorination, and In Vitro Evaluation of Pyrazolo[1,5-a]pyridine-Based Dopamine D4 Receptor Ligands: Discovery of an Inverse Agonist Radioligand for PET. J Med Chem, 51: 1800-1810

Stadlbauer A, Prante O, Nimsky C, Salomonowitz E, Buchfelder M, Kuwert T, Linke R, Ganslandt O (2008) Metabolic Imaging of Cerebral Gliomas: Spatial Correlation of Changes in O-(2-18F-Fluoroethyl)-L-Tyrosine PET and Proton Magnetic Resonance Spectroscopic Imaging. J Nucl Med, 49: 721-729

International Cooperation

Dr A.H. Vija, Molecular Imaging, Siemens Medical Solutions, Hoffman Estates, Chicago, USA

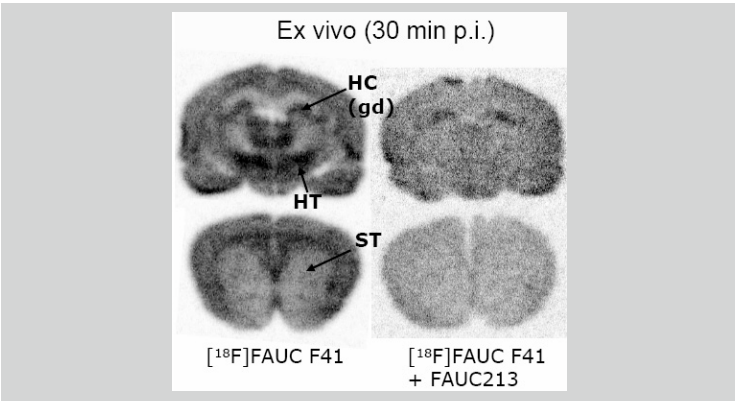
Dr. rer.nat. R. Haubner, Klinik fuer Nuklearmedizin, Medizinische Universitaet Innsbruck, Austria

Research Equipment

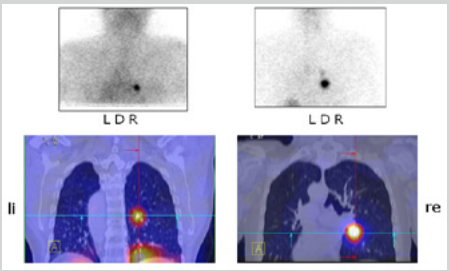
Siemens Tier PET "Inveon"

Siemens SPECT/CT Symbia T6

Siemens PET/CT Biograph 64



Ex vivo autoradiography of rat brain slices after i.v. injection of [18F]FAUC F41 (10 MBq, 30 min p.i. coronal, 20 µm; left column). Co-injection of the D4 selective neutral antagonist FAUC 213 (1mg/kg; right column) inhibited the binding of [18F]FAUC F41 in hippocampus (HC; gd: dentate gyrus) and hypothalamus (HT), cortical regions and septum. The striatum (ST; lower row) is known as a brain region with low D4 receptor expression



Patient with iodine arid pulmonal metastases of thyroid carcinoma. The SPECT / CT allows a precise anatomical mapping of metastasis once in the lung and once in the left hilus. This information is crucial for further therapeutic management (surgery, irradiation)

Institute of Radiology

Chair of Diagnostic Radiology

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Research Focus

- Non-invasive diagnostic of cardiovascular disease
- Functional and metabolic magnetic resonance imaging (MRI)
- Biological assessment of DNA damage due to diagnostic irradiation
- Imaging of the head and neck
- Breast imaging
- Contrast media induced nephropathy

Structure of the Institution

The Department of Radiology of the University of Erlangen-Nürnberg has six subsections (internal medicine, surgery, otorhinolaryngology, pediatric radiology, gynecology, and neuroradiology). The staff of the department consists of 4 professors, 4 assistant professors, 31 medical doctors, 2 experimental scientists, 69 radiographers and assistant medical technicians and 21 employees in the office and controlling. The Department of Radiology provides the full range of radiologic imaging modalities. Furthermore a variety of interventional procedures as 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. Focuses of research are the imaging of the head and neck, breast, heart, vessels and the evaluation of functional MRI respectively. Furthermore experimental laboratory studies play a well-established role in our scientific activities.

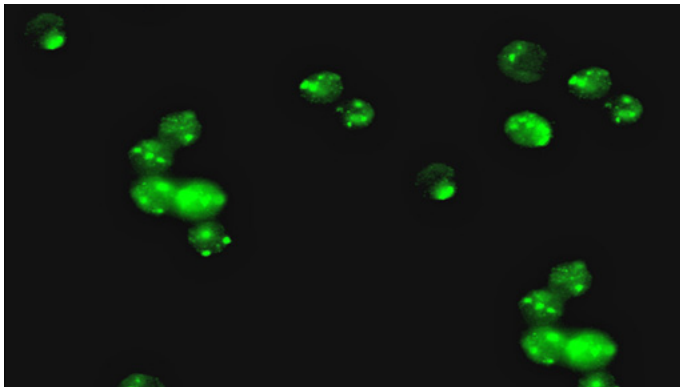
Research

Non-invasive diagnostic of cardiovascular disease
Project manager: K. Anders, A. Kuettner, R. Janka, A. Schmid, M. Lell
Due to the technical progress of computed tomography and magnetic resonance imaging both methods offer new possibilities in the diagnostic assessment of cardiovascular disease which are explored *in vitro* and clinically in cooperation with the Departments of Cardiology (Prof. Daniel), Otorhinolaryngology (Prof. Iro), Vascular Surgery (Prof. Lang), Maxillofacial Surgery (Prof. Neukam), Department of Computer Science – Pattern Recognition (Prof. Dr. Ing. J. Hornegger), as well as the Institute for Medical Physics (Prof. Kalender), Siemens Healthcare and the Department of Radiology, UCLA, David Geffen School of Medicine (Prof. Dr. D. Enzmann).
New CT angiography examination protocols are developed to assess adult and pediatric cardiovascular disease (coronaries, carotids, aorta and peripheral vasculature). A special aspect is the minimization of radiation exposure as well as establishing suitable measurement models. Another focus is the optimization of contrast media injection protocols. Novel CT techniques such as dual spectral analysis are used for vessel visualization. After testing in models the clinical potential is explored. Focus point is the automated vessel segmentation and analysis of atherosclerotic plaque.
MRI allows for precise functional assessment of cardiac chambers as well as valves. Focuses of research are the functional analysis of the entire heart in patients with impaired cardiac function and the evaluation of novel therapies.

Functional and metabolic magnetic resonance imaging (MRI)
Project manager: M. Uder, R. Janka, S. Alibek
Diffusion weighted imaging (DWI) visualizes the diffusion of free water molecules in tissue. The use of this technique in other body regions than the brain is a new field of research. Improvements of the MR hardware and software enable DWI measurements in a reasonable time, even in free breathing. We use this technique to differentiate malignant from benign tissue and inflammatory from tumour tissue in selected patient groups.
In MRI perfusion measurements without the use of contrast material are possible. For that purpose the inflowing (arterial) spins become labelled and their concentration in the organ of interest can be measured as signal strength. Our focus of interest is the kidney. *In vivo* experiments of the physiologic change of the kidney perfusion after drug therapy or after contrast media applications become possible.

Biological assessment of DNA damage due to diagnostic irradiation
Project manager: M. Uder, M. Kuefner, S. Schwab, M. Heckmann, C. Engert
The established dose parameters in radiologic procedures can determine exposition, but they do not adequately evaluate the dose deposition and the biological x-ray interactions in the patient. The determination of DNA double-strand breaks using an immunofluorescence microscopic technique, which was established in collaboration with Prof. Dr. Loebrich (TU Darmstadt), provides an accurate and sensitive estimate of biological radiation effects. The method is based on the phosphorylation of the histone variant H2AX after DSB formation, which can be stained with a specific antibody. Recent studies have shown a strong correlation between DSB levels and dose length product in patients undergoing CT scans and within 24 hours after exposure the number of DNA lesions returned to the baseline levels. In angiography DNA damages were dependent on the dose deposed, 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) on the biological dose is investigated in patients and in biological phantom models as well. Furthermore the potential protective effect of radical binding substances should be assessed.

Imaging of the head and neck
Project manager: M. Lell, S. Alibek, F. Hinkmann, M. Kramer, 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 Ear, Nose and Throat - Head and Neck Surgery (Prof. Iro), Department of Maxillofacial Surgery (Prof. Neukam) and the Department of Radiation Therapy (Prof. Fietkau).
Methodological and clinical studies evaluating the use of CT and MRI in the preparation and planning of reconstructive surgery in coopera-



Double strand breaks in blood lymphocytes are visualized using fluorescence microscopy after staining against the phosphorylated histone variant γ-H2AX. The bright spots are called foci, each focus represents one double strand break.

tion with the Department of Oral and Maxillofacial Surgery (Prof. Neukam).
Methodological and clinical studies in dose reduction techniques in CT in cooperation with the Institute of Medical Physics (Prof. Kalender).

Breast imaging
Project manager: R. Schulz-Wendtland, E. Wenkel, S. Schwab, R. Janka, B. Adamietz
Breast imaging is an important research domain of the Institute of Radiology. 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). In cooperation with the Fraunhofer Institut, Erlangen and the Definiens AG (Prof. Binnig) a CAD system is being developed. Furthermore, a new MRI-based method for diagnosting ductal disease was implemented. Another main focus in breast MRI lies in the development of new MRI sequences for better differentiation between malignant and benign breast disease and the development of an automated breast ultrasound.

Contrast media induced nephropathy
Project manager: M. Uder, M. Heinrich
Contrast media induced nephropathy (CIN) is a common cause of hospital-acquired acute renal failure and is associated with increased rates of mortality and morbidity as well as longer hospital stays and poor long-term prognosis. A working group from the Institute of Radiology is investigating *in vitro* mechanisms involved in the pathogenesis of contrast media induced nephropathy. Tubulotoxic effects are being investigated in renal tubular cell cultures. Important features of these experiments are the comparisons between isoosmolar and low-osmolar contrast media and between iodinated and gadolinium based contrast agents. In addition, the Institute of Radiology is involved in multicenter studies comparing the incidence of CIN in high-risk patients with different types of contrast media.

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

Alibek S, Zenk J, Bozzato A, Lell M, Grunewald M, Anders K, Rabe C, Iro H, Bautz W, Greess H (2007) The value of dynamic MRI studies in parotid tumors. Acad Radiol, 14: 701-10

Heinrich MC, Kuhlmann MK, Kohlbacher S, Scheer M, Grgic A, Heckmann MB, Uder M (2007) Cytotoxicity of iodinated and gadolinium-based contrast agents in renal tubular cells at angiographic concentrations: *in vitro* study. Radiology, 242: 425-34

Lell MM, Ditt H, Panknin C, Sayre JW, Klotz E, Ruehm SG, Villablanca JP (2008) Cervical CT angiography comparing routine noncontrast and a late venous scan as masks for automated bone subtraction: feasibility study and examination of the influence of patient motion on image quality. Invest Radiol, 43: 27-32

Lell MM, Gmelin C, Panknin C, Eckel KT, Schmid M, Bautz WA, Greess H (2008) Thin-slice MDCT of the neck: impact on cancer staging. AJR Am J Roentgenol, 190: 785-9

Schwab SA, Uder M, Schulz-Wendtland R, Bautz WA, Janka R, Wenkel E (2008) Direct MR galactography: feasibility study. Radiology, 249: 54-61

Kuefner MA, Grudzenski S, Schwab SA, Azoulay S, Heckmann M, Heinrich MC, Lobrich M, Uder M (2009) X-ray-induced DNA double-strand breaks after angiographic examinations of different anatomic regions. Rofo, 181: 374-80

International Cooperation

Prof. Dr. D. Enzmann, Department of Radiology, UCLA, Los Angeles, USA

Dr. J. Petersen, Department Radiologie, Medizinische Universitaet Innsbruck, Austria

Meetings and International Training Courses

Fortbildungskurs Mammadiagnostik 03.2007, Erlangen

MR-Compact 06.2007, Bamberg

Mammasonokurs 09.2007, Erlangen

Forum interventionelle Neuroradiologie 11.2007, Erlangen

Fortbildungskurs Mammadiagnostik 04.2008, Erlangen

Mamma-MRT Kurs 05.2008, Erlangen

Angiographiekurs 06.2008, Erlangen

MR-Compact 06.2008, Bamberg

Kinderradiologie-Symposium 09.2008, Erlangen

Mammasonokurs 09.2008, Erlangen

Herz-MRT Kurs 10.2008, Erlangen

Mamma-MRT Kurs 12.2008, Erlangen

Research Equipment

Siemens Magnetom Trio

Siemens Magnetom Avanto

Siemens Sensation Definiton AS+

Siemens Sensation 64

Siemens Axiom Artis with flat panel detector

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Division of Neuroradiology

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Research Focus

- Clinical and experimental validation of flat-panel volume CT
- Multimodal CT and MR imaging in of cerebrovascular disease
- Preoperative comprehensive imaging of epilepsy
- 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 Institution

In the Division of Neuroradiology a total of 32 stuff members are employed. Research is performed by 11 medical doctors, 5 postgraduates, and externally funded by one biologist, one computer scientist and one veterinarian, respectively.
The Division of Neuroradiology performs the neuroradiological work-up for patients of the University Hospital of Erlangen and for many patients referred from external hospitals. A special focus lies on the endovascular therapy of neurovascular diseases such as 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 Institute 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.

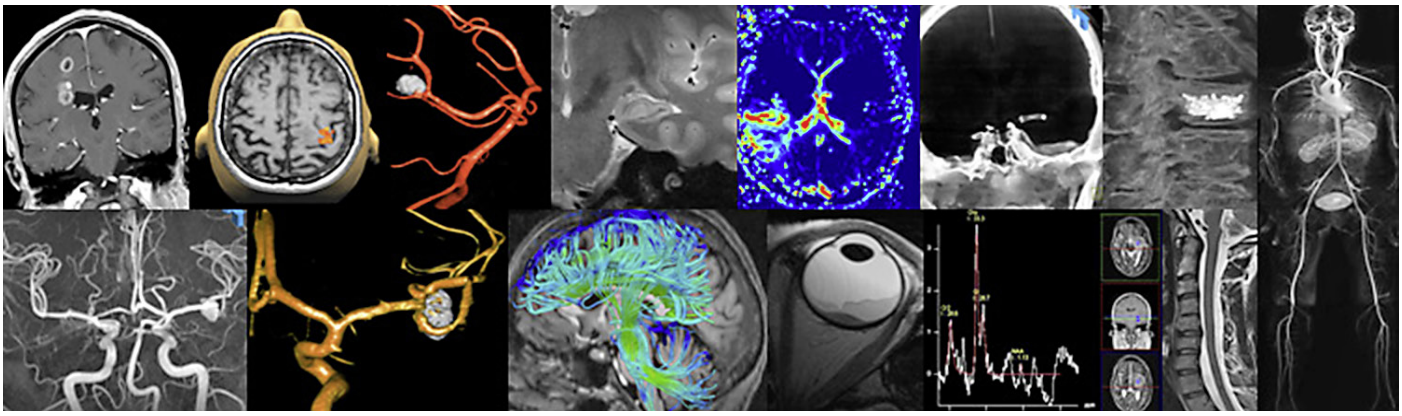
Multimodal CT and MR imaging in of cerebrovascular disease
In cooperation with the Department of Neurology we participate in several acute stroke studies. Using multimodal imaging algorithms including perfusion-, diffusion- and angiographic imaging by CT and mainly MRI we evaluate the individual indication for acute stroke therapies such as thrombolysis and/or other neuroprotective therapies. 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.

Preoperative comprehensive imaging of epilepsy
In cooperation with the Epilepsy Centre/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.

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 (KFO 661) we evaluate multimodal imaging strategies to assess brain gliomas using micro-CT, high-field MRI and micro-PET. We closely cooperate with the Institute of Medical Physics, the Institute of Experimental and Clinical Pharmacology and Toxicology, Core Unit small animal imaging, and the Department of Nuclear Medicine. Additionally, using an elastase-induced aneurysm model, we evaluate different imaging techniques and new materials and techniques for endovascular treatment.



The Division of Neuroradiology focuses mainly on visualisation and cerebrovascular therapy

Teaching

The Division of Neuroradiology is involved in training medical students. We offer a large variety of lectures and practical courses partly in cooperation with the neurological and neurosurgical department, ophthalmology, psychiatry and radiology. In addition, we train residents in Neurororadiology and general radiology and radiological technicians.

Selected Publications

Doelken MT, Richter G, Stefan H, Doerfler A, Noemayr A, Kuwert T, Ganslandt O, Nimsky CH, Hammen T (2007) Multimodal coregistration in patients with temporal lobe epilepsy--results of different imaging modalities in lateralization of the affected hemisphere in MR imaging positive and negative subgroups. AJNR Am J Neuroradiol, 28: 449-54

Richter G, Engelhorn T, Struffert T, Doelken M, Ganslandt O, Hornegger J, Kalender WA, Doerfler A (2007) Flat panel detector angiographic CT for stent-assisted coil embolization of broad-based cerebral aneurysms. AJNR Am J Neuroradiol, 28: 1902-8

Engelhorn T, Hufnagel A, Weise J, Baehr M, Doerfler A (2007) Monitoring of acute generalized status epilepticus using multilocal diffusion MR imaging: early prediction of regional neuronal damage. AJNR Am J Neuroradiol, 28: 321-7

Doelken M, Struffert T, Richter G, Engelhorn T, Nimsky C, Ganslandt O, Hammen T, Doerfler A (2008) Flat-panel detector volumetric CT for visualization of subarachnoid hemorrhage and ventricles: preliminary results compared to conventional CT. Neuroradiology, 50: 517-23

Savaskan NE, Heckel A, Hahnen E, Engelhorn T, Doerfler A, Ganslandt O, Nimsky C, Buchfelder M, Eyuepoglu IY (2008) Small interfering RNA-mediated xCT silencing in gliomas inhibits neurodegeneration and alleviates brain edema. Nat Med, 14: 629-32

Engelhorn T, Struffert T, Richter G, Doelken M, Ganslandt O, Kalender W, Doerfler A (2008) Flat panel detector angiographic CT in the management of aneurysmal rupture during coil embolization. AJNR Am J Neuroradiol, 29: 1581-4

International Cooperation

Dr. A. Bose, Department of Radiology and Neurology, Lenox Hill Hospital New York, USA

Department of Neuroscience/Neuroimaging, Ospedale San Raffaele, Mailand, Italy

Institut fuer Radiologie und Neuroradiologie, Landesnervenklinik Linz, Austria

Institut fuer Neuroradiologie, Klinikgruppe Hirslanden, Zuerich, Switzerland

Meetings and International Training Courses

07.–08.02.2008: Workshop "Hands-on Angiography", ECR Wien, Austria

07.–08.02.2008: Workshop "Hands-on MRI", ECR Wien, Austria

23.02.2008: Workshop "Neuroradiologie fuer die Praxis", Leipzig, Germany

14.06.2008: Workshop "Hands-on Stroke MRI", Erlangen

17.–19.10.2008: Refresherkurs: Neuroradiologie. 61. Jahrestagung der Bayerischen Roentgengesellschaft Bad Windsheim

24.–25.10.2008: Workshop "Interventionelle Neuroangiographie", Erlangen and Forchheim

22.11.2008: Workshop "Hands-on Stroke MRI", Erlangen

13.12.2008: Workshop "Hands-on Stroke-MRT", Linz, Austria

Research Equipment

Siemens Axiom Artis dBA; Biplanare Flachdetektor-Angiographieanlage mit integrierter CT-Option

Siemens Somatom Sensation 64; 64-Zeilen-CT

Siemens 1.5 Tesla Magnetom Sonata MRT

Siemens 3 Tesla Magnetom TimTrio MRT

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Research Focus
- Clinical trials office
- Clinical cancer registry
- Anorectal dysfunction
- Molecular mechanisms of inflammatory related angiogenesis
- Molecular mechanisms of infection related angiogenesis
- Clinical-experimental research

Structure of the Institution

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, with its principle task being the efficient initiation and monitoring of the clinical trials. From the very beginning numerous trials targeting the improvement of cancer therapy, optimization of presently available surgical techniques and to establish new surgical techniques have been supervised.
The fundamental molecular research has been conducted at the Division of Molecular and Experimental Surgery (AMEC), also founded in 2003.
Main focus of the research of the AMEC is molecular oncology with focus on new markers for prognosis and molecular regulation of inflammation associated angiogenesis in tumor and infectious diseases. In the reported period the department consisted of eleven scientific researchers (three post-docs, eight postgraduates). In over 80% funding came from grants from German Research Foundation (DFG), Deutsche Krebshilfe, IZKF and ELAN-awards from the University Hospital Erlangen for equal opportunity for women. This department takes part in subprojects of the DFG with focus on "Infection of the endothelium" (1130) and Graduiertenkolleg 1071 "Viruses of the immune system". During the reported period two patents have been developed. Results of the research were transformed into economics by issuing a licence for an ELISA by two companies in the USA (Genway Biotech, Quest Diagnostics).

Research

Clinical trials office
Project manager: 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 Radiation Therapy whereas a total of 63 patients haven been included until 2/2009 (Prof. Hohenberger, Prof. Goehl).
A prospective-randomised, multi-center phase III trial investigates if preoperative chemo radiation of a resectable tumor of the pancreatic head leads towards better median overall survival (ISRCTN78805636) (Prof. Hohenberger, Dr. Golcher).
Further multi-center trials investigate malignant melanoma, gastrointestinal stroma tumors and colon carcinoma. There are also other diseases evaluated by clinical trials like anorectal dysfunction, acute cholecystitis, prevention of incisional hernias and resection of deviating ileostomies (Prof. Hohenberger, Prof. Matzel, Dr. Golcher).

Clinical cancer registry
Project manager: W. Hohenberger, S. Merkel
Since 1978 a Clinical Cancer Registry is kept for prospective, structured and organ specific documentation of cancer. At present more than 20.000 patients are registered. The main focus is the colorectal cancer with nearly 9 000 documented cases. Patients are tracked live-long and the rate of `lost cases` is 0.5%.
The main target of the science based evaluation of these data are an improvement of classification of tumors, identification of prognostic markers, definition of indicators for quality and the implementation of the German S3-guidelines. The specific diagnostics and the multimodal therapeutical strategies administered in many patients result 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 stimulation per pace maker combined with gracilis plastic for therapy of faecal incontinency has been implanted at this clinic. Since then the method has been continuously improved. The patients are participating in an extensive post operational review program, which allows documenting sustainable therapeutic effects for the first time. Repeated workshops on a national and international scale, which are dedicated to convey innovative therapeutic methods, initiate 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 in cooperation.

Molecular mechanisms of inflammatory related angiogenesis
Project manager: M. Stuerzl
In studies conducted beforehand, the study group managed to identify the great GTPase guanylate binding protein 1 (GBP-1) as the main regulator of the inflammatory related angiogenesis inhibitor. New studies on the mechanism of the effects of GBP-1 have shown that GBP-1 is definitely reducing the migration and invasion capability of endothelial cells through Integrin mediated signal processes (Weinlaender et al., 2008).
First available indications are suggesting that this mechanism could result in an improved survival of colorectal carcinoma with inflammatory stroma reactions. In order to study the epigenetic effects of inflammatory stroma reactions on the angiogenic behaviour of tumor vascular endothelial cells, it was managed for the first time to cultivate vital microvascular endothelial cells of more than 20 various colorectal carcinomas. This included taking comparable cell samples of not affected healthy colorectal tissue from the very same patients. At comparable examinations, significant differences were detected between the two groups of cell samples (Schellerer et al., 2007). This suggests that at tumor endothelial cells, an epigenetic imprinting is in effect on the micro milieu in

the tumor. Hopefully, new starting points can be developed for a more specific anti-angiogenic therapy through the detected differences

Molecular mechanisms of infection related angiogenesis
Project manager: M. Stuerzl
For the examination of the infection associated angiogenesis, analysis for the development of the AIDS associated Kaposi's sarcoma (KS) is at the centre of attention. This sarcoma is an endothelial tumor which is initiated through the human herpes virus-8 (HHV-8). The target of the study is to determine which of the 86 genes that comprise HHV-8 is playing a part in the angiogenic activation of KS and whether several of these genes concur in the context of the development of KS. For these studies new systemized biologic approaches were introduced at the clinic for the first time in order to allow conducting a great number of genetic functional analyses simultaneously. With this approach 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 systemized biological application for the high-throughput analysis of viral proteins to cellular signal transduction. Comparing proteomic analysis for genetic effects complements this approach.

Clinical-experimental research
Project manager: R. Croner
The objective of this study group is the individualization of the multi modal therapy for gastrointestinal tumours based on molecular predictors and factors for prognosis. In cooperation with 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 metastasis of lymph nodes from primary tumors of 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 the industry. The functional characterization of the genes identified is currently conducted through cooperation projects (PD Croner, Prof. Stuerzl).

Groundbreaking for a new building at the Department of Surgery. Source: University Hospital Erlangen

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, intensive prep classes are offered alongside other measures. In order to gain a realistic perspective of the clinical routine, smaller, supervised groups are allowed to visit the operation room and the intensive care unit. During the winter term 2007/2008 Prof. I. Schneider was granted the Lecturer's Award of the Medical Faculty. 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

Schellerer VS, Croner RS, Weinlaender K, Hohenberger W, Stuerzl M, Naschberger E (2007) Endothelial cells of human colorectal cancer and healthy colon reveal phenotypic differences in culture. Lab Invest, 87: 1159-70

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

Golcher H, Brunner T, Grabenbauer G, Merkel S, Papadopoulos T, Hohenberger W, Meyer T (2008) Preoperative chemoradiation in adenocarcinoma of the pancreas. A single centre experience advocating a new treatment strategy. Eur J Surg Oncol, 34: 756-64

Naschberger E, Croner RS, Merkel S, Dimmler A, Tripal P, Amann KU, Kremmer E, Brueckl WM, Papadopoulos T, Hohenadl C, Hohenberger W, Stuerzl M (2008) Angiostatic immune reaction in colorectal carcinoma: Impact on survival and perspectives for antiangiogenic therapy. Int J Cancer, 123: 2120-9

Weinlaender K, Naschberger E, Lehmann MH, Tripal P, Paster W, Stockinger H, Hohenadl C, Stuerzl M (2008) Guanylate binding protein-1 inhibits spreading and migration of endothelial cells through induction of integrin alpha4 expression. FASEB J, 22: 4168-78

Hohenberger W, Weber K, Matzel K, Papadopoulos T, Merkel S. (2009) Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. Colorectal Dis. 11: 354-64

International Cooperation

Prof. JX . Chen, Shanghai Renji Krankenhaus der Shanghai Jiaotong Universitaet, China

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

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

Prof. Dr. Christine Hohenadl, Austrianova Biomanufacturing AG, Wien, Austria

Univ.-Prof. Dr. Hannes Stockinger, Abteilung Molekulare Immunologie, Medizinische Universitaet, Wien, Austria

Dr. Terry Robins, Quest Diagnostics, Madison, USA

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Research Focus

- Prospective, psychological evaluation of dysmorphic disease pattern (thoracic wall deformities) in the course of surgical correction
- Reduction of pulmonary hypertension and expression of pro-inflammatory interleukins 1β/8.
- Palliative Chemotherapy in patients with advanced colorectal cancer
- Constitution and implementation of an interdisciplinary VACTERL consultation-hour.
- Sealing in pediatric surgery: Innovative surgical management of NEC
- Sealing in pediatric surgery: Fast-track surgery of recurrent pneumothorax

Structure of the Institution

Locations: Department of Surgery and Department of Pediatrics. Closest relation to the Department of Pediatrics (Prof. Rascher) and its specific departments. Envolvement into the expert network of the franconian perinatal centre (Prof. Schild, Prof. Doetsch). In the frame of the Erlangen University Pediatric Operative Centre (KIOZ) close cooperation with the pediatric institutions of anaesthesiology (Prof. Schuettler), urology (Prof. Schott), cardiac surgery (Prof. Cesnjevar), traumatology (Prof. Hennig), orthopedics (Prof. Forst), and neurosurgery (Prof. Buchfelder). Close connections and cooperations to university associated teaching academic pediatric hospitals in Bamberg (Prof. Deeg), Bayreuth (Prof. Rupprecht) and Fuerth/B. (Prof. Klinge).

Research

Prospective, psychological evaluation of dysmorphic disease pattern (thoracic wall deformities) in the course of surgical correction

Project manager: P. G. Weber, A. Mueller, B. Reingruber

Since 1956, more than 3,000 procedures on chest wall deformities had been performed in the Erlangen Division of Pediatric Surgery The experiences obtained include not only the operative features but also psychological situation in those patients. Body shape and contouring mark major impact to the patients and normally result in a critical, ambiguous and psychologically striking behaviour. It's a fact that psychological strain does not correlate rationally with the grade of chest deformity. Sometimes, the patients are seriously affected caused by their body shape even in the time after surgical correction. This study aims on those patients who are not satisfied with their body shape even though the objective result seems to be. Such patients should be found out by preoperative evaluation in order to provide an individually performed path of treatment, e.g. to dog them with psychotherapy before, during and after surgery. Perhaps, with the help of corresponding psychological tests, one can be discouraged from the operation.

A collective of male patients with pectus excavatus is prospectively searched in a standardized comprehensive questionaire at given times (pre-operatively, 3 vs 6 months post-operatively, 1 year post-operatively).

Reduction of pulmonary hypertension and expression of pro-inflammatory interleukins 1β/8. Large animal model for neonatal respiratory distress syndrom

Project manager: A. Rueckel

In neonatal respiratory distress syndrome (IRDS) with pulmonary hypertension, interleukins (IL-1ß, IL-8) are involved in the pulmonary inflammatory reaction. The purpose of this study was to determine whether systemic or aerosolized administered IL-1 receptor antagonist (IL-1Ra) Anakinra (Kineret™) affects lung mechanics and pulmonary artery pressure in surfactant depleted newborn piglets. After induction of severe lung injury by bronchoalveolar lavage, neonatal piglets received repetitive treatment of either aerosolized IL-1Ra (IL-1Ra-Aerosol) or intravenous IL-1Ra (IL-1Ra-i.v.), or saline solution as control. Cardiopulmonary data were recorded for 12 hours. Gene expression of IL-1β and IL-8 in lung tissue was quantified by TaqMan real-time polymerase chain reaction (PCR). A lung injury score was calculated based on the results of histological examination.

IL-1Ra given as aerosol or intravenously significantly reduced mean pulmonary artery pressure (MPAP) and did not influence mean systemic arterial pressure (MAP) compared with the control group. IL-1β and IL-8 mRNA expressions normalized to β-actin and hypoxanthine-guanine-phosphoribosyl transferase were significantly reduced in the IL-1Ra-Aerosol group but not in IL-1Ra-i.v. group compared to the control group. The lung injury score were not significantly different between IL-1Ra groups and the control group. Application of aerosolized IL-1Ra reduced MPAP without affecting MAP in a piglet model of surfactant depletion with pulmonary hypertension. Furthermore, there is evidence for reduction of early pro-inflammatory pulmonary reaction following treatment with topical admission of IL-1Ra as aerosol that might become a therapeutic option to reduce induction of lung fibrosis and the subsequent risk of bronchopulmonary dysplasia (BPD) after lung injury.

Palliative Chemotherapy in patients with advanced colorectal cancer

Project manager: N. Spychalski

Prolonged infusion with 5-fluorouracil/folinic acid protcols with view on the toxicity profile of sodium folinic acid versus calcium folinic acid. In the study palliative high dose chemotherapy was inspected by 5-fluorouracil (NaF) respectively calciumfolinat (CaF) for 100 consecutive non selected patients with an advanced colorectal cancer. 5-FU and NaF were infused simultaneously for 24 h. The incompatibility of CaF and 5-FU by simultaneous infusion effected a sequential application of CaF as 2h quick infusion and 5-FU as 24h-infusion (acc. AIO/Ardalan-scheme). Among NaF there was no case of catheter occlusion caused by salt sedimentation as described by CaF. So it is assumed that NaF and 5-FU are compatible for simultaneous application. Regarding the application of NaF it was observed a saw similar frequency and severity of toxicity as for CaF, also as equieffective data of progress in the intern comparison of the therapy groups as conventional studies. A significant benefit of NaF was shown by the economy of time. Out of this it results an increase of quality of life and a decrease in costs. Con-

sequently the application of NaF in the high-dose therapy with 5-FU in colorectal cancer is a matter for further approval.

Constitution and implementation of an interdisciplinary VACTERL consultation-hour.
Project manager: N. Spychalski
In long-term support of patients with multiple extensive malformations such as VACTERL, different departments were involved. By logistic management it is possible to offer an optimal support to those patients. Ambition is a prospective registration for recording patient's development and standardization of follow-up care. The VACTERL consultation-hour is well-established since December 2006. It takes place twice a month with a high patients compliance, a significant quality of care and collecting scientific relevant data.

Sealing in pediatric surgery: Innovative surgical management of NEC
Project manager: R.T. Carbon
Necrotizing enterocolitis (NEC) is a severe septic disease of preterm infants and newborns and is characterized by mortality rates of 40%. Around 50% of the children survive the invasion with conservative measures (parenteral nutrition, antibiotics). There is no binding concept for operative treatment, with the spectrum of therapy ranging from pure drainage insertion to extensive resection measures. After experimental evaluation, (DDS, tensile strength, elasticity, adhesive strength), an innovative, antimicrobially effective gluing system (manual application of gentamicin-impregnated Tacho-Sil®) was introduced into the regimen, with this system supporting atraumatic, reconstructive and augmenting enteroplasties. A total of 52 preterm infants (1998-2005, Ø 1183 g, Ø week 31, 41 patients Bell II, 11 patients Bell III) underwent a total of 84 operations, 252 gluings, 122 intestinal re-sections and 83 ostomies. Gluing saved Ø 17.8 cm of intestine (range: 1.8-38 cm)/patient, and short-bowel syndrome was prevented in three patients (5.8%). There were no septic complications and the mortality rate was 13.5%.

Sealing in pediatric surgery: Fast-track surgery of recurrent pneumothorax
Project manager: R. T. Carbon
Fast-track surgery involves an interdisciplinary concept of accelerating the rehabilitation of patients who have undergone surgery. To better advance this aim, the surgical procedure must meet minimal invasion criteria. Tissue management must be effective and efficient so as to minimize and prevent complications. Such an appropriate concept has been developed for patients with cystic fibrosis and recurrent pneumothorax, consisting of thoracoscopy in connection with minimally invasive tissue management (ATSS: AMISA-TachoSil®-System, ready-to-use sealing). Evidence-based results for fast-track parameters were obtained for 131 patients (1993-2006) and compared to a patient collective that had been treated with conventional surgery (284, 1985-1996): Drainage requirements: 38.5 vs. 100.0 %, drainage time: 0.5 vs. 17.2 d, time in ICU: 1.2 vs. 4.7 d, time on ward: 4.8 vs. 34.3 d, complications: 1.8 vs. 34.9 %, recurrence: 9.9 vs. 45.1 %.

Zebra maneuver. Patch sealing of small bowel anastomoses in an earlyborn (1220 g, 33rd GW)

Teaching

The presentation of pediatric surgery as a subject occurs in three segments: 1. curricular (contents are composed of general and special topics from pediatric surgery in theory and practical experience. The knowledge is deliverd in single lectures/events, partly integrated in the main lecture of general surgery, according to IMPP-regulations. The presentation is characterized by a problem-orientated method (POL) of instruction/teaching and/or interactive features. The whole package is completed by teaching units in cooperation with the technical schools (pediatric nursing, physiotherapy, medical massage)). 2. interdisciplinary (contents are assorted from pediatric surgery topics, e.g. "emergency in pediatric surgery", in the context of cycles of lectures/tutorials). 3. specific (contents consists of questions/problems out of pediatric surgery in theory and practical experience which might be worked out systematically and/or innovative. Therefore seminars for doctoral researchers/graduates are organized. Practical experience to promote specialization occurs in phantom courses/tutorials for minimally invasive pediatric surgery ("Skills-lab", "Hands-on courses").

Selected Publications

Carbon R, Carbon R, Reingruber B, Weber P, Baar S, Kriegelstein S (2007) Innovative surgical management of NEC – Results of 52 consecutive cases. Inflamm Res, 56 Suppl.: S203-S203

Henrich K, Huemmer HP, Reingruber B, Weber PG (2008) Gastroschisis and omphalocele: treatments and long-term outcomes. Pediatr Surg Int, 24: 167-73

International Cooperation

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

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Division of Trauma Surgery

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Research Focus

- Development of a ceramic knee endoprothesis
- Biomechanical studies of a minimal-invasive internal fixation method
- Factors and molecular mechanisms of chondrocyte differentiation and cartilage repair
- "Molecular" magnetic resonance imaging
- Early diagnosis and monitoring of osteoarthritis
- Bone physiology and its pharmacokinetics

Structure of the Institution

The Division of Trauma Surgery of the University Hospital 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)", "Bavarian Research Fund", IZKF, German Society for Orthopaedics and Orthopaedic Surgery (DGOOC), and ELAN (fund of the university hospital).

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 medical technology, Peter Brehm surgery mechanics and the Department of Glass & Ceramics of the University Erlangen, focuses on the development of an innovative ceramic knee endoprothesis. This project is supported by the "Bavarian Research Fund". 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 promising with respect to functionality and operability.

Biomechanical studies of a minimal-invasive internal fixation method
Project manager: 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 stabilisation. Such lesions can be treated by various surgical approaches which often coincide with considerable trauma by the surgical approach. However, the surgical stabilisation 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 reliability 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 golden standard of conventional plate osteosynthesis. Preliminary results demonstrate that, with respect to biomechanical properties, the minimal-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-1α 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 German Research Foundation (DFG) and the Interdisciplinary Centre for Clinical Research (IZKF).

"Molecular" magnetic resonance imaging
Project manager: G. Welsch
The research project of musculoskeletal magnetic resonance imaging are performed in cooperation with the MR Centre 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 orthopaedic-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 remodelling processes of repair tissues could be visualized and quantified leading to important additional information on the properties of cartilage.

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.

Development of a ceramic knee endoprothesis

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.

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 focussing 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

Brem MH, Pauser J, Yoshioka H, Brenning A, Stratmann J, Hennig FF, Kikinis R, Duryea J, Winalski CS, Lang P (2007) Longitudinal *in vivo* reproducibility of cartilage volume and surface in osteoarthritis of the knee. Skeletal Radiol, 36: 315-20

Brem MH, Schlechtweg PM, Bhagwat J, Genovese M, Dillingham MF, Yoshioka H, Lang P (2008) Longitudinal evaluation of the occurrence of MRI-detectable bone marrow edema in osteoarthritis of the knee. Acta Radiol, 49: 1031-7

Gelse K, Mühle C, Franke O, Park J, Jehle M, Durst K, Göken M, Hennig F, Mark KV, Schneider H (2008) Cell-based resurfacing of large cartilage defects: Long-term evaluation of grafts from autologous transgene-activated periosteal cells in a porcine model of osteoarthritis. Arthritis Rheum, 58: 475-488

Gelse K, Mühle C, Knaup K, Swoboda B, Wiesener M, Hennig F, Olk A, Schneider H (2008) Chondrogenic differentiation of growth factor-stimulated precursor cells in cartilage repair tissue is associated with increased HIF-1alpha activity. Osteoarthritis Cartilage, 16: 1457-65

Welsch GH, Mamisch TC, Hughes T, Domayer S, Marlovits S, Trattnig S (2008) Advanced morphological and biochemical magnetic resonance imaging of cartilage repair procedures in the knee joint at 3 Tesla. Semin Musculoskelet Radiol, 12: 196-211

Welsch GH, Trattnig S, Scheffler K, Szomonanyi P, Quirbach S, Marlovits S, Domayer S, Bieri O, Mamisch TC (2008) Magnetization transfer contrast and T2 mapping in the evaluation of cartilage repair tissue with 3T MRI. J Magn Reson Imaging, 28: 979-86

International Cooperation

Prof. Dr. S. Trattnig, Exzellenzzentrum Hochfeld MRT, Klinik fuer Radiodiagnostik, Medizinische Universitaet Wien, Wien, Austria

Prof. Dr. P. Lang, Prof. Dr. Duryea, Brigham and Women`s Hospital, Harvard Medical School, Boston, USA

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Research Focus

- Separation of progenitor cells from peripheral blood or cord blood
- Preparation and characterization of white cell-poor platelet concentrates by apheresis
- Preparation of dry platelet concentrates and platelet storage in additive solutions
- Platelet-derived growth factors for wound healing and angiogenesis
- Autologous blood donation and haematopoiesis
- Collection of monocytes for the generation of dendritic cells
- Clinical research related to hemotherapy
- Clinical research related to haemostaseology

Structure of the Institution

The Division of Transfusion Medicine and Haemostaseology is located at the Department of Surgery of the University Hospital Erlangen. The head of the Division is Extraordinarius for Transfusion Medicine and Haemostaseology.
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 for diagnostics in the fields of immunohematology and haemostaseology, 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 9001:2000 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 German Accrediation System for Testing (DAP).

Research

Separation of progenitor cells from peripheral blood or cord blood
Project manager: J. Zingsem
Haematopoietic 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. Aggressive novel strategies for therapy of malignant diseases require the isolation and storage of these cells. The infusion of concentrates of progenitor and stem cells following high-dose chemo- and radiotherapy enables the reconstitution of haematopoiesis. A major focus of research is the isolation of haematopoietic 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.

Preparation and characterization of white cell-poor platelet concentrates by apheresis
Project manager: J. Zingsem, J. Ringwald
Platelet apheresis processing large blood volumes to produce platelet-rich plasma has become a standard procedure. In the past, platelet concentrates collected by apheresis were contaminated by large amounts of white cells. Contamination of platelet concentrates with white cells may cause typical secondary effects associated with blood transfusion as cytomegalovirus transmission, immunization to HLA class I antigens and other antigens of white cells and secretion of cytokines during storage. Therefore, 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 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. Additionally, the portion of plasma that may be used otherwise is higher if "dry platelets" are produced. Clinically, the reduction of the plasma portion in platelet components may reduce the frequency of adverse reactions, e.g. of allergic reactions. The resuspension of platelets 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 platelet preparations using the TRIMA separator by Gam-broBCT. Platelet 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 platelet concentrates.

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 haematopoiesis
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 risks of homologous transfusion, which shall be avoided by autologous blood, have been permanently

decreasing during the past several years. Thus, if preoperative autologous blood donation is performed at all, it has to be performed in an optimal way to improve the overall transfusion risk for an individual patient considering the very low risks nowadays associated with homologous blood transfusion. 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.

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 systems 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 collegues 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.

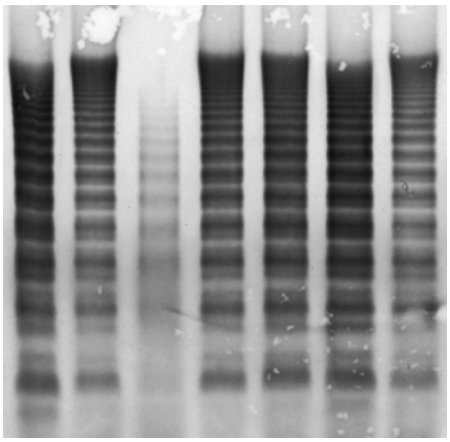
Clinical research related to hemotherapy

Other research interests regard to the examination of antibodies against red cell antigens (Prof. Weisbach), the characterization of factors influencing the quality of stored red cell concentrates (Prof. Weisbach, Prof. Zimmermann) and complex dysfunctions of the coagulation system (PD Dr. Ringwald, PD Dr. Strasser).

Clinical research related to haemostaseology

Project manager: J. Ringwald, E. Strasser

Other research interests regard to thrombophilia, traveller´s thrombosis and haemostasis dysfunctions resulting in bleeding disorders. A study on traveller´s thrombosis ("traveller´s thrombosis – a state of practice in Germany") was awarded in 2003 by the der ISTM (International society for travel medicine) (PD Dr. Ringwald). Other current study objectives are preanalytical determinants of fibrinolysis tests, hemostasis tests in systemic lupus erythematodes and other currently relevant topics.



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

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, Schroth M, Faschingbauer F, Strobel J, Strasser E, Schild RL, Goecke TW (2007) Intrauterine use of hyperconcentrated platelet concentrates collected with Trima Accel in a case of neonatal alloimmune thrombocytopenia. Transfusion, 47: 1488-93

Strasser EF, Keller B, Hendelmeier M, Ringwald J, Zingsem J, Eckstein R (2007) Short-term liquid storage of CD14+ monocytes, CD11c+, and CD123+ precursor dendritic cells produced by leukocytapheresis. Transfusion, 47: 1241-9

Weisbach V, Strobel J, Hahn B, Roedel F, Lotter M, Zingsem J, Ringwald J, Eckstein R (2007) Effect of gamma irradiation with 30 Gy on the coagulation system in leukoreduced fresh-frozen plasma. Transfusion, 47: 1658-65

Zingsem J, Strasser E, Ringwald J, Zimmermann R, Weisbach V, Eckstein R (2007) Evaluation of a new apheresis system for the collection of leukoreduced single-donor platelets. Transfusion, 47: 987-94

Weiss DR, Thiel C, Strasser EF, Zimmermann R, Eckstein R (2008) An optimized electrophoresis method for high-resolution imaging of von-Willebrand multimers. Thromb Haemost, 100: 949-51

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

International Cooperation

BEST group der ISBT, International Society of Blood Transfusion (ISBT), Amsterdam, Netherlands

Meetings and International Training Courses

16.–17.11.2007: Fortbildungsveranstaltung 2007 der Bayerischen Landesaerztekammer "Qualifikation als Transfusionsverantwortlicher/ Transfusionsbeauftragter", Erlangen

21.–22.11.2008: Fortbildungsveranstaltung 2008 der Bayerischen Landesaerztekammer "Qualifikation als Transfusionsverantwortlicher/ Transfusionsbeauftragter", Erlangen, Bayerische Landesaerztekammer

Department of Plastic and Hand Surgery

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Research Focus

- Gene expression profiles and intracellular signal pathways in acute wounds under vacuum therapy
- Histological and molecular biological analyses of the pathologies of the discus ulnocarpalis
- Engineering of axially vascularised bone tissue using biomorph ceramics
- Vascularisation of bioartificial tissue via embryonic endothelial progenitor cells
- Imaging tools and molecular biological analyses of ischemia and reperfusion in human free flaps
- Generation of axially vascularised neo-tissue in the large animal model of the sheep
- Tissue engineering of skeletal muscle with nanofibers

Structure of the Institution

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 student are working in a number of different teams on various topics of basic and clinical / applied science. Besides clinical studies and research based on *in vitro* investigations of clinical samples, different large and small animal models are established. With these *in vivo* studies many issues are addressed in the field of plastic and reconstructive surgery, especially concerning angiogenesis and tissue engineering.

Research

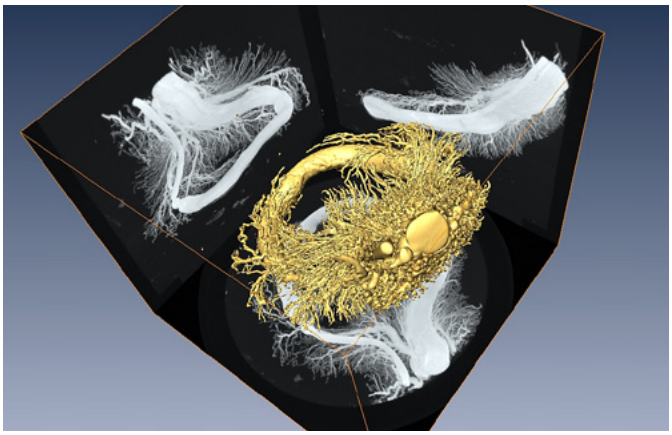
Gene expression profiles and intracellular signal pathways in acute wounds under vacuum therapy
Project manager: M. Leffler
Vacuum therapy leads to a significant improvement in the treatment of problematic wounds, but the underlying biological mechanisms are still not fully understood. The aim of this project is to examine gene expression profiles of tissue biopsies before and after vacuum therapy. Tissue samples were analysed using microarray technology and molecular biology methods (PCR, Western Blot). Differences in gene expression profiles and in the activity of single genes will be analysed. Besides this corresponding signal pathways will be examined. The aim is to find a distinct gene expression profile which correlates with an improved wound healing under vacuum therapy.

Histological and molecular biological analyses of the pathologies of the discus ulnocarpalis
Project manager: F. Unglaub
The working group concentrates on experimental investigations regarding the pathologies of the discus ulnocarpalis of the wrist. Degenerative lesions and traumatic lesions are included in the investigative studies. The studies' aim is to uncover degeneration and regeneration mechanisms occurring in the fibrocartilage of the wrist. For these purposes, biopsies, which are retrieved during arthroscopic wrist procedures, are examined regarding their molecular biological properties: apoptotic pathways are immuno-histochemically analyzed, and the role of inflammation in the development of fibrocartilage degeneration is investigated. Other main focuses of the investigations are the vascularization of the fibrocartilage, and its regeneration potential.

Engineering of axially vascularised bone tissue using biomorph ceramics
Project manager: U. Kneser, A. Arkudas, E. Polykandriotis
Aim of this project in cooperation with Prof. Greil, Material Research Centre, Department of Glass and Ceramics, is to generate axially vascularised bone tissues based on biomorph calcium phosphate scaffolds. In the first phase matrices are evaluated in the subcutaneous screening model (rat) with regard to vascularisation, biocompatibility and bone generation following application of osteoinductive factors. In the second phase vascularisation and bone formation following application of vital autologous osteoblasts into optimized matrices are investigated in the arteriovenous loop model (rat). At the end the axially vascularised constructs will be implanted into critical-sized bone defects.

Vascularisation of bioartificial tissue via embryonic endothelial progenitor cells
Project manager: O. Bleiziffer
Endothelial progenitor cells (EPC) may support vascularisation of bioartificial tissues due to their angiogenic potential. In the present project EPC are transplanted in a fibrin matrix *in vivo* inside an arteriovenous loop and their impact on construct vascularisation is investigated. Transgenic EPC expressing pro-or anti-angiogenic mediators, respectively, will be employed to modulate neoangiogenesis. EPC localization and construct vascularisation are investigated by morphometric analysis, immunohistochemistry and micro CT scan. The results may support creation of functional blood vessel networks in bioartificial constructs or support antiangiogenetic cancer therapy.

Imaging tools and molecular biological analyses of ischemia and reperfusion in human free flaps
Project manager: A. Dragu
The use of free flaps in plastic and reconstructive surgery represents an established microsurgical procedure, for the successful closure of defects of the human body. However, the postoperative monitoring of viability and perfusion of the transplanted tissue represents a clinical problem (e.g. buried flaps). The limited time of free flap ischemia also represents a clinical problem. Innovative imaging tools in nuclear medicine are used on an interdisciplinary basis to evaluate viability and perfusion of the free flap. Additionally, gene expression analyses are performed in order to understand more about ischemia and reperfusion in free flaps.



Micro-CT visualisation of axial vascularisation via an arteriovenous loop in the rat animal model

Generation of axially vascularised neo-tissue in the large animal model of the sheep

Project manager: J. Beier, U. Kneser

In the newly developed arteriovenous loop model in the sheep, axial vascularisation in neo-tissues is induced in various hard- and soft matrices. Besides histomorphometrical and immunohistological analyses, up-to-date intravital, three-dimensional imaging studies are performed in cooperation with the Institute of Pharmacology (PD Dr. A. Hess, PhD) to assess vascularisation. In the future we will investigate the potential role of osteogenic growth factors in this large animal model as well as the transplantation of mesenchymal stem cells.

Tissue engineering of skeletal muscle with nanofibers

Project manager: J. Beier

In this research project the generation of neo-muscle tissue is aimed for by *in vitro* and *in vivo* application of novel electrospun nanofibers. Primary myoblasts as well as mesenchymal stem cells are used as cell source. Besides FACS- and molecular biology analysis *in vitro*, the implantation of these cell-containing constructs in the rat AV-loop model is a promising step towards cultivation of axially vascularized skeletal muscle tissue *in vivo*.

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
- Course on examination of the bracial plexus and peripheral nerves of the upper extremity

Selected Publications

Arkudas A, Beier JP, Heidner K, Tjiawi J, Polykandriotis E, Srour S, Sturzl M, Horch RE, Kneser U (2007) Axial prevascularization of porous matrices using an arteriovenous loop promotes survival and differentiation of transplanted autologous osteoblasts. Tissue Eng, 13: 1549-60

Arkudas A, Tjiawi J, Bleiziffer O, Grabinger L, Polykandriotis E, Beier JP, Stuerzl M, Horch RE, Kneser U (2007) Fibrin Gel-Immobilized VEGF and bFGF Efficiently Stimulate Angiogenesis in the AV Loop Model. Mol Med, 13: 480-7

Bleiziffer O, Eriksson E, Yao F, Horch RE, Kneser U (2007) Gene transfer strategies in tissue engineering. J Cell Mol Med, 11: 206-23

Leffler M, Hrach T, Stuerzl M, Horch RE, Herndon DN, Jeschke MG (2007) Insulin attenuates apoptosis and exerts anti-inflammatory effects in endotoxemic human macrophages. J Surg Res, 143: 398-406

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

Unglaub F, Kroeber MW, Thomas SB, Wolf MB, Arkudas A, Dragu A, Horch RE (2009) Incidence and distribution of blood vessels in punch biopsies of Palmer 1A disc lesions in the wrist. Arch Orthop Trauma Surg, 129: 631-4

International Cooperation

Prof. Dr. Alois Lammetschwandtner, Lehrstuhl fuer Biologie, Universitaet Salzburg, Austria

Prof. Dr. Dietmar Hutmacher, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia

Prof. Elof Eriksson, M. D., Ph. D., Plastic Surgery Division, Harvard Medical School, Boston, USA

Meetings and International Training Research Equipment

Zeiss 2 Zeiss Operationsmikroskope

Leica 1 Leica-Operationsmikroskop

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Chair of Cardiac Surgery

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Research Focus

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

Structure of the Institution

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

Research

Therapy of end-stage heart failure: heart transplantation or support with a left- or right ventricular assist device
Project manager: M. Weyand, R. Tandler, M. Kondruweit
The survival rate of patients with end stage heart failure (prevalence approx. 0.1%) with optimised 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 stabilised ('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.

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 vascularised 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 characterised 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 programme 750 "Vaskulaere Schaeden 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 vascularised allografts. Therefore, the major aim of this project is to develop a human peripheral blood lymphocyte (hu-PBL)/severe combined immunodeficiency (SCID) mouse Xenograft-model to investigate the immunological and pathological mechanisms of HCMV in the modulation and progression of transplant arteriosclerosis. 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 University of Erlangen-Nürnberg.

Tissue engineering of cardiovascular implants
Project manager: M. Weyand, O. Roerick
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 neededd 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 derivatised with RGD (fibronectin) and YIGSR (laminin) in comparison to a matrix derivatised 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.

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 Aδ- 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.

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 Anaesthesiology we perform a study analysing 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.

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

Arnold ML, Ensminger SM, Doxiadis II, Spriewald BM (2008) Effect of Donor Cell Type on Complement-Dependent Cytotoxicity Crossmatch Outcome for Patients Immunized Against HLA Class-II Antigens. Exp Clin Transplant, 6: 1-6

Ensminger SM, Helm SN, Ohl L, Spriewald BM, Abele S, Wollin M, Wood KJ, Weyand M, Foerster R (2008) Increased transplant arteriosclerosis in the absence of CCR7 is associated with reduced expression of Foxp3. Transplantation, 86: 590-600

Schmid C, Jurmann M, Birnbaum D, Colombo T, Falk V, Feltrin G, Garatti A, Genoni M, Gerosa G, Goettel P, Gummert J, Halfmann R, Hammel D, Hennig E, Kaufmann F, Lanfranconi M, Meyns B, Mohr F, Mueller J, Nikolov D, Rucinskas K, Scheld HH, Schmid FX, Schneider M, Sirvydis V, Tandler R, Vitali E, Vlasselaers D, Weyand M, Wilhelm M, Hetzer R (2008) Influence of inflow cannula length in axial-flow pumps on neurologic adverse event rate: results from a multi-center analysis. J Heart Lung Transplant, 27: 253-60

International Cooperation

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

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

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Research Focus

- Systemic tumor therapy, clinical trials
- Establishment of a clinically annotated tumor tissue repository containing urologic tumors
- Tumor genetic research with focus on identification of biomarkers
- MRT-guided needle biopsy for the diagnosis of prostate carcinoma

Structure of the Institution

University hospital:
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:
Adult urology (inpatients' department), private insurance patients (outpatients' department).
Trial documentation centre.

Research

Systemic tumor therapy, clinical trials
Project manager: P.J. Goebell
The medical care and treatment of patients with uro-oncologic diseases represent an integral part of the urologic specialty and systemic therapy forms besides the provision of surgical treatment one of the fundamental sources of competence in urology. For this purpose the outpatient centre for uro-oncologic diseases (AURONTE) was founded together with the Department of Urology and the Department of Medicine 5. Any therapeutic decision concerning systemic drug therapy, including indications for neoadjuvant or adjuvant systemic treatment, is based on a common interdisciplinary conference.
Any particular decision on treatment is also discussed in the context of the current clinical trials. With this it is assured that all currently activated or planned clinical trails are open to all common patients. Since April 2008 the study registry is staffed with our quality managing intern intern (Dr. Kerscher, K. Jalalian). Currently open clinical trials mainly focus on new therapeutic options for patients with kidney cancer or prostate cancer:
- Registry for advanced kidney cancer
Epidemiologic registry to provide information on treatment and current regimen of patients with metastatic or locally advanced kidney cancer
- Registry STAR – TOR
Registry for the assessment of safety, tolerance and efficacy of Temsirolimus (Torisel®) for the treatment of advanced kidney cancer
- 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
- CRAD001L2401
Advanced open-access, multicentre trial of RAD001 (Everolimus), for patients with metastatic renal cell cancer, following tyrosinkinase-inhibition failure
- FLARE DOCT/L03323
Evaluation of the use of Taxotere® in hormone-refractory prostate cancer and the assessment of the PSA FLARE phenomenon
- H6Q-MC-SO32
Randomized double-blind first-line placebo controlled phase II trial with or without enzastaurin in combination with docetaxel and prednisone, followed by enzastaurin maintenance therapy in hormone-refractory metastatic prostate cancer
- CA180-227
Randomized double-blind first-line placebo controlled phase III trial to evaluate the combination of docetaxel w/o dasatinib for patients with hormone-refractory prostate cancer

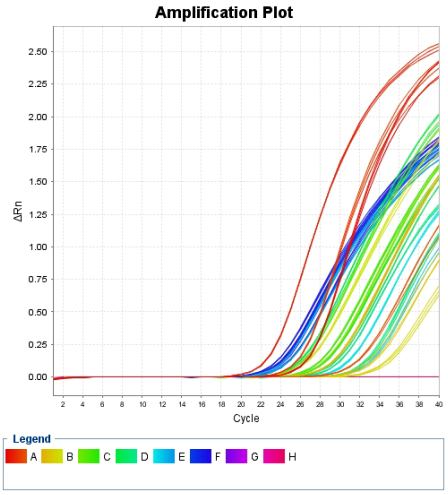

Fig.1: Real-time analysis of microRNA expression in tumor tissue

- HAROW-Study
Prospective, multicentre german registry trial to evaluate the provision of care and treatment for newly diagnosed, localized prostate cancer
Further Information:
http://www.urologie.uk-erlangen.de/informationen_fuer_aerzte/studienzentrale/aktuelle_studien/index_ger.html

Establishment of a clinically annotated tumor tissue repository containing urologic tumors
Project manager: B. Wullich
New insights about the occurrence of malignant tumors and the identification of new and reliable prognostic biomarkers are dependent on the molecular characterization of rather large cohorts of tissue samples, since the currently used morphologic criteria only poorly reflect the progression behavior of one patient's specific tumor. To facilitate this research, the collection of tissue samples originating from tumors and corresponding non-tumorous tissue as well as blood, serum, and other body fluids like urine is crucial 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 samples carried out by an experienced pathologist. In close cooperation with the local Institute of Pathology a repository of urologic tissue samples has been established, in which tissue samples of all surgically treated malignant uro-

logic tumors are introduced. 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. Additionally, the documentation of patients' clinical parameters is carried out with the valuable assistance of the Medical information and communication centre (Prof. Prokosch) on the basis of a SOARIAN-generated clinical database. This database has currently been optimized for prostate cancer patients and will soon be extended to other urologic tumors. All incorporated procedures are consistent with the legal, ethical, technical and organizational regulations of tissue repositories and databases (patients' informed consent, data security, standard operating procedures and quality management) according to the recommendations of the BMBF associated telematics platform for medical research networks.

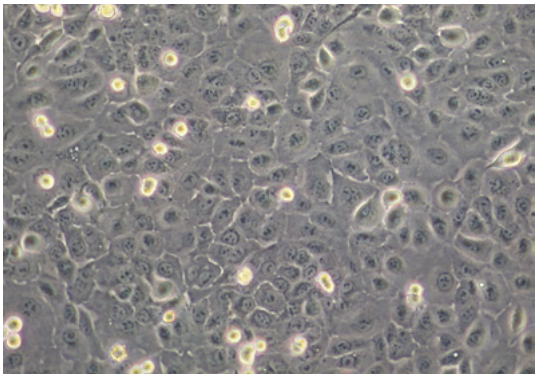

Fig. 2: Cell culture of the prostata carcinoma cell line DU145

Tumor genetic research with focus on identification of biomarkers

Project manager: S. Wach

The identification and characterization of specific biologic properties of prostate cancer as well as other malignant tumors like bladder or kidney cancer is the main focus of the biologic research projects. By conducting correlation analyses of certain specific molecular characteristics of tumors with histopathologic criteria and clinical progression data new biomarkers will be identified. These biomarkers are thought to provide a more accurate prediction of the individual patient's course of the disease (prognostic value) and enable optimized therapy decisions (predictive value). The complete spectrum of molecular cytogenetic techniques including fluorescence in situ DNA and RNA hybridization and microarray based hybridization techniques (oligonucleotide microarrays for genomic, expression and microRNA profiling analysis) has been established in the laboratory. The quantification of microRNA and gene expression (Fig.1) as well as the determination of gene copy numbers using real time PCR approaches is a central part of the experimental methods.

Another important aspect of our tumor biology research are functional studies using short- and long-term cultures of tumor cells (Fig.2). Using RNA interference or expression vector constructs it is possible to modulate the activity of target genes. The functional alterations of tumor cells are then analyzed using proliferation, invasion, migration, or apoptosis assays.

MRT-guided needle biopsy for the diagnosis of prostate carcinoma

Project manager: D. Engehausen

Magnetic resonance tomography (MRT)-guided biopsy is a novel diagnostic approach in cases of suspected prostate cancer. It combines sophisticated MRT imaging techniques with the guided extraction of prostate biopsy samples therefore incorporating the radiologist's (visualization of the target area) and the urologist's (targeting the biopsy needle and extraction of the sample) expertise. With the patients lying in a supine position, two biopsy samples from every suspect area and one reference sample are extracted, each taken under visual control of the biopsy needle. The examination takes between 40 and 70 minutes. A mild sedation as well as local anesthesia are administered. This procedure is intended for patients with persistent suspect for prostate cancer after negative transrectal ultrasound (TRUS) biopsy and shows a high detection rate in this cohort with 40%, in a sub cohort with even 60%. This procedure is available in only a few centres worldwide (at this time 4, including Erlangen), requiring the interdisciplinary cooperation between urologists and radiologists and is constantly improving. Before conducting this type of examination, the modalities of payment should be clarified. The total cost of about 1.350 € are at this time not approved by the health insurance Chamber Law for Health Care professions.

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

Kindich R, Florl AR, Jung V, Engers R, Mueller M, Schulz WA, Wullich B (2005) Application of a modified real-time PCR technique for relative gene copy number quantification to the determination of the relationship between NKX3.1 loss and MYC gain in prostate cancer. Clin Chem, 51: 649-52

Jung V, Kindich R, Kamradt J, Jung M, Mueller M, Schulz WA, Engers R, Unteregger G, Stoeckle M, Zimmermann R, Wullich B (2006) Genomic and expression analysis of the 3q25-q26 amplification unit reveals TLOC1/SEC62 as a probable target gene in prostate cancer. Mol Cancer Res, 4: 169-76

Jung V, Wullich B, Kamradt J, Stoeckle M, Unteregger G (2007) An improved in vitro model to characterize invasive growing cancer cells simultaneously by function and genetic aberrations. Toxicol In Vitro, 21: 183-90

Hugo C, Schott G, Eckardt KU, Wullich B (2008) ABO-incompatible renal transplantation – why and how? Urologe A, 47: 1074-8

Jungwirth N, Haeberle L, Schrott KM, Wullich B, Krause FS (2008) Serotonin used as prognostic marker of urological tumors. World J Urol, 26: 499-504

Keck B, Stoehr R, Goebell PJ, Fritsche HM, Wullich B, Hartmann A (2008) Plasmacytoid carcinoma: Five case reports of a rare variant of urothelial carcinoma. Pathologe, 29: 379-82

International Cooperation

OA Dr. Peter J. Goebell, Secretary General, International Bladder Cancer Network (IBCN), Barcelona, Spain

Prof. Colin Dinney, MD Anderson Comprehensive Cancer Centre, SPORE Bladder Cancer (funded by the National Cancer Institute), Houston, USA

Prof. Pierre Hainaut, IARC, International Consortium of Biological Resource Centres for Cancer, Lyon, France

Peter J. Geary, Marble Arch Working Group on Global Biorepositories, Montreal, Canada

Meetings and International Training Courses

10.03.2007: Erlanger Urologie, Waldkrankenhaus

23.10.2007: Neues vom Prostatakarzinom, Waldkrankenhaus

28.11.2007: Kinderurologische Gespräche, Waldkrankenhaus Erlangen

02.04.2008: Neues vom Nierenzellkarzinom, Waldkrankenhaus

17.09.2008: Kinderurologische Gespräche, Waldkrankenhaus

24.10.2008: Erlanger Gesundheitstag Prostatakrebs Expertensymposium

25.10.2008: Erlanger Gesundheitstag Prostatakrebs

21.–22.11.2008: dpkk Workshop mit 6. Mitgliederversammlung, Vierzehnheiligen Staffelstein

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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 anaesthesia
- Intensive care and emergency medicine: systemic inflammation, acute lung and cardiac failure, resuscitation
- Research in teaching and learning

Structure of the Institution

The Department of Anaesthesiology 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 University Hospital Erlangen. The Department of Anaesthesiology also includes an outpatient's anesthesia division with an unit for lung function diagnostics and a pain clinic. The Department of Anaesthesiology is responsible for the management of the interdisciplinary surgical ICU of the University Hospital with 25 beds and, together with the Department of Neurology, holds the Centre for Interdisciplinary Pain Therapy. Additionally, the Department of Anaesthesiology is responsible for the management of the ambulance service for the city of Erlangen, the region of Erlangen-Hoechstadt 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.
At the Department of Anaesthesiology is located the Chair of Anaesthesiology of the Friedrich-Alexander University Erlangen-Nürnberg (Chair and Chairman of the department: Prof. Dr. Dr. med h. c. Jürgen Schüttler) with extra Ordinariates for Experimental Anaesthesiology (Prof. Dr. Dr. rer. nat. Helmut Schwilden) and Anaesthesiology / Pain Research (Prof. Dr. med. Carla Nau). An autonomous unit with an Extraordinariate for Molecular Pneumology (Prof. Dr. Dr. Susetta Finotto) was affiliated to the Chair of Anaesthesiology in 2009. The establishment of an endowed chair for palliative medicine is nearing completion. The Anaesthesiology Department employs 95 medical doctors and 9 scientific members with responsibilities in research and teaching.
The main research focus is in pain research, which is represented by the interdisciplinary clinical research unit "Determinants and modulators of post-operative pain" (Scientific Head: Prof. Dr. med. Carla Nau). It is supplemented by the group of Prof. Dr. med. Wolfgang Koppert with a focus on pharmacology of analgesic agents in humans. Other focuses are the monitoring in anesthesia and intensive care medicine and the exploration of medical processes in the medical care for inpatients and outpatients. The latter is accomplished in cooperation with the Fraunhofer Institute for Integrated Circuits, which holds a medical test and application centre at the Medical Faculty.
Other groups work on aspects of clinical and experimental pharmacology of anesthesia including muscle relaxation, and in the context of intensive care and emergency medicine explore generalized inflammation, acute lung and cardiac failure and resuscitation by means of clinical and animal models.
The working group "Research in Teaching" is operating at the intersection between teaching and research and applies simulation of medical processes to optimize teaching and to establish a scientific foundation for risk and process management.

Research

Pain research: determinants and modulators of perioperative and palliative pain
An interdisciplinary clinical research unit (DFG KFO 130) focuses 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
To monitor the effect and efficacy of anaesthetic drugs head related biosignals (spontaneous EEG and auditory evoked potentials) were examined and mathematically analyzed to extract therapeutic features and to model their time course using the pharmacokinetics of the drugs. Especially the particularities in pediatric anaesthesia patients were analyzed. Within the field of vital data monitoring methodologies were investigated to measure non-invasive and continuously pulse waves and blood pressures of the arterial systems and to compare it with the common invasive technique. The research grant project "Teletherapy of chronic pain" investigated and developed technical options to improve the location-independent integrated home care of palliative patients. The analysis with respect to medical technology aimed particularly at the telemedical human interaction with infusion pumps for the automated supply with analgesic drugs and documentation via diverse technical signal pathways. Focus of the palliative medicine oriented research was the analysis of application pattern of the analgesic drugs.

Clinical and experimental pharmacology of anaesthesia
The importance of genotype CYP3A5 for the pharmacokinetics and pharmacodynamics of midazolam for the treatment of intensive care patients was investigated in cooperation with the Chair of Clinical Pharmacology with respect

Analysis on research projects of the Clinical Research Unit 130
Source: University Hospital Erlangen

to interindividual variations. For the muscle relaxants mivacurium and rocuronium the impact of the mutation of the dystrophin gene at locus Xp21 (M. Duchenne) on the pharmacokinetics and pharmacodynamics was modelled and analyzed with respect to its influence on the progression of the disease. In animal studies (rats) we explored the relationship between drug concentrations of desflurane, sevoflurane and isoflurane and its induced EEG effects. In contrast to the relationship between drug concentrations and MAC value this is rather unknown. These concentration-effect relationships are essential for further investigations concerning the additivity respectively non-additivity of these substances in combination with other anaesthetics which in turn are of great importance with respect to the unitary theory of narcosis.

Intensive care and emergency medicine: systemic inflammation, acute lung and cardiac failure, resuscitation

In this research focus, studies about pharmacological therapies in cardiopulmonary resuscitation are performed as well as studies about immunomonitoring and options for immunomodulation of patients suffering from a systemic inflammatory response syndrome or sepsis. Here, immunological methods as well as animal models and clinical studies are exhibited.

Research in teaching and learning

The projects in this area serve both increase in scientific knowledge and quality assurance and improvement. The Anaesthesiology Department is involved in the development of a national curriculum which is redesigned in view of new ways of examination (so-called OSCE exams = Objective Structured Clinical Examination).

Research in teaching focuses on learning in a virtual environment. In the field of Anaesthesia and Emergency Medicine, gain in knowledge and learning are intertwined with a high degree of "exposure", which is perceived as stressful. It is investigated, whether a careful introduction to a stressful situation improves learning as compared to an unsparing confrontation with the virtual reality and the consecutive "learning from mistakes." Here, psychological conditions play a prominent role that are related to the respective model of learning. Due to the scientific relatedness to psychology and pedagogy, a collaboration with the Department of Educational Psychology was launched.

Teaching

The cross-sectional area Emergency medicine accounts, in addition to the lecture "clinical anaesthesiology", for the main part of the teaching curriculum in anaesthesiology. Professional lecturers and instructors of the Department of Anaesthesiology 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 centre of the Department of Anaesthesiology. The cross-sectional area Q12 rehabilitation has a focus in pain therapy at the Medical Faculty and is organized by the Department of Anaesthesiology. 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 Anaesthesiology, intensive care medicine, emergency medicine, pain therapy, and palliative medicine as lectures, internships, seminars, and exercises.

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

Selected Publications

Fromm MF, Schwilden H, Bachmakov I, Koenig J, Bremer F, Schuettler J (2007) Impact of the CYP3A5 genotype on midazolam pharmacokinetics and pharmacodynamics during intensive care sedation. Eur J Clin Pharmacol, 63: 1129-1133

Leffler A, Reiprich A, Mohapatra DP, Nau C (2007) Use-dependent block by lidocaine but not amitriptyline is more pronounced in tetrodotoxin (TTX)-Resistant Nav1.8 than in TTX-sensitive Na+ channels. J Pharmacol Exp Ther, 320: 354-64

Palmaers T, Albrecht S, Heuser F, Leuthold C, Schuettler J, Schmitz B (2007) Milrinone combined with vasopressin improves cardiac index after cardiopulmonary resuscitation in a pig model of myocardial infarction. Anaesthesiology, 106: 100-6

Filitz J, Ihmsen H, Guenther W, Troester A, Schwilden H, Schuettler J, Koppert W (2008) Supra-additive effects of tramadol and acetaminophen in a human pain model. Pain, 136: 262-70

Jeleazcov C, Ihmsen H, Schmidt J, Ammon C, Schwilden H, Schuettler J, Fechner J (2008) Pharmacodynamic modelling of the bispectral index response to propofol-based anaesthesia during general surgery in children. Br J Anaesth, 100: 509-16

Leffler A, Fischer MJ, Rehner D, Kienel S, Kistner K, Sauer SK, Gavva NR, Reeh PW, Nau C (2008) The vanilloid receptor TRPV1 is activated and sensitized by local anesthetics in rodent sensory neurons. J Clin Invest, 118: 763-76

International Cooperation

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

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

Prof. G. K. Wang, Dept. of Anaesthesiology, Perioperative, and Pain Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, USA

Meetings and International Training Courses

01.–02.06.2007: 1. Erlanger Schmerztage fuer Pflegekraefte

30.11.–01.12.2007: 12. Erlanger Notfallmedizinische Tage "Großschadensereignisse"

07.–08.12.2007: Winter School – Methods in Pain Research, Erlangen

08.–09.02.2008: 8. Erlanger Schmerz- und Palliativtage – Schmerztherapie und Palliativmedizin – Forschung und Klinik

24.–25.10.2008: 38. Bayerische Anaesthesietage BAT, Erlangen

28.–29.11.2008: 13. Erlanger Notfallmedizinische Tage – Polytrauma Management – Chirurgische Notfaelle

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Research Focus
- Clinical Trial Centre (CTC) and Institute for Women's Health (IFG®)
- Laboratory for molecular medicine (LMM) and gynaecological oncology
- Gynaecological endocrinology and reproductive medicine
- Specialized obstetrics and perinatal medicine

Structure of the Institution

During the reporting period, the Department of Gynaecology has successfully continued the structural transformation that was initiated at the start of the decade, with the setting up of nationally and internationally certified interdisciplinary centres. The three traditional pillars of the specialty (gynaecology and gynaecological oncology, obstetrics and perinatal medicine, along with endocrinology and reproductive medicine) are now represented clinically and scientifically by the following organizational units:
- University Breast Centre for Franconia (UBF)
- University Gynaecological Cancer Centre for Franconia (GKF)
- University Perinatal Centre for Franconia (UPF)
- University Centre for Reproductive Medicine for Franconia (UFF) and
- University Endometriosis Centre for Franconia (UEF)

Interfaces for scientific work in the department are provided by the Laboratory for Molecular Medicine (LMM) and the associated Clinical Trial Centre (CTC, Institute for Women's Health, IFG®). In all, some 40 physicians are involved in clinical and scientific work in the department. They are supported by three researchers and four study nurses.

The department is recognized by the European Board and College of Obstetrics and Gynaecology (EBCOG) as a training hospital for european qualification as a physician specializing in obstetrics and gynaecology.

Research

Clinical Trial Centre (CTC) and Institute for Women's Health (IFG®)
More than 100 research projects have been carried out at the IFG® since 2001. These include clinical phase I–IV studies, as well as investigations on new surgical techniques. The clinical studies have concerned innovative approaches to the etiology, diagnosis, and treatment of breast, ovarian, endometrial, and cervical carcinoma. In addition to modern genetic studies and chemotherapy protocols, "target therapies" that are of particular current interest are being investigated.
Of particular note currently in connection with genital carcinomas is the AGO Cervix 1 study. In this randomized phase III study, the chemotherapy regimens of paclitaxel plus topotecan and topotecan plus cisplatin are being compared in patients with recurrent or persistent cervical carcinoma. For women with breast carcinoma, the years 2008 and 2009 are marked by the "Evaluate" study program. This is investigating therapy management, prospective pharmacoeconomics, and the basis for pharmacogenetic treatment in aromatase inhibitor therapy with letrozole in postmenopausal patients with hormone-sensitive breast carcinoma. The IFG® coordinates both studies in Germany.

Laboratory for molecular medicine (LMM) and gynaecological oncology
The basis for research in the LMM (Dr. Strick) is provided by a DNA and tissue bank, which at the end of 2008 already held more than 11,000 DNA samples from patients' blood, as well more than 6000 tissue samples from benign and malignant tumors, in collaboration with the Institute of Pathology at the University of Erlangen (Director: Prof. Hartmann).
Breast cancer research at the LMM (PD Dr. Fasching) is mainly focused on the search for genetic mutations and their possible correlation with the risk of the disease and its prognosis. This also includes the effect of mutations on enzymes such as CYP2D6 which influences the metabolic degradation of drugs. The LMM is a member of the international Breast Cancer Association Consortium (BCAC), which holds data for more than 30,000 breast cancer patients and matched controls. In large-scale epidemiological studies, the BCAC is investigating genetic risk factors and prognostic factors.
Research work on ovarian carcinoma (PD Dr. Fasching, Dr. Thiel), in collaboration with the international Ovarian Cancer Association Consortium (OCAC), is also aimed at identifying genetic mutations linked to cancer. In addition, the functional role of five human endogenous retroviruses and their significance for invasiveness and for cell–cell fusion has been investigated at the molecular level. In close collaboration with the Chair of Biochemistry and Molecular Medicine (Prof. Becker), it has been shown that a neuronal gene (neuron-restrictive silencer factor, NRSF) is a susceptibility marker in patients with ovarian carcinoma.
In the investigation of endometriotic tissue samples (Dr. Renner, Dr. Strissel) for DNA from herpes simplex virus (HSV) and human papillomavirus (HPV), as well as Chlamydia, 13.2% of the samples were found to be HPV-positive. Further studies are now in progress to examine whether HPV may be linked with endometriosis-associated malignant diseases.
In the normal endometrium of patients with breast carcinoma who are treated with or without tamoxifen, the LMM researchers found significant overexpression of various genes (IGF1 and its receptor, estrogen-receptor alpha and beta, syncytin-1, PAX2). In addition, it has been shown that tamoxifen enhances the phosphorylation of proteins such as AKT and mTOR in the endometrium, leading to overstimulation of the estrogen receptor (Dr. Strick, Dr. Strissel).

Gynaecological endocrinology and reproductive medicine
In the field of gynaecological endocrinology, research has continued successfully on methods of preserving fertility in young women with cancer who need to undergo treatments that are toxic to the ovaries. At the end of 2008, the department's tissue bank, where ovarian tissue that has been removed before treatment and cryoconserved for later sterility therapy if desired, held samples from over 150 patients.
In 2007, the research group achieved the first successful retransplantation of this type of conserved ovarian tissue in Germany. The patient, a 28-year-old woman, had undergone combined chemoradiotherapy. Five months after orthotopic retransplantation of the cryocon-

served ovarian tissue, there was an increase in estradiol from less than 20 pg/mL to a value of 436 pg/mL, and the patient reported her first spontaneous hormone withdrawal bleeding after the cancer treatment (Prof. Dittrich, PD Dr. Mueller, Prof. Beckmann).
Additional studies have focused on metabolic risks (hyperinsulinemia and insulin resistance) in women who meet the criteria for polycystic ovary syndrome (PCOS) or who have hyperandrogenemia. It was found that these risks are most strongly associated with body weight (BMI) and with ovarian function. By contrast, androgen levels and the extent of clinical androgenization phenomena (e.g., hirsutism and the ultrasound appearance of the polycystic ovaries) did not have any predictive significance (PD Dr. Mueller, PD Dr. Cupisti, Prof. Dittrich).

Specialized obstetrics and perinatal medicine

Through collaboration between the LMM and obstetricians (Prof. Schild, Dr. Goecke), it was demonstrated in connection with the pathophysiology of preeclampsia and the HELLP syndrome that syncytin-1, which is essential for human placental development, is a target for the transcription factors PPARγ/RXRα. In the placenta of patients with these diseases, the expression of syncytin-1 was reduced as a result of DNA methylation. In addition, it was shown in an investigation of the placenta in patients with intrauterine growth retardation (IUGR) that the expression of the envelope genes syncytin-1, -2, and -3 was significantly reduced.
The Perinatal Centre is working in close cooperation with the Department of Pediatrics (Director Prof. Rascher) on studies concerning the role of the placenta in fetal programming. It was shown that simultaneously reduced gene expression of cortisol-activating and -inactivating enzymes can be found in the placenta of small-for-gestational age (SGA) neonates. In children with IUGR, there was an inverse correlation between placental gene expression of 11β-HSD2 and the speed of growth during the first year of life.
In a large-scale collaborative project with the Department of Psychiatry and Psychotherapy (Director: Prof. Kornhuber) on pre-, peri-, and postpartal depression, it was shown that the development of postpartal depression, with all of its negative effects on the neonate's later cognitive and intellectual performance, is significantly dependent on prepartal factors, the birth experience, and the partnership (Dr. Goecke, Dr. Reulbach).

Sculpture in front of the perinatology building of the artist Prof. Stephan Balkenhol
Source: University Hospital Erlangen

Teaching

During the reporting period, teaching work was improved and strengthened by the implementation of a special area of responsibility (Dr. Frobenius, PD Dr. Cupisti). The integration of all teaching duties into the department's duty roster and responsibility rosters made it possible to ensure that there is now adequate staffing available for all curricular teaching courses and that these are now running to plan. In addition, a skills laboratory has been established for students in the department.
These new structures have also made it possible to substantially improve the practical course and expand the teaching program overall. Related to this, the introduction of a six-hour peer teaching program for participants in the practical course and the modification of the marked final examination into a small, objective, structured clinical examination (mini-OSKE) were monitored using a prospective randomized study. In addition, the department has been running since 2007 a two-day intensive course twice a year to provide preparation for the second state examination.

Selected Publications

Strick R, Ackermann S, Langbein M, Swiatek J, Schubert SW, Hashemolhosseini S, Koscheck T, Fasching PA, Schild RL, Beckmann MW, Strissel PL (2007) Proliferation and cell-cell fusion of endometrial carcinoma are induced by the human endogenous retroviral Syncytin-1 and regulated by TGF-beta. J Mol Med, 85: 23-38

Struwe E, Berzl GM, Schild RL, Beckmann MW, Doerr HG, Rascher W, Doetsch J (2007) Simultaneously reduced gene expression of cortisol-activating and cortisol-inactivating enzymes in placentas of small-for-gestational-age neonates. Am J Obstet Gynecol, 197: 43.e1-6

Dittrich R, Mueller A, Hoffmann I, Oppelt PG, Beckmann MW (2008) The transplantation of cryo-preserved ovarial tissue as option of the fertility preservation in cancer disease: Experience from the transplantation of human ovarial tissues on the immune deficient mouse and a 30-year old patient. Geburtsh Frauenheilk, 68: 538-539

Fasching PA, Loehberg CR, Strissel PL, Lux MP, Bani MR, Schrauder M, Geiler S, Ringleff K, Oeser S, Weihbrecht S, Schulz-Wendtland R, Hartmann A, Beckmann MW, Strick R (2008) Single nucleotide polymorphisms of the aromatase gene (CYP19A1), HER2/neu status, and prognosis in breast cancer patients. Breast Cancer Res Treat, 112: 89-98

Mueller A, Gooren LJ, Naton-Schoetz S, Cupisti S, Beckmann MW, Dittrich R (2008) Prevalence of polycystic ovary syndrome and hyperandrogenemia in female-to-male transsexuals. J Clin Endocrinol Metab, 93: 1408-11

Strissel PL, Ellmann S, Loprich E, Thiel F, Fasching PA, Stiegler E, Hartmann A, Beckmann MW, Strick R (2008) Early aberrant insulin-like growth factor signaling in the progression to endometrial carcinoma is augmented by tamoxifen. Int J Cancer, 123: 2871-9

International Cooperation

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

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

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

Meetings and International Training Courses

12.–13.05.2007: 8. Erlanger Kolposkopie Workshop, Erlangen, Arbeitsgemeinschaft Zervixpathologie und Kolposkopie der Deutschen Gesellschaft fuer Gynaekologie und Geburtshilfe

19.–20.10.2007: Intensiv-Fortbildungskurs "Geburtsmedizin", Erlangen, Deutsche Gesellschaft fuer Praenatal- und Geburtsmedizin

18.–19.01.2008: FertiPROTEKT – Deutsches Netzwerk fuer fertilititaetsprotektive Maßnahmen bei Chemo- und Strahlentherapie, Erlangen

07.–08.06.2008: 9. Erlanger Kolposkopie Workshop, Erlangen, Arbeitsgemeinschaft Zervixpathologie und Kolposkopie der Deutschen Gesellschaft fuer Gynaekologie und Geburtshilfe

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Research Focus
- Clinical trials
- Biological aspects of radiooncology
- Physical aspects of radiooncology

Structure of the Institution

Research in the department focuses on clinical, biological and physical aspects of radiooncology. Research on clinical aspects takes place mainly within the framework of phase I, II and III trials and is carried out on the ward, in the outpatient department, the treatment planning department as well as the therapeutics department harbouring the linear accelerators and the hyperthermia unit. A total of 5 registrars and 12 residents are involved in running the various trials and clinical studies. Coordination of the clinical trials is through the clinical trials office which is staffed by a chief secretary, two assistant secretaries as well as a secretary involved in documentation. For hyperthermia treatments the department has two machines to administer deep tissue hyperthermia one of which is equipped with an integrated MRI scanner for non- invasive temperature monitoring. In addition there is one appliance for interstitial hyperthermia and one appliance for superficial hyperthermia. Radiotherapy treatments are carried out at one of four linear accelerators and four brachytherapy afterloading machines. Radiobiological research is done by two group leaders, one scientist, two post docs, 4 laboratory assistants, two PhD students as well as several medical students as part of their doctoral thesis work. The department of radiobiology consists of two research groups who are interested in classical aspects of radiobiology (Project manager Dr. Distel) and in the field of radioimmunobiology (Project manager Dr Gaipel), respectively. The research group "Medical radiation physics" consists of five research associates, one of whom is habilitated and four of whom are PhD graduates, as well as four PhD students and two to three additional staff. Research work is carried out mainly by PhD students under the individual supervision of research associates.

Research

Clinical trials
1. Phase-III-multicentre trial: preoperative radiochemotherapy and adjuvant chemotherapy with 5-fluorouracil vs preoperative radiochemotherapy and adjuvant chemotherapy with 5- fluorouracil combined with oxaliplatinum in patients with locally advanced UICC stage II and III rectal cancer. (Prof. Sauer)
2. Phase-III-multicentre trial: comparison of partial breast interstitial brachytherapy with whole breast external beam radiotherapy in patients with low risk invasive and in-situ breast carcinomas. (Prof. Strnad C. Polgar, Budapest)
Sponsoring Deutsche Krebshilfe
3. Phase-III-multicentre trial: reducing total radiation dose in the context of a simultaneous radiochemotherapy of head and neck tumours (PacCis trial) (Prof. Fietkau and Prof. Iro)
Sponsoring Deutsche Krebshilfe
4. Phase-III-multicentre trial: Nutritional therapy of patients with head and neck tumours (Supportan trial) (Prof. Fietkau)
Sponsoring company: Fresenius
5. Phase-III-trial: Assessing the influence of an adjuvant chemotherapy following a simultaneous radiochemotherapy in patients with inoperable lung tumours (GILT-CRT-1) (R. Huber, M. Flentje and R. Fietkau)
Sponsoring company: Pierre Fabre
The department participates in the following externally- led phase-III-trials:
- Phase-III-trial: radiation dose intensity study in breast cancer young women
Randomized trial of additional dose to the tumour bed (Barteling)
- Phase-III-trial: hyperfractionated accelerated radiotherapy (HART) with mitomycin C/5-fluorouracil vs cisplatinum/ 5- fluorouracil in locally advanced head and neck tumours (V. Budach, J. A. Werner)
- German Hodgkin trials, coordinated by Cologne

In addition the department runs a number of phase I and II trials.

Biological aspects of radiooncology
1. Individual sensitivity to radiation
(Dr. Distel)
Individual differences in the sensitivity of normal tissues to radiation are the most important determinant for the occurrence of dose-limiting side effects of radiotherapy. In a project run jointly with the University of Würzburg (Dr. T. Djuzenova) the usefulness of of a bed-side test in determining the β H2AX phosphorylation status is compared to the established assay based on the analysis of chromosomal aberrations in peripheral blood lymphocytes. Patients with both rectal and breast tumours serve as study population.
2. Tumour infiltrating lymphocytes
(Dr. Distel)
Sponsoring: IZKF
The role played by tumour 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 Essen (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 tumours, gastric cancer and carcinoma of the rectum.
3. Non targeted effects of ionizing radiation
(PD Dr. Gaipl)
Sponsoring: Euopean Union
The non targeted effects of low dose irradiation have an influence on a number of different immune cell types. The mechanisms underlying the anti-inflammatory immune response have not yet been sufficiently elucidated. The project addresses the question of whether cells that have been exposed to low doses of radiation have the ability to induce an immunosuppressive state or to modulate inflammatory cells
4. Cell death and immunogenicity of cells from colorectal tumours after combined treatment with irradiation (X-rays) and hyperthermia (HT)
(PD Dr. Gaipl)
Sponsoring: ELAN fonds of the university hospital.
A combined anti-tumour therapy should lead to the cessation of cell proliferation and cell death on the one hand and should stimulate an immune response to the surviving tumour (stem) cells on the other. In this project the mode of cell death following individual (X- ray or HT) or combined modality treatment (X- ray and HT) is thoroughly characterized in colorectal tumour cell lines and the immunogenicity of dying tumour cells is tested in a xenogenic mouse model.

5. Characterisation of stress signals induced by application of high pressure (HHD) and their influence on the immunogenicty of tumour cells (Dr. Frey and Dr. Meister)
Sponsoring: ELAN fonds of the university hospital
In the treatment of tumour patients with whole-cell tumour vaccines the application of high pressure technology is thought capable of making an important contribution by acting as a tool to inactivate tumour cells while at the same time preserving or ideally even enhancing immunogenicity. The project looks at whether unfolded proteins accumulate in the endoplasmic reticulum (ER) following HHD treatment thus inducing an ER stress response called the "unfolded protein stress response" that causes cell death. The immunogenicity of tumour cells is analysed in the mouse model and is correlated with the UPR.
6. Influencing inflammatory states through low dose radiotherapy
(PD Dr. Gaipl and PD Dr. Keilholz)
Sponsoring: Thomas-Wildey Institute e.V.
The project focuses on the study of the systemic effects of low dose radiotherapy. To this end we use *in vitro* cell culture models as well as *in vivo* mouse models such as the one transgenic for the pro-inflammatory cytokine TNF-α where mice go on to develop a polyarthritis
7. Modulation of the NALP3 infammasome through low dose irradiation
(PD Dr. Gaipl)
Sponsoring: DFG, GRK of the Collaborative Research Centre (SFB) 643
The immunasome is a multi-protein complex that participates in the inflammatory response. The projects looks at whether and how low dose irradiation modulates the immunasome thereby exerting its anti-inflammatory effect. Stimulated macrophages are used as model system.

Physical aspects of radiooncology
Developing and setting up a tomotherapy treatment system
Patents: D, EU, US
Businessplan Competition 2008-2009
BPWN, MBPW, Science4Life
Monte Carlo algorithm to plan treatments with carbon ions. Development of an "optimiser" for the calculation of treatment parameters in the planning of treatments with e.g. protons and carbon ions.
Measuring absolute temperature in hyperthermia using MR- spectroscopy
Computer modelling in the development and construction of a ring-shaped electron beam CT (TOM'AGE)
Patents: D, EU, US
Monte Carlo Algorithm addressing geometrical problems concerning structural radiation protection
Cooperation partners: GSI, Darmstadt, GANIL, Caen, France
Sponsoring: Spiral2 FP7

Teaching

Apart from the traditional radiotherapy teaching sessions embedded in the course covering the related fields of medical imaging, radiotherapy treatment and radiation protection the department organizes an interdisciplinary lecture series in collaboration with the University Cancer Centre (UCC). In these lectures tumours 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 student 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 has been set up. For students doing practical clinical work in their pre-registration year a complementary teaching programme is offered.

Selected Publications

Fietkau R, Roedel C, Hohenberger W, Raab R, Hess C, Liersch T, Becker H, Wittekind C, Hutter M, Hager E, Karstens J, Ewald H, Christen N, Jagoditsch M, Martus P, Sauer R, German Rectal Cancer Study Group (2007) Rectal cancer delivery of radiotherapy in adequate time and with adequate dose is influenced by treatment center, treatment schedule, and gender and is prognostic parameter for local control: results of study CAO/ARO/AIO-94. Int J Radiat Oncol Biol Phys, 67: 1008-19

Wittlinger M, Grabenbauer GG, Sprung CN, Sauer R, Distel LV (2007) Time and dose-dependent activation of p53 serine 15 phosphorylation among cell lines with different radiation sensitivity. Int J Radiat Biol, 83: 245-57

Ott OJ, Hildebrandt G, Poetter R, Hammer J, Lotter M, Resch A, Sauer R, Strnad V (2007) Accelerated partial breast irradiation with multi-catheter brachytherapy: Local control, side effects and cosmetic outcome for 274 patients. Results of the German-Austrian multi-centre trial. Radiother Oncol, 82: 281-6

Achterberg N, Mueller RG (2007) Multibeam tomotherapy: a new treatment unit devised for multileaf collimation, intensity-modulated radiation therapy. Med Phys, 34: 3926-42

Frey B, Munoz LE, Pausch F, Sieber R, Franz S, Brachvogel B, Poschl E, Schneider H, Rödel F, Sauer R, Fietkau R, Herrmann M, Gaipl US (2009) The immune reaction against allogeneic necrotic cells is reduced in AnnexinA5 knock out mice whose macrophages display an anti-inflammatory phenotype. J Cell Mol Med 13:1391-9

International Cooperation

Prof. Dr. P. Rovere-Querini, Prof. Dr. A. Manfredi, H.S. Raffaele, Mailand, Italy

Dr. C. N. Sprung, Monash University, Clayton, Australia

Dr. Michael Lacniel, GANIL, Caen, France

Meetings and International Training Courses

30.–31.03.2007: 33. Erlanger Weiterbildungsveranstaltung, Erlangen, DEGRO

20.–22.09.2007: Interdisziplinaere Onkologie Rothenburg 2007, Rothenburg o.d.T., Verein zur Foerderung der Radioonkologie im Universitaetsklinikum Erlangen e.V

10.–11.10.2008: 34. Erlanger Weiterbildungsveranstaltung, Erlangen, Deutschland, DEGRO

Research Equipment

BSD Medical Corporation, Salt-Lake-City, Utah, USA BSD2000/3D-MRI

Siemens, Deutschland Siemens Symphony MRT 1,5 Tesla

BSD Medical Corporation, Salt-Lake-City, Utah, USA Sigma 30 MRI

BSD Medical Corporation, Salt-Lake-City, Utah, USA Sigma 40 MRI

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Research Focus

- Perinatal programming
- Perinatal hypoxic-ischemic brain injury
- Genetic diseases of the neonate
- Genomic aberrations in childhood malignancies
- Pediatric cell therapy
- Involvement in the Collaborative Research Centre 423 "Kidney injury: pathogenesis and regenerative mechanisms"

Structure of the Institution

The Department of Pediatrics comprises five specialized divisions (neonatology, neuropediatrics, paedeatric oncology/cell therapy, nephrology, and molecular paedeatrics), an endowed professorship for paedeatric endocrinology and diabetology, a social paedeatrics unit, and a number of specialized outpatient clinics. Academic staff of the department includes 91 physicians and scientists. Of these, 12 positions are financed by external funds.
Research continues to be focussed on the field of perinatal medicine, which has been strengthened by the recent establishment of a professorship for experimental perinatal medicine. Other main research activities are related to paedeatric oncology 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 or infection epidemiology, RECALTOX trial in children who received a kidney transplant, LESS study investigating long-term effects of anti-cancer therapy, clinical trials testing growth hormone as a treatment of short stature in children). 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 Division of Pediatric Cardiology as well as with various, mostly surgical subspecialties, often planned and carried out by interdisciplinary teams (Centre for Perinatal Medicine, Centre for Epilepsy, Heart Centre, Cleft Lip and Palate Centre, Transplantation Centre).

Research

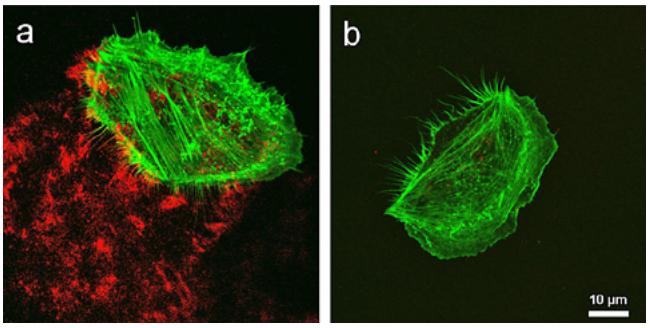
Perinatal programming
Project manager: J. Dötsch, I. Knerr
The term "perinatal programming" refers to permanent modifications of physiological processes by the intrauterine or early postnatal environment. Although the phenomenon has been well described also in humans, its mechanisms have remained unclear. 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.
Further research is aimed at understanding developmental abnormalities of the human placenta and the role of the fusion protein syncytin-1. Our studies have provided initial evidence that this protein may exert anti-apoptotic functions at the mitochondrial level.

Perinatal hypoxic-ischemic brain injury
Project manager: R. Trollmann, M. Schroth
Aiming at an early detection and prevention of perinatal brain injury caused by acute or chronic hypoxia, we investigate the role of hypoxia-inducible transcription factors (HIF). Such 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 analyzed. Experimental approaches to stabilizing HIF pharmacologically appear as a promising neuroprotective strategy.
In clinical studies, the potential of hypertonic-hyperoncotic saline solutions for minimizing cerebral edema in paedeatric intensive care patients is being evaluated.

Genetic diseases of the neonate
Project manager: H. Schneider, H. G. Dörr, 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. In a mouse model of Herlitz disease, presenting from birth with widespread blistering and erosions of skin and mucosae, we investigated for the first time the feasibility of gene therapy in utero. The most important advantage of this strategy proved to be the possibility to induce long-lasting immune tolerance of therapeutic proteins.
Long-term studies also include the documentation and retrospective analysis of prenatal treatment of adrenogenital syndrome in Germany. 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 (NEC) of preterm neonates.

Genomic aberrations in childhood malignancies
Project manager: M. Metzler, T. Langer
Analysis of patient-specific genomic aberrations in paedeatric tumors, particularly in childhood leukemia, allows insight into tumor initiation and clonal evolution. For clinical use, we try to employ such individual genetic tumor markers 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.

Pediatric cell therapy
Project manager: 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



Immunofluorescence study of individual keratinocytes from a neonate: Healthy keratinocytes (a) secrete laminin-5 leaving a distinct migration track behind (red). This anchoring protein is absent in keratinocytes from a patient with Herlitz disease (b), resulting in blistering and erosions of the skin subsequent to minor mechanical stress. Prof. Schneider 2007.

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.

In another research project we demonstrated that mesenchymal progenitor cells can be isolated from umbilical cord blood and – subsequent to expansion *in vitro* – are capable of differentiating into osteoblasts, chondrocytes, skeletal myoblasts and cardiomyocytes. Such 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.

Involvement in the Collaborative Research Centre 423 "Kidney injury: pathogenesis and regenerative mechanisms"

Project manager: A. Hartner, C. Plank, J. Dötsch

Typical features of progressive kidney diseases are fibrotic changes due to extracellular matrix accumulation and hyperplasia. In this connection, integrins as matrix receptors are known to play a pivotal pathogenetic role. Therefore we investigate the function of integrins and their ligands which are relevant to the kidney. We were able to show that α8-integrin can regulate cell adhesion, migration, differentiation and proliferation, thereby contributing significantly to the maintenance of renal tissue homeostasis. Further studies aim 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 and hands-on training in paedeatrics), special lectures, research seminars and interdisciplinary courses are offered to medical students. Individual members of the research staff participate in 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 paedeatric 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

Wixler V, Hirner S, Müller JM, Gullotti L, Will C, Kirfel J, Günther T, Schneider H, Bosserhoff A, Schorle H, Park J, Schüle R, Buettner R (2007) Deficiency in the LIM-only protein Fhl2 impairs skin wound healing. J Cell Biol, 177: 163-72

Cisse B, Caton ML, Lehner M, Maeda T, Scheu S, Locksley R, Holmberg D, Zweier C, den Hollander NS, Kant SG, Holter W, Rauch A, Zhuang Y, Reizis B (2008) Transcription factor E2-2 is an essential and specific regulator of plasmacytoid dendritic cell development. Cell, 135: 37-48

Knerr I, Dost A, Lepler R, Raile K, Schober E, Rascher W, Holl RW, Diabetes Data Acquisition System for Prospective Surveillance (DPV) Scientific Initiative Germany and Austria (2008) Tracking and prediction of arterial blood pressure from childhood to young adulthood in 868 patients with type 1 diabetes: a multicenter longitudinal survey in Germany and Austria. Diabetes Care, 31: 726-7

Müller T, Hess MW, Schiefermeier N, Pfaller K, Ebner HL, Heinz-Erian P, Ponstingl H, Partsch J, Röllinghoff B, Köhler H, Berger T, Lenhartz H, Schlenck B, Houwen RJ, Taylor CJ, Zoller H, Lechner S, Goulet O, Utermann G, Ruemmele FM, Huber LA, Janecke AR (2008) MYO5B mutations cause microvillus inclusion disease and disrupt epithelial cell polarity. Nat Genet, 40: 1163-5

Metzler M, Staege MS, Harder L, Mendelova D, Zuna J, Fronkova E, Meyer C, Flohr T, Bednarova D, Harbott J, Langer T, Gesk S, Trka J, Siebert R, Dingermann T, Marschalek R, Niemeyer C, Rascher W (2008) Inv(11)(q21q23) fuses MLL to the Notch co-activator mastermind-like 2 in secondary T-cell acute lymphoblastic leukemia. Leukemia, 22: 1807-11

Nüsken KD, Dötsch J, Rauh M, Rascher W, Schneider H (2008) Uteroplacental insufficiency after bilateral uterine artery ligation in the rat: impact on postnatal glucose and lipid metabolism and evidence for metabolic programming of the offspring by sham operation. Endocrinology, 149: 1056-63

International Cooperation

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

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

Dr. Simon Waddington, Department of Haematology, University College London, U.K.

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

Dr. Ornella Parolini, Fondazione Poliambulanza, Brescia, Italy

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

Prof. Dr. Georg Simbruner, Department of Pediatrics, Innsbruck Medical University, Austria

Meetings and International Training Courses

13.–16.09.2007: 103. Jahrestagung der Deutschen Gesellschaft fuer Kinder- und Jugendmedizin, Nürnberg

05.–07.06.2008: 16. Jahrestagung der Deutschen Gesellschaft fuer Paediatrische Infektiologie, Erlangen

Research Equipment

Beckman Coulter DNA-Sequenzierautomat

Becton Dickinson FACS Calibur

Applied Biosystems 2 Tandem-Massenspektrometer

Tecan Analyseplattform EVO 150

Carl Zeiss "Life cell imaging"-System

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Research Focus

- B-type natriuretic peptide as a diagnostic and prognostic tool for patients with congenital heart defects
- A biomaterial bank for patients with congenital heart defects
- Candidate gene approach for coarctation of aorta
- Gene hunting in a monogenic form of arterial hypertension

Structure of the Institution

The independent Division of Paedeatric Cardiology was newly established at the July 1st 2007. Clinical work and research activities are performed in close cooperation with the Division of Pediatric Cardiac Surgery founded at the 1st of September 2008, and the Department of Paedeatrics. A total of 9 medical doctors are employed splitting clinical work, teaching, and research. At the moment, there are 3 graduate students studying for a doctorate. There are several projects 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 and 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 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, and 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.

A biomaterial bank for patients with congenital heart defects

The evaluation of genetic factors and cellular mechanisms responsible for congenital heart malformation are in the focus of Dr. Toka's investigations. For this purpose, our department of paedeatric cardiology has established a biomaterial bank consisting of DNA and cardiac tissue samples recruited during routine cardiac surgery in children with congenital heart defects. This has been enabled by collaboration with the department of paedeatric cardiac surgery. Hereby we could recruit about 500 DNA samples and about 250 cardiac tissue sample of all four chambers of the heart and the great vessels since September 2008. The recruitment of sample is still ongoing. Due to the high genetic variability of cardiac malformations the establishment of a biomaterial bank will be a crucial element for our future investigations. It will be the fundament for a systematic approach to identify genetic key players in cardio genesis and congenital malformation.

Candidate gene approach for coarctation of aorta

The coarctation of the aorta accounts for a common type of heart defects with an incidence of about 7 % of all congenital heart malformations. We are conducting a positional candidate gene approach on a gonosomal locus to get more insights into the genetic mechanism of aotic isthmus stenosis. The genes we are interested in are so called homologue genes. These genes encoded and expressed on both gonosomal chromosomes and escape x-chromosomal inactivation in female. Thus, everyone has two functional copies of these genes, independent from once gender. Homologues genes have no sex-specific function. Their role in organogenesis and congenital malformations is mostly unknown. We are currently screening a cohort of 86 patients with sporadic coarctation of the aorta and identified two different mutations in one of this homologue genes so far. The biological relevance of the mutation is currently subject to our ongoing investigations.

Gene hunting in a monogenic form of arterial hypertension

Genetic research in the field of arterial hypertension with mendelian inheritance is an established approach to investigate the genetic contributors of essential hypertension. We are investigating a large Turkish kindred with a monogenetic form of arterial hypertension which co-segregates 100% with a complex type of brachydactyly (HBS) within a long-standing cooperation with Prof. Luft, Max-Delbrueck-Centre for Molecular Medicine, Berlin. Since 1994 numerous manuscripts have been published to describe this complex syndrome (Omin 112410). HBS patients resemble essential hypertension with normal water and sold homeostasis with no evidence of reno-tubulare defects. Investigating to evaluate the pathogenetic pathways responsible for this phenotype are still ongoing.

View of the Department of Pediatrics
Source: University Hospital Erlangen

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 in 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, Singer H (2006) B-type natriuretic peptide in paediatric patients with congenital heart disease. Eur Heart J, 27: 861-6

Koch A, Kitzsteiner T, Zink S, Cesnjevar R, Singer H (2007) Impact of cardiac surgery on plasma levels of B-type natriuretic peptide in children with congenital heart disease. Int J Cardiol, 114: 339-44

Baehring S, Kann M, Neuenfeld Y, Gong M, Chitayat D, Toka HR, Toka O, Plessis G, Maass P, Rauch A, Aydin A, Luft FC (2008) Inversion region for hypertension and brachydactyly on chromosome 12p features multiple splicing and noncoding RNA. Hypertension, 51: 426-31

Koch AM, Zink S, Singer H (2008) B-type natriuretic peptide in patients with systemic right ventricle. Cardiology, 110: 1-7

Koch AM, Zink S, Singer H, Dittrich S (2008) B-type natriuretic peptide levels in patients with functionally univentricular hearts after total cavopulmonary connection. Eur J Heart Fail, 10: 60-2

Wolf CM, Arad M, Ahmad F, Sanbe A, Bernstein SA, Toka O, Konno T, Morley G, Robbins J, Seidman JG, Seidman CE, Berul CI (2008) Reversibility of PRKAG2 glycogen-storage cardiomyopathy and electrophysiological manifestations. Circulation, 117: 144-54

International Cooperation

Seidman Laboratory, Department of Cardiovascular Genetics, Harvard Medical School, Boston, USA

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Research Focus

- Dendritic Cell (DC) vaccination (notably malignant melanoma)
- DC subpopulation and T-cell response
- Interaction between DC and viruses, especially HSV-1
- Tolerance induction using modified DC
- Basic research on DC's and T-cells
- Signal transduction and intercellular communication in the tumor microenvironment

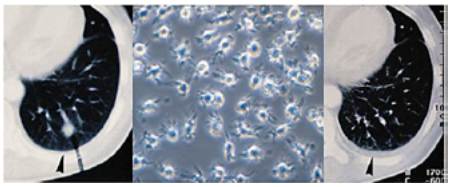
Structure of the Institution

Over 70 medics and scientists work at the Department of Dermatology. The research activities are organized in three main areas, (i) "Experimental Immunotherapy", (ii) "Experimental Dermatology" group and (iii) "Biology of Dendritic Cells". The Department of Dermatology pursues several immunologically oriented research areas. (i) The development of new and innovative immunotherapies based on DC. DC are specialized cells, able to induce antigen-specific cytotoxic as well as helper T-cell responses upon *ex vivo* antigen loading and injection into patients. Such approaches are currently used to vaccinate patients against cancer (melanoma as a prime model). Several clinical trials have already been conducted using peptide-loaded DCs in over 200 melanoma patients. With the help of these studies the "proof of principle", i.e. that modified DC can induce potent immune responses in melanoma patients has been obtained. (ii) An additional research focus concentrates on basic immunological aspects in order to understand the role of specific cells involved in the regulation of the immune system. New findings gained from these studies will firstly increase basic scientific knowledge and secondly represent the basis for innovative future clinical applications. All these projects are manly financed by extra mural fundings. In addition the Department of Dermatology coordinates the collaborative research project Collaborative Research Centre (SFB) 643 "Strategies of cellular immune intervention" sponsored by the German Research Foundation (DFG).

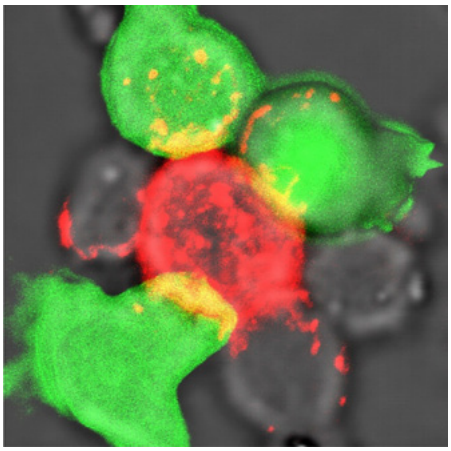
Research

Dendritic Cell (DC) vaccination (notably malignant melanoma)
Project manager: B. Schuler-Thurner
The major aim of the "Experimental immunotherapy" group is the development of new and innovative immunotherapies based on DC. DC are specialized white cells able to induce antigen-specific T-cell responses upon *ex vivo* antigen loading and injection into patients. 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 (Dr. Koch) for DC from peptide-loaded DC to those loaded with autologous tumor-RNA. Moreover we were preparing for a randomized, multicentric phase III trial for the indication uveal melanoma (with the collaboration of Prof. Kaempgen). In addition a clinical trial, using DC loaded with defined RNA for the tumor antigens MAGE-3, MelanA und Survivin was carried out for the treatment of patients suffering from metastasized melanoma.
The RNA-project group (Dr. Schaft and Dr. Doerrie) 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.

DC subpopulation and T-cell response
Project manager: D. Dudziak
This research group focuses on the antigen presentation of DC. In mice it could be shown that antigens can be targeted by antigen-coupled antibodies against C-type lectins and endocytosis receptors to DCs *in vivo*. Depending on the DC subpopulation we found that the T cell response could be directed and was either a more prominent CD4 T-helper response when CD11c+CD8- DCs presented the antigen or was a more dominant cytotoxic T-cell response, when CD11c+CD8+ DCs presented the antigen. This approach allows the maintenance/initiation of antigen-specific tolerance as well as the implementation of immunity. Now the strategy concept of "*in vivo* antigen targeting" of DCs will 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 studies we will be able to



Following dendritic cell vaccination (middle) lung metastases (arrow, left) regress (right side)



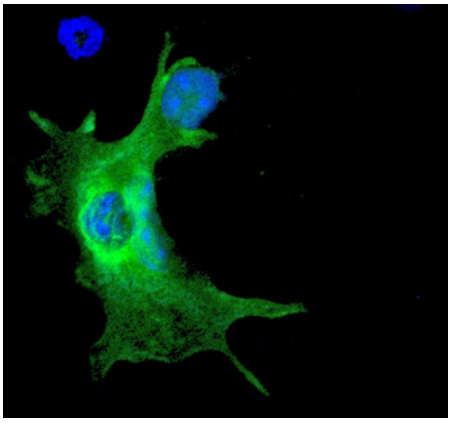
Trogocytosis of a HIV Nef activated T-cell (red) onto resting bystander T-cells

analyze the tissues for distinct DC subpopulations. Further, cell sorting and microarray analysis of the distinct DC subpopulations will help to identify molecules in these subpopulations that can be used for specific antigen targeting *in vivo*. Further, we will focus our work 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.

Interaction between DC and viruses, especially HSV-1

Project manager: M. Kummer, A. Goldwich

The project group "DC and viruses" analyses the interaction between DC and viruses, in particular in respect to the HSV-1 infection. A new immune-escape mechanism could be identified, namely that in HSV-1 infected DC, CD83 is completely degraded, which interestingly correlates with a reduced immuno-stimulatory capacity of these infected DC. This degradation is mediated by the viral immediate early protein ICP0 and the cellular proteasome. In addition we could show that HSV-1 interferes with the



A dendritic cell interacts with a T-cell

chemokine mediated DC-migration, which is an absolutely essential step in order to induce potent antiviral immune responses.

Tolerance induction using modified DC

Project manager: E. Zinser, I. Knippertz, M. Lechmann

The project group "DC-specific molecules" focuses on new, functionally relevant DC-specific molecules. A major aim is the functional characterization and elucidation of signal transduction and transcription events for CD83 which is one the best known cell surface markers for mature DC. In this respect, using CD83-specific siRNAs, we could show that CD83 is very important for the immunostimulatory capacity of mature DC. Furthermore we found that a soluble form of CD83 completely blocks DC-mediated T cell stimulation *in vitro* and *in vivo*. A recombinant soluble CD83 molecule showed great therapeutic potential in the treatment of experimental autoimmune encephalomyelitis (EAE) and in transplant studies using animal models. Interestingly, the abundance of an endogenously encoded soluble CD83 molecule was increased in the serum of cancer patients and certain viral infections. We will continue to study and analyze the therapeutic potential of the soluble CD83 molecule in additional autoimmune and transplantation models.

Using ChIP-chip™ microarray analyses we could further characterize the human CD83 promoter which in the long run should allow the targeted *in vivo* gene expression in mature DC. With the help of CD83 expressing reporter mice we will investigate the role of CD83 during tolerance induction as well as in T- and B-cell activation. Using the aptamer technology we will identify DC- and T-cell- (esp. Treg) specific surface molecule and characterize them on functional level.

Basic research on DC's and T-cells

Project manager: A. Steinkasserer

This research unit focuses on the basic research of DC, antigen loading, induction of tolerance, as well as DC- and T-cell- mediated signalling and transcription events. The aim of this research unit is several fold: (i) the establishment of new scientific basics for future therapy concepts and (ii) the investigation of molecular mechanisms regulating immune responses.

Signal transduction and intercellular communication in the tumor microenvironment

Project manager: A. Baur

The project group investigates MAP kinase-dependent signal transduction and intercellular communication in the tumor microenvironment of malignant melanoma. In our projects we investigate novel mechanisms of intercellular communication between tumor-cells and the immune system. In the course of these mechanisms cellular molecules are transferred to bystander cells through nanotubes, microvesicles and by trogocytosis. The functional consequences of this cellular hardware transfer, as well as its molecular basis are not understood. It is likely, however, that signal transduction events are transferred from one cell to the other leading to functional changes in the whole microenvironment. 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 hnRNPK-depend formation of a signaling complex leads to the activation of MAP kinase and subsequently to increased secretion of microvesicles and activation of trogocytosis. Preliminary data indicate that these events also lead to the activation of matrix metalloproteinase. These events are currently investigated in primary melanoma cell lines.

Teaching

The coworkers 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 Centre (SFB) 643 (strategies of cellular immune intervention).

Selected Publications

Erdmann M, Doerrie J, Schaft N, Strasser E, Hendelmeier M, Kaempgen E, Schuler G, Schuler-Thurner B (2007) Effective clinical-scale production of dendritic cell vaccines by monocyte elutriation directly in medium, subsequent culture in bags and final antigen loading using peptides or RNA transfection. J Immunother, 30: 663-74

Prechtel AT, Turza NM, Theodoridis AA, Steinkasserer A (2007) CD83 knockdown in monocyte-derived dendritic cells by small interfering RNA leads to a diminished T cell stimulation. J Immunol, 178: 5454-64

Albert H, Collin M, Dudziak D, Ravetch JV, Nimmerjahn F (2008) *In vivo* enzymatic modulation of IgG glycosylation inhibits autoimmune disease in an IgG subclass-dependent manner. Proc Natl Acad Sci U S A, 105: 15005-9

Doerrie J, Schaft N, Mueller I, Wellner V, Schunder T, Haenig J, Oostingh GJ, Schoen MP, Robert C, Kaempgen E, Schuler G (2008) Introduction of functional chimeric E/L-selectin by RNA electroporation to target dendritic cells from blood to lymph nodes. Cancer Immunol Immunother, 57: 467-77

Reinwald S, Wiethe C, Westendorf AM, Breloer M, Probst-Kepper M, Fleischer B, Steinkasserer A, Buer J, Hansen W (2008) CD83 expression in CD4+ T cells modulates inflammation and autoimmunity. J Immunol, 180: 5890-7

Witte V, Laffert B, Gintschel P, Krautkraemer E, Blume K, Fackler OT, Baur AS (2008) Induction of HIV transcription by Nef involves Lck activation and protein kinase C theta raft recruitment leading to activation of ERK1/2 but not NF kappa B. J Immunol, 181: 8425-32

International Cooperation

Prof. Dr. R. M. Steinman, The Rockefeller University, New York, USA

Prof. Dr. J. Banchereau, Dr. Karolina Palucka, Baylor Institute for Immunology, Dallas, Texas, USA

Prof. Dr. T. Boon, Prof. Dr. P. Coulie, Prof. Dr. van der Bruggen, Ludwig Institute of Cancer Research, Bruessel, Belgium

Prof. K. Thielemanns, Dr. J. Corthals, Free University of Brussels, Belgium

Prof. Dr. C. G. Figdor, Tumor Immunology, University Hospital, Nijmegen, Netherlands

Meetings and International Training Courses

16.–18.07.2007: DC2007 Kongress, Bamberg

Research Equipment

Becton Dickinson FACS Aria II

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Research Focus
- Neurootology/vestibular laboratory
- Computer aided surgery/robotics
- Laboratory for sleep disorders/somnology
- Experimental otolaryngology
- Magnetic drug targeting/nanomedicine
- Ultrasound and endoscopy
- Allergology/clinical immunology and rhinology
- Individual speech processor programming in cochlear implant users
- Neurophysiology

Structure of the Institution

In the Department altogether 255 act as coworkers, out of these 31 coworkers are engaged the clinical-scientific area, 7 coworkers exclusively within basic research and 217 coworkers in nursing and administration.
Within different scientific groups clinical-relevant research concerning neurootology, somnology, oncology, ultrasound and endoscopy, allergology and neurophysiology is performed.

Research

Neurootology/vestibular laboratory
In the year 2007 the integration of a dynamic Posturography system (Smart Equi Test®, NeuroCom Int.) into the clinic was the main focus of the neurootology/vestibular laboratory. The present equipment with videooculography combined to computernystagmography, laser target projector, rotary-/pendularchair system and static posturography could be extended thus by this very important functional spectrum. The emphasis was in particular on the pre- and postoperative diagnostics concerning cochlear implants and oktavusneurinomas. Further the dynamic, computerized posturography was used not only to the improved diagnostics of vestibular disturbances but also very successfully to the respective therapy of these diseases in cooperation with physiotherapists.

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 sofar 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.

Laboratory for sleep disorders/somnology
The projects are focused 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.

Experimental otolaryngology
The research lab experimental otolaryngology focused its research on projects on 1. pathogenesis of juvenile angiofibromas (JA), 2. inner ear biology, and 3. neurophysiology of the central auditory system. Results yielded e.g.:
1. evidence of tumor origin at early developmental stage by specific laminin expression patterns in tumor vessels and evidence that the prominent extracellular matrix component collagen type VI may exert growth-stimulatory effects on vascular as well as stromal cells in JAs.
2. the first description of glycine receptors in the rat cochlea and its developmental regulation which supports our hypothesis of a glycinergic component in cochlear efferent signal transduction.
3. the description of a new mechanism for sound source segregation in the auditory cortex of the Mongolian gerbil which is based on the neurophysiological implementation of a winner-take-all-algorithm (in cooperation with the University of Ulm and the Leibniz Institute for Neurobiology in Magdeburg).

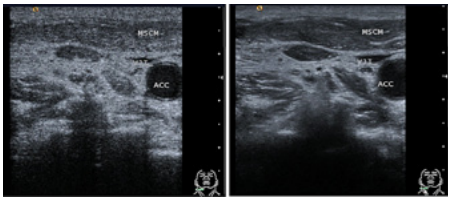
Magnetic drug targeting/nanomedicine
The therapeutical and the toxic effects of chemotherapeutics are often closely connected. Therefore, even small changes of their distribution in favour of the respective body compartment can result for the patients in a better

Neurootology/Vestibulardiagnostics

treatment of the malignancy while a often severe side effects should be reduced. Magnetic drug targeting is a new and inovative cancer therapy. Here, nanoparticles bound reversibly to cy-tostatic drugs are injected close to the tumor into the tumor supporting vessels and are enriched under the presence of an external magnetic field in the tumor. The nanoparticles serve as vehicles for concentrating the bound chemotherapeutic agents over the blood stream in the desired target area which is in the focus of an appropriate external magnetic field. In the laboratory for nanotechnology/local tumor therapy of the department extensive work is accomplished for the synthesis of biocompatible nanocarrier systems and their application in animal models. The aim of these studies is to lay the foundations for human trials ("Translational cancer research").

Ultrasound and endoscopy

A key issue of the high resolution ultrasound remains identification and classification of head and neck disease and salivary gland alterations. Using state of the art ultrasound devices we were able to develop in cooperation with the Competence Centre of Medical Technology of the Ruhr University of Bochum (Professor Ermert) computer-assisted diagnostic algorhytms, which could detect different tumours of the parotid gland with high sensitivity. Diagnostic quality of parotid gland tumours was critically tested in a nation wide multicenter study.



Ultrasound and Endoscopy

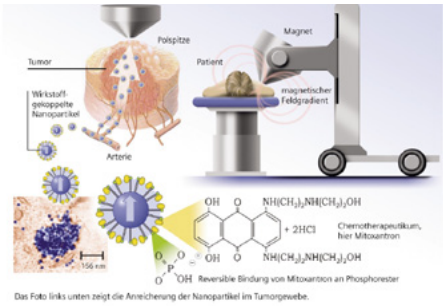
The application of current sonographic applications such as tissue harmonic imaging and compound imaging are the subject of up-to-date accomplished studies. Here these applications can contribute to clarify architecture and improve contrasting pathologies. Analyses of contrast agent application in patients with unclear lymph node enlargements could identify new objective characteristics in the distinction of benign and malignant nodes. Minimalinvasive techniques in the treatment of obstructive salivary gland disease remained another mainstay of research of the endoscopy team. In the context of an european-wide cooperation the experiences of this modern diagnosis and therapy procedure were evaluated and published. Salivary duct-, and gland endoscopy and their areas of application could be corroborated in their value of gland preserving treatment options.

Academic workshops and academic projects enabled Erlangen to assume leading position of salivary gland diseases in Germany and Europe. Many people visited the facilities and numerous international invitations were used to refer our personal experiences.

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



Schematic drawing of Magnetic Drug Targeting (www.siemens.de/pof)

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

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.

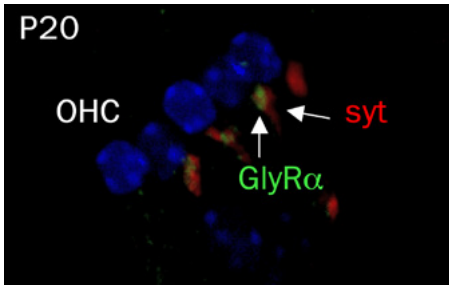
Neurophysiology

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.

Teaching

Traditional instruction forms (main lecture with case-demonstration and live transmission of operations, block practical courses) are supplemented by interdisciplinary meetings. Further more all the year the possibility exists for hospitation in the outpatient clinic and the operating theater.



Immunofluorescence staining of glycine receptors in the murine cochlea (P20) GlyRa protein (GlyRa, green) is detected at the basolateral end of outer hair cells (OHCs), in close apposition to efferent synaptic terminals, which are labelled with an antibody against synaptotagmin (syt, red). Cell nuclei are counterstained with DAPI (blue).

Selected Publications

Iro H, Wurm J, Zenk J (2004) Complications with inflammatory diseases of the nasal sinuses. HNO, 52: 395-408

Zenk J, Bozzato A, Steinhart H, Greess H, Iro H (2005) Metastatic and inflammatory cervical lymph nodes as analyzed by contrast-enhanced color-coded Doppler ultrasonography: quantitative dynamic perfusion patterns and histopathologic correlation. Ann Otol Rhinol Laryngol, 114: 43-7

Alexiou C, Jurgons R, Seliger C, Iro H (2006) Medical applications of magnetic nanoparticles. J Nanosci Nanotechnol, 6: 2762-8

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Duerr S, Wendler O, Aigner T, Karosi S, Schick B (2008) Metalloproteinases in juvenile angiofibroma--a collagen rich tumor. Hum Pathol, 39: 259-68

International Cooperation

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

Meetings and International Training Courses

International Course on Aesthetic and Reconstructive Rhinoplasty and Otoplasty, Blepharoplasty and Face Lift, Erlangen

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

Structure of the Institution

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 University Erlangen-Nürnberg and is supervising scientific works in all of these fields. Totally, 21 employees work at the department, four financed via third-party funds.

Research

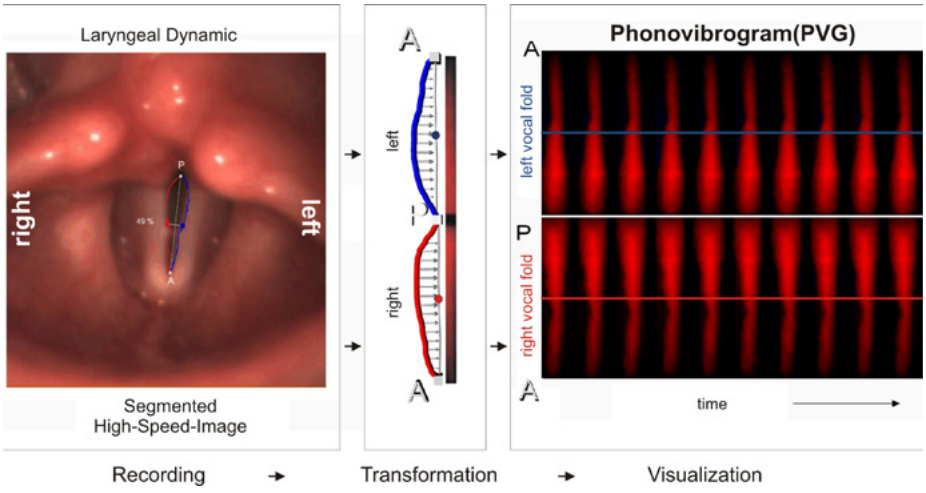
Evaluation of tracheoesophageal voice
After laryngectomy, the loss of natural voice is the most prominent functional defect. It can be rehabilitated best by means of shunt valves. So far, there is no consensus on how to evaluate tracheoesophageal voice. In a study funded by the German Cancer Aid Foundation it was shown that tracheoesophageal voice can be evaluated by an automatic speech analysis device. Results correlate significantly with expert evaluation, and expert evaluation correlates significantly with an evaluation obtained from naïve listeners. Different measures of self perception correlate significantly but not with the parameters extracted from voice analysis.

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 proved 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 are analyzed, captured at a frame rate of 4000 Hz. 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. For further quantification a laser projection device was developed which enables a quantification of the image data. Thus, absolute measures of vocal fold elongation and velocities can be performed.

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. The automatic speech analysis, as used for automatic speech recognition systems, is a new objective method for global evaluation, i.e. for the quantification of the intelligibility. Automatic evaluation agrees with the perceptive estimation by a panel of human experts. It is qualified to replace laborious subjective evaluations. Moreover, the application is tested for different forms of speech disorders and adapted for the automatic classification and quantification of different typical speech disorders. The new method will improve outcome measurements of different therapy strategies, e.g. for children with cleft lip and palate or adults with tumours of the head and neck.

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 approach auditory evoked potentials were used, whereat event related voltage deflections are derived from the scalp (EEG). Our workgroup detected a previously unknown speech evoked component in the time course of auditory potentials (N170), which is supposed to be generated due to changes of spectral and temporal stimulus features. The successful reconstruction of complex speech evoked potentials on the basis of acoustic stimulus features confirms this assumption. Thus, N170 allows conclusions about the auditory perception of speech. In children, N170 emerges over the years of infancy, i.e. it can be interpreted as an attribute of maturation, and support diagnostics of childish speech processing. In another project, 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
The segmented vocal fold oscillations can be analyzed with means of non-linear dynamics by simulating vocal fold motion curves with a biomechanical two-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 pattern can be quantified within a 2D parameter domain. The model simulations were designed in that way to quantify stationary and non-stationary vocal fold vibrations. Thus, different kinds of dysphonia were quantified within the parameter domain of the biomechanical model.



Assessment of vocal fold dynamics demands a computerized analysis of high-speed videos. After segmentation vocal fold edges are transformed and the distances to the glottal midline become color coded. Applying this strategy to an entire high-speed video generates a color image, denoted Phonovibrogram (PVG) which can be regarded as fingerprint of vocal fold dynamics.

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. Analysing 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 FOR894/1 is performing highly frontier research. 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 besides 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, Kummer P, Lohscheller J, Eysholdt U, Doellinger M (2007) Wavelet-based analysis of MMN responses in children. Biomed Tech (Berl), 52: 111-6

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Lohscheller J, Doellinger M, McWhorter AJ, Kunduk M (2008) Preliminary study on the quantitative analysis of vocal loading effects on vocal fold dynamics using phonovibrograms. Ann Otol Rhinol Laryngol, 117: 484-93

Lohscheller J, Eysholdt U (2008) Phonovibrogram visualization of entire vocal fold dynamics. Laryngoscope, 118: 753-8

Lohscheller J, Eysholdt U, Toy H, Dollinger M (2008) Phonovibrography: mapping high-speed movies of vocal fold vibrations into 2-d diagrams for visualizing and analyzing the underlying laryngeal dynamics. IEEE Trans Med Imaging, 27: 300-9

Wurzbacher T, Voigt I, Schwarz R, Doellinger M, Hoppe U, Penne J, Eysholdt U, Lohscheller J (2008) Calibration of laryngeal endoscopic high-speed image sequences by an automated detection of parallel laser line projections. Med Image Anal, 12: 300-17

International Cooperation

Melda Kunduk (PhD), Department of Communication Sciences & Disorders, Louisiana State University, Baton Rouge, USA

D.A. Berry, PhD, Laryngeal Dynamics Laboratory, Division of Head and Neck Surgery, University of California Los Angeles, USA

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Research Focus

- Pseudoexfoliation syndrome/glaucoma
- Corneal stem cells
- Ocular hem- and lymphangiogenesis and their relevance for corneal transplant immunology and tumor metastasis
- Biomorphometry of the optic nerve
- Clinico-pathologic concepts in diagnosis and management of ocular diseases
- Circulation of the eye and the visual Pathway and Computer-aided-Diagnosis & Virtual Education
- Functional aspects of retinal neurodegeneration
- Retinal physiology

Structure of the Institution

In total 168 Persons are employed at the Eye Hospital. Of these, 42 are physicians, 10 scientific staff member. 7 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 are 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, ourpatients 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 centre, 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

At the Department of Ophthalmology several aspects of ocular and eye diseases are investigated. The range of research includes studies on disease of the orbit and ocular media but also the retina and the central visual pathways. A multitude of techniques are available for these studies, including molecular biological methods, imaging techniques, electrophysiological recordings and psychophysical procedures.
Research in the Department of Ophthalmology is financially supported from various sources. The collaborative research centre 539 "Glaucoma including pseudoexfoliation syndrome (PEX)" should be explicitly mentioned. In addition many projects are supported by the German Research Council and other public and private institutions. In total 16 positions are externally funded: one professorship, 4 physicians, 5 scientific and 6 non-scientific staff members.

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.

Corneal stem cells
Project manager: 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.

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 morphometric reading centre of several multicentre antiangiogenic trials. The role of pathologic lymphangiogenesis for tumor metastasis of ocular tumors is examined.

Biomorphometry of the optic nerve
Project manager: C. Mardin, R. Tornow
The objective, measurable glaucoma damage at the optic disc and the peripapillary tissue and its early progression often precede functional defects. The project's aim is to measure the morphologic damage with new and established techniques *in vivo*, to find progression indicators and to differentiate between early glaucoma tissue loss and age related changes. Current focus is to establish high-resolution OCT to measure the retinal nerve fibre layer as the earliest tissue to be lost in glaucomas.

Clinico-pathologic concepts in diagnosis and management of ocular diseases
Project manager: 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.

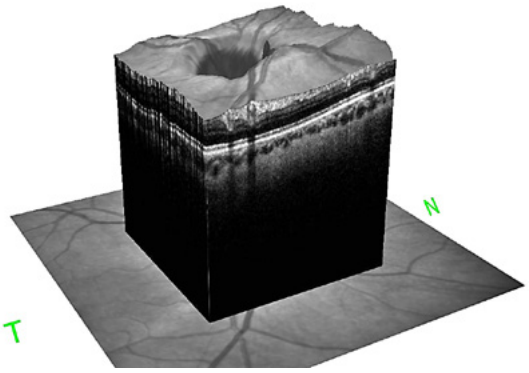
The aim of this study is the long-term evaluation of surgical results following intraoperative frozen section control and immediate plastic repair regarding recurrence rates and adequacy of reconstructive techniques.

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.

Circulation of the eye and the visual pathway and computer-aided-diagnosis & virtual education

Project manager: G. Michelson, S.Waerntges, M. Scibor



3-D imaging of a focal retinal nerve fibre layer defect in an early glaucoma eye with SPECTRALIS-OCT

1. Ocular circulation of the eye and the visual pathway.

The tissues and vessels of the eye reflect systemic diseases are a merely perfect system for the visualisation of physiologic processes of the body. Immunological processes, diabetes and arterial hypertension can be evaluated quantitatively in the eye.

2. Computer-aided-diagnosis & virtual education.

Ophthalmology needs new methods for medical information processing to optimize diagnosis and therapy. Automated analysis of ophthalmic images combined with automated classification leads to a fast and bias-free evaluation, which is an important prerequisite for screening.

3. Diffusion measurement of the visual pathway based on magnetic resonance images.

Neurodegenerative eye diseases often involve the 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.

Functional aspects of retinal neurodegeneration

Project manager: A. Juenemann, J. Kremers, F. Horn

In this research centre 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.

Retinal physiology

Project manager: 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 observers 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.

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

Heindl LM, Naumann GO, Kruse FE, Holbach LM (2008) Aggressive metastasising adenocarcinoma of the retinal pigment epithelium with trisomy 21. Br J Ophthalmol, 92: 389-91

Hos D, Bock F, Dietrich T, Onderka J, Kruse FE, Thierauch KH, Cursiefen C (2008) Inflammatory corneal (lymph) angiogenesis is blocked by VEGFR-tyrosine kinase inhibitor ZK 261991, resulting in improved graft survival after corneal transplantation. Invest Ophthalmol Vis Sci, 49: 1836-42

Kremers J, Link B (2008) Electroretinographic responses that may reflect activity of parvo- and magnocellular postreceptoral visual pathways. J Vis, 8: 11.1-14

Laemmer R, Mardin CY, Juenemann AG (2008) Visualization of changes of the iris configuration after peripheral laser iridotomy in primary melanin dispersion syndrome using optical coherence tomography. J Glaucoma, 17: 569-70

Ritt M, Harazny JM, Ott C, Schlaich MP, Schneider MP, Michelson G, Schmieder RE (2008) Analysis of retinal arteriolar structure in never-treated patients with essential hypertension. J Hypertens, 26: 1427-34

Schloetzer-Schrehardt U, Pasutto F, Sommer P, Hornstra I, Kruse FE, Naumann GO, Reis A, Zenkel M (2008) Genotype-correlated expression of lysyl oxidase-like 1 in ocular tissues of patients with pseudoexfoliation syndrome/glaucoma and normal patients. Am J Pathol, 173: 1724-35

International Cooperation

Claude Burgoyne, Devers Eye Institute, Discoveries in Sight Research Laboratories., Portland, USA

Prof. Luiz Silveira, Universidade Federal do Pará, Belém, Brasilia

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

Wolfgang Drexler, Institute f. Optometry, Cardiff, UK

Research Equipment

Zeiss Transmissionselektronenmikroskop

Zeiss Lasermikrodissektionssystem

Heidelberg Engineering SPECTRALIS-FLA und OCT

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Research Focus
- Stroke
- Public health
- Telemedicine and systems of care
- Neurocognition, headache and neuropathic pain
- Autonomic nervous system
- Neuromuscular diseases
- Epilepsy

Structure of the Institution

The Department of Neurology of Erlangen University Hospital is one of the largest neurological centres in Germany treating 3500 inpatients and more than 7000 outpatients each year. Our Stroke unit is the largest one in the state of Bavaria, and there is a huge intensive care unit integrated in the department. Additionally the department hosts one of the most important units for specialized diagnosis and treatment of epilepsy (ZEE) and runs a telemedical network for regional stroke care.
Within all these features 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

Stroke
Project manager: P. Schellinger, R. Kollmar, J. Bardutzky.
Intensive care medicine: A main focus of the neurocritical care unit consists of clinical research and transferring experimental research into clinical practice. In a larger cohort we studied the benefit of intraventricular thrombolysis and lumbar drainage after intraventricular haemorrhage. In a randomised clinical study of hypothermia treatment in patients with large intracerebral haemorrhage, preliminary data show a beneficial effect of therapeutic cooling. Further on, we conduct a throughout europe unique hypothermia trial in awake stroke patients. Other main fields of interest concern diagnostics of autonomic disorders and multimodal monitoring in severe neurologic disorders.
Stroke unit: After opening of the dedicated neuro emergency unit in 2006 and expansion of our stroke unit to 14 beds we are able to supply state-of-the-art stroke therapy in Erlangen around the clock. Therefore stroke patients get immediate treatment according to guidelines and have the opportunity to participate in promising national and international clinical trials. Main focus of research interest here are intraarterial and intravenous thrombolysis, advanced imaging guided therapy, treatment with growth factors and management of body temperature.

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 centre 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. The aim of register 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 manager: R. Handschu
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 focussing 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.

Neurocognition, headache and neuropathic pain
Project manager: C. Maihoefner
Our research team investigates mechanisms of adaptive and maladaptive sensorimotor plasticity in several diseases (neuropathic pain, headache, 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 several times awarded (European Pain Price 2007, Sertuener Price 2007; 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).

Autonomic nervous system
Project manager: M.-J. Hilz
The autonomic research laboratory evaluates cardiovascular autonomic sequelae of cerebral disorders involving the central autonomic network, e.g. after stroke, traumatic brain injury, in epilepsy, or other autonomic diseases. We developed methods for an early diagnosis of altered cerebral autoregulation, e.g. in diabetes mellitus or in congenital autonomic diseases, such as familial dysautonomia which we study in cooperation with New York University.

Neuromuscular diseases
Project manager: D. Heuss, R. Schroeder
The Neuromuscular Disease Centre 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 Rican family (2) CK2-deficient myopathies (3) Vaskulitic neuropathies / clinical follow up (4) Intermediate 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 and cardiac pathology in a R155C-VCP knock-in mouse. (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 desmin protein. Therapeutical trials (A) A Study in Early Onset ALS (SIRONA) ONO-2506POE014 (B) Deflazacort in Dysferlinopathies – double-blind, placebo-controlled study/BMBF-subproject R19 MD-NET.

Epilepsy
Project manager: H. Stefan
As a degree-four-centre ZEE provides the highest level of medical care for patients suffering form therapy resistant seizures. A model program for the management of epilepsy centres was developed. Important research goals are further developments of non-invasive preoperative localization diagnosis with the help of a high resolution functional magnetic resonance tomography and spectroscopy (MRS) and magnetencephalography, quantitative EEG-analysis and SPECT- and PET registrations (cooperation with neuroradiology and nuclear medicine). Neurobiological and molecular genetic methods allow the examination of epileptogenic tissue gained by surgery. This opens promising perspectives for experimental clinical research and will further support the understanding of epileptogenesis (cooperation with the institute of neuropathology and biochemistry). Analyzing the course of focal epilepsies shall contribute to the recognition of pharmacoresistence mechanisms, therapy and prognosis. Innovation strategies for drug treatment of epilepsy with new substances, new surgical procedures and focal radiotherapy will be developed (cooperation with neurosurgery and radiotherapy). A new multi-channel MEG-system is currently installed.

Teaching

Clinical education has been restructured primarily in the practical week. Elements for practical skill such as lumbar puncture training and OSCE have been included. For the following year, further state-of-the-art implementations are panned according to student assessment and recent knowledge of master of medical education studies.

Selected Publications

Duetsch M, Burger M, Doerfler C, Schwab S, Hilz MJ (2007) Cardiovascular autonomic function in poststroke patients. Neurology, 69: 2249-55

Hammen T, Schwarz M, Doelken M, Kerling F, Engelhorn T, Stadlbauer A, Ganslandt O, Nimsky C, Doerfler A, Stefan H (2007) 1H-MR spectroscopy indicates severity markers in temporal lobe epilepsy: correlations between metabolic alterations, seizures, and epileptic discharges in EEG. Epilepsia, 48: 263-9

Hilz MJ, Devinsky O, Szczepanska H, Borod JC, Marthol H, Tutaj M (2007) Right ventromedial prefrontal lesions result in paradoxical cardiovascular activation with emotional stimuli (vol 129, pg 343, 2006). Brain, 130: 879-879

Seifert F, Maihoefner C (2007) Representation of cold allodynia in the human brain--a functional MRI study. Neuroimage, 35: 1168-80

Huttner HB, Janich P, Koehrmann M, Jászai J, Siebzehnrubl F, Bluemcke I, Suttorp M, Gahr M, Kuhnt D, Nimsky C, Krex D, Schackert G, Loewenbrueck K, Reichmann H, Juettler E, Hacke W, Schellinger PD, Schwab S, Wilsch-Braeuninger M, Marzesco AM, Corbeil D (2008) The stem cell marker prominin-1/CD133 on membrane particles in human cerebrospinal fluid offers novel approaches for studying central nervous system disease. Stem Cells, 26: 698-705

Schellinger PD, Köhrmann M, (2008) MRS/DWI mismatch: a novel concept or something one coud get easier and cheaper? Stroke, 39: 2423-4

International Cooperation

New York University, USA

Prof. P. Chauvel, Service de Neurophysiologie Clinique, Aix-Marseile-Université, France

Prof. Ch. Baumgartner, Neurologische Universitaetsklinik Vienna, Austria

Prof. J. Duncan, National Hospital Queen Square London, United Kingdom

Prof. Achten, Katholieke Universiteit Leuven, Belgium

Prof. Zong-Zou, Universitaet Chengdu, China

Prof. G. del Valle, University of Costa Rica, San José

Prof. G. Wiche, University of Vienna, Austria

Prof. Denise Paulin, Pierre et Marie Curie University, Paris, France

Prof. Lee Schwamm, Havard Medical School, Boston, USA

Prof. S. Anderman, Montreal Neurological Institute (MNI), Canada

Prof. W. Theodore, National Institute of Health, Bethesda-Maryland, USA

Dr. G. Kraemer, Schweizerische Epilepsieklinik, Zuerich, Swiss

Meetings and International Training Courses

15.–16.06.2007: 3rd Epilepsy Colloquium Erlangen

05.07.2007: STENO-Netzwerk Schlaganfall, Forchheim

06.10.2007: Eroeffnung Stroke Unit mit wissenschaftlichem Symposium, Erlangen

17.04.2008: 1. STENO-Symposium, Erlangen

Research Equipment

Schwarzer Neurophysiologie Netzwerk

Magnes MEG 4D Neuroimaging Biomagnetismusanlage

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Division of Molecular Neurology

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Research Focus
- Neurodegenerative diseases
- Translational research
- Clinical research and development

Structure of the Institution

The Division of Molecular Neurology within the Department of Neurology, newly formed in September 2008, aims to establish the link from daily patient care towards the neuroscientific development in the field of neurodegenerative diseases. 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 projects with the neighbouring Departments of Neurology, Psychiatry, Neurosurgery, Ophthalmology, Neuropathology as well as the Division of Neuroradiology.
Clinically, an outpatient clinic for movement disorders was established where the entire spectrum of clinical, electrophysiological, imaging and genetic diagnostics is provided for patients affected with these diseases.

Research

Neurodegenerative diseases
The scientific focus of the newly formed division emphasizes on adult neurogenesis and neurodegenerative mechanism in Parkinson's disease, Huntington's disease and hereditary spastic paraplegia. Neuroregenerative processes with emphasis on adult neurogenesis (generation of new neurons in the adult brain) are assessed in movement disorders using cell culture and transgenic models of Parkinson's and Huntington's disease. In an complementary approach neurodegenerative mechanism in synucleinopathies are analysed in order to understand the molecular mechanism in the development of Parkinson's disease and Lewy body dementia.

Translational research
The Division is interested in the molecular and cellular biology of adult neural stem and progenitor cells in two regions of the adult brain, the subventricular zone and the hippocampus, where new neurons are generated throughout the whole life span. Adult neurogenesis is seriously altered in the context of neurodegenerative diseases. Numerous findings indicate that impaired adult neurogenesis may be one of the underlying pathophysiological events in the development of non-motor symptoms like depression, cognitive impairment and olfactory dysfunction. These symptoms are likely to reflect the compromised ability of the brain to generate new neurons in the hippocampus as well as the olfactory bulb. Moreover, cell and molecular techniques have been established to delineate and modify pathological mechanism associated with protein aggregation of alpha-synuclein in Parkinson's disease and atypical Parkinson syndromes. This strategy may lead to a causal therapy of synucleinopathies.

Clinical research and development
The outpatient clinic for movement disorders (in particular Parkinson's disease, Huntington's disease and hereditary spastic paraplegia) is offering state of the art diagnostic procedures and long-term care for patients and their caregivers. Furthermore, the integration of scientific projects will be consequently followed up in close cooperation with the Department of Neurology which provides the care for inpatients. Using modern structural imaging and functional diagnostics workups such as high-resolution magnetic resonance tomography, SPECT and PET analysis, the precise diagnostic classification of these movement disorders will be completed by a detailed molecular genetic testing. The ultimate goal of this combined approach is to develop an individualized therapy for each patient.
In addition to the clinical and neurobiological activities deep brain stimulation (DBS) procedures for movement disorders is prepared in close cooperation with the Department of Neurology and Neurosurgery in order to provide the entire spectrum of therapies for movement disorders at the University Hospital Erlangen.

Selected Publications

Kohl Z, Kandasamy M, Winner B, Aigner R, Gross C, Couillard-Despres S, Bogdahn U, Aigner L, Winkler J (2007) Physical activity fails to rescue hippocampal neurogenesis deficits in the R6/2 mouse model of Huntington's disease. Brain Res, 1155: 24-33

St Martin JL, Klucken J, Outeiro TF, Nguyen P, Keller-McGandy C, Cantuti-Castelvetri I, Grammatopoulos TN, Standaert DG, Hyman BT, McLean PJ (2007) Dopaminergic neuron loss and up-regulation of chaperone protein mRNA induced by targeted over-expression of alpha-synuclein in mouse substantia nigra. J Neurochem, 100: 1449-57

Nuber S, Petrasch-Parwez E, Winner B, Winkler J, von Hoersten S, Schmidt T, Boy J, Kuhn M, Nguyen HP, Teismann P, Schulz JB, Neumann M, Pichler BJ, Reischl G, Holzmann C, Schmitt I, Bornemann A, Kuhn W, Zimmermann F, Servadio A, Riess O (2008) Neurodegeneration and motor dysfunction in a conditional model of Parkinson's disease. J Neurosci, 28: 2471-84

Winner B, Couillard-Despres S, Geyer M, Aigner R, Bogdahn U, Aigner L, Kuhn HG, Winkler J (2008) Dopaminergic lesion enhances growth factor-induced striatal neuroblast migration. J Neuropathol Exp Neurol, 67: 105-16

Winner B, Rockenstein E, Lie DC, Aigner R, Mante M, Bogdahn U, Couillard-Despres S, Masliah E, Winkler J (2008) Mutant alpha-synuclein exacerbates age-related decrease of neurogenesis. Neurobiol Aging, 29: 913-25

Marxreiter F, Nuber S, Kandasamy M, Klucken J, Aigner R, Burgmayer R, Couillard-Despres S, Riess O, Winkler J, Winner B (2009) Changes in adult olfactory bulb neurogenesis in mice expressing the A30P mutant form of alpha-synuclein. Eur J Neurosci, 29: 879-90

International Cooperation

Prof. Dr. B.T. Hyman, Massachusetts General Hospital – MIND, Harvard University, Boston, USA

Dr. M. Ingelsson, Rudbeck Laboratory, Uppsala University, Sweeden

Dr. T.F. Outeiro, Institute for Molecular Medicine – Cellular and Molecular Neuroscience Unit, University of Lisbon, Portugal

Prof. Dr. F. Gage, Laboratory of Genetics, The Salk Institute for Biological Studies, La Jolla, California, USA

Prof. Dr. E. Masliah, Department of Neurosciences, University of California San Diego, California, USA

View of the "Kopfklinikum" in the background with the Division of Molecular Neurology
Source: University Hospital Erlangen

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Research Focus
- Neuroendocrinology
- Neurooncology
- Functional neuronavigation and intraoperative imaging

Structure of the Institution

The Department of Neurosurgery of the University of 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 in the microsurgical treatment of processes of the skull base, particularly in the sellar region, in eloquent brain areas (e.g. central region, brain stem), the vascular neurosurgery, spine surgery, pediatric neurosurgery and epilepsy surgery. Aside of modern microsurgical techniques, endoscopic procedure, intraoperative electrophysiological monitoring, neuronavigation and intraoperative MRI are used. A molecular biological laboratory with an integrated cell culture and a wide range of cellular and molecular biological methods are available for basic scientific issues.

Research

Neuroendocrinology

The Department of Neurosurgery represents a nationally and internationally specialized centre for the whole spectrum of sellar pathologies. Clinically we investigate the influence of interventional/operative, radiotherapeutic, and pharmacological approaches on normal and hypersecretory pituitary gland function in the course of the "Acrostudy" (treatment and MRI follow-up of the medicinal therapy with Somavert). Also, investigations on Somatostatin analoga and their clinical relevance in the treatment of growth hormone secreting pituitary adenoma represent a central part. Our clinical and laboratory chemical analysis and screening studies are supported by Pfizer and Novartis. The efficacy of novel intra-operative technologies in pituitary adenoma surgery and craniopharyngiomas 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 tumours. Goal of these clinical long term studies is to define the relapse frequencies of sellar tumours including different prognostic factors.
The field of Neuroendocrinology in the Department of Neurosurgery was established in 2007 in the framework of a foundation professorship for clinical and experimental neuroendocrinology. In cooperation with the Institute of Radiology body composition, liver and muscle fat content are determined by MRI in patients with various hypothalamic-pituitary diseases (e.g. pituitary deficiency, acromegaly and M. Cushing). The results are correlated with various metabolic characteristics and with novel parameters involved in the metabolic control. The aims of these studies are to obtain novel insights in the neuroendocrine control of metabolic and energetic processes. Another translational scientific project involves the functional characterization of mutations of the metabotropic calcium-sensing receptor (CaSR), that occur in patients with specific disorders of calcium homeostasis. The CaSR is also expressed in pituitary cells and in hypothalamic nuclei involved in the control of endocrine systems. In this project the patients are screened for clinical evidence of neuroendocrine dysfunction, and clinical and *in-vitro* data are correlated to define a potential genotype-phenotype relation. Furthermore, agonists and antagonists of the CaSR are tested *in vitro* whether they can rescue the molecular defect of the mutated CaSR. This potentially offers a therapeutic approach specifically tailored to patient´s molecular CaSR defect (individualized medicine). Further projects investigate various aspects of growth-hormone secreting human adenoma cells *in vitro* like the expression of certain membrane receptors (e.g. somatostatin receptors) and the characteristics of signalling cascades (cAMP- and Ca2+-PI-signalling 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 tumours of the brain, and about 70% of these tumours are malignant gliomas. Currently, there do not exist any promising therapy for the treatment of malignant tumours 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 tumour-associated cell interaction represents the protein MIF. This cytokine is secreted by glioma cells and interacts with the adjacent parenchyma. The aim of this project is the analysis of MIF effects on immune competent cells in the brain such as microglial cells and its role in glioma proliferation and invasion. Moreover, the preliminary data indicate that microglial cells participate at edema formation surrounding malignant gliomas. The presented studies are funded by a grant from the "Wilhelm Sander-Stiftung" and from the "Institut Danone Ernaehrung fuer Gesundheit e.V.".

Functional neuronavigation and intraoperative imaging

The reseach group "functional neuronavigation and intraoperative imaging" is divided into three subgroups that work in part independently. The common interface represents the BrainSuite, consisting of intraoperative 1.5 T MRI-scanner and integrated navigation:

Subgroup I (Intraoperative imaging): A major effort of this group is the acquisition of all parameters that are connected to intraoperative imaging of 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 magnetoencephalographie. Moreover studies of implementation of tractography data in the surgical treatment of brain stem lesions were completed. Two important studies analysed the connectivity of eloquent brain areas with different DTI algorithms using probabililistica fiber tracking and investigated the amount of susceptibility artefacts 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 (in collaboration with the Department of Nuclear Medicine). 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.

In the forthcoming period we intend to 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 glioma resection adjacent to eloquent brain areas and intraoperative MR spectroscopy in gliomas. The presented studies are funded by a grant from the "Wilhelm Sander-Stiftung".

Operation according to state-of-the-art technology
Source: University Hospital Erlangen

Teaching

Aside of the neurosurgical main lecture with case demonstrations and live broadcasts from the operating theatre, 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 theatre.

Selected Publications

Stadlbauer A, Nimsky C, Buslei R, Salomonowitz E, Hammen T, Buchfelder M, Moser E, Ernst-Stecken A, Ganslandt O (2007) Diffusion tensor imaging and optimized fiber tracking in glioma patients: Histopathologic evaluation of tumor-invaded white matter structures. Neuroimage, 34: 949-56

Tanrikulu L, Hastreiter P, Troescher-Weber R, Buchfelder M, Naraghi R (2007) Intraoperative three-dimensional visualization in microvascular decompression. J Neurosurg, 107: 1137-43

Kreutzer J, Buslei R, Wallaschofski H, Hofmann B, Nimsky C, Fahlbusch R, Buchfelder M (2008) Operative treatment of prolactinomas: indications and results in a current consecutive series of 212 patients. Eur J Endocrinol, 158: 11-8

Rus R, Haag C, Bumke-Vogt C, Baehr V, Mayr B, Moehlig M, Schulze E, Frank-Raue K, Raue F, Schoefl C (2008) Novel inactivating mutations of the calcium-sensing receptor: the calcimimetic NPS R-568 improves signal transduction of mutant receptors. J Clin Endocrinol Metab, 93: 4797-803

Savaskan NE, Heckel A, Hahnen E, Engelhorn T, Doerfler A, Ganslandt O, Nimsky C, Buchfelder M, Eyuepoglu IY (2008) Small interfering RNA-mediated xCT silencing in gliomas inhibits neurodegeneration and alleviates brain edema. Nat Med, 14: 629-32

Stadlbauer A, Buchfelder M, Nimsky C, Saeger W, Salomonowitz E, Pinker K, Richter G, Akutsu H, Ganslandt O (2008) Proton magnetic resonance spectroscopy in pituitary macroadenomas: preliminary results. J Neurosurg, 109: 306-12

International Cooperation

Prof. Dr. David L. Kleinberg, Department of Endocrinology, New York University Langone Medical Centre, USA

Prof. Dr. Ting Lei, Department of Neurosurgery, Huazhong University of Science and Technology, Tongji Medical College, Wuhan, China

Research Equipment

Zeiss Opmi Pentero

BrainLab Neuronavigationssystem VectorVision Sky

BrainLab Neuronavigationssystem VectorVision Square

Siemens Intraoperative Kernspintomographie Sonata

Siemens Patientenmonitoring Intensivstation

BrainLab Stereotaktischer Linearbeschleuniger Novalis

4D Neuroimaging Magnes II Biomagnetometer

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Research Focus
- Depression research
- Research in dementia
- Addiction research
- Clinical neurochemistry
- Psychometric research
- Health services research in psychiatry

Structure of the Institution

All the psychosocial professions are united under one roof and fall under the organisational umbrella of the Department of Psychiatric and Psychotherapeutic Clinic, and include 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 9001:2000.
We provide a qualified, interdisciplinary team, which are involved with 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 department are multifaceted with a broad diversity. Particularly visible research projects have been developed in the disease areas depression, addiction and dementia. The department is a member of the Dementia Competence Network Society and plays a leading role with its diagnostic centre 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 emphasised. 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 centre for the neurochemical dementia diagnostic in the frame work of the Dementia Competence Network, is a part of the psychiatric core clinic. In addition, the laboratories for molecular neurobiology and sensorics are part of the Clinic.
The Clinic strives at an above-average teaching performance. The courses are regularly evaluated as particularly good by Erlangen's students. Nationwide, the Erlanger medical psychology and medical sociology students regularly hold first place.

Research

Depression research

In Depression research, the stimulation procedures electroconvulsion therapy, repetitive transcranial magnetic stimulation and vagus nerve stimulation were evaluated for their clinical efficacy. Significant improvements over common treatment procedures were found in the clinical treatment of therapy-resistant depressions. Moreover, the cognitive concepts "rumination" and "worry" were differentially analyzed in depression, anxiety disorders and the high rate of comorbid occurrence of depression and anxiety disorders to clarify the model presentations in order to enable improvement in psychotherapeutic interventions. The cell-biological basis of depressive disorders, especially intracellular lipid-associated signal transduction mechanisms was investigated.

Research in dementia

In this area, research focuses on the improvement of the early and differential diagnosis of dementias. By using our newly-developed two-dimensional Western-immunoblot method (2D-Aβ-WIB) a complex pattern of 30 distinct Aβ peptide species was detected in human blood plasma. Similarly, in supernatants from human mononuclear phagocyte (MNP) cultures a complex signature of released Aβ peptides was observed. To improve our understanding of immunological processes in age-dependent neurodegenerative diseases, current research focuses on the identification of cellular and signalling molecule patterns which may serve as biomarkers of dementias. The studies were supported by grants from the German Federal Ministry of Education and Research – Dementia Competence Network, NGFN2-SMP Proteomics, HUPO – and the European Union – cNEUPRO, neuroTAS – (total amount: 800,000 Euro).

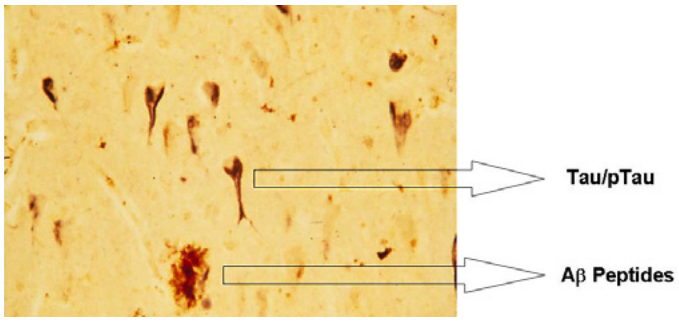
"MAKS aktiv!" – training in motion, activities of daily living and cognition for dementia patients

Addiction research

In the area of addiction, scientifically important findings were obtained in not only neurobiological foundations (genetics, epigenetics, fMRI, event-correlated potentials) but also in clinical, epidemiological and supply research. The research interest focused on processes of chemoperception, "liking" and "craving" for addictive substances, the vulnerability to addictive substances and the effect of substance use and withdrawal on epigenetic, neurotrophic and neuroprotective control systems. Likewise, clinical questions about the treatment of withdrawal and also new aspects of classification were addressed.
The vulnerability concept of alcoholism was investigated with respect to neuropsychological, neurobiochemical influence factors and comorbidity according to the classfication of Lesch

type I-IV. Third-party fundings were used. Scientists in this research area received two ERAB travel awards and one ECNP Fellowship Award.

Clinical neurochemistry
Clinical neurochemistry focuses on the search for novel cerebrospinal fluid (CSF) and blood/plasma biomarkers for improved early- and differential diagnosis of the diseases of the nervous system, with particular focus on neurodegenerative conditions (like Alzheimer's disease). The goal is their integration into routine analytical procedures. Furthermore, we are working to improve the analytical performance of already available biomarkers of neurodegeneration (amyloid β-peptides, tau proteins), for example by optimizing the standard operating procedures (SOPs) for collection and storage of relevant body fluids, and by their integration into novel analytical platforms, like e.g. multiplexing. In parallel, we have organized and maintain one of the world-wide largest prospective multicenter biobank of human body fluids from patients with early dementias. The research is funded by the BMBF and the EU.



Senile plaques, composed predominantly of amyloid beta peptides, and neurofibrillary tangles with hyperphosphorylated Tau proteins: the two hallmarks of Alzheimer's disease neuropathology

Psychometric research
Therapeutic success, especially in typical age-associated diseases, depends on how efficient the methods are which scientifically deal with the individual links in the treatment chain "awareness-prevention-early diagnosis-therapy-rehabilitation." It appears possible to achieve considerable strengthening of this treatment chain by including psychological methods and using art objects as part of awareness concepts and screening methods for information transport. This is the approach of the "informArtik Project" sponsored by the Bavarian Research Foundation BFS. In addition, a novel performance test, the E-ADL Test, was developed, validated and published internationally. This test enables for the first time measurement of everyday practical capabilities in dementia patients.

Health services research in psychiatry
Health Services Research in Psychiatry has become increasingly important, as investigation of the effectiveness and efficiency of diagnostic, therapeutic and support services for patients is becoming more important. The IDA project, "Dementia Care Initiative in Primary Care", with a total budget of € 3,200,000 is one of the largest clinical trials ever about the homecare of dementia patients. The controlled, randomised longitudinal study "MAKS aktiv!" – motor function and cognitive and mental training coupled with managing everyday practical activities – is sponsored within the framework of "Leuchtturm Demenz" an initiative supported by the German Ministry of Health. We identified a general central mechanism increasing the age-dependent perception of olfactory pleasure which can be used to protect against malnutrition in advanced age. Long-term catamnestic studies over 6 decades in patients with chronic posttraumatic stress disorders revealed a significant increase of late onset schizophrenias in women.

Teaching

In the clinical phase of the curriculum, we offer a wide range of learning opportunities like lectures, seminars, electives, clinical rotations, postgraduate education and blended E-Learning. Evaluation regularly rates psychiatry among the best clinical disciplines. Curriculum organization and evaluation are planned on a scientific basis at a high professional level. Our medical education is accompanied by a didactic research group (Professor Weih, master of medical education (MME)) and based on principles of quality management. In addition, medical psychology and medical sociology are offered as subjects in the preclinical phase of medical studies and taken by 480 students per semester. Professor Graeßel, Head of the above-named area, received a teaching prize in the 2006/07 winter semester, based on student evaluation. In 2008, the average results of the written examination in these subjects in the preliminary medical examination in Erlangen took first place nationwide.

Selected Publications

Frieling H, Gozner A, Roemer KD, Lenz B, Boensch D, Wilhelm J, Hillemacher T, de Zwaan M, Kornhuber J, Bleich S (2007) Global DNA hypomethylation and DNA hypermethylation of the alpha synuclein promoter in females with anorexia nervosa. Mol Psychiatry, 12: 229-30

Henkel AW, Dittrich PS, Groemer TW, Lemke EA, Klingauf J, Klafki HW, Lewczuk P, Esselmann H, Schwille P, Kornhuber J, Wiltfang J (2007) Immune complexes of auto-antibodies against A beta 1-42 peptides patrol cerebrospinal fluid of non-Alzheimer's patients. Mol Psychiatry, 12: 601-10

Frieling H, Bleich S, Otten J, Roemer KD, Kornhuber J, de Zwaan M, Jacoby GE, Wilhelm J, Hillemacher T (2008) Epigenetic downregulation of atrial natriuretic peptide but not vasopressin mRNA expression in females with eating disorders is related to impulsivity. Neuropsychopharmacology, 33: 2605-9

Kornhuber J, Tripal P, Reichel M, Terfloth L, Bleich S, Wiltfang J, Gulbins E (2008) Identification of new functional inhibitors of acid sphingomyelinase using a structure-property-activity relation model. J Med Chem, 51: 219-37

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 (2008) Soluble amyloid precursor proteins in the cerebrospinal fluid as novel potential biomarkers of Alzheimer's disease: a multicenter study. Mol Psychiatry, 2008 Jul 29. DOI 10.1038

Graessel E, Viegas R, Stemmer R, Kuechly B, Kornhuber J, Donath C (2009) The Erlangen Test of Activities of Daily Living: first results on reliability and validity of a short performance test to measure fundamental activities of daily living in dementia patients. Int Psychogeriatr, 21: 103-12

International Cooperation

Prof. Dr. med. J. Leszek and Dr. M. Zboch, Alzheimer's Disease Diagnostic and Therapy Centre, University of Wroclaw, Scinawa, Poland

Prof. Dr. Dr. Klaus R. Liedl, Centre for Molecular Biosciences, Leopold-Franzens-University Innsbruck, Austria

Dr. med. Trine Brogaard, Forschungsbereich Allgemeinmedizin, Universitaet Aarhus, Denmark

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Research Focus
- Neurophysiology in child and adolescent psychiatry
- Neurobiology in child and adolescent psychiatry

Structure of the Institution

The Division of Child and Adolescent Mental Health at the Department of Psychiatry and Psychotherapy is a self-contained division of the University Hospital. It is subdivided in the areas research, outpatient division/policlinic, day hospital and inpatient division. Furthermore, in cooperation with the Fuerth 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, emotional disorders in childhood, depressive disorders, post-traumatic stress disorders, eating disorders, psychic disorders in childhood with comorbid obesity, obsessive-compulsive disorders, tic disorders, autistic disorders.

Research

Neurophysiology in child and adolescent psychiatry

Project manager: H. Heinrich
The working group "Neurophysiology in child and adolescent psychiatry" carries out 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.
Neurofeedback: training effects on the behavioural and neurophysiological level. In a large randomised 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 attention deficit/hyperactivity disorder (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 computerised attention training. A further study with healthy adults examines the effects of different neurofeedback protocols on attentional processes, the motor system and well-being.
Inhibitory processes in children with ADHD: event-related potentials and transcranial magnetic stimulation. We developed a methodological approach combining transcranial magnetic stimulation and event-related potentials to study inhibitory processes in a differentiated manner. This approach is applied to investigate the neurophyisological basis of ADHD and the mechanisms of the medication that is most commonly used for this disorder (methylphenidate).
Interaction of cognition and emotion in children and adolescents with emotional, affective, anxiety and eating disorders. In cooperation with the Chair of Pattern Recognition (Technical Faculty) a psychophysiological working station was established that allows to measure several levels of investigation simultaneously: the central nervous system (EEG, event-related potentials), the autonomic nervous system (heart rate variability, skin conductance), and the behavioural level (eye movements, speech). A study with adolescents with anorexia nervosa and healthy controls compares their responses to emotion inducing pictures and movies as well as their attentional focus when viewing body scheme pictures.

Neurobiology in child and adolescent psychiatry

Project manager: R. Dawirs
One main focus of the working group "Neurobiology in child and adolescent psychiatry" comprises investigations of structural neuroplasticity in various regions of the mammalian brain focusing on the role of monoamine neurotransmitter systems in development and function of said various brain regions. The appearance of monoamine systems in early development suggests that they may play a key role in morphogenesis of the mammalian CNS, wherein during postnatal development critical periods exist in which crucial events may determine the way of subsequent development of the brain. Therefore, the fundamental mechanisms of postnatal activity dependent structural and functional development of the brain and their lifelong impact on CNS functions need to be clarified in more detail.
In one study with gerbils, it could be detected that subchronic administration of oral methylphenidate during adolescence prevented suppressive development of dopamine projections into prefrontal cortex and amygdala induced by methamphetamine. In a further study with gerbils, it could be detected that environmental enrichment during adolescence and administration of oral methylphenidate had no effect on the development of dopaminergic and GABAergic fibers in the prefrontal cortex and amygdala. In still a further study with gerbils, it could be detected that early methamphetamine application (postnatal day 14) and subsequent postweaning rearing conditions interfered with development of peripheral stress parameters and neural growth factors.

Teaching

The teachings are composed of lectures, seminars, tutorials and case presentations that comprise the clinical disorders of child and adolescent psychiatry and its therapy 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.
Furthermore, it is possible to do an internship in all subdivisions of our department at any time.

Neurofeedback
A boy controls a computer game (goalkeeper at a penalty kick) by modulating his brain electrical activity. The training intends to help children with ADHD to improve attention and self-control.

Psychophysiological working station
A girl is viewing an emotion inducing picture on the monitor. Her brain electrical activity, heart rate, skin conductance, speech and eye movements are measured.

Selected Publications

Grund T, Teuchert-Noodt G, Busche A, Neddens J, Brummelte S, Moll GH, Dawirs RR (2007) Administration of oral methylphenidate during adolescence prevents suppressive development of dopamine projections into prefrontal cortex and amygdala after an early pharmacological challenge in gerbils. Brain Res, 1176C: 124-132

Heinrich H, Gevensleben H, Strehl U (2007) Annotation: neurofeedback – train your brain to train behaviour. J Child Psychol Psychiatry, 48: 3-16

Lehmann K, Rodriguez EG, Kratz O, Moll GH, Dawirs RR, Teuchert-Noodt G (2007) Early preweaning methamphetamine and postweaning rearing conditions interfere with the development of peripheral stress parameters and neural growth factors in gerbils. Int J Neurosci, 117: 1621-38

Brummelte S, Grund T, Moll GH, Teuchert-Noodt G, Dawirs RR (2008) Environmental enrichment has no effect on the development of dopaminergic and GABAergic fibers during methylphenidate treatment of early traumatized gerbils. J Negat Results Biomed, 7: 2

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 randomised controlled clinical trial. J Child Psychol Psychiatry, 50: 780-9

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

International Cooperation

Prof. Dr. D. Brandeis, Dr. R. Drechsler, Kinder- und Jugendpsychiatrie, Universitaet Zuerich, Switzerland

Prof. J. Yordanova, Prof. V. Kolev, Institut fuer Physiologie, Bulgarische Akademie der Wissenschaften, Sofia, Bulgary

EU Projekt COST Action B27, Bruessel, Belgium

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Research Focus
- Eating disorders
- Obesity
- Psycho-oncology
- Excessive behaviors/behavioral addictions
- Somatoform disorders

Structure of the Institution

In total, 24 scientific staff are working in the Department, of whom 3 are entirely funded through grants. The Department offers inpatient, day-patient, and outpatient treatment settings, as well as a psychosomatic liaison service. 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 consists of a multimodal and multidisciplinary evidence-based psychotherapy. On April 1st 2008 we hired Dr. Alexandra Martin to fill our new faculty professorship in "Psychotherapy Research". We will be able to expand our research capabilities by utilizing her expertise in somatoform disorders and biofeedback.

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 first 3-year funding period will end 2009; however, the research consortium was successful also in the second funding period (2010-2012). The 4 large randomized multi-center psychotherapy studies of the first funding period will be finished at the end of 2010. In the second funding period a new randomized multi-center trial for the treatment of Binge-Eating-Disorder will be conducted with Erlangen being the study centre. The efficacy of an internet-based therapist-guided intervention will be compared with individual cognitive-behavioral therapy.
Besides the engagement in EDNET we have conducted and published studies covering different areas in the field of eating disorders in part in collaboration with the Department of Psychiatry and the Department of Internal Medicine 1. These include: the need for support of carers of patients with eating disorders, night eating, studies on epigenetic regulation, and structural neuroimaging in patients with anorexia nervosa focusing on DTI tractography.

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, Prof. de Zwaan is deputy speaker of the Competence Network. The Division of Psychosomatics and Psychotherapy in Erlangen will initiate 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 will include clinical samples as well as volunteers from the general population who have intentionally lost at least 10% of their initial body weight and have kept it off at least 1 year. All participants will be subsequently followed annually. For data capture a participant-centered approach with secure data entry directly by the participants is planned and 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 Institute of Medical Informatics at the University Erlangen-Nürnberg.
A long-term follow-up investigation of 150 consecutive patients with obesity grade 3 pre and 2 years post bariatric surgery will be finished at the end of 2009. The goals of the study are the examination of the long-term course of psychosocial parameters after bariatric surgery (psychopathology, eating behavior, quality of life) and the assessment of predictors of post-surgery weight loss.

Psycho-oncology

Project manager: H. Sinzinger

This research area focuses on the problems and needs for support of careers of patients with cancer and on the evaluation of screening instruments for patients to assess the necessity of psycho-oncological care.

Excessive behaviors/behavioral addictions

Project manager: A. Mueller

If normal behavior becomes excessive, senseless, impulsive, escalating and is associated with significant distress it can be called "behavioral addiction". For example, compulsive buying, pathological gambling, and excessive internet usage may be considered typical behavioral addictions. The maladaptive behaviors cause psychological, social, occupational, financial, and often legal problems. A randomized trial comparing the efficacy of a disorder specific group cognitive-behavioral therapy (CBT) designed for the treatment of compulsive buying disorder to a waiting list control group was completed in 2008. Sixty patients (51 women, 9 men; age 20-61 yrs) with compulsive buying participated in the study. The standardized outpatient treatment lasted 12 weeks with one group session per week. The therapy specifically aimed at reducing the number of buying episodes, at identifying and modifying cues and consequences for compulsive buying, at restructuring maladaptive thoughts, and feelings associated with shopping, and at establishing healthy purchasing patterns. The CBT intervention resulted in a reduction of the compulsive buying behavior, and the improvement was maintained during 6-month follow-up. Poorer attendance of the group therapy sessions and higher pretreatment hoarding traits were significant predictors for non-remission.

Somatoform disorders

Project manager: A. Martin

The common feature of the somatoform disorders is the presence of physical symptoms that cannot be fully 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.

One of the current research projects is a longitudinal survey aiming at clarifying predictors of health care utilization and symptom persistence in somatoform disorders, and is conducted in cooperation with the Universities of Marburg and Leipzig (DFG grant to Rief, Braehler and Martin).

Additional studies regarding unspecific chest pain and body dysmorphic disorder have been started in 2008:

1) Unspecific chest pain: More than 50 % of patients in cardiology are found to have no cardiac basis for their persisting chest pain. As a result patients often suffer from emotional distress and significant restrictions in daily life both leading to an increased health care utilization. Routine reassurance about normal test results often does not seem to be sufficient to prevent chronic manifestations of chest pain; therefore a brief and early cognitive-behavioral intervention is developed and 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.
2) Body dysmorphic disorder (BDD): BDD is characterized by excessive concerns about and preoccupations with an imagined or minor defect in physical appearance which causes clinically significant distress or impairment in important areas of functioning. The concerns can focus on general aspects of appearance or specific locations, e. g. skin, hair, nose, face shape, breasts. Often BDD is 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.

Teaching

The Division is significantly involved in the curriculum of the medical school. 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 within the curriculum of the medical school and also offers courses for psychology students. Medical students can chose psychosomatic medicine as a clinical elective and as an internship during their final year rotation. The Division also offers courses for advanced training in psychotherapy for psychotherapist with a university degree in psychology.

In the newly created study program Medical process management the Division of Psychosomatics and Psychotherapy is responsible for a seminar on "communication and cooperation aspects within the health care system".

Kompetenznetz Adipositas

Competence Network Obesity, funded by the BMBF

Selected Publications

Mueller A, Mueller U, Albert P, Mertens C, Silbermann A, Mitchell JE, de Zwaan M (2007) Hoarding in a compulsive buying sample. Behav Res Ther, 45: 2754-63

de Zwaan M, Hilbert A, Herpertz S, Zipfel S, Beutel M, Gefeller O, Muehlhans B (2008) Weight Loss Maintenance in a Population-based Sample of German Adults. Obesity (Silver Spring), 16: 2535-40

Graap H, Bleich S, Herbst F, Trostmann Y, Wancata J, de Zwaan M (2008) The needs of carers of patients with anorexia and bulimia nervosa. Eur Eat Disord Rev, 16: 21-9

Mewes R, Rief W, Braehler E, Martin A, Glaesmer H (2008) Lower decision threshold for doctor visits as a predictor of health care use in somatoform disorders and in the general population. Gen Hosp Psychiatry, 30: 349-55

Mueller A, Mueller U, Silbermann A, Reinecker H, Bleich S, Mitchell JE, de Zwaan M (2008) A randomized, controlled trial of group cognitive-behavioral therapy for compulsive buying disorder: posttreatment and 6-month follow-up results. J Clin Psychiatry, 69: 1131-8

Nestoriuc Y, Martin A, Rief W, Andrasik F (2008) Biofeedback treatment for headache disorders: a comprehensive efficacy review. Appl Psychophysiol Biofeedback, 33: 125-40

International Cooperation

Prof. Dr. J.E. Mitchell, Chairman and Professor of Psychiatry, Neuropsychiatric Research Institute and University of North Dakota School of Medicine and Health Sciences, Fargo, USA

Prof. Dr. Johannes Wancata, Klinische Abteilung fuer Sozialpsychiatrie und Evaluationsforschung, Universitaetsklinik fuer Psychiatrie, Medizinische Universitaet Wien, Austria

Meetings and International Training Courses

21.–24.03.2007: 58. Jahrestagung des Deutschen Kollegiums fuer Psychosomatische Medizin (DKPM) und 15. Jahrestagung der Deutschen Gesellschaft fuer Psychosomatische Medizin und Aerztliche Psychotherapie (DGPM), Erlangen-Nürnberg, DKPM und DGPM

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Research Focus
- Biomedical technics
- Tumor research
- Infection and inflammation

Structure of the Institution

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. Faculty includes twenty medical doctors/ dentists and two biologists.

Research

Research mainly focusses on biomedical technology, infection and inflammation as well as tumours of the head and neck. Topics of particular interest are augmentation of osseous defects by transplantation of autogenous tissues or vector transfected bone marrow stromal cells, 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

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.

Clinical focus is the surgery of malformations of the head/ neck and cleft lip palate in particular, oncologic and reconstructive surgery for tumours of the head and neck, orthognathic surgery, traumatology of the facial skeleton, esthetic surgery as well as dental implantology.

Biomedical technics

Project manager: E. Nkenke, K. A. Schlegel

The focus "biomedical technology" comprises research projects on regeneration of soft and hard tissues, intraoperative imaging, and laser applications.

Bone substitutes promote formation of new bone in pre-existing osseous defects by different biologic mechanisms including inflammatory and proliferative cellular reactions. As opposed to autogenous bone, the application of anorganic bone substitutes results in a prolongation of the inflammatory phase. The project "biomimetic materials" funded by the German Research Foundation (DFG) aims at creation, application, and evaluation of biomimetic materials in an interdisciplinary approach including the School of Sciences and the School of Engineering of the University of Erlangen-Nürnberg. Modification of titanium surfaces (e.g. nano tubes) for adsorption of several cells populations, poly-ether-ether-ketone (PEEK), as well as ceramic materials based on biodegradable polysaccharide templates were applied in *in vitro* and *in vivo* experiments.

Optical three-dimensional (3D) imaging has been validated for the assessment of the facial surface (former Collaborative Research Centre (SFB) 603). Using the principle of phase measuring triangulation, volume changes following craniofacial operations were measured quantitatively and used to predict the result of surgical interventions. By fusing optical 3D data with ultrasound measurements of tissue thickness in patients undergoing maxillary advancement, it could for example be shown that maxillary advancement leads to a more pronounced shifting of the soft tissues in the malar-midfacial area than of the upper lip. The new parameters will help to assess normative soft tissue data based on 3D imaging with a view to an improved three-dimensional prediction of the operative outcome of orthognathic surgery.

In cooperation with the Bavarian Laser Centre a sensor-assisted laser system for selective bone ablation was tested in cadaver bone as well as in an *in vivo* setting. By connecting the Er:YAG laser to a process control for material-specific ablation, the system is able to differentiate cortical and cancellous bone as well as soft tissues. In oral and maxillofacial surgery the selective bone ablation offers a new perspective to preserve nerval structures during surgery such as the nervus mandibularis during osteotomy of the lower jaw.

Tumor research

Project manager: E. Nkenke

Research aims at improving function as well as facial esthetics following resection of tumours 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.

Resection of tumours of the oral cavity often leads to an impairment of speech function. For evaluation and analysis of different degrees of speech intelligibility an automatic and objective tool was developed in cooperation with the Chair of Pattern Recognition (University of Erlangen-Nürnberg). The tool was applied in a cohort of patients following resection of oral squamous cell carcinoma (grant by Wilhelm-Sander-Stiftung). Prospective follow-up will yield insight into the degree of dependence between speech disorders and tumor stage, localization, and type of reconstruction. Further development of the technique will allow additional analysis of spectral and temporal characteristics of distorted phones. This will improve diagnostics of the individual speech disorder and in the long run enhance therapeutic options for these patients.

The tumour specific antigen MAGE-A is part of the apoptotic pathway and capable of inducing a humoral and cellular immune response. Current research focusses on detection of tumour cells in histology and zytology as well as evaluation of the prognostic value of MAGE-A in patients undergoing resection and adjuvant therapy for oral squamous cell carcinoma. Also the association of phosphorylated AKT (pAKT) expression and radiation resistance as well as tumour specific outcome is currently being evaluated in a cohort of patients diagnosed with squamous cell carcinoma of the head and neck.

Infection and inflammation

Project manager: E. Nkenke, K.A. Schlegel

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 the bisphosphonate-associated osteonecrosis of the jaw (BONJ).

Aseptic operations as a precondition for clinical research
Source: University Hospital Erlangen

As BONJ is restricted to craniofacial bone structures, research focusses on jaw bone specific signal transduction processes during development, bone remodelling 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 modelling 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.

Teaching

Oral and maxillofacial surgery is 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.

Traditional methods of teaching (lectures, lectures with case demonstrations, practical training for medical and dental students) are completed by problem based and interdisciplinary approaches. 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

Nkenke E, Eitner S, Radespiel-Troeger M, Vairaktaris E, Neukam FW, Fenner M (2007) Patient-centred outcomes comparing transmucosal implant placement with an open approach in the maxilla: a prospective, non-randomized pilot study. Clin Oral Implants Res, 18: 197-203

Ries J, Toyoshima T, Neukam F, Wiltfang J, Nkenke E (2007) Expression pattern of MAGE gene families in oral squamous cell carcinoma: Identification of diagnostic markers and potential targets for immunotherapy. Oral Oncol, 2 Suppl. S: 184-185

Nkenke E, Vairaktaris E, Kramer M, Schlegel A, Holst A, Hirschfelder U, Wiltfang J, Neukam FW, Stamminger M (2008) Three-dimensional analysis of changes of the malar-midfacial region after LeFort I osteotomy and maxillary advancement. Oral Maxillofac Surg, 12: 5-12

Ponader S, Vairaktaris E, Heinl P, Wilmowsky CV, Rottmair A, Koerner C, Singer RF, Holst S, Schlegel KA, Neukam FW, Nkenke E (2008) Effects of topographical surface modifications of electron beam melted Ti-6Al-4V titanium on human fetal osteoblasts. J Biomed Mater Res A, 84: 1111-9

Schlegel A, Hamel J, Wichmann M, Eitner S (2008) Comparative clinical results after implant placement in the posterior maxilla with and without sinus augmentation. Int J Oral Maxillofac Implants, 23: 289-98

von Wilmowsky C, Vairaktaris E, Pohle D, Rechtenwald T, Lutz R, Muenstedt H, Koller G, Schmidt M, Neukam FW, Schlegel KA, Nkenke E (2008) Effects of bioactive glass and beta-TCP containing three-dimensional laser sintered polyetheretherketone composites on osteoblasts in vitro. J Biomed Mater Res A, 87: 896-902

International Cooperation

Prof. Dr.Dr. Vairaktaris, Department of Oral and Maxillofacial Surgery, University of Athens, Greece

Prof. Dr. K. Smetana, Institut fuer Anatomie, Universitaet Prag, Czech Republic

Dr. E. Felzshegy, Gerichtsmedizinisches Institut, Semmelweiss-Universitaet Budapest, Hungary

Dr. U. Thams, Chair for Animal Pathology II, University of Complutense, Madrid, Spain

Research Equipment

BrainLab, Heimstetten Neuronavigationsgeraet Vector Vision II

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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Research Focus
- Wear simulation on dental mastication surfaces
- Development of peptide-based bioadhesives
- Prospective clinical study on glassionomer-cements using the a.r.t. – technique
- Cyclic fatigue principles of resin composite restoratives
- Current problems in adhesive dentistry
- Restoration of endodotically treated teeth using frc-posts
- Dentoalveolar trauma

Structure of the Institution

The Dental Department 1 – Operative Dentistry and Periodontology – employs 50 staff members, thereof 6 professors and associate professors, 13 assistant professors, 19 dental nurses and 4 dental technicians. The Dental Clinic 1 further hosts a Research Laboratory with 10 Research Associates (3 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 based 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

Wear simulation on dental mastication surfaces
Project manager: U. Lohbauer
Dental filling materials in direct contact with the antagonist teeth suffer from a continuous wear process due to mastication. Wear can be categorized into direct interaction of two surfaces (2-media abrasion: chewing simulation (artificial mouth)) and further interaction by an abrasive slurry (3-media-abrasion: toothbrush abrasion, ACTA abrasion). Defined contact area between test material and human enamel antagonists account for a standardized in-vitro testing in 2- or 3- media test setup. Worn volumina will be quantitatively analyzed under a confocal laser scanning microscope (CLSM) and qualitatively assessed under scanning electron microscopy (SEM). This research project is focused on assessment of direct, restorative dental materials with respect to three-body wear.

Development of peptide-based bioadhesives
Project manager: 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, Fig.). Polymerspacers link the Mefp-1 decapeptides to functionalised hydroxyapatite nanoparticles which in turn serve as centres of cohesion. Thus, chemical binding in addition to micromechanical anchorage should be responsible for stronger adhesion to dentin. 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 functionalised nanoparticles. Fundamental insight is expected by investigating the process of synthesis, the surface modifications of oxidic dental ceramics, developing the funtionalisation of nanoparticles and controlling adhesive mechanisms on collagen scaffolds. Interactions between peptides, polymers and oxidic ceramics will be examined using novel IR and VCD techniques. Molecular simulation approaches will be applied to investigate adhesion mechanisms and guide the peptide synthesis. Adhesive properties, behaviour and bonding effectiveness to human collagen as well as to oxidic surfaces will be investigated by analytic techniques, fractography, high resolution microscopy and quantitatively described in terms of microtensile bond strength measurements.

Prospective clinical study on glassionomer-cements using the a.r.t. – technique
Project manager: 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 glassionomercement 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 are planned after 6 months and 1, 2, and 3 years.

Cyclic fatigue principles of resin composite restoratives
Project manager: U. Lohbauer
Modern restorative materials were developed with a focus on amalgam like characteristics, excellent aesthetics and biocompatibility. These materials were improved for an application in stress bearing areas. Therefore mechanical properties under masticatory load and above all fatigue resistance are an important property. Fatigue fractures after years in clinical use were found to be a common failure reason. Damages of restorations like bulk, cusp, or marginal fractures were reported frequently. Fatigue in dental restoratives is influenced by corrosive water attack at a certain temperature (37°C) and by cyclic masticatory forces. Contemporary approaches to fatigue principles consider a fracture process in three phases: crack initiation, slow crack growth and fast fracture. The latter phase is very short in duration and thus the time of crack initiation and of slow crack growth account for the useful fatigue resistance of a material. The purpose of this work is to determine the strength of today's resin composite materials under fatigue conditions, simulating the clinical situation. The methodology is developed considering the findings on materials degradation above.

Adhesion of a mussel on Teflon via the Mytilus edulis foot protein Mefp-1
Source: Ingo Grunwald, IFAM.

Current problems in adhesive dentistry
Project manager: R. Frankenberger
Major goal of the WGAD is a consequent *in vitro* and *in vivo* evaluation regarding adhesive potential of biomaterials, i.e. resin composites and ceramics. It is our main interest to thoroughly link preclinical and clinical investigations. Beside a standardized portfolio of *in vitro* investigations, primarily prospective clinical trials are conducted. Central publications in this field were awarded with the Walkhoff Award of the German Association of Conservative Dentistry and the Research Award Full Ceramics of the Workgroup Ceramics in Germany.

Restoration of endodotically treated teeth using frc-posts
Project manager: C. Berthold
As a result of the research that took place between the University of Texas Houston and the University of Erlangen, since 2005, different biomaterial research aspects of bonding for fiber reinforced composite posts (FRC-posts), were investigated. These are used for restoration of endodontically treated teeth. In 2008, three young researches and the project leader conducted studies at the UT Houston.
Particular studies are third-party founded (ELAN-fund of the university hospital, Staedler-Foundation, Ilse and Dr. Alexander Mayer Foundation, Fritz and Maria Hofmann-Foundation).

Dentoalveolar Trauma
Project manager: C. Berthold
Since 2002, *in vitro* and *in vivo* investigations involving diagnostics and therapy of dentoalveolar trauma were performed. The research focussed specifically on the methods for tooth mobility measurement and investigations about mechanical properties of dental trauma splints.

Teaching

The main lectures of the Dental Department 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 trend 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 practical oriented. Therefore, the Dental Department 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

Frankenberger R, Kramer N, Lohbauer U, Nikolaenko SA, Reich SM (2007) Marginal integrity: Is the clinical performance of bonded restorations predictable *in vitro*? J Adhes Dent, 9 Suppl. 1: 107-116

Muller FA, Gbureck U, Kasuga T, Mizutani Y, Barralet JE, Lohbauer U (2007) Whisker-reinforced calcium phosphate cements. J Am Ceram Soc, 90: 3694-3697

Roggendorf MJ, Ebert J, Petschelt A, Frankenberger R (2007) Influence of moisture on the apical seal of root canal fillings with five different types of sealer. J Endod, 33: 31-3

Lohbauer U, Kraemer N, Petschelt A, Frankenberger R (2008) Correlation of *in vitro* fatigue data and in vivo clinical performance of a glassceramic material. Dent Mater, 24: 39-44

Lohbauer U, Nikolaenko SA, Petschelt A, Frankenberger R (2008) Resin tags do not contribute to dentin adhesion in self-etching adhesives. J Adhes Dent, 10: 97-103

Thaler A, Ebert J, Petschelt A, Pelka M (2008) Influence of tooth age and root section on root dentine dye penetration. Int Endod J, 41: 1115-22

International Cooperation

Prof. R. Braga, University of Sao Paulo (USP), Brasil

Prof. G. Eliades, University of Athens (UOA), Greece

Prof. J. Powers, University of Texas, Houston, USA

Prof. E. Schubert, University of Joinville (Univille), Brasil

Prof. N. Baratieri, University of Santa Catarina, Florianopolis, Brasil

PD Dr. S. Scherrer, University of Geneva, Switzerland

Dental Department 2 - Prosthetic Dentistry

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Research Focus

- Biomechanical factors of implant retained superstructures
- Evaluation of full-field three-dimensional optical inspection systems in dentistry
- Dental CAD/CAM systems and high-strength oxide ceramics
- Assessment of psychogenic influence on dental health and alternative treatment methods

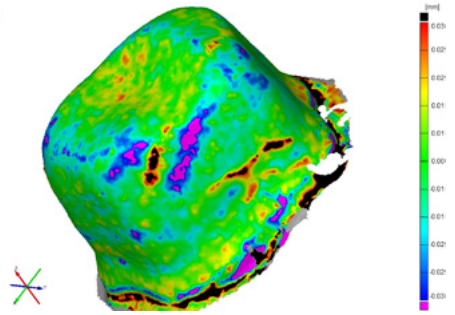
Structure of the Institution

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 faculty 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 specialist 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 ageing population and the resulting demographic changes into consideration and investigates the relation between oral and general health.

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 analysed 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 precision 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.

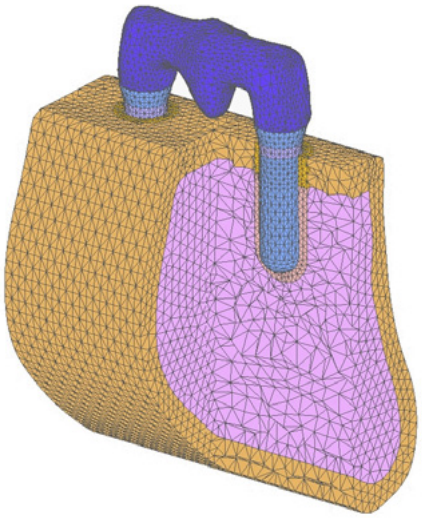
Evaluation of full-field three-dimensional optical inspection systems in dentistry
Project manager: S. Holst, M. Goellner
Quantitative assessment of biomechanical effects *in vivo* intraoral required highly complex reaserch set-ups due to lack of adequate measurement technology in the past. The aim of the research group is to establish and evaluate full-field three-dimensional (3D) optical inspection systems for clinical application in biomechanic research. The system will allow real time quantitative depiction of biomechanical influences in the oral cavity. 3D image correlation provides strain measurements in all dimensions, which are critical for accurate strain and loading response measurements in objects. The results of these optical measurements are compatible with finite element analysis software, and facilitate verification and iteration of models that solely cannot be used to draw general conclusions regarding specific questions related to biomechanics. The system available in the Dental Department 2 uses photogrammetric principles. Relevant parameters for future *in vivo* applications were identified in current and completed studies and first *in vivo* applications revealed promising results.



STL-matching: Verification of scan precision

Dental CAD/CAM systems and high-strength oxide ceramics
Project manager: S. Holst, M. Karl, J. Schmitt
Dental restorations generated with computer aided design/computer aided manufacturing (CAD/CAM) are making a considerable impact in dentistry. Advantages related to material and manufacturing will promote the continuous adoption of CAD/CAM systems over conventional casting techniques. The advantages CAD/CAM technology offers include: standardized quality guaranteed by industrial fabrication methods, excellent precision of fit, and outstanding biocompatibility, combined with adequate mechanical strength and provisions for aesthetic design. The research group focuses on assessment and analysis of various segments of industrial manufacture of current dental CAD/CAM systems. At the same time 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 back-



Area of research biomechanics: 3-dimensional FEA-model based on µCt and construction data

ground. Amongst other factors are a subjects appraisal of his own body, or the aetiologic 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.

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 focussing on biologic interactions and material properties. While theoretical knowledge remains integral part of dental education, manual manufacture of dental restoration will be taught exemplarily.

Selected Publications

Eitner S, Wichmann M, Schlegel A, Holst S (2007) Clinical study on the correlation between psychogenic dental prosthesis incompatibility, oral stereognosis, and the psychologic diagnostic tools SCL-90-R and CES-D. Int J Prosthodont, 20: 538-45

Holst S, Blatz MB, Bergler M, Goellner M, Wichmann M (2007) Influence of impression material and time on the 3-dimensional accuracy of implant impressions. Quintessence Int, 38: 67-73

Karl M, Graef F, Taylor TD, Heckmann SM (2007) In vitro effect of load cycling on metal-ceramic cement- and screw-retained implant restorations. J Prosthet Dent, 97: 137-40

Nickenig HJ, Eitner S (2007) Reliability of implant placement after virtual planning of implant positions using cone beam CT data and surgical (guide) templates. J Craniomaxillofac Surg, 35: 207-11

Holst S, Geiselhoeringer H, Wichmann M, Holst AI (2008) The effect of provisional restoration type on micromovement of implants. J Prosthet Dent, 100: 173-82

Karl M, Fischer H, Graef F, Wichmann MG, Taylor TD, Heckmann SM (2008) Structural changes in ceramic veneered three-unit implant-supported restorations as a consequence of static and dynamic loading. Dent Mater, 24: 464-470

International Cooperation

Weber, HP, University of Harvard, Boston, USA

Taylor, TD; Kelley JR, University of Connecticut, Farmington, USA

Blatz, MB, University of Pennsylvania, USA

Dental Department 3 – Orthodontics and Orofacial Orthopedics

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Research Focus
- 3D-morphometrical evaluation of complex craniofacial deformities
- 3D-evaluation of orthodontic casts using the "fringe projection system"
- Cleft lip palates (CLP)
- Evalutation of morpho-functional relations
- Material-scientific investigations
- Quality based evaluation of orthodontic treatment therapy concepts
- Distractionosteogenesis
- Investigation of biomechanical aspects of orthodontic compontents

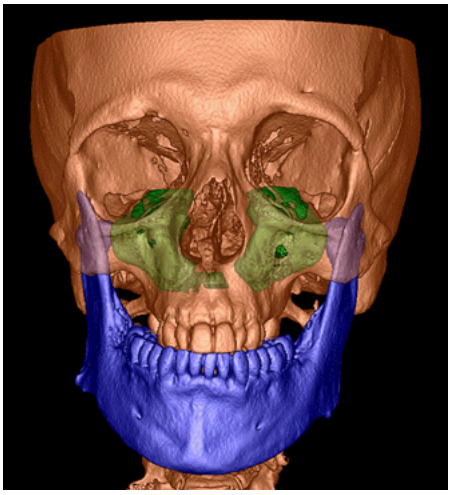
Structure of the Institution

The Chair of Dental Department 3 is integrated in the department of dentistry since 2004 with regular rotation of the head of department every second year.
All together, 27 employees are working in the Dental Department 3. The research is carried out by 11 scientists and 22 doctorates. Technical assistants are not available.
The prime alignment of our research is the 3D-evaluation of dentofacial anomalies with development of practice near 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 misalignment 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 Centre of Cleft Lip and Palate of the University of Erlangen-Nürnberg. In this interdisciplinary centre, therapy concepts are continuously updated and initiated by the team.

Research

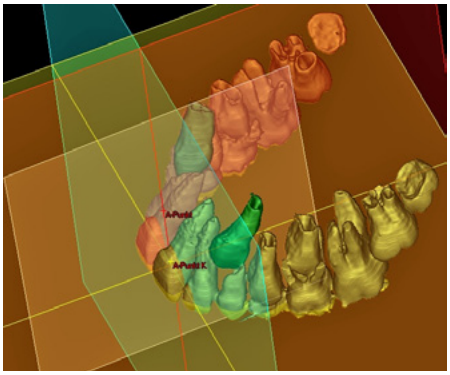
3D-morphometrical evaluation of complex craniofacial deformities
Project manager: U. Hirschfelder, K. Hertrich
In context of these scientific emphasis craniofacial deformities and asymmetries are characterized by using modern imaging techniques with respect to differential diagnostic typed with application modern imaging procedures in craniofacial diagnostics. In context with the application of a new CT software (Voxim®) available CT data are reevaluated. The possibility of three-dimensional measurements will arise new metrical possibilities concerning the face morphology in cases of craniofacial deformities. The anatomically based evaluation of the facial skeleton is completed by application of the new VRT technique (Volume Rendering technique) and the "Inspace Software program" in order to assess muscular and skeletal parameters correlatively on the basis of CT data records.
Different subjects of this topic research area will be evaluated by in actual thesis works using the Voxim® software program.

3D-evaluation of orthodontic casts using the "fringe projection system"
Initially the optical scanning method of diagnostic study models will be applied in cases of CLP patients by applicating an optical sensor based on coded illumination. The surface shape of the object is calculated according to the displacement of the fringes. After data acquisition well definied 3D measurements are carried out (3D distances, angles and volumes of anatomical areas) by using the Voxim® software program (Fa. IVS Solution, Chemnitz) in order to analyse changes of the study casts threedimensionally by means of high accuracy (resolution: 175 µm, measurement error: 30 µm). It is also the aim of this scientific project to develop and to establish realistic computer-aided 3D method for evaluating diagnostic orthodontic casts.

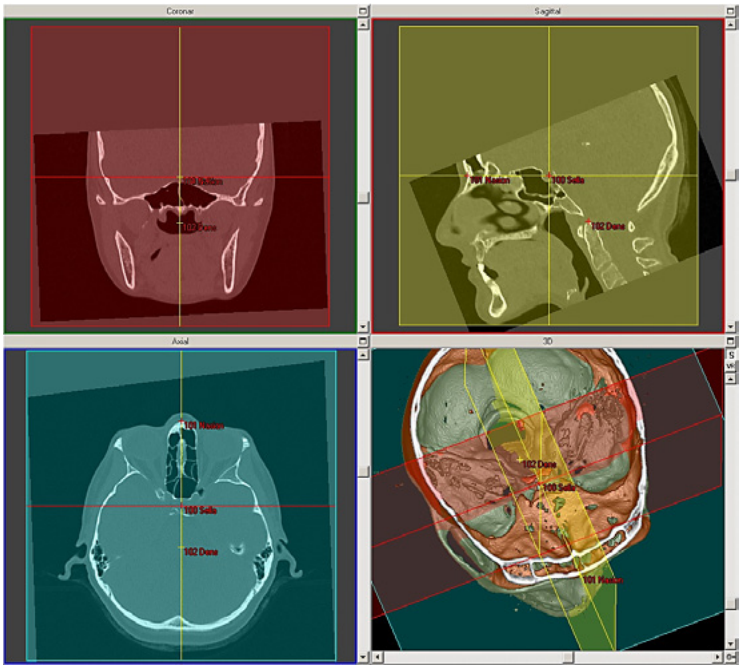


Volumetric CT-based 3D-data analysis

Cleft lip palates (CLP)
Project manager: U. Hirschfelder, A. Holst, K. Strobel-Schwarthoff
In the framework of a long-term study a current project is to evaluate the facial development in cases with cleft lip palates also according to secondary osteoplasty. A further project deals with a measurement system of the pneumatisation of the petrosus bone and the prozessus mastoideus on the basis of computertomographic data in relation to the Division of Phoniatrics and Pediatric Audiology. Furthermore the result of a growth control study of the upper jaw development is evaluated in the context to the early orthodontic therapy in babies with cleft lip palates using optical scanning method by the "fringe projection system" of study casts and subsequent measurements of well defined 3D distances, angles and volumes of the jaws (detailed description of the project, see above).
In a further project the dimension of the bony cleft defect will be analysed metrically on the basis of CT data acquisition with the Voxim® software program.



3D-CT-based localization of a dislocated upper right canine (23) in relation to a virtual reference system



CT-based craniofacial 3D-diagnosis

Evalutation of morpho-functional relations
In context of a current project functional sequences with the maxillo-facial complex are evaluated by applications of sonographic and electromyography procedures and bite force measurements.

Material-scientific investigations
Project manager: U. Hirschfelder
In the year 2004 the present scientific project was dealing with the adhesive bond strength of different adhesive materials were tested, as well as the adhesive bond strength using different ceramic brackets. This project was promoted by the industry. Within this framework also the tooth surface was examined by using scanning electron microscopy.
In the year 2006 began a second present scientific project. Examination of the efficiency of GC Tooth Mousse to reduction and to avoid to 'White Spots' during the orthodontics treatment.

Quality based evaluation of orthodontic treatment therapy concepts
In the context of introduces quality management system several studies are executed on the evaluation of orthodontic handling success with application internationally of valid indices.

Distractionosteogenesis
In the context of a current research project long term studies are made on facial development of distraction osteogenesis of the midface and the mandible on the basis of lateral teleradiographs.

Investigation of biomechanical aspects of orthodontic compontents
Another special research area is the investigation of biomechanical aspects of orthodontic components and their biocompatibility. In cooperation with the Institute of Mineralogy, studies concerning the corrosive potential of metallic brackets were initiated.
Additionally, correlations between biomechanical characteristics of orthodontic mini-implants and bone-features are examined in cooperation with the Institute of Medical Physics and the Anatomical Institute, Chair II.

Teaching

Traditional teaching methods (curricular teaching programs, patient-orientated preparatory and clinical courses and seminary's, policlinical programs and optional teaching programs) are completed with interdisciplinary programs and psychosomatic-orientated teaching offers. Additionally, chair side-lectures are offered during the entire semester to allow the students to gain insight in the clinical practice.
Diagnostic material of selected cases (plaster models, photos and x-rays) is offered to the students for self-study.
The development of a workable e-learning-platform is in progress and will be explicitly supported.

Selected Publications

Greiner M, Greiner A, Hirschfelder U (2007) Variance of landmarks in digital evaluations: comparison between CT-based and conventional digital lateral cephalometric radiographs. J Orofac Orthop, 68: 290-8

Holst S, Hegenbarth EA, Schlegel KA, Holst AI (2007) Restoration of a nonrestorable central incisor using forced orthodontic eruption, immediate implant placement, and an all-ceramic restoration: A clinical report. J Prosthet Dent, 98: 251-5

Lovrov S, Hertrich K, Hirschfelder U (2007) Enamel Demineralization during Fixed Orthodontic Treatment – Incidence and Correlation to Various Oral-hygiene Parameters. J Orofac Orthop, 68: 353-363

Stec-Slonicz M, Szczepa?ska J, Hirschfelder U (2007) Comparison of caries prevalence in two populations of cleft patients. Cleft Palate Craniofac J, 44: 532-7

Holzmeier M, Schaubmayr M, Dasch W, Hirschfelder U (2008) A new generation of self-etching adhesives: comparison with traditional acid etch technique. J Orofac Orthop, 69: 78-93

Stauber I, Vairaktaris E, Holst A, Schuster M, Hirschfelder U, Neukam FW, Nkenke E (2008) Three-dimensional analysis of facial symmetry in cleft lip and palate patients using optical surface data. J Orofac Orthop, 69: 268-82

Meetings and International Training Courses

19.–20.04.2007: Lingualtechnik – Dr. Wiechmann, Erlangen

08.–10.11.2007: Troubleshooting – Prof. Hasund, Erlangen

01.01.–31.12.2007: Curriculare Weiterbildung zum Fachzahnarzt fuer Kieferorthopaedie – Erlangen

20.–22.11.2008: Klasse III – Behandlung – Prof. Hasund, Erlangen

01.01.–31.12.2008: Curriculare Weiterbildung zum Fachzahnarzt fuer Kieferorthopaedie – Erlangen

Collaborative Research Centre (SFB) 423: Kidney injury: pathogenesis and regenerative mechanisms

Speaker
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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 Centre (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 centre grant. Currently scientists from nine clinics and institutes are collaborating in this research centre at the University of Erlangen-Nürnberg. The aim of the SFB 423 is 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 centre founded by the German Research Foundation (DFG) and one of the few research consortia in Europe, focusing on kidney disease. Funding period: 1999 – 2010.

Research

Section A: Pathophysiology of renal cells and initial mechanisms of renal injury
Section A encompasses 8 projects that focus on the pathophysiology and mechanisms of initial injury of glomerular and tubular cells. The first project (A1) analyses 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) deals with cell matrix interactions in the mesangium and in the renal tubular interstitium focusing on the special role of α8 integrin. Project A12 is focusing on the regulation of the epithelial sodium channel (ENaC) in distal tubular cells and addresses mechanisms which are potentially relevant for the pathogenesis of secondary hypertension in patients with kidney disease.
Two projects (A14, A16) deal with the regulation and pathophysiological relevance of hypoxia inducible gene expression mediated by HIF transcription factors. Project A14 focuses on studying the expression, regulation and functional relevance of HIF prolylhydroxylases, enzymes that are of the critical relevance 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 deals 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 analyzes 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 (Fig. 1).

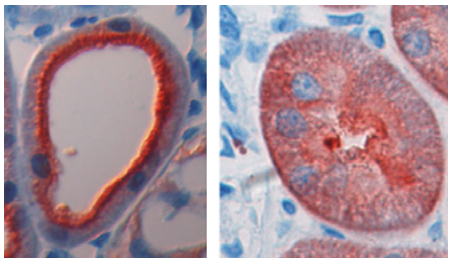

Fig. 1: Staining for Survivin in proximal tubular cells of the kidney under normal, physiological conditions (left) and following the application of the nephrotoxic drug cisplantinum. While the protein is normally strictly localized to the brush border, it is distributed over the whole cytoplasm following injury.

Project A17 deals with the role of p38MAPK during the development of rapid progressive glomerulonephritis and thereby attempts to identify a novel, drugable therapeutic target for this serious disease, which can so far only be treated with unspecific immunosuppression. The 8th project within this area (A18) deals with the analysis of syndromal diseases characterized by congenital or infantile nephrosis. Using complex genetic approaches, this project aims to identify critical, pathogenetically relevant molecules that may also play an important role in noninheritable nephrotic diseases.

Section B: Mechanisms of progressive renal disease
Section B focuses on complex mechanisms that influence the progression of renal disease. These studies also aim to identify novel targets for intervention. Project B5 uses 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 deals with the functional relevance of Thrombospondin 1 and 2 in the regulation of chronic kidney disease and during this funding period focuses on the impact of these molecules on chronic allograft nephropathy. Two additional projects in this project area study different modulators of inflammatory processes. Project B12 deals with the functional relevance of renal afferent neurons for mechanisms of inflammation and sclerosis within the kidney. This project combines complex neurophysiological investigations with the application of pharmacological modulators of neurotransmitter release and function. Project B13 deals 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 are complemented by a third area, which includes an administrative project and two core units that focus on methodological aspects. The goal of these core units is to rationalize and structure the cooperation between different projects in two important areas. Prof. Dr. K. Amann leads a core unit for quantitative structural analysis of kidney injury and Prof. Dr. T. Winkler coordinates the development of genetically modified mice.

Collaborative Research Centre (SFB) 466: Lymphoproliferation and Viral Immunodeficiency

Speaker
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Aims and Structure

The AIDS epidemy is threatening the world. An effective preventive vaccine would be required, but there is no sufficient biological basis so far. Antiretroviral therapy made enormous progress during the past years. However, this is very expensive and remains dependent on comprehensive diagnostic therapy steering. A health problem of this dimension requires more fundamental research on virus replication and immunobiology. Research on the pathogenesis of immunodeficiency relates in numerous aspects to the basic problems of activation, differentiation, growth control and destruction of the cells of the lymphatic system and other hematopoietic elements. Thus, immunodeficiency research is closely interconnected with the mechanisms of oncogenic transformation by viral gene products and cellular oncogenes in the hematopoietic system. The program of the SFB 466 is oriented towards the basic problems relevant for pathogenesis at an intersection of cell biology. The SFB 466 consists of research groups of the Medical Faculty and the Department of Biology in the University of Erlangen-Nürnberg as well as structural biologists of the University of Bayreuth. It includes the junior research group of PD Dr. Stefan Poehlmann, whose laboratory was localized in the Nikolaus-Fiebiger-Research Centre until March 2008. Funding period: 1996 – 2008.

Research

The SFB 466 deals with mechanisms of control in lymphocyte activation and proliferation, with the transformation by viral gene products as well as apoptosis and destruction of lymphatic cells. Lymphocyte activation and destruction are largely following similar signaling cascades. Thus, the SFB 466 finds its identity in research projects on the molecular and cellular biology of pathogenesis in immunodeficiency and leukemogenesis. This is aiming at a molecular understanding of the pathogenesis in viral immunodeficiency and in the controlled and autonomous proliferation of lymphocytes. The SFB 466 contributes to understanding the transformation of hematopoietic cells and the progression in tumors of the lymphatic system. The SFB 466 is the sole German cooperative German Research Foundation (DFG) project that deals with the molecular biology of acquired immunodeficiency.

Section A: Structure and function of retroviral proteins
The Section A encompasses five subprojects on structural and regulatory proteins of human immunodeficiency viruses. It deals with the persistence of HIV under highly active anti-retroviral therapy. The projects try to understand what cell compartments are containing the viruses and how the variability of HIV quasispecies develops. Further studies deal with the molecular structure and function of the viral polyprotein Pr55Gag and its functions for maturation of the human immunodeficiency viruses and the interaction of HIV with the native immune system, as well as the role of Dendritic Cells (DC) in pathogenesis for mechanisms of immune evasion in immunodeficiency viruses. The Junior Research Group investigates the role of DC in pathogenicity. The lectin DC-SIGN appears relevant for the DC-mediated transmission of HIV.

Section B: Signaling cascades in T cell activation and destruction
The Section B consists of six individual projects that are dealing with signal transduction in hematopoietic cells and investigating activation and destruction in hematopoietic cells. One subproject investigates multiprotein complexes that are formed with NFAT transcription factors in lymphoid cells, and further projects are investigating the function of the soluble CD83 protein that influences T cell activation and the T cell response against HIV proteins. Further work is focused on the analysis of intracellular signal cascades that are controlling the proliferative expansion and differentiation in early B lymphoid cells under the control of the pre-B cell receptor and the analysis of signal transduction from cytokine receptors and signaling cascades in B lymphocytes.

Section C: Lymphocyte transformation and malignant progression
The Section C consists of five subprojects and is oriented at molecular oncology. Two subprojects are dealing with basic mechanisms of transformation in T lymphocytes by the human T cell leukemia virus and signalling cascades in T cell transformation by retroviral oncoproteins. A further project investigates a rhadinovirus, the human Kaposi's Sarcoma-associated herpesvirus 8. Finally, a subproject investigates how Epstein-Barr-virus is persisting in B lymphocytes in the organism.

Collaborative Research Centre (SFB) 473: Switch Processes of Transcription

Speaker
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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 is funded since 1997 and represents a scientific conglomerate of 13 groups from the Faculty of Natural Science and the Faculty of Medicine.
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 signalling 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: Signalling pathways to transcriptional regulatory proteins
The transcription factors studied in these projects have their coupling to signalling pathways in common, so that their switching reaction is dependent on a number of signalling proteins. Molecular genetic and theoretical aspects of signalling are cooperatively studied to elucidate catabolite repression in Gram-positive bacteria, nitrogen metabolism in Corynebacteria and the role of ß-catenin in tumorigenesis, lending substantial medical importance to this transcriptional switch. These projects have in common that more or less complicated signalling 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 haematopoiesis 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 Centre (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 Centre, which has been funded by the German Research Foundation (DFG) since 1997, integrates 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 SFB 539 represents the only Research Centre in Ophthalmology.
The focus of the Research Centre lies 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.
Funding period: 1997 – 2009.

Research

Section A: Glaucomatous damage of optic nerve and retina
This section deals with the structural and functional glaucomatous damage of the sensory retina and optic nerve head. It comprises projects developing and evaluating novel diagnostic tools for the detection of early structural changes and functional deficits. The most specific and sensitive imaging methods and physiological tests have been implemented in clinical practice (e.g. Spectral domain OCT, FDT perimetry) or have even been developed into commercially available instruments (e.g. Erlanger flicker test, RETI-Port). 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 retinal ganglion cell death, e.g. receptor mechanisms of neurotoxic processes, mechanisms of oxidative cell damage, ion transport mechanisms, and alterations in gene and protein expression of glaucomatous ganglion cells.

Section B: Pathogenetic factors
Projects in this section aim at the investigation of multifactorial pathogenetic factors contributing to glaucoma development, particularly regarding the ocular outflow pathways and ocular microcirculation. Analyses of human glaucoma eyes, in vitro models and established mouse models lead to the identification of crucial molecular pathomechanisms of intraocular pressure rise, including extracellular matrix components, growth factors, oxidative stress, immune mechanisms, and COX-2-regulated prostaglandins and matrix metalloproteinases. The molecular analysis of pseudoexfoliation syndrome, a generalized disorder of the extracellular matrix and frequent cause of glaucoma, yielded a conclusive and generally accepted pathogenetic concept of a stress-induced elastosis. Changes in various intraocular vascular beds including their accompanying innervation were analyzed in glaucomatous donor eyes and animal models by using morphologic methods. Taken 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.

Section C: Clinical biometry and genetic analyses
This section comprises both, the analysis of genetic factors for glaucoma and the medical-bioinformatic integration, processing and analysis of clinical data. 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. Instructed planning and evaluation of clinical-epidemiologic studies as well as the statistical analysis of research data were further improved by novel approaches of computerized learning, mathematic modeling, and strategies of classification. Finally, the clinical data collected from more than 1500 patients since 1991 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, particularly the evaluation of the prognostic and predictive value of diagnostic procedures in long-term analyses.

Teaching

The study groups of the SFB 539 are involved in the training of doctoral students in medicine, molecular medicine, natural science and technical science. Supervision of doctoral theses is in part integrated into the graduate school "Advanced Optical Technologies". In addition, the principal investigators participate 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.

Collaborative Research Centre (SFB) 603: Model-Based Analysis and Visualization of Complex Scenes and Sensor Data

Speaker
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Aims and Structure

Participating institutions from the Faculty of Engineering Sciences: Chair of Pattern Recognition, Chair of Computer Graphics, Chair of Manufacturing Technology, Chair of Flow Mechanics, Chair of Quality Management and Production Measurement Technology, Chair of Sensorics.
Participating institutions from the Faculty of Natural Science: Chair of Optics.
Participating institutions from the Faculty of Medicine: Department of Oral and Maxillofacial Surgery, Division of Phoniatrics and Paediatric Audiology.
Funding period: 1998 – 2007.

Research

This research centre aims to develop an uniform and practically approved methodology for analysis and design of information processing systems which interprete and visualize pictures, sensor data, and scene descriptions of realistic complexity. Application examples will be taken from medicine and engineering systems which autonomously recognize, analyze, model, track in motion or use in a simulation on real objects and relations between objects have to meet high requirements. Innovative solutions of corresponding problems should be applicable for image analysis and computer graphics. Central topics of long term research programs are model based approaches, optimization procedures, resolution hierachies and fusion of sensor data. Models for time invariant 3D-surfaces, for time variable 3D-surfaces, and for volumes and structures of higher dimension will be investigated in three project fields.

Collaborative Research Centre (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 centre 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: A) basic immunology B) immune intervention in animal models and C) therapeutic applications.
Funding period: since 2004.

Research

Several representative projects will be described shortly: 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 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.

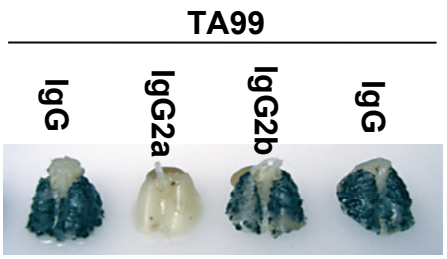

Fig. 1: Pulmonary metastasis in mices after injection of melanoma cells, which were treated with different versions of the therapeutic antibody TA99

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. Support of the patient's immune defense against the virus is a major goal in transplantation medicine. Memory B cell transfer provided long-term protection from the lethal course of the infection that is invariably seen in immunodeficient animals. The data provide evidence that a cell based strategy to support the humoral immune response can be effective to combat infectious pathogens in severely immunodeficient hosts.

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 transplant studies in murine models. This represents the basis for further preclinical and clinical developments.

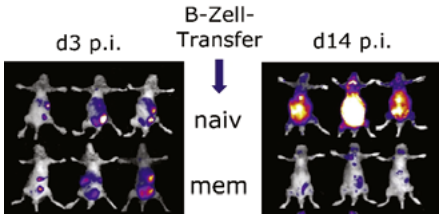

Fig. 2: Memory B lymphozytes are able to protect immunodeficient mices against CMV infection

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.

Clinical Research Unit (KFO) 106: Target Organ Damage in Hypertension

Speaker
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Aims and Structure

The contributing institutions are the Division of Nephropathology, Department of Medicine 2, Department of Medicine 4, Department of Nuclear Medicine and the Department of Ophthalmology.

Research

Arterial hypertension induces clinically relevant injury in several target organs, including heart, kidney, eye and blood vessels. The highly variable extent of injury to these target organs cannot be explained solely by the degree of blood pressure elevation. Our clinical research unit identified pathogenetic factors other than blood pressure which contribute to the development of hypertensive target organ injury. Further, we used interdisciplinary approaches to analyze whether hormonal, neural and inflammatory factors can be affected by therapeutic interventions. As a central part of our research group, we established a specialized clinical research unit devoted exclusively to clinical studies in patients with hypertension and/or vascular diseases. After the scheduled end of funding by the German Research Foundation (DFG; 2 periods of 3 years each), continued funding for the clinical research unit will be provided by the University Hospital Erlangen. The clinical research unit will continue its mission to perform clinical studies in patients with hypertension and/or vascular disease according to the regulatory framework and quality control standards of investigator-sponsored clinical pharmaceutical studies. In an interdisciplinary and translational approach, we will also perform experimental studies in models of cardiovascular disease, and apply modern methods of molecular and cell biology.

The role of the hormone aldosterone for the development of target organ injury was the main focus of subprojects 2 and 5. In animal experiments, we demonstrated that mineralocorticoid effects contributed directly to kidney injury, independent from blood pressure. In patients with resistant hypertension, a placebo-controlled trial showed that blockade of mineralocorticoid effects improved left ventricular hypertrophy independent from blood pressure effects. Further clinical studies supported the notion that aldosterone exerts important, non-genomic, direct vascular effects.

Impaired endothelial function and vascular inflammation were investigated in subprojects. We improved the methods for analysis of vascular structure and endothelial function in resistance arteries of patients. In particular, we demonstrated that laser-doppler flow measurement of the retinal arteries is highly suitable to analyze impaired endothelial function in this important vascular bed. Structural alterations of retinal vessels were associated with cardiovascular risk. We identified several factors which mediate the impaired endothelial function in hypertension. In a subproject, we obtained evidence that patients with impaired endothelial function display an impaired cellular uptake of L-arginine. A further factor causing impaired endothelial is asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NO-synthase. We started experimental studies in a transgenic animal model which will permit to analyze the role of ADMA for hypertensive target organ injury.

In patients with hypertension, an increase of serum markers of inflammation became evident only with severe hypertension. Experimental studies in rodents provided clear evidence that local inflammation, in particular infiltration of macrophages, contributed to hypertensive target organ injury. Statins exerted anti-inflammatory and protective effects in these experimental models. Local inflammation was particularly evident when the renin-angiotensin-aldosterone system was stimulated, and this effect was not due to high blood pressure alone.

The autonomic innervation of the kidney can also stimulate local inflammation, as shown

in experimental studies. This effect of the innervation is partly but not completely due to sympathetic, efferent nerve activity. Proinflammatory factors are also released from afferent peptidergic nerves which may thus exert a local, paracrine function. Members of our group are now part of a consortium which started a clinical trial on percutaneous catheter-based transluminal high-frequency ablation of the renal innervation in patients with hypertension and kidney disease („Native Kidney Denervation in Patients with End Stage Renal Disease", Clinical.Trials.gov NCT00551304).

In summary, the translational studies pursued by our clinical research unit provided evidence that non-hemodynamic factors play a very important role in determining the extent of target organ injury in hypertension. In addition, we improved the methods to assess endothelial function as a prognostic parameter in patients with hypertension.

Teaching

Junior scientists were educated in methods of patient-oriented clinical research in our clinical research unit. Between 1.5 and 2.0 positions per year for junior physician-scientists were continuously used. For the most part, these positions were used for full-time or part-time rotations in the clinical research unit. Some junior scientists in our team obtained additional educational or research grants by the DFG which permitted research abroad for up to two years. Most of these scientists rejoined our clinical research group after completion of their grants, and some of them became leaders of independent subprojects. Medical students were integrated in our team to perform MD thesis work.

Clinical Reserach Unit 130: Determinants and Modulators of postoperative pain

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Aims and Structure

Contributing Departments are: Anaesthesiology, Pharmacology, Physiology, Neurology, Human Genetics, Physiological Psychology (University Bamberg), Pharmacology (University Zurich)
The clinical research unit KFO 130 has been established at the Department of Anaesthesiology in August 2005. In July 2008, on the ground of a re-evaluation process, it has been decided to fund the clinical research unit for a second period from 2008 – 2011.

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, modern methods of molecular and cell biology as well as experimental pathophysiology and clinical studies are combined to identify neurobiological, pharmacological, genetic, and psycho-social factors of postoperative pain, and to characterize clinical and pathophysiological situations that may facilitate the development of persistent pain.
Long-term goal is the development of perioperative screening parameters, therapies and interventional strategies to treat postoperative pain more effectively and to prevent the development of persistent pain in patients at risk. The scientific management has Prof. Dr. med. Carla Nau.

Teaching

In December 2007, the clinical research unit has hosted an international Winter School "Methods in Pain Research". This event aimed to offer 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.

Clinical Research Unit Bavarian Immunotherapy Network (BayImmuNet): Adoptive Immunotherapy

Speaker
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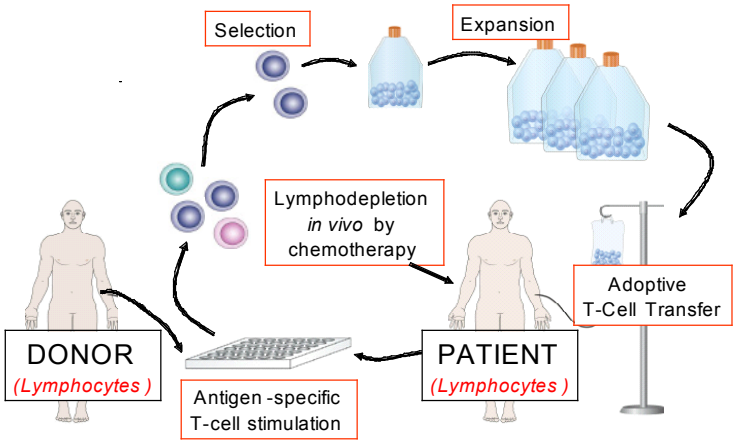

Schematic description of the goals of the Clinical Research Group "Adoptive Immuntherapy"

Aims and Structure

Immunotherapy – therapeutic influencing of 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 Mio. €, has set itself the goal of achieving faster translation of new approaches in immunotherapy into clinical application. Five clinical research units were established at the University of Erlangen, Regensburg, Würzburg and Munich.

Research

The realization that cellular immune reactions, mediated primarily by activated T lymphocytes recognizing defined antigens, are responsible for the rejection of tumours 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 tumour-specific T cells has fuelled 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 tumour cells [graft versus tumour (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 under the guidelines of good manufacturing procedure (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 tumours that express the gene of interest due to low level expression or impaired antigen processing by the tumour 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 the 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 system 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 haematologic diseases after allogeneic BMT.

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 programme for basic and translational research.

Research Unit (FOR) 661: Multimodal Imaging in Pre-clinical Research

Speaker
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Aims and Structure

The German Research Foundation (DFG) is supporting a team of researchers from different faculties and research areas working on multimodal imaging in pre-clinical research with emphasis on computed tomography and small animal imaging. This research unit is objected for three years and funded with 3.5 million €.
The Research Unit 661 consists of the following 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. Doerfler, T. Engelhorn, Department 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, Institute of High Frequency Technology, Ruhr-University Bochum)
TP6: Combination of optical fluorescence imaging with Micro CT procedures for fusion imaging on small animals (A. Langenbucher, Institute of Medical Physics)
TP7: The 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, Faculty: Immunology/Rheumatology; K. Engelke, Institute of Medical Physics)

Research

Using the field of small animal imaging, a multidisciplinary team endeavors to improve the assessment of structure-function relationships in the same animal under comparable conditions and in repetitive sequences using CT, MR, PET, US and OI, 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 to enhance and to 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 Magnetic Resonance Tomography (MR), Positron Emission Tomography (PET), Ultrasound (US) and Optical Imaging (OI), 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 and clinical application (P3, P4 and P7).
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, alternatively, minimal dose for a given level of image quality. The combination of modern optical procedures with fluorescence imaging that allows for minimally invasive investigations of molecular, cellular and physiological processes in vivo with micro CT imaging is an additional goal to evaluate its potential for displaying functional and anatomical information of physiological processes in vivo. At the Institute of High Frequency Engineering at the Ruhr University Bochum the application of various ultrasound imaging modalities in small animal imaging, the comparison of these modalities to MRT, micro-CT and PET, are further subjects. Another research topic is the technical combination of ultrasound and micro-CT in a multimodal system to make use of the spatial resolution of micro CT and the contrast resolution of soft tissue of ultrasound.
In the Division of Neuroradiology at the University Hospital Erlangen the work focus 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 that is widely available to encircle ischemic tissue that is not yet irreversibly damaged and still treatable. At the Institute of Pharmacology 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 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 animal. The research focus is to be expanded on the quantification of vasculogenese in arthritic inflamed joints in correlation to architecture and extent of the vessel net.

Research Unit (FOR) 832: Regulators of humoral immunity

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Faculty of Natural Science
Prof. Dr. rer. nat. Hans-Martin Jäck
Faculty of Medicine

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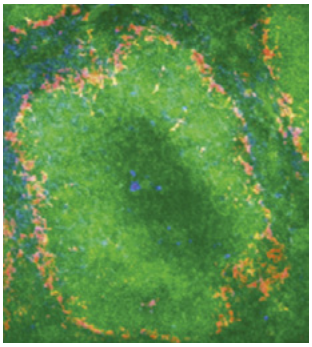
Aims and Structure

Since 2008, the German Research Foundation (DFG) has been sponsoring a new interdepartmental research group 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 Natural Sciences Faculty and the University Hospital of the Medical Faculty (five projects) are participating in the research group. Five of the eight participating project leaders, which include both biologists and clinicians, are based at the Nikolaus-Fiebiger-Centre 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 used. Meetings on a regular basis (such as 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, additionally promote the mutual scientific objective.
The educational concept for the doctoral students can be seen as a special feature of the DFG research group. 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 group participate in all of the events and courses of the research training group. This is intended to ensure an excellent education for the new generation of scientists, also in the context of international networking.

Research

The B cell is at the centre of attention for the research group FOR832. 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 group concentrates its work on these complex regulatory processes during the maturation and activation of B cells.
On the one hand, congenital and acquired disorders of the complex differentiation scheme 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 group directs the focus of its work towards the clarification of such undesirable developments. The approach of the research group 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



Histology of a B cell follicle in the spleen

suitable animal models through appropriate cell-sorting methods. Consequently, one experimental focus of the research group 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 the mouse and in humans. The possibility of using and also establishing "genetically tailored" mouse models here in Erlangen will be employed by the research group in a special way, especially for better understanding such molecular and cellular processes during the humoral immune response that cannot be specifically investigated in either the cell cultures or the human being.

Teaching

In addition to classic lectures (such as concepts of immunology, literature seminars, etc.) and practical courses within the bachelor and master programs in biology, molecular and cell biology (Department of Biology) and molecular medicine (Medical Faculty), all of the project leaders also participate in a methods seminar organized by one of the doctoral students of the research group. Furthermore, all 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 group are also actively involved in the public relations work of the Research Training Group GK 592 (such as the 2008 "International Day of Immunology").

Research Unit (FOR) 894: Fundamentals on Fluid and Physical Dynamics in Human Voice Production

Speaker
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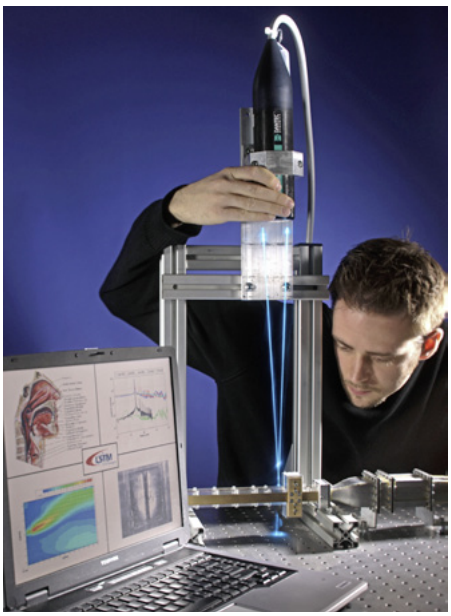
Aims and Structure

Participating Institutions: Division of Phoniatrics and Paediatric Audiology, Chair of Applied Mathematics II, Chair of Sensorics, 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 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 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 highly frontier research. For coordination and leading the interdisciplinary group, the German Research Foundation (DFG) established a W2-professorship. The scientific management has Prof. Dr. Ing. Michael Doellinger.

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 is endoscopic high speed digital video recordings from healthy and pathological subjects. At the department 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 was developed by the Institute of Fluid Mechanics (Fig.) presenting a realistic model of human voice production. Vocal folds consisting of a silicon mixture are set into vibration and enable to experimentally analyse 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 analysed. However, irregularities cannot be separated regarding their cause and resulting effect.
For investigation pre defined clinical observed irregularities and their impact on voice quality a water driven model was developed by the group from Freiberg. Here, the fluid dynamics are easier to observe due to the increased time scale. This model is especially appropriate for observing eddy induced acoustics.
The experimental work is supplemented by a numerical finite element method model of the Institute of Sensorics. Hereby fluid volume as well as mechanical induced acoustics can be directly analysed. However, this model is only two dimensional due to the high computational costs.
By these approaches the different acoustic sources can be investigated and analysed. In future, conclusions based on the cause-and-effect chain, for medical conservative as well as surgical treatments will be driven.



Air driven channel for simulation of human vocal fold dynamics. The vocal folds consist of a silicon mixture. Adjustment of the laser doppler anemometry (LDA) hardware for supraglottal volume flow measurements. (Picture: Institute of Fluid Mechanics)

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 of three different faculties: medical, engineering sciences and natural sciences.

National Reference Centre for Retroviruses

Speaker
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Aims and Structure

In 1996, the Robert Koch Institute (RKI) established the National Reference Centre for Retroviruses (NRC) at the Institute for Clinical and Molecular Virology, University of Erlangen-Nürnberg, headed by Prof. Bernhard Fleckenstein. The main tasks of the reference centre focus on epidemiologic surveillance and the generation and provision of standards for diagnostic methods and therapeutic procedures. In addition, they distribute reference materials (like virus stocks) and give advice how to handle unclear and rare clinical cases.

Diagnostic

The NRC has extensive experience in testing antiretroviral drug susceptibility. A major 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 resistance interpretation system HIV-GRADE. Both interpretation tools are freely online available (www.geno2pheno.org bzw. www.hiv-grade.de).

Within the last two 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. During the last year, sequence analyses of the HIV-1 integrase gene derived from patients' plasma viruses were sufficient to explain therapy failures in Raltegravir treated patients. In contrast, due to a higher natural level of alternate coreceptor usage by the virus, sequencing the V3-loop of the viral env gene has to be performed before the treatment with CCR5 antagonists is started. For this drug class, discrepancies between the results obtained from functional tests and sequence analyses have been observed, indicating that it is essential to make possible further comparisons and validation of the methods. In parallel, therapy response data were generated by more than ten clinical centres in Germany and were collected and analyzed under the coordination of the NRC in order to support and validate the more cost effective and faster sequence analyses based method. According to this data, the method is now recommended in first line and has been implemented in the German therapy guidelines. A similar development can be expected for the European guidelines within this year.

In order to assure standardized testing, the NRC is engaged in quality control trials concerning diagnostic methods for human retroviruses. In cooperation with the German Society for Virology, a standardized operational protocol was developed how to analyze a quality control trial based on sequence analyses in order to detect HIV-1 drug susceptibilities. The protocol can be transferred to other microbiological pathogens and may contribute to a higher level of standardization in future quality control trials.

In cooperation with several other institutions, the NRC could show that one of the commercially available HIV-1-RNA detection systems was not able to quantify some isolates appropriately. Meanwhile, an updated version of the system is distributed by the company, which seems to overcome most of the disadvantages described before.

The NRC quarterly publishes the Retrovirus-Bulletin to provide scientific and clinical information on HIV, AIDS and other retroviral infections like HTLV-1/2. The Bulletin is freely distributed by mail to a broad and diverse 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

In December 2008 a database was generated in cooperation with the HIV competence network, and the collection of HIV-1 sequences has been started which may facilitate the surveillance of emerging resistance pattern in the future. Further epidemiologic research at the NRC is also focused on HIV-1 drug resistance. In close cooperation with the Robert Koch Institute, the NRC continues to study the role of transmission of HIV-1 drug resistance on the European level. 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, the European Union and by several companies.

Teaching

The members of the NRC offer a broad range of HIV-related seminars to students of human medicine, 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.

National Genome Research Network – Infection and Inflammation – Work package "Viral Infections", Erlangen

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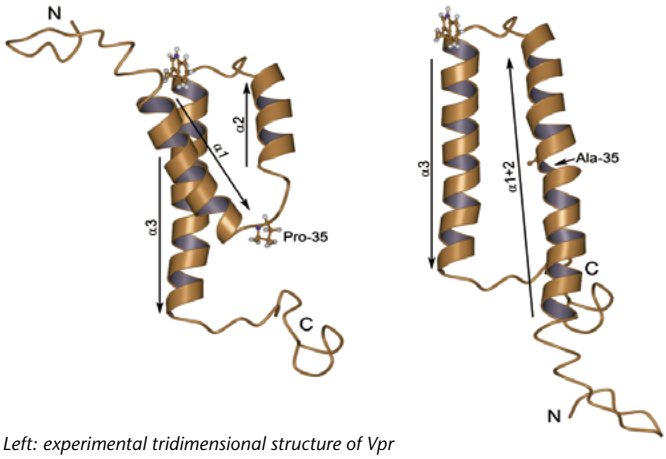


Left: experimental tridimensional structure of Vpr
Right: evaluated conformation of the P35A-mutant where both helices 1 and 2 fusion to a antiparallel helix

Aims and Structure

The comprehension of the very specific interaction between viral and host cells is a basic precondition for the understanding of pathologic mechanisms of viral infections. This knowledge provides eventually a decisive assumption for the development of new antiviral methods of treatment as well as improved vaccination strategies. The genomic structures of many viruses are quite simple and extensively explored for the known human pathogen viruses. The bulk of viral gene products have already been molecularly characterized. However, there is a huge discrepancy between detailed knowledge about the viral genome- and proteom organisation and the complex virus-host interactions in the viral replication.

Research

The following sub-projects of the work package "viral infections" have been treated:
The sub-project of Prof. Alexander Steinkasserer (NIE-S10T02) dealt with the identification of new cellular target structures of HSV-1 in dendritical cells in order to develop new therapeutical strategies. The HSV infection of mature dendritical cells causes a nearly entire down regulation of the surface molecule CD83. As CD83 is decomposed very quickly, maybe viral IE-proteins could be responsible therefore. Infection experiments with diverse HSV specific deletion mutants have shown that the infection with a ICPO-specific deletion mutant caused a considerable minimized CD83 decomposition and this indicates that ICPO has an important role in decomposition of CD83. To analyze this hypothesis there have been made cotransfection experiments with plasmids, which coded for CD83 and ICPO. The cotransfection of CD83 and ICPO caused a considerable down regulation of the CD83 molecule. Contrariwise, the cotransfection of CD83 with a ICPO deletion mutante, which had no ubiquitin ligase domain, did not cause any reduction of CD83. This confirms the relevance of ICPO at the HSV-1 interfered CD83-decomposition and indicates that the ubiquitin proteasome system (UPS) of the host cell is involved in this degradation. Hence, as next step we have been carried out infection experiments with HSV in dendritical cells after treatment with specific proteasome inhibitors. Interestingly, the CD83-surface expression was unvaried strong, despite HSV infection. The hypothesis, that cellular proteasomic protein decomposition and the HSV-1-gene transcript ICPO have a significant role at CD83 decomposition, could be definitely demonstrated with these trials.

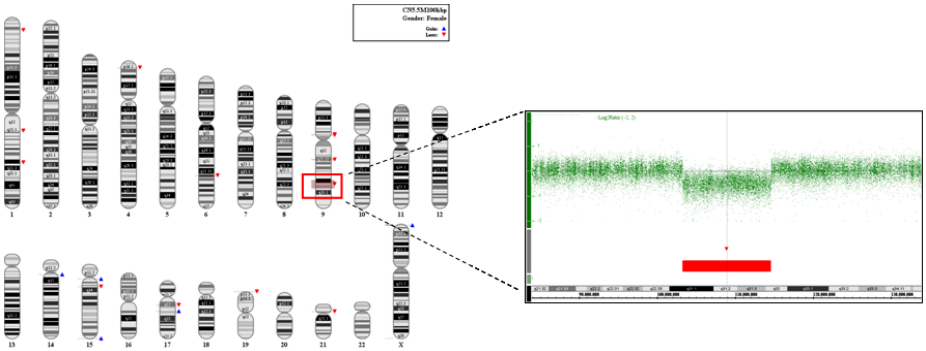
The sub-project NIE-S10T01 of Prof. Schubert analyzes the interaction of host cell and virus proteins on a molecular level. Aim is the determination of cellular target structures for the therapy of infections with HIV, HCV and influenza A viruses. Thereby, the UPS and certain folding enzymes take a centre stage. Following cellular factors have been identified: (1) the 26S proteasome, (2) the ubiquitin ligase POSH, (3) the peptidyl-prolyl-isomerase (PPIase) Cyclophilin A (CypA). Studies with proteasome inhibitors in numerous virus systems have been continued. The realization that these inhibitors do not inhibit only release and maturation of HIV but also block replication of further viruses, demonstrate a central role of UPS in viral replication cycles.

The E3 ubiquitin ligase POSH was identified by searching further targets in collaboration with cooperation partners. It regulates the transport of HIV Gag proteins from the trans-Golgi network to the cell membrane. Essential is that inactivation of this E3-ligase has only weak toxic effects on the cell vitality, compared to the multiple effects of the deactivation of the proteasom on different aspects of the cell metabolism.

The accessory protein Vpr of HIV-1 represents a virus associated protein which performs a series of functions during the retroviral replication cycle. Amongst others Vpr regulates the transport of the pre-intergration complex in the cell nucleus and induces G2-cell cycle arrest of the infected cell. By means of Biacore spectroscopy, Far Western Blot and Pull down experiments, an interaction of Vpr with the cellular PPIase could be proven. These studies are based on previous structure analyses of small viral proteins and their binding partners. Amongst others, the structure of HIV-1 p6 protein has been determined which interferes via two so called late (L)-domains with the efficient release of the virions from the host cell membrane.

National Genome Research Network – Mental Retardation Network (MRNET), Erlangen

Logo of the MRNET



Molecular karyotyping reveals genomic aberration.
Schematic chromosome representation of a female patient with mental retardation (left). The boxed region on chromosome 9 is enlarged at the right. Red bar indicates a deleted region with reduced signal intensities (green points).

Speaker
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Aims and Structure

Mental retardation (MR) has a prevalence of about 2% in the general population and is one of the most important cost factors in health care. During the last years it has become evident that genetic factors play an important role in the aetiology of MR. The German Mental Retardation Network (MRNET) is the first national network dedicated to the systematic investigation of genetic causes of MR. Identification and characterization of molecular networks involved should allow identification of targets for therapeutic intervention.

MRNET is funded within the medical genome research programme (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 10 centres distributed throughout Germany and the Netherlands. The network combines the clinical and scientific expertise of researchers and physicians from 7 german universities (Bonn, Dresden, Erlangen, Essen, Heidelberg, Muenster and Tuebingen), one institute of the Max-Planck-Society (Berlin), a research centre of the Helmholtz-Society (Munich) 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. In a multi centre study a total of 3,000 patients will be recruited and receive a standardized clinical evaluation based on an 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 using modern micro-array based technologies. We expect to detect de novo aberrations in about 10-15% of cases. Patients with similar phenotype to those with the genomic aberration will be screened for point mutations in candidate genes from the respective genomic region.
Familial cases will be explored for cosegregation of genetic markers with the disease (linkage analysis) to likewise reveal candidate genes from linked regions. Furthermore, some patients will be subject to comprehensive sequencing of large genomic intervals with next-generation sequencing technologies.
Candidate genes and their respective signalling pathways will be functionally explored in cellular assays and in animal models, specially the fruit fly drosophila melanogaster.
Finally, genotype-phenotype correlation will help reveal new clinical entities and to better describe the natural history of diseases. Findings will be transferred into clinical practice in a timely manner and made available to affected families and thus improve diagnostic options.

Project group of the Academy of Science and Literature, Mainz

Speaker
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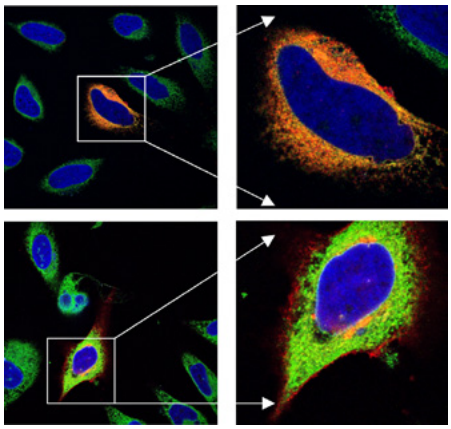
Aims and Structure

Persistence of pathogens is the pathogenetic principle 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 immunodeficiency viruses

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 non-pathogenic virus from the flavi-group, the GB virus C, which delay the prolonged development to AIDS. The clarification of the underlying mechanism led to the identification of several flaviviral components. It could be demonstrated that the non structural proteins NS3 and NS5A of GBV-C can inhibit HIV after host cell entry, whereas the glycoprotein E2 of GBV-C specifically interferes with very early replication steps of HIV, like binding, fusion or uncoating. This so called new Entry-inhibitor is active against a wide spectrum of HIV isolates independently of the co-receptor tropism. In accordance with these findings, recent results suggest that there is an E2-like epitope on the HIV particle, which is involved in the HIV entry process. Indeed, using human polyclonal anti-GBV-C E2 positive sera as well as some specific monoclonal anti-GBV-C E2 antibodies, a variety of lab adapted or primary HIV strains can be potently neutralized. If these cross reactive antibodies will prove to be broad and potent reactive against HIV in the animal model, these findings establish a new perspective for the development of HIV vaccine strategies.



Confocal laser scanning microscopy for demonstration of the glycoproteins of the Kaposi sarcoma associated human herpesvirus 8

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. In 2008, novel ligands for two HHV-8 glycoproteins were identified. 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 envolved in the pathogenesis of Kaposi's sarcoma. Thus, HHV-8 encouters 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 research group of PD Dr. med. Barbara Schmidt is investigating the role of the innate immunity for the defense against viral pathogens like immunodeficiency and herpesviruses. Hereby the plasmacytoid dendritic cells (PDC), which are the main producer of Type 1 interferons, contribute substantially to the control of viral pathogens. There is a direct correlation between PDC cell counts and helper cell counts and clinical status and a inverse correlation with the virus load. The research group could demonstrate that a PDC depletion during HIV pathogenesis is not caused by the HIV infection accompanied with a cytopathic effect, but by an increased migration of PDC into secondary lymphatic organs. The PDC-specific interferon secretion is mainly induced by HIV infected cells, whereby this process is critically affected by the affinity of the HIV-1 envelope protein to the CD4 receptor. However the induction of interferon is ambiguous, since not only the required immune protection is activated, but also the programmed cell death of bystander cells that can increase the immune deficiency during the HIV infection. Thus, inhibitors of the CD4/gp120 interaction will not only suppress virus replication, but also reduce the HIV-1 induced immune stimulation.

Research Training Group 516: Cultural Transfer in the European Middle Ages

Speaker
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The Research Training Group comprises an interdisciplinary research and study program in which the Medical Faculty collaborates with the Philosophical Faculty and the Division of Theology as well as the Faculty of Engineering Sciences. In the centre of this program lays the european cultural transfer during the middle ages. The main focus is on the identification of the process itself in terms of the persons, the ways, methods and aims of transfer. On the other hand research is directed to the changes which knowledge or human artefacts undergo by being assimilated within a different culture. The project of the Chair of the History of Medicine concentrates on the impact of the Arabian medicine on western medicine from the 11th century onwards and the 16th century restaurative efforts in occidental science.
Funding period: 1999 – 2008.

Research Training Group 592: Lymphocytes – Differentiation, Activation and Deviation

Speaker
Prof. Dr. rer. nat. Hans-Martin Jäck

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Aims and Structure

Since 1st May 2000, the German Research Foundation (DFG) and Bavaria have sponsored the first Research Training Group (GK) 592 on Lymphocytes: Differentiation, Activation & Deviation at the Erlangen University Hospital. Sixteen university lecturers from the Medical Faculty and the Natural Sciences Faculty participate in the program as mentors. In order to both the doctoral students and the project leaders to participate in the important decision-making processes of the research training group, 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 sponsoring 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. 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 programme 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 Würzburg (speaker: Prof. Huenig) and Tübingen (speaker: Prof. 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 GK 592 doctoral students. Twenty high-calibre immunologists from all over 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 leukaemia. This also includes immunotherapeutic approaches for the treatment of tumors. The research programme of the GK 592 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 leukaemic diseases. Research-oriented and clinical aspects of lymphocyte biology are integrated within this research programme. 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 experimental findings and discussing them under consideration of published data. This means that the GK 592 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 programme for molecular medicine (Medical Faculty), all of the project leaders also participate in a methods seminar organised 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 are also actively participating in the public relations work of the research training group (such as the 2008 "International Day of Immunology") and projects conducted with the Erlangen grammar schools (Gymnasium). A definite highlight of this was the cooperation of the GK 592 in a pilot project called W-Seminar in Immunobiology within the scope of the G8 Secondary School Reform. This was initiated by the Ministry of Education and Cultural Affairs and organised at the Emmy-Noether-Gymnasium in Erlangen by Ms. Brigitte Kraml. The findings of this project, which was coordinated for 1.5 years, were presented by members of the research training group during a symposium in Munich that was organised by the Ministry of Education and Research and was met with a considerable response.

Day of Immunology 2008

Research Training Group 1071: Viruses of the Immune System

Speaker
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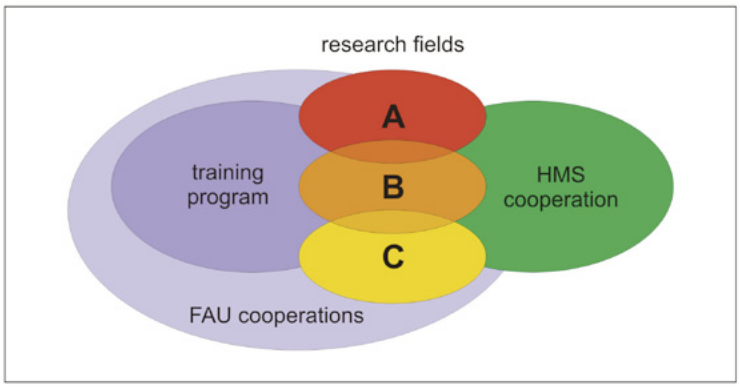

Network of Research Training Group 1071

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 established interdisciplinary cooperation among scientists of the Medical Faculty and the Faculty of Natural Science at the Friedrich-Alexander-University (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. First funding period: 2005 – 2009.

Research

The scientific focus of the research training group 1071 is at 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 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 (http://www.lymphozyten.de/symposium.html), realized for the second time in October 2008 together with students of Research Training Group 592 and Research Unit 832, was again a great success.

BioMedTec International Graduate School of Science (BIGSS): Lead structures of Cell Function

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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. Michael Hensel, Institute of Clinical Microbiology, Immunology and Hygiene, 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, Institute of Biochemistry and Pathobiochemistry.
Funding period: since 2004.

Announcement poster of the Bayreuther Strukturtage

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 17 PhD students. These eight female and nine male PhD students have been selected out of 600 national and international applicants. The graduate school resulted from an initiative of the BioMedTec Franken e.V., which forms a network of the Universities of Bayreuth, Würzburg 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. That needs primarily a best possible supervision of the projects. Consequently, the PhD students are supported by their two local supervisors plus an additional external supervisor from a foreign country. 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.
Together with the international summer school of Bavaria California Technology Centre, the University of San Francisco (UCSF, Prof. Dr. Thomas James) and the degree programm Macromolecular Science the summer school Structure in Biology – Key to Understanding (October 2008) was organized. In addition, in cooperation with the research centre for Biomacromolecules of the university of Bayreuth, a symposium named Bayreuther Strukturtage was established for the first time under the participation of international researchers. This meeting become 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 14 publications within the last two years in important journals. In 2008, the first five students finished their PhD and meanwhile have changed in carrying on positions in research and industry.

Erlangen Graduate School in Advanced Optical Technologies (SAOT)

Speaker
Prof. Dr.-Ing. Alfred Leipertz

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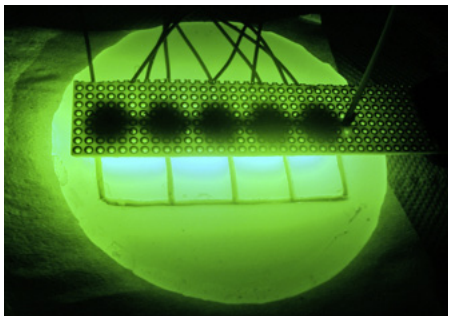

Fig. 1: Measurements on biotissue phantom: proof of principle phase of the Epithelium Capillary Grid Real Time Monitoring project

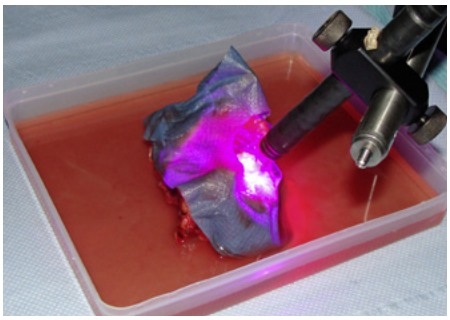

Fig. 2: Development of surgery navigation technology for laser ablation cancer resection

Aims and Structure

In November 2006, the SAOT was established at the Friedrich-Alexander University Erlangen-Nürnberg (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 a structured, internationally oriented (working language English) and interdisciplinary education programme to doctoral candidates. It is hosted by the Faculties of Engineering, of Natural Science and of Medicine and is embedded into an international network of distinguished experts in their respective fields of optical technologies. The scientific topics SAOT focuses on optical metrology, optical material processing, optics in medicine, optics in communication and information technologies, optical materials and systems and computational optics.

Research

Intensive research work is carried out in each of the different SAOT topics which are in their activities partly overlapped with other topics. This in particular is true for the topic "Optics in Medicine" which can be considered to form an application field of the other topics. Thus it is inherently interdisciplinary covering, e.g., optical diagnostics as well as optical therapy and surgery. Thus, the further development of optical techniques in medicine demands an intensive and comprehensive exchange and collaboration between the different schools involved. The topic "Optics in Medicine" deals with the fundamental functioning principles of the human body, its organs and tissues under the exposure of optical radiation covering a broad field of frequencies and light strength. These detailed investigations of the interaction of light and tissue promote the development of improved diagnostics, therapy and surgery techniques. Moreover technical specifications are defined which will serve as the basis for future development and engineering of bio-optical sensors and apparatuses for medical applications. To realize these objectives, the Clinical Photonics Laboratory (CPL) which is headed by guest professor 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 spread all over the world and inside FAU with several medical and clinics research institutes. To intensify the interdisciplinary and international collaborations, SAOT organizes international workshops routinely. In 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 programme comprise seminars, workshops and academies. Outstanding scientists from international leading institutions are invited to give an one hour talk on specialised themes at the SAOT seminar. Workshops with several speakers of leading international research institutions contributing with a talk to a major subject usually last up to three days. This has already been done with 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.

Interdisciplinary Centre for Clinical Research (IZKF)

interdisziplinäres Zentrum für Klinische Forschung

Logo of the IZKF

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Aims and Structure

The Interdisciplinary Centre for Clinical Research (IZKF) was founded in 1996 under the major topic "Inflammatory Processes: Aetiopathogenesis, Diagnostics and Therapy". During the first 8 years (1996-2004) it received funding from the Federal Ministry of Research and Technology within the programme "Health related research 2000". Beginning with the funding period 2004-2007 the IZKF's budget of 3.600.000 € was defrayed entirely by the state allowance for education and research of the University Hospital Erlangen. Since several years, the University contributes to the budget - currently 150.000 € yearly - to support the participation of the institutes outside the hospital.

Currently 150 scientists from 31 departments, institutes and divisions participate in the IZKF in altogether 42 projects from 4 major scientific topics. Through the support of mainly clinically oriented research projects of high quality and through fostering of collaborations between clinically and theoretically working groups the IZKF aims to increase the overall quality of clinical research at the Medical Faculty. New projects are established during triennial peer-review visits of the scientific advisory board as well as at yearly internal and external review sessions. After a single 3-year funding period projects should be transferred to extramural funding. Exceptionally, projects can receive additional funding for another 2 years.

Support and development of young scientists continues to be a main goal of the IZKF. The IZKF supports two junior research groups, housed in the Nikolaus-Fiebiger-Center for Molecular Medicine. In the reporting period two very successful junior research groups are supported by the IZKF - junior group 2 (PD Dr. med. Reinhard Voll) with the topic „The role of NF-kappaB in the pathogenesis of inflammatory diseases" and the junior group 3 (PD Dr. med. Michael Wiesener) on „The role of hypoxia-inducible transcription factors in the context of the development and progression of renal cell carcinoma.

Participation from the IZKF was key to attract Prof. Falk Nimmerjahn for a third (associated) junior group to Erlangen funded by the Bavarian Genome Research Network.

Support of young scientists is also achieved through supporting young clinicians to rotate for a certain period of time into the laboratory to follow up their research projects. This programme is also directed to projects not directly funded by the IZKF. The IZKF also supports young medical students within IZKF projects with grants and a special training programme. An annual seminar for MD and PhD students participating in all the different research programmes at the Medical Faculty is organised by the IZKF.

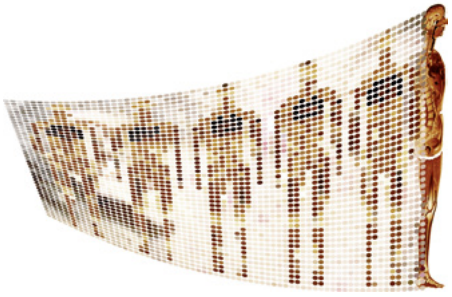
Furthermore, core units represent a strong structuring element. Currently, 3 core units are funded:

Z2 – Non-invasive high-resolution imaging of small animals (since Oct. 2002)
Z3 – Affymetrix Platform (since Oct. 2007)
Z4 – DNA-Extraction Platform (Biobank) (since Jan. 2009)

Supporting activities also include the "Visiting Professor Programme" and a triennial international scientific meeting.

Research

The Interdisciplinary Centre for Clinical research (IZKF) has established itself as a strong central institution in the research environment of the Medical Faculty. The initial focus on inflammation research could be developed further to also accommodate other research areas, without sacrificing this distinctive topic,



Graphic illustrating the IZKF

thus allowing more institutions of the Medical Faculty to successfully participate in the IZKF. Almost half of the projects are so called "tandem-projects" between clinically and theoretically working institutions while 2 projects are collaborations between different clinical institutions. The stringent, two-stage peer-review process (first internal, then external) based solely on scientific criteria, ensures a high scientific quality of the projects with current funding rates at about 50%. This helped further increase the acceptance of internal peer-review and thus increasing the ability to successfully applying for extramural funding. In the last years both, junior groups and IZKF projects have been very successful in this respect. The high standard of research done at IZKF also becomes evident through the large number of scientists appointed to external chairs and professorships.

Interdisciplinary Centre for Public Health (IZPH)

Speaker
Prof. Dr. med. Hans Drexler

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Successful evaluation of the IZPH by the Governing Body of the University: IZPH Executive Board (Speaker: Prof. Drexler; Managing Director: PD Dr. Kolominsky-Rabas; Prof Gräßel) with the Governing Body of the University of Erlangen-Nürnberg (Vice-President Prof. Steinrück, Dipl.-Ing. Kramp) and the reviewers (Prof. Siebert, Austria, Prof. Röllinghoff, Germany)

Aims and Structure

„Networking across scientific borders" is the unique selling proposition of the Interdisciplinary Centre for Public Health (IZPH). The IZPH is a multidisciplinary research centre consisting of different faculties of the University of Erlangen-Nürnberg: the primary objective of the centre is to merge medical, economical and social sciences and management in order to advance research in public-health and resolve current health care challenges of the aging society. Within the Nürnberg Metropolitan Region the IZPH bundles all relevant stakeholders of the health care management industry i.e. medical professionals (doctors, hospital 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 centre 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 centre performed a number of large-scale studies addressing research topics as need of care and resource use in chronically ill patients (dementia, cancer, stroke) as well as assessment of health care services funded externally with 2.5 mio. Euro. With its emphasis on health promotion/preventive medicine, health economics/health technology assessment and federal health monitoring the centre acts as the scientific platform for outcomes research at the Friedrich-Alexander-University and as the main regional promoter.

Teaching

Members of the IZPH are providing interdisciplinary lectures and courses in the field of public health, such as health economics, health system research, health promotion and prevention. Special focus is also given to lectures on public health issues for students of the Faculty of Economics and to the master program medical process management (M.Sc.).

Interdisciplinary Centre for Gerontology (ICG)

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Aims and Structure

Since the foundation in 2003 the Interdisciplinary Centre of Gerontology (ICG) is active in the fields of biological, medical, psychiatric, psychological, behavioral, humanistic, economical and technological aging research. The centre initiates and supports interdisciplinary collaboration on aging research at the University of Erlangen-Nürnberg. The Centre of Gerontology is also actively collaborating with communal institutions of medical care and with nursing homes of the region. Currently the ICG has 27 members coming from four different faculties and four 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.

Section: Nutrition
Fully aware of the higher risk for malnutrition and it's negative consequences for older people, different screening instruments of the nutritional status were analysed in residents of acute geriatric hospitals and of homes for the aged (Project "MNA"). A one-year longitudinal study in a population of old people home residents showed a higher survival-rate in obese persons (BMI > 30 kg/m^2) compared to those with a low body mass index (< 20 kg/m^2) and to those with normal BMI. The outstanding disposition of older people for malnutrition seems to be caused by age-associated changes in the regulation of appetite. Hormonal influences (e. g. Ghrelin) seem to be of special importance in this case.

Section: Physical activity
Targeted activation of physical activity can improve physical function and thus help to maintain independence in older persons (Project "EUNAAPA"). The "PASEO" project intends to improve the implementation of programs for the promotion of physical activity among sedentary older people by supporting the development of new political capacities. Physical activity also seems to play a major role in the treatment of mild cognitive impairment (Project "Sports and Cognition"). Common understanding is that multifactorial physical exercise helps to prevent falls and increases physical ressources like strength and balance. But the process of transfer from research into practice still needs to be more investigated (Project "Stable in old age"). The risk for falls is increasing with age, due to physiological and pathologic processes. 50 % of community dwelling older persons report at least one fall per year in the age-cohort 80 years and over. To prevent further falls the first important step is a screening process to identify older persons at risk of falls (Project "Falls in the Nürnberg-Erlangen-Fürth-Area").

Section: 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. Research also focuses on the biomedical, psychological, and cognitive processes that enhance the quality of social ties in later life ("RELATE" project). Another research focus is on the situation of family caregiver, particularly with respect to caregiver burden, and to the potentials of psychoeducation of family caregiver ("GesA" project). Additional projects focus on quality of caregiving in nursing homes.

Teaching

The majority of the ICG-members is engaged in the interdisciplinary course offerings of the masters 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 organiseded by numerous members of the ICG at the Medical Faculty of the Friedrich-Alexander-University.
Furthermore, the ICG operates a collective graduate school of gerontology, which provides structured lecturing for PhD students in gerontology as well as in psychology, psychiatry and sport sciences.

Interdisciplinary Centre for Functional Genomics (FUGE)

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Aims and Structure

The "Interdisciplinary Centre for Functional Genomics (FUGE)" was founded in 2001 as an organizational framework to focus and advance activities in all areas of genomics research at the FAU. Through initiation and fostering of interfaculty cooperation FUGE integrates the research field of "genetics and genomics" of the Faculty of Engineering Sciences into the life sciences profile of the university. As a methodological platform, FUGE opens access to the complex methodology of genome research for groups working in other focus areas of research of the medical faculty, e.g. cancer research, infectiology and immunology as well as neurosciences and strengthens them through interaction.

As an university facility FUGE acts so far as a dislocated centre without having any edificial structure of its own. About 15 groups are currently involved in the centre. They originate from three faculties, the Medical, Natural Sciences and Engineering Sciences. Members of the Medical Faculty come from the Institutes of Biochemistry, Experimental Medicine I and II, Human Genetics, Neuropathology, Microbiology, Pathology, Pharmacology and Virology and Department of Gynaecology and that of Medicine 3 as well as the Divisions of Molecular and Experimental Surgery and Molecular Immunology. Members from the Natural Sciences Faculty include the chairs of Biotechnology, Genetics, Microbiology and Molecular Plant Physiology. From the Faculty of Engineering Sciences are involved the Chair of Bioprocess Engineering and the Computer Science Department 2 (Programming Systems).

The micro array facility started its operation in October 2007 after successful application for a HBFG-grant initiated by several members lead-managed by the speaker. It is operated by the Interdisciplinary Centre for Clinical Research (IZKF) which has taken over the interim financing of the personnel until the funds from the Bavarian Innovation Fund become available probably early 2009. These had been previously raised by Prof. A. Reis together with Prof. Sticht (Institute of Biochemistry, Medical Faculty). The laboratory is managed by the Institute of Human Genetics. During the reporting period the laboratory performed numerous analyses for many different groups, both in expression profiling as well as genome wide genotyping of SNPs. The availability of the Core Unit was instrumental in obtaining a large grant from the Federal Ministry of Research within the National Genome Research Network (NGFN) for research on the genetic basis of mental retardation. The "German Mental Retardation Network" (MRNET) aims at systematically screening large patient groups for copy number variation (CNVs) in order to identify novel genes for mental retardation. This national network is coordinated by the FUGE-Speaker A. Reis. A detailed report on the activities of MRNET is found at page 150.

Several seminars were held during the reporting period under the auspices of FUGE on different topics including Next-Generation-Sequencing technologies. After extensive discussion of the properties of the different platforms of this important technique, several FUGE members from the Medical and Natural Science Faculties developed a concept for implementation of this technique in Erlangen and prepared a grant application to introduce this method here. FUGE offers an excellent structure to house this interfaculty endeavour.

ELAN programme for supporting clinical research and teaching

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„Spannungsfeld" by Silvia Stabel

Aims and Structure

The ELAN programme 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 1.2 Mio € 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 programme are financial support for research projects, promotion of innovative didactic models and internationalization of clinical teaching as well as its evaluation.

Research project support

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. 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. From mid 1998 until the end of 2008, a total of 616 grant applications have been submitted (2007: 63, 2008: 47) coming from virtually all clinical departments including the IZKF. The numbers of grant proposals from the respective departments reflected both their sizes and research activities, though to different extents. The average requested funding was about 33.000 € in 2007 and increased in 2008 to 39.000 €, at least in part because of rising personnel expenses. The total amount of funding requested ranged from 2.1 Mio € in 2007 to 1.8 Mio € in 2008. The total amount of granted money oscillated around 1.2 Mio € 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 programme, e. g. start or young investigator support. Since 1998 a total of 405 out of 422 projects were completed, representing a total funding of 9.5 Mio €. From these projects, 223 papers (37 in 2007, 20 in 2008), were produced mostly in high ranking or well respected journals. Additionally 74 (8 in 2007, 8 in 2008) grants were acquired from external funding sources (1.1 Mio € in 2007, 2.8 Mio € in 2008) amounting since 1998 to a total of 13.5 Mio €.

In conclusion, the ELAN programme has successfully stimulated a surge in high quality research projects from all clinical departments. This emphasizes the value of this programme for dynamically improving clinical research in our faculty.

Johannes and Frieda Marohn-Foundation

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Aims and Structure

According to the founders' will, the purpose of the J.F.M. Foundation is the promotion of new innovative projects of the Medical Faculty of the Friedrich-Alexander-University 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 explicitily 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-University Erlangen-Nürnberg.

According to the rules of the foundation, 5 members of the faculty have to be elected for a 3 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 conflict of interests.

Only clearly definde, 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 2007 – 2008)

Financial year	Budget	Number of accepted applications
2007	360,199.- €	12 = 337,375.- €
2008	341,194.- €	6 = 150,565.- €

Finalized projects (Time of funding 2004 – 2006)

Number of projects	Number of publications	Continued funding by other foundations *
31	50 (from 26 projects)	13 projects

* DFG = 7 projects; other foundations = 6 projects
18 projects could not obtain further financial support

Further foundations for research support

In addition to the ELAN programme and the Marohn Foundation, a number of foundations and endowments are established at the Medical Faculty, which support research. There are more than 20 supporting associations, who in most cases work closely with an institution. 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 advancement. Amongst the foundations that are administrated by the university or closely connected to the Medical Faculty, only the most important ones are to be 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 2005 the prize was given to Prof. Dr. Friedrich Magerl, Switzerland, for his outstanding contributions to spinal surgery. The Dr. Fritz Erler junior prize was newly established and first given to Prof. Stephan Ensminger, cardiac surgery, to appreciate his results in the role of CD40-CD154 blockade in the pathological mechanisms leading to the development of transplant arteriosclerosis. The Gottfried and Lieselotte Naumann Fund make contributions to ophthalmology, especially to clinical ophthalmo-pathology and to microsurgery of the eye. In a four-year rhythm the prize is given to an extraordinary researcher. 2006 the first-time award was donated to Prof. Thaddeus Dryja, Harvard Medical School, Boston, USA, for his fundamental contribution to the molecular basics of retinitis pigmentosa, at the World Meeting for Ophthalmology and Vision in Sao Paulo, Brasilia. The Dr. Norbert Henning Foundation gives every two years a prize for research in the field of gastroenterology. 2007 Prof. Dr. Robert Thimme of the University Hospital Freiburg was awarded for his scientific achievements in the field of immunopathogenesis of hepatitis B and C viral infection.

End of 2007 the Research Foundation of Medicine at the University Hospital Erlangen was founded at the initiative of the professors of the University Hospital Erlangen and the Medical Faculty of the Friedrich-Alexander University Erlangen-Nürnberg. Purposes of the foundation are advancement of science and research in all areas of basic and clinical medicine, also the advancement of apprenticeship and further training of scholars as well as physicians and scientists, the advancement of public health system (particularly with regard to the area of prevention and early diagnosis of disease) and 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 learners will be awarded.

In 2006 the Dr. Kurt and Magarete Groß Donation was founded for the advancement of special achievements in the field of cardiology, cardiac-physiology or cardiac surgery. The Ria Freifrau von Fritsch Foundation (contact: Mr. V. Paul, Ref. F3, ZUV) 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: Mr. H. Riepel, Ref. F3, ZUV) also supports cancer research, especially highly gifted young researchers interested in oncology by travel grants to enable a research project in 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, ZUV). 2007 a project of Prof. Dr. H. Drexler, Institute for Occupational, Social and Environmental Medicine, to environmental medical lead exposure of hobby shooters via shooting sport was cofinanced. 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 (contact: Prof. Dr. J. Kornhuber, Department of Psychiatry ans Psychotherapy) supports research in the field of Alzheimers disease, especially by giving grants for doctoral theses. The Dr. Ernst and Anita Bauer Foundation is an unaffiliated donation with base in Nürnberg. Its aim is to support gifted young physicians who come from the franconian area. To achieve this goal there are awards for extraordinary research results, benefits for doctorate theses, postdoctoral qualifications and research projects as well as grantships for a stay in a foreign laboratory. The best and most concise postdoctoral qualification (Habilitation) is awarded anually by the Thiersch Prize. Most outstanding doctoral theses are awarded by the Staedtler Prize. The Foundation for Teaching (www.stiftung-lehre.de) was founded to support and improve the education of young clinicians.

Society for Physics and Medicine Erlangen

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Aims and Structure

The Erlangen Society for Physics and Medicine, also known as Societas physico-medica Erlangensis, was founded on March 20, 1808 in order to exchange "ideas, observations and experiences between all the areas of natural sciences and medicine". These first statutes and articles, defined in the year 1808, are still valid; by amendment of the statutes in 1990 the technical disciplines have also been admitted.
At present, the society has about 490 members inside and outside Germany, six of them honorary and 55 corresponding members.

Every semester the society holds three regular meetings with lectures given by members or invited guests. From 1984 to 2008 nine volumes of reports were published, each of them consists of four single issues (ISSN 0371-2117). 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 Faculty of Medicine of the University of Erlangen.
On June 18th 2008 the Erlangen Society for Physics and Medicine celebrated its 200th birthday in a ceremony at the castle of the University of Erlangen. After the greeting from Prof. Dr. Karl-Dieter Grueske, president of the University of Erlangen-Nürnberg, Prof. Dr. Renate Wittern-Sterzel, head of the Chair of the History of Medicine, gave a lecture on the early history of the Physico-Medica. The invited lecture on "Illuminating Post-Genome Biology with Tomographic Photoning Imaging" was held by Prof. Dr. Vasilis Ntziachristos, Director of the Institute of Biological and Medical Imaging at the GSF-Research Centre on Environment and Health.
On the occasion of the 200th birthday the society presented a festschrift (Ritter, Marco: Isidor Rosenthal. Forscher - Arzt - Politiker. Festschrift zur 200-Jahrfeier der Physikalisch-Medizinischen Sozietät zu Erlangen. Verlag Palm & Enke, Jena und Erlangen 2008 (ISBN 978-3-7896-0441-6)). Marco Ritter describes the life of Isidor Rosenthal (1836-1915) who was the first independent physiologist of the University Erlangen. In this work not only the aspects of life and work of Isidor Rosenthal but also detailed information on the former circumstances in Poland, Berlin, Erlangen and in the war of 1870/1871 between Germany and France were given.

In the year of celebrating the 200th birthday the Medical Society that had been separated in 1958 after the 150th celebration of the Physico Medica united again with the Society for Physics and Medicine Erlangen.

Degree Program in Medicine

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Auscultation on a phantom in the skills lab

Aims and Structure

The Medical Department consists of three study programs: Medicine, Dentistry, and Molecular Medicine. In the 2007/08 winter term 2,680 students were enrolled in these three study programs, of which 1,660 were female. Thus, the percentage of women studying in the Medical Department remained constant at 62 %. According to the statistics of the University of Erlangen-Nürnberg for the 2007/08 winter term, 227 of the students enrolled in the Medical Department were foreigners, which is about 8.5 %. Compared to the last year that constitutes a rise in the percentage of foreigners enrolled in the Medical Department of about 2.5 percentage points.

In the 2007/08 winter term, 273 of the students began their first semester in the Medical Department, 176 in the study program Medicine, 62 in Dentistry, and 35 in Molecular Medicine. Applicants for the study programs Medicine, Dentistry, and Molecular Medicine are chosen according to the criteria of the Central Office for the Allocation of university places in Germany (ZVS). The number of places in the study programs Medicine and Dentistry is reassessed each semester by the Administrative Court Ansbach due to the fact that applicants for a place in the study programs take their cases to court.

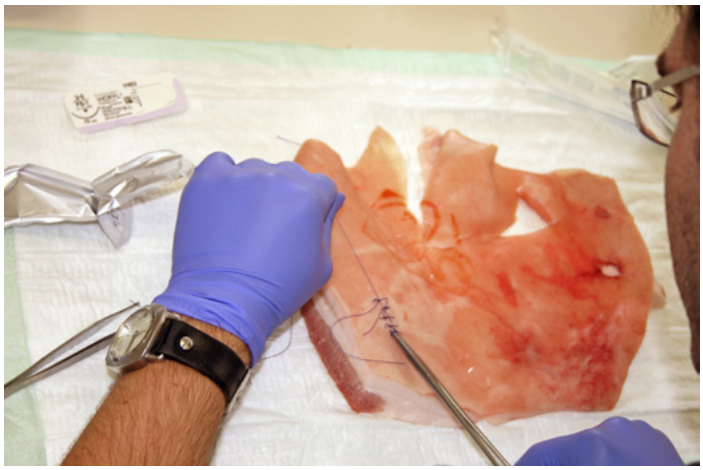
Online-Evaluation

Each semester, all courses are evaluated online by the students with the help of the online evaluation system EVALuna (Dr. Ganslandt, Institute for 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 (semester 5 – 10) for Medicine receive grants of 30.000, 20.000 and 10.000 Euro. 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 respective semester.

In the winter term 2007/2008 2015 students participated in the online evaluation, 1.414 of them enrolled in the study program Medicine, 471 in Dentistry, and 130 in Molecular Medicine. Thus, the Medical Department evaluates all medical courses in all semesters, thus fulfilling the requirements of the approbation regulations (ÄAppO). The last year of the study program medicine, the practical training year (PJ), is also evaluated by the students online.

Skills Lab PERLE

Since the introduction of student fees in Germany in 2007, the Medical Faculty has had the means to expand the activities in the Skills Lab PERLE. Medical students now take one mandatory class in the Skills Lab in the fifth semester.



Training of surgical suturing in the skills lab

The approbation regulation's goal for improvement in teaching basic practical medical skills has thus been furthered. 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. In the near future, the Skills Lab will offer special courses for students in the dentistry study program in the field of surgical suturation.

Medical State Examination

In 2008 students in Erlangen achieved very good results in the Medical State Examination part one and two. All medical students in Germany take the same examination. Therefore, results are objective and comparable. According to the students' State Examination results, the Medical Faculty in Erlangen belongs to the top group of Medical Faculties in Germany.

Degree Program in Dentistry

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Aims and Structure

The school of dentistry at the University of Erlangen-Nürnberg currently admits 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). Cases of unexpected rises in enrollment resulting from lawsuits successfully filed against admissions restrictions have become fewer in recent years, so that in fact there have been no further unexpected increases in enrollment. 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 a leading position in German university rankings published by the CHE (Centre for University Development).

Degree Program in Molecular Medicine

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Aims and Structure

The degree program in Molecular Medicine combines both, the subjects of experimental medicine and the approaches of molecular biology, biochemistry, and genomics. This program acknowledges the fact that boundaries which traditionally separate 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 universities. Nationwide, this program in Molecular Medicine has been met by an extraordinary interest. Each academic year, 34 students are admitted, as compared to more than 700 applications. The winter semester 2007/2008, the first class has been admitted to the novel B.Sc./M.Sc program, consistent with the declaration of Bologna. Accordingly, the traditional, very successful ‚diploma track' program will end.

Objectives of the degree program in Molecular Medicine

Under the influence of molecular and cellular methods, medicine has changed fundamentally. Yet, higher education in Germany has only begun to reflect these changes. Traditionally, subjects and methods of molecular medicine are distributed over different ‚Fakultäten' of our universities. Degree programs in the biological sciences offer many of the methods used in molecular medicine, but do so without a systematic presentation of medical subjects. In medical programs, on the other hand, basic science aspects are widely restricted to the needs of medical practice. This contrasts the situation at medical schools in the USA: in addition to the doctoral degree in medicine (M.D.), curricular programs in the basic medical sciences (biochemistry, pharmacology, physiology etc.) are offered leading to M.Sc. or Ph.D. degrees (Master of Science / Doctor of Philosophy).

The B.Sc./M.Sc program in Molecular Medicine in Erlangen addresses these needs and offers an interdisciplinary curriculum in the medical basic sciences, which also covers clinical aspects. The B.Sc. program covers 6 semesters, emphasising a solid and thematically diversified education in basic science. The first semesters its syllabus heavily draws on contributions from the science faculties (physics, inorganic/physical/organic chemistry). The second year focuses on preclinical aspects, the curriculum of the third year will be extended with a focus on pathology and experimental therapy. The B.Sc. program ends with a scientific thesis.
Starting in winter semester 2010/11, when first graduate students of Molecular medicine have finished, a consecutive master program will be offered to them as well as for applicants with similar qualifications. The main training goal of this four semester program is to acquire a deeper understanding of science by working with original publications and ambitious practical training. Whereas the B.Sc. focuses on functional aspects the M.Sc. program mediate interdisciplinary themes which are taught together by different institutes. This profile is already practised in the course of 'molecular pathomechanisms' performed by biochemistry, pathology and physiology institutes. The M.Sc. ends with a 6 month master thesis.

Compared to the 'Diploma' program, the degree program will be able to address an additional topic by receiving additional support from the Innovation Initiative at the University of Erlangen-Nürnberg: a newly established professorship for molecular medicine will further extend the curriculum by the new module 'Molecular imaging'. This module will reflect another scientific strength of Erlangen, as it will bridge the gap between the degree program and industrial applications. The Master program Molecular Medicine offers 4 groups (A-D) of compulsory optional subjects, one of each has to be selected and a single has to be selected for specialisation.
A. Structure and development
B. Signal cascades and active components
C. Infection and pathogenesis
D. Molecular imaging

The freshmen in Molecular Medicine are welcomed by an annual symposium, introducing them to the program and the Medical Faculty of the University of 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 a close feedback from students to faculty.

Applications, development of student numbers and implementation of the program

Potential applicants are introduced to the program in Molecular Medicine by the Chair of Biochemistry and Molecular Medicine, the central advisory service of the Friedrich-Alexander-Universität, as well as by brochures and the internet homepage www.MolMed.de. The program has been registered with internet services (studieren.de) and search engines (Google, Lycos etc.). Indeed, the internet represents the single most important source of information among freshman students: about 70 % of first contacts with Molecular Medicine have been made via the internet. Asking students for their alternative choices in case they would not have been admitted to Molecular Medicine, most students listed medicine, biochemistry, or biotechnology. At present, half of the students enrolled in Molecular Medicine are in-state students from Bavaria, while the other half originate from other German ‚Länder' (states) or are international students. This situation demonstrates the nationwide attractiveness of our study program.

Presently, more than 22 applicants compete for one admission slot in Molecular Medicine. For the Winter term of 2008/2009, admission requirements for the program had reached the highly selective grade point average of 1.2, 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. Both, the admission procedure and the underlying capacity regulations have been approved by the Administrative Court of Bavaria (Bayerischer

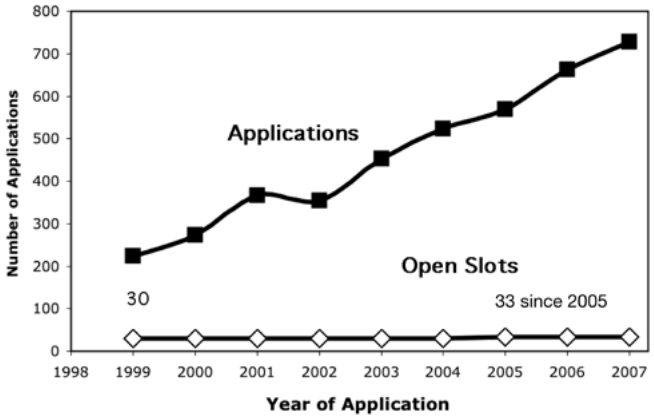
Verwaltungsgerichtshof) in Munich. These rulings underscore the right of the university to adapt educational programs to current scientific developments.

Since winter term 2007/2008, the new B.Sc. program is offered. It has been our experience that a small number of students drop out of the program before completing the first semester and, again, after the fourth semester when the ‚Vordiplom' examinations are due. When asked for their reasons to quit, the students leaving the program frequently attribute their decision to the demanding requirements of basic science studies. We have responded to this drop out rate by intensifying counselling of applicants and offering an online admission test at www.MolMed.de. The number of students leaving, however, is exceeded by the number of applicants trying to enter from medicine, biochemistry or biotechnology. Generally, these applicants are advised to continue their current academic programs.

The undergraduate phase of the 'Diploma' program ended with the ‚Vordiplom' examinations taken place for the last time in winter semester 2008/09. The fraction of students, who successfully passed these examinations in the minimum period of time, has exceeded 80 %. In summer of 2004, the ‚Diplom' degree has been conferred to the first class of the program. In each graduation class, several excellent theses have won prices from the university or external foundations.

In contrast to the 'diploma' program, the B.Sc. Molecular Medicine according to the declaration of Bologna is characterized by close-meshed and course-related exams which are continuously documented in an electronic management system. A lot of students -also high-capacity course participants- feel this situation incriminating. As the more flexible time schedules of Diploma program are no longer available, the formal specifications and recordings have urgently been to liberalise. Otherwise the number of drop out students will rigorously increase.

The core curriculum in Molecular Medicine is mainly taught by preclinical and theoretical institutes, and the Nikolaus-Fiebiger-Centre. In its first decade, the degree program in Molecular Medicine has been implemented in a very efficient way, with no additional university budget or outside funding available. In the meantime, a new professorship for molecular imaging has been awarded by the Innovation Initiative at University of Erlangen-Nürnberg. The laborious restructuring of the Diploma program Molecular Medicine to the two-stage Bologna schema is currently supported by a half administration position.



As expected from its interdisciplinary approach, the program in Molecular Medicine offers strong interactions with the pure science programs. In particular, the Molecular Science program run by the departments of chemistry and pharmacy offers complementary topics in the life sciences, bio- and nanotechnology. Since the Erlangen program in Molecular Medicine has been established, similar courses have also been introduced by the Universities of Freiburg, Würzburg, Bonn, Göttingen and Ulm.

Perspectives

The degree program in Molecular Medicine has paved the way for a high-quality doctoral program at Friedrich-Alexander-University of Erlangen-Nürnberg. Graduates may enrol in a doctoral program (Dr. rer. nat.) offered in collaboration with the Faculty of Sciences. At present, the first graduates of Molecular Medicine program are in a stage of completing their doctoral theses. The degree program in Molecular Medicine is intended to enable 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 will be open to 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. In a longer perspective, the degree program in Molecular Medicine will prove its concepts through successful professional and academic careers of its graduates.

Medical Process Management

Speaker
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Aims and Structure

The degree programme in Medical Process Management is structured as a non-consecutive master programme in order to attract graduate students of different faculties, primarily natural sciences, social and economic sciences, engineering, as well as dentistry and molecular medicine. The curriculum aims to give insight into three major areas: first of all the economical aspects of healthcare are an important subject as well as management and organization of patient care in hospitals and office-based medicine. Finally, much emphasis will be put into the knowledge transfer from clinical medicine into the diverse fields of patient care. This master programme offers 30 different major topics provided within three faculties of Erlangen University. A total of 120 ECS-points are necessary to complete successfully this programme. 20 and 30 students respectively have started with the first and second study years 2008/2009 and 2009/2010. With the master degree in Medical Process Managemnet an improved understanding of administration and management in healthcare systems should provide best chances to get employment in diverse fields of healthcare management, development of new medical technologies, and optimized clinical pathway management.

Honorary Doctorate

Honorary Doctorate 2007

Prof. Dr. Hermona Soreq
Faculty of Mathematics and Natural Sciences of the Hebrew University Jerusalem, Israel

Honorary Doctorate 2008

Prof. Dr. Dontscho Kerjaschki
Medical University of Vienna, Austria

A Selection of Awards 2007 – 2008

Ernst Jung-Karriere-Förderpreis für Medizinische Forschung 2007
Dr. med. Jörg Distler
Department of Medicine 3 – Rheumatology and Immunology

Ferdinand Sauerbruch Forschungspreis der Berliner Chirurgischen Gesellschaft
PD Dr. med. Ulrich Kneser
Department of Plastic and Hand Surgery

Innovationspreis der Deutschen Gesellschaft für Arbeitsmedizin und Umweltmedizin (DGAUM)
Prof. Dr. med. Hans Drexler, Prof. Dr. rer. nat. Jürgen Angerer and Dipl.-Chem. Karl-Heinz Schaller
Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine

BRAHMS-Forschungspreis der Deutschen Gesellschaft für Nuklearmedizin
Herr cand. med. Daniel Bläser
Department of Nuclear Medicine

Helen-Keller-Prize for Vision Research
Prof. Dr. med. Elke Lütjen-Drecoll, Chair of Anatomy II
Prof. emerit. Dr. med. Johannes Wilhelm Rohen
Chair of Anatomy II

Innovations-Preis 2007 der Familie-Klee-Stiftung
Prof. Dr. med. Georg Michelson
Department of Ophthalmology

Wissenschaftspreis 2007 der Deutschen Gesellschaft der Plastischen-, Rekonstruktiven- und Ästhetischen Chirurgen und der Vereinigung der Deutschen Ästhetischen Plastischen Chirurgen (Habilitationsschrift)
PD Dr. med. Alexander Bach
Department of Plastic and Hand Surgery

Wissenschaftspreis der Deutschen Gesellschaft der Plastischen, Rekonstruktiven und Ästhetischen Chirurgen
Prof. Dr. med. Raymund Horch
Department of Plastic and Hand Surgery

Auszeichnung der Habilitationsschrift mit dem Wissenschaftspreis 2007 der Deutschen Gesellschaft für Zahnärztliche Hypnose (DGZH) e.V.
PD Dr. med. dent. Stephan Eitner
Dental Department 2 - Prosthetic Dentistry

Hans-Jörg Weitbrecht-Preis für Klinische Neurowissenschaften
Prof. Dr. med. Rolf Schröder
Institute of Neuropathology

Gerhard-Fürst-Preis des Statistischen Bundesamtes
Dr. rer. nat. Matthias Schmid
Institute of Medical Informatics, Biometry and Epidemiology

Zweiter Preis der Kategorie Grundlagenforschung des Förderpreises für Schmerzforschung
Dr. med. Katharina Zimmermann
Institute of Physiology and Pathophysiology
Dr. med. Andreas Leffler
Department of Anaesthesiology

XVI. International Blindness Prevention Award
Prof. emerit. Dr. med. h. c. mult. Gottfried O.H. Naumann
Chair of Ophthalmology

Latsis-Preis der Europäischen Wissenschaftsstiftung ESF
Prof. Dr. med. Dr. habil. Willi Kalender, Ph.D.
Chair of Medical Physics

Pettenkofer-Preis
Prof. Dr. rer. nat. Michael Hensel
Institute of Clinical Microbiology, Immunology and Hygiene

Innovationspreis und Wissenschaftlicher Vortragspreis der Deutschsprachigen Arbeitsgemeinschaft für Mikrochirurgie (DAM)
Dr. med. Justus Beier
Department of Plastic and Hand Surgery

Forschungsförderungspreis der Deutschen Gesellschaft für Geriatrie
Prof. Dr. med. Karl G. Gassmann
Institute of Biomedicine of Aging

Ehrenpreis der Deutschen Gesellschaft für Geriatrie
Dr. med. Jürgen Bauer
Institute of Biomedicine of Aging

Hans J. Dengler-Preis für Klinische Pharmakologie
Dr. rer. nat. Hartmut Gläser
Institute of Experimental and Clinical Pharmacology and Toxicology

Wilhelm-Feuerlein-Forschungspreis 2007
Prof. Dr. med. Stefan Bleich
Institute of Experimental and Clinical Pharmacology and Toxicology

Sertürner-Preis 2007
Prof. Dr. med. Dr. h. c. Kay Brune
Doerenkamp-Chair of Innovations in Animal and Consumer Protection

Innovationspreis eHealth 2008
Prof. Dr. med. Georg Michelson
Department of Ophthalmology

Ernst-Derra-Preis 2008
Prof. Dr. med. Robert Cesnjevar
Department of Cardiac Surgery

Forschungspreis 2008 der Dr. Geisenhofer-Stiftung
Dr. med. Tamme Goecke
Department of Obstetrics and Gynaecology
Dr. med. Udo Reulbach
Department of Psychiatry and Psychotherapy

Ted Stanley Award for Innovation in Anaesthetic Pharmacology
Prof. Dr. med. Dr. Dipl.-Phys. Helmut Schwilden
Department of Anaesthesiology

Auszeichnung der Diplomarbeit mit dem Werner von Siemens Excellence Award 2008
Philip Stenner
Institute of Medical Physics

Preis für die beste wissenschaftliche Arbeit aller Bayerischen Frauenkliniken
Prof. Dr. rer. nat. Ralf Dittrich
Department of Obstetrics and Gynaecology

Preis für gute Lehre an Bayerns Universitäten
Dr. med. Wolfgang Frobenius
Department of Obstetrics and Gynaecology

Forschungspreis für geburtshilfliche Forschung in Europa 2008
Dr. med. Tamme W. Goecke
Department of Obstetrics and Gynaecology
Dr. med. Udo Reulbach
Department of Psychiatry and Psychotherapy

Franz Kölsch-Preis 2008
Dr. med. Gintautas Korinth
Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine

Georges-Koehler-Preis der Deutschen Gesellschaft für Immunologie
Prof. Dr. rer. nat. Diana Dudziak
Department of Dermatology

PHOENIX-Phamazie-Wissenschaftspreis 2008
Prof. Dr. med. Torsten Kuwert
Chair of Clinical Nuclear Medicine

Hauptpreis 2008 der Stiftung der Deutschen Gesellschaft für Hygiene und Mikrobiologie
Prof. Dr. rer. nat. Michael Hensel
Institute of Clinical Microbiology, Immunology and Hygiene

Forschungsförderungspreis der Deutschen Zöliakie-Gesellschaft e. V. 2008
PD Dr. rer. nat. Walburga Dieterich und Dr. Birgit Esslinger
Department of Medicine 1 – Gastroenterology, Lung Diseases and Endocrinology

Erster Preis der Kategorie Grundlagenforschung des Förderpreises für Schmerzforschung 2008
PD Dr. rer. nat. Andreas Hess
Institute of Experimental and Clinical Pharmacology and Toxicology

Sir Hans Krebs-Preis 2008
Prof. Dr. med. Anita Rauch
Institute of Human Genetics

Kulturpreis Bayern der E.ON Bayern AG
Dr. med. Teja W. Groemer
Department of Psychiatry and Psychotherapy

Auszeichnung der Diplomarbeit mit dem Friedrich-Wingert-Nachwuchspreis
Herr cand. Dipl. Inf. Andreas Beck
Institute of Medical Informatics, Biometry and Epidemiology

Förderpreis 2008 der Albert-J.B.-Sturm Stiftung
Dr. med. Frank Unglaub
Department of Plastic and Hand Surgery

Preis der Union of European Neonatal and Perinatal Societies (UENPS)
Prof. Dr. Holm Schneider
Department of Pediatrics

Doctorate Theses, Board Qualifications, Additional Qualifications, Habilitations

Anatomical Institute
Chair of Anatomy I

Doctorate Theses

Ganns, Daniela, Dr. med. (2007): *Untersuchung allgemeiner und zytoskelettaler Marker zur quantitativen Bestimmung von Neuronenpopulationen im menschlichen Darm*

Kapp, Sonja, Dr. med. (2007): *Chemische Kodierung der submukösen Typ V-Neuronen im Ileum des Schweins*

Lennerz, Jochen, Dr. med. Dipl. Mol. Med. (2007): *Elektrophysiologische Charakterisierung vagaler Afferenzen im oberen Ösophagus der Ratte - Relevanz für die mukosale Nozizeption*

Ewald, Philipp, Dr. med. (2008): *Immunreaktivität des vesikulären Glutamattransporter 1 in der extrinsischen und intrinsischen Innervation des Rattenösophagus*

Kallmünzer, Bernd, Dr. med. (2008): *Enterische Co-Innervation von quergestreifter Muskulatur im menschlichen Ösophagus*

Kraus, Tobias, Dr. med. (2008): *Distribution of vesicular glutamate transporter 1 in the mouse esophagus*

Weidmann, Simone, Dr. med. dent. (2008): *Quantifizierung des Anteils der mutmaßlichen primär-afferenten Neuronen im Plexus myentericus des menschlichen Dünndarms*

Wolf, Matthias, Dr. med. (2008): *Calcitonin gene-related Peptide: Ein Marker für mutmaßliche primär-afferente Neuronen im Plexus myentericus des Schweinedünndarms*

Institute of Physiology and Pathophysiology
Chair of Physiology

Doctorate Theses

Denekas, Thomas, Dr. med. (2007): *Inhibition of stimulated meningeal blood flow by a calcitonin gene-related peptide binding mirror-image RNA oligonucleotide*

Derow, Alexandra, Dr. med. (2007): *Prostaglandine steigern die Hitzeantwort von Nozizeptoren, nicht aber deren CGRP-Freisetzung in isolierter Rattenhaut*

Engel, Matthias, Dr. med. (2007): *Cannabinoide hemmen und fazilitieren konzentrationsabhängig die reizinduzierte calcitonin gene-related peptide-Freisetzung aus Ratten- und Maushaut*

Hullard-Pulstinger, Caroline, Dr. med. dent. (2007): *Darstellung und Vergleich der kortikalen Repräsentation von sowohl willkürlich- aktiv als auch unwillkürlich-passiv provoziertem Tiefenschmerz mit Hilfe von funktioneller Magnetresonanztomographie und eines computergestützten Hirnatlas*

Kaschka, Miriam, Dr. med. dent. (2007): *Vergleich der Lokalisationen der durch Oberflächen– und Tiefenschmerz aktivierten Hirnareale mit Hilfe der funktionellen Magnetresonanztomographie*

Lennerz, Jochen, Dipl. Mol. Med. (2007): *Elektrophysiologische Charakterisierung vagaler Afferenzen im oberen Ösophagus der Ratte – Relevanz für die mukosale Nozizeption*

Mayer, Stephanie, Dr. med. (2007): *Bradykinin-induzierte Nozizeptorsensibilisierung gegen Hitze hängt ab von COX-1 und COX-2-Aktivität in isolierter Rattenhaut*

Rickeheer, Sebastian, Dr. med. (2007): *Signalanalyse in der funktionellen Kernspintomographie (fMRI): Detektion schmerzinduzierter Aktivität im Gehirn durch Klassifikation von BOLD-Signalen ohne Vorkenntnis des Stimulationsmusters*

Schödel, Andrea, Dr. med. (2007): *Der Einfluss von Rating auf BOLD Effekte in verschiedenen Regionen des menschlichen Kortex während taktiler und schmerzhafter mechanischer Stimulation*

Spitzer, Martin, Dr. med. (2007): *Mechanismen der stimulierten axonalen Neuropeptid-Freisetzung aus isolierten Ischiasnerven der Ratte*

Tröltzsch, Markus, Dr. med. (2007): *The calcitonin gene-related peptide (CGRP) receptor antagonist BIBN4096BS reduces neurogenic increases in dural blood flow*

De Col, Roberto, Dr. med. (2008): *Die Leitungsgeschwindigkeit unmyelinisierter Nervenfasern der Dura mater encephali wird von der Verfügbarkeit der spannungsgesteuerten Natriumkanäle bestimmt*

Hager, Ulrich, Dr. med. (2008): *Die morphologische Charakterisierung des MrgC-Rezeptors der Ratte und eine funktionelle Analyse von Rezeptoragonisten*

Herde, Lina, Dr. med. (2008): *Juckreiz, der durch eine neue Methode induziert wird, führt zur limbischen Deaktivierung - Eine Untersuchung mit funktionellem Kernspin*

Langhammer, Andreas, Dr. med. (2008): *Forward and Backward Enhancement" bei ballistischer Stoßreizung der Haut – eine taktile Sinnestäuschung?*

Rühle, Belinda, Dr. med. (2008): *Zentrale Repräsentation von mechano sensitiven versus mechano insensitiven C-Nozizeptoren – funktionelle Kernspintomographie am menschlichen Gehirn*

Habilitation

Fischer, Michael, Dr. med. habil. (2008): *Beiträge zur Sensibilität und Sensibilisierbarkeit primärer nozizeptiver Afferenzen mit Fokus auf Calcitonin Gene-Related Peptide*

Institute of Biochemistry – Emil-Fischer-Centre
Chair of Biochemistry and Molecular Medicine

Doctorate Theses

Grömer, Teja Wolfgang, Dr. med (2007): *Vesikel-Populationen bei spontaner und aktivitätsabhängiger synaptischer Übertragung*

Meiselbach, Heike, Dr. rer. nat. (2007): *Computergestützte Untersuchung der Struktur, Dynamik und Energetik von Proteininteraktionen*

Müller, Wolfgang, Dr. rer. nat. (2007): *Strukturbasierte Bewertungsfunktionen zur Vorhersage neuer Protein-Protein-Interaktionen*

Braune, Marlen, Dr. rer. nat. (2008): *Die hypertone Bewegungsstörung der Mausmutante spastic*

Dinkel, Holger, Dr. rer. nat. (2008): *A computational strategy for the prediction of functional interaction motifs*

Homeyer , Nadine, Dr. rer. nat. (2008): *Untersuchung des Einflusses von Phosphorylierung auf Struktur, Dynamik und Funktion des HPr-Proteins*

Habilitation

Schiebel, Katrin, Prof. Dr. rer. nat. (2007): *DNA-Polymorphismen und ihre pathobiochemische Bedeutung* (Erweiterung der Lehrbefähigung für die Fächer Biochemie und Molekularbiologie)

Institute of Biochemistry – Emil-Fischer-Centre
Chair of Biochemistry and Pathobiochemistry

Doctorate Theses

Kosian, Thomas, Dr. rer. nat. (2007): *Interaktion und Modifikation des HMG-Box Transkriptionsfaktors Sox10*

Werner, Torsten, Dr. rer. nat. (2007): *Untersuchungen zur genregulatorischen Aktivität evolutionär konservierter, nicht-kodierender regionen im Sox10 Locus.*

Zoubek, Robert, Dr. rer. nat. (2007): *Subzelluläre Verteilung von Thymosin-b4 in Abhängigkeit seiner G-Aktin-Bindungssequenz*

Hoser, Melanie, Dr. rer. nat. (2008): *Entwicklungsbiologische Studien zur Funktion von SoxC-Proteinen während der Mausembryogenese.*

Schubert, Steffen, Dr. rer. nat. (2008): *Identifikation der mit dem Transkriptionsfaktor GCMa assoziierten Signalwege und die Herstellung eines konditionalen GCMa-Knockout-Mausmodells*

Habilitations

Stolt, Claus, PD Dr. rer. nat. (2007): *Sox-Proteine in der Entwicklung von Oligodendrozyten*

Schlierf, Beate, PD Dr. rer. nat (2008): *Untersuchungen zur transkriptionellen Regulation durch Sox10*

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

Doctorate Theses

Adler, Werner, Dr. rer. biol. hum. (2007): *Development and evaluation of an automated classification method for early detection of glaucoma*

Menezes de Pádua, Cristiane Aparecida, Dr. rer. biol. hum. (2007): *Allergic Contact Dermatitis to Topical Drugs - Epidemiological Risk Assessment*

Tartler, Bärbel, Dr. med. (2007): *Diagnostik von Kontaktallergien gegen Inhaltsstoffe von Haarkosmetika*

Rabe, Christina, Dr. rer. biol. hum. (2008): *Verfahren zur Schätzung partieller attributabler Risiken bei multifaktoriell bedingten Erkrankungen*

Wolf, Carmen Christine, Dr. med. (2008): *Sonnenschutz bei Kindern. Die Erlanger Kindergarten-Studie -- aktueller Wissensstand und daraus resultierende Präventionskampagnen im weltweiten Kontext*

Institute of Medical Informatics, Biometry and Epidemiology
Endowed Chair of Medical Informatics

Doctorate Theses

Dumitru, Corina, Dr. med. (2007): *A systematic approach for the evaluation of Web-based personal health records in Germany*

Gerdsen, Frederic, Dr. hum. biol. (2007): *Entwicklung eines Referenzmodells zur Unterstützung von integrierter Glaukomversorgung und -forschung durch standardisierte Kommunikation auf Basis der Clinical Document Architecture*

Jantsch, Stefan, Dr. med. (2008): *Evaluation von Pathifier. Ein zeitstrahlbasiertes Präsentationsprogramm integrierter Patientendaten als Basis für vielseitige klinische Anwendungen*

Klein, Andreas, Dr. hum. biol. (2008): *Ein generischer Ansatz zur Realisierung verteilter Datenerfassung in der vernetzten klinischen Verbundforschung*

Lang, Martin, Dr. hum. biol. (2008): *Prozessmining und Prozessoptimierung zur Verbesserung klinischer Workflows im Umfeld bilderzeugender Fächer*

Pálffy, Péter, Dr. hum. biol. (2008): *Konzeption und Einführung eines DV-basierten OP-Planungs- und OP-Dokumentationssystems in einem Universitätsklinikum*

Sojer, Reinhold, Dr. hum. biol. (2008): *Transformation des Arzneimittelsicherheitsystems KLASSE in eine standardisierte Wissensrepräsentation*

Institute of the History of Medicine and Medical Ethics
Chair of the History of Medicine

Doctorate Theses

Krüger, Dorothea Irene Edith, Dr. phil. (2007): *„Zwangssterilisationen im Nationalsozialismus: Das „Gesetz zur Verhütung erbkranken Nachwuchses" vom 14. Juli 1933 und seine Durchführung an der Universitäts-Frauenklinik Erlangen"*

Schlee, Steffen Dieter, Dr. phil. (2007): *Maximilian Anton Wintrich (1812-1882) Die Einführung der physikalischen Diagnostik an der Universität Erlangen im 19. Jahrhundert*

Habilitation

Steger, Florian, PD Dr. phil. (2008): *„Keine Stoffwechselstörung im Gehirn, sondern eine persönliche Geschichte" Geschichte und Ethik der Psychiatrie und Psychotherapie im 20. und 21. Jahrhundert*

Institute of Pathology
Chair of General Pathology and Pathological Anatomy

Doctorate Theses

Frangou, Phroso, Dr. med. (2007): *Epstein-Barr Virus-Replikation in Epithelzellen in vivo*

Greiner, Axel, Dr. med. (2007): *Expression von B-Zell-Differenzierungsantigenen in Hodgkin Lymphomen*

Grimm, Roland, Dr. med. (2007): *Auswirkungen von Anämie und Urämie auf das Myokard: Strukturelle und hämodynamische Veränderungen im Modell der subtotal nephrektomierten Ratte*

Kolb, Jochen, Dr. med. (2007): *Reduktion der Cdx2-Expression in kolorektalen Karzinomen durch ß1-Integrin Stimulation*

Lange, Oliver, Dr. med. (2007): *Morphometrische Veränderunge in der Frühphase der STZ-induzierten experimentellen Diabetischen Nephropathie nach 5 und 15 Tagen*

Porzner, Marc, Dr. med. (2007): *Die Bedeutung von Mutationen im APC-Gen für die subzelluläre Lokalisation von APC und ß-Catenin in humanen kolorektalen Karzinomen*

Päzolt, Doreen, Dr. med. (2007): *Expression von TH2 Zytokinen und Chemokinen beim Hodgkin Lymphom und beim Nasopharynxkarzinom*

Tyralla, Karin, Dr. med. (2007): *Untersuchung des regressiven Einflusses einer hochdosierten Behandlung mit dem Angiotensin-Converting-Enzym-Hemmer Enalapril auf kardiovaskuläre Veränderungen im experimentellen Modell der chronischen Niereninsuffizienz*

Walcher, Felix, Dr. med. (2007): *Einfluß von humanem Endothelin-2 auf die myokardiale Schädigung bei Diabetes mellitus am Tiermodell der ET-2 transgenen Ratten*

Wernicke, Konstanze, Dr. med. (2007): *Der Einfluß von nativem und modifiziertem C-reaktiven Protein auf die Atherosklerose Entwicklung in Apolipoprotein E-knockout-Mäusen*

Bacmann, David, Dr. med. (2008): *Die Herunterregulierung des TGF-beta-Rezeptor 2 in tumorassoziiertem Stroma verschlechtert die Prognose und High-grade Tumore zeigen mehr tumorassoziierte Makrophagen und geringere Expression von TGF-beta 1 in colorektalen Karzinomen*

Casper, Sandra, Dr. med. (2008): *Systemische Wirkung von Tabak- und Asbestexposition auf Niere und Gefäßsystem im Tierversuch*

Forster, Christian, Dr. med. (2008): *Morphologische und stereologische Untersuchungen der Mesangiolyse in der murinen Habutoxin Nephropathie der Maus*

Friebel, Daniela, Dr. med. (2008): *Prognostische Bedeutung tumorinfiltrierender T-Zellen beim klassischen Hodgkin Lymphom*

Koch, Stefan, Dr. med. (2008): *Auswirkungen einer oralen Therapie mit Atorvastatin auf renale Schäden im Tiermodell der ApoE-/-Knock out Maus*

Lang, Katrin, Dr. med. (2008): *Einfluss des P2Y1-Rezeptors mit und ohne adjuvante Gabe des P2Y12 Rezeptorblockers Clopidogrel auf den Krankheitsverlauf im anti-GBM-Glomerulonephritis-Mausmodell*

Lill, Maria, Dr. med. (2008): *Auswirkungen einer oralen Therapie mit Perindopril, Candesartan und S 18886 auf renale Schäden im Tiermodell der unilateral nephrektomierten obese Zucker Ratte (OZR)*

Sachs, Albrecht, Dr. med. (2008): *Die Butyrat-induzierte Expression des Zellzyklusinhibitors p21 Cip1/Waf1 erfolgt unabhängig von CDX2*

Institute of Neuropathology
Chair of Neuropathology

Doctorate Theses

Siebzehnrübl, Florian A., Dr. rer. nat (2007): *Therapeutic applicability of adult brain stem cells*

Coras, Roland, Dr. med. (2008): *The peroxisome proliferator-activated receptor-y agonist troglitazone inhibits transforming growth factor-ß–mediated glioma cell cell migration and brain invasion*

Institute of Microbiology – Clinical Microbiology, Immunology and Hygiene
Chair of Microbiology and Immunology of Infection

Doctorate Theses

Eckert, Melanie, Dr. rer. nat. (2007): *Untersuchungen zur Expression und Funktion von murinem bactericidal/permeability increasing protein (BPI)*

Gerlach, Roman, Dr. rer. nat. (2007): *Characterization of Virulence Genes in Salmonella Pathogenicity Island 4*

Halici, Serkan, Dr. rer. nat. (2007): *Molekulare Mechanismen der Interferenz von intrazellulären Salmonellen mit der Antigen-Präsentation von murinen Dendritischen Zellen*

Aichele, Diana, Dr. rer. nat. (2008): *Analysis of the function of human bacteridical/permeability-increasing protein (BPI) and of the expression of selected BPI-family members*

Braun, Tobias, Dr. med. (2008): *Charakterisierung Lipid-reaktiver T-Zell-Subpopulationen beim Menschen*

Braun, Joachim, Dr. med. (2008): *Untersuchungen zur Expression und Regulation zytotoxischer Effektormoleküle in Lymphozyten*

Groer, Gerhard, Dr. rer. nat. (2008): *Immunotagmine (IMTAGs)-Struktur, calciumabhängige Lipidbindung und Expression in Lymphozyten*

Henning, Dorothée, Dr. med. (2008): *Die entzündungshemmende Wirkung einer niedrigdosierten Strahlentherapie beinhaltet eine verminderte CCL20-Chemokin-Expression und Adhäsion von Granulozyten an Endothel*

Saake, Marc, Dr. med. (2008): *Analyse der Expression der Komponenten des Prostaglandinsystems bei der Mukoviszidose und der experimentellen Pseudomonas aeruginosa-Pneumonie*

Board Qualification

Lang, Roland, PD Dr. med. (2007): *Mikrobiologie, Virologie und Infektionsepidemiologie*

Institute of Virology – Clinical and Molecular Virology
Chair of Clinical Virology

Doctorate Theses

Gramberg, Thomas, Dr. rer. nat. (2007): *Analyse der Interaktion viraler Hüllproteine mit zellulären Anheftungsfaktoren*

Hochstein, Norbert, Dr. rer. nat. (2007): *Der epigenetische Status eines Transgenoms in Hamsterzellen*

Hülsmann, Peter, Dr. rer. nat. (2007): *RNA-Interferenz und das Suizidgen tBid als neue Ansätze gentherapeutischer Strategien gegen HIV-1*

Klinger, Patricia, Dr. rer. nat. (2007): *Rolle des UPS in der HIV-1-Virusassemblierung*

Marzi, Andrea, Dr. rer. nat. (2007): *Die Bedeutung zellulärer Anheftungsfaktoren für die Filovirus-Infektion*

Tschochner, Monika, Dr. rer. nat. (2007): *Korrelation von Replikationskapazität und Pathogenität zum Resistenzmuster von HIV-1-Varianten*

Wucherpfennig, Frank, Dr. rer. nat. (2007): *Transfer und Freisetzung von Episomen für die somatische Gentherapie durch einen Herpesvirus/Adenovirus-Hybridvektor*

Alberter, Barbara, Dr. rer. nat. (2008): *Die Epigenetik des Herpesvirus saimiri-Genoms*

Berndt, Anja, Dr. rer. nat. (2008): *Characterization of covalent and non-covalent interactions of the cellular ubiquitin-homologous protein SUMO with the major immediate-early transactivator IE2p86 of human cytomegalovirus*

Gack, Michaela , Dr. rer. nat. (2008): *Regulation of RIG-I-mediated anti-viral innate immunity*

Glanz, Anja, Dr. rer. nat. (2008): *Wechselwirkungen von StpC mit Signalwegen der T-Zell-Aktivierung*

Kaiser, Nina, Dr. rer. nat. (2008): *Selektion und Charakterisierung von pUL84-bindenden Peptid-Aptameren zur Hemmung der Cytomegalovirus-Replikation*

Kittan, Nicolai, Dr. med. (2008): *Native Immunabwehr plasmazytoider dendritischer Zellen (PDC) bei Patienten mit akuter retinaler Nekrose (ARN) durch Herpesviren*

Knöpfel, Stefanie, Dr. rer. nat. (2008): *Einfluss der Prozessivität der Reversen Transkriptase des humanen Immundefizienzvirus Typ I auf die G-zu-A Mutationsrate induziert durch APOBEC3-Proteine*

Silbermann, Katrin, Dr. rer. nat. (2008): *Antiapoptose durch das Onkoprotein Tax menschlicher T-Zell-Leukämieviren*

Tavalai, Nina, Dr. rer. nat. (2008): *Analysis of the role of the cellular subnuclear structure ND10 for human cytomegalovirus replication*

Habilitation

Metzner, Karin, PD Dr. med. (2007): *Genomic diversity and population dynamics of simian and human immunodeficiency viruses (SIV/HIV)*

Institute of Experimental and Clinical Pharmacology and Toxicology
Chair of Pharmacology and Toxicology

Doctorate Theses

Blaich, Anna, Dr. rer. nat. (2008): *Untersuchung der Rolle des Schrittmacherkanals HCN4 im Gehirn adulter Mäuse*

Erhardt, Annette, Dr. rer. nat. (2008): *Toleranzinduktion in der Leber nach T- und NKT-Zellaktivierung*

Hoesl, Evelyn, Dr. rer. nat. (2008): *Konditionelle Gendeletion im Reizleitungssystem der Maus*

Vogel, Eva-Maria, Dr. rer. nat. (2008): *Bedeutung der autonomen renalen Innervation für Entzündungsvorgänge bei experimentellen Nephritiden*

Institute of Experimental and Clinical Pharmacology and Toxicology
Chair of Clinical Pharmacology and Clinical Toxicology

Doctorate Theses

Gradhand, Ulrike, Dr. rer. nat. (2007): *Expression, Lokalisation und Regulation der ABC-Transporter Multidrug Resistance Protein 3 und Multidrug Resistance Protein 4 in der humanen Leber*

Neuwald, Sebastian, Dr. med. (2007): *Pharmakokinetische und pharmakodynamische Effekte von Etoricoxib und Valdecoxib im experimentellen Schmerzmodell*

Stadelmann, Alexander, Dr. med. (2007): *Interaktion von Geruch und Geschmack unter besonderer Berücksichtigung des Sättigungszustands*

Eberl, Sonja, Dr. rer. nat. (2008): *Die Inhibition des OATP1B3- und P-Glykoprotein-vermittelten Arzneimitteltransports: Untersuchungen zur Relevanz bei Arzneimittelinteraktionen*

Krajcik, Rastislav, Dr. rer. nat. (2008): *Funktionalisierte Kohlenstoffnanoröhren als neuartiges Transfektionsmittel für effizientes gene silencing in Rattenkardiomyozyten*

Seithel, Annick, Dr. rer. nat. (2008): *Der humane Aufnahmetransporter OATP1B1: Bedeutung für Arzneimittelinteraktionen und funktionelle Charakterisierung von Sequenzvariationen*

Board Qualifications "Klinische Pharmakologie"

Zolk, Oliver, Dr. med. (2007)
Bachmakov, Iouri, Dr. med. (2008)

Habilitation

Zolk, Oliver, PD Dr. med. (2007): *Bedeutung der humoralen Faktoren Endothelin-1 und Cardiotrophin-1 für die Entwicklung der Herzinsuffizienz*

Institute of Experimental and Clinical Pharmacology and Toxicology
Doerenkamp-Chair of Innovations in Animal and Consumer Protection

Doctorate Theses

Eichele, Karin, Dr. rer. nat. (2007): *Decisive role of cyclooxygenase-2 and lipocalin-type prostaglandin D synthase in R(+)-methanandamide- and chemotherapeutics-induced apoptosis of human cancer cells.*

Hille, Sandra, Dr. rer. nat. (2007): *Die Rolle von Caspasen bei der T-Zell-Aktivierung und der Pathogenese des Asthma*

Puljic, Ruzica, Dr. rer. nat. (2007): *Anti-Zytokin Strategien zur Therapie von COPD*

Amon, Annette, Dr. rer. nat. (2008): *Die Rolle des MAP-Kinase-Signalwegs bei der antientzündlichen Wirkung von Glucocorticoiden und PDE4-Inhibitoren*

Besz, Dominika, Dr. med. (2008): *Untersuchung der Zyklooxygenasehemmwirkungen von Naproxen: Kardioprotektion im Gegensatz zu gastrointestinaler Toxizität*

Institute of Human Genetics
Chair of Human Genetics

Doctorate Theses

Chavarria Soley, Gabriela, Dr. rer. nat. (2008): *Genome-wide identification and characterisation of well-defined genes involved in glaucoma and pterygioum corneae*

Lascorz Puertolas, Jesús, Dr. hum. biol. (2008): *Systematic association studies and functional characterization of positional and functional candidate genes for psoriatic arthritis and psoriasis vulgaris*

Institute of Forensic Medicine
Chair of Forensic Medicine

Doctorate Theses

Eckardt, Gerlinde, Dr. rer. biol. hum. (2008): *Quantifizierung von Betäubungsmitteln in Haaren – Praktische Untersuchungen zur Aufnahme von Betäubungsmitteln in Haare bei beruflich exponierten Personen im Vergleich zu Drogenkonsumenten*

Meier, Maria, Dr. med. (2008): *Entwicklung und Validierung eines Short Tandem Repeat Multiplex Systems für die Typisierung degradierter DNA-Proben*

Board Qualification

Bock, Horst, Dr. med. (2007): *Rechtsmedizin*

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

Doctorate Theses

Krückert, Kerstin, Dr. med. (2007): *Frühdiagnostik asbestbedingter Bronchialkarzinome mit Hilfe der low - dose Spiral-CT Wertigkeit einer 3 D-Software zur Detektion kleiner pulmonaler Rundherde in einem ehemals Asbest-exponierten Hochrisikokollektiv.*

Förster, Katrin, Dr. rer. nat. (2008): *Entwicklung und Anwendung analytischer Verfahren für ein Human-Biomonitoring von Naphtalin im Rahmen arbeits -und umweltmedizinischer Fragestellungen*

Jacobs, Stephanie Elisabeth, Dr. med. (2008): *Bestimmung der Herzfrequenzvariabilität mit dem Prototyp eines „stand-alone"-Plethysmographen: Validierung der implementierten Algorithmen mit einem „gold-standard".*

Korinth, Gintautas, Dr. med. (2008): *Vergleich von in-vivo- und in-vitro-Methoden zur Erfassung der dermalen Penetration von Arbeitsstoffen durch exzidierte Humanhaut und bei der Ratte am Beispiel von 2-Butoxyethanol und Toluol.*

Board Qualifications "Arbeitsmedizin"

Zöbelein, Petra, Dr. med. (2007)
Ochsmann, Elke, Dr. med. (2008)

Institute of Medical Physics
Chair of Medical Physics

Doctorate Theses

Henke , Maria, Dr. rer. biol. hum. (2008): *Multidimensionale adaptive Filterung zur Rauschreduktion in der Computertomographie: Vergleich und Kombination faltungs- und splinebasierter Verfahren*

Niebler, Christine, Dr. rer. biol. hum. (2008): *Vermessung und Korrektur des Misalignments robotergeführter C-Bogen-Systeme*

Reinhart, Christian, Dr. rer. biol. hum. (2008): *Bild- versus rohdatenbasierte Zwei-Spektren-Computertomographie*

Vollmar, Sabrina, Dr. rer. biol. hum. (2008): *Dosisreduktion in der weiblichen Brust bei Thorax CT*

Nikolaus-Fiebiger-Centre of Molecular Medicine
Chair of Experimental Medicine I
(Connective Tissue Research)

Doctorate Theses

Surmann-Schmitt, Cordula, Dr. rer. nat. (2007): *Struktur, Funktion und Expression von UCMA, einem neuen Knorpelspezifischen Protein*

Mühle, Christiane, Dr. rer. nat. (2008): *Molecular basis and characteristics of the polyclonal antibody response to exogenous coagulation factor VIII in patients with hemophilia A*

Nikolaus-Fiebiger-Centre of Molecular Medicine
Chair of Experimental Medicine II
(Molecular Oncology)

Doctorate Theses

Bauer, Katja, Dr. rer. nat. (2007): *Untersuchung molekularer Mechanismen der transendothelialen Migration von Tumorzellen: Bedeutung von Integrin ß3 und EVA1*

Stemmer, Volker, Dr. rer. nat. (2007): *Interaktion von Snail mit beta-Catenin und deren Bedeutung für den Wnt-Signalweg*

Wacker, Ingrid, Dr. rer. nat. (2007): *Activin B - ein Schlüsselmolekül in der zellulären Transformation infolge Inaktivierung des von Hippel-Lindau Tumorsuppressors*

Dehner, Manuel, Dr. rer.nat. (2008): *Identifizierung und funktionelle Charakterisierung von SGK1 als neues Zielgen der Wnt-Signaltransduktion*

Kohler, Eva Maria, Dr. rer. nat. (2008): *A general model that explains the complex pattern of biallelic APC mutations in colorectal carcinoma, duodenal and desmoid tumours*

Institute of Biomedicine of Aging
Chair of Internal Medicine - Geriatrics

Board Qualification

Singler, Katrin, Dr. med. (2007): *Innere Medizin und Endokrinologie und Diabetologie*

Additional Qualifications "Notfallmedizin"

Heppner, Hans-Jürgen, Dr. med. (2007)
Singler, Katrin, Dr. med. (2007)

Department of Orthopaedics in the Waldkrankenhaus
Chair of Orthopaedics and Orthopaedic Surgery

Doctorate Theses

Betz, Tobias Oliver, Dr. med. (2007): *Langzeituntersuchungen zur knöchernen Reaktion auf einen zementfreien Hüftendoprothesenschaft mittels CT-gestützter Osteodensitometrie*

Böhm, Roland Alexander, Dr. med. (2007): *Langzeitergebnisse mit der Wagner Metall-Metall Schalenprothese*

Forster, Silvia Irene Maria, Dr. med. (2007): *Morphologische Veränderungen des Tractus-iliotibialis und des Septum intermusculare femoris laterale bei Jungen mit Duchenne-Muskeldystrophie*

Kandemir, Bahadir, Dr. med. (2007): *Spätergebnisse knöcherner Eingriffe am Hüftgelenk des Zerebralparetischen Kindes Beschreibung der Behandlungsmethoden und Analyse der Ergebnisse von knöcherner Eingriffe, funktioneller*

Behandlung und Hilfsmittelversorgung von 73 Patienten

Nowak, Tobias Eckhard, Dr. med. (2007): *Computertomographie-gestützte Osteodensitometrie nach Implantation eines zementfreien Hüftendoprothesenschaftes - Untersuchungen 3 Jahre postoperativ -*

Peykan-Sepahi, Nilufar, Dr. med. (2007): *MRT-basierte Darstellung der Knorpelverteilung im Hüftgelenk bei Patienten nach sphärischer Hüftpfannenosteotomie nach WAGNER*

Vornlachner, Michael Paul, Dr. med. (2007): *Das Beschwerdebild nach Halswirbelsäulendistorsion Zeitliche Dynamik und Einflussfaktoren*

Pfitzner, Tilman, Dr. med. (2008): *Die operative Rekonstruktion der rupturierten Rotatorenmanschette - klinische, radiologische und magnetresonanztomographische Analyse*

Röhr, Markus, Dr. med. (2008): *Ergebnisse der operativen Therapie der juvenilen Knochenzyste unter Berücksichtigung der Rezidivrate*

Board Qualification

Müller, Lutz Arne, PD Dr. med. (2007): *Orthopädie und Unfallchirurgie*

Habilitation

Müller, Lutz Arne, PD Dr. med. (2007): *Die femorale und periacetabuläre Knochendichte nach Hüfttotalendoprothesen - Implantation: Validität der Methodik, Reproduzierbarkeit der Messung und in-vivo Langzeitergebnisse mittels CT-gestützter Osteodensitometrie*

Department of Orthopaedics in the Waldkrankenhaus
Division of Orthopaedic Rheumatology

Additional Qualification

Eichinger, Stephan, Dr. med. (2008): *Orthopädische Rheumatologie*

Habilitation

Carl, Hans-Dieter, PD Dr. med. (2007): *Untersuchungen zur Effizienz orthopädisch-rheumatologischer Interventionen*

Department of Medicine 1 – Gastroenterology, Lung Diseases and Endocrinology
Chair of Internal Medicine I

Doctorate Theses

Ackermann, Andreas, Dr. med. (2007): *Computergestützte Detektion unerwünschter Arzneimittelwirkungen auf der Basis von Laborwerten, Medikation und Diagnosen*

Asshoff, Gerald, Dr. med. (2007): *Oszillometrie versus Ösophagusdruckmessung zur Früherkennung einer Atemwegsobstruktion unter nasaler nCPAP-Überdruckbehandlung des obstruktiven Schlafapnoesyndroms*

Batz, Hans-Bernd, Dr. med. (2007): *Schlafbezogene Atmungsstörungen und diastolische Dysfunktion - Hat die nächtliche Beatmung bei Patienten mit schlafbezogener Atmungsstörung einen Effekt auf die diastolische linksventrikuläre Funktion des Herzens?*

Brückner-Schmutt, Kerstin, Dr. med. (2007): *Effekte einer continuous positive airway pressure-Therapie auf die sekundäre Insulinresistenz bei Patienten mit obstruktivem Schlafapnoe-Syndrom und Diabetes mellitus Typ 2*

Bölükbas, Servet, Dr. med. (2007): *Untersuchung zur Pharmakokinetik von Ceftazidim (Fortum i.v.(R)) bei Intensivpatienten mit akutem Nierenversagen unter kontinuierlicher venöser Hämofiltration (CVHF) und hämofiltrationsfreien Intervall*

Döltz, Stefanie, Dr. med. (2007): *Häufigkeit und Prognose von ambulant erworbenen Pneumonien 2002*

Döltz, Thomas, Dr. med. (2007): *Retrospektive Erfassung von Prädiktoren für das Überleben nach PEG-Anlage*

Frank, Michael, Dr. med. (2007): *Untersuchungen zur Induktion von Arousalreaktionen durch Variationen des Therapiedruckes während einer APAP-Therapie bei obstruktivem Schlafapnoe-Syndrom*

Freiin Marschall von Bieberstein, Kerstin, Dr. med. (2007): *Einführung eines Behandlungspfades für ambulant erworbene Pneumonie. Bedeutung für die Dauer der intravenösen und oralen Antibiose*

Karakurt, Zeynep, Dr. med. (2007): *Auswirkungen der Einführung eines klinischen Behandlungspfads für ambulant erworbene Pneumonie unter besonderer Berücksichtigung der Effekte auf die Wahl und Dauer der initialen Antibiotikatherapie und der Häufigkeit peroraler Sequenztherapie*

Kleinecke, Caroline, Dr. med. (2007): *Vaskularisationsmuster hepatozellulärer Karzinome in der dynamischen Kontrastmittelsonographie in Korrelation zum Goldstandard Histologie*

Ludwig, Rayk, Dr. med. (2007): *Identifikation von Helicobacter spezies in Leberbiopsaten ägyptischer Patienten mit chronischer Hepatitis C Infektion mit und ohne hepatozellulärem Karzinom*

Matthes, Kai, Dr. med. (2007): *Prospektive Evaluation von zusätzlichen praktischen Trainingskursen an einem Simulationsmodell (CompactEASIE) im Vergleich zur rein klinischen Ausbildung in endoskopischer Blutstillung - Ein Pilotprojekt an neun New Yorker Kliniken*

Neukirchner, Claudia, Dr. med. (2007): *Objektive und subjektive Effektivität einer oszillometrisch gesteuerten Auto-CPAP-Therapie des obstruktiven Schlafapnoe-Syndroms während der Therapieeinleitung im Schlaflabor*

Otto, Patrick, Dr. med. (2007): *Das Eosiniphile Kationische Protein im Serum als Aktivitätsparameter bei Morbus Crohn nach resektiver Operation*

Peter, Gisela, Dr. med. (2007): *Beeinflussung des Wachstumshepatozellulärer Karzinomzellen durch Inhibitoren der Angiogenese, der Histondeazetylase und zyklin-abhängiger Kinasen in vitro*

Premm, Wolfgang, Dr. med. (2007): *Untersuchungen zur mittleren Apnoedauer beim obstruktiven Schlafapnoesyndrom*

Rößner, Elke, Dr. med. (2007): *Diagnostische Bedeutung von Natürlichen Killer-Zellen in der Bronchoalveolären Lavage*

Seegara Heenen, Luisa, Dr. med. (2007): *Der Effekt von zusätzlichem Unterricht in einem Medizischen Trainings- und Prüfungszentrum im internistischen, chirurgischen und urologischen Blockpraktikum auf die Ergebenisse in Objektiven Strukturierten Klinischen Examina*

Steinebrunner, Niels, Dr. med. (2007): *Hepatische Transitzeit bei benignen und malignen Leberraumforderungen kontrastverstärkten Ultraschall*

Walter, Benjamin, Dr. med. (2007): *Mukosaprotektive Eigenschaften von Ghrelin bei durch Ischämie und Reperfusion verursachten Magenläsionen im Rattenmodell*

Wasmeier, Alexandra, Dr. med. (2007): *Eine prospektive Untersuchung zur Lebensqualität von Patienten einer internistischen Intensivstation im zeitlichen Verlauf unter Berücksichtigung des Alters*

Wiesnet, Johannes, Dr. med. (2007): *Europäisches Pilotprojekt: Prospektive Evaluation des Wertes von zusätzlichen intensivierten praktischen Trainingskursen an einem Simulationsmodell (ComacptEASIE(R)) im Vergleich zur herkömmlichen Ausbildung für die endoskopische Blutstillung*

Baumbach, Christina, Dr. med. (2008): *Hämodynamische Effektivität eine neuartigen Hämoclips im Vergleich zur Injektionstherapie bei der Versorgung von Blutungen im oberen Gastrointestinaltrakt*

Bermbach, Daniela, Dr. med. (2008): *Koagulopathien bei Intensivpatienten*

Busch, Ekaterina, Dr. med. (2008): *Klinische Bedeutung der lymphatischen Hyperplasie am unteren Gastrointestinaltrakt*

Dorlaque, Laure, Dr. med. dent. (2008): *Die Bedeutung der Genexpression von Matrix-Metalloproteinasen bei metastasierten kolorektalen Karzinomen*

Fritsche, Berit, Dr. med. (2008): *Nachsorgeverhalten nach Resektion relevanter (<10mm) kolorektaler Adenome*

Geyer, Dietmar, Dr. med. (2008): *Evaluierung klinischer und laborchemischer Parameter sowie Befunden der apparativen Diagnostik bezüglich ihrer Aussagekraft für die Etablierung*

der Diagnose gastrointestinal vermittelte Allergie

Grimm, Verena, Dr. med. (2008): *Untersuchungen zur Mortalität bei akuten Blutungen am oberen Gastrointestinaltrakt*

Herbst, Alexandra, Dr. med. (2008): *Analyse der prädiktiven und prognostischen Faktoren beim kleinzelligen Bronchialkarzinom unter palliativer Erstlinien-Therapie mit ACE - eine retrospektive Analyse von 16 Jahren*

Hiemer, Eva, Dr. med. (2008): *Untersuchungen zur Bedeutung von Spirometrie und Bodyplethysmographie bei der Diagnostik des obstruktiven Schlafapnoe-Syndroms*

Kimpel, Silke, Dr. med. (2008): *Langzeitverlauf der Methylhistamin- und Leukotrien-Ausscheidung im Urin bei Morbus Crohn Patienten unter Medikation mit Omega-3-Fettsäuren im Vergleich mit Mastozytose Patienten*

Kollmann, Sylvia, Dr. med. (2008): *Untersuchung von Geschmack und Ernährung bei Patienten mit Morbus Crohn*

Korn, Corinna, Dr. med. dent. (2008): *Komplikationen der endoskopisch-retrograten Cholangio-pankreatikographie (ERCP) von 1990-2000 in einem norddeutschen Krankenhaus der Regelversorgung*

Kölln, Sandra, Dr. med. (2008): *Untersuchungen der Adipozytokine Leptin und Adiponektin, sowie Resistin bei Zystischer Fibrose*

Lampel, Emilia, Dr. med. (2008): *Biochemische Evaluation des Effektes von Pankreasenzymen auf die Allergenstruktur von wichtigen Nahrungsmittelallergenen*

Lechler, Annette, Dr. med. (2008): *Toxizität/ Nebenwirkungen der ACE-Chemotherapie beim kleinzelligen Bronchialkarzinom - eine retrospektive Analyse über 16 Jahre*

Leu, Thorsten, Dr. med. (2008): *Beeinflussung von Apoptose, Proliferation und Differenzierungs-Mustern durch Zebularine und SAHA in Pankreaskarzinom-Modellen*

Mösch, Christian, Dr. med. (2008): *Prognostische Bedeutung der Mikrosatelliteninstabilität (MSI) bei metastasierten sporadischehn kolorektalen Karzinomen unter palliativer Chemotherapie*

Nürnberger, Andreas, Dr. med. (2008): *Lokale peristomale Infektion nach PEG-Anlage - eine prospektive Studie zur Erfassung von Risikofaktoren*

Rienecker, Helmut, Dr. med. (2008): *Protektiver Effekt von H. pylori auf die Entstehung einer gastro-intestinal vermittelten Allergie*

Scheibner, Claudia, Dr. med. (2008): *Pharmakologische Interventionen bei experimenteller Entzündung des Darmes im Mausmodell*

Stegemann, Tanja, Dr. med. (2008): *Die Auswirkungen von Alkohol- und Nikotinabusus auf die Rate von unerwünschten Arzneimittelwirkungen während der stationären Behandlung*

Vogler, Marcus, Dr. med. (2008): *Entwicklung metachroner kolorektaler Karzinome nach Polypektomie: Retrospektive Analyse klinikopathologischer- und Verlaufsdaten*

Zimmermann, Annette, Dr. med. (2008): *Medikamentöse Kombinationstherapie des HCC mit Biomodulatoren an einem syngenen Hepatommodell*

Board Qualifications "Innere Medizin"

Geise, Arnim, Dr. med. (2007)
Krauss, Norbert, Dr. med. (2007)
Ganslmayer, Marion, Dr. med. (2008)
Zopf, Steffen, Dr. med. (2008)

Additional Qualifications

Bernatik, Thomas, PD Dr. med. (2007): *Gastroenterologie*

Boxberger, Frank, Dr. med. (2007): *Medikamentöse Tumortherapie*

Brückl, Wolfgang, PD Dr. med. (2007): *Pneumonologie*

Fuchs, Florian, Dr. med. (2007): *Pneumonologie*

Riel, Rosina, Dr. med. (2007): *Endokrinologie*

Brückl, Wolfgang, PD Dr. med. (2008): Schlafmedizin

Geise, Arnim, Dr. med. (2008): *Pneumonologie*

Department of Medicine 2 – Cardiology and Angiology
Chair of Internal Medicine II

Doctorate Theses

Becker, Clemens Franz Maria, Dr. med. (2007): *Dreidimensionale Echokardiographie: Algorithmenvergleich der „average - rotation - method" und Scheibchensummationsmethode in der linksventrikulären Volumetrie aneurysmatisch nachempfundener pulsierender Herzmodelle*

Derlien, Hans-Joachim, Dr. med. (2007): *Klinische Evaluation der nichtinvasiven Darstellung von Koronararterien und aorto-koronaren Bypassgefäßen mittels kontrastverstärktem Mehrzeilen-Spiral-CT und retrospektivem EKG-Gating*

Frimmel, Sonja Alexandra Frizzi, Dr. med. (2007): *Langzeitverlauf der Progression koronarer Kalzifizierungen*

Marquart, Andreas, Dr. med. (2007): *Überprüfung der Abbildungsgenauigkeit bei der Koronararteriendarstellung durch 16-Zeilen-Spiral-Computertomographie mittels Vergleich zur quantitativen Koronarangiographie*

Ruthrof, Susanne Margarete Rose, Dr. med. (2008): *Interventionelle Therapie und 30-Tage-Prognose des akuten ST-Streckenelevations-Myokardinfarktes (STEMI) bei Frauen im Vergleich zu männlichen Patienten -Erfahrungen an der Universitätsklinik Erlangen 1999-2005-*

Board Qualifications

von Erffa, Johannes, Dr. med. (2007): *Innere Medizin und Kardiologie*

Zimmermann, Stefan, Dr. med. (2007): *Innere Medizin*

Schneider, Reinhard, Dr. med. (2008): *Innere Medizin und Kardiologie*

Wolf, Tobias, Dr. med. (2008): *Innere Medizin und Kardiologie*

Additional Qualifications

Ropers, Dieter, PD Dr. med. (2007): *Intensivmedizin*

Schneider, Reinhard, Dr. med. (2007): *Sportmedizin*

Achenbach, Stephan, Prof. Dr. med. (2008): *Intensivmedizin*

Garlichs, Christoph, Prof. Dr. med. (2008): *Intensivmedizin*

Stumpf, Christian, PD Dr. med. (2008): *Intensivmedizin*

Department of Medicine 3 – Rheumatology and Immunology
Chair of Internal Medicine III

Doctorate Theses

Franz, Sandra, Dr. rer. nat. (2007): *Fingerprinting Apoptotic Cell Surfaces: Alterations of Glycocalyx and Membrane Composition*

Munoz, Luis, Dr. med. (2007): *The influence on the immunomodulatory effects of dying and dead cells of Annexin V*

Neubert, Kirsten, Dr. rer. nat. (2007): *Eliminierung autoreaktiver Plasmazellen durch Proteasominhibition in Lupus-Mausmodellen*

Barbara, Fürnrohr, Dr. rer. nat. (2008): *Hitzeschockproteine bei der Pathogenede des systemischen Lupus erythematodes*

Department of Medicine 3 – Rheumatology and Immunology
Division of Molecular Immunology

Doctorate Theses

Herrmann, Kai-Uwe, Dr. rer. nat. (2007): *Untersuchungen zur Transport- und Signalkompetenz von schweren IgM-Ketten*

Vettermann, Christian, Dr. rer. nat. (2007): *Funktion der Unique-Region von Lambda-5 für die Entwicklung von B-Lymphozyten*

Department of Medicine 4 – Nephrology and Hypertensiology
Chair of Internal Medicine IV

Doctorate Theses

Friedrich, Chris, Dr. med. (2007): *Antiproteinurische Wirksamkeit von Angiotensin-Rezeptor-*

Blockern bei diabetischen und nicht-diabetischen Patienten: Systematischer Review mit Meta-Analyse
Handtrack, Claudia, Dr. med. (2007): *Einfluss des Angiotensinogen-Genotyps auf Hypertonie und Nephrosklerose in der Maus*
Porstner, Martin, Dr. med. (2007): *Plasminogen-Aktivierung und die Nierenschädigung beim Diabetes mellitus*
Segitz, Verena, Dr. med. (2007): *Induktion von CTGF durch Aldosteron in Mesangiumzellen der Ratte*
Özcan, Zehra, Dr. med. (2007): *Einfluss von Integrin alpha 8 auf die Zytoskelettorganisation*
Lechler, Philipp, Dr. med. (2008): *Expression des antiapoptotischen Faktors Survivin in der Niere*
Oehmer, Sebastian, Dr. med. (2008): *Nachweis u. Untersuchung erythropoietin-bedingter Änderung auf den Vasotonus der Unterarmarterie bei Hypertertonikern und Normotonikern*
Ott, Christian, Dr. med. (2008): *Einfluss von Veränderungen des Zytoskeletts auf die CTGF Expression*
Schafflhuber, Markus, Dr. med. (2008): *Bedeutung extrazellulärer Matrix für die Speicherung von Natrium in osmotisch inaktiver Form*
Schneider, Andreas, Dr. med. (2008): *Spironolacton in nicht bludruckwirksamer Dosierung reduziert die linksventrikuläre Masse*

Board Qualifications

Forster, Christian, Dr. med. (2007): *Innere Medizin*
Griesbach, Daniela, Dr. med. (2007): *Innere Medizin und Nephrologie*
Heider, Annette, Dr. med. (2007): *Innere Medizin und Nephrologie*
Jacobi, Johannes, Dr. med. (2007): *Innere Medizin und Nephrologie*
Jank, Sabine, Dr. med. (2007): *Innere Medizin und Nephrologie*
Kueri, Nadia, Dr. med. (2007): *Innere Medizin*
Radtke, Steffen, Dr. med (2007): *Innere Medizin und Nephrologie*
Raff, Ulrike, Dr. med. (2007): *Innere Medizin*
Stein, Holger, Dr. med. (2007): *Innere Medizin und Nephrologie*
Zapf, Arnd-Oliver, Dr. med. (2007): *Innere Medizin und Nephrologie*
Zeltner, Raoul, Dr. med. (2007): *Innere Medizin und Nephrologie*
Kraß, Christine, Dr. med. (2008): *Innere Medizin*
Schneider, Markus, Dr. med. (2008): *Innere Medizin*
Seitz, Randolf, Dr. med. (2008): *Innere Medizin*

Additional Qualification

Willam, Carsten, PD Dr. med. (2008): *Intensivmedizin*

Habilitations

Hohenstein, Bernd, PD Dr. med. (2008): *Modulators of microvascular endothelial injury and repair in the kidney*
Jacobi, Johannes, PD Dr. med. (2008): *Rolle von ADMA bei entzündlichen Gefäßschäden*
Lindner, Tom Herbert, Dr. med. (2008): *Typ-2 Diabetes und arterielle Hypertonie: ein gemeinsamer genetischer Lokus auf Chromosom 1* (Erweiterung der Lehrbefähigung Innere Medizin)

Department of Medicine 5 – Haematology and Oncology
Chair of Haematology and Oncology

Doctorate Theses

Fierl, Andrea Marita, Dr. med. dent. (2008): *Hemmung des Ras-Raf-MAPK-Signalweges beim Multiplen Myelom durch neuartige spezifische Inhibitoren*
Rolbetzki, Stefan, Dr. med. (2008): *Assoziation von MHC Klasse II und CTLA-4 Polymorphismen mit Wespengiftallergie*
Unger, Martina, Dr. med. (2008): *Die Bedeutung der Biographie für die Ausbildung salutogener Ressourcen im Umgang mit chronischer Krankheit. Eine biographie-analytische und fallvergleichende Untersuchung*
Völkl, Simon, Dr. rer. nat. (2008): *Immunregulatorische Funktion humaner TCRab+ CD4- CD8- T-Lymphozyten*

Board Qualifications "Innere Medizin"

Kallert, Stefan, Dr. med. (2007)
Ferstl, Barbara, Dr. med. (2008)

Department of Nuclear Medicine
Chair of Clinical Nuclear Medicine

Doctorate Theses

Ketelsen, Dominik, Dr. med. (2007): *Arten der Informationsvermittlung im radiologisch-anatomischen Studentenunterricht - Auswirkungen auf die Leistungen der Studenten*
Knickenberg, Ines, Dr. med. (2007): *www.HNO-Rad.de Eine interdisziplinäre interaktive Fallsammlung in HNO-Radiologie im Internet*
Spörl, Markus, Dr. med. (2007): *PEDBONE: Online-Referenzdatenbank für Standardröntgenaufnahmen in der Pädiatrie*
Bläser, Daniel, Dr. med. (2008): *In vitro Studien zur Signaltransduktion der Aufnahme von 2 [18F]Fluor-2-desoxy-D-glucose und [131I]Jodid in die Schilddrüse*
Wolz, Gabriele, Dr. med. (2008): *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 Qualification

Reiermann, Jung, PD Dr. med. (2007): *Nuklearmedizin*

Habilitation

Prante, Olaf, PD Dr. rer. nat. (2008): *Entwicklung Subtyp-selektiver Dopamin-D4-Radioliganden für die Positronen-Emissions-Tomographie*

Institute of Radiology
Chair of Diagnostic Radiology

Doctorate Theses

Brand, Martin, Dr. med. (2008): *Dosisreduktion in der pädiatrischen Computertomographie unter Anwendung einer Dosisautomatik*
Kerl, Josef, Dr. med. (2008): *Split-Bolus Contrast Medium Injection with Diluted Contrast Material for Visualization of The Right Heart at Coronary CT Angiography*
Klemm, Christine, Dr. med. (2008): *Stereotaktische Vakuumbiopsie - Erfolg, Korrelation von Histologie und BI-RADS™-Klassifikation, Patientenakzeptanz*
Runck, Frank, Dr. med. (2008): *Magnetic resonance imaging: Influence of imaging modality and post processing on measurement*
Rüdel, Christina, Dr. med. (2008): *Mehrzeilen-Spiral CT (MSCT) der Halsregion: Dosisoptimierung unter Berücksichtigung der Bildqualität*
Spörl, Markus, Dr. med. (2008): *PEDBONE: Online-Referenzdatenbank für Standardröntgenaufnahmen in der Pädiatrie*

Board Qualifications "Diagnostische Radiologie"

Anders, Katharina, Dr. med. (2008)
Küfner, Michael, Dr. med. (2008)
Radkow, Tanja, Dr. med. (2008)

Habilitations

Janka, Rolf, PD Dr. med. (2007): *Magnetresonanzangiographie der Becken- und Beingefäße: Untersuchungstechnik und klinische Bewertung*
Engelhard, Karl, PD Dr. (2008): *Wertigkeit der Magnetresonanz-Tomographie in der Primärdiagnostik und der Stadieneinteilung des Prostatakarzinoms*

Institute of Radiology
Division of Neuroradiology

Doctorate Theses

Thek-Ling , Eddy, Dr. med. (2007): *Diffusionsgewichtete MRT in der Akutphase des experimen-*

tellen generalisierten Status epilepticus. Prädiktion von neuronalem Zelluntergang

Okorn, Christine, Dr. med. (2008): *Effekte des AT1-Rezeptor-Blockers Candesartan auf den zerebralen Blutfluß, Infarktgröße und neurologischen Status bei fokaler zerebraler Ischämie. Experimentelle Untersuchungen am Tiermodell*

Additional Qualifications "Röntgendiagnostik"

Gölitz, Philipp, Dr. med. (2007)
Schulz-Heise, Susanne, Dr. med. (2007)
Engelhorn, Tobias, PD Dr. med. (2008)
Kloska, Stephan, PD Dr. med. (2008)
Richter, Gregor, Dr. med. (2008)

Habilitation

Engelhorn, Tobias, PD Dr. med. (2007): *Neue Therapieansätze beim Schlaganfall. Pathophysiologische und magnetresonanztomographische Untersuchungen am tierexperimentellen Ischämiemodell*

Department of Surgery
Chair of Surgery

Doctorate Theses

Klug, Eva Maria, Dr. med. (2007): *Effizienz und Tolerabilität der Hämorrhoidopexie nach Longo*

Melling, Nathaniel Timon, Dr. med. (2007): *Dreidimensionale Ganganalyse vor und nach Anschlussheilbehandlung bei hüftendoprothetisch versorgten Patienten*

Pross, Annette, Dr. med. (2007): *Die volare Plattenosteosynthese als Standardverfahren bei handgelenksnahen Frakturen Ergebnisse am Klinikum Bayreuth*

Richter, Norbert Rudolf, Dr. med. (2007): *Die Operation nach Graner II zur Therapie der Lunatumnekrose*

Schürger, Irina-Doris, Dr. med. (2007): *Pseudarthrosenbehandlung durch extrakorporale Stoßwellentherapie (ESWT) - Klinische Ergebnisse -*

Ziegler, Christian Björn, Dr. med. (2007): *Ein Vergleich verschiedener Rekonstruktionsmethoden nach Fingerkuppenamputationen bezüglich Sensibilität, Funktionalität und kosmetischem Ergebnis*

Bialecki, Diana, Dr. med. (2008): *Prä- und posttherapeutische Schätzung der Prognose bei Resektion kolorektaler Lebermetastasen am Krankengut der Chirurgischen Klinik am Universitätsklinikum Erlangen im Zeitraum 1995-2006*

Decker, Martin Georg, Dr. med. (2008): *Der Einfluss der hyperthermen intraperitonealen Chemoperfusion (HIPEC) auf die Heilung kolorektaler Anastomosen im Tiermodell*

Engert, Alexandra Barbara Elisabeth, Dr. med. (2008): *Gastroplastik nach Mason und Law: Eine retrospektive Verlaufsbeobachtung an 27 operierten, übergewichtigen Patientinnen*

Gugger, Christine Yoko, Dr. med. (2008): *Narbenhernienentstehung nach Laparotomie Evaluation der Tensiometrie und weiterer potenzieller Prognosefaktoren*

Langenbach, Andreas, Dr. med. (2008): *Immunhistochemische und molekulargenetische Untersuchungen von Mannose-bindendem Lektin (MBL) in gesundem und entzündlich verändertem Darmgewebe bei Morbus Crohn*

Perrakis, Aristotelis, Dr. med. (2008): *Integrierte Operationssysteme in der minimal invasiven Chirurgie - Bedeutung der Sprachsteuerung*

Rosenbauer, Siegfried Ulf, Dr. med. (2008): *Chirurgische Therapie des Rektumprolaps an der Frankenwaldklinik Kronach von 1999 bis 2004*

Spiegel, Astrid, Dr. med. (2008): *Bedeutung der Lymphangiogenese bei der Lymphknotenmetastasierung des Kolonkarzinoms*

Votteler, Birgit, Dr. med. (2008): *Chronische Pankreatitis und Duodenumerhaltende Pankreaskopfresektion an der Chirurgischen Klinik der Friedrich-Alexander-Universität Erlangen-Nürnberg: Operatives Risiko und Follow up*

Wanninger, Sebastian, Dr. med. (2008): *Evaluation des postoperativen Verlaufs bei parastomalen Hernien - eine Analayse des Patientenguts der Chirurgischen Klinik des Universitätsklinikums Erlangen*

Wetzler, Dirk-Andreas, Dr. med. (2008): *Mittelfristige Ergebnisse nach vorderer Kreuzbandersatzplastik mit dem mittleren Patellarsehnendrittel als bone-tendon-bone-Transplantat unter besonderer Berücksichtigung des Operationszeitpunktes*

Yildirim, Ümit, Dr. med. (2008): *Mammakarzinom beim Mann Retrospektive Analyse des Patientengutes des Klinikums Nürnberg-Nord 1988-2003*

Zimmermann, Patrick, Dr. med. (2008): *Risikoabschätzung für septische Komplikationen nach großen abdominalchirurgischen Eingriffen anhand der Zytokine IL-6 und TNF-a*

Board Qualifications

Dürsch, Markus, Dr. med. (2007): *Chiurgie*
Förtsch, Thomas, Dr. med. (2007): *Chirurgie*
Schildberg, Claus, Dr. med. (2007): *Chirurgie*
Croner, Roland, PD Dr. med. (2008): *Gefäßchirurgie*
Herrmann, Olaf, Dr. med. (2008): *Gefäßchirurgie*
Hoffmann, Martin, Dr. med. (2008): *Chirurgie*

Department of Surgery
Division of Pediatric Surgery

Doctorate Theses

Kolbeck, Michael, Dr. med. (2007): *Prä- und postpubertäre Teratome und Keimzelltumore mit Teratom-Anteilen männlicher Patienten. 221 Fälle (1969–2007) und Literaturübersicht*

Pfrang, Sven, Dr. med. (2008): *Besonderheiten des Morbus Crohn im Kindes- und Jugendalter aus kinderchirurgischer Sicht. Erlanger Krankengut 1987–2005*

Schöll, Petra Hannelore, Dr. med. (2008): *Laparoskopische und konventionelle Appendektomie in der Kinderchirurgie. Ein retrospektiver Vergleich (Erlanger Patienten 2000–2004)*

Board Qualification

Knorr, Christian, Dr. med. (2007): *Chirurgie*

Department of Surgery
Division of Trauma Surgery

Doctorate Theses

Bogsch, Heike, Dr. med. (2007): *Nichtoperative Behandlung von Verletzungen der Brust- und Lendenwirbelsäule*

Fischer, Stefan Erwin, Dr. med. (2007): *Die winkelstabile Plattenosteosynthese bei Mehrfragmentfrakturen und Pseudarthrosen der Klavikula*

Keller, Kristin, Dr. med. (2007): *Prospektiv randomisierte Studie zur Untersuchung der Auswirkung des Wunddrainagesystems auf die Entstehung eine postoperativen Seroms in der Hüftendoprothetik*

Kolvenbach, Carl Paul, Dr. med. (2007): *Retrospektive Untersuchung nach operativer Korrektur des Hallux valgus durch subkapitale Metatarsalosteotomie nach Stoffella*

Schindler, Andreas Christoph, Dr. med. (2007): *Der internationale militärisch-medizinische Einsatz am Beispiel des Schiffsarztes von heute*

Grimm, Andreas Hilmar, Dr. med. (2008): *Biomechanische Push-out-Überprüfung der Osseointegration von laserstrukturierten TiA16V4-Titan-Endoprothesenoberflächen*

Haferkamp, Ines, Dr. med. (2008): *Ganganalytische Funktionsprüfungen nach Hüftendoprothesen - Implantation im Verlauf eines halben Jahres*

Board Qualifications "Orthopädie und Unfallchirurgie"

Blanke, Matthias, Dr. med. (2007)
Gusinde, Johannes, Dr. med. (2007)

Additional Qualifications

Brem, Matthias, Dr. med. (2007): *Sportmedizin*
Gelse, Kolja, Dr. med. (2007): *Sportmedizin*
Müller, Olaf, Dr. med. (2007): *Spezielle Unfallchirurgie*
Blanke, Matthias, Dr. med. (2008): *Manuelle Medizin/Chirotherapie*

Olk, Alexander, Dr. med. (2008): *Spezielle Unfallchirurgie*
Olk, Alexander, Dr. med. (2008): *Ärztliches Qualitätsmanagement*
Schulz-Drost, Stefan, Dr. med. (2008): *Notfallmedizin*

Habilitation

Schöffl, Volker, PD Dr. med. (2007): *Sportartspezifische Verletzungen der Hand und Finger im Klettersport*

Department of Surgery
Division of Transfusion Medicine and Haemostaseology

Doctorate Theses

Frank, Maren, Dr. med. dent. (2007): *Diagnosestatistik für Empfänger von Plasmaderivaten aus dem Blutdepot der Transfusionsmedizinischen und Hämostaseologischen Abteilung des Universitätsklinikums Erlangen*
Friedrich, Iris, Dr. med. (2007): *Ist es nicht höchste Zeit, die Blutspender gegen Hepatitis B zu impfen?*
Hendelmeier, Martin, Dr. med. (2007): *Gewinnung CD14-positiver Zellen und Rekrutierung monozytärer Subpopulationen durch Apherese*
Strobel, Julian, Dr. med. (2007): *Einfluss von Gammastrahlung auf die Gerinnungsaktivierung in Gefrorenem Frischplasma*
Helmer-Krex, Martina, Dr. med. (2008): *Der Einfluss der Veränderung des Azetat- und Zitratanteils auf die in-vitro Qualität von in additiver Lösung gelagerten Thrombozytapheresekonzentraten*
König, Julia, Dr. med. (2008): *Die Wirkung der Antikoagulation von Proben auf die Messung von zirkulierenden Wachstumsfaktoren, die aus Thrombozyten freigesetzt werden*
Wintzheimer, Simone, Dr. med. (2008): *In-vitro-Qualitätskontrollen von mit verschiedenen Methoden leukozytendepletierten und teilweise mit 30 Gray bestrahlten Erythrozytenkonzentraten*

Additional Qualifications

Achenbach, Susanne, Dr. med. (2008): *Hämostaseologie*
Ringwald, Jürgen, PD Dr. med. (2008): *Ärztliches Qualitätsmanagement*

Department of Plastic and Hand Surgery

Doctorate Theses

Brockmann, Silke, Dr. med. (2007): *Vergleichende Betrachtung des distal gestielten Suralis- und Peroneuslappens zur Rekonstruktion des distalen Unterschenkels und Fußes*
Cevikel, Ufuk, Dr. med. (2007): *Die stadienabhängige Expression von TGFß1-spezifischen Signalproteinen beim Morbus Dupuytren – Eine immunhistochemische Studie an Resektionspräparaten*
Euler, Simon, Dr. med. (2007): *Früh- und Spätangiogenetische Ereignisse der Gefäßinduktion, -adaptation und –reifung in einem Isolationskammermodell durch den Einsatz einer arteriovenösen Gefäßschleife*
Heidner, Kristina, Dr. med. (2007): *Osteoblastentransplantation in axial prävaskularisierte Hartmatrizes: Untersuchungen im Modell der arterio-venösen Gefäßschleife*
Lippert, Marion, Dr. med. (2007): *Zur Effektivität der Keratinozytentransplantation bei der Behandlung von Brandwunden, im Vergleich zur Spalthauttransplantation – eine Metaanalyse*
Konzi, Melanie, Dr. med. (2008): *Evaluation von Wirkung und Effizienz verschiedener Transplantationstechniken autolog und allogen gewonnener Keratinozyten bei chronischen, therapierefraktären Wunden unterschiedlicher Genese: Eine Metaanalyse*
Lanczak, Johanna, Dr. med. (2008): *Aktivierung des Jak1-Stat1-Cross-Talks hzur Blockade des profibrotischen TGFß1-Signalweges – Adenoviral codiertes IFNy agiert via Überexpression von Smad 7*

Board Qualifications "Plastische und Ästhetische Chirurgie"

Kneser, Ulrich, Dr. med. (2007)
Loos, Bernd, Dr. med. (2007)
Dragu, Adrian, Dr. med. (2008)
Polykandriotis, Elias, Dr. med. (2008)

Additional Qualification

Bach, Alexander, PD Dr. med. (2007): *Handchirurgie*

Habilitation

Kneser, Ulrich, PD Dr. med. (2008): *Tissue Engineering von Knochen: von der zellbesiedelten Hartmatrix zum axial vaskularisierten bioartifiziellen Knochenhgewebe*

Department of Cardiac Surgery
Chair of Cardiac Surgery

Doctorate Theses

Heckel, Matthias Karl, Dr. med. (2008): *Frühpostinterventionelle Stentkomplikationen und operative Myokardrevaskularisation bei koronarer Herzerkrankung - eine Situationsanalyse unter Berücksichtigung der aktuellen Versorgungsleitlinien*
Helm, Stephanie Nadine, Dr. med. (2008): *Die Rolle des Chemokinrezeptors CCR 7 bei der Pathogenese der Transplantatarteriosklerose*

Department of Urology
Chair of Urology

Doctorate Theses

Strasser, Hans, Dr. med. (2007): *DNA double-strand break induction and repair in irradiated lymphoblastoid, fibroblast cell lines and white blood cells from ATM, NBS and radiosensitive patients*
Bogner, geb. Goeb, Katja, Dr. med. (2008): *MRI-Spectroscopy in screening for prostate cancer*
Landsmann, Dr. med. (2008): *Treatment of advanced transitional cell carcinoma of the bladder (TCC) by irinotecan in an experimental animal model*

Board Qualifications "Urologie"

Rith, Torsten, Dr. med. (2008)
Strasser, Hans, Dr. med. (2008)

Additional Qualifications "Medikamentöse Tumortherapie"

Krause, Frens Steffen, PD Dr. med (2008)
Walter, Bernhard, Dr. med. (2008)

Habilitation

Zugor, Vahudin, PD Dr. med (2008): *Solide renale Raumforderungen: Therapie, Klinik und Prognose unter besonderer Berücksichtigung des Kindes- und Jugendalters*

Department of Anaesthesiology
Chair of Anaesthesiology

Doctorate Theses

Donhauser, Andreas, Dr. med. (2007): *Simulation eines Mehrwellenpulsoximeters zur Bestimmung der technischen Spezifikationen für eine nicht-invasive Messung der Carboxyhämoglobinfraktion*
Frötsch, Katrin, Dr. med. (2007): *Renale Nebenwirkungen von Paracetamol oder Parecoxib nach orthopädischen Operationen bei älteren Patienten*
Herrndobler, Franz, Dr. med. (2007): *Modulation der kortikalen Schmerzverarbeitung durch Cyclooxygenase-Hemmung in einem UV-B induzierten Hyperalgesiemodell: eine funktionelle Kernspintomographie-Studie*
Koch, Yvonne, Dr. med. (2007): *In vitro Untersuchung der Auswirkungen von neuen Volumenersatzmitteln auf die Gerinnung*
Meyer, Verena, Dr. med. (2007): *Zuverlässigkeit von Pulsoximetern der dritten und vierten*

Generation bei raschen Änderungen von Herzfrequenz und Sauerstoffsättigung während der Elektrokrampftherapie

Reindl, Michael, Dr. med. (2007): *Die Ärztliche Übergabe als wichtige Schnittstelle zwischen Intensivstation und Normalstation*

Singler, Boris, Dr. med. (2007): *Modulation der Remifentanil-induzierten Hyperalgesie durch Propofol in einem experimentellen Schmerzmodell am Menschen*

Sittl, Ruth, Dr. med. (2007): *Modulation der Remifentanil-induzierten Analgesie und Hyperalgesie durch Parecoxib in einem experimentellen Schmerzmodell am Menschen*

Wick, Stefanie, Dr. med. (2007): *Studie zur Erfassung der Anschlagszeit und Dauer einer neuromuskulären Blockade durch Rocuronium bei Patienten mit Duchenne Muskeldystrophie*

Arlt, Verena, Dr. med. (2008): *Wirkungsprofil des Muskelrelaxans Mivacurium bei Patienten mit Muskeldystrophie Typ Duchenne*

Feuchter, Sonja, Dr. med. (2008): *Wirksamkeit und Verträglichkeit von transdermalem Buprenorphin bei einer Applikationsdauer von 4 Tagen im Vergleich zu 3 Tagen*

Göhring, Markus, Dr. med. (2008): *Effekte einer oralen Gabe von Pregabalin und Aprepitant auf Schmerz und zentrale Sensibilisierung in einem experimentellen Schmerzmodell beim Menschen*

Günther, Werner, Dr. med. (2008): *Supra-additive Effekte von Tramadol und Paracetamol in einem Schmerzmodell am Menschen*

Heinl, Kathrin, Dr. med. (2008): *Einfluss einer multimodalen Gruppentherapie auf Medikamentenverhalten und Symptomatik bei chronischen Kopfschmerzpatienten*

Körber, Nicole, Dr. med. (2008): *Unterschiedliche Profile von Analgesie und Antihyperalgesie nach Buprenorphin in einem menschlichen Schmerzmodell*

Leuthold, Christian, Dr. med. (2008): *Entwicklung eines neuen Tiermodells für Reanimation bei akutem Myocardinfarkt und Evaluation der Hämodynamik nach Wiederkehr des Spontankreislaufes am Hausschwein*

Plettke, Regina, Dr. med. (2008): *Pharmakodynamische Modellbildung anästhesieassoziierter Veränderungen quantitativer EEG-Variablen während Sevofluranapplikation bei der Ratte*

Priller, Michael, Dr. med. (2008): *Pharmakodynamische Modellbildung anästhesieassoziierter Veränderungen quantitativer EEG-Variablen während Isofluranapplikation bei der Ratte*

Radünz, Sonia, Dr. med. (2008): *Totale intravenöse Anästhesie mit Fospropofol (Aquavan Injection) - einem wasserlöslichen Prodrug von Propofol - während koronarchirurgischer Operationen*

Schulte, Klaus, Dr. med. (2008): *Klinische Anwendungsbeobachtung zum Vergleich der postoperativen Schmerztherapie nach endoprothetischer Versorgung des Kniegelenkes mit Patienten kontrollierter Periduralanalgesie versus intravenöser/peroraler Schmerztherapie*

Wilderer, Jürgen, Dr. med. (2008): *Diskriminanzanalyse des spontanen und evozierten EEG zur Unterscheidung und Vorhersage verschiedener klinischer Narkosestadien*

Zapke, Tobias, Dr. med. (2008): *Alcuronium und Atracurium im Vergleich hinsichtlich ihrer lytischen Wirkung auf Succinylcholin-induzierte Muskelfaszikulationen*

Board Qualifications "Anästhesiologie"

Klein, Carsten, Dr. med. (2007)
Lang, Anna-Katharina, Dr. med. (2007)
Schwalb, Rebecca, Dr. med. (2007)
Strube, Marion, Dr. med. (2007)
Tzabazis, Alexander, Dr. med. (2007)
Aumiller, Thomas, Dr. med. (2008)
Jeleazcov, Christian, Dr. med. (2008)
Müller, Susanne, Dr. med. (2008)
Rieß, Simon, Dr. med. (2008)
Schmidt, Astrid, Dr. med. (2008)
Schön, Christoph, Dr. med. (2008)
Strembski, Dieter, Dr. med. (2008)
Wilhelm, Ilca-Ricarda, Dr. med. (2008)

Habilitations

Münster, Tino, PD Dr. med. (2007): *Muskelrelaxation bei Patienten mit neuromuskulären Erkrankungen: Wirkprofil von Mivacurium und Rocuronium*

Schmidt, Joachim, PD Dr. med. (2007): *Perioperativer Einsatz moderner nicht-depolarisierender Muskelrelaxanzien: Untersuchungen zu Anwendungsgewohnheiten, Monitoring, Pharmakodynamik an verschiedenen Muskelgruppen sowie zur Pharmakodynamik bei Patienten mit neuromuskulären Erkrankungen*

Jeleazcov, Christian, PD Dr. med. (2008): *Parametrization and pharmacodynamic modelling of spontaneous and evoked EEG to optimize anaesthetic drug therapy by simultaneous trend monitoring in children and adults*

Schiessl, Christine, PD Dr. med. (2008): *Patientenkontrollierte Analgesie (PCA) in der Tumorschmerztherapie: Indikation, Management und Behandlungsergebnisse*

Department of Obstetrics and Gynaecology

Chair of Obstetrics and Gynaecology

Doctorate Theses

Grabbert, Martina, Dr. med. (2007): *Fetal outcome bei Sectio caesarea in Spinalanästhesie, Periduralanästhesie und Intubationsnarkose*

Hoffmann, Frederike, Dr. med. (2007): *Einfluss von Maillard-Produkten vom Typ Chelatbildner auf die kupferkatalysierte Oxidation von Low Density Lipoprotein*

Schreiner, Stefanie, Dr. med. (2007): *Der Konzentrationsabhängige Einfluss von 17ß-Estradiol und Progesteron auf das Kontaktionsverhalten des Myometriums*

Geiler, Sonja, Dr. med. (2008): *Polymorphismen im Aromatasegen (CYP19A1) und deren Assoziation mit dem histopathologischen Phänotyp beim Mammakarzinom*

Heusinger, Katharina, Dr. med. (2008): *Genauigkeit der Tumorgrößenbestimmung im Rahmen des klinischen Stagings von Brustkrebspatientinnen – eine vergleichende, prospektive klinische Studie*

Kollmannsberger, Bettina, Dr. med. (2008): *Polymorphismen in den 5-Hydroxytryptaminrezeptorgenen HTR3B und HTR3C und deren Bedeutung für chemotherapieinduziertes Erbrechen*

Kusuma Widjaja, Widya, Dr. med. (2008): *Etablierung eines Mikrochip-Präzisionsdruckkatheters zur Messung intrauteriner Druckverläufen sowie Einführung der Perfusionsdruckmessung mit einem digitalen Transducer im ex vivo Schweineuterusperfusionsmodell*

Kösztner, Heike, Dr. med. (2008): *Die Kryokonservierung von Geweben und Organen am Beispiel des Schweineuterus*

Langbein, Manuela, Dr. rer. nat. (2008): *Die Rolle des PPARγ Signalweges für die Trophoblasten-Differenzierung im Verlauf normaler und pathologischer humaner Plazentogenese*

Rauh, Claudia, Dr. med. (2008): *Einfluss von hormonellen und reproduktiven Faktoren auf die Entstehung und Prognose eines Mammakarzinoms*

Board Qualifications "Frauenheilkunde und Geburtshilfe"

Fasching, Peter, Dr. med. (2007)
Mehlhorn, Grit, Dr. med. (2007)
Meurer, Britta, Dr. med. (2007)
Siemer, Christian, Dr. med. (2007)
Allali, Faouz, (2008)
Hart, Nicola, Dr. med. (2008)
Lux, Michael Patrick, Dr. med. (2008)
Oppelt, Patricia, Dr. med. (2008)
Reißmann, Christine, Dr. med. (2008)

Additional Qualifications

Goecke, Tamme, Dr. med. (2007): *Spezielle Geburtshilfe und Perinatalmedizin*

Oppelt, Peter, Dr. med. (2007): *Gynäkologische Onkologie*

Cupisti, Susanne, Dr. med. (2008): *Spezielle Geburtshilfe und Perinatalmedizin*

Cupisti, Susanne, Dr. med. (2008): *Gynäkologische Exfoliativ-Zytologie*

Frobenius, Wolfgang, Dr. med. (2008): *Spezielle Geburtshilfe und Perinatalmedizin*

Thiel, Falk, Dr. med. (2008): *Gynäkologische Onkologie*

Habilitations

Fasching, Peter, PD Dr. med. (2007): *Risikoeinschätzung für das Mammakarzinom in Prävention und Früherkennung*
Binder, Helge, PD Dr. med. (2008): *Untersuchungen zur Genetik, Klinik und Kostenanalyse des ovariellen Überstimulationssyndroms (OHSS) in der Sterilitätstherapie*
Cupisti, Susanne, PD Dr. med. (2008): *Endokrine und metabolische Evaluation der klinischen Kriterien des Polyzystischen Ovar-Syndroms und Einfluß des Body-mass-Index*

Department of Radiation
Chair of Radiation Therapy

Doctorate Theses

Baierlein, Sammy, Dr. med. (2007): *Kombinierter Effekt von Tumor Nekrose Faktor alpha und ionisierender Strahlung auf die Induktion von Apoptose in 5637 Harnblasenkarzinomzellen*
Lahmer, Godehard, Dr. med. (2007): *Der Einfluss immunkompetenter Zellen auf die Prognose des Analkarzinoms nach einer Radiochemotherapie*
Metz, Anja, Dr. med. (2007): *Resultate der neoadjuvanten Radiochemotherapie bei Patienten mit fortgeschrittenen Mundhöhlenkarzinomen*
Schilcher, Florian, Dr. med. (2007): *Radiotherapie der medialen Lymphabflusswege gleicht die ungünstigere Prognose eines medialen und zentralen Primärtumorsitzes beim kleinen Mammakarzinom aus*
Strasser, Hans, Dr. med. (2007): *DNA-Doppelstrangbruch-Induktion und Reparatur in bestrahlten Lymphoblastoiden Zellen, Fibroblasten und Leukozyten von ATM-, NBS- und strahlensensiblen Patienten*
Uhl, Matthias, Dr. med. (2007): *Veränderungen der NBS-Phosphorylierung nach Bestrahlung von Säugerzellen im zeitlichen Verlauf*
Waas, Alexandra, Dr. med. (2007): *Kann mit Hilfe des G2/M-Arrests die individuelle Strahlenempfindlichkeit von Patienten vorhergesagt werden?*
Wittlinger, Michael, Dr. med. (2007): *Zeit- und dosisabhängige Phosphorylierung von p53 an Serin 15 in Zelllinien mit unterschiedlicher Strahlensensibilität*
Albrecht, Christine, Dr. med. (2008): *Expression und Modulation von p53 und Mdm2 in Kopf-Hals-Tumoren*
Brandl, Isabella, Dr. med. (2008): *Die Bedeutung von p53-Mutationen für die Wirksamkeit einer adjuvanten Radiotherapie bei Plattenepithelkarzinomen des Oropharynx*
Dietel, Katrin, Dr. med. (2008): *Der Einfluss tumorinfiltrierender Lymphozyten auf die Prognose des Oropharynxkarzinoms*
Fickenscher, Rainer, Dr. med. dent. (2008): *Der prognostische Einfluss von tumorinfiltrierenden Lymphozyten im Plattenepithelkarzinom des Oropharynx ist abhängig von der Art der Behandlung*
Gebel, Philipp, Dr. med. (2008): *Gemcitabine aktiviert H2AX über blockierte Replikationsgabel*
Hofmann, Anne, Dr. med. (2008): *Unterschiede in der Signaltransduktion einer normalen menschlichen Zelllinie im Vergleich zu einer Zelllinie mit Nijmegen Breakage Syndrom*
Kühn, Leonhard, Dr. med. (2008): *Bildung der Nuklear Bodies in Abhängigkeit von der p53-Posphorylierung in bestrahlten lymphoblastoiden Zellen und Fibroblasten von einem Gesunden und einem NBS-Patienten*
Lettmaier, Sebastian, Dr. med. (2008): *Langzeitergebnisse zur Wirksamkeit von Amifostin in der Prävention der chronischen radiogenen Xerostomie*
Mese, Mesut, Dr. med. (2008): *Einfluss der Operationstechnik auf die Rezidivhäufigkeit beim Rektumkarzinom nach standardisierter Radiochemotherapie Eine retrospektive Analyse des Krankenguts einer fränkischen Klinik im Zeitraum 01.04.1993 bis 30.04.2002*
Schendel, Roy, Dr. med. (2008): *Tumor und Stroma beim lokal fortgeschrittenem duktalen Pankreaskarzinom: Die Expression von molekularen Markern und deren Korrelation mit dem Überleben bei Patienten mit definitiver, simultaner Radiochemotherapie*
Ullmann, Christian, Dr. med. (2008): *Der Einfluss tumorinfiltrierender Lymphozyten auf die Prognose des Oropharynxkarzinoms*
Wolze, Carolin, Dr. med. (2008): *Die organerhaltende Therapie des Harnblasenkarzinoms durch transurethrale Resektion und kombinierte Radiochemotherapie*

Board Qualifications "Strahlentherapie"

Melzner, Winfrid, Dr. med. (2007)
Windschall, Andrea, Dr. med. (2007)

Habilitations

Fahrig, Antje, PD Dr. med. (2007): *Innovative Techniken in der Hochpräzisions-Strahlentherapie: experimentelle Grundlagen und klinische Ergebnisse*
Gaipl, Udo, PD Dr. rer. nat. (2008): *Dying and dead cells as inducer of chronic autoimmunity and as tool for immune intervention*

Department of Pediatrics
Chair of Pediatrics

Doctorate Theses

Eitel, Annelie-Beate, Dr. med. (2007): *Immunglobulin-G-Subklassen-Verteilung und Erkrankungsmuster bei Kindern mit rezidivierenden Infekten*
Falkenberg, Christian, Dr. med. (2007): *Todesursachen der juvenilen chronischen Arthritis*
Graml, Michael, Dr. med. dent. (2007): *Prospektive Erfassung von endokrinen Spätschäden bei Kindern und Jugendlichen nach Hirntumortherapie im Rahmen der GPOH-Studie HIT 2000*
Klaffenbach, Daniela, Dr. med. (2007): *Regulation und Signaltransduktion der Toll-like-Rezeptoren in humanen Plazentazellen*
Krauß, Alexander, Dr. med. dent. (2007): *Prolaktin-Konzentrationen im Serum von Kindern und Jugendlichen*
Kunz, Katharina, Dr. med. dent. (2007): *Pulmonalatresie mit intaktem Ventrikelseptum: operative Therapie und mittelfristige Ergebnisse*
Mahfoud, Suleiman, Dr. med. (2007): *Inhalative Anwendung von Adrenomedullin im Modell surfactantdepletierter neonataler Ferkel mit pulmonaler Hypertension*
Neuner, Andrea, Dr. med. (2007): *Evaluierung einer pränatalen Gentherapiestrategie für die Behandlung des Morbus Herlitz*
Pickel, Naemi, Dr. med. (2007): *Unterschiedliche ontogenetische Regulation der mRNA-Expression konstitutiver und induzierbarer peptiderger und nitriderger Systeme in der Plazenta*
Popp, Karolin, Dr. med. (2007): *Hemmung der pulmonalen Fibroseinduktion durch inhalatives Adrenomedullin im Modell surfactantdepletierter neonataler Ferkel*
Tell, Kai, Dr. med. dent. (2007): *Der Diabetes-Situations-Test: Statistische Evaluierung von Objektivität, Reliabilität, Validität und Testscoreveränderungen im Rahmen des „Projekt D"*
Todoric, Teofil, Dr. med. (2007): *Die diagnostische Aussagekraft visuell evozierter Potentiale nach Blitz- und Musterreizung bei Säuglingen und Kleinkindern mit Mehrfachbehinderung und permanenter kortikaler Blindheit*
Weigel, Corina, Dr. med. (2007): *Einfluss experimenteller Hypoxie auf die Expression von Syncytin und dessen Rezeptor ASCT2*
Albert, Christian, Dr. med. (2008): *Untersuchungen zur intrakapillären Hämoglobinoxygenierung bei Kindern mit Wachstumshormonmangel unter Wachstumshormontherapie mit dem Erlanger Mikrolichtleiter-Spektrophotometer*
Berzl, Gabriele, Dr. med. (2008): *Veränderungen endokriner Parameter in der Plazenta bei hypotrophen Früh- und Neugeborenen*
Bosselmann, Stephan, Dr. med. (2008): *Therapie des akuten Lungenversagens mit aerosolisiertem Perfluorcarbon im tierexperimentellen Modell des neonatalen ARDS: Vergleich der Wirkung von kontinuierlich und atemphasenabhängig appliziertem Perfluorcarbon in unterschiedlichen Testdosen*
Bäcker, Silke, Dr. med. (2008): *Bakterielle Transmigration an Darmepithelzellinien unter dem Einfluss verschiedener Ingredienzien*
Denekas, Anja, Dr. med. dent. (2008): *Parodontitis – eine Frage der körpereigenen Abwehr?*

Fischer, Barbara, Dr. med. (2008): *HLA-DRalpha- und DRbeta-spezifische Antikörper zur Lyse maligner B-Zellen*

Klingmüller, Karin, Dr. med. (2008): *Expression Hypoxie-induzierbarer metabolischer Faktoren in der humanen Plazenta in vivo unter akuter und chronischer Hypoxie*

Marek, Ines, Dr. med. (2008): *Molekulare Unterschiede im Ablauf der experimentellen mesangioproliferativen Glomerulonephritis nach intrauteriner Wachstumsrestrikton in der Ratte*

Otto, Stephanie Johanna , Dr. med. (2008): *Kombinierte ösophageale pH- und Impedanzmessung nach operierter Ösophagusatresie*

Rückel, Aline, Dr. med. (2008): *Reduktion der pulmonalen Hypertonie sowie der Expression der proinflammatorischen Interleukine 1beta und 8 im Rahmen eines Großtiermodells des neonatalen Atemnotsyndroms durch den Interleukin-1-Rezeptorantagonisten Anakinra*

Schrey, Dominik, Dr. med. (2008): *Findung der Dosis und der Applikationsart für die aerosolisierte Perfluorcarbon-Beatmung an surfactantdepletierten Ferkeln mit ARDS*

Walther, Julia, Dr. med. (2008): *Verbesserung von Gasaustausch und Lungenmechanik, Reduktion der pulmonalen Hypertonie durch aerosolisiertes Perfluorcarbon am surfactantdepletierten Ferkel mit ARDS*

Wich, Christina, Dr. med. (2008): *Genexpression des plazentaren Fusionsproteins Syncytin und dessen Transkriptionsfaktors GCMa, des Syncytin-Rezeptors ASCT2 und des Effektormoleküls Connexin 43 unter Normoxie und Hypoxie in humanen trophoblastären Zellen*

Wolst, Andreas, Dr. med. (2008): *Chylothorax nach Herzoperation im Kindesalter*

Board Qualifications "Kinder- und Jugendmedizin"

Karle, Stephanie, Dr. med. (2007)
Metzler, Markus, Dr. med. (2007)
Richter, Markus, Dr. med. (2007)
Sauerstein, Katja, Dr. med. (2007)
Topf, Hans-Georg, Dr. med. (2007)
Galiano, Matthias, Dr. med. (2008)
Gratzki, Nils, Dr. med. (2008)
Melichar, Volker, Dr. med. (2008)
Zapke, Maren, Dr. med. (2008)
von Goessel, Heiko, Dr. med. (2008)

Habilitations

Rauh, Manfred, PD Dr. rer. nat. (2007): *LC-Tandem-Massenspektrometrie. Neue analytische Möglichkeiten für das klinische Labor*

Utsch, Boris, PD Dr. med. (2008): *Hand-Fuß-Genitalsyndrom – Polyalanin-Expansionen*

Department of Pediatrics
Division of Pediatric Cardiology

Doctorate Thesis

Spicher, Janna-Kristin, Dr. med. (2008): *Ballondilatation der valvulären Aortenstenose: Prädiktoren für den unmittelbaren Erfolg und Langzeitergebnisse*

Department of Dermatology
Chair of Skin and Venereal Diseases

Doctorate Theses

Bekou, Vassiliki, Dr. med. (2007): *Entwicklung eines ELISA zum Nachweis von Autoantikörpern gegen Laminin 5 beim Schleimhautpemphigoid*

Eisemann, Jutta, Dr. rer. nat. (2007): *Untersuchungen zur Interaktion von HSV-1 mit reifen dendritischen Zellen*

Busch, Marion, Dr. med. (2008): *Surrogatproteine in Latexhandschuhen induzieren allergenspezifische IgE-Antikörper im Mausmodel: Etablierung einer Microarray-basierten Diagnostik muriner Antikörper*

Erfurt-Berge, Cornelia Susanne, Dr. med. (2008): *Erstmaliger Nachweis einer CD4+ T-Zell-vermittelten Immunantwort auf das Tumorantigen „Melanom-assoziiertes Chondroitinsulfat-Proteoglykan (MCSP)" und Identifizierung des immunogenen Epitopes*

Gagg, Tina Brigitte, Dr. med. (2008): *Epidemiologische Untersuchungen zur chronischen Urtikaria unter besonderer Berücksichtigung des Krankheitsverlaufes und der Abheilung*

Horstmann, Brigitte, Dr. med. vet. (2008): *Immunmodulation Dendritischer Zellen durch niedrigmolekulare, makrozyklische Inhibitoren in vivo und in vitro*

Knippertz, Ilka, Dr. rer. nat. (2008): *Genetic and physical modification of human DC in order to improve vaccination protocols*

Kosmides, Daniela, Dr. rer. nat. (2008): *Modulation of Viral Gene Expression and Capsid Components to Engineer Oncolytic Adenoviruses for Virotherapy of Cancer*

Schierer, Stefan, Dr. rer. nat. (2008): *Modulation Of Dendritic Cell Biology By Oncolytic Adenoviruses And By Melanoma Cells Lysed By Oncolytic Adenoviruses*

Seidel, Helmut Andreas, Dr. med. dent. (2008): *Prognose von Berufsdermatosen - Eine Follow-up Untersuchung des Berufskrankheitenregisters Haut Nordbayern (BKH-N)*

Board Qualifications "Haut- und Geschlechtskrankheiten"

Hezel, Svea, Dr. med. (2008)
Zajitschek, Jörg, Dr. med. (2008)

Habilitations

Nettelbeck, Dirk Manfred, PD Dr. rer. physiol. (2007): *Engineering of Oncolytic Adenoviruses for Targeted Treatment of Malignant Melanoma*

Department of Ear, Nose and Throat – Head and Neck Surgery
Chair of Otorhinolaryngology

Doctorate Theses

Brase, Christopher, Dr. med. (2007): *Antwortprofile individueller olfaktorischer Glomeruli im Bulbus olfactorius principalis von Xenopus-laevis-Larven.*

Gill, Sandra, Dr. med. (2007): *Sonographische Kontrastmittelkinetikanalyse in der Dignitätsbestimmung von Lypmphknoten im Kopf-Hals Bereich*

Göderer, Lisa, Dr. med. (2007): *Das CRPS (= komplex regionales Schmerzsyndrom) - eine Langzeit Follow-up-Studie*

Miller, Ludwig Andreas, Dr. med. dent. (2007): *Der Erfolg der adaptiven Desaktivierung gegen Acetylsalicylsäure bei Patienten mit Polyposis nasi und Analgetika-Intoleranz gemessen am postoperativen Beschwerdebild*

Müller, Oliver, Dr. med. dent. (2007): *Ergebnisse der chirurgischen Therapie des Zenker Divertikels: Endoskopische Schwellendurchtrennung versus transzervikale Methoden*

Nguyen, Danny Tho, Dr. med. (2007): *Stapedotomie - Stapedektomie Eine Langzeitstudie zweier Operationsmethoden unter Betracht des Innenohr- und Mittelohrbereiches*

Reißenweber, Christian Matthias, Dr. med. dent. (2007): *Langzeitergebnisse zur adaptiven Desaktivierung gegen Acetylsalicylsäure (ASS) bei Patienten mit Polyposis nasi et sinuum und Analgetika-Intoleranz-Syndrom Eine retrospektive Krankengutanalyse von 1986 bis 2004 der Hals-Nasen-Ohrenklinik*

Schmidt, Manfred Georg, Dr. med. (2007): *Parotidektomien der Jahre 1990-2001 an der Hals-Nasen-Ohren-Klinik, Kopf- und Hals-Chirurgie des Universitätsklinikums Erlangen*

Zeidelhack, Nicole Florentine Inge Hilde, Dr. med. dent. (2007): *Komplikationen akuter Rhinosinusitiden Eine Analyse stationärer Aufenthalte*

Birk, Stephanie, Dr. med. (2008): *Genetische Markierung von humanen mesenchymalen Stammzellen mittels enhanced green fluorescent protein.*

Gaitzsch, Christian, Dr. med. dent. (2008): *Hörverlauf nach transtemporaler mikrochirurgischer Entfernung von Vestibularisschwannomen*

Hechtel, Christina, Dr. med. (2008): *Mediane Halszysten und Halsfisteln Untersuchung am Patientengut der Hals-Nasen-Ohren-Klinik,*

Kopf- und Halschirurgie Erlangen von 1992 bis 2002

Häusler, Marcus Alexander, Dr. med. (2008): *Analyse der Immunogenität von Plattenepithelkarzinomen des Kopf-Hals-Bereiches mit der Serex-Methode*

Kapsreiter, Markus, Dr. med. (2008): *Über die Innervation der Arteria centralis retinae des Menschen.*

Kluge, Sonja Elisabeth, Dr. med. dent. (2008): *Identifizierung immunogener Strukturen eines Cholesteatoms*

Prillwitz, Heino Torsten, Dr. med. (2008): *Anwendung und Versuch der Validierung der Funktionellen Eicosanoid-Typisierung (FET-AIT®) bei Patienten mit Polyposis nasi*

Rogler, Katrin, Dr. med. (2008): *Einfluss von Phosphatase- und Kinase- Inhibitoren auf die Phosphorylierung und Aggregation des Tau-Proteins in Zellkulturen.*

Schardt, Katharina, Dr. med. (2008): *Untersuchungen zu Tumorantigenen an einem Adenokarzinom der Nasennebenhöhle mittels „SER-EX"*

Schnell, Jennifer-Lisa, Dr. med. (2008): *Retrospektive Analyse von operativen Defektdeckungen im Bereich der Rhinobasis unter besonderer Berücksichtigung von intraoperativ verursachten Schädelbasisdefekten bei endoskopischen Nasennebenhöhlenoperationen der Jahre 1990 - 2004*

Tziridis, Konstantin, Dr. rer. nat. (2008): *The role of the pontine nuclei in visually guided hand and eye movements*

Board Qualifications "Hals-Nasen-Ohrenheilkunde"

Bumm, Klaus, Dr. med. (2007)
Bohr, Christopher, Dr. med. (2008)

Department of Ear, Nose and Throat – Head and Neck Surgery
Division of Phoniatrics and Pediatric Audiology

Doctorate Theses

Brauner, Kristof, Dr. med. (2007): *Früherkennung von Sprachentwicklungsstörungen – Bewertung des Screenings anhand der Grenzsteine der kindlichen Entwicklung nach Michaelis*

Burger, Martin, Dr.-Ing. (2007): *Assessment of the Individual Auditory Perception via Evoked Potentials*

Haderlein, Tino, Dr.-Ing. (2007): *Automatic evaluation of tracheoesophageal substitute voices*

Paal, Sonja-Gerda, Dr. med (2007): *Evaluation of speech disorder in children with cleft lip and palate*

Rasp, Oliver, Dr. med (2007): *The pitch raise paradigm: a new task for real-time endoscopy of non-stationary phonation*

Schwarz, Raphael, Dr.-Ing. (2007): *Model-Based Quantification of Pathological Voice Production*

Weigl, Veronika, Dr. med (2007): *Ängstlichkeit, Depressivität und gesundheitsbezogene Lebensqualität der Mütter von Kindern mit Lippen-Kiefer-Gaumenspalten*

Wurzbacher, Tobias, Dr.-Ing. (2007): *Vocal Fold Dynamics - Quantification and Model-based Classification*

Bößenecker, Arno, Dr. med. (2008): *Analyse der Dreidimensionalen Stimmlippendynamik*

Preclik, Markus , Dr. med (2008): *Anamnesebogen für Auditive Verarbeitungs- und Wahrnehmungsstörungen – Psychometrische Korrelation im Vorschulalter*

Schmitt, Claudia, Dr. med (2008): *Screening der kognitiven Entwicklung von Vorschulkindern – Bewertung der essentiellen Grenzsteine der kindlichen Entwicklung nach Michaelis*

Vogt, Beate, Dr. med (2008): *Numerische Quantifizierung der Verständlichkeit von Schulkindern mit isolierter und kombinierter Gaumenspalte*

Board Qualifications "Sprach-, Stimm- und kindliche Hörstörungen"

Toy, Hikmet, Dr. med. (2007)
Schützenberger, Anne, Dr. med. (2008)

Habilitation

Lohscheller, Jörg, PD Dr.-Ing. (2007): *Analyse, Visualisierung und Klassifikation stimmerzeugender Strukturen basierend auf endoskopischen Hochgeschwindigkeitsaufnahmen*

Department of Ophthalmology
Chair of Ophthalmology

Doctorate Theses

Link, Barbara, Dr. med (2007): *Einfluss des spontanen Venenpulses auf morphometrischen Papillenmessungen mit dem HRT*

Raum, Christoph, Dr. med (2007): *Planimetrische Langzeitbeobachtung von Patienten mit stabilem und progressivem Glaukom*

Rödl, Johannes, Dr. med (2007): *Glaukomatöse Neurodegeneration - Homocystein als neuer Risikofaktor*

Schröder, Sabine, Dr. med (2007): *Planimetrische Langzeitbeobachtung von Normalen und Patienten mit okulärer Hypertension*

Düz, Melek, Dr. med (2008): *Semiautomatische Messung parapapillärer Autofluoreszenz bei Normalen, Patienten mit Glaukomverdacht und Glaukom*

Hösel, Laura, Dr. med (2008): *Wertigkeit unterschiedlicher Methoden zur semi-automatischen Diagnosestellung bei Glaukomen mit dem HRT*

Schrems, Wolfgang, Dr. med (2008): *Diagnostische Wertigkeit von GDxVCC und Stratus-OCT bei Glaukomen*

Steinhäuser, Maike, Dr. med. (2008): *OCT gestützte Referenzebene für das HRT-eine neue Option?*

Department of Neurology
Chair of Neurology

Doctorate Theses

Breuer, Lorenz, Dr. med. (2007): *Megaphen- die Rolle der Universitäts-Nervenklinik Erlangen bei der klinischen Einführung der ersten Neuroleptika in Deutschland*

Kiphuth, Ines-Christine, Dr. med. (2007): *Entwicklung einer Methode zur molekularen Haplotypisierung: allelspezifische Bestimmung von Mutationen und genetischen Markern im PAH-Gen*

Porsche, Christian, Dr. rer. nat. (2007): *Neuronale Plastizität im Hippocampus der Maus: Die Rolle von Neurotrophinen und Cytokinen*

Pohle, Rebecca, Dr. med. (2008): *Zusammenhang zwischen Schlaganfallentitäen gemäß den Diagnosekriterien der TOAST Klassifikation und dem Auftreten von funktioneller Behinderung nach einem Schlaganfall im Erlanger Schlaganfall Projekt*

Racz, Attila, Dr. rer. nat. (2008): *Molecular determinants of hippocampal oscillatory activity*

Board Qualifications "Neurologie"

Kollmar, Rainer, Dr. med. (2007)
Ulrich, Kathrin, Dr. med. (2007)
Bardutzky, Jürgen, Dr. med. (2008)
Schramm, Axel, Dr. med. (2008)

Habilitations

Bardutzky , Jürgen, PD Dr. med. (2008): *Magnetresonaztomographische Untersuchungen zur Entwicklung und Dynamik der Perfusions/Diffusions Mismatches am tierexperimentellen Ischämiemodell*

Huttner, Hagen, PD Dr. med. (2008): *Neue intensivmedizinische Behandlungsaspekte bei der intrazerebralen Blutung*

Kollmar, Rainer, PD Dr. med. (2008): *Experimentelle Untersuchungen zu induzierter Hypothermie als Therapieverfahren nach akutem ischämischen Schlaganfall*

Schäuble, Barbara, PD Dr. med. (2008): *Diagnose und Therapie der Epilepsie*

Stemper, Brigitte, PD Dr. med. (2008): *Störungen der kardiovaskulären und zerebrovaskulären Regulation bei Erkrankungen des peripheren und zentralen Nervensystems*

Department of Neurosurgery
Chair of Neurosurgery

Board Qualifications "Neurochirurgie"

Nestler, Dirk, Dr. med. (2007)
Weigel, Daniel, Dr. med. (2007)
Eyüpoglu, Ilker, Dr. med. (2008)

Habilitations

Stadlbauer, Andreas, PD Dr. techn. (2008): *Magnetresonanzspektroskopie und Diffusionstensor-Bildgebung bei hirneigenen Tumoren*

Department of Psychiatry and Psychotherapy
Chair of Psychiatry and Psychotherapy

Doctorate Theses

Bartl, Christina, Dr. med. (2007): *Optische Visualisierung und Analyse der Exozytose singulärer Vesikel in Phaeochromozytoma – Zellen mittels Total-Reflexions-Mikroskopie (TIRF)*

Bauer, Christiane, Dr. med. (2007): *Die Borderline-Störung: aktuelle Konzepte, therapeutische Ansätze und erste Ergebnisse des Nürnberger Kriseninterventionsprogramms*

Breuer, Lorenz, Dr. med. (2007): *Megaphen®: Die Rolle der Universitäts-Nervenklinik Erlangen bei der klinischen Einführung der ersten Neuroleptika in Deutschland*

Bruckmoser, Ralf, Dr. med. (2007): *Die Rolle der präanalytischen Probenbehandlung in der neurochemischen Demenzdiagnostik*

Dütsch, Carmen, Dr. med. (2007): *Dantrolen und das Maligne Neuroleptische Syndrom: ein meta-analytischer Ansatz zur Evidenzprüfung der therapeutischen Effektivität*

Greiner, Annette, Dr. med. (2007): *Veränderungen der Serumaktivität der Semicarbazid-sensitiven Aminooxidasen bei verschiedenen psychiatrischen Erkrankungen*

Hauenstein, Tobias, Dr. med. (2007): *Der Einfluss des Homocystein-Serumspiegels auf die Kurzspeicherkapazität – die HomEMed-Studie an Medizinstudenten*

Jacob, Harald, Dr. med. (2007): *Früherkennung qualitativ hochstehender Forscher der deutschen Psychiatrie durch global zugängliche bibliometrische Indikatoren*

Jacobi, Andrea, Dr. med. (2007): *Der Einfluss der Vagusstimulation auf trigeminale Schmerzreize*

Krieglstein, Christian, Dr. med. dent. (2007): *Der Einfluss des Plasma-Homocysteinspiegels und des Alkoholkonsums auf die (epigenetische) DNA-Methylierung bei Gesunden. Genomische und Gen-spezifische Analysen unter Berücksichtigung des circadianen Rhythmus*

Lenz, Bernd, Dr. med. (2007): *Homocysteinassoziierte epigenetische Veränderungen von DNA-Methylierung bei Alkoholabhängigkeit. In-vitro- und in-vivo- Untersuchungen*

Rischer, Angela, Dr. phil. (2007): *Sorgen und Grübeln: Zwei Seiten derselben Medaille? Ein Konzeptvergleich von Worry und Rumination in einer multizentrischen Studie an Patienten mit Depression und einer nichtklinischen Vergleichsstichprobe.*

Scheer, Raimund, Dr. med. (2007): *Saisonale Auffälligkeiten bei Patienten mit Schizophrenie hinsichtlich Zeitpunkt der Geburt und stationärer Aufnahme*

Struck, Ingo, Dr. med. (2007): *Vorhersage von pharmakologisch induzierten Gewichtsveränderungen durch Körpergewicht, Body Mass Index (BMI), Körperfettmasse und Alter*

Stößel, Christina, Dr. med. (2007): *Geschmacksstörungen bei Patienten mit akutem Schlaganfall*

Summ, Elisabeth, Dr. rer. nat. (2007): *Psychoedukation Angst bei stationären Patienten – PASTA*

Tripal, Philipp, Dr. rer. nat. (2007): *Gemeinsamkeiten und Unterschiede der humanen Guanylatbindeproteine*

Bock, Eva, Dr. med. (2008): *Körperliche Beschwerden bei Müttern von Kindern mit Sprachentwicklungsstörungen*

Carl, Marco, Dr. med. (2008): *Alkoholismus-assoziierte Hyperhomocysteinämie und deren Verlauf im Alkoholentzug*

Cimmino, Natalie, Dr. med. (2008): *Einfluss moderner Antidepressiva auf Körperzusammensetzung, Körpergewicht, Tumor-Nektrose-Faktor, Leptin und Psychopathologie*

Degirmenci, Ümüt, Dr. med. (2008): *Homocystein, ApoE4 und akute postoperative neuropsychologische Defizite nach aorto-coronaren Bypassoperationen*

Freiberger, Verena, Dr. med. (2008): *Einfluss der Antipsychotika Quetiapin und Ziprasidon auf Gewicht, Leptin, TNF-alpha System und Psychopathologie*

Hoeß, Uta, Dr. med. (2008): *Versorgung von Schlaganfallpatienten mit ambulanten Heil- und Hilfsmitteln im Langzeitverlauf nach stationärer neurologischer Rehabilitation*

Koch, Marlene, Dr. med. (2008): *Der Plasmahomocysteinspiegel: Circadianer Rhythmus und Zusammenhang mit der geistigen Leistungsfähigkeit*

Koloschin, Tatjana, Dr. med. (2008): *Vergleich der in den Zitationsindizes erfassten und zitierten Publikationen in Nachautorenschaft mit denen in Allein-/Erstautorenschaft – eine Verlaufsstudie am Beispiel der Ordinarien der deutschen Psychiatrie*

Krauß, Katharina, Dr. med. dent. (2008): *Circadianer Rhythmus der Reaktionszeit bei Depressiven verglichen mit gesunden Kontrollpersonen*

Löwe, Nadine, Dr. med. (2008): *Verminderte Methylierung der DNA im Sperma und Änderungen in der Expression der Methyltransferasen DNMTs und alkoholgesteuerten Genen sowohl im Blut als auch im Sperma nach akuter Alkoholintoxikation*

Mertens, Florian, Dr. med. (2008): *Verordnung von Benzodiazepinen bei der Behandlung von depressiven Erkrankungen*

Mertens, Andreas, Dr. med. (2008): *Kombinations- und Augmentationsstrategien bei der Behandlung depressiver Störungen*

Rauh, Johannes, Dr. med. (2008): *Genetische Variationen des Serotonin-Transporter-Gens im Zusammenhang mit Craving bei Patienten mit Alkoholabhängigkeit*

Rogler, Katrin, Dr. med. (2008): *Einfluss von Phosphatase- und Kinase-Inhibitoren auf die Phosphorylierung und Aggregation von Tau in Zellkulturzellen*

Rotter, Andrea, Dr. med. (2008): *Der Effekt von Antidepressiva auf die Expression von Wachstumsfaktoren am Zellmodell von differenzierten Neuroblastomzellen SH-SY5Y*

Scholz, Sarah, Dr. med. (2008): *Die Rolle epigenetischer Faktoren bei der Kontrolle des dopaminergen Systems bei Essstörungen*

Schütz, Patricia, Dr. med. (2008): *Untersuchung von Biomarkern der neuronalen Zellschädigung bei der Elektrokonvulsionsbehandlung von Patienten mit Depression*

Sieling, Swantje, Dr. med. dent. (2008): *Früherkennung qualitativ hoch stehender Forscher der deutschen Neurologie durch global zugängliche bibliometrische Indikatoren*

Zimmermann, Rüdiger, Dr. med. (2008): *Der Stellenwert der ß-Amyloid-Quotienten Aßx-42/Aß1-42/Aßx-40 für die Neurochemische Demenzdiagnostik*

Board Qualifications "Psychiatrie und Psychotherapie"

Maler, Juan Manuel, Dr. med. (2007)
Nowak, Magdalena, Dr. med. (2007)
Weih, Markus, Dr. med. (2007)
Bayerlein, Kristina, Dr. med. (2008)
Biermann, Teresa, Dr. med. (2008)

Additional Qualifications

Hillemacher, Thomas, PD Dr. med. (2008): *Geriatrie*
Maler, Juan Manuel, Dr. med. (2008): *Geriatrie*
Nowak, Magdalena, Dr. med. (2008): *Schlafmedizin*

Department of Psychiatry and Psychotherapy
Division of Child and Adolescent Mental Health

Board Qualification

Fehn, Thomas, Dr. med. (2008): *Kinder- und Jugendpsychiatrie und -psychotherapie*

Department of Psychiatry and Psychotherapy
Division of Psychosomatics and Psychotherapy

Doctorate Theses

Krajinovic, Ljubica, Dr. med. (2007): *Erfassung der Psychopathologie von Essstörungen bei adipösen Patienten vor Magenbandoperation: Interview oder Selbstbeurteilungsverfahren?*

Doll, Michael, Dr. med. (2008): *Dissoziative Symptomausprägung einer psychosomatischen Stichprobe im Verlauf der Psychotherapie*

Oumard, Daniela Gabriela, Dr. med. (2008): *Geschlechtsspezifische Unterschiede in Psychopathologie, Lebensqualität und Essverhalten vor chirurgischer Adipositastherapie*

Postler, Peter, Dr. med. (2008): *Beschreibung und Prä-Post-Vergleich der vollstationären und tagesklinischen Behandlung des Psychosomatischen und Psychotherapeutischen Abteilung des Universitätsklinikums Erlangen*

Department of Oral and Maxillofacial Surgery
Chair of Dental, Oral and Maxillofacial Medicine – especially Oral and Maxillofacial Surgery

Doctorate Theses

Bieth, Anna Silke Caroline, Dr. med. dent. (2007): *Entstehung von Osteoradionekrosen als Folge kurativ-intendierter Radio- bzw. Radiochemotherapie bei Karzinomen des Oberen Aerodigestivtraktes - Einfluss auf Funktion und Lebensqualität*

Gadner, Klaus, Dr. med. dent. (2007): *Der klinische Einsatz von periostalen osteoblastenähnlichen Zellen für „Bone tissue engineering" am Beispiel des Sinuslift*

Jehle, Marc, Dr. med. (2007): *MAGE-A-, p53- und p21-Expression als prognostischer Marker bei oralen Plattenepithelkarzinomen*

Kamm, Tobias, Dr. med. dent. (2007): *Mikroradiographische - und immunhistologische Untersuchung zweier knochenersatzmaterialien*

Schinhammer, Martin, Dr. med. dent. (2007): *Expression der Proliferationsmarker Repp86, Ki- 67 und Topoisomerase IIa beim Plattenepithelkarzinom der Mundhöhle - eine immunhistochemische Analyse*

Berger, Susanne, Dr. med. dent. (2008): *Die Beurteilung unterschiedlicher Materialien bei der Sinusaugmentation Eine retrospektive Studie*

Beyer, Kathrin, Dr. med. dent. (2008): *In vivo Modell zur Analyse der CD105-Expression im ersatzschwachen Wundheilungsgebiet nach mikrovaskulärem freien Weichgewebetransfer im Rahmen ablativer Tumorchirurgie im Kopf- und Halsbereich*

Bilwatsch, Stefanie, Dr. med. dent. (2008): *Dreidimensionale Analyse des Einflusses des Verschlusses einer einseitigen Lippen-Kiefer-Gaumenspalte nach Tennison-Randall auf die Gesichtssymmetrie des Spaltpatienten*

Bloch-Birkholz, Alexandra Ellen, Dr. med. dent. (2008): *Lebensqualität von Patienten mit Plattenepithelkarzinomen der Mundhöhle unter Vergleich zweier Therapiestrategien*

Geidl, Achim, Dr. med. dent. (2008): *Immunhistologische Untersuchung der ossären Heilung am Modell des „critical-size-defects" unter Verwendung von autologem Knochen als Füllmaterial*

Kramer, Manuel Rolf, Dr. med. dent. (2008): *Intraoperative noncontact, nonionizing, optical 3D exophthalmometry during repositioning of dislocated globes: first results*

Lederer, Jean Wolfgang, Dr. med. dent. (2008): *Tierexperimentelle Untersuchung der knöchernen Regeneration um enossale Implantate mit Vakuum-Titanplasma-Spray oder Calciumphosphat-Beschichtung*

Stauber, Irene, Dr. med. dent. (2008): *Dreidimensionale Analyse der Gesichtssymmetrie von Patienten mit einseitiger Lippen-Kiefer-Gaumenspalte anhand optischer Oberflächendaten*

Board Qualification

Kühnel, Thomas, Dr. Dr. (2008): *Mund-Kiefer-Gesichtschirurgie*

Dental Department 1 - Operative Dentistry and Periodontology
Chair of Dental, Oral and Maxillofacial Medicine – especially Operative Dentistry, Periodontology and Pediatric Dentistry

Doctorate Theses

Aly, Tarek, Dr. med. dent. (2007): *Polymerisationsleistungen von LED- und Halogenlampen*

Back, Michael, Dr. med. dent. (2007): *Einfluss verschiedener Befestigungstechniken auf die interne Dentinhaftung von Kompositinlays*

Basel, Miriam, Dr. med. dent. (2007): *Polymerisationsbedingte Stressentwicklung in zahnärztlichen Kompositwerkstoffen*

Boos, Melanie, Dr. med. dent. (2007): *Polymerisationsstress von Kompositen bei konventioneller und gepulster Polymerisation*

El-Komi, Samira, Dr. med. dent. (2007): *Zur Schmelzhaftung selbstätzender Adhäsivsysteme im Kavitätendesign*

Karl, Christina, Dr. med. dent. (2007): *Adhäsiver Verschluss von Wurzelkanalfüllung nach unterschiedlicher Versäuberung der Trepanationsöffnung*

Kentsch, Caroline, Dr. med. dent. (2007): *Mikroleakage-Untersuchung von Wurzelkanalfüllungen nach unterschiedlichen Abschluss- Spülungen - zwei klassische Wurzelkanalsealer im Vergleich zu einem selbstadhäsiven Zement*

Löffler, Christian, Dr. med. dent. (2007): *Adhäsiver Verschluss direkt nach endodontischer Behandlung: Dichtigkeit vor und nach Kausimulation*

Medelnik, Jürgen, Dr. med. dent. (2007): *Wurzelkanalsauberkeit nach Aufbereitung und Revision mit modernen rotierenden Nickel-Titan-Instrumenten: Eine zweiteilige rasterelektronenmikroskopische Studie*

Meier, Bettina, Dr. med. dent. (2007): *Sekundärkaries - Möglichkeiten der Frühdiagnostik mit Clinpro Cario Diagnosis*

Meißner, Thomas, Dr. med. dent. (2007): *Bruchzähigkeit von modernen Füllungskompositen in Abhängigkeit von der Füllstoffstruktur*

Onczul, Christian, Dr. med. dent. (2007): *Einfluss optimierter Applikationsstrategien auf die marginale Adaptation von Kompositfüllungen im Seitenzahnbereich*

Radon, Claudia, Dr. med. dent. (2007): *Optimierung der Randqualität von Klasse V Kompositfüllungen bei Verwendung simplifizierter Adhäsive*

Schiller, Thomas, Dr. med. dent. (2007): *Zur Dentinhaftung verschiedener Adhäsivsysteme an Milchzähnen*

Schußmüller, Marc, Dr. med. dent. (2007): *Einfluss von Applikation und Polymerisation auf die Randqualität von Klasse-II-Kompositfüllungen*

Seltmann, Thomas, Dr. med. dent. (2007): *Microtensile-Untersuchungen zu einem selbstadhäsiven Universalzement*

Stein, Julia, Dr. med. dent. (2007): *Randverhalten ästetisch optimierter Komposite in Klasse-II-Kavitäten*

Teubner, Alexander, Dr. med. dent. (2007): *Retentionsstärke von Goldinlays in Abhängigkeit vom Befestigungszement*

Weise, Miriam, Dr. med. dent. (2007): *Effektivität verschiedener Wurzelkanalreinigungsmethoden in gekrümmten Wurzelkanälen - Eine rasterelektronenmikroskopische Studie -*

Zwerger, Stefan, Dr. med. dent. (2007): *Flowable Komposite in extendierten Kavitäten- eine Langzeitstudie -*

Aßmann , Irene, Dr. med. dent. (2008): *Vergleich von Geräten zur Kinetischen Kavitätenpräparation untereinander und zu einem rotierenden Instrument*

Beck, Philipp, Dr. med. dent. (2008): *Einfluss der Schmelzabschrägung auf das Dentinrandverhalten zervikaler Kompositfüllungen*

Bienert, Karin, Dr. med. dent. (2008): *Einfluss des Sauerstoffgehalts der Umgebungsluft auf*

die Festigkeit des Komposit-Dentinverbunds im Microtensile-Verfahren

Brügel, Philip, Dr. med. dent. (2008): *Haftverbund zweier selbstätzender und selbstadhäsiver Befestigungszemente am Wurzelkanaldentin unter dem Einfluss endodontischer Spüllösungen*

Deines, Irene, Dr. med. dent. (2008): *Der Einfluss verschiedener Wurzelkanalsealer auf das Wachstum unterschiedlicher Bakterien*

Dennerlein, Michael, Dr. med. dent. (2008): *Untersuchung der apikalen und koronalen Undichtigkeit von adhäsiven und nicht-adhäsiven Wurzelkanalsealern*

Fereidouni, Amir, Dr. med. dent. (2008): *Scherfestigkeit von verschiedenen Befestigungszementen am Wurzelkanaldentin*

Fink, Martin, Dr. med. dent. (2008): *Experimentelle Untersuchung zu Prüfparametern des Farbstoffpenetrationstestverfahrens an bovinem Zahngut*

Flassig, Thomas, Dr. med. dent. (2008): *Detailerkennbarkeit von Lufteinschlüssen im Wurzelkanalfüllmaterial AH Plus™ bei Zahnfilmaufnahmen*

Freiberger, Hannes, Dr. med. dent. (2008): *Einfluss von C-Faktoren und Vorbehandlung auf die Haftung eines selbstadhäsiven Befestigungszements*

Freyberger, Sina, Dr. med. dent. (2008): *Inhibition des Bakterienwachstums durch verschiedene Wurzelkanalsealer - eine In-vitro-Studie*

Grötsch, Marisa, Dr. med. dent. (2008): *Einfluss eines Kalziumhydroxidpräparats auf die Dentinhaftung unterschiedlicher Adhäsivsysteme*

Herbstleb, Edith, Dr. med. dent. (2008): *Mikroleakage-Untersuchungen von Wurzelkanalfüllungen nach unterschiedlichen Abschluss-Spülungen - zwei neue Wurzelkanalsealer im Vergleich zu AH Plus-*

Hock, Katrin, Dr. med. dent. (2008): *Vergleich der Schmelzhaftung von vier selbstätzenden Adhäsivsystemen unter Anwendung unterschiedlicher Applikationsmodi*

Keller, Michael, Dr. med. dent. (2008): *Einfluss der Etch-and-rinse-Technik auf die Dauerhaftigkeit des Komposit-Dentinverbundes selbstätzender Adhäsive*

Kent, Hamdi, Dr. med. dent. (2008): *Klinische Überprüfung eines ionenaktiven Komposits im Milchgebiss -Ergebnisse einer 2-Jahres-Prospektivstudie im Vergleich zu einem Kompomer-*

Kägi, Ute, Dr. med. dent. (2008): *Quantitative Randspaltanalyse von Hytac/Dyract AP nach 4 Jahren - in vivo*

Ritzmann, Claus, Dr. med. dent. (2008): *Ein automatisiertes Kariesmodell zur Erzeugung sekundärkariöser Läsionen*

Rödl, Stefanie, Dr. med. dent. (2008): *Haftverbund eines kunstharzbasierten und methacrylatbasierten Sealers am Wurzelkanaldentin unter dem Einfluss endodontischer Spüllösungen*

Schultes, Camilla, Dr. med. dent. (2008): *Haftverbund zweier adhäsiver Sealer am Wurzelkanaldentin unter dem Einfluss unterschiedlicher Spüllösungen*

Taranu, Ramona, Dr. med. dent. (2008): *Langzeitpenetrationsuntersuchung zur Dichtigkeitsüberprüfung von Wurzelkanalfüllungen mit drei modernen Sealer*

Todorova, Milena, Dr. med. dent. (2008): *Koronale Dichtigkeit von Wurzelkanalfüllungen nach Präparation einer Stiftkavität in vitro*

Ungvári, Stefan, Dr. med. dent. (2008): *Bakteriendichtigkeit von Wurzelkanalfüllungen unter Verwendung verschiedener Wurzelkanalsealer - Eine In-vitro Studie*

Welz-Reitinger, Fabian, Dr. med. dent. (2008): *Einfluss unterschiedlicher Verarbeitungsmodi moderner Adhäsivsysteme auf die Dentinhaftung*

Habilitation

Lohbauer, Ulrich, PD Dr.-Ing. (2007): *Long-term performance of the tooth-restoration compartment - dynamic fatigue simulation*

Dental Department 2 - Prosthetic Dentistry

Chair of Dental, Oral and Maxillofacial Medicine – especially Prosthetic Dentistry

Doctorate Theses

Göllner, Matthias, Dr. med. dent. (2007): *Untersuchung zur Evaluierung und Etablierung photogrammetrischer Messtechnik in der Zahnmedizin*

Helbig, Isabella, Dr. med. dent. (2007): *Rissbildung und Rissverhinderung bei keramisch verblendeten Implantatbrücken - eine in vitro Studie an zementierbaren und verschraubbaren Implantatbrücken*

Krug, Florian, Dr. med. dent. (2007): *Einfluss statischer und dynamischer Belastung auf die Stabilität keramisch verblendeter Implantatrestaurationen*

Scholz, Nicola, Dr. med. dent. (2007): *Neurophysiologische Effekte bei mund-, kiefer-, gesichtschirurgischen Eingriffen unter Hypnose – Eine vergleichende klinische Studie zur Evaluation kardiopulmonaler Parameterveränderungen unter Hypnose*

Zillmann, Elke, Dr. med. dent. (2007): *Neurophysiologische Effekte bei mund-, kiefer-, gesichtschirurgischen Eingriffen unter Hypnose – Eine vergleichende klinische Studie zur Beurteilung subjektiver Parameter und von EEG-Veränderungen unter Hypnose*

Kirchner, Elena, Dr. med. dent. (2008): *Lexikalische Analyse des implantologischen Wortschatzes der russischen Sprache*

Rill, Ulrich, Dr. med. dent. (2008): *Vergleichende klinische Studie zur Wirksamkeit von Akupunktur beim CMD in Zusammenwirken mit progressiver Entspannung mittels Stützstiftregistrat*

Schlaupe, Alexander, Dr. med. dent. (2008): *Präzision in der Meistermodellherstellung für implantatgetragene Restaurationen – der Einfluss unterschiedlicher Abformmaterialien auf die Präzision*

Habilitation

Karl, Matthias, PD Dr. med. dent. (2008): *Biomechanische und materialkundliche Untersuchungen zur Passgenauigkeit festsitzenden implantatgetragenen Zahnersatzes*

Dental Department 3 - Orthodontics and Orofacial Orthopedics

Chair of Dental, Oral and Maxillofacial Medicine – especially Orofacial Orthopedics

Doctorate Theses

Hilbert, Tanja, Dr. med. dent. (2007): *In-vitro Untersuchung zur Scherfestigkeit von Keramikbrackets auf humanem Zahnschmelz und Bewertung der Schmelzoberfläche*

Knorr, Kristin, Dr. med. dent. (2007): *Vergleich des Korrosionsverhaltens von Metallbrackets der Firma 3M Unitek und Forestadent und dessen Einfluss auf die Haftfestigkeit*

Lorenz, Stefan, Dr. med. dent. (2007): *Zur Entwicklung der vertikalen und sagittalen Relation bei Patienten mit ein- und beidseitigen Lippen-Kiefer-Gaumenspalten*

Neuroth, Jeannette, Dr. med. dent. (2007): *Bewertung der Verbundfestigkeit von verschiedenen Bracket-Adhäsiv-Befestigungssystemen in der Kieferorthopädie*

Rodich, Melanie, Dr. med. dent. (2007): *Topographie von Oberkiefer-Eckzahnverlagerungen. Eine metrische Analyse im dreidimensionalen Computertomogramm mit vergleichender Einschätzung im Orthopantomogramm*

Roesel, Nina, Dr. med. dent. (2007): *Quantitative systemische Bestimmung von Legierungsbestandteilen im Zusammenhang mit der Eingliederung festsitzender kieferorthopädischer Mulitbracketapparaturen - eine prospektive klinische Studie*

Schirm, Harald, Dr. med. dent. (2007): *Einflussfaktoren auf die Entwicklung des retromolaren Raumes hinsichtlich der Prognose des Weisheitszahndurchbruchs*

Siegmund Teixeira Soares, Verena, Dr. med. dent. (2007): *Dreidimensionale CT-basierte Evaluation der Spaltmorphologie einschließlich der Nase bei Lippen-Kiefer-Gaumenspalten*

Slotta, Regina, Dr. med. dent. (2007): *Differenzialdiagnostische Bewertung und Klassifikation der Angle-Klasse II,1 nach morphologischen Kriterien*

Münch, Susanne, Dr. med. dent. (2008): *Multizentrischer Ringversuch zur Scherhaftfestigkeit von Adhäsiven für kieferorthopädische Befestigungselemente nach Normvorlage DIN*

Schaubmayr, Martin, Dr. med. dent. (2008): *Untersuchung der Haftfestigkeit von Kompositzylindern und Brackets auf bovinem Schmelz bei Einsatz neuartiger Adhäsivsysteme*

Siegel, Peggy Dr. med. dent. (2008): *Testung der Scherfestigkeit und des Bruchlinienverlaufs verschiedener Adhäsive in Verbindung mit Keramikbrackets*

Weinelt, Thorsten Dr. med. dent. (2008): *Untersuchung des Musculus masseter in Ruhe und Funktion mittels Sonographie, Elektromyographie und Bisskraft*

Board Qualifications "Kieferorthopädie"

Holzmeier, Marcus, Dr. med. dent. (2007)
Meurer, Annika, Dr. med. dent. (2007)
Forster, Hedwig, Dr. med. dent. (2008)
Lovrov, Sylvia, Dr. med. dent. (2008)

In Memoriam

2007 – Deceased Person

Prof. Dr. med. Erich Rügheimer
Professor emeritus of the Department of Anaesthesiology
Dean 1974 – 1979

2008 – Deceased Persons

Dr. med. Heinrich Baust
Medical researcher in the Department of Radiology

Prof. Dr. med. Werner Bautz
Chair of Diagnostic Radiology 1996 – 2008
Medical Director 2006 – 2008

Prof. Dr. med. Volker Becker
Professor emeritus of the Chair of General Pathology and Pathological Anatomy
Dean 1981 – 1983

Prof. Dr. rer. nat. Ralph Grassmann
Scientist in the Institute of Clinical and Molecular Virology

Walburga Forster
General duty nurse in the University Hospital Erlangen

Thomas Holz
Radiographer in the Department of Medicine 2 – Cardiology and Angiology

Petra Kandler
Housemaid in the Department of Obstetrics and Gynaecology

Dr. med. h. c. Kurt Köhler
Syndikus and Chancellor of the Friedrich-Alexander-University Erlangen-Nürnberg
1966-1988
Honorary Doctorate of the Medical School

Hannelore Macher
Administration secretary in the University Hospital Erlangen

Andreas Stark
Former male nurse and member of the Employee Committee of the University

Prof. Dr. med. Helmut Valentin
Professor emeritus of the Chair of Occupational and Social Medicine
Dean 1969 – 1970

Marcus Voigtmann
Laboratory technician in the Division of Neuroradiology of the Institute of Radiology

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Cover
The cover shows the motif „Orientation“
by the artist Silvia Stabel
www.silvia-stabel.de
E-Mail: sistabel@web.de
A further motif you will find at page 161
acrylic on canvas