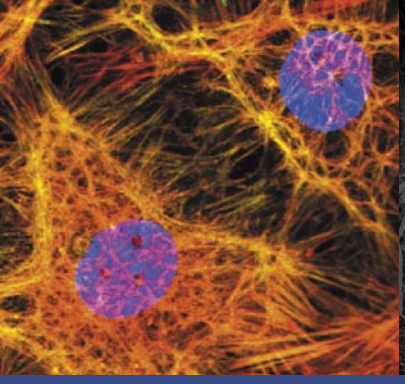
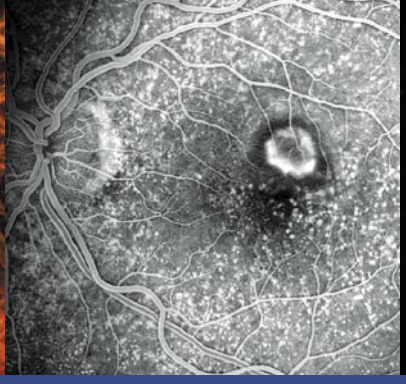
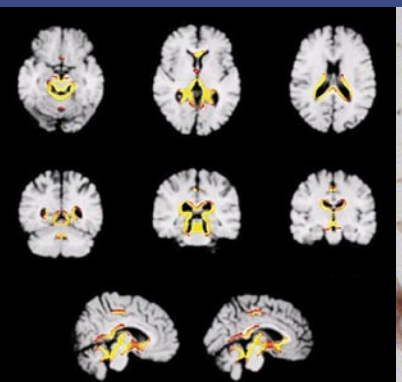
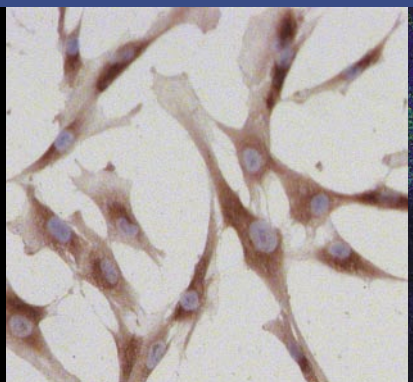
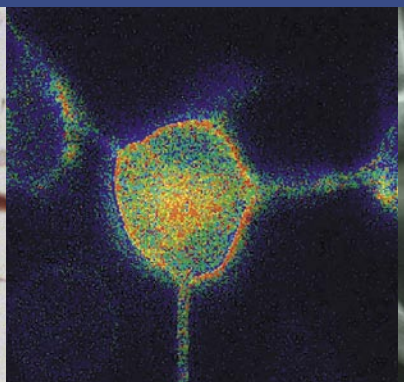
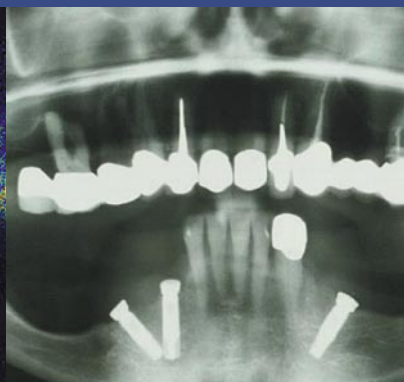



University of Würzburg
Medical Faculty

Research Report 2008

University of Würzburg
Medical Faculty

Research Report 2008

Content

1 General Part
1.1 Preface

After having issued the last research report in 2002, the Faculty of Medicine is again presenting a report documenting the achievements and activities of the institutes, clinics and research units and opening this information to the public.

Both, the Faculty of Medicine's scientific foci and its strength particularly with regard to the biomedical basic science, are decisively shaping the university of Würzburg. Targeted appointments and a very close cooperation with the scientific faculties were regarded as decisive premises for the development of the scientific profile and the development of productive research structures in the past. The foundation of the Biocentre (Biozentrum), the setup of the Research Center for Infectious Diseases (in which chairs of the Faculties of Biology, Physics, Chemistry and Pharmacy besides diverse sections of the Faculty of Medicine are integrated), as well as the installation of the Rudolf-Virchow Centre for Experimental Biomedicine - one of the first DFG-funded research centres – represent outstanding examples, not only for the thematic breadth of the various biomedical disciplines represented in Würzburg, but also for the close cooperation between the faculties and the interdisciplinarity of the research approaches. The close cooperation between the theoretical institutes and the clinical departments is a further characteristic of the university medicine in Würzburg. The Interdisciplinary Centre for Clinical Research (IZKF) highlights this interaction between basic research and disease oriented research. Research institutes and departments which are closely linked to the clinics have been installed, measures which help to realize and structure the transformation of the biomedical and disease oriented basic research into clinical research involving human subjects. The Medical Faculty is further promoting these processes and will set forward-looking impulses to the clinical and patient-oriented research and the translational health research. A special emphasis in this context will be given to the further expansion of disease focussed centres, following thus the examples of the already established Cardiovascular Centre, the Breast Centre and the Tumor Centre.

The Faculty of Medicine puts a special focus on the following thematic fields:

- Infection and Immunity
- Cardiovascular system
- Neuroscience
- Cancer, growth and differentiation
- Structure and function of proteins

The mentioned core themes are becoming evident by interdisciplinary joint activities which are supported by external third-party funds; these joint activities comprise collaborative research centres, post graduate programmes, DFG research groups, the DFG Research Centre for Experimental Biomedicine (Rudolf-Virchow-Centre) and integrated projects funded by the BMBF and the EU. Members of the Faculty of Medicine are taking an active part in all of the nine collaborative research centres of the University of Würzburg from which five are especially closely linked to the Faculty of Medicine via their speakers. Würzburg's Faculty of Medicine is standing out for its reinforced support by third-party money for the joint projects. According to DFG records, the University of Würzburg is unique in Germany for raising more funds in medicine and biology for joint research activities than for individual projects. The most recent DFG fund ranking proves that 80 % of the DFG allocations at the University of Würzburg account for biology and medicine. A 60 % share of the third-party fund expenditures go on medical facilities at the University of Würzburg. This extraordinary position is also made evident by the statistics of the DFG fund ranking: Würzburg's Faculty of Medicine is holding the 1st rank with € 50.9 mio. (Fig. 1), followed by LMU Munich (€ 36.9 mio.) and Tübingen (€ 35.5 mio.). These figures show that the Faculty of Medicine is extremely productive, making obvious that the Faculty of Medicine essentially shapes the scientific profile and underline it's strategic importance for the University of Würzburg.

After having visited the Faculty of Medicine in 2005, the German Council of Science and Humanities has released a statement in 2006 about the faculty's further development. The document expressly acknowledges the extraordinary level of performance as a location of biomedical basic research. It also highly acknowledges the faculty's research profile with the above mentioned five research priorities which have been developed within the past decade. This profile has made Würzburg a biomedical research area of supra-regional, in parts even of international reputation, taking into special account that apart from the university no other research institutions are present in Würzburg.

The statement of the German Council of Science and Humanities also reconfirms the Faculty of Medicine's concepts which are giving support to the development of junior scientists.

In this respect, the Faculty has perfectly achieved to substantiate the scientific focus through new, respectively complimentary teaching concepts. During the past years, the Faculty of Medicine has complemented the studies of Human Medicine and Dentistry by innovative educational structures and two new courses of studies. The course of studies Biomedicine, concluding with the Bachelor of Science (B.Sc.) and being complemented by the masters programme (M. Sc.), is concentrating on the basic molecular and cellular principles of life. The curriculum, which has been developed in cooperation with the Faculty of Biology, promotes the practical training in the laboratory. This course of studies aims at producing scientists for the promising area of biomedical research at universities and in the industry. A training programme for medicine students, complimentary to the research foci, has been developed by the implementation of the accompanying study course *Experimental Medicine*. This course of studies shall arouse the students' interest for basic research at a very early stage and thus contribute to incrementing the number of junior researchers. The efforts for recruiting and educating junior researchers have been followed up by the implementation of the *Graduate School of Life Sciences (GSLS)* in 2006 which is an important tool for graduate training and which also gives evidence of the excellent cooperation between the Faculty of Medicine and the scientific faculties.

The further development of the Faculty of Medicine will depend on the creativity of its scientists and a purposeful appointment policy on the one hand. On the other hand, it will essentially depend on the further improvement of the edificial substance. Moving into the Centre for Operational Medicine (ZOM) in 2004 as well as the imminent completion of the Centre for Internal Medicine (ZIM) are milestones for the development of the Faculty of Medicine, rendering more attractive the location for patients. These measures also contribute to develop and implement new concepts for the training of medical students and to support the faculty's efforts for further developing and strengthening the clinical research. The room situation for laboratories has partially improved when the Centre for Experimental Molecular Medicine (ZEMM) was taken into operation in 2007/2008. The new facilities which will be gained for the working groups of the Rudolf-Virchow-Centre and the Institute for Molecular Infection Biology by the move of the Surgical

Clinic into the ZOM will again decisively improve the working conditions for basic research and experimental clinical research. The mentioned building projects as a whole are forming part of a comprehensive concept bringing together all the institutes and clinics of the Faculty of Medicine on the medical campus within the next few years. I should like to use the opportunity in order to express my sincere thanks for the huge support for the realization of this concept which the Faculty of Medicine is being given by the Bavarian State Government and the Bavarian Parliament. My special thanks goes to MR (ret.) R. Külb from the Bavarian State Ministry for Sciences, Research and the Arts, his successor, MR H. Dierl, the member of the Budget Committee of the Bavarian Parliament, M. Ach (MdL) and Prof. Dr. W. Eykmann (MdL), for their efficient support for the Faculty of Medicine.

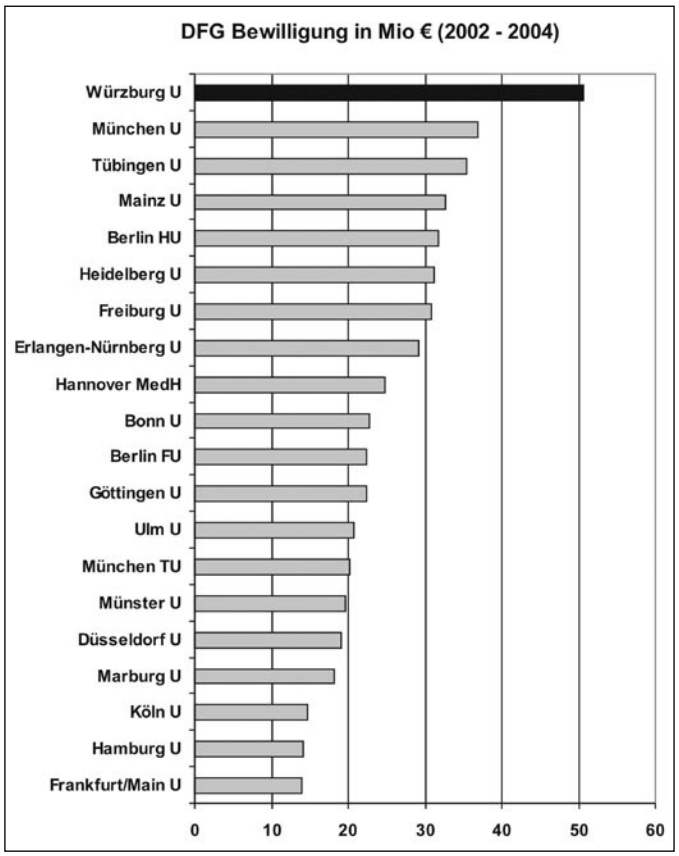


Fig. 1: Nationwide comparison of the DFG allocation 2002 – 2004 (source: DFG).

Finally, I am very grateful for the numerous suggestions which we have received from externs, the critical and constructive advice of our assessors of our research centres and research cooperation, who essentially contribute to the positive development of our faculty. I also thank the members of the science council, who have given valuable advice and impulse with their statements for the further development of our faculty. Sincere thanks go further to the members of the closer and wider Faculty Board and to the persons affiliated to the Faculty of Medicine, who are notably contributing to the reputation and further development of the faculty with their engagement and creativity. The fruits of the concerted efforts are described in detail in the reports on the following pages.

Würzburg, January 2008
Professor Dr. med. Matthias Frosch
Dean

1.2 Medical Education

The requirements of the new Medical Licensure Act (ÄAppO) were implemented in the clinical studies in the summer term of 2004. A thorough reorganization of the curriculum and study schedule was necessary for this purpose. The essential intention of the new Medical Licensure Act is to extend and improve the clinical practical education as well as to create interdisciplinary educational contents. For this purpose, 12 new interdisciplinary courses and required two-week clerkships in five clinical disciplines had to be integrated in the curriculum. Under the new regulations, the two written state exams formerly held during the clinical studies (1st and 2nd state examination) are not part of the curriculum any more. Therefore, a large part of the responsibility for carrying out appropriate examinations had been transferred to the faculties. For each discipline, for each interdisciplinary course and each new required clerkship during the clinical studies a graded certificate of achievement had to be issued. The three graded certificates of achievement for the new interdisciplinary courses constitute a special challenge.

In conjunction with the curricular changes described, the Faculty of Medicine has issued regulations for studies and examinations conforming in every detail to the requirements of the new Medical Licensure Act.

Students

At present 1,923 students are enrolled at the University of Würzburg for Human Medicine, 625 for Dental Medicine, 76 for Biomedical Sciences (Bachelor) and 36 for the master course in Biomedical Sciences (status quo: winter term 2007/2008). 154 medical students are first-year students; 23 of them were granted admission guaranteeing them a university place only until the end of their preclinical studies including the first part of the State Medical Licensing Examination (Physikum). 122 students are enrolled per term in the clinical study.

Skills Lab

The new Skills Lab, a practical clinical skills teaching facility for Medical students, was put into operation for the first time in the summer term of 2004. The investment budget of 50,000 Euro permitted the purchase of numerous models and other equipment. Furthermore, 1,5 positions were created and various tutors were contracted for the operation of the Skills Lab. Several required courses are held in the Skills Lab and represent an essential element in the curriculum. Through an intensive training with special phantoms and models students learn and develop practical skills needed for their profession. Since summer 2007, skills acquired during these courses are tested with a standardized protocol (OSCE: Objective Structured Clinical Examination). The skills lab is open for medical students all day long, so that all facilities are available for free training.

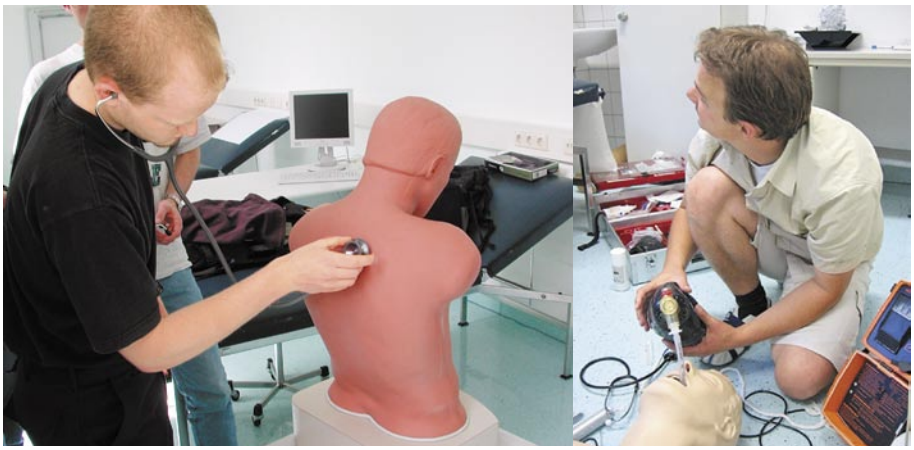


Fig. 1: Practicing with phantoms in the Skills Lab.

General Medicine

The new Medical Licensure Act is giving more importance to the subject of general medicine in medical studies. Medical students in Würzburg now have to complete a two week clerkship at a general practitioner's office, and they are offered "general medicine" as an optional subject during their internship. In addition to the existing net of general practitioners' offices, the Medical Faculty has contracted numerous new general practitioners for this purpose. A part-time position for a physician has been created to coordinate the students' training in general medicine.

New required clerkships

In addition to the clerkship in general medicine, the students have to complete two week clerkships in surgery, internal medicine, paediatrics and gynaecology. In order to improve the educational conditions for each student during this training, tuition fee-based financing has been used to employ teaching coordinators for surgery, internal medicine, paediatrics and gynaecology.

Electives

As the Free State of Bavaria has discontinued to grant financial support for hospitals involved in the education of Medical students, the Faculty of Medicine has concluded new agreements concerning the medical students' education during the last-year internship (Praktisches Jahr) with all hospitals associated with the University (Juliusspital Würzburg, Missionsärztliche Klinik Würzburg, Klinikum Aschaffenburg, Klinikum Coburg, Leopoldina-Krankenhaus Schweinfurt) in 2005/2006. Comprehensive evaluations have highlighted critical points and possibilities for improvement of the education during the internship, and have served as a basis for developing and implementing a structured internship curriculum in cooperation with the involved hospitals. For this curriculum a so-called logbook has been devised, which serves as a guideline for the students' training during the internship. Anamneses, medical examinations, diagnostic and therapeutic measures, etc. that have been performed by the student are documented by the mentoring doctor. The first evaluations which were made after the reorganization of the curriculum show that the implemented measures have helped to improve the internship training considerably.

Evaluation

Students' evaluations of courses and lectures have been regularly performed since 1999. More than 80 % of the students regularly participate in the evaluation process and thus provide extensive and significant data, which have led to different adjustments and improvements of the educational program. For the respective teachers as well as for the clinics and institutes the evaluation results offer an excellent basis for critically reviewing their own teaching quality. Extraordinary evaluation results are criteria considered in the assignment of the achievement-based financial support (Leistungsorientierte Mittelverteilung, LOM).

Examination performance

In comparisons of results of the written examination included in the First Part of the State Medical Licensing Examination ("Physikum"), the University of Würzburg

scores top ranks among German medical schools. In spring 2006, 2007, Würzburg medical students ranked first. Moreover, medical students in Würzburg were very successful in the written examination of the Second Part of the State Medical Licensing Examination: in spring 2007 and autumn 2007 they ranked third among the 35 German faculties. Thus, the Würzburg medical students were obviously very well prepared for this demanding final medical examination.

Albert-Koelliker teaching price

Since winter term 2003, the Albert-Koelliker teaching price endowed with 10,000 Euro is awarded for extraordinary teaching achievements. A commission composed in equal parts of professors and students chooses the laureate from the proposals. Laureates honoured to date are listed in paragraph 6 ("Essential Data of the Faculty"). The Albert-Koelliker teaching price is awarded each term in June and in December in the course of the Medical Faculty's graduation ceremony in the Neubaukirche of the University.

Fig. 2: Awarding ceremony of the Koelliker teaching price to doctors and tutors of the Skills Lab by the Dean of Student Affairs, Prof. D. Drenckhahn. Picture taken during the exam celebration in the Neubaukirche on 1st December 2007.

Tuition fees

Starting with the summer term of 2007, students studying in Bavaria have to pay tuition fees of 500 Euros per term. Tuition fees have to be used exclusively for the improvement of teaching and learning conditions, and it is important to clearly distinguish this purpose from financing staff and basic equipment by the University`s budget provided by the state of Bavaria. Tuition fees amount to approx. 1 Mio Euros per year, with 700,000 Euros available for educational purposes in preclinical and clinical medicine including Biomedicine, and 270,000 Euros for education in dental medicine. Expenditure of the fees is decided by a commission with equal representation of students and professors.

In the beginning, equipment designed to improve practical training conditions was purchased such as modern microscopes, photometers, cardiograms, phantoms, plastinated body slices and anatomical models. Numerous student tutors were employed for course mentoring and practical training. Financial support is also granted to doctoral students to allow them to participate at international congresses in order to present the results of their thesis research. Further means are used for the improvement of childcare facilities for students' children.

About half of the fees are used for the employment of teaching coordinators, who organize and improve course curricula preferentially for the clinical education. Teaching coordinators were granted for surgery, internal medicine, neurology, psychiatry, gynecology, pediatrics and for interdisciplinary oncology. A further part-time position has been created for the promotion and coordination of international student exchange programs. For the future, the clinical-practical training shall be further expanded and improved. For this purpose, a skills clinic (teaching clinic) shall be built up, into which the present skills lab will be integrated.

E-learning – blended learning

The virtual Bavarian University (Virtuelle Hochschule Bayern – vhb) has been financing numerous E-learning projects, for example in dermatology, rheumatology and internal medicine. At present, a university-wide project of E-learning is being promoted, partially financed by tuition fees. The final goal is to integrate E-learning into all curricula ("blended learning"). In this project, the Faculty of Medicine is cooperating with other faculties, for example informatics, law, economics, philosophy and biology. The E-learning platform WueCampus which is also partially financed by tuition fees, facilitates access and orientation for all students.

E-learning in Würzburg can rely on further financial support thanks to the installation of a "centre of competence in medical education in Bavaria" ("Kompetenzzentrum Lehre in der Medizin in Bayern") by the Bavarian State Ministry for Science, Research and Art, which provides means for the employment of 5 scientists over a period of three years. Among the five Medical faculties of Bavarian universities participating in the Bavarian centre for medical education, Würzburg represents the competence centre for E-learning. The competence centres based at the other Medical faculties are the centres for examinations (LMU Munich), training during the internship (TU Munich), medical-didactic qualifications (Regensburg) and evaluation (Erlangen).

Accompanying study course for Experimental Medicine

In order to offer medical students the possibility of an intensive education in the field of biomedical basic research, an "accompanying study course for experimental medicine" was launched in winter term 2005/2006. This study course is mainly focussed on research and imparts current scientific issues in the biomedical field as well as basic methods and experimental approaches at the interfaces of medicine, biology, chemistry and physics. The study programme is based on an interdisciplinary cooperation between the faculties of medicine, biology, chemistry and physics.

The number of course participants per term is limited to 5, which permits an intensive mentoring of the students. At present, 17 students (5 of them female) are enrolled in this programme.

The study course programme is designed to prepare the participating students for their medical dissertation. The students are expected to submit an experimental dissertation about a topic of the training program. After completion of the whole programme including the medical dissertation all conditions are fulfilled to prepare a dissertation in natural sciences at

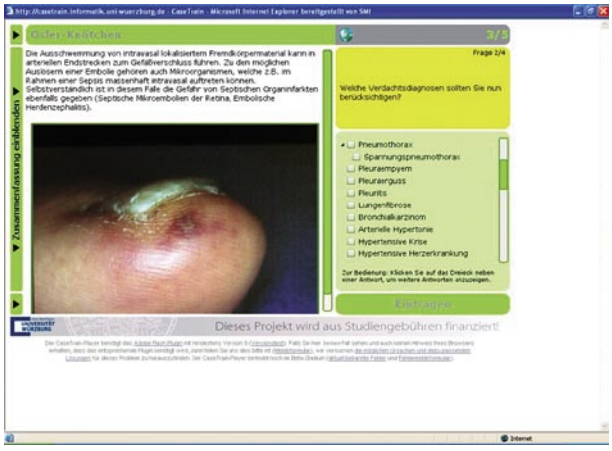


Fig. 3: Example of an E-learning case in internal medicine in WueCampus.

the Faculty of Biology of the University of Würzburg, and to finally receive the degree of "Dr. rer. nat" (PhD). This program thus complements the successful MD/PhD programme of the Faculties of Medicine and Biology.

Dental medicine

At present, more than 600 dentistry students are enrolled at the University of Würzburg. About 260 of the students are in the preclinical, 350 in the clinical part of their education. The clinical studies are organized according to the currently valid Medical Licensure Act for dentistry students, and all required practical and theoretical courses are offered. The recently refurbished dental clinic is located in the city centre. The dental clinic's location guarantees a high patient accessibility and an immediate proximity to the local population. This becomes evident by the high patient influx: more than 28,000 out-patients and more than 1,300 in-patients were treated in 2007.

All departments are equipped according to the newest technical standard. State-of-the-art equipment necessary for a modern dentist training is available. In most departments, interactive teaching concepts and problem-based learning integrated in the clinical training are now offered. Students have access to an extensive library with numerous computer work stations with internet connection.

The tuition fees allotted to the dental clinic are mainly used for the financing of tutors and a part-time teaching coordinator as well as for the financing of partly extremely expensive instruments and expendable items for student courses. A part of the financial burden, which dental students have to bear today, is thus taken off.

In winter term 2007/2008, for the first time, a Committee and Dean of Student Affairs and a Committee for Student Affairs were appointed for the dental school. The new Medical Licensure Act (ZAppO) for dentistry which has been announced for a long time will apparently be issued soon and will require a significant effort for restructuring the studies of dental medicine.

Biomedical Sciences

The first students of Biomedical Sciences were enrolled in winter term 2000/2001. The curriculum comprises six terms with courses and lectures in natural sciences and preclinical and theoretical clinical medicine and final graduation with the degree of "Bachelor of Science (B.Sc.)". The undergraduate study course is complemented by a postgraduate course, comprising three terms during which participants acquire the "Master of Science (M.Sc.)" degree, and can then go on in order to receive a PhD (Dr. rer. nat.). For PhD students, a special class "Biomedical Sciences" is available within the Graduate School of Life Sciences at the University of Würzburg. This interdisciplinary study course is also open for postgraduate students of the faculties of Biology, Medicine, Physics, Chemistry and Mathematics.

Outlook for the future

The Faculty of Medicine aims at expanding the international network by building up new partnerships with foreign universities and by establishing a special study course programme for Human Medicine taught exclusively in English. Furthermore, a teaching clinic as well as a mentoring programme for female students shall be implemented in the near future. Moreover, it is of great concern for the faculty to improve the child care conditions for students' children.

Professor Dr. med. D. Drenckhahn, Dean of Student Affairs for Human Medicine
Professor Dr. med. Dr. med. dent. A. Kübler, Dean of Student Affairs for Dental Medicine
Dr. rer. nat. E. Lüneberg, Dean's Office

Fig. 4: Students of dental medicine at the phantom course.

1.3 Students' Representatives

Josef-Schneider-Str. 2
97078 Würzburg

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Fax: 0931 201-53858

E-mail: info@fi-med.de

The group students` representatives are both elected as well as non-elected students who are committed to work voluntarily for the interests of medical students at the University of Wuerzburg Medical School. We have an office at our disposal which is located in building No. D7 of the University Hospital.

Our work mainly consists of two parts: On the one hand we officially represent the medical students in various committees: the faculty and the student council and the several appeal commissions of the faculty. The second part includes several projects, such as working in our office, giving advice to students, organizing different information events as well as contributing to students' social life at university by carrying through various parties or other meetings.

The committees

The students´ representatives are entitled to vote on many concerns of the faculty. Here, we opine the students' point of view on all topics being discussed. According to the Bavarian university- law of October 2006, at least one student member is part of every committee. Our representatives in these committees are being elected by all medical students. In this context, a topic with exorbitant interest are the newly implemented study fees. By constituting a committee of equal numbers of students and professors, we set up a successful system of how to manage the allocation, reviewing and evaluation process. In any case, the study fees represent a new challenge for all persons concerned, especially within the context of a responsible and effective allocation.

Projects

During the past three years we have been publishing a guideline for medical students in their first semester (so called "Vorklinik") and for students in their fifth semester (i.e. beginning of "Klinik"). It informs students about the faculty, lectures, courses, exams, books, ongoing events and many more topics. We provide further information to all students of the faculty on our homepage or in the rooms of our office, where we also have at our disposal specific learning material for most of the subjects. In addition, the local representatives of the exchange section of the German Medical Students' Association (bvmd-Germany), helping students in Wuerzburg to organize their international internships, and SEG-Med stand to the students' disposal in our faculty. SEG-Med is a cooperation of numerous medical students throughout Germany that enables its members to purchase medical equipment (stethoscopes e.g.) to a lower price. Once a week our students' council meeting takes place, which is supposed to enhance the exchange of information between all members and to give room to discussions on current topics. Additionally, students may contact us for advice with problems, conflicts or new ideas which concern the faculty, the students' council, lectures, courses, professors etc. At the beginning of every semester we organize the so-called freshmendays where freshmen at the university get a chance to get to know the university, their fellow students and the city of Wuerzburg. Furthermore, we contribute in the organization of several social events, such as film evenings, parties and opening days for students and pupils. On our permanent effort to improve students' curricula and the system of education, we carried out an online survey in December 2007, in order to evaluate the structure of the schedule. All students from third year (fifth semester) on were asked to pronounce their opinion to furnish an overview on the broad interest of students at our faculty.

Susanne Keilig
Sophia Danhof

1.4 The History of the Würzburg Medical Faculty

The Medical Faculty of Würzburg ranks among the four oldest medical faculties in Germany. It was preceded only by Heidelberg, Cologne and Erfurt, and thus has today a history of more than 600 years behind it. Together with theology and law, medicine had its place assigned among the three higher faculties in 1402 already, at the original foundation of Würzburg University. It remains unclear to this day, however, to what degree formal medical teaching was inaugurated at the time. Certainly, any regular teaching activities must have come to an end with the rapid decline of the University as a whole. Long before 1402 already, Würzburg was held in high esteem as a center of medical learning, however. Already in the late 13th century the abbot of the monastery of Aldersbach in Lower Bavaria undertook a journey of more than 300 kilometers to consult the learned physicians in Würzburg about his failing health. About the same time, probably around 1280, one of the most influential vernacular medical handbooks of the Middle Ages was written, the "Arzneibuch" of Ortolf von Baierland who called himself explicitly a "physician from Würzburg". Compiled "from all the Latin medical books I have ever read", Ortolf's "Arzneibuch" offered of *summa* of medieval medical learning. From the mid-14th century, an topographical illustration of the brain by the Würzburg canon Berthold von Blumentrost has come down to us, which attributed the major rational faculties – imagination, cogitation and memory – to the various cerebral ventricles. This made perfect sense within the ruling Galenic paradim, which associated the rational faculites with very subtle and mobile animal spirits in the ventricles rather than with the cerebral substance itself.

In the 16th century, various learned physicians of renown were active in Würzburg, Burckhard von Horneck, for instance, and Johannes Posthius. Only with the second foundation of the University in 1582, however, formal academic medical teaching was put into place again. Again, medicine ranked among the University's three higher faculties from the start, though it took several years until the Medical Faculty truly came to life. In 1587, the faculty's statutes were approved. By 1593, finally, the professors had been appointed and began teaching. Würzburg had come to offer exceptionally good conditions for a sound medical education. Adrian van Roomen, also known as Adrianus Romanus, had been appointed to the first and most prestigious professorship, the chair for medical theory. Within a couple of years, van Roomen, who was also a mathematician of international acclaim, succeeded in establishing a flourishing culture of medical dissertations and disputations and promoted a number of medical students to doctors. At the same time, conditions for clinical, practical training had markedly improved, thanks to the newly founded Julius-Spital. In contrast to many other contemporary hospitals which cared almost exclusively for the aged and invalid, the Julius-Spital was, from its very beginning, explicitly designated also as a hospital "in aegrorum curationem", i.e. for the medical treatment of the curable sick. With its many patients, the Julius-Spital thus offered a welcome opportunity to medical students to observe manifold diseases and to experience the effects of different curative approaches. Such bedside teaching was very popular among contemporary medical students and was a major reason, why a number of medical students crossed the Alps and frequented one the Northern Italian universities, where they were commonly allowed to accompany the professors on the visits to the large municipal hospitals.

After van Roomen's retirement and death and due to the recurring outbreaks of plague and the Thirty Years' War the Würzburg Medical University lost much of its international renown, however. Only very few medical students continued to find their way to Würzburg and even fewer were promoted to doctors of medicine. From the late 17th century, the government tried to counteract this trend and initiated important reforms. The number of medical chairs was raised to five in 1709; originally there were only two or three. Following the example of leading protestant universities such as Leiden and Halle a botanical garden was set up; botanical gardens were then considered important teaching tools which helped medical students get familiar with the various plants used as medicinal drugs. An anatomical theater was built in the garden pavilion of the Julius-Spital and the famous Parisian surgeon Louis Sievert was brought in to improve anatomical teaching. The professor of anatomy was instructed to dissect a corpse at least every four weeks in the winter time, in the presence of the other professors. Academic disputations and dissertations were encouraged. Yet these efforts bore little fruit, at first. The Faculty lacked professors whose fame could attract medical students from further away, and the teaching methods remained rather old-fashioned. In 1739, the professors still had to be explicitly forbidden to dictate their lectures were by word. In 1758, Karl Philipp von Greiffenklau began his request for a survey of the Faculty's state bluntly by asking: "Wherein lies the cause of the immense decline of the Medical Faculty?"

It was due primarily to the incessant activities of one man, Carl Caspar Siebold, that this rather desolate situation changed within a couple of decades and the Würzburg Medical Faculty became one the foremost institutions of its kind in Germany. Siebold, since 1769 professor of anatomy, surgery and obstetrics, began a systematic drive to improve medical education, introducing new modern teaching methods. Since 1766, medical students had been offered regular clinical instruction again, in the Julius-Spital. Towards the end of the 18th century, large scale reconstructions work created space for about 200 curable patients and thus markedly improved the conditions for practical bedside teaching. Siebold was also a driving force behind the rebuilding of the *Theatrum anatomicum* and behind the establishment, in 1805, of a modern operation theatre in the Julius-Spital. Siebold's sons were to follow their father's footsteps and like him contributed to the modernization of the hospital care and medical instruction. Johann Barthel von Siebold who worked primarily as an anatomist and surgeon lectured about pathological anatomy for the first time. Adam Elias von Siebold continued his father's efforts to improve obstetrical training for medical students and midwives. In 1805, he opened the first obstetrical hospital in Würzburg in a building which formerly housed epileptics.

The rapid ascent of the Medical Faculty under Siebold and his sons was ultimately crucial for the survival of the University as a whole. When Würzburg came under Bavarian rule in 1803, it was the university in Bamberg rather than the one in Würzburg which was closed. In the process, the Würzburg Medical Faculty even saw its fame further promoted by leading professors from the former Bamberg institution. One of Germany's foremost anatomists, physiologists and embryologists, Ignaz Döllinger, joined its ranks. Like Döllinger, Wilhelm von Hoven, a former school mate of Friedrich Schiller, came from Bamberg to Würzburg. Later he became a major medical figure in Nuremberg, and was, by all appearances, the driving force behind the first double-blind trial in history, which was organized in Nuremberg 1835 in an attempt to disprove the efficacy of homeopathic drugs. The strongest attraction on German medical students was exerted, for a couple of years, by the Philosopher Schelling who sought to put medicine on new, philosophical foundations. At the

height of his fame in Würzburg, 270 students wrote their names into the matricles in one year. Soon, growing disillusionment set in, however, and his audience shrank rapidly.

Over the following decades, Würzburg increasingly turned into a center of empirical-observational and, finally, laboratory-based, experimental approaches. Clinical instruction was further thanks to a massive expansion of policlinical care. Thousands of out-patients provided medical students with unique possibilities to visit and observe the patients in their homes and to take responsibility for their care, guided by a more experienced physician. Johann Lukas Schönlein, the foremost representative of the so-called "natural history school" in medicine, introduced scores of students to his approach. He focused on a detailed and unprejudiced observation of signs and symptoms as the basis of a new, empirically founded nosology. Thanks to his method Schönlein described various diseases for the first time and some like the Schoenlein-Henoch purpura (*Vasculitis allergica*) carry his name to this day. Nikolaus Anton Friedreich gave an account of facial nerve paralysis. Johann Georg Pickel and Johann Joseph von Scherer helped lay the groundwork for a modern science of pharmaceutics and medical chemistry respectively. Around the middle of the 19th century, Franz von Rinecker was the Faculty's dominant figure. He made important contributions to pediatrics, psychiatry and dermatology alike and thanks to his efforts Würzburg can boast one the first pediatric hospitals at any university in the world. Under Rinecker's leadership, Rudolf Virchow and Albert Kölliker were appointed professors, who helped turn anatomy and pathology into modern laboratory sciences and, in the case of Virchow's cellular pathology, provided contemporary medicine as a whole with a new theoretical basis. Outstanding contributions came from researchers outside of the Medical Faculty, from the biologists Julius Sachs and Theodor Boveri, for example, and, above all, from the physicist Wilhelm Conrad Röntgen who discovered the x-rays.

By 1900, the Julius-Spital – in 1800 still to a large degree a last resort for poor, single patients and invalids – and the various university hospitals had become the most important providers of medical care in Würzburg. In the 1920s, the close and fruitful, though sometimes conflict-ridden ties between the Juliusspital and the Medical Faculty were somewhat loosened when the new Luitpold-Hospital was built in Grombühl.

The National Socialist period left deep marks on the Würzburg Medical Faculty. The Institut für Vererbungswissenschaft und Rasseforschung (Institute of Genetics and Racial Research) conducted large scale genetic surveys of the population in the area around Würzburg. The Werner Heyse, who was appointed professor of psychiatry in Würzburg in 1939 in disregard of the Faculty's preferences, played a leading role in the so-called „Aktion T4", the organized mass murder of 10.000s of psychiatric and handicapped men, women and children between 1939 und 1941. Based on the „Gesetz zur Verhütung erbkranken Nachwuchses" (1933) forced sterilizations and abortions were performed in the Maternity Hospital under Carl Gauß. George Schaltenbrand, professor of neurology and later widely acknowledged as one of the leading researchers on multiple sclerosis in the world, vaccinated inmates of the psychiatric hospital in Werneck with the cerebral fluid of monkeys who, he believed, suffered from multiple sclerosis, in order to prove the contagious nature of the disease. Most of the other hospitals and institutes were also in some way or other implicated in National Socialist medicine and almost all professors lost their chairs after 1945.

The massive air raid in the spring of 1945 also damaged or destroyed large parts of the university and the hospitals. Already a couple of days after the raid, the first operations were performed again, however, and out-patient care as well as work on the wards was resumed. Only ten years after the end of the war, the Faculty counted three of the big names in contemporary Western medicine among its members, the surgeon Werner Wachsmuth, the internist Ernst Wollheim and the otorhinolaryngologist Horst Wullstein. Wullstein not only acquired international fame with his new method of tympanoplasty and his operation microscope. As the driving force behind the foundation of a "head clinic" he also set the path for a development towards the establishment of interdisciplinary centers which increasingly came to shape the Faculty and which acted as crucial catalysts for cutting edge biomedical research. In 1992, a new center for biomedical research was opened on the Hubland, which today brings together members of ten different institutions, from the faculties of medicine, chemistry and pharmacy as well as biology., In 2002, the *Virchow Zentrum* was established as a national research center for experimental biomedicine, endowed with a number of research professorships and research groups headed by junior researchers, which plays a major role in the new *Graduate School for Life Science*. Würzburg also has come to house a center for research on infectious diseases and a center for interdisciplinary clinical research. In addition, since 1971, a fair number of so-called "Sonderforschungsbereiche" (special research areas) have been active, financed by large grants from the Deutsche Forschungsgemeinschaft. The trend towards interdisciplinary research and medical care gained further momentum over the last years, with plans for the creation of a "Zentrum Operative Medizin" (Center for Operative Medicine), opened in 2004, a "Zentrum Experimentelle Molekulare Medizin" (Center for Experimental Molecular Medicine) and a "Zentrum Innere Medizin" (Center for Internal Medicine).

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2 Research Institutes
2.1 Institute of Anatomy and Cell Biology I

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Mission and Structure

The research at Chair I is dedicated to the structure, function, distribution and regulation of membrane proteins, in particular to transporters of sugars and drugs. Furthermore, the function of an intracellular regulatory protein for plasma membrane transporters is investigated. This regulatory protein represents a novel target for the modulation of transport processes. The methods used in this research include molecular biology, cell biological and biochemical investigations, transport measurements, electrical measurements on Xenopus laevis oocytes, and breeding and characterisation of transgenic mice.

Members of chair I are: the department head, four assistant professors, three technicians and MD-students. Two Post-Docs, two PhD-students funded by the Collaborative Research Centre (SFB 487) are also included.

Major Research Interests

The main focus is the elucidation of the molecular mechanisms of function and regulation of physiologicaly important transport proteins in the plasma membrane. One project deals with polyspecific cation transporters of the SLC22-family, which are involved in the absorption of drugs in small intestine as well as in excretion of drugs and drug metabolites in kidney and liver. Furthermore, these transporters are essential for the distribution of neurotransmitters in the brain. The first member of this family (OCT1, SLC22A1) of polyspecific drug transporters was cloned in 1994 in this department. Another project deals with the sodium-dependent D-glucose transporter SGLT1. SGLT1 absorbs dietary D-glucose in the small intestine and reabsorbs D-glucose from the primary urine in the proximal tubule of the kidney. A key element in this project is the investigation of the regulator protein RS1 (RSC1A1), which was cloned in 1992 in this group. RS1 regulates the trafficking of SGLT1 to the plasma membrane and modulates SGLT1 transcription in the nucleus.

Substrate recognition and transport mechanism of the polyspecific transporters of the SLC22-family

The SLC22-family of transporters includes transporters for organic cations, organic anions, and the zwitterion carnitine. Using site directed mutagenesis we identified seven amino acids in OCT1 that are critical for the binding of substrates and inhibitors. Computer modeling of the OCT1 tertiary structure in analogy to the elucidated structure of a bacterial transporter (lactose permease) revealed a large binding pocket in which the critical seven amino acids are directed to the aqueous phase. Using fluorescent labeling of single amino acids of OCT1 we could demonstrate motion of the 11th transmembrane domain during transport of organic cations. A detailed analysis of the currents induced by translocation of organic cations in wildtype OCT1 and rOCT1 mutants suggests a transport mechanism according to the “alternating access” model. In a first step substrate binds to the outward-facing substrate binding pocket. Thereafter the binding pocket undergoes a conformational change after which the subtrate binding pocket is accessible from the intracellular side (inward-facing conformation). This allows release of the substrate to the cytosol. We have successful expressed members of the SLC22-family in insect cells and in a cell free expression system. Furthermore, we purified and reconstituted active transporters in proteoliposomes. In collaboration with another research group attempts will be undertaken to crystallize expressed and purified transporters and to determine tertiary structures by X-ray diffraction.

Function and regulation of the sodium D-glucose cotransporter SGLT1

We generated SGLT1-specific antibodies, which are used to investigate the function and localization of SGLT1 in intestine, kidney, liver, lung, and different glands. Furthermore, we generated mice with a SGLT1 (SLC5A1 gene) knock out, which survive on a D-glucose and D-galactose free diet. A couple of years ago we cloned the intracellular regulator protein RS1, which is encoded by the intronless gene RSC1A1. RS1 is localized at the *trans*-golgi network, where it inhibits the budding of SGLT1-containing vesicles. During mitosis or in less differentiated cells, RS1 is localized in the nucleus, where it inhibits SGLT1-transcription. In mice with a RS1 (RSC1A1 gene) knock out, absorption of D-glucose in the small intestine was increased; furthermore, these mice developed adipositas. We identified two RS1 domains, which are responsible for the post-transcriptional inhibition of SGLT1. Tripeptides derived from these domains inhibited SGLT1 function at nanomo-

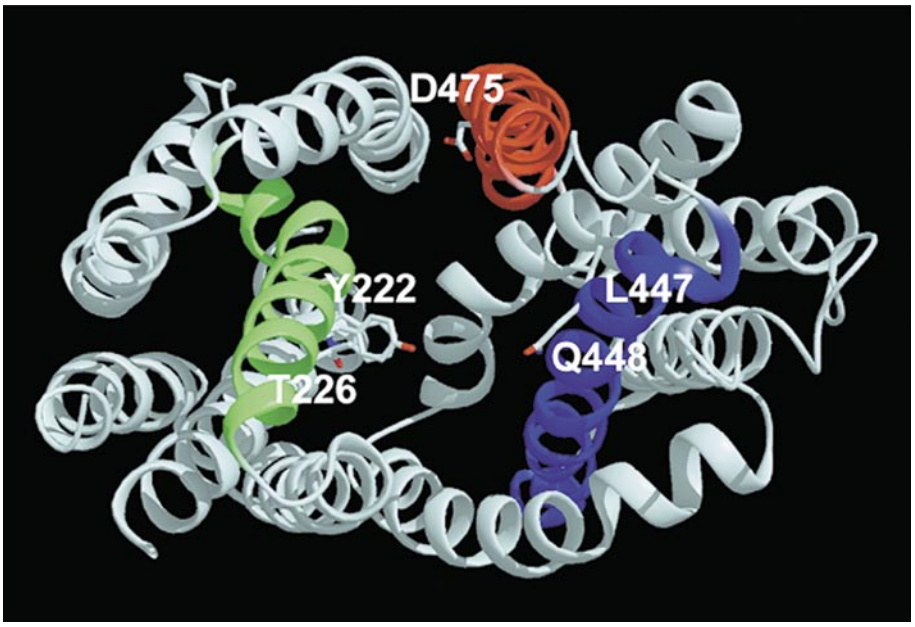

Fig. 1: Model of the inward-facing substrate binding pocket of the organic cation transporter rOCT1. The 4th transmembrane α-helix (TMH) is coloured in green, TMH10 is coloured in red. For the indicated amino acids a contribution to substrate binding has been shown experimentally.

lar intracellular concentrations. The inhibiting tripeptides are taken up by enterocytes via a peptide transporter and are, therefore, potential drugs for the treatment of adipositas.

Teaching

Education of medical and dental medical students in microscopical and macroscopical anatomy and in cell biology. Education of PhD and MD students. Classes in transporters and channels.

SELECTED PUBLICATIONS

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Vernaleken A, Veyhl M, Gorboulev V, Kottra G, Palm D, Burckhardt B-C, Burckhardt G, Pipkorn R, Beier N, van Amsterdam C, Koepsell H (2007) Tripeptides of RS1 (RSC1A1) inhibit a monosaccharide-dependent exocytotic pathway of Na^+-D-glucose cotransporter SGLT1 with high affinity. J. Biol. Chem. 282, 28501-28513.

2.2 Institute of Anatomy and Cell Biology II

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Mission and Structure

Research in the department is focused on two main areas of interest. The research group on cell biology (head scientist: Prof. Dr. D. Drenckhahn) analyses structural, molecular and functional properties of the cytoskeleton and the regulation of endothelial barrier.

The research group on neurobiology (head scientist: Prof. Dr. P. Kugler, Prof. Dr. E. Asan) studies the transport and metabolism of neurotransmitter glutamate and investigates the organization and ultrastructure of various CNS regions (e.g. amygdala).

Research in the department is carried out by 11 postdoctoral scientists, 18 Ph.D.-students, and 12 technical assistants.

Two existing experimental systems to measure forces between molecules and cells (atomic-force-microscopy, laser-tweezers) were further improved. In the years 2004-2006 a new technique to measure vascular permeability in rats in vivo (single-microvessel perfusion technique) was established.

Major Research Interests

Endothel barrier regulation in vivo and in vitro
(D. Drenckhahn, J. Waschke, N. Schlegel, A Hübner)

The endothelium lines the inner surface of the vascular wall. We investigate how inflammatory mediators induce the formation of gaps between endothelial cells which allow the leakage of plasma into the surrounding tissue and thereby may lead to severe edema. We focus on the regulation of cell adhesion molecules (cadherins, claudins, integrins) and of the cytoskeleton.

Molecular mechanisms of steroid-induced regulation of permeability in the haematoencephalic barrier
(C. Förster)

The integrity of the blood brain barrier (BBB) is compromised in many disorders of the human CNS leading amongst others to increased vascular permeability and reduced expression of tight junction and adherens junction proteins. Therapeutical strategies include treatment with the vasoprotective steroid hormones, glucocorticoids (GC) and estrogen which improve permeability properties of the BBB. Research projects concentrate on elucidating the molecular basis how GCs and estrogen regulate BBB permeability. Effects of GCs and estrogen are known to be mediated by their cognate steroid hormone receptors, the GC and estrogen receptor, so that a special emphasis is laid on their function acting as ligand-dependent transcriptional regulators.

Pemphigus pathogenesis
(D. Drenckhahn, J. Waschke, A Hübner)

The life-threatening blistering skin disease pemphigus is primarily caused by antibodies against cell adhesion molecules (desmocadherins). We investigate whether these autoantibodies directly interfere with binding of these adhesion molecules or whether cell signalling pathways are responsible for skin blistering.

Proteins of the nucleus
(S. Hübner)

The nucleus represents the “control center” of eukaryotic cells with many proteins playing an important role in maintaining its structural and functional integrity. We focus on such proteins (i.e. lamins and kanadaptin) and perform investigations in the context of fundamental and pathophysiological aspects (i.e. lamino-pathies).

Glutamate transporters in the brain
(P. Kugler)

Glutamate is used as an excitatory neurotransmitter by numerous neuronal systems in the brain. Synaptically released glutamate has to be eliminated rapidly from the extracellular space via glutamate transporters (EAAT1-5), since otherwise it would overexcite and damage neighboring neurons. We try to obtain insights into the subcellular localization and translocation of glutamate transporters in glutamatergic neurons.

Emotions
(E. Asan)

The corpus amygdaloideum (amygdala) is of decisive importance for emotional processes. Malfunctions in interconnections of

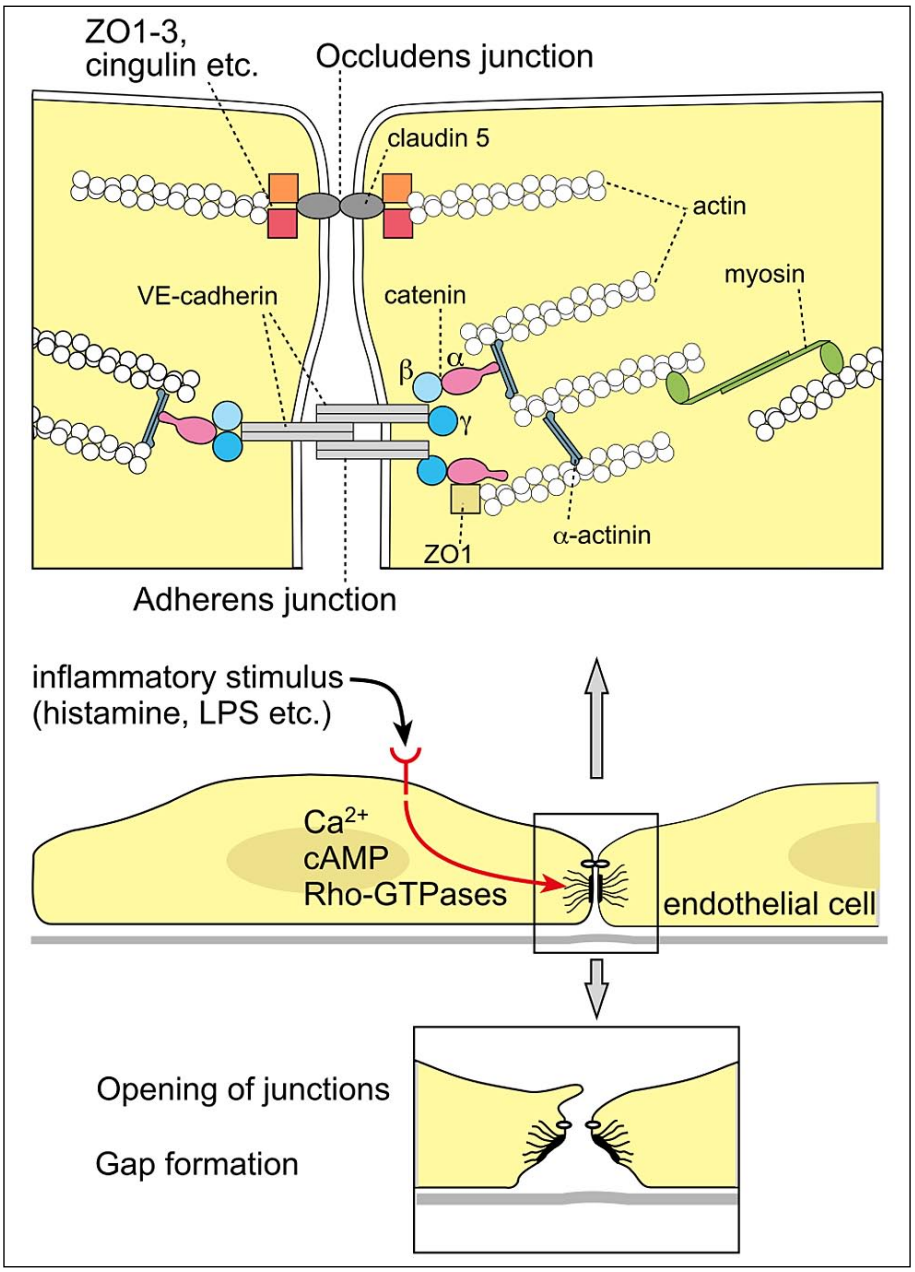

Fig. 1: Cytoskeleton and adhesion molecules (cadherins) control the barrier between blood and tissue (endothelial layer). How inflammatory stimuli modify the barrier is one aspect investigated by the group.

this brain area may contribute to neuropsychiatric, especially affective disorders. We analyze the structure of amygdaloid network and investigate which factors could be responsible for normal function and pathologic changes.

Ultrastructure of tissues and cells of the nervous system
(E. Asan)

Morphological investigations, especially on an electron microscopy level, deliver important contributions to the analysis of changes in the nervous system which may be the cause of neuropsychiatric disorders. By carrying out such investigations, we support studies in numerous clinical and basic science projects dedicated to elucidate molecular mechanisms of nervous system disorders.

Teaching

Courses in microscopic and macroscopic anatomy, neuroanatomy and cell biology are held for medical and dentistry students (a total of 430 students per year). The department hosts a yearly meeting of the Anatomical Society (last week of September).

SELECTED PUBLICATIONS

Asan E, Yilmazer-Hanke DM, Eliava M, Hantsch M, Lesch K-P, Schmitt A (2005) The corticotropin-releasing factor (CRF)-system and monoaminergic afferents in the central amygdala: investigations in different mouse strains and comparison with the rat. Neuroscience, 131:953-967.

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2.3 Institute of Physiology I

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Mission and Structure

Our research activities are in the field of cardiovascular physiology and pathophysiology. Our investigation has focused on understanding the molecular mechanisms associated with specific forms of arterial hypertension and cardiac hypertrophic remodeling. Another major point of interest is the function of SPRED proteins in cellular proliferation and differentiation. In particular, by application of gene targeting technology in mice, we obtained new insights into the diverse physiological functions of natriuretic peptides, nitric oxide (NO) and their guanylyl cyclase (GC) receptors as well as of SPRED proteins. These different projects are supported by the DFG (SFB 688 and 487, besides personal fundings) and the IZKF Würzburg.

Major Research Interests

Endothelial effects of the cardiac hormone atrial natriuretic peptide (ANP)
(M. Kuhn, B. Gaßner, B. Schreier)

The cardiac hormone atrial natriuretic peptide (ANP), via its vasodilating and diuretic effects, has an important physiological role in the maintenance of arterial blood pressure and volume. Its guanylyl cyclase-A (GC-A) receptor is highly expressed in vascular endothelium, but the functional relevance of this is controversial. To dissect the endothelium-mediated actions of ANP in vivo, we inactivated the *GC-A* gene selectively in endothelial cells. Mice with endothelium-restricted GC-A deletion exhibited reduced vascular permeability to plasma protein, resulting in chronically increased plasma volume, arterial hypertension and cardiac hypertrophy. Renal excretion and vasodilation did not account for these changes. Thus ANP-induced increases in endothelial permeability may be critical to the ability of ANP to lower arterial blood pressure. Our current studies supported by the SFB 688 are directed to dissect the cellular pathways mediating these effects.

Posttranslational modifications of the ANP receptor
(M. Kuhn, M. Hartmann, J. Schröter, A. Gazinski)

In some forms of arterial hypertension and as one of the earliest and pathognomonic events in cardiac hypertrophy and insufficiency, the cardiac synthesis and release of ANP is markedly enhanced, but the cardiovascular effects are clearly diminished, indicating a receptor or postreceptor defect of GC-A. Biochemical studies in transfected GC-A–overexpressing cells showed that phosphorylation of GC-A within the intracellular domain is essential for its activation process. In turn, desensitization and/or inactivation of GC-A probably involves ANP-dependent dephosphorylation of GC-A. Notably, the responsiveness of GC-A to ANP is also reduced by exposure to growth hormones such as Angiotensin II and endothelin and in vitro this correlates with receptor dephosphorylation. In collaboration with Professor Albert Sickmann (Protein Mass Spectrometry, Rudolf-Virchow-Center) our project in the SFB 487 attempts to identify (in)activating modifications of GC-A and the mediating regulatory proteins.

Cardiac effects of ANP
(M. Kuhn, K. Völker, S. Krautblatter, M. Klaiber)

Cardiac hypertrophy is a common and often lethal complication of arterial hypertension. Cardiac myocytes have signaling pathways that agonize and antagonize hypertrophic growth. In chronic hemodynamic overload, there is a significant increase in ANP expression in the cardiac ventricles. Our studies in cultured myocytes and genetically engineered mice showed that in this situation the ANP / GC-A pathway exerts not only endocrine but also local antihypertrophic actions (Figure 1). The molecular mechanism(s) by which ANP and GC-A inhibit cardiac hypertrophy is not definitively known. Our observations suggest that ANP modulates myocyte intracellular pH and $Ca^{2}+$ homeostasis and counter-regulates calcium-dependent hypertrophic signaling pathways such as CaMKII and calcineurin.

Interaction of Ca^{2+}- and NO-dependent Pathways in the Cardiovascular System
(K. Schuh, D. Fetting, T. Fischer, R. Freudinger)

Aim of this project is the generation of transgenic mouse models to investigate the interactions of Ca^{2+}- and NO/cGMP-dependent signaling pathways in components of the cardiovascular system. To do so, we combine the tetracycline-regulated Tet-Off system with corresponding transgenes under control of tetracycline responsive elements. As a result, expres-

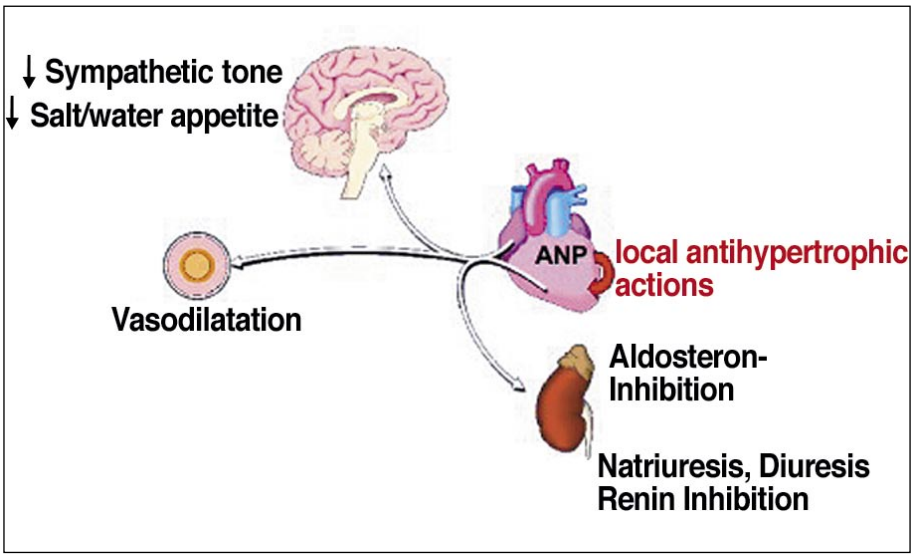

Fig. 1: The guanylyl cyclase A (GC-A) receptor mediates the endocrine effects of atrial natriuretic peptide (ANP) regulating arterial blood pressure and volume homeostasis and also local antihypertrophic actions in the heart.

sion of various proteins can be induced tissue-specifically e.g. in vascular smooth muscle cells (SM22 alpha promoter) or in cardiac myocytes (alpha MHC promoter). Subsequently, the effects of transgenic overexpression on our model systems will be investigated.

In vivo Relevance of the MAPK Pathway Inhibitor SPRED
(K. Schuh, M. Ullrich, P. Benz)

Spreds form a new protein family with an N-terminal Enabled/VASP homology 1 domain, a central c-Kit binding domain, and a C-terminal Sprouty-related domain. They are able to inhibit the Ras/ERK signaling pathway after various mitogenic stimulations. They inhibit cellular proliferation and differentiation and have a high potential as tumor markers and suppressors of carcinogenesis. One aim of this project is getting a deeper insight into the physiological functions of SPRED proteins in an entire organism. In order to achieve this, we used a gene trap model, which results in an ablation of the spred2 gene and in the replacement of the endogenous gene by a reporter gene, allowing expression profiling of spred2. Furthermore, we are interested in the inhibitory function of SPREDs in cellular systems, i.e. which are the interacting partners necessary to exert the inhibitory role. Based on this integrated approach, we hope to gain detailed insights into the molecular mechanisms as well as into the in vivo functions of SPRED proteins.

Teaching

Physiology and pathophysiology (together with Chair II) for the students of medicine, dentistry, pharmacy, psychology, and informatics (lectures, seminars, integrated seminars, and practical courses as well as examinations).

SELECTED PUBLICATIONS

Sabrane K, Kruse MN, Fabritz L, Zwiener M, Zetsche B, Skryabin BV, Baba HA, Yanagisawa M, Kuhn M (2005) Vascular endothelium is critically involved in the hypotensive and hypovolemic actions of atrial natriuretic peptide. J Clin Invest. 115: 1666-1674.

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2.4 Institute of Physiology II

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Professor Dr. rer. nat. Erhard Wischmeyer (acting Head since 1. 1. 2008)
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Mission and Structure

The research activities of the department focus on the molecular, biochemical and pharmacological/functional characterization of two different classes of ion channels: tandem-pore potassium channels and acid-sensing ion channels. Another focus of our research is the analysis of the molecular gating mechanism of mechanically activated ion channels, in particular the transduction channel of sensory hair cells.

In addition to the chairman, the staff includes two associate professors, four research associates, four technical assistants and several academic co-workers that are financed through third-party funds.

Major Research Interests

Molecular understanding of the proton gating of ASICs
(S. Gründer, X. Chen)

Protons are the simplest transmitter; they participate in the synaptic transmission in the CNS as well as in the excitation of nociceptors in the PNS. One of the most important class of neuronal receptors for protons are acid-sensing ion channels (ASICs). Activation of ASICs contributes to neuronal death associated with stroke. Our aim is it to elucidate the activation mechanism of ASICs by protons. This will also increase our understanding of the role of these receptors in situations such as stroke, ischemia, and metabolic acidosis for example during exercise.

Regulation of neuronal excitability and synaptic transmission by potassium channels
(M. Weber)

The efficacy of synaptic transmission depends on pre- and postsynaptic ion currents. Synaptic transmission in a pontine brain stem nucleus (PnC) plays a crucial role during processing of the startle response. This nucleus integrates a number of different synaptic inputs, e.g. inputs from the amygdala in fear and anxiety. However, the detailed characteristics and regulation of the synapses remain to be clarified. Possibly, background potassium currents play an important role because they modulate neuronal excitability. Tandem-pore potassium channels carry these currents and can be inactivated by neurotransmitters such as serotonin. We could show that these channels significantly regulate the excitability of the neurons in the PnC as well as in the amygdala.

Tandem-pore potassium channels as therapeutical targets of antidepressants
(E. Wischmeyer)

Tandem-pore potassium channels are the molecular correlate of background potassium currents. They control the excitability of neurons in the central nervous system and are expressed e.g. in the limbic system of the brain and in the heart. Pathological changes in the limbic system may cause symptoms from mood disorders to depressions. Antidepressants are the main pharmacological tools for therapy. However, their use is limited by unwanted cardiac side effects, which might be caused by an interaction with the same target protein in heart cells. So far, one member of the tandem-pore potassium channel family has been identified to be sensitive to several antidepressants. This potassium channel is also expressed in cardiac cells, suggesting that it causes the cardiac side effects of antidepressants.

Molecular characterisation of a mechanically gated ion channel
(S. Gründer, D. Wiemuth, I. Kadurin)

Mechanically activated ion channels are arguably the least characterised ion channels, and this in spite of the fact that they serve many physiological functions. We have cloned a new ion channel that is a good candidate for a mechanosensitive ion channel from sensory hair cells. We want to identify proteins that are associated with this channel and that are important for its mechanical gating. We use this system as a model to define the molecular organisation of a mechanosensitive complex.

Cellular excitability modulates the expression of potassium channel genes
(F. Döring)

The excitability of neurons crucially depends on the resting potassium conductance. This conductance is predominantly mediated by inwardly rectifying potassium channels

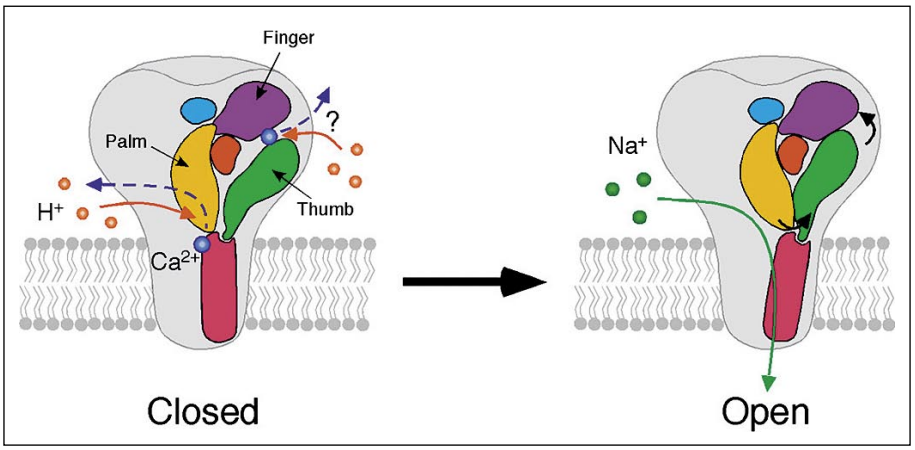

Fig. 1: The figure shows a preliminary model for the activation of an acid-sensitive ion channel (ASIC) by protons (From: Paukert et al. (2008) J. Biol. Chem.).

(Kir) and tandem-pore potassium channels (K2P). Studies using in vitro models of neuronal cell cultures have shown that gene expression of potassium channels is modulated by changes in the resting membrane potential. Our investigations on K2P channel knockout mice demonstrated that the loss of individual potassium channels, accompanied by a reduction of neuronal potassium conductance, is compensated by increased expression of related potassium channels. We want to identify i) the individual potassium channel genes that are regulated by changes in the membrane potential and ii) the signalling pathways that couple gene expression of ion channels to cellular excitability.

Molecular characterisation of peptide-gated ion channels
(S. Gründer, A. Golubovic)

It is textbook knowledge that neuropeptides activate exclusively G-protein-coupled-receptors that mediate slow neurotransmission. We have cloned form the freshwater polyp Hydra an ion channel that is directly gated by a neuropeptide. This result shows that simple nervous systems use neuropeptides also for fast neurotransmission. The human genome contains ionotropic receptors that are related to the peptide-gated channel of Hydra. We are currently investigating whether these human channels are also directly gated by neuropeptides.

Teaching

The department teaches physiology and pathophysiology to students of medicine, dentistry, pharmacy, psychology and neurobiology (lectures, seminars and practical courses as well as examinations). Together with colleagues from the university hospital, the institute offers seminars that deepen the understanding of the clinical aspects of physiology.

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2.5 Biocenter Würzburg
Chair of Physiological Chemistry I

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Mission and Structure

Complying to the perspectives of research at the Biocenter, extending from functional molecular biology to the development of the total organs and its interactions with the environment, all individual research groups of our chair contribute to research in basic biochemistry as well as cell biology. The multi-faceted approach is well reflected in the fact that the scientists of the institute are biologists, chemists and physicians and that the head of the institute is a member of the Medical as well as the Biological Faculty of the University.

The research interests of the individual groups range from functional molecular and cellular biology to questions concerning the development of entire organs and their interactions with the environment, in line with the mission of research at the Biocenter. The multi-faceted approach is well reflected in the fact that the scientists of the institute are biologists, chemists and physicians and that the head of the institute is a member of the Medical as well as the Biological Faculty of the University.

Major Research Interests

Molecular analysis of melanoma formation
(M. Schartl)

Due to the enormous complexity and variety of human cancerous diseases, animal models are especially suited to analyse basic mechanisms of tumour development and progression on the genetic and molecular level. Small laboratory model fish species, the Medaka and Xiphophorus are used to study melanoma formation in-vivo in a comparative approach with mouse and human melanoma cell lines. This led to a better understanding of the intracellular processes, which are responsible for the transformation of normal, healthy pigment cells to tumour cells. Through proteome and microarray analyses interesting, novel melanoma molecules were identified. The usefulness of these as tumour markers or therapeutic targets is currently evaluated. Of special importance was the finding that a high signalling output of the melanoma inducing growth factor receptor Xmrk leads to senescence of melanocytes and a nevus cell-like appearance. This contributes a new aspect to the clinical important, but still unsolved question whether nevi are a benign, precancerous state of the malignant melanoma.

Functional analysis of Hey genes
(M. Gessler)

Hey genes are essential transducers of Delta/Notch signals and they control embryonic development of the cardiovascular system. Hey1, Hey2 and HeyL are needed for epithelial to mesenchymal transformation (EMT) of the endocardium in the developing heart, a prerequisite for the formation of the septum and valves. Furthermore, Hey1 und Hey2 participate in the positioning of the atrioventricular canal as an organizing center. These findings were supported by high resolution magnetic resonance imaging of knockout embryos (Figure). Hey genes are induced by hypoxia and they mediate arterialization of endothelial cells. They repress expression of the venous regulator Coup-TFII and thereby control angiogenesis. A lack of Hey1 and Hey2 leads to a lethal angiogenesis defect.
Our work on the fjx1 ligand as part of the planar cell polarity (PCP) pathway showed that fjx1 regulates dendrite growth in the CNS and it seems to participate in additional PCP processes in other organs.

Analysis of Wilms tumors
(M. Gessler)

Within the framework of the German Wilms Tumor Study our tumor bank has been expanded and we could identify several new genes whose expression correlates with tumor prognosis. A parallel re-evaluation of all previously known candidate genes in a large cohort of more than 200 Wilms tumors revealed that significant associations could be substantiated in only a fraction of cases. Further validation and functional analyses of these genes are currently under way.

The role of the pRB/E2F pathway in gene expression and cell cycle progression
(S. Gaubatz)

Research focuses on E2F transcription factors, the retinoblastoma protein and related pocket proteins. These proteins play key roles in the regulation of cellular proliferation, differentiation and apoptosis and they have been implicated in tumorigenesis. We have recently identified LINC, a novel E2F/pocket protein complex in human cells that is related to similar complexes in inverte-

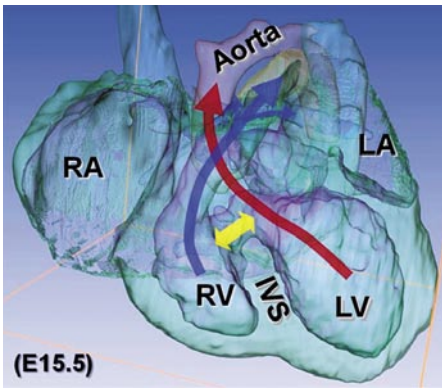

Fig. 1: Ventricular septum defect of a Hey2 knockout embryo. Failure to close the interventricular septum (IVS) leads to an open connection (double arrow) between the right and left cardiac chamber (RV, LV). (Picture: Lang and Gessler).

brates. LINC regulates the expression of mitotic genes and is essential for cell cycle progression through the G2 phase and for entry into mitosis. Inactivation of the LIN9 subunit of LINC in the mouse results in early embryonic lethality at the peri-implantation stage. In contrast, the incomplete depletion of LIN9 promotes tumorigenic transformation. We are currently investigating the possibility that the knockdown of LIN9 promotes tumorigenesis by weakening the mitotic spindle checkpoint and increasing genomic instability.

Teaching

The chairs of Physiological Chemistry offer a broad spectrum of lectures, seminars and practical courses. A focus is on the theoretical and practical training of more than 400 students of Medicine and Dentistry in their curricular subjects Biochemistry and Molecular Biology. In addition, 24 students of Biomedicine (B.Sc./M.Sc.) are taught intensively in Biochemistry, Molecular Biology and Developmental Biology. For Biology students advanced courses are offered as minor subject in Physiological Chemistry and in conjunction with the Institute for Biochemistry as major subject Biochemistry. Additional training courses for PhD students are offered within the framework of the Institute-based research training groups 639 and 1048 (Graduiertenkollegs) and the Graduate School of Life Sciences (GSLS).

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2.6 Biocenter Würzburg
Chair of Physiological Chemistry II

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Mission and Structure

The department of Physiological Chemistry II (PCII) is part of the „Biozentrum“ founded in 1990, where 10 institutions from the faculties of Biology, Chemistry and Medicine cooperate in teaching and research. PCII teaches biochemistry for large numbers of preclinical students in Medicine and Dentistry. Research at PCII is organized across traditional borders of disciplines and faculties. The aim of PCII is to contribute to therapy and diagnosis of several human disorders (asthma, allergies, cancer, organ and tissue regeneration, cardiac hypertrophy, fatty acid metabolism) by the establishment of biological model systems and the set up of chemical/biochemical methodology.

Major Research Interests

Strukture, mechanism and cellular functions of growth and differentiaton factors
(W. Sebald)

We are focussing on Interleukins involved in generation and maintenance of allergic diseases and asthma, as well as on BMP´s/ TGF-b´s, which regulate the development and regeneration of tissues and organs.

Ongoing projects concern:

- Molecular recognition and primary activation steps in BMP/GDF-receptor complexes (W. Sebald).
- Osteogenic stem cell-differentiation and therapies of bone loss (W. Sebald).
- Structure and specificity of VWC domains from crossveinless-2 (T. Müller, W. Sebald).
- BMP heterodimers.
- L51P BMP-2 as Nogginblocker.
- Large scale production of rekombinant proteins.
- Interleukin-4 antagonists.

Metabolic pathways in peroxisomes: alpha-methylacyl-CoA-racemase
(E. Conzelmann)

- Elucidation of structure and mechanism of the enzyme
- Significance of the enzyme in the metabolism of cholesterol and of branched-chain fatty acids, i.a. by analysis of a mouse knock-out model
- Simultaneous targeting of the same enzyme to different cellular compartments
- Role as marker for tumours of the prostate and of other organs

Role of the murine Caspase-12
(J. Hoppe)

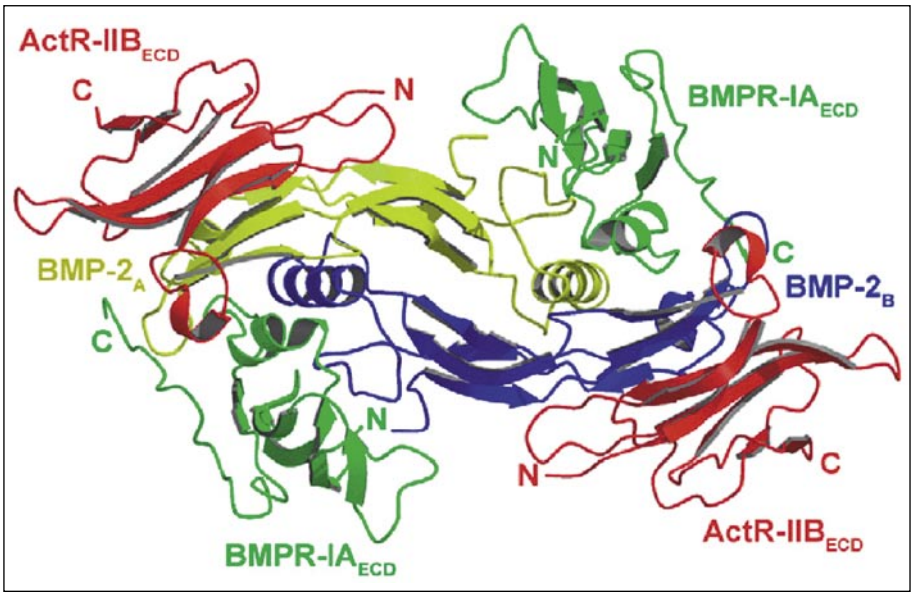

Fig. 1: The bone morphogenetic protein BMP-2 signals into target cells by assembling two types of receptor kinases in the cell membrane. We have elucidated the structure of the ternary complex consisting of the dimeric BMP-2 and two ectodomais of each BMP receptor IA and Activin receptor IIB.

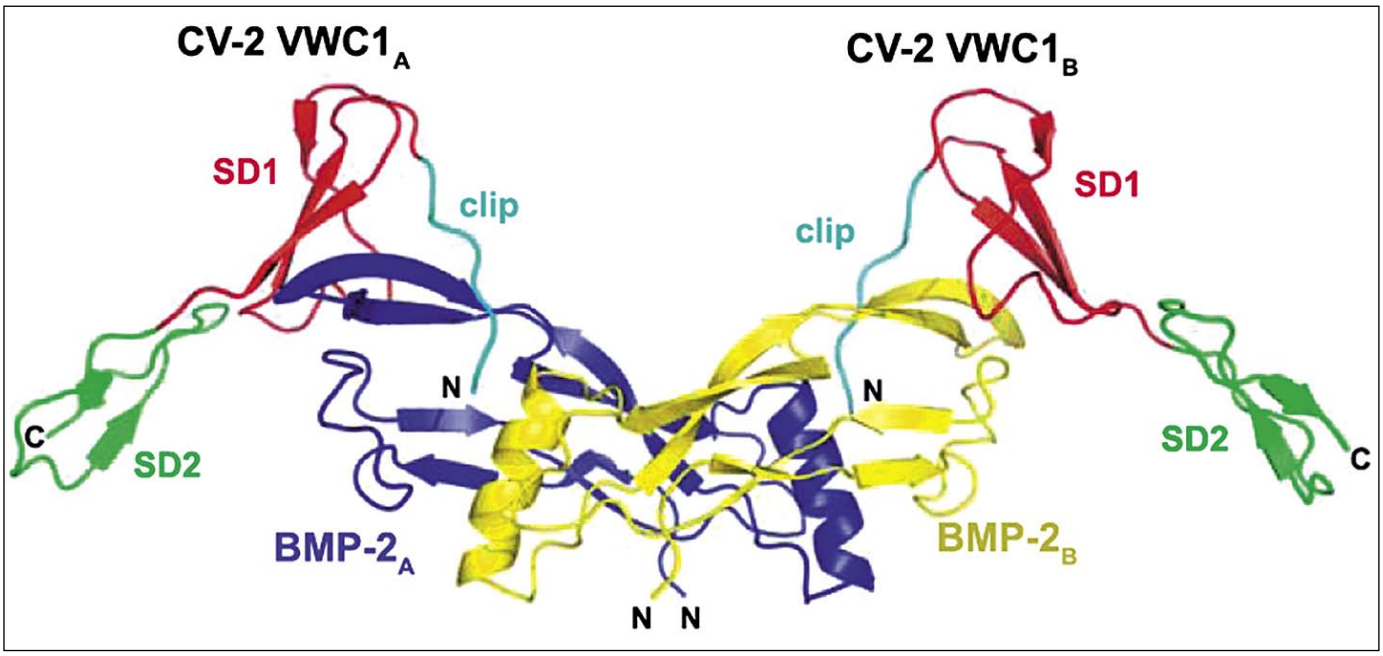

Fig. 2: The activity of BMP-2 in the organism is regulated by the binding of proteins containing VWC domains. We have solved the structure of the complex between dimeric BMP-2 and two VWC domains of the BMP modulator protein crossveinless-2.

Caspase-12 was originally described as initiator caspase, which is avtivated in a [Ca2+] i dependent manner after ER-Stress. Our results do not support this model. In contrast caspase-12 was found to be cleaved after asp-94 by caspase-3 independently of ER-stress. By using cleavages site specific antibodies we could exclude a further processing of caspase-12 in the intersubunit regions. Our model locates caspase-12 downstream of caspase-3, questioning its proposed role as initiator caspase.

Teaching

The chair of Physiological Chemistry II in conjunction with the Chair of Physiological Chemistry I is in charge of all teaching in Biochemistry and Molecular Biology for more than 400 students of Medicine and Dentistry per year as well as 24 annual students of Biomedicine (B.Sc./M.Sc.).

SELECTED PUBLICATIONS

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Zhang, J. L., Huang, Y., Qiu, L. Y., Nickel, J., and Sebald, W. (2007): von Willebrand factor type C domain-containing proteins regulate bone morphogenetic protein signaling through different recognition mechanisms. J Biol Chem 282: 20002-20014.

2.7 Institute for the History of Medicine

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Mission and Structure

The Institute for the History of Medicine is the only institution of the Medical Faculty which approaches medical issues primarily from the perspective of the humanities. During the last years, the relatively small scientific staff (head of department and two collaborators) was complemented by about twice that number of scientists employed through outside funding (Deutsche Forschungsgemeinschaft, Fritz-Thyssen-Stiftung, KAAD, private sponsoring). About a dozen more scientists support the teaching activities. Large parts of the Institute are housed in a former ONT-clinic donated for the purpose by the former Würzburg Professor Horst Wullstein and his wife Sabina. Further rooms are in the former Zoology building in the city center. The Institute's library comprises about 60.000 volumes and ranks among the largest of its kind in the German speaking area.

Major Research Interests

Research at the Institute focuses on premodern medicine (ca. 1400-1850). More recently, the history of medical ethics from the Middle Ages until today has emerged as a second area of special interest. A number of research projects are currently undertaken at the Institute or are just about to be concluded.

Medical Ethics in Ordinary Medical Practice
(M. Stolberg, K. Nolte)

While a fair amount of research has been done on the historical development of the theological und philosophical debates about euthanasia and other major ethical issues, we know very little, so far, about the way ordinary physicians, nurses, relatives and patients dealt with these issues on a day-today basis. Our research has thus shown, for example, that various means to achieve active euthanasia were widely accepted among the population across Europe in the early modern period and we have been able to identify physicians who already around 1800, publicly endorsed active euthanasia on dying patients, a century earlier than had hitherto been assumed. Analysing the attitudes towards truth-telling in the case of fatal progrnosis and towards informed consent to painful and risky operations we have been able to show the crucial importance of changing roles and patterns of interaction among patients, relatives, physicians, nurses and priests.

Physicians and the Physician's Authority in the Early Modern Period
(M. Stolberg, D. Groß, J. Steinmetzer, T. Walter)

In this project, we have followed the careers and typical career patterns of early modern learned physician and analyzed the various strategies they used to achieve and secure professional status and personal authority, at a time when their curative skills were, in hindsight, not superior to those of their numerous less learned competitors.

Out-Patient Medical Care 1600-1850
(M. Stolberg, K. Nolte)

Little is known, so far, about the history of ordinary physicians' medical practice, neither about the structure and social extraction of ordinary physicians' clientele nor about the ways in which they applied the medical theories which they had acquired during their studies to their daily diagnostic and therapeutic practice. Using physicians' case books kept by ordinary physicians as well as journals from the newly established policlinics in Würzburg and Göttingen around 1800 we are embarking on an international cooperative research project designed to approach these issues in a comparative perspective.

Research Group Monastic Medicine
(J. G. Mayer, R. Windhaber)

This interdisciplinary research group was formed at the Institute several years ago bringing together medical historians and specialists of pharmacology. The group works on the history of Western monastic healing and more generally on the history of medicinal plants in the medieval and early modern period. One of its major aims is also to preserve this historical knowledge and make it accessible to modern medical practitioners.

History of Palliative Medicine
(M. Stolberg, H. Langrieger, K. Max)

The long pre-history of modern palliative medicine is virtually unknown. In this project we pursue for a period spanning from the 16th to the 20th centuries how physicians and nurses dealt with incurable and

Fig. 1: Doctor's visit (Egbert van Heemskerk III, ca. 1725).

dying patients and analyse the role which hospitals, poor-houses and similar institutions played in taking care of such patients over the centuries.

Cultural History of Uroscopy, 1500-1850
(M. Stolberg)

Based on printed and manuscript medical writing, on court records and on letters and autobiographies written by physicians and patients and on visual evidence in early modern painting this project traces the changing fate of uroscopy as the major means of diagnosis from the 16th to the 19th centuries.

Teaching

The Institute offers 16 compulsory courses in Medical Terminology and Professional Orientation every term, for students of medicine and of dentistry. It is also responsible for the course in "History, Theory and Ethics" which all medical students have to do in their third year. In addition, a wide variety of elective courses and seminars is offered, ranging from „Medical English" and courses in bibliography and palaeography to seminars dealing with specific topics of medico-historical interest. The Institute is also responsible for the teaching of medical history and medical theory at the University of Regensburg. Individual staff members and collaborators have also assumed teaching responsibilities at the Historical Faculty in Würzburg and at the Universities of Ulm and St. Gallen.

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2.8 Institute of Psychotherapy and Medical Psychology

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Mission and Structure

The Institute of Psychotherapy and Medical Psychology was founded in 1958 as the first of its kind in Germany. Its focus areas include research, education, and patient care. The interdisciplinary research topics comprise methodological and clinical psychotherapy research as well as research of the processes involved in coping with illness and rehabilitation. In the area of medical education, the institute is responsible for the following subjects: Medical Psychology and Sociology in the first study section, Psychotherapy and Psychosomatic Medicine as well as Rehabilitation Sciences in the second. For patient care, psychotherapeutic out-patient department and consultation-liaison services for the University Hospital are provided.

Currently, 8 researchers are financed by the institute's budget and another 13 by third-party payer. Several close clinical and research co-operations with the University Hospital exist. The institute is a member of the Comprehensive Cancer Center, the Breast Center and the Center of Cardiovascular Disorders of the University Hospital. Its section of Rehabilitation Sciences coordinates the Rehabilitation Research Network of Bavaria (RFB; see Ch. 5.6 Research Networks).

Major Research Interests

Psychocardiology
(H. Faller)

The prevalence of depression in patients with chronic heart failure is high. In our research, which is performed in cooperation with the Department of Internal Medicine I (Prof. Angermann, Prof. Ertl), we examine the factors that put patients at risk for depression and whether depression itself is a risk factor for heightened mortality in chronic heart failure (Fig. 1). Moreover, we evaluate an intervention for optimizing disease management programs, including telephone-based patient education, in regards to mortality, morbidity, re-hospitalisation, and quality of life (INH Study). In a future study, the efficacy of pharmacotherapy of depression in reference to mortality in chronic heart failure will be examined (MOOD-HF Study).

Psychooncology
(H. Faller)

As an extension of various projects on coping with illness in cancer patients and its prognostic significance, the following questions are examined in an ongoing multi-center study: What is the prevalence of psychological distress and psychological disorders among cancer patients? What are cancer patients' needs for psychosocial support? In this study, patients with various cancer types, from various treatments stages (acute care, rehabilitation) and settings (in-patient and out-patient care) are included.

Psychonephrology
(S. Neuderth)

In transplantation medicine, living donor kidney transplantation is becoming increasingly important. In cooperation with the Department of Internal Medicine I (Nephrology), both donors and recipients who had been psychologically evaluated before the kidney transplantation are followed up. The various aspects of the transplantation process, such as decision making, risk-perception and information status as well as health-related quality of life, psychological distress, sense of self-worth, and benefit finding, are evaluated.

Obesity Treatment
(M. Schowalter)
In cooperation with the Obesity Center of the University Hospital of Würzburg, a comprehensive evaluation of pre- and post-operative psychological factors in patients with morbid obesity undergoing bariatric surgery is performed. Furthermore, behavioral criteria of decision making before surgery and a post-surgical after-care program are de-

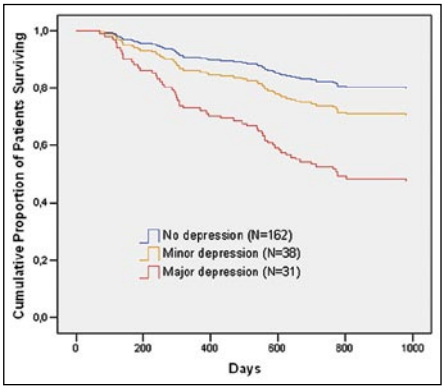

Fig. 1: Depression and survival rate of patients with chronic heart failure according to degree of depression.

veloped. We evaluate both the success of this after-care program and the short and long-term psychosocial outcomes of the surgical treatment.

Patient Education
(H. Faller, H. Vogel, A. Reusch)

Patient education is a central feature of medical rehabilitation in chronic diseases. Several research projects aim to advance the concepts of patient education, to enhance patient orientation, to perform a survey on the present state of education practice, to develop an education database, and to evaluate the effectiveness of educational programs in various disorders (e.g. chronic low back pain). Specific strategies are implemented to increase the sustainability of education effects and to transfer newly learned skills to every-day life situations. Examples include behavioral planning and after-care using modern media (telephone-based after-care, live-online after-care via the internet) (see also RFB, Ch. 5.6 Research Networks).

Occupational Rehabilitation
(H. Vogel, S. Neuderth)

To increase the rehabilitants' chance of returning to work, early identification of patients with occupational impediments and corresponding occupational treatments are necessary. Thus, several projects aim at developing screening instruments for occupational impediments, creating a survey of the present state of work-related treatments in rehabilitation and fostering shared decision making regarding treatment selection (see also RFB, Ch. 5.6 Research Networks).

Quality Management
(H. Vogel, S. Neuderth)

Quality management programs have been developed for a large number of institutions. These include a concept for quality management in medical rehabilitation carried out by the statutory accident insurance and a quality management concept for prevention and rehabilitation in mother-child-clinics. Another method of quality assurance is the development of guidelines for the rehabilitation process. In the context of the guideline program of the German Statutory Pension Insurance, the institute is responsible for the field of rehabilitation for children and youth.

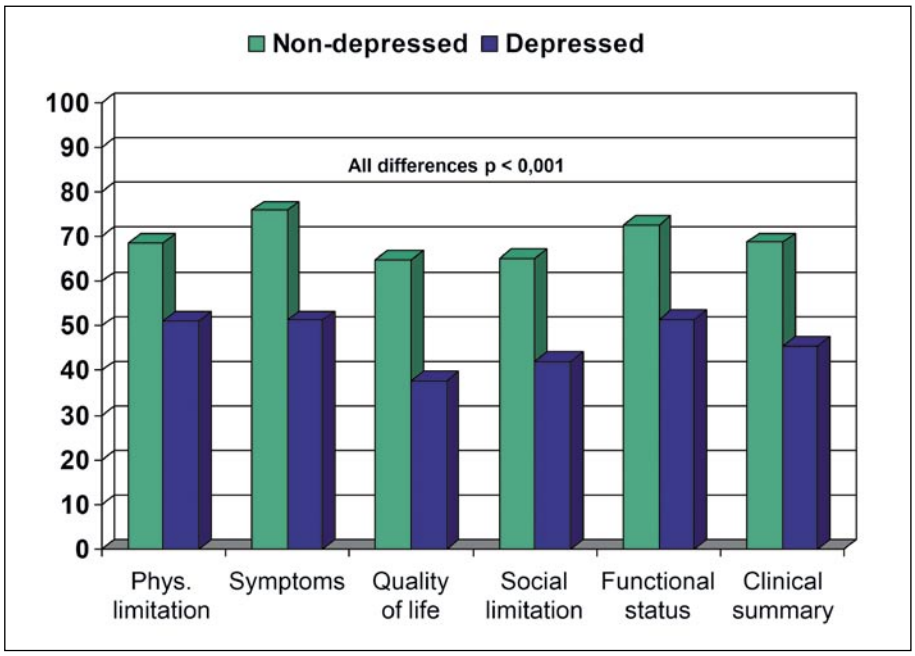

Fig. 2 Impact of depression on disease-specific quality of life in chronic heart failure (Kansas City Cardiomyopathy Questionnaire).

Quality of Life Measurement
(H. Faller)

A final research focus of the Institute is the development and psychometric evaluation of self-assessment instruments for health-related quality of life. In collaboration with the Department of Internal Medicine I (Prof. Angermann, Prof. Ertl), an innovative tool for the assessment of disease-specific quality of life in chronic heart failure has been psychometrically evaluated (Kansas City Cardiomyopathy Questionnaire; Fig. 2). In cooperation with the Orthopedic University Hospital (Prof. König), the German version of the Short Musculoskeletal Function Assessment Questionnaire, has been developed and evaluated. In a large multi-center study, several quality of life questionnaires, which are frequently used in medical rehabilitation (SF-36, IRES, SCL-90-R), have been examined regarding their sensitivity to change. In an ongoing multi-center study, the Health Education Impact Questionnaire (heiQ) is being translated and psychometrically evaluated in collaboration with the Medical University of Hannover and the University of Melbourne, Australia.

Teaching

Within the subjects of Medical Psychology and Medical Sociology, the following compulsory classes are provided: Lectures, Courses, and Integrated Seminars/Seminars with Clinical Aspects. An optional seminar on Research Methods and Evaluation (Evidence-Based Medicine) is also offered. Moreover, the Institute takes part in the Integrated Lecture and Integrated Practical Courses of Psychiatry, Psychosomatics, and Psychotherapy. (Teachings within the cross-sectional subjects are presented under RFB, Ch. 5.6 Research Networks).

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Faller H, Schmidt M (2004) Prognostic value of depressive coping and depression in survival of lung cancer patients. Psycho-Oncology 13:359-363.

Faller H, Störk S, Schowalter M, Steinbüchel T, Wollner V, Ertl G, Angermann CE (2007) Depression and survival in chronic heart failure: Does gender play a role? Eur J Heart Fail 9:1018-1023.

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Schowalter M, Benecke A, Lager C, Heimbucher J, Bueter M, Thalheimer A, Fein M, Richard M, Faller H (2008) Changes in depression following gastric banding operation: a 5 to 7-year prospective study. Obesity Surgery 18:314-320.

2.9 Institute for Hygiene and Microbiology

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Professor Dr. med. Dr. rer. nat. Bhanu Sinha
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Professor Dr. med. Ulrich Vogel
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Mission and Structure

The main tasks of the Institute for Hygiene and Microbiology are the laboratory diagnosis of infectious diseases caused by bacteria, fungi and parasites, the advice of clinicians with respect to diagnosis, therapy and prevention of infectious diseases, the research on infectious diseases and their causative agents, hospital hygiene as well the education of students in medicine, dentistry and related subjects.

In addition to the comprehensive range of routinely used diagnostic tools the institute also provides special molecular and serological test systems. Our commitment to patient care also includes the development of strategies for the prevention of hospital infections and the monitoring of hospital hygiene. Annually approximately 85.000 microbiological analyses are performed.
The research activity of the institute mainly focuses on the elucidation of the molecular mechanisms in the pathogenesis of infectious diseases. Using tools from molecular genetics, cell biology, immunology and genome research the pathogenicity of bacteria, fungi and parasites is investigated and novel strategies for the diagnosis, therapy and prevention of infectious diseases are developed.

At the institute the "Bundesministerium für Gesundheit" established the national reference centre for meningococci (NRZM). The activities of the NRZM include the identification as well as the serological and molecular typing of meningococci, an advisory service in case management and the counselling of public health departments in the epidemiological monitoring of putative outbreaks of meningococci diseases. The institute is part of the pan-European network of reference centres the "European Monitoring Group on Meningococci". Moreover, on behalf of the Robert-Koch Institute the institute also functions as consiliary laboratory for Haemophilus influenzae and echinococcosis, employing special diagnostic tests and providing advice on diagnosis, therapy, prevention and epidemiology.

Major Research Interests

Infection biology of meningococcal disease
(O. Kurzai, A. Schubert-Unkmeir, M. Frosch)

Meningococci, an important cause of septicemia and meningitis in infants and adolescents, are in the focus of research on infection biology and population genetics. The molecular basis of transmission across the blood-brain barrier and the interaction of meningococci with the complement system and dendritic cells as central effectors of the human innate immune system are major points of interest in our research.

Population biology and biofilm formation of meningococci
(U. Vogel, H. Claus)

The population biology of N. meningitidis and its spread among human hosts is analyzed by bacterial finetyping. To study the molecular mechanisms effective during asymptomatic colonization of the nasopharynx, a biofilm model is applied. Furthermore, the group works on the impact of the capsular polysaccharide and its biochemical modifications, since this surface structure is believed not only to support invasive disease, but also to have a pivotal role in host-to-host transmission.

Genome research on pathogenic bacteria
(C. Schoen, M. Frosch)

Genomics of pathogenic bacteria is one main research focus at the institute encompassing different pathogenic species. The comparison of the genomes from pathogenic as well as non-pathogenic species provides insight into the genetic basis of the observed differences in the pathogenic phenotypes and the evolution of pathogens. Whole-genome sequences are also required for the construction of DNA microarrays which allow for a genome-wide analysis of gene regulation and genome variation. This work has been performed in the frame of the BMBF funded competence network „Genomforschung an pathogenen Bakterien (PathoGenoMik)". A microarray facility was established at the institute which allows the fabrication of microarrays and the conduction of experiments not only for all pathogens for which the genome sequence is available but also for eukaryotic genes with known sequences (e. g. from human or mouse).

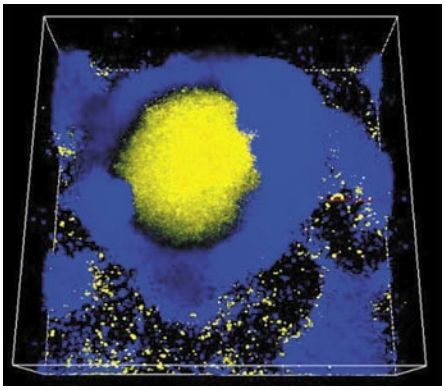

Fig. 1: Bacterial biofilm formed by two variants of Neisseria meningitidis. The strains are expressing different fluorescent proteins to allow the visualization of their growth in a dynamic "Flussmodell". The biofilm model is used for the analysis of DNA exchange between meningococci, which is of fundamental importance for the genetic diversity of the bacteria.

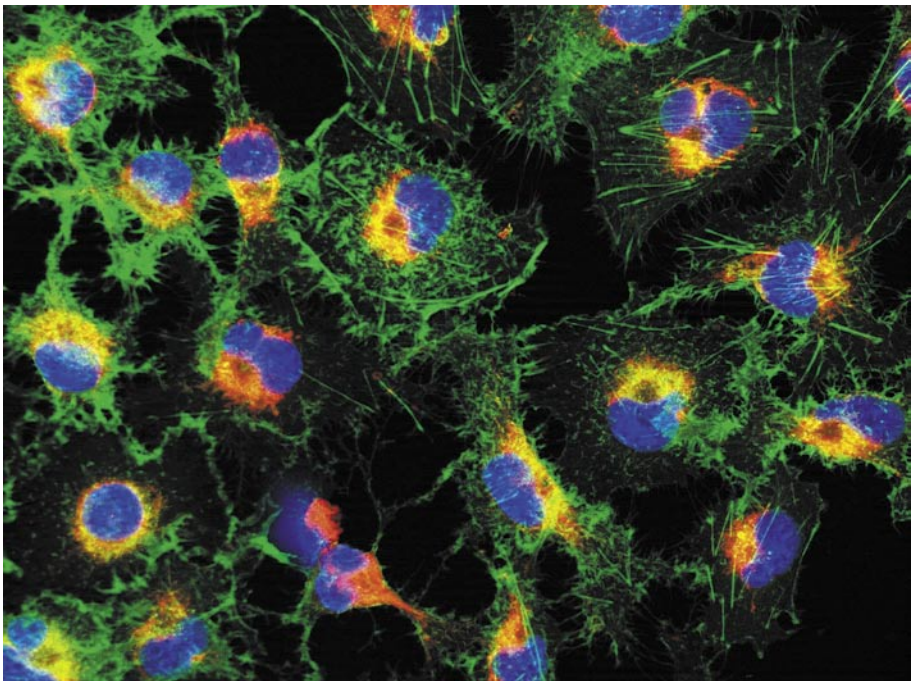

Fig. 2: Human brain microvascular endothelial cells incubated with MitoTracker Red CMXRos to label the mitochondria. After fixation and permeabilization, the cells were stained with Alexa Fluor 488 phalloidin to label the filamentous actin (F-actin) and finally counterstained with DAPI to label the nucleus.

Staphylococcus aureus
(B. Sinha)

Staphylococcus aureus is one of the most common causes of bacterial infection in humans. Despite this, a high proportion of the healthy population is colonized without suffering from infection. To understand this interaction we characterize the interplay between S. aureus and host cells. We have shown that S. aureus is able to invade host cells and persist intracellularly during infection. Invasion of host cells involves a phagocytosis related process. The maturation of S. aureus containing phagosomes and a possible correlation between invasive potential and virulence are in the focus of current research. Beside these experiments, the response of S. aureus to contact with biocides is analyzed.

Immune-response against fungal pathogens
(O. Kurzai)

Fungal infections are an increasing threat for immunocompromised patients. By characterizing the molecular basis of interaction between Candida albicans and Aspergillus fumigatus and the innate immune system we try to identify correlates of protective immunity and possible ways for adjuvant immune therapy.

Fox-tapeworm and alveolar echinococcosis
(K. Brehm)

Alveolar echinococcosis is a life-threatening parasitosis in humans causing destruction of liver tissue by the tapeworm larva. We have shown that cells of this parasite make use of hormone based communication systems which are closely related to cell-cell communication systems of the host. The possibility of cross-communication between the parasite and the host, which could be one reason for the long persistence of tapeworm infections and their modulation of human immune responses is in the focus of current research. In genome- and proteome-based approaches parasite specific factors suited as targets for anti-infective therapy are identified.

Teaching

Student's courses are organised for students of medicine, dentistry, biomedicine, pharmacy and food chemistry. Scientists at the institutes participated in the organization of several scientific and medical meetings.

SELECTED PUBLICATIONS

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Schoen, C., Blom, B., Claus, H., Schramm-Glück, A., Brandt, P., Müller, T., Goesmann, A., Joseph, B., Konietzny, S., Kurzai, O., Schmitt, C., Friedrich, T., Linke, B., Vogel, U., Frosch, M. (2008). Whole genome comparison of disease and carriage strains provides insights into virulence evolution in Neisseria meningitidis. Proc. Natl. Acad. Sci. U.S.A., 105: 3473-34788.

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2.10 Institute of Virology and Immunobiology, Chair of Virology

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Mission and Structure

Research within the Chair of Virology is focussed on the analysis of the regulation of viral replication and gene expression, complex investigations of the pathogenesis of viruses, research into the sensitivity to antivirals and the development of viral vectors towards gene therapy. The Chair of Virology is also responsible for the provision of virus diagnostics to the University Hospital. We host approx. 65 scientists and work in close cooperation with the Chair of Immunology at our Institute as well as the Centre For Infectious Diseases, a number of Basic Research Programmes (SFBs), Graduate Schools and the Interdisciplinary Centre for Clinical Research.

Major Research Interests

Molecular mechanism of Measles virus induced immunosuppression
(S. Schneider-Schaulies)

Measles virus (MV) infections cause a generalised immunosuppression which almost exclusively accounts for their high morbidity rates. Typically, peripheral blood T lymphocytes, fail to expand in response to polyclonal stimulation ex vivo, indicating they received anergising signals. The MV glycoprotein complex, identified as effector structure in this process, targets activation of the phosphatidyl-inositol-3-kinase via contact with an unknown receptor which is currently being identified. Most likely, dendritic cells (DCs) are central to MV-induced immunosuppression. DCs take up MV by specific receptors (CD150 and DC-SIGN), mature, yet fail to promote expansion of cocultured allogenic T cells in mixed leukocyte reactions. This is because they do not support formation of stable conjugates with T cells as required for their activation. Amongst other proteins, the MV glycoprotein complex present at the DC/T cell interface contributes to synapse destabilisation.

Neuroimmunology and Neurodegeneration of Prion Diseases
(M. Klein)

Prion diseases or transmissible spongiform encephalopathies (TSE) belong to a group of infectious, fatal, neurodegenerative diseases, which affect both animals and humans. During disease, PrPSc, an abnormal, detergent-insoluble, relatively protease-resistant isoform of the host encoded cellular prion protein (PrPC) accumulates within infected tissues. After infection prions accumulate in a first step within the lymphoreticular system before degeneration of the nervous system occurs. The mechanisms of neuroinvasion into the brain, the role and function of PrPC, and the molecular aspects of prion-induced neurodegeneration are analyzed within various projects. Furthermore immunotherapeutic concepts are currently explored to develop a vaccination strategy against the disease.

Pathogenesis of Pneumoviruses
(C. Krempl)

Respiratory Syncytial virus (RSV) is major viral cause of serious lower respiratory tract disease in the pediatric world, in the elderly and in severely immunocompromized patients. However, an effective antiviral therapy or a licensed vaccine is lacking, possibly due to a fragmentary understanding of pathogenicity mechanisms and lack of a permissive animal model. Infection of mice with the closely related pneumonia virus of mice (PVM) causes symptoms that are similar to those induced by RSV-infection of humans. Thus, the group is using PVM-infections as surrogate model. By using reverse genetics that permits introduction of defined mutations into the PVM genome, the group is identifying and characterizing viral and host factors involved in pathogenicity. The results of these studies will contribute to a better understanding of the mechanism of RSV-induced disease and might help to optimize the rational design of a live-attenuated RSV vaccine.

Modellsysteme für Virusaufnahme und Mechanismen der Virusausbreitung
(J. Schneider-Schaulies)

The group investigates mechanisms of virus spread in various model systems. In the focus of interest are uptake and spread of measles virus, which is accompanied by a transient immunosuppression and may persist in the central nervous system. Recently, the group has established a model of persistent CNS infection in immunocompetent mice using a recombinant neurotropic measles virus to find new posibilities of therapy. The role of cytotoxic and regulatory T cells, as well as application of possibly therapeutically usable antiviral short interfering RNA (siRNA) against measles are investigated. An effective inhibition of virus replication was achieved with siRNAs directed against

transcripts of the components of the viral replicative complex. Similar test systems to identify inhibitors of virus uptake and spread are being developed for canine distemper, Nipah- and Dengueviruses.

Molecular Biology of Foamy Viruses
(J. Bodem, A. Rethwilm)

The foamy virus mechanisms of replication are distinct from all other retroviruses (orthoretroviruses). In particular, they show an extremely high degree of genome conservation, have developed own mechanisms of transcriptional and posttranscriptional regulation of gene expression, and show distinct features of particle assembly and maturation. We are elucidating these phenomena using various techniques in molecular virology.

Development of Foamy Virus Vectors for Gene Therapy
(C. Scheller, A. Rethwilm)

The benign character of natural foamy virus infections and a variety of other favourable features has led to the development of foamy virus vectors for somatic gene therapy. Such vectors for the efficient transduction of mesenchymal and haematopoietic stem cells are under development.

CNS Gene Transfer
(E. Koutsilieri, C. Scheller, M. Klein, A. Rethwilm)

We investigate the application of foamy viral vectors in the transduction of haematopoietic stem cells as a tool for a novel gene therapeutic approach to generate transgenic microglia for the treatment of Parkinson's disease in a mouse animal model. Moreover, we use Adeno-Associated Viral Vectors for intracerebral delivery of allele-specific amyloid precursor protein (APP)-shRNA for the treatment of hereditary Alzheimer's disease in an APP-transgenic mouse model.

Pathogenesis of SIV/HIV dementia
(E. Koutsilieri, C. Scheller)

HIV/SIV dementia is probably a result of an initial microglial activation in CNS, production of inflammatory mediators with subsequent direct cytocidal effect on non-infected neural cells or indirect actions on the regulation of the functional elements of synapses and neurodegeneration. In this research group, the pathogenesis of these disease entities are studied using SIV-infected rhesus macaques in a cooperation with the German Primate Center and HIV-infected patients in a clinical study including 3 clinical and 2 theoretical institutes. The studies include the role of the NMDA receptors on the progression of neurodegeneration as well as their relation to the excitatory amino acid transporters which are responsible for the removal of glutamate from the extrasynaptic space and thereby the protection of neurons from excitotoxic death. The plastic adaptations at the glutamatergic synapse are correlated to the presynaptic regulation of the dopaminergic pathways in order to gain insight on the primary and secondary pathogenetic cascades following initiation of inflammative processes in HIV/SIV dementia.

Clinical Virology
(B. Weißbrich, J. Schubert, U. Herre)

30-35 thousand clinical samples are processed each year. Furthermore, a variety of clinical virological questions are being addressed. In a cooperation with the children's hospital of the university clinic, new respiratory viruses are being studied. The human bocavirus (first described in 2005) has been detected in 11 % of nasopharyngeal samples from children who were hospitalised for acute respiratory diseases. Strikingly, we detected a high number of coinfections with other respiratory viruses among the children who were positive for bocavirus DNA. Further studies including antibody determinations are currently ongoing in order to elucidate if bocavirus is a "real pathogen" or just an "innocent bystander".

Cooperations with Mwanza/Tanzania and Cape Town/South Africa
(C. Scheller, J. Bodem, E. Koutsilieri, A. Rethwilm)

We are enforcing the collaborations with African countries to characterize African HIV isolates and to improve anti-retroviral therapy. We are in particular interested to determine the resistance profile of African HIVs. The HIV pandemia strikes Africa most and has considerable medical and social economical consequences. Here we want to offer our virological and research expertise that should be embedded in a higher order collaborative effort between Wuerzburg University and African hospitals/universities.

Teaching

In addition to lectures, colloquia for students of biology, biomedicine and medicine we offer practical courses for interested students.

SELECTED PUBLICATIONS

Yun SW, Ertmer A, Flechsig E, Gilch S, Riederer P, Gerlach M, Schätzl HM, Klein MA (2007) The tyrosine kinase inhibitor imatinib mesylate delays prion neuroinvasion by inhibiting prion propagation in the periphery. J. Neurovirol. 13, 328-337.

Müller N, Avota E, Schneider-Schaulies J, Harms H, Krohne G, Schneider-Schaulies S (2006) Measles virus contact impedes cytoskeletal remodeling associated with T cell adhesion, spreading and CD3 clustering in the immunological synapse. Traffic 7, 849-858.

Neske F, Blessing K, Tollmann F, Schubert J, Rethwilm A, Kreth HW, Weissbrich B (2007) Real-time PCR for diagnosis of human bocavirus infections and phylogenetic analysis. J. Clin. Microbiol. 45, 2116-2122.

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Sopper S, Nierwetberg D, Halbach A, Sauer U, Scheller C, Stahl-Hennig C, Mätz-Rensing K, Schäfer F, Schneider T, ter Meulen V, Müller JG (2002) Impact of simian immunodeficiency virus (SIV) infection on lymphocyte numbers and T-cell turnover in different organs of rhesus monkeys. Blood 101, 1213-1219.

2.11 Institute of Virology and Immunobiology, Chair of Immunology

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Professor Dr. rer. nat. Manfred Lutz
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Mission and Structure

The research groups of this chair are particularly interested in the differentiation, activation and mutual interactions of T and B lymphocytes, as well as NKT cells, myeloid suppressor cells and dendritic cells. The approaches in basic research will allow a better understanding of the immune system and immunologically mediated diseases which lead to new experimental therapies against allergies, autoimmune diseases, transplant rejection and graft-versus-host-disease. There exist multiple interactions with other groups of our University but also within Germany and internationally. Research is complemented by the laboratory of immunodiagnostics which analyses autoantibodies from patient samples (head Dr. T. Kerkau).

Major Research Interests

Function of the costimulatory receptor CD28
(T. Hünig)

Using newly developed monoclonal antibodies with specificity for the mouse CD28 molecule, we are studying the effects of blockade versus stimulation of this receptor on the composition and function of the murine immune system.

Regulatory T-cells in mice and rats
(T. Hünig)

Besides the search for novel, functionally important cell surface receptors on regulatory T-cells, we are particularly interested in the mechanisms by which stimulatory CD28-specific monoclonal antibodies increase the number and enhance the function of regulatory T-cells in vivo.

CD8 T-cell-mediated autoimmunity in mouse model of Multiple Sclerosis
(T. Hünig)

Through transgenic expression of a cytosolic model antigen in oligodendrocytes which form the myelin sheath around the axons, CD8 “killer” T-cells, but not CD4 “helper” T-cells, specific for the model antigen can induce MS-like lesions in the CNS of mice.

T cell activation by non-conventional antigens
(T. Herrmann)

Most T cells recognize complexes of peptide antigens bound to MHC molecules. Moreover there are non-conventional antigens such as glycolipids and „Phosphoantigens“. The group of T. Herrmann investigates the activation of T-cells with specificity for such non-conventional antigens (rat NKT cells and human Vγ9Vδ2 T cells). Furthermore the function of a „new“ non-polymorphic rat MHC class II molecule (RT1D2) is investigated.

Tolerance induction by dendritic cells
(M. Lutz)

Dendritic cells are key mediators of immune responses but they are also essential to maintain tolerance. Tolerogenic functions are mediateted through “immature” or “semi-mature” activation stages while “mature” or “licensed” dendritic cells induce immunity. We are investigating physiological T cell tolerance mechanisms induced by dendritic cells in antigen-transgenic K5-mOVA mice such as anergy, immune deviation and regulatory T cells. We also use in vitro generated tolerogenic dendritic cells to modulate immune responses in mouse models of allergy, autoimmunity and transplantation.

Immunosuppression by myeloid suppressor cells
(M. Lutz)

Myeloid suppressor cells in mice and humans represent early differentiation stages of the myeloid lineage. At a certain level of their development they can be activated to produce nitric oxide and suppress overshooting CD4 and CD8 T cell responses. This is however also exploited by tumors and microbial pathogens such as Mycobacteria. The knowledge about the induction of myeloid suppressor cells will help to improve immune responses against tumors and lead to new strategies for vaccine development.

Regulation of maturation and differentiation of B cells
(I. Berberich, M. Herold)

B cells mature in the bone marrow and finally differentiate in spleen and lymph nodes after contact with their cognate an-

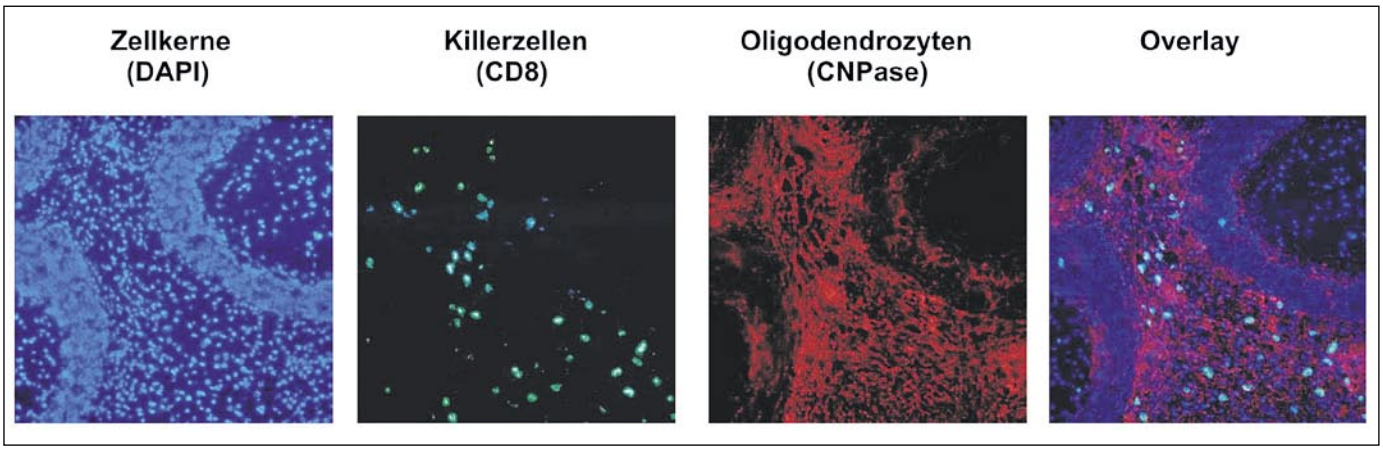

Fig. 1: Attack of cytotoxic T-lymphocytes on the brain´s white matter. The section through the cerebellum of a mouse shows the accumulation of cytotoxic T-lymphocytes (green) in the central region, the so-called white matter, where oligodendrocytes (red) form the myelin sheaths around the axons which transmit neuronal impulses. The section was taken from transgenic mice expressing the model-antigen ovalbumin (OVA) in oligodendrocytes and killer cells specific for OVA. Similar accumulations of cytotoxic cells are seen in lesions of human Multiple Sclerosis.

tigen. During all these steps, survival of B cells depends on the fact that the cell is potentially beneficial for the organism, i.e. can recognize foreign antigen, and does not attack the own body. In the latter case, such autoreactive cells have to be deleted. This decision about life and death among other things depends on the integrity of the cell's mitochondria assured by so-called anti-apoptotic proteins of the Bcl-2 family. Research focuses on the analysis of the regulation and functionality of A1/Bfl1, a member of this protein family.

Regulation of misguided immune reactions
(T. Kerkau, N. Beyersdorf)

The team is working on the significance and therapeutic manipulation of regulatory T cells in the context of pathological immune reactions. Here, in addition to animal models of multiple slerosis, we are particularly interested in the study of Graft-versus-host-disease, a major complication after allogeneic bone marrow transplantation.

Teaching

Basic lecture for students of medicine, biomedicine and biology are offered. These are complemented by a series of seminars for advanced students together with practical courses of 8 weeks per year.

SELECTED PUBLICATIONS

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2.12 Institute for Molecular Infection Biology

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Mission and Structure

The Institute for Molecular Infection Biology was founded 1993 as an interdisciplinary institution at the Medical Faculty of the University of Würzburg and is a part of the „Research Center for Infectious Diseases". As the chairman is also a member of the Faculty of Biology, the institute represents a link between these two faculties. The institute is closely associated with the young investigator groups of the Research Center for Infectious Diseases. The research of the institute aims to elucidate fundamental aspects of infection processes. The research groups at the institute study several molecular aspects of infections caused by bacteria, parasites and fungi. Additionally, the interactions between parasitic pathogens and the host immune system are investigated in detail.

Major Research Interests

The main interest of the working groups of the institute is the analysis of the mechanisms that allow pathogens to trigger infections. Furthermore, the reactions of the host cells in response to contact with pathogens is studied. In addition to microbiological, molecular and cell biological methods, genomic (genome analysis) and proteomic (protein expression analysis) approaches are applied within the following projects:

Virulence mechanisms and genome diversity of enterobacteria
(U. Dobrindt)

Pathogenic enterobacteria possess, in contrast to many of their non-pathogenic commensal relatives, additional DNA regions, i.e. the so-called Pathogenicity- or Genomic Islands. The group characterizes processes involved in genetic diversity and genome optimization of pathogenic and commensal enterobacteria. The structure, function and distribution of virulence-associated genes as well as the regulation of gene expression are studied. Furthermore, we aim at the functional characterization of novel virulence-associated genes of pathogenic enterobacteria.

Enterobacterial adhesins/ invasins and countermeasures
(T. Ölschläger)

Special attention is paid to the analysis of invasion and adherence of pathogenic enterobacteria. The research group aims at the specific interference of adhesion-mediated host-pathogen interaction. Besides mechanisms of molecular pathogenicity, the use of probiotics in order to counteract bacterial infection is investigated using probiotic *E. coli* strain Nissle 1917 as a model organism.

Immunological and cell biological studies on the pathogenicity of *Leishmania* parasites
(H. Moll, K. Remer)

Leishmania cause different clinical pictures, whose expression depends on the immune response of the infected host. This model allows to study the immunological mechanisms of defense against infectious pathogens. The group investigates the role of chemokines and dendritic cells in host resistance against Leishmania and works on the identification and characterization of leishmanicidal compounds.

Biology and Pathogenicity of *Candida albicans*
(J. Morschhäuser)

The group aims at the characterization of molecular mechanisms of infection by *Candida albicans* and of the nature of antifungal resistance. For this purpose, the signals and signal transmission routes that control morphogenesis, virulence gene expression and antifungal drug resistance in *C. albicans* are studied.

Molecular and cellular studies of *Legionella pneumophila*
(K. Heuner)

The causative agent of Legionnaires' disease, *Legionella pneumophila*, is able to invade and destroy human lung macrophages. The natural niche of these pathogens are protozoa in the environment. The group studies the interaction of these protozoa with *Legionella pneumophila* and focuses on the investigation of the host-pathogen interaction as well as the function and regulation of various specific virulence factors of this pathogen.

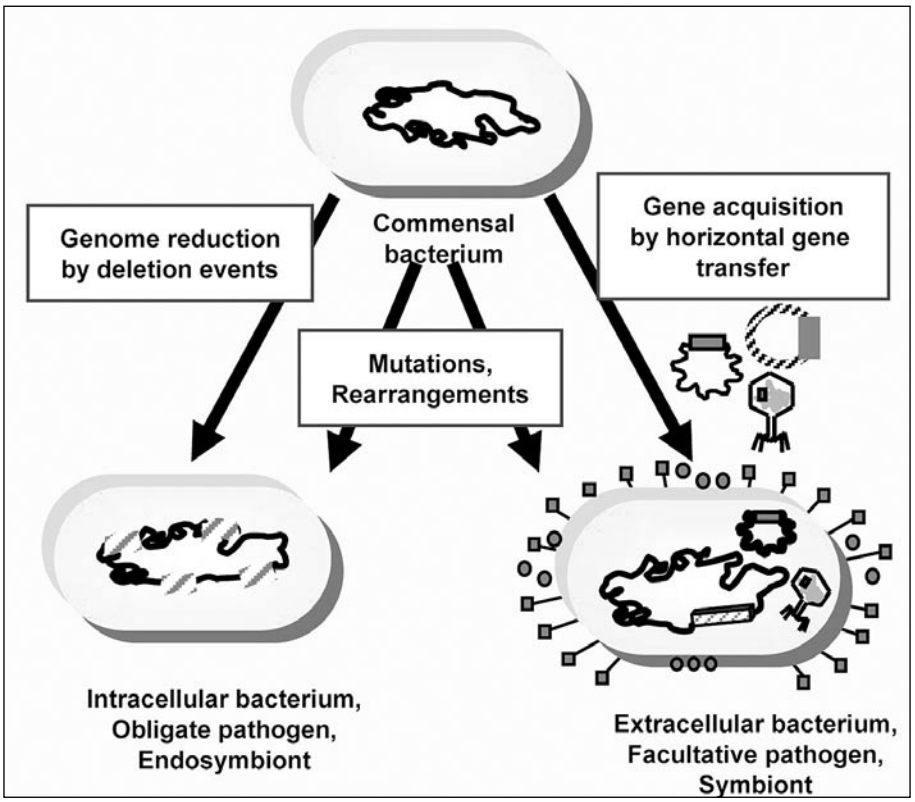

Fig. 1: Impact of genome plasticity on the evolution of pathogenic bacteria due to genome rearrangements, gene loss and the acquisition pathogenicity islands, phages and plasmids.

Virulence- and resistance mechanisms of pathogenic staphylococci
(W. Ziebuhr, K. Ohlsen)

Staphylococci are among the most important nosocomical pathogens. The ability of these pathogens to form biofilms and to develop antibiotic resistance is intensively studied in this group. The gene expression of these pathogens is studied under conditions that mimic the host by the use of *in vivo*-infection models. These studies also include methods of functional and comparative genomics and proteomics.

Molecular characterisation of pathogenic reactions of *Entamoeba histolytica*
(H. Bruhn)

Entamoeba histolytica causes human amoebiasis, the second leading cause of death due to parasitic infections worldwide. The amoeba lives as a commensal in the human intestine and can occasionally penetrate into the surrounding tissue thereby exciting severe tissue destruction which mostly results in severe liver abscesses. The factors involved in the destruction of the host cells by the amoeba are characterized at the molecular level.

Teaching

A considerable part of the teaching activities contribute to the training of biologists in the Department of Microbiology. These activities include lectures in general microbiology, on issues of pathogenicity and immunology, as well as seminars on current topics of Infection Biology and courses and internships. Some of these events are also part of the curriculum of the Biomedical Education. The institute organizes lectures, courses, seminars and summer schools for the members of the Graduate College "Infectiology" in association with the International Graduate School "Life Sciences" at the University of Würzburg.

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2.13 Institute of Pharmacology and Toxicology, Chair of Toxicology

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Mission and Structure

The departments of Pharmacology (chaired by Prof.Dr. Martin J. Lohse), and Toxicology constitute the Institute of Pharmacology and Toxicology. The building accommodates the research laboratories and offices, a lecture hall seating 300 students, course laboratories, a seminar room, and a library for pharmacology and toxicology. Facilities for animal husbandry, work with high levels of radioactive isotopes, a repair shop, and computer facilities for medical students are also available.

The workforce of the department of Toxicology comprises between 50 and 60 members. Six research groups are led by the University Professors Dr. Werner K. Lutz (Head since 1994), Dr. Helga Stopper, Dr. Gilbert Schönfelder, the Associate Professors Dr. Erwin Eder and Dr. Wolfgang Dekant, and the Research Associate Dr. Angela Mally. Postdocs and on average 15 Ph.D. students with degrees in chemistry, food chemistry, biology, pharmacy, and medicine accomplish the experimental work, supported by about an equal number of technicians.

Major Research Interests

Most of our research is funded by grants. We rank first among the Chairs of Toxicology of the Bavarian Universities in this respect. This is also reflected by the number of publications in refereed Journals reaching 20 per year on average over the last 12 years.

Chemical Carcinogenesis

Our research focuses on elucidating the first-line interactions of mutagenic and carcinogenic chemicals with biological target, with the aim of a mechanistically supported risk characterization of chemically induced cancer in humans. We investigate the kinetics and metabolism of chemicals in vitro, in cells, animals and humans, paying special attention to the metabolic activation to chemically reactive intermediates, their interaction with biological macromolecules such as DNA and protein, and their detoxification. Numerous assays have been developed to study the genotoxicity by covalent DNA binding, induction of other types of DNA damage (see Figures) and the course of events leading to mutations. Epigenetic mechanisms include hormonal effects, changes in the cell cycle and disturbance of cell differentiation.

Biomarkers

A second research focus is biomarkers in both animals and humans. Biomarkers of exposure are based mainly on the analysis of metabolites in urine, including metabolic profiling of major classes of conjugates. Analysis of biofluids is also used for metabonomics, in an attempt to find treatment- or disease-related changes. Early cytological alterations are investigated in the search of early biomarkers of toxicity and carcinogenicity in kidney and liver, including idiosyncratic reactions. Biomarkers of genotoxicity include investigation of genomic damage in blood cells. Oxidative stress and advanced glycation end products should also be mentioned. Biomarkers of individual susceptibility are studied in connection with side effects of radiotherapy and differences in metabolism due to genetic polymorphisms or inhibition of enzymes involved in resorption, metabolism and excretion.

Risk Assessment

Knowledge on the mode of toxic action is a prerequisite for biologically based extrapolation from cells in culture or laboratory animals to humans, from high dose to low dose, and from the reproducible situation of experimental systems to the heterogeneity of a human population. Efforts on dose-response relationships and mixture effects are based on experimental data but include elaborate statistical analysis as well as kinetic modeling.

Investigated Compounds

The list of investigated compounds comprises a variety of chemical classes and sources. Exposure at the work place and in the environment include aromatic hydrocarbons and substituted derivatives, as well as chlorinated and fluorinated chemicals. Dietary exposure includes mycotoxins (ochratoxin A), heat-derived products (acrylamide, furan), migrants from polymers, phytoestrogens, as well as different types of fat and their (per)oxidation products. For drugs, we focus on agents for which the probability of side effects is modulated by pharmacogenetic differ-

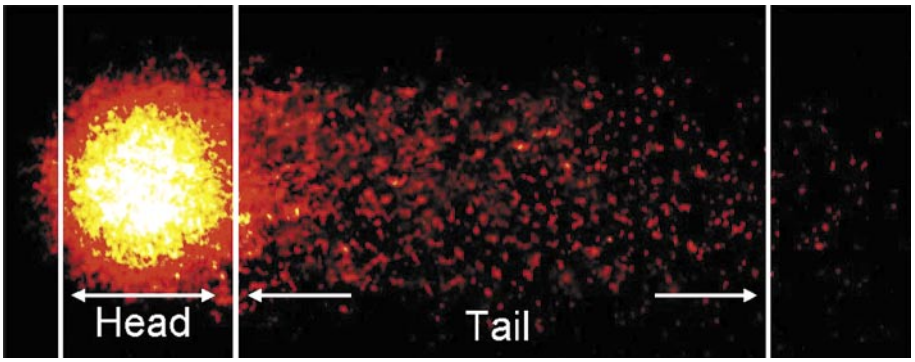

Fig. 1: "The Comet Assay": DNA fragments induced by a genotoxic agent migrate in an electric field out of the cell nucleus (Head) into a tail.

Fig. 2: "The Micronucleus Test": Chromosome damage is indicated by the presence of a DNA-containing fragment in the cytoplasm of the bi-nucleated cell in the middle of the three cells.

ences and/or enzyme inhibition. Compounds with estrogenic and antiestrogenic activity are used primarily in connection with the investigation of epigenetic effects. Endogenous and unavoidable DNA-damaging agents and processes that contribute to "spontaneous" tumor formation are also of interest. Oxidative stress is considered a major factor in this respect.

Teaching

Our staff covers all aspects of toxicology and shares the responsibility with the Pharmacology Department for teaching general and systematic pharmacology for students of medicine and biomedicine, pharmacy, dentistry, and biology. For chemistry students, a special course meets the legal requirements according to the "Gefahrstoffverordnung" to allow graduates to do business in chemical manufacture and sale. Prof. Lutz is Chairman of the Study Committee for the Curriculum in Biomedicine and chairs the admission committee for the respective M.Sc. Program. Prof. Stopper is Coordinator of the Graduate Program „Target Proteins". All professors teach in the postgraduate courses organized by the Society of Toxicology of the DGPT to register as DGPT and EUROTOX-certified Toxicologist. Editing and reviewing for scientific journals, membership in national and international scientific committees and consulting of political and governmental bodies is another part of our activities in the field. For the chemical and pharmaceutical industry, we offer both theoretical and experimental expertise for cooperations.

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2.14 Institute of Pharmacology and Toxicology, Chair of Pharmacology

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Mission and Structure

The Institute of Pharmacology and Toxicology comprises Chairs for Pharmacology (Prof. Lohse) and for Toxicology (Prof. Lutz). Presently, the institute also houses several research groups of the Rudolf Virchow Center that was funded in 2002 and that is chaired by Prof. Lohse.

The chair comprises a total of 75 people, 40 of whom are paid from grants. All research groups are devoted to the investigation of molecular mechanisms of cellular communication, their role for physiological functions and their potential to serve as drug targets. In addition to standard biochemical and molecular biology equipment the chair has a SPF unit for the generation of transgenic mouse models as well as equipment for rapid microscopic imaging, for confocal, 2-photon and TIRF microscopy and for electrophysiology.

The chair also provides a drug information service for the university hospital and medical faculty as well as outside physicians and pharmacists.

Major Research Interests

Research in pharmacology is primarily concerned with cell surface receptors for the stress hormones adrenaline and noradrenaline, and with related receptors that bin, for example, opiates, somatostatin and adenosine. These receptors are being investigated with a large array of methods and questions that range from the structures of receptors and ligands to transgenic disease models and studies on patient samples. Our research is funded by grants from the DFG, in particular the SFB487 and 688, the EU, the BMBF (Federal Ministry of Research), the Bavarian research Foundation and others.

Mechanisms und Function of G-Protein-coupled Receptors
(M. Lohse, C. Hoffmann, V.O. Nikolaev)

Communication between receptors occurs via hormones and neurotransmitters that are recognized by specific receptors, which constitute the primary class of drug targets. We investigate their function and regulation in various model systems, most importantly receptors for adrenaline and noradrenaline and for parathyroid hormone. We are also studying the mechanisms that lead to desensitization of receptors, i.e. their habituation to prolonged stimuli, which may be the basis of tolerance against drugs. In the past few years we have developed a variety of techniques to visualize receptor activation and inactivation with the aid of new sensors and fluorescence microscopy methods. This permits the direct study of receptors and signaling mechanisms „at work“, and the analysis of the speed and localization of cellular signals.

G-Proteins und Regulation of Ion Channels
(M. Bünemann)

Many ion channels are regulated by receptors and G-proteins. We investigate the molecular mechanism of this control, and use fluorescence methods to visualize an entire signaling chain from the receptor to the activation of the ion channel.

Somatostatin and Opiate Receptors
(S. Schulz)

Opiate receptors are the targets for morphine and heroin and play a central role in pain perception; somatostatin receptors regulate cell growth and appear to be important in several types of cancer. Both receptor families belong to the G-protein-coupled receptors. We investigate their regulation and cellular trafficking, with the aim of identifying ligands for improved pain and tumor therapy.

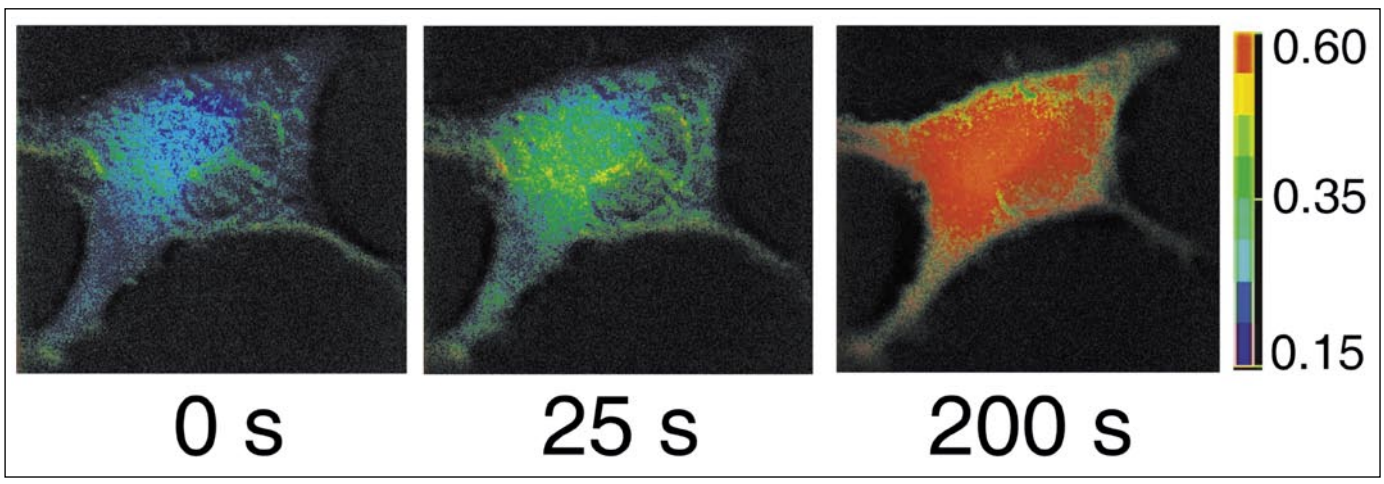

Fig. 1: A newly developed fluorescence sensor shows an increase (red color) of the second messenger cGMP in primary mesangial cells of the kidney.

Adenosine Receptors and their Ligands
(K.-N. Klotz)

Adenosine is a ubiquitous mediator that acts on cells via four different receptors. In collaboration with chemists we develop selective ligands for these receptors and investigate the principles of their specific recognition.

Mechanisms of Heart Failure and Cardiac Signaling
(S. Engelhardt, K. Lorenz)

Chronic heart failure is one of the main health problems of old age. Based on a mouse model of slowly developing heart failure we are searching for genes and mechanisms that contribute to heart failure and dilatation and may offer new therapeutic avenues. Several such candidates have been identified in recent years: the sodium/proton exchanger NHE1, the interleukin converting enzyme ICE, the transcriptional regulator NAB1, and the protein kinase inhibitor RKIP. More recently, we have begun to elucidate the role of newly discovered micro RNAs in heart failure.

Receptor-Antiodies in Heart Failure
(R. Jahns, in collaboration with the Department of Medicine)

Over many years we have demonstrated the presence of antibodies against β_1-adrenergic receptors in about a third of patients with chronic heart failure. These auto-antibodies reduce the chance of survival of these patients by 50%. We have now generated a corresponding animal model by immunizing rats with receptor epitopes. In a project funded by the BMBF GoBio program we now want to try to develop a therapeutic strategy based on cyclic peptides.

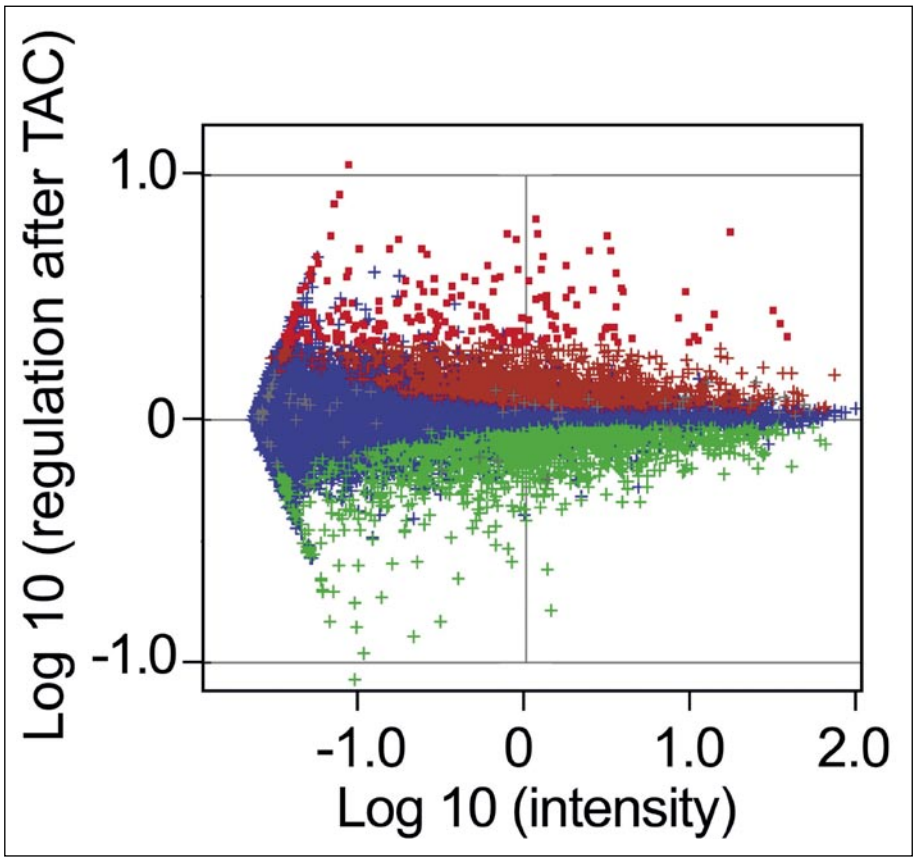

Fig. 2: Cardiac gene expression – many of the 20.000 investigated genes are less (green) or more (red) active in failing compared to healthy heart.

Teaching

The Institute is responsible for teaching pharmacology and toxicology to students in medicine, dentistry, biology and biomedicine. The focus is on general and clinical pharmacology for medical students (5th, 6th and 8th term) and pharmacy students (5th-8th term). We also play a key role in the conception of the new research oriented BSc/MSc curriculum in Biomedicine and participate in the curriculum in Experimental Medicine. We also offer the full curriculum for the medical specialties of pharmacology and clinical pharmacology.

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2.15 Institute of Forensic Medicine

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Mission and Structure

The Institute of Forensic Medicine at the University of Würzburg has an academic staffing plan which comprises the head of the institute and four physicians, two toxicologists and a molecular biologist. The existing staff situation reflects the specialist requirements in respect of research, teaching and the forensic medical equivalent of medical care.

Forensic medical care encompasses practical medicolegal work in Lower Franconia and adjacent areas of Upper Franconia and Baden-Württemberg that is conducted at the request of courts, state attorneys and police. The main task is to investigate deaths from unnatural causes, to appraise physical injuries to live persons that are relevant in penal law terms, and forensics as a service to resolve capital crimes, to clarify contentious paternity and forensic toxicological analysis to establish the cause of death as well as to clear up road traffic offences.

Major Research Interests

Forensic medical research is oriented to the special needs of legal practice. Accordingly, it has forensic pathological, forensic molecular biological and forensic toxicological aspects. Forensic medicine in Würzburg focuses on natural science. Legal and forensic psychiatric matters are therefore no longer dealt with.

In clarifying the cases of death from unnatural causes, establishment of the time of death within the 24-hour period is entirely feasible; after this time, it is largely impossible. The RNA analysis introduced by our institute has opened up a novel avenue to resolve this problem: by measuring the stability of the mRNA using real-time PCR, the range of changes in the body that are associated with the time of death can be extended.

Before we presented our own molecular genetic research results, the origin of blood, e.g. menstrual blood or blood deriving from injuries, could not be determined. Internationally, this was feasible for the first time only subsequent to our research on receptor-specific endometrial mRNA.

The age of bloodstains and the age of persons who have left stains cannot be adequately determined: a forensic approach to appraising the age of the respective individuals has been presented using procedures of mRNA analysis or detection of 4977 base pair deletions in the mitochondrial genome.

Molecular biological species diagnostics were conducted and DNA was analyzed in hair and stored skeletal material, in some cases by doctoral students. Finally, it has become feasible to make an individual identification on the basis of semen from vasectomized men.

Transplantation surgery, prenatal medicine and stem cell research have raised ethical questions on the borderline zones of human life. Our institute has presented a distinction between the anthropological category human and the biological category human life that has led to a more objective discussion.

Teaching

Medical students are instructed in forensic medicine in the main lecture course, by means of practicals and seminars. In the main lecture course, chiefly the correct procedure for a medical autopsy is taught. This requires comprehensive knowledge of forensic traumatology and toxicology and is consolidated in an obligatory autopsy practical in small groups. Teaching consists of thanatology, forensic traumatology, forensic serology/molecular genetics, forensic toxicology and questions of medical law. The latter is gaining importance since medicine is increasingly subject to legal consider-

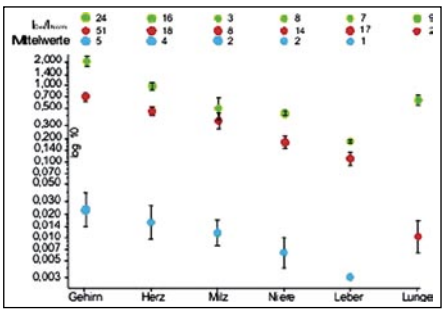

Fig. 1: Age estimation on the basis of mitochondrial sequence analysis (age-dependent raised incidence of the 4977 bp deletion): The mean value and the standard deviation for the respective tissue in the three age groups ≤ 30 years (blue), ≤ 70 year (red) and ≤ 90 years (green) is shown. The number of samples investigated is also specified.

ations. Future physicians are trained to take the legal background into account in their work in such a way that they cannot be accused of not meeting their obligations. One focus of forensic traumatology is detecting signs of domestic violence. In the interdisciplinary subjects, Prevention and Treatment of Addiction is dealt with under the banner title of preventive medicine and a seminar Ethics in Medicine is conducted as one of the selectable compulsory subject which can be chosen.

Forensic Medicine for Lawyers is a well-attended lecture course for law students. Moreover, legal interns are instructed on the effects of alcohol and drugs in road traffic in conjunction with a scientifically supervised drinking experiment.

SELECTED PUBLICATIONS

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Patzelt D (2004) Grenzbereiche menschlichen Lebens. Rechtsmedizin 14: 247 – 250.

2.16 Institute of Pathology

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Mission and Structure

The Institute of Pathology of Wuerzburg University is a medical facilty with a staff of over 100, including 6 professors and about 15 pathologists, with a dual function in clinical support and research. Its main clinical tasks include histologic and cytologic diagnosis of biopsies and other materials, and autopsies. Specialized departments for Applied Cytology and Tumor Genetics, Neuropathology, and Molecular Pathology concentrate on specific diagnostic topics. The institute has established itself as a successful scientific facility with broad research interests, with an emphasis on hematopathology (especially lymph node pathology). With its large consultation service for other pathology institutes with respect to diagnostically difficult neoplastic alterations of bone marrow and lymph nodes, the institute acts as a national diagnostic reference center for all german multicentric clinical therapeutic trials of malignant lymphomas.

Major Research Interests

Hematopathology Research and Consultation Center for Lymph Node Pathology
(H. K. Müller-Hermelink)

Several research groups operate within the national consultation center for lymph node pathology. (1) The group of Dr. E. Haralambieva analyses the biologic heterogeneity of multiple myeloma after succeeding in developing reliable fluorescence in situ hybridization (FISH) protocols that enable the detection of various chromosomal translocations in routinely fixed paraffin embedded tissue samples. (2) Within the Peripheral T-cell Lymphoma Research Group, Dr. E. Geissinger demonstrated that anaplastic large cell lymphomas (ALCL) lack the expression of a T-cell receptor (TCR) and associated signalling molecules. Priv.Doz Dr. A. Zettl established the genetic differences among peripheral T-cell lymphomas and showed two genetically and clinically different variants of enteropathy-type intestinal T-cell lymphoma.. The group of Dr. P. Adam focuses on indolent B-cell non-Hodgkin lymphomas (MALT-type lymphoma / follicular lymphoma). In the past especially early stages of lymphoma development were investigated. Ongoing research projects include the association of infectious agents with and the analysis of chromosomal imbalances in MALT-type lymphoma.

The consultation center for lymph node pathology coordinates histologic evaluation of patients enrolled in one of several clinical therapeutic trials of the “German study group for high-malignant non-Hodgkin Lymphoma” (DSHNHL), and the european multicentric study of peripheral T-cell lymphomas.

Molecular Pathogenesis of Malignant B-cell-Lymphomas
(A. Rosenwald)

The research group is focused on the molecular characterization of malignant lymphomas. By using gene expression profiling (Affymetrix technolgy) and correlating global transcriptional profiles with morphologic, cytogenetic und molecular features, it is working towards a molecular classification of lymphomas, a goal recently accomplished in the case of Burkitt´s lymphoma in collaboration with 2 scientifc consortia. Furthermore the research group acts on a global level as one of seven FDA-approved centers for the development of a diagnostic microarray for lymphomas.

Therapeutic Relevance of CD56 Dependant Signalling Pathways in Ischemic Cardiomyopathy and Malignant Hematopoietic Neoplasias
(S. Gattenloehner)

Preliminary work demonstrated that the specific overexpression of the cell adhesion molecule CD56 (NCAM) in the myocardium from patients with ischemic cardiomyopathy is regulated by novel isoforms of the transcription factor RUNXI. Tansfection assays proved that murine cardiomyocytes with stable overexpression of CD56 have a strong induction of apoptosis and decreased calcium influx, resulting in cardiomyocyte loss and reduced contractility, representing the hallmarks of heart failure. By contrast in malignant hematopoietic neoplasias such as acute myeloid leukemia or multiple myeloma, CD56 induced nuclear translocation of NF-kappaB and increased bcl2L12 expression blocked by the NF-kappaB wedelolactone. Since the overexpression of

DC56 and its dependant downstream cascades has impact on progression of ischemic cardiomyopathy and malignant hematopoietic neoplasias, the inhibition or regulation of such pathways might open new aspects in the therapy of these diseases with mostly fatal course.

Immunotherapy for Rhabdomyosarcoma and Rhabdoid Differentiated Tumors
(S. Gattenloehner)

Rhabdomyosarcoma (RMS) is the leading malignant soft tissue tumor in children with high mortality rates in spite of modern multimodality tratments. Since strong expression of the gamma-subunit of the acetylcholine receptor (AChR) defining the fetal AChR isoform is specific for rhabdomyoblasts, the question arose whether RMS cells could be killed by an anti-fetal AChR-directed immunotherapy. Based on a fully human Fab-fragment with anti-fetal AChR specificity, the research group generated a chimeric T-cell receptor (TCR) harbouring the fAChR specific antibody fragment (single chain Fv scFv) attached to the zeta chain of the TCR and a Pseudomonas exotoxin A based immunotoxin that both kill human embryonal and alveolar RMS cell lines in vitro and delay RMS development in a transplantation model in mice. Since the fAChR is also expressed on rhabdoid differentiated tumors other than RMS such as malignant melanomas and is induced by conventional chemotherapy on RMS cells in vivo, anti-faChR scFv based immunotherapies might be a promising alternative therapeutic strategy for such aggressive and high-malignant tumors.

Transcriptional Control of Lymphokine Genes in T-Lymphocytes
(E. Serfling)

The experimental work of the department of molecular pathology within the institute of pathology of Wuerzburg university is devoted to the transcriptional control of lymphokine genes in T lymphocytes, in particular to that of IL-2, IL-4 and IL-5 genes. This work lead to a detailed analysis of NFAT transcription factors whose induction – by elevated Ca++ levels and calcineurin-mediated signals – appears to be unique for the activation of lymphocytes. In the future the research group plans to study expression and function of individual NFATc isoforms, to characterize DNA sequence elements and tissue factors controlling NFATc1 expression in vivo, and to analyze interaction of NFATc factors with other transcription factors such as GATA-3, STAT6 and Foxp3. To this aim, the research group cooperates with the proteomics facility at the Rudolf-Virchow-Center of experimental biomedicine and with the department of molecular plant physiology and biophysics of Wuerzburg university.

Human Immunity to Cancer
(H.P. Vollmers)

The experimental work of this research group is focused on human immunity to cancer in which antibodies play an important role. To investigate their nature, function, and targets, the group screened thousands of human monoclonal antibodies. All tumor-specific antibodies proved to be natural antibodies, mostly of IgM isotype, coded by distinct germ line genes, their targets being post-transcriptionally modified carbohydrate epitopes on cell surface receptors like CD55, CFR-1 or GRP78. Furthermore, all tested antibodies remove malignant cells in vitro and in vivo by inducing apoptosis. In collaboration with Australian and US pharma companies, several antibodies are in preclinical development. The ongoing scientific work is concentrated on the characterisation of the antibody targets and the apoptotic pathways.

Neurooncology and Neurodegeneration
(W. Roggendorf)

Ependymomas are primary tumors of the central nervous systems occurring relatively often in childhood. The pathogenesis of these tumors is poorly understood, and prognostic assessment based on histologic features is difficult. With the goal to analyse ependymomas on a molecular level, the research group detected deletions to occur especially on chromosomes 6, 9, and 22, and used cDNA microarrays and RT-PCR to examine gene expression. These results were correlated with clinical parameters yielding prognostic factors influencing survival. – Another project about neurodegeneration investigates the role of impaired microcirculation in the pathogenesis of M. Alzheimer. In cooperation with other european tissue banks, the group participates in developing standardizied operation procedures (SOP) for further research on tissue of the central nervous system of humans.

Teaching

The institute of pathology is responsible for teaching pathology within the medical curriculum of Wuerzburg medical school. Five professors and about 10-15 lectures share in the teaching, its major element being a concentrated course of pathology comprising lectures, seminars, practical classes (histology) and macropathologic case demonstrations (autopsies). Additional courses for graduate students cover a wide range of specific subjects, techniques, and skills. Pathology lecturers also participate in interdisciplinary teaching projects (e.g. interdisciplinary oncology) and clinico-pathologic conferences for several hospitals and departments.

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2.17 Institute for Medical Radiation and Cell Research

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Mission and Structure

The Institut für Medizinische Strahlenkunde und Zellforschung (MSZ) was founded in 1993 and adjusted to modern safety standards by extensive remedial actions, which were completed in 2006. The MSZ is the Bavarian Center for Experimental Cancer Research of the University of Würzburg and is endowed with one full, two associate and six assistant professorships. In addition, in 2007 an independent junior group of the Bavarian Genome Research Network BayGene (Eugen Kerkhoff) and a DFG Emmy-Noether group (Krishnaraj Rajalingam) were settled at the MSZ. The objective of the approximately 70 employees is to better understand cancer in order to develop novel therapeutic approaches. Special emphasis is on the analysis of signaling pathways, which are disrupted in tumors. In addition, in cooperation with pharmaceutical companies the MSZ is involved in the development of small molecule inhibitors and therapeutic vaccines for cancer. Because of the intimate relationship between cancer and regenerative stem cells a group is also devoted to the biology of stem and tumor stem cells (Prof. Albrecht Müller). This work is supported by experiments with model organisms including the fruit fly Drosophila (Prof. Thomas Raabe). The MSZ is working together closely with several institutes of the faculties of medicine, biology and chemistry.

Major Research Interests

Investigations on the mechanisms of cell growth, differentiation and survival are the main research areas at the MSZ. Disruption of these processes is directly associated with the development of a variety of disorders such as cancer. Current methods of modern molecular biology, biochemistry, cell biology, genetics and structural analysis are utilized. Some of the research groups are mentioned in detail below:

Tumor Genetics
(U. R. Rapp, R. Götz)

Lung cancer is the most prevalent neoplasm in the industrialized world with 1.2 million annual deaths. Mouse models of lung cancer offer not only the opportunity to study the impact of oncogenes and other genetic factors on tumor initiation and progression but also provide a powerful system for the pre-clinical evaluation of novel therapeutic modalities. We have generated a mouse model for non-small cell lung cancer. These mice express in specific cells of the lung an oncogenic form of the RAF kinase, called C-RAF BXB, and develop lung tumors within two weeks after birth. No progression of these adenomas towards metastasis has ever been observed. However, when cell-cell adhesion was compromised by interference with the function of E-cadherin, the lung adenomas progressed to highly invasive and aggressive adenocarcinomas (Ceteci et al, 2007). There was a massive formation of intratumoral vessels and vascularized tumors gave rise to metastases. In ongoing studies the molecular details of the progression from benign to malignant lung tumors are further investigated. This should lead to the identification of novel molecular targets for cancer therapy.

Neurobiology
(U. R. Rapp, R. Götz)

The RAF kinase family encompasses three family members, A-RAF, B-RAF and C-RAF. The neurobiology group is using genetic approaches in mice to dissect the individual and common functions of these three isoforms. In the past the group neurobiology was able to show that specific cell populations in the developing embryo require either C-RAF or B-RAF for their survival. In order to further evaluate the function of RAF in the suppression of cell death, the role of Bag1, a co-chaperone for the heat shock protein Hsp70, which interacts with RAF and other proteins, was examined. By targeted gene disruption in mice, we showed that Bag1 plays an essential role in survival of differentiating neurons and hematopoietic cells and identified the mechanism of action (Götz et al, 2005). In order to delineate the function of B-RAF in the brain, mice with conditional inactivation of B-RAF and B-RAFKIN/KIN mice lacking B-RAF and expressing A-RAF under the control of the B-RAF locus were created. Our data revealed distinct, non-redundant functions for B-RAF and A-RAF during brain development and demonstrate that B-RAF is an important mediator of neuronal survival, migration and dendrite formation (Camarero et al, 2006).

Tumor Therapy
(U. R. Rapp, B. Bergmann)

Immunotherapy is a promising approach for the treatment of cancer. The idea is to en-

Fig. 1: The MSZ building.

gage the immune system of a tumor patient in a way that it is able to detect and to destroy the tumor. Due to the limited efficiency of current approaches, new methods have to be developed. It has been shown recently that immune therapies are particularly successful when different parts of the immune system work together in the fight against the tumor. In the group tumor therapy modified intracellular bacteria strains are used as carriers for tumor proteins. These infectious bacteria do not harm humans but increase the specific immune response against the tumor. The greatest progress has been made so far with a salmonella-based vaccine, which is expressing a RAF oncogene. In a lung tumor mouse model it was shown that after the administration of this vaccine tumor mass was reduced and the life span of mice was increased (Gentschev et al, 2005). In partnership with the company Æterna Zentaris the MSZ is in preparation for clinical trials of a salmonella-based vaccine against prostate cancer. If successful, this approach will be adapted to other tumor types.

Stem Cell Biology
(A. Müller)

Stem cells are rare but essential cell types for development and tissue regeneration. Research on stem cell biology and cellular pluripotency is one of the most promising research fields in human medicine. The possibility to reprogram cells into any type of adult stem cells for the purpose of cell replacement holds tremendous therapeutic promise and may circumvent ethical considerations concerning the derivation of new human embryonic stem cells. The molecular pathways controlling pluripotency and cellular reprogramming are now only beginning to be unravelled. The stem cell biology group focuses on embryonic, hematopoietic and mesenchymal stem cells and asks how global chromatin states guide stem cell behavior (Schmittwolf et al, 2005). Also, we are analysing the developmental potential of mesenchymal and uniparental embryonic stem cells. Albrecht Müller is speaker of the national DFG priority program 1356: Pluripotency and cellular reprogramming and member of the bioethics committee of the Bavarian state government.

Molecular Genetics
(T. Raabe)

One of the central challenges in neurobiological research is the elucidation of cellular and molecular mechanisms of brain development. Despite major anatomical differences between vertebrate and invertebrate nervous systems, the astounding similarity in their molecular mechanisms of development is becoming increasingly clear. Therefore, Drosophila melanogaster offers the opportunity to develop a general understanding of brain development through the use of genetic, molecular and functional studies. The group is focusing on signaling pathways regulating neuronal stem cell proliferation, specification and differentiation.

Teaching

Prof. Rapp is speaker of the German-French Research Training Group “Signal Transduction: Where cancer and infection converge” (http://www.gcwn.de) and deputy speaker of the BioMedTec International Graduate School of Sciences “Lead Structures of Cell Function” (Elitenetwork Bavaria; http://www.bigss.de). At the MSZ more than 30 students are currently doing research for their diploma, MD or PhD theses. Lectures, seminars and practical courses are offered for medicine, biology and biomedicine students with focus on radiology, neurobiology, cell biology and genetics.

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2.18 Institute of Human and Medical Genetics

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Mission and Structure

Human Genetics is an important area of biomedicine with increasing impact on the practice of medicine. Human Genetics investigates evolution, structure, function, inheritance and disorders of the human genome. Results of these studies are applied to genetic diagnosis, genetic counseling and patient care. At the University of Würzburg, human genetics is represented by a basic science-oriented Chair (Prof. Hoehn) and a Division of Medical Genetics (Prof. Grimm) providing genetic services. Both chair and division participate in patient care and teaching for students in the fields of medicine, biomedicine and biology. Located in the Würzburg Biocenter, the Department belongs to the University of Würzburg School of Medicine.

Major Research Interests

Cytogenetics and comparative genome research
(M. Schmid)

Using classical and molecular cytogenetic methods, the group headed by Michael Schmid analyses mechanisms of chromosome evolution and chromosome pathology. Cooperating with Manfred Schartl (Chair of Physiological Chemistry I), the group uses several model systems, including amphibians, fish, birds and mammals to improve our understanding of chromosomal and genomic evolution in vertebrates. In addition, the group provides access to cytogenetic methos (including FISH, SKY and CGH) to a variety of other groups within the biocenter and the medical school. Michael Schmid serves as editor of a number of genetics journals and serials (including Cytogenetics and Genome Research, Sexual Development, and Monographs in Human Genetics).

Molecular human genetics
(C. R. Müller-Reible)

Using a positional cloning approach and collaborating with Johannes Oldenburg, the group was able to identify VKORC1 as the central gene of the vitamin K dependent blood clotting cascade. Subsequently, mutations in VKORC1 were recognized as cause of warfarin-resistance in both humans and rodents. Current efforts are directed at improving our understanding of disorders of the vitamin K dependent clotting factors. In addition, the group has a long standing interest in the genetics of inherited muscle disorders, including the muscular dystrophies, the myotonias, and malignant hyperthermia. Clemens Müller-Reible serves as a member of several European committees on quality assurance in genetic diagnostics.

Somatic cell genetics
(D. Schindler)

This group investigates the role of human caretaker genes (including ATM, WRN, NBS, RAD50, LIG IV, MCPH1 and the FANC-family of genes) in the maintenance of genomic stability.

Most recently, the group participated in the discovery of three novel FANC-genes (FANCJ, FANCN, FANCI). Collaborating with groups from Germany and abroad, the Schindler laboratory has made major contributions to the cell genetic, epidemiological and functional aspects of Fanconi anemia (FA) and other caretaker gene syndromes, including Ataxia telangiectasia and the Nijmegen breakage syndrome. Current efforts are directed at finding the gene defects in unclassified FA patients, and at understanding the close connection between genetic instability and the emergence of neoplastic cell growth.

Human Progeroid Syndromes
(H. Hoehn)

In close collaboration with the Schindler laboratory, genetic instability syndromes with progeroid manifestations are used as models for the understanding of normal and pathological ageing. Cells derived from patients with the Werner adult progeria syndrome (WS) show multiple chromosome rearrangements that have been defined via spectral karyotyping. It remains unclear how this genetic instability related to the pleiotropic manifestations of WS which only superficially mimic normal ageing. Cells derived from patients with Fanconi anemia show frequent somatic reversions and are exceedingly sensitive to oxygen, rendering this disorder to the only human model system for the investigation of the free radical theory of ageing.

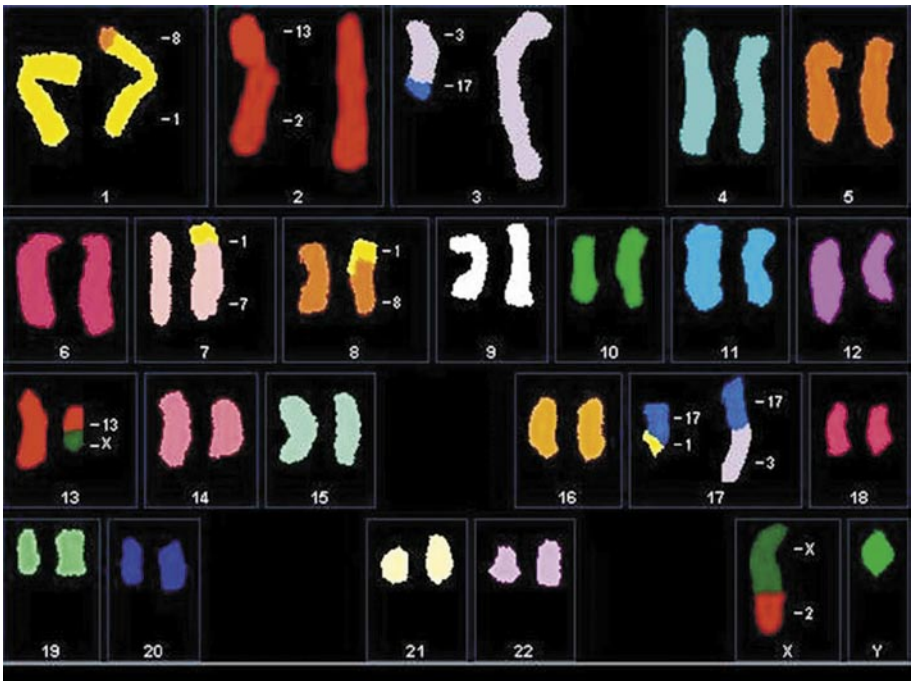

Fig. 1. Genomic instability typical of the Werner adult progeria syndrome: spectral karyotype showing multiple chromosomal rearrangements in a patient-derived fibroblast culture.

Teaching

The medical school curriculum includes a lecture course entitled "Clinical Human Genetics" which is taught in the 6th semester, together with an interdisciplinary course on "Disease prevention". Medical students can choose human genetics as an elective during their rotating internships, with emphasis on genetic diagnosis, dysmorphology and genetic counseling. In addition to teaching medical students, the Department also offers courses to students of biomedicine and biology, including laboratory courses in human cytogenetics and human molecular genetics. Undergraduate biology students can choose human genetics as one of their major subjects. Graduate students can obtain their M.S. or Ph.D. degrees within one of the research groups of the Department.

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2.18.1 Division of Medical Genetics

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Mission and Structure

The Division of Medical Genetics is part of the Department of Human and Medical Genetics at the University of Würzburg School of Medicine. Medical genetics represents the applied branch of human genetics. As such, medical genetics translates the results of human genetics research into the practice of medicine. Medical genetics deals with the medical implications of inherited diseases as they are encountered in many of the medical subspecialties. Patient contact is established via genetic counselling and genetic consultations. Genetic counselling is a process of communication with patients and families that is guided by the principle of patient autonomy. The genetic counsellor listens to patients´ fears and concerns, explains the nature and possible risks of inherited disease, and provides information on therapeutic and preventive measures. Important subspecialties of medical genetics are syndromology and teratology, which aim at recognizing and classifying congenital malformations and malfunctions. Comprehensive diagnostic and counselling services are provided in close cooperation between physicians in private practice, University hospital physicians, and members of the Department of Human and Medical Genetics. Participating physicians and geneticists belong to the "Würzburg Center of Medical Genetics".

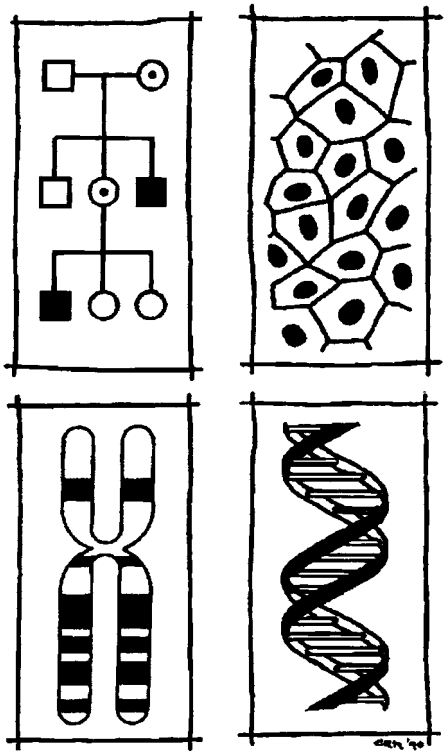
The Division of Medical Genetics includes the following centers:

Center for muscle diseases (operated by the German society for muscle diseases)
(Co-Directors: Prof. Dr. K. Reiners, Department of Neurology, University Hospital, and Prof. Dr. T. Grimm, Division of Medical Genetics; Coordinator and social worker: Angelika Eiler)

In close cooperation with the clinical Department of Neurology, the Center for muscle diseases coordinates diagnostic efforts, medical and social counselling, and long-term care of patients affected by neuromuscular diseases and their families

Center for hereditary breast and ovarian cancer
(Co-Directors: Prof. Dr. T. Grimm, Division of Medical Genetics and Prof. Dr. J. Dietl, Department of Obstetrics and Gynecology, University Hospital)

The center provides diagnostic, therapeutic and counselling services, including preventive measures, for women and families affected by or at risk for inherited breast and ovarian cancer. (cf. section 5.2.6)



Major Research Interests

Major research topics are genotype-phenotype correlations, aspects of formal and population genetics with emphasis on neuromuscular diseases, and the nosological classification of birth defects. Special research projects:

Genetics of proximal myotonic dystrophy (PROMM or DM2)
(W. Kress, T. Grimm)

The group tries to answer the questions of clinical heterogeneity and highly variable incidence of DM2. An interesting result with respect to genotype-phenotype correlations relates to the observation that rare homozygous DM2 patients (carrying the CCTG expansion) apparently are not more severely affected than their heterozygous counterparts.

Statistical and formal genetics
(T. Grimm)

T. Grimm has longstanding interest and expertise in genetic models, including non-mendelian models of inheritance. Numerous investigations of mutation rates as function of gender and mutation types in various diseases, including the X-linked muscular dystrophies, have provided the scientific basis for clinically relevant risk calculations.

Genetics of dyslexia
(T. Grimm)

Taking into account that approximately 5% of students are affected by various forms of dyslexia, T. Grimm became interested in the population genetics of dyslexia. Family studies provide evidence for familial clustering of dyslexia, including rare pedigrees suggesting monogenic inheritance. Novel candidate dyslexia genes are evaluated in close cooperation with the Max Planck Institute of Molecular Genetics (Berlin).

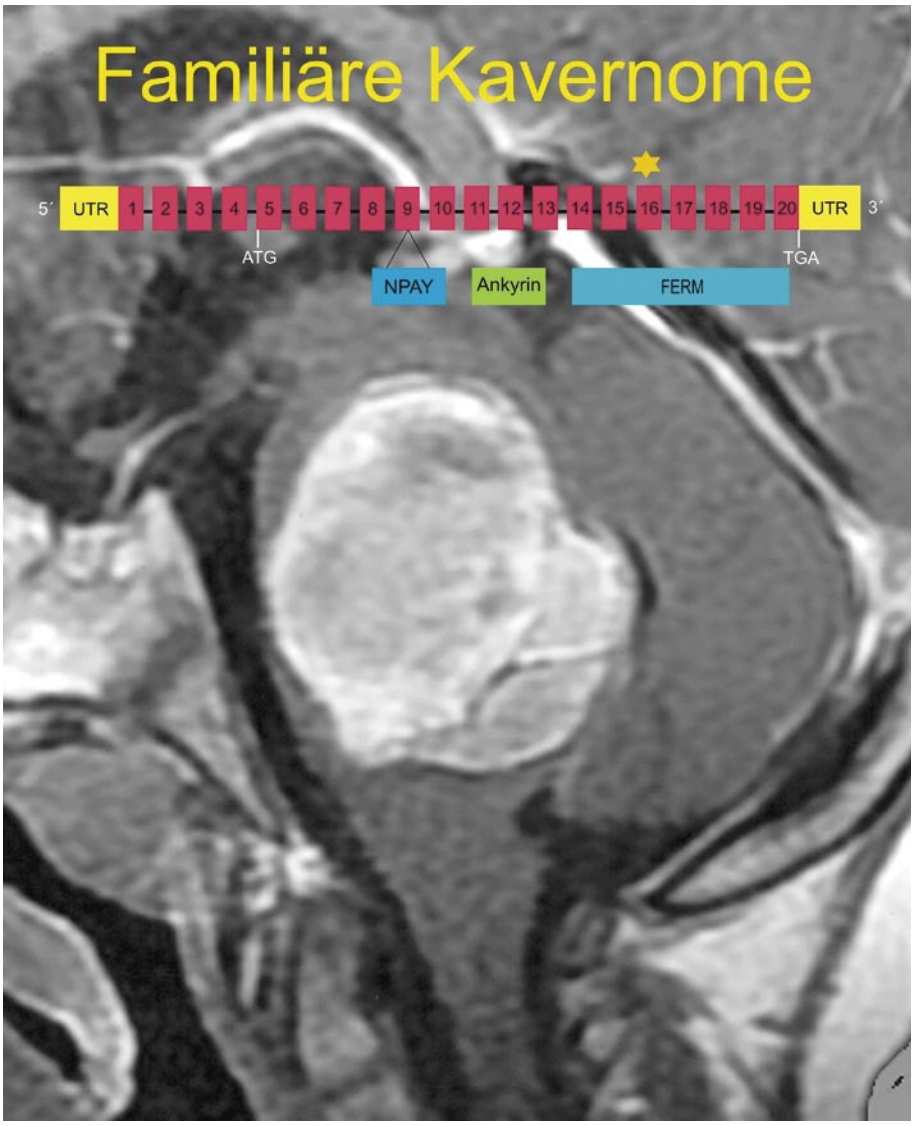


Fig. 1: Large brainstem cavernous malformation of a 3-year-old CCM1 mutation carrier with right-sided hemiparesis, epilepsy, and headaches.

Genotype-phenotype correlations in craniosynostosis
(W. Kress)

In close cooperation with the University Hospital Department of Pediatric Neurosurgery W. Kress was able to show that around 20% of patients with evidence for premature closure of cranial sutures display additional symptoms (e.g. malformations of the distal extremities). These complex disease entities are caused by a number of gene defects in receptors and transcription factors (e.g. FGFR3, TWIST1).

Genetics of vascular diseases
(U. Felbor)

The group headed by U. Felbor focuses on the molecular pathogenesis of hereditary vascular malformations. A rare monogenic form of hemorrhagic stroke caused by mutations in either of three genes (CCM1, CCM2 or CCM3) has most recently provided experimental evidence that CCM3 forms a protein complex with CCM1 and CCM2. Functional characterization of the CCM gene products is performed in endothelial cell cultures and in zebrafish using knockdown techniques. Systematic genetic testing for CCM gene defects has been established for the first time in Germany. With a mutation detection rate of >90% for familial CCM and of >60% for isolated CCM, the group has set new diagnostic standards. Previous projects of the group addressed the mechanism of action of the angiogenesis inhibitor endostatin, and the molecular events underlying neurodegeneration in cathepsin B and L-deficient mice.

Ethical aspects of Human and Medical Genetics
(T. M. Schroeder-Kurth)

Prenatal and predictive genetic testing cause a variety of ethical dilemmas and questions. In her capacity as a guest scholar, Professor emerita T. Schroeder-Kurth provides consultations and recommendations, guidelines and critical evaluations concerning ethical issues in human and medical genetics.

Teaching

The Division of Medical Genetics participates in lectures and courses for advanced students of medicine, biomedicine and biology. In addition, the division offers theoretical and practical training (clerkships, interships, "practical year") in areas such as genetic diagnosis, genetic testing, and genetic counselling. Postgraduate training is provided for MD and PhD professionals specializing in human genetics.

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3 University Hospital
3.1 Introduction

Tradition and progress don't contradict each other. Both distinguish the University Hospital of Würzburg: In the year 1581, the first university clinic evolved from the combination of the faculty of medicine and the Juliusspital. In times of highly developed health care, Würzburg is among the large clinics for high end medical care in Germany and enjoys a good reputation as a "prime address" for patient care not only in the region but also internationally, especially in the field of research and teaching.

Today, 19 clinics and 22 outpatient departments as well as four clinical institutes are part of the University Hospital. Four experimentally-orientated institutes, respectively departments, are integrated. Furthermore there are 6 affiliated training colleges of health care, which together offer more than 500 apprenticeship training positions.

Multidisciplinary collaboration is the focus of attention in nine Centers: the IZKF – Interdisciplinary Center for Clinical Research, the Center for Heart/Cardiovascular Diseases, the Breast Center, the Perinatal Center, the Center for Stem Cell Transplantation, the Transplant Center, the Center for Rheumatism and the Interdisciplinary Center for Cleft Lip and Palate.

The new Center for Experimental Molecular Medicine (ZEMM) will intensify the translation between basic research and clinical research. Another step in that direction was the setup of a central office for clinical studies (ZKS).

According to the official plan 2006, the University Hospital provides 1,509 hospital beds; the utilization ratio of the 1,456 beds having been set up was 76.1% with an average residence time of 8.3 days. In the year 2006, 48,603 patients received inpatient treatment and a total amount of 401,925 care days were performed. A total of 176,035 patients received outpatient treatment. Approximately 81% of all patients originate from the administrative regions of Lower, Middle and Upper Franconia as well as from other parts of Bavaria. 12.5% of all patients come from the adjacent Baden-Wuerttemberg, the remaining 6.5% from the rest of Germany or from abroad.

The University Hospital employs a total of more than 4,200 full-time employees, among them 742 physicians, 1219 nurses, 348 employees working as ancillary staff and 992 employees active in medical-technical work.

Surgical departments, which used to have different locations on the campus, are now combined in the Centre of Operative Medicine (ZOM) which started its work in 2004: the Department of Anesthesia and Intensive Care, the Department of Surgery, the Department of Trauma, Hand, Plastic & Reconstructive Surgery, the Department of Thoracic and Cardiovascular Surgery as well as the Department of Urology/Paediatric Urology. These departments make use of optimized structures, such as the service of the Institute of Transfusion Medicine and Haematotherapy or of the Institute of Radiology that both employees and patients benefit from. Apart from state-of-the-art medical services, the patient is offered the latest comfort available in the Center of Operative Medicine.

In the immediate vicinity of the Center of Operative Medicine, the Center for Internal Medicine (ZIM) is currently under construction. In the future it will house the Medical Clinics (I and II), the Department of Nuclear Medicine with the Centre for Radiation Accidents, the Institute of Radiology, the Institute for Transfusion Medicine and Haemotherapy as well as the Institute of Clinical Biochemistry and Pathobiochemistry with Division of Laboratory Medicine. Its opening is planned for 2009.

Among the constructional activities in the future are the reconstruction of the "Kopfklinik", which is a Center harboring Neurology, Neurosurgery, Neuroradiology, Ophthalmology and Ear, Nose and Throat Surgery and the construction of a „Mother-Child-Center", where the Department of Obstetrics and Gynaecology and the Department of Pediatrics will be housed in the future.

Comprehensive reconstruction work is currently carried out in the Center of Dentistry, Oral and Macillofacial Surgery, the Department of Dermatology and in the Department of Obstetrics and Gynaecology.
In view of an ideal collaboration between departments and the field of service and logistics, modernization works – especially on the kitchen and the pharmacy – are being planned. Furthermore the infrastructure for information and communication systems is currently being expanded and unified in all departments. Compre-

Fig. 1: Entrance hall of the Center of Operative Medicine (ZOM).

hensive reorganization in the field of patient management (e.g. in terms of medical informatics, quality management, medical controlling and risk management) and especially the establishment of a separate division for strategy and development are to support the University Clinic of Würzburg cope with the challenges of a constantly changing health care market with increased competition and simultaneously ensure that a prosperous working environment in the fields of research and teaching is fostered.

Professor Dr. med. Chr. Reiners
Managing Medical Director

3.2 Department of Anaesthesia and Critical Care

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Mission and Structure

The Department of Anaesthesiology annually performs anaesthesia for approximately 24.000 surgical and diagnostic procedures in the various clinical departments including orthopaedic cases (König-Ludwig-Haus). The pain centre and the outpatient department of Anaesthesiology in each case exhibit more than 5.500 patient contacts per year of patients suffering from acute and chronic pain. The department has an interdisciplinary Intensive Care Unit with 12 beds for critically ill patients after major surgery or for those suffering from severe multiple traumas. Each intensive care bed is fully equipped with new state-of-the-art bedside monitoring and data management systems as well as ventilators and all available systems to treat all kinds of organ failure.

The department further consists of a section for trauma and emergency medicine, which is responsible for clinical education as well as research in this field of medicine.

The department provides as well a modern simulation centre for anaesthesia and emergency cases. An artificial patient, equipped with computer technology, allows the realistic training of routine anaesthetic procedures as well as the handling of rare emergency events.

In addition to patient care and education of students and residents the department runs a laboratory for the diagnosis of malignant hyperthermia. Malignant hyperthermia is a rare hereditary disorder, which might occur quickly and life-threatening during anaesthesia.

Major Research Interests

Pain research
(G. Sprotte)

Different research groups focus on the pathophysiology of the immunological system and its role in the development of chronic pain, using in-vivo approaches with chronic pain patients or experimental in-vitro techniques.

Intestinal hypomotility in ICU patients
(M. Herbert)

ICU patients show a dysfunction of the intestinal motility. Consequence of which may develop systemic inflammation and further aggravation of the patients condition. With the help of experimental animal models the interdependency between drugs used in intensive care and the motility of the intestine is investigated.

Evidence Based Medicine
(P. Kranke)

“Evidence Based Medicine” tries to provide best up-to-date quality data for special questions concerning the treatment of patients. The facilitation of an evidence based way of thinking and behaviour in the perioperative medicine is the aim of the research group. For this purpose systematic reviews in the field of anaesthesia, pain therapy, palliative medicine, intensive care medicine and cognate disciplines are generated.

Ultrasound applications in anaesthesiology
(U. Schwemmer)

By means of modern portable ultrasound devices it is possible to gently identify detailed anatomic structures under the body surface. The accomplishment of regional anaesthesia requires the injection of local anaesthetics with a potential sharp needle close to neural structures. Ultrasound guided injections allow the clear identification of neural structures and the subsequent blockade of the nerve. The research group tries to enhance the safety and success rate of ultrasound guided regional anaesthesia through clinical studies. The impact of the usage of ultrasound devices on complications, difficulties and the expenditure of time during the installation of central venous and arterial catheters are investigated as well.

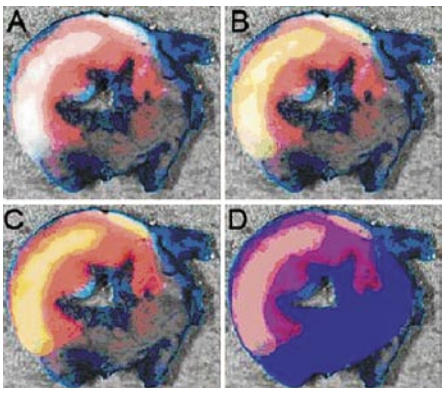

Fig. 1: Planimetry of myocardial infarction (mouse).

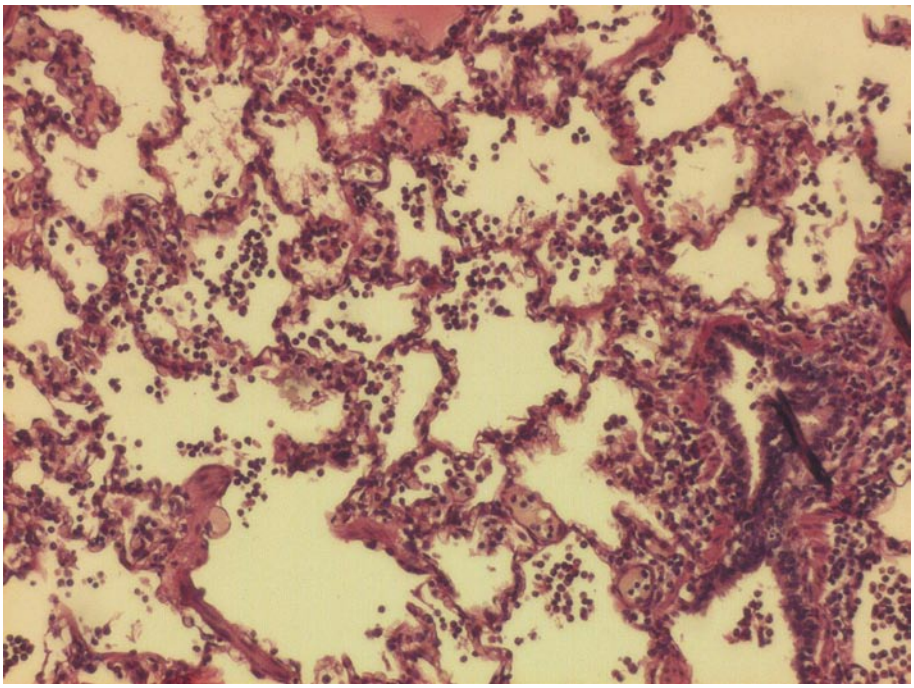

Fig. 2: Acute lung injury (pig).

Transesophageal Echocardiography
(B. Steinhübel)

The Transesophageal Echocardiography allows via a miniaturized probe in the esophagus the evaluation of the function and performance of the heart with its cavities and valves. This examination method is performed during anesthesia in the theatre or during treatment on the intensive care unit.

Organ-Protection
(F. Kehl)

Volatile anesthetics not only induce anesthesia, but also render organs resistant against ischemic damage. The intracellular mechanisms underlying anesthesia induced reduction of ischemia/reperfusion injury are under intense investigation. The projects performed by the research group aim to identify triggers, mediators and end-effectors of anesthetic-induced pre- and postconditioning and to characterize their complex intracellular interaction in the heart and the brain.

Acute lung injury
(J. Brederlau)

Acute lung injuries in adults, caused by pneumonia, sepsis and multiple traumas still show a lethality of 40-60%. The key to survive for patients is a ventilation strategy which allows the lung to recover and heal. The choice of a ventilation profile with optimal pressure amplitudes for the individual patient needs is of vital importance. With the help of experimentally induced acute lung injury in pigs the influence of different ventilation modes and profiles on the inflammation and function of the lungs are investigated. In patients the usages of high oscillatory ventilation modes in combination with extracorporal lung assist devices in patients with acute lung injuries are scientifically accompanied.

Microcirculation
(C. Wunder)

The term microcirculation denotes the bloodflow in the smallest vessels and capillaries. The perpetuation of the microcirculation in the different organs is fundamental for the function and metabolism of the different cell populations. The patho-physiological coherences of the microcirculatory disturbances in the liver and the intestine during systemic inflammatory states and shock are the aim of the investigated projects. The organ failure of the liver and / or the intestine is associated with a high mortality. By means of small animal models and clinical studies the underlying mechanisms of microcirculatory failure in the liver and intestine and the potential therapeutic interference are investigated.

Intelligent diagnosis and monitoring systems
(J. Broscheit)

The development of intelligent knowledge based systems, which support the anaesthesiologist during daily work, is the aim of this group. Databases about special question fields are created and with the help of a web-based surfaces the system provides the user solutions for the previously programmed questions. The research group is cooperation with the Lehrstuhl IV, Künstliche Intelligenz und Angewandte Informatik, Instituts für Informatik of the University of Würzburg.

Trauma emergency room management
(T. Wurmb)

The initial diagnostic and therapeutic treatment of polytraumatized patients is performed by a multidisciplinary medical staff team in the trauma emergency room. The development of algorithms and operating procedures to provide optimal support for these patients at high risk are performed by clinical investigations.

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3.3 Department of Surgery I

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Mission and Structure

The Clinic of Surgery I offers services in general, visceral, vascular, and pediatric surgery. The clinic has 132 beds, including intermediate and intensive care units. Six thousand surgical procedures are performed every year. The health care centre offers specialized services include surgeries for tumours (interdisciplinary), oesophagus and gastric illness, gallbladder and pancreas, endocrine diseases, gastrointestinal diagnosis, endoscopy, proctology with endosonography, and vascular and pediatric surgery.

Clinical Services

Onological surgery is an important focal point of the clinic. The patients are treated following recommendations from the interdisciplinary tumour board. Special expertise exists in the care of gastric, pancreatic and intestinal cancer, primary and secondary liver cancer, and thyroid cancer. In the last two year oesophagus, colon, and rectal cancer have been treated with minimally invasive surgery. The endocrinology surgery offers thyroid surgery with monitoring of the recurrent laryngeal nerve. The dysfunction of parathyroid and adrenal glands is treated with minimally invasive surgery. The coloproctology offers therapeutic procedures for hemorrhoids, constipation, and complicated anal fistulas. Special expertise also exists for the care of abdominal wall hernias. Patients with morbid adiposity are cared for by an interdisciplinary team of surgeons, internists and psychologists ("Würzburger Model"). The pediatric unit provides the best of care for the full range of clinical pediatric needs. These include the operative care of premature infants, therapy of birth deformities, basic pediatric urology, and pediatric traumatology. The vascular surgery treats abdominal aortic aneurysms with aorta-iliacal bifurcation prostheses. Aorta and iliacal vascular diseases are treated with endovascular procedures. Our surgeons are well experienced in femur crural artery bypass surgery and in carotid artery surgery.

Major Research Interests

Clinical Research

The clinic applies the latest suture systems and laparoscopic operating procedures. The vascular surgery evaluates modern combined endovascular and operative procedures for the treatment of aneurysms and the peri-arterial obstructive disease. The clinic is part of one international and several national multi-centre studies, involving, among other things, the therapy of reflux gastritis, therapy of rectal cancer, liver metastases, and acute cholecystitis. In addition, procedures for distal/caudel pancreatectomy are evaluated. The oncological group carried out a random trial on the reconstruction of the food passage following gastrectomy and a trial following deep anterior rectum resection. Several publications demonstrate the quality of the clinic's medical health care in all working groups.

Experimental Research

Experimental Surgery and Molecular Oncology have both established their own working groups for experimental research. Experimental Surgery, with their main focus on immune biology/cell therapy, analyzes tolerance mechanisms following experimental organ transplantation and cell therapy approaches to heal diabetes mellitus. Molecular Oncology analyzes the immune response to gastrointestinal tumours to develop diagnostic and therapeutic approaches. Close cooperations exist with the Harvard Medical School in Boston/USA, the universities of Oxford/UK and Rochester (New York)/USA, the Prince of Wales Hospital in Sydney/Australia, the Ludwig-Maximilians University in Munich and, of course, the institutes and clinics of the University of Würzburg Hospital and the university.

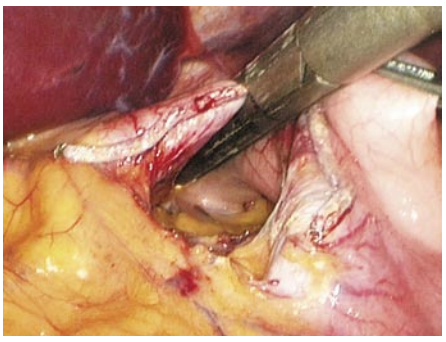

Fig. 1: Creation of a gastric pouche with minimally invasive surgery.

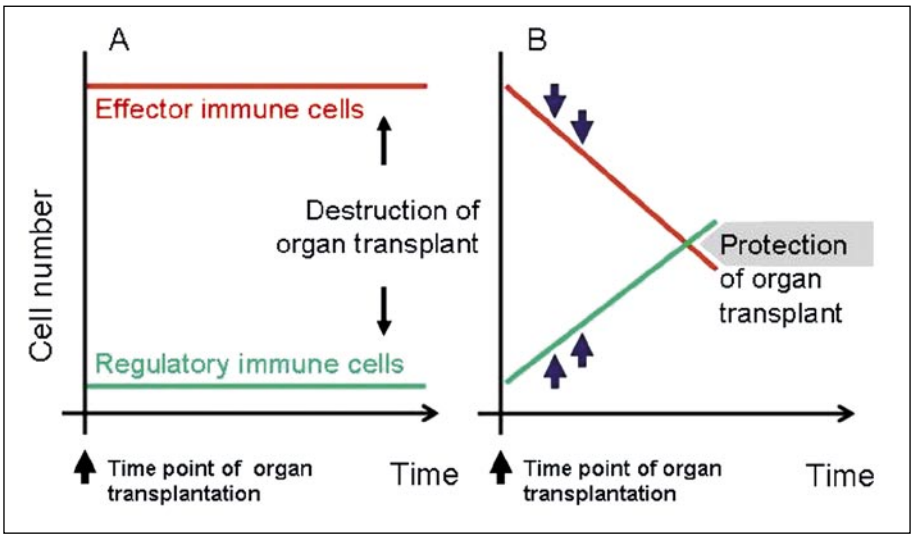

Fig. 2: The goal of transplantation research is to prevent the destruction of organ transplants. In addition to effector immune cells the immune system also has so called regulatory immune cells. They are able to stop immune responses but normally their amount is too low to protect organ transplantats (A). Therefore, increasing the amount of regulatory immune cells and reducing the amount of effector cells after transplantation (B) seems to be promising for experimental and clinical research.

Teaching

All aspects of modern surgery are covered in lectures and seminars; bedside teaching was optimized. An Interdisciplinary Training and Simulation Centre (INTUS) was established in the SkillsLab to give the students more opportunities to improve their operating skills on training simulators under realistic conditions. Training courses for thyroid surgery and microsurgery, laparoscopic operation procedures, as well as advanced training in gastrointestinal diagnostics and endosonoscopy are offered on a regular basis.

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3.4 Department of Trauma, Hand, Plastic and Reconstructive Surgery

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Mission and Structure

With appeal of the new ordinay the division of trauma became an independent Department of Trauma, Hand, Plastic & Reconstructive Surgery on 01.01.2007. Within our department we dispose of an independent section for plastic and aesthetic surgery.

The Department of Trauma, Hand, Plastic & Reconstructive Surgery employs 18 medical doctors. Currently, we are responsible for 52 patients on the regular wards. In addition, together with the department of anaethesiology and the department of surgery we operate jointly the units for surgical intensive care and the Intermediate Care ward.

Within the Center for operative medicine we collaborate closely with the departments of general surgey, of anaesthesiology and of radiology in particular view of the treatment of severely injured patients. In July 2007 we have founded the trauma networtk of „North Bavaria – Würzburg“. 19 medical centres of the region join the new network for improving the rescue system and treatment for trauma victims up to now.

A state-of-the-art shock-trauma unit equipped with spiral CT as well as all modern functional facilities, as for example a central sterilisation, operating theatres, intensive care unit and physiotherapy facilities are on the spot. Besides, the department of radiology enacts of the modernest devices for angiography, CT and MRI diagnostics.

Patient-Care

Because of the different main focuses of the Department of Trauma, Hand, Plastic and Reconstructive Surgery, consultation hours on account of the further specialisations were required. Next to the consultation hour for spinal fractures, pelvic fractures and complex fractures we established further ones for workers compensation insurance, for hand surgery, for arthroscopic surgeries of the knee and shoulder as well as for arthroplasties and foot injuries. Beyond it, we offer special consultation hours for plastic and aesthetic operations.

To improve the patient´s service we have introduced fixed outpatient appointment hours to reduce the average waiting period while being able to treat the numerous emergency patients. The main focuses are also reflected in our care statistics of more than 3000 operations. Beside approx. 180 interventions in the traumatised cervical, chest or lumbar spine, approx. 60 interventions involving the pelvic ring, approx. 150 osteosyntheses of long long bones and approx. 300 complex joint injuries are performed annualy. Another considerable proportion is performed by the hand surgery with approx. 500 interventions and the plastic surgery with approx. 300 interventions. Within the scope of the trauma network 100 polytraumatized patients were treated interdisciplinary in the shock trauma emergency room of our hospital.

Clinical research and studies

Not a complete year passed by since the new department was founded. As a result both clinical and experimental research are developing in structural process. One of the established main interests of the clinical research refers to the injuries of the vertebral column. Moreover, we are participating in the study group spine of the german society for trauma surgery. Therefore we are in a steady exchange with other main medical centres. Another main focus concerns the treatment of unstable pelvic fractures. We also analyze the oucome of pelvic ring fractures as a participating clinic of the “pelvic group” of the German Society for Orthopaedic Trauma Surgery.

Within the scope of restructuring the new department a research professorship was granted for 2008.

Major Research Interests

The facilities of the trauma research labaratory extend over 70 m ². Included are an microscopic analysis area combined with a full-digital workplace which enables to further analyze analogly contact radiographs e.g.. Besides the labs are provided with newest computer equipment which allows not

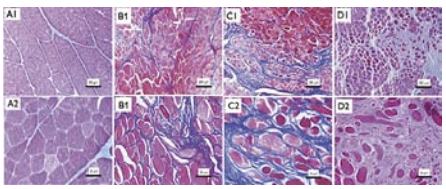

Fig. 1: Histological image of muscle: No trauma (A), increasing soft tissue trauma with connective tissue displacing muscle tissue in ascending order.

only our doctoral students to be up-to-date concerning literature based knowledge finding. For biomechanical investigations and analyses we installed a Zwick-Roell-2020 as a 2 chanal device. At present we analyze different installations of mini locking implants in bovine metacarpal bones which are of interest for hand surgery. Furthermore, at present we develop new implants with improved anchorage in osteoporotic bone.

In 2007 we have mainly concentrated on the experimentally induced soft tissue and osseous trauma as well as on muscle and bone regeneration.

Almost every day we see heavily injured patients with complicated extremity injuries which involve damage of the bone and the surrounding soft tissue.

By means of an experimental model to simulate the described clinical situation we are able to produce a defined musculoskeletal trauma which leads to a compartment syndrom (picture 1). This is treated by shortening of the extremity followed by distraction osteogenesis (picture 2). Moreover we quantified the muscle strength invivo which gave us information about the muscle strength regeneration. Additionally, we analysed the preparations histologically, histomorphologically and radiographically.

Next, based on these results, we will examine the regeneration of the soft tissue and bone influenced by angiogentetic and neurotrophic growth factors. Aim of these investigations is to transfer positive results into clinical applications. This project is supported by the IZKF-Würzburg.

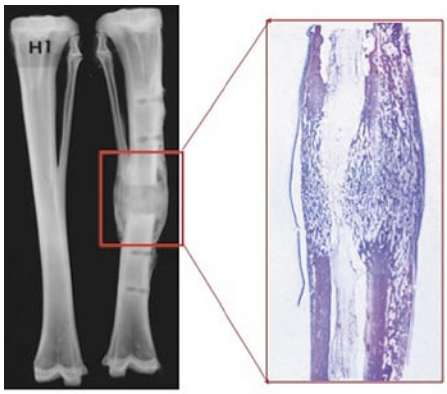

Fig. 2: Newly regenerated bone (Callus) via distractionosteogenesis.

Teaching

The apprenticeship is divided into the education of the students and the advanced training and continuing education of residents and senior registrars. Beside the regular main lecture for trauma, hand, plastic and reconstructive surgery we offer an extensive teaching for the students. Moreover we provide training periods including bedside-teaching, weekly block training periods with concluding final examinations, clinical investigation courses during our special consultation hours as well as the possibility to assist in surgeries. Students of the last year are invited to attend a specially taylored weekly seminar which is an optimal preparation for their exam. For advanced training of the junior doctors and to discus indications we meet twice daily. Four times a year we organize additional trauma meetings. Alike these we also oragnize topic-related, interdisciplinary polytrauma conferences as well as lectures of plastic and hand surgery to which we invite members of the rescue services and of the surrounding hospitals and disciplines. In cooperation with the institute of anatomy (Prof. Drenckhahn) we carry out operation courses in body donators for the first time in 2008.

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3.5 Institute for Transfusion Medicine and Haemotherapy

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Mission and Structure

The Institute of Transfusion Medicine and Haemotherapy is localized at three positions within the hospital area. It provides

- a laboratory for blood group serology
- a laboratory for HLA-typing
- a GMP-laboratory for modification and cryopreservation of stem cell concentrates
- a blood bank for supplying the university hospital with blood components
- a blood donation department
- a department for therapeutical apheresis
- a register for stem cell donors

Clinical activities

The Institute of Transfusion Medicine and Haemotherapy supplies the university hospital of Wuerzburg with all required blood products, e.g. red cell concentrates, platelet concentrates and fresh frozen plasma. Additionally, it is competent for the production of autologous and allogenic stem cell concentrates for adult patients of the hospital. Beside immunohaematological laboratory analyses (e.g. blood group serology, red blood cell cross match, antibody screening, antibody differentiation) the Institute of Transfusion Medicine and Haemotherapy provides HLA-testing for the patients of the hospital with serological and DNA-based methods. It is responsible for the search of compatible stem cell donors and organizes a stem cell donor registry for the national and international donor mediation. In addition, the Institute of Transfusion Medicine and Haemotherapy is specialized in the enforcement of therapeutical aphereses (e.g. plasmapheresis, immunoadsorption, cell-apheresis). Furthermore, quality assurance in haemotherapy for the university hospital is one of the central functions of the institute.

Major Research Interests

Biochemical and functional comparison of different platelet concentrates

Platelet concentrates are obtained by apheresis or by buffy coat method. One of the research activities of the Institute of Transfusion Medicine and Haemotherapy is the biochemical and functional characterization and comparison of these two types of platelet concentrates.

Storage and transport of red cell concentrates under different conditions

According to the German directions of blood processing and transfusion red cell concentrates have to be stored at 4° C ± 2° C in special blood storage refrigerators. However, less information is available, how long this cooling process can be interrupted without harming the concentrates. Therefore, different storage and transport conditions of red cell concentrates are evaluated.

Teaching

- Main lecture “transfusion medicine”
- Lecture “Blood group serology and transfusion therapy”
- Lecture “Immunohaematology”
- Lecture “Therapeutical and preparative apheresis”
- Lecture “Transfusion in difficult patients”

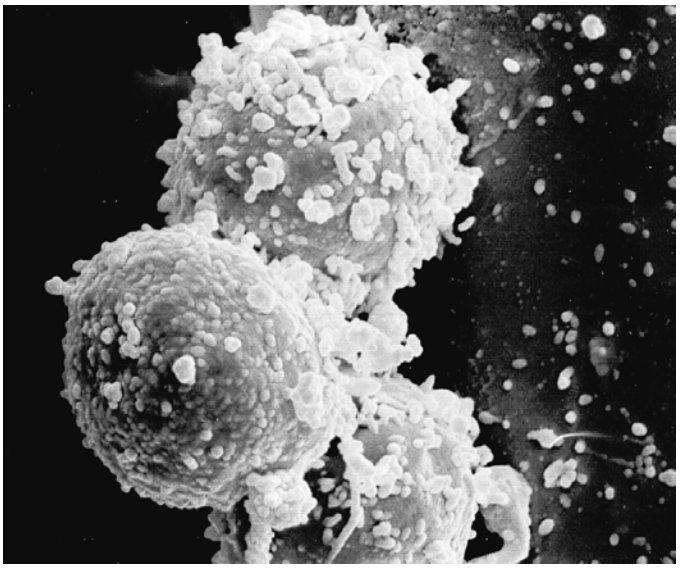

Fig. 1: Leucocytes from stored and concentrated erythrocytes.

- Lecture “Production of blood components”
- Lecture “Biology and function of red cells”
- Lecture “Transfusion therapy with and without red cells”
- Lecture “Stem cell transplantation: from the donor to the transplant”
- Lecture “The HLA-system”
- Pracitcal training “Transfusion medicine and immunohaematology”
- Pracical training “Blood group serology”

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3.6 Department of Thoracic and Cardiovascular Surgery

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Mission and Structure

The department of Thoracic and Cardiovascular Surgery is a 56-bed department with 3 operating theaters and operates ist own 14 bed intensive care/intermediate care unit plus. At present 24 physicians and 1 psychologist are working in this department.

Approximately 1600 procedures are peformed annually covering the entire field of adult heart and thoracic surgery. 700 procedures are open heart surgeries with extracorporeal circulation.

In 2007 an assist device program was established and the heart transplant program relaunched. Specialized outpatient clinics care for transplant and VAD patients and for patients requiring aortic surgery. In addition there is a tumour outpatient clinic for thoracic tumours.

Within a radius of 100 kms we represent the sole institution which offers the full range of adult heart surgery including heart transplantation and simultaneous management of any kind of thoracic surgery including tracheal surgery.

Main areas of interest are total arterial revascularization, beating heart bypass surgery, reconstrucitve valve surgery including DAVID-, YACOUB-procedures. In selected patients we also offer the ROSS procedure.

Recently, we have introduced a mobile heart-lung-machine (Lifebridge) for further improving the management of heart or lung failure patients. Such patients are transferred to our hospital through a dedicated team from our department.

Approx. 400 thoracic cases are performed per year. Main areas of interest are extrapleural pneumonectomies for mesothelioma and minimally-invasive procedures and laser resections. We are proud to offer the only laser system in this region. The laser enables us to perform cancer surgery with a maximum protection of healthy tissue.

In addition we cover the entire field of arrhythmia surgery. Apart from pacemaker, ICD and biventricular device implantations we routinely perform Mini-MAZE proceudres fort he surgical treatment of atrial fibrillation.

Major Research Interests

Cardiac surgery:

Ross operation:
By means of MR and CT-scanning we evaluate the impact of different implant techniques of the pulmonary autograft on postoperative RV function (Dr. Gorski, Dr. Sommer). Data from all Ross procedures are forwarded to the German Ross registry.

Transplant vasculopathy after heart transplantation:
After establishing a heterotopic rat heart transplant model (Dr. Lange) we are currently investigating the effect of CD28-antibodies on tolerance induction. The second step will be the reversal of tolerance induction by CTLA4-antibodies.

Furthermore, we are preparing experimental studies to assess the immunosuppressive properties of inhibitory blocking peptide (IBP, Dr. Lange in cooperation with PD Dr. Ritter from the department of cardiology). IBP inhibits the protein which is respponsible for transferring calcineurin into the nucleus without the dramatic side effects of classical calcineurin inhibitors like cyclosporine A or tacrolimus.

Knock-out- mice will serve as study animals for Nrf-2 transcription factor and ist effect on oxidative stress.

Heart / lung transplantation:
Two large animal studies will assess the role of resveratrol for amelioration of pulmonary and cardiac ischemia/reperfusion injury (IRS), respectively. Resveratrol had favourable effects on IRS of different organs like kidneys and liver. However, effects on cardiac and pulmonary function after transplantation have not been elucidated fully yet (Dr. sommer, Dr. Oezkur).

Transfusion requirements:
Due to the large need for blood products in cardiac surgery studies with cryopreserved erythrocytes have been initiated by Dr. Hickethier. Funding through the German army was available. Dr. Hickethier has resumed his previous acitivities and will obtain new data on in vitro function of cryopreserved leucocytes and platelets. Additional studies highlighting the function of the coagulation system after cryopreservation are in preparation.

Neuropsychological studies and cardiac surgery:
Dr. Krannich, our clinical psychologist, is investigating neuropsychological deficts and ist reversability during rehabilitation therapy after surgery for coronary artery disease.

Prior to bypass surgery 45 to 80% of patients have cognitive deficits. This proportion increases postoperatively. Data on these defects and their potential reversibility during rehabilitation are scarce. Since rehabilitation is performed after percutaneous interventions as well, different interventions and their impact on neuropsycholgical function can be compared.

A similar test battery will examine patients after operations uitlizing deep hypothermic circulartory arrest. By comparison with coronary artery disease patients operated upon without circulatory arrest the effects of deep hypothermia, circulatory arrest and extracorporeal circulation, respectively can be determined.

Thoracic surgery
Surgery for pulmonary metastases is an established therapeutic approach. However, the psychological benefit of these procedures has not been investigated at all yet. At the same time, this is the main justification for these procedures, because there is hardly any symptomatic improvement in these mostly asymptomatic patients. Therefore, all our patients referred for metastasectomy are investigated by means of questionnaires pre- and postoperatively (Dr. Krannich, Dr. Bohrer, Dr. Neukam).

Ongoing projects assess the role of liver cirrhosis on outcome after cardiac and thoracic surgery and the impact of concomitant meningiomas on neurological outcome after cardiac surgery utilizing the heart-lung-machine (PD Dr. Aleksic, Dr. Gorski, Dr. Sommer).

Teaching

All topics of cardiothoracic surgery relevant to the medical student are covered by a lecture series and regular „bed-side“-teaching plus grand rounds. Since 2007 2-3 medical students spend one week in the department as part of a mandatory surgical rotation. Final year medical student spend a 16 week rotation in our department.

A new weekly crdiology7 cardiac surgery conference is a mainstay for the education of our residents.
In addition we are proud to offer a new seminar on „ethics in surgery“ starting in fall 2007.

This department ist the only one in the state of Bavaria which offers German board certified training in cardiac surgery, cardiac surgical intensive care medicine and thoracic surgery within one department.
In 2008 we are planning to host two clinical fellows from Serbia and Jordan, respectively.

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3.7 Department of Urology and Paediatric Urology

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Mission and Structure

The Department of Urology and Paediatric Urology is a tertiary referral centre with two general wards (54 beds), intensive care unit (8 beds) with haemodialysis facility, a busy outpatient clinic with uroradiology section, point-of-care lab and a research laboratory with an emphasis on molecular urooncology. Three state-of-the-art operating theatres allow the surgical treatment of approximately 2.500 adults and 350 children and adolescents with 2.500 conventional open and laparoscopic procedures and more than 1.800 endourologic interventions per year. The equipment comprises a multi-function unit for extracorporal shockwave lithotripsy, a computer-assisted (video)urodynamic set-up, lasers of the most recent generation and several ultrasound machines with colour-coded duplex sonography and transrectal probes.

The surgical spectrum encompasses the entire speciality of urology (high volume centre) with special expertise in urooncology (particularly orthotopic bladder substitution and continent cutaneous/heterotopic urinary diversion following radical cystectomy, nerve-sparing; radical perineal and retropubic prostatectomy/nerve-sparing; nephron-sparing resection of renal cell cancer; polychemotherapy; immunemodulation); paediatric urology (correction of complex congenital malformations), reconstructive urology (ileal ureter replacement, open urethral reconstruction, complex fistula repair) including implantation of artificial urinary sphincters and penis prosthesis, urogynaecology and renal transplantationen (cadaver and living related transplantation).

Major Research Interests

Impact of mismatch repair defects on pathogenesis and prognosis of prostate cancer
(B. Kneitz, E. Gerharz)

Defects in the mismatch repair (MMR) system play a critical role for the development of microsatellite instable colorectal cancer and cancer of various other tissues. Prostate cancer (PCa) is the most common malignancy in men. However, the impact of MMR defects on pathogenesis and prognosis of these tumors is not well defined and up to now it is unknown whether MMR defective tumors represent a distinct clinical risk group. To answer the question what impact MMR defects play for tumor development we generated novel mouse models that will allow to study the biological function of MMR defects during development and progression of PCa in vivo. One of the proposed mouse models is based on a prostate specific inactivation of the MMR system using the Cre-LoxP system. It will provide the opportunity to study the molecular and genetic mechanisms of the early development, progression and eventually metastasis of the PCa and will further allow to functionally explore different therapies in vivo.

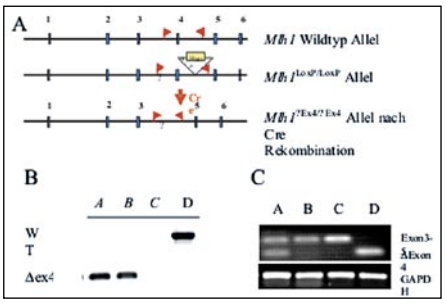

Fig. 1: Generation of a transgenic mouse model to inactivate mismatch repair activity in the prostate using the Cre-loxP system.

Aberrant expression of spindle checkpoint genes in high grade prostate cancer
(B. Kneitz, E. Gerharz)

Defects in the mitotic spindle checkpoint (MSC) are discussed to be involved in cancer development. To understand the role of aberrant expression of MSC genes for the development of prostate cancer (PCa) we analysed the expression of two MSC genes in PCa specimens. In addition we studied the effect of Bub1b haplo- insufficiency for induction of genomic instability and resistance against therapeutic agents in vitro. We could show that spindle checkpoint genes are frequently down regulated in high grade PCa. Our results suggest that the expression of MSC genes may be helpful biomarkers for advanced PCAs and that spindle checkpoint defects caused by aberrant expression of spindle checkpoint genes might be involved in malignant progression of PCa and failure of treatment using cytotoxic agents.

Identification of tumor supressors or onco- microRNAs in prostate cancer and renal cell cancer
(B. Kneitz, M. Spahn, F. Hillig)

Micro-RNAs (miRNA) are a class of small (19-25-nt long) non-coding regulatory RNAs. According to the current understanding the main function of miRNAs is to regulate gene expression. A number of previous studies detected frequent alterations of miRNA expression in various cancers. Functional studies of individual miRNAs have shown that they might function biologically either as tumor suppressor or oncomiRs. The aim of our studies is to analyse the role of miRNAs for the development and progression of prostate cancer and renal cell cancer.

Using microarrays and qRT-PCR miRNA analysis we detected specific miRNA signatures for both types of cancer (Figure 2). By bioinformatics and statistical analysis specific miRNAs were identified, which are linked to the development and progression of cancer. To study the molecular mechanisms of such miRNAs we are currently studying the function of specific miRNAs in vitro.

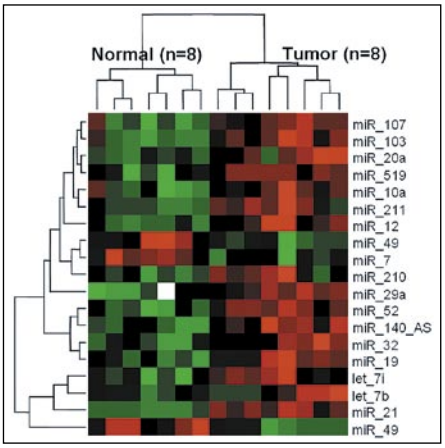

Fig. 2: MiRNA expression signature of renal cell cancer.

Characterization of the humoral immune response and identification of new diagnostic molecular marker in transitional cell carcinoma
(P. Ardelt)

The aim of this project is to identify a serological marker in transitional cell carcinoma of the bladder for early detection and followup.

Using the phage display technique three oligopeptide sequences were isolated. They are recognized by the circulating patient's antibody pool and represent fragments of tumor-associated antigens. For these oligopeptides binding specificity was verified by competitive binding inhibition studies. The antibody response against one sequence indicates the presence of a carcinoma in situ (flat lesion) of the bladder, which is notoriously difficult to detect by plain cystoscopy; a drop in titer suggests successful treatment. For this sequence mycobacterial heat shock protein HSP65 could be identified as corresponding antigen.

Corresponding antigens of all selected oligopeptides will be characterized (Western Blot, affinity chromatography, MALDI-TOF) and both, sensitivity and specificity of antibody response will be determined by ELISA in patients sera samples. In further screening tests immune response specifically induced by BCG immunotherapy will be investigated.

Treatment of patients with high risk prostate cancer
(M. Spahn, H. Riedmiller)

In the era of PSA based screening a trend towards more favourable stages at initial clinical presentation is observed. Unfortunately, the percentage of patients with high risk prostate cancer (1992 AJCC clinical category >T2c, or PSA >20 ng/ml, or Gleason score >8) is still significant (1990: 39%; 2003: 22%). In this group of patients the risk of biochemical progression within a 5-year period is approximately 40%.

Treatment of these patients is controversial and radiation therapy is often combined with androgen deprivation as the preferred option. Only few studies analysed surgical strategies in these patients. We therefore evaluate the outcome of different surgical techniques (radical prostatectomy, radical cystoprostatectomy) combined with stage dependent androgen deprivation in patients with high risk and locally advanced prostate carcinoma.

Teaching

Traditional teaching formats (lecture with clinical case presentation and live transmission of surgical procedures from the operating theatre; clerkships/electives) are offered along with integrated and interdisciplinary approaches. Participation in skills lab, e-learning-programmes, interdisciplinary oncology (seminar and lecture), emergency medicine, integrated seminars in tumor biology, interdisciplinary paediatric pathophysiology and courses in prevention, epidemiology and biostatistics. Hospitation in the operating theatre and outpatient clinic is possible throughout the entire academic year.

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3.8 Department of Orthopaedics

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Mission and Structure

The Orthopedic Clinic König-Ludwig-Haus is a top level hospital for musculoskeletal diseases and injuries and their sequelae. The hospital is operated by the district of Unterfranken. The chair for Orthopedics, the University Outpatient Clinic for Orthopedics and a Competence Center for Osteology are integrated into this hospital. The director in Chief of the Chair and Department, 1 full Professor of Osteology, 6 Senior Physicians and 22 Residents are running patient care and teaching. The hospital holds 140 beds, more than 3.800 operations per year are performed in 5 operating theatres. The University Outpatient Clinic provides ambulatory care for app. 10.000 patients per year. The König-Ludwig-Haus also runs own departments for x-ray diagnosis and physiotherapy.

The Orthopedic Center for Musculoskeletal Research is an interactive platform between basic science, translational research and clinical implementation of innovative therapeutic strategies. Its main topics of research are Mesenchymal Stem Cell Biology and their differentiation into mesenchymal tissues and the development of cell based therapeutic strategies for tissue regeneration. The Center especially supports the chair in the representation of teaching and research. It is also an important partner for the development of the emerging Wuerzburg Interdisciplinary Musculoskeletal Research and Treatment Center.

Key Issues in ambulatory and in-patient care for orthopedic patients are

- Shoulder and Elbow Surgery
- Ankle and Foot Surgery
- Pediatric Orthopedic Surgery
- Spine Surgery
- Endoprostheses of hip, knee, shoulder and elbow joints
- Arthroscopies of knee, shoulder, elbow, ankle and wrist joints
- Sports Orthopedics
- Osteology (metabolic and degenerative diseases with a special focus in osteoporosis and malignant bone disease)

Orthopedic Advice is offered for several other hospital and centers for disabled.

Major Research Interests

The Orthopedic Centre for Musculoskeletal Diseases is located in a 500 sq. m laboratory area which comprises scientific laboratories and working rooms (S1, S2, radioactivity). The Center is supported by the District of Unterfranken. It is funded by the German Research Society (Clinical research Unit KFO 103, DFG Research unit FOR 793, several single projects), by the German Ministry of Research BMBF, the IZKF of our Medical Faculty, the Arbeitsgemeinschaft Osteosynthese (AO), Arbeitsgemeinschaft Arthrose, and by the Research Fund of the State of Bavaria as

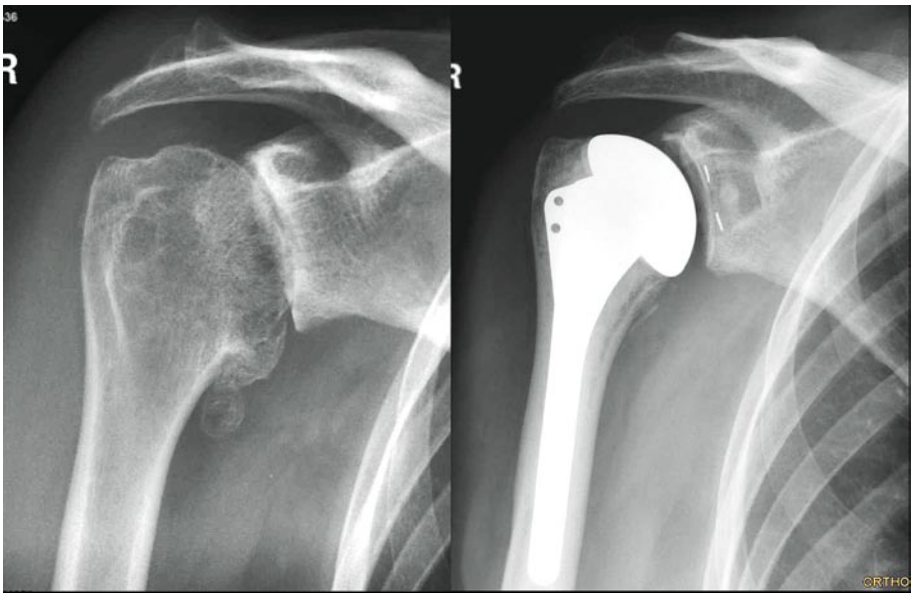

Fig. 1: Endoprosthesis of the shoulder for treatment of omarthrosis.

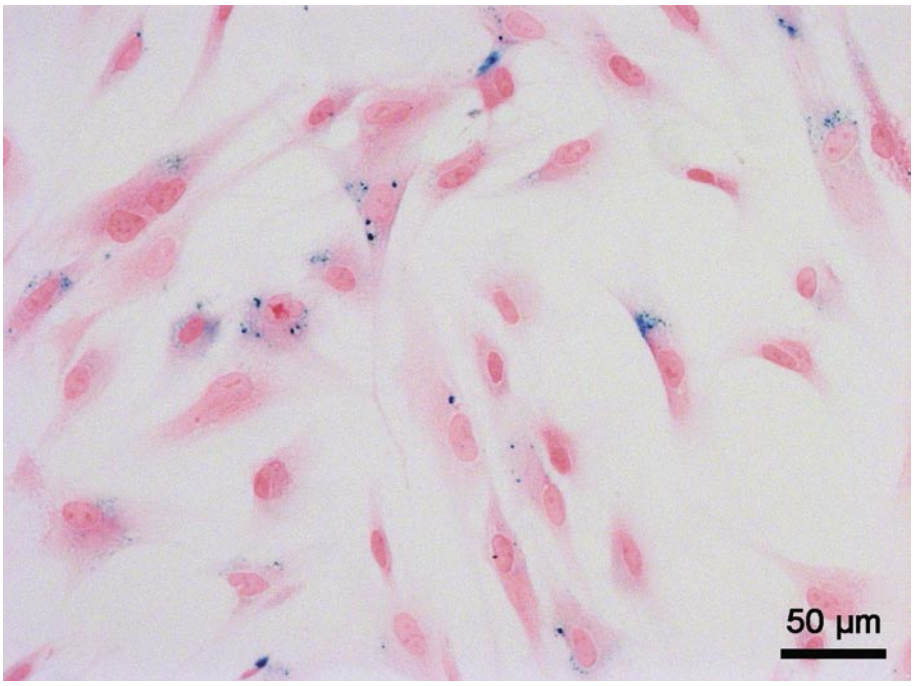

Fig. 2: Tracking of human mesenchymal stem cells using superparamagnetic Iron-oxide nanoparticles (VSOP): histological demonstration of particles in the cytoplasm using Berliner Blau Staining (Heymer et al. 2008).

well as several industry sponsored unrestricted grants. The number of positions funded is 19 as of 2007.

Key Issues in Research

- Biology of Mesenchymal Stem Cells (F. Jakob, R. Ebert, T. Schilling)
- Molecular Orthopedics and Cell Biology (N. Schütze, T. Schilling, R. Schenk, K. Schlegelmilch)
- Tissue Engineering (U. Nöth, M. Weber, A. Heymer)
- Gene therapy in Musculoskeletal Diseases (A. Steinert, N. Armbruster, C. Weber)
- Molecular and Classical Biomechanics (F. Jakob, L. Seefried, J. Stehle, S. Müller-Deubert)
- Fracture Healing in Trauma and Osteoporosis (KFO 103 in Kooperation mit KFO 102 Berlin; FOR 793)
- Particle Disease (B. Baumann)
- Special techniques in shoulder joint reconstruction (F. Gohlke, O. Rolf)
- Special pediatric surgery and spine surgery (P. Raab, V. Ettl)
- Clinical Studies on Osteoporosis (F. Jakob, L. Seefried, S. Goebel)
- Development of innovative cell based therapeutic strategies for Musculoskeletal Diseases (U Nöth, A. Steinert, L. Rackwitz, T. Barthel)
- Endoprosthesis of hip and knee joints (J. Eulert, B. Baumann, O. Rolf)
- Pain Research in Orthopedics (S. Goebel, J. Eulert)

Teaching

- Course in clinical examination techniques for operative and conservative orthopedics
- Lectures in Basics of Orthopedics (also accompanying the practical course)
- Practical Course in Orthopedics (bedside teaching in small groups, demonstrations in physiotherapy, plaster techniques and orthopedic technical devices and corselets
- Clinical ward Rounds, x-ray discussions, orthopedic colloquia
- Molecular Aspects of Bone Diseases – Genes and Cell Biology
- Molecular Methods for osteology in basic science
- Integrated Seminar on the Molecular Basis of Musculoskeletal Diseases

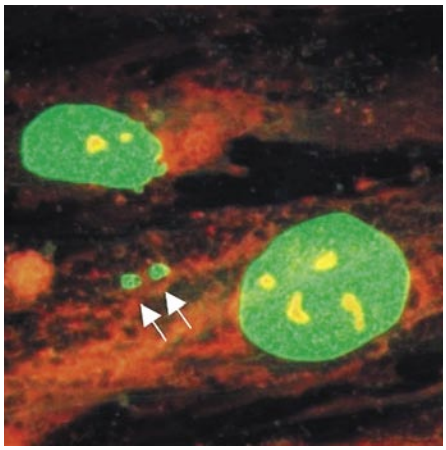

Fig. 3: Demonstration of micronuclei in human mesenchymal Stem Cells. Antioxidative enzymes are able to reduce these indicators of genotoxic stress during ex vivo cell culture (Ebert et al. 2006).

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3.9 Department of Obstetrics and Gynecology

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Mission and Structure

The Woman's Hospital (bed capacity of 84, 33 doctors, 102 nurses, 14 midwives, 6 assistant medical technicians) has two obstetrical and three gynecological wards, 5 labour and delivery rooms and a Level I Perinatal Centre with six neonatal intensive-care beds, three operating rooms of most modern standards, an operating room for caesarean sections, an intermediate-care unit, outpatient clinics for gynecology and obstetrics, gynaecological oncology, breast cancer, dysplasias of the cervix, child and adolescence gynecology, urogynecology, endocrinology and reproductive medicine, prenatal diagnostics. There are laboratories for endocrinology, cytology and reproductive medicine with andrology. Programs include a midwifery school. In the women's clinic are also department of the Clinic for Radiation Therapy (external radiation; brachytherapy) and the Institute of Radiology (mammography, vacuum biopsy) and the Department of Anaesthesiology (pain ambulance).

In 2007, 2,264 operations, 1,386 deliveries, 5411 DRG cases, 22,080 outpatient therapies (3577 chemotherapies) have been performed. Centres of the clinic are: The interdisciplinary treatment of gynecological cancers, including breast (certified breast centre), the centre for hereditary breast and ovarian cancer, the treatment of urinary incontinence and pelvic floor dysfunction, care of risk pregnancies and infertility treatment including in vitro fertilisation.

Major Research Interests

Fetomaternal interface
(U. Kämmerer, L. Rieger, S. Segerer, J. Dietl)

The interactions between the maternal immune system and placenta are that lead to tolerance of the fetus analyzed,. A subproject studies the effect of soluble factors, such as cytokines, growth factors and hormones, which influence cellular interactions. As part of a clinical research group (KFO 124, cooperation with the department of dermatology, J. Becker), placentation serves as a model system for tumours. Under a new "first applicant" programme by the IZKF Wuerzburg, a project on the role of thrombopoietin in early pregnancy is promoted (Dr. S. Segerer).

Research Project „Immune escape of tumours"
(J. Wischhusen, C. Weidler, Y. Dombrowski, S. Häusler)

Funded by the IZKF, a group of young researchers investigates the mechanisms that underlie the immune escape of tumour cells. Particular attention is paid the members of the TGF-β superfamily, as TGF-β with promoting effects on migration, invasion and angiogenesis seems to be a factor of tumour progression in various tumours. In addition, members of the TGF-β family exert extensive immune-inhibitory effects on immune cells and thus contribute to the "immune escape" of tumour cells. Further, in cooperation with the department of dermatology (JC. Becker) the group participates in a DFG project (BE: 1394/9-1) on the research of tumour stem cells.

In close association with the junior research group, the role of the macrophage migration inhibitory factor (MIF) in the interactions between the immune system and ovarian cancer cells is analyzed (IZKF project Z-4/72). (M. Krockenberger, A. Hönig).

Studies on function and prognostic value of LASP in the dissemination of breast and ovarian cancer
(PA. Hönig, M. Kapp, U. Kämmerer)

LIM and SH3 domain protein (LASP) is an actin-binding protein that plays a role in cellular migration. In a study in collaboration with the institute of clinical biochemistry (E. Butt), we try to analyze the expression of LASP in breast cancer metastases in order to elucidate a possible significance of this protein in tumour progress. Cell culture studies investigate the function of LASP in the biology of tumour cells. The project is funded by the Deutsche Krebshilfe (No 107706).

Therapeutic strategies for the treatment of premature labour (IZKF Project E-38)
(T. Frambach, M. Ivanisevic)

Tocolytic drugs have different mechanisms of action. During long-term treatment, however, it comes to a rapid loss of effect, and often a premature birth cannot be avoided. In a collaborative project with the institute of pharmacology (M. Lohse), fundamental mechanisms of these substances at the myometrium of pregnant uteri are elucidated. The goal is to identify new and to optimize established therapeutic strategies to reduce fetal morbidity and mortality due to preterm delivery caused by premature labour.

Metabolism of tumours / Clinical study on carbohydrate deficient nutrition in malignant tumours
(M. Schmidt, N. Pfetzer, U. Kämmerer)

Many tumour cells show a strikingly high sugar uptake. The reason for this is usually a disproportionate increase in glycolysis. Possible therapeutic approaches by targeted inhibition of glycolytic enzymes are investigated both in vitro (cell cultures) and in vivo (in mice, cooperation with the experimental transplant surgery, C. Otto). In a clinical study, the effect of carbohydrate deprivation under a carbohydrate-poor oil/protein-rich diet on tumours of different entities is analyzed. The study was sponsored by „Hilfe im Kampf gegen Krebs e.V.".

New GnRH antagonists in the treatment of gynaecological malignancies
(J. Engel, A. Hönig, M. Ivanesevic)

GnRH seems to act as a local growth factor in a variety of tumours. GnRH antagonists show anti-tumour efficacy in vitro and in vivo, but it remains unclear whether atypical GnRH I- or GnRH II-receptors mediate these effects. „Peptidomimetic"-GnRH antagonists, whose advantage lies in the oral bioavailability, represent a new pharmacologic strategy. With the help of in vitro tu-

Fig. 1: Premature infant in the incubator.

mour models of endometrium, ovarian and breast cancer, the effect of these new non-peptidic GnRH antagonists in terms of their effectiveness and mechanism of action is investigated.

Matrix Metalloproteases and galectines in placentation and tumours
(J. Anacker, A. Köhrmann, N. Kohrenhagen)

Matrix Metalloproteases (MMPs) are enzymes, which play an essential role in cell migration. Galectines are important components of the cellular matrix. In addition to their function regarding tissue structure they possess immunoregulatory properties. The role of these important factors in the placentation and dissemination of tumours (cancer of the breast and cervix) is investigated.

Interstitial brachytherapy versus external radiation therapy after breast-conserving surgery
(A. Hönig, J. Dietl)

In collaboration with the department of radiation therapy (M. Flentje, J. Goebel), we investigate the influence of partial interstitial brachytherapy (partial breast irradiation) versus conventional external radiation therapy on local relapse in low-risk invasive breast cancer in a multi-centre study.

Optimization of In Vitro Fertilisation (IVF)
(C. Rennemeier, E. Horn)

The focus of the work of the IVF laboratory consists in the continuous improvement of existing protocols in order to increase the success rates of IVF. On this regard, we optimized laboratory procedures concerning the processing of gametes and embryos and their culture conditions. A new method for vitrification of multi-cellular embryos or blastocysts has been introduced.
Additionally, several research projects have been initiated. They include the study on the influence of seminal plasma on the function of different cell types in the uterine endometrium.

Teaching

The curricular teaching in Obstetrics and Gynaecology consist of a main lecture (8th semester), seminars, clinical visits (9th semester) and a practical training (10th semester). Additionally, a „Skills Laboratory" focuses on practical aspects of the subject.

With gynaecological models and case studies, students learn to deal with clinical situations and to handle diagnostic equipment. The training is complemented by a number of interdisciplinary subjects like ethics, preventive medicine, emergency medicine, infectious diseases, tumour biology and oncology. For doctors in private practice, we organize regular interdisciplinary conferences as part of the perinatal centre.

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3.10 Department of Pediatrics

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Mission and Structure

The Children's` Hospital of the University of Würzburg (staff: 53.2 MD`s, 163.5 nurses, 33.75 technicians / administrative staff) comprises 113 beds including a pediatric-neonatal intensive care unit (12 beds) and a neonatal intensive care unit (12 beds) in the perinatal centre (obstetrics and gynaecology). The Children's` Hospital is divided into the following functional sections: neonatology (Prof. Dr. C. P. Speer, Dr. W. Thomas, Dr. J. Wirbelauer, Dr. R. Wössner), pediatric intensive care (Prof. Dr. C. P. Speer, Dr. W. Thomas, Dr. J. Wirbelauer), oncology / haematology / stem cell therapy (Prof. Dr. P.-G. Schlegel, Dr. F. Deinlein, PD Dr. M. Eyrich, PD Dr. S. Rutkowski), cardiology (Dr. J. Wirbelauer), pulmonology / cystic fibrosis / sports medicine (Prof. Dr. H. Hebestreit), gastroenterology (Dr. A. Dick), nephrology (Fr. Dr. A Beissert), endocrinology (Prof. Dr. H. Hebestreit), diabetes (Dr. R. Wössner), neuropediatrics / social pediatrics (Prof. Dr. H.-M. Straßburg), immunology / infectiology (Prof. Dr. H. Girschick), rheumatology (Prof. Dr. H. Girschick), and others. Patients of all pediatric age groups ranging from premature infants up to adolescents are treated for the entire spectrum of pediatric diseases in hospital as well as in outpatient clinics. The Children's Hospital is in close cooperation with pediatric neurosurgery, pediatric surgery, urology with pediatric urology and the section for pediatric neurosurgery. Every year, around 6500 patients are treated as inpatients and 7500 as outpatients.

Major Research Interests

Inflammation of the lungs during acute and chronic diseases in premature infants and newborns.

The aim of this project is to analyze pathogenetic mechanisms in order to establish new strategies for prevention and therapy for this disease.

Characterization of "airway remodelling" processes in chronic pulmonary inflammatory reactions

The purpose of this set of studies is the molecular characterization of transmitters that are involved in pulmonary remodelling processes in premature infants with bronchopulmonary dysplasia (BPD), as well as in children with asthma.

Malignant brain tumors in children and adolescents

For more than 20 years, the Children's Hospital of the University of Würzburg has been coordinating the prospective multicenter phase II and phase III studies of the "Society for Pediatric Oncology and Hematology" (GPOH) to optimize treatment for medulloblastomas, PNETs, and ependymoma conducted in Germany and Austria. In order to increase survival rates these studies evaluate age-adapted treatment strategies such as radiation and chemotherapy, and investigate the value of biological parameters for prognostic assessment (see Fig. 1).

Reconstitution of the immune system after stem cell therapy

After the opening of the stem cell transplantation unit in 2005 the reconstitution of the immune system after the transplantation of highly purified hematopoietic stem cells across beyond HLA-barriers is studied. The objective of this project is to optimize established immunotherapeutic approaches such as the transfusion of donor lymphocytes in order to enhance the antileucemic effect of stem cell transplantation.

New cellular therapeutic concepts for brain tumors

With the establishment of a new EU Network cellular therapies like vaccination with patient-specific dendritic cells loaded with the patient's tumor antigens and tumor-specific cytotoxic T-cells are being developed for the treatment of malignant brain tumors.

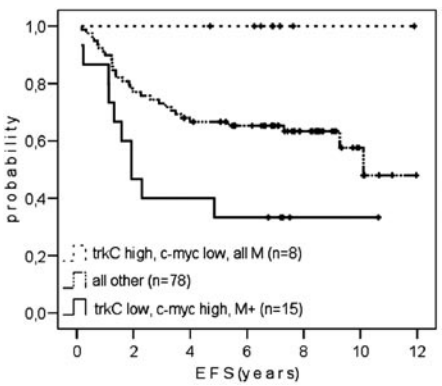

Fig. 1: Event-free survival of 101 children with medulloblastoma participating in the HIT´91 study grouped according to clinical criteria and the biological markers c-myc and trkC (Rutkowski et al., Clinical Cancer Research 2007).

Inflammation processes in autoimmune diseases

A series of research projects entailing basic research and clinical studies investigates pathomechanisms, diagnostic and therapeutic options for inflammatory processes in autoimmune diseases (rheumatism, systemic lupus erythematosus), infections (Lyme disease, borreliosis, see Fig. 2), and metabolic disorders (hypophosphatemia) in the human organism.

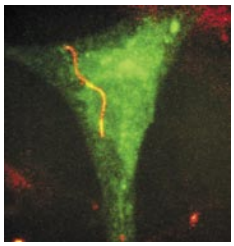

Fig. 2: Borrelia within a synovial fibroblast (confocal laser scanning microscopy); the bacterium may persist intracellularly for months and hence induce the inflammatory responses associated with Lyme-arthritis.

Magnetic resonance imaging techniques for examination of the lungs

This interdisciplinary project assesses the value of low- and high-field MRI scans of the thorax for the diagnosis of pathological changes in the lungs and for the functional evaluation of ventilation and perfusion.

Exercise testing methodology and training effects in healthy children and in children with chronic diseases

Several studies evaluate the preventative effects of physical activity in healthy children, and the positive effects on patients with chronic diseases. Furthermore, the mechanisms possibly involved are investigated. The validity of exercise testing for diagnosis and the follow-up of therapeutic effects is determined in other studies.

Teaching

The Children's Hospital of the University of Würzburg offers several courses for medical students. Students have repeatedly evaluated the main lecture in pediatrics regularly as one of the best courses in the faculty of medicine. Prof. Dr. C. P. Speer is authorized to fully train MD`s in pediatrics, as well as in neonatology and pediatric intensive care. The heads of the sections for pediatric haematology and oncology, neuropediatrics, pediatric pulmonology and pediatric rheumatology are qualified to train MDs in their respective subspecialties. The Children's Hospital organizes regularly clinical rounds and educational seminars for pediatricians on a regional and national level. In addition every year scientific meetings and symposia are organized in Würzburg, e.g. every 3rd year the international symposium "Recent Advances in Neonatal Medicine" with participants from more than 45 nations. Outside of the United States of America this symposium represents the largest scientific forum for neonatology. In 2007 the Annual Meeting of the "Süddeutsche Gesellschaft für Kinderheilkunde" took place in Würzburg.

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3.11 Department of Internal Medicine I

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Mission and Structure

The Department of Medicine I includes six sections of internal medicine in research, teaching, and patient care: angiology, endocrinology, cardiology, intensive care medicine, nephrology, and pneumology. The department has 57 MD positions and 33 postdoctoral research positions from third-party funding. There are 165 planned beds (including an intensive care unit with 24 beds), and some 10,000 patients a year receive inpatient treatment. 1,200 outpatients are attended to in the emergency room every year. More than 12,000 patients are attended to in numerous special outpatient clinics.

Angiology
The Division of Angiology has been rapidly developing since May 2007. Since that time, 60 patients per month (with a steady upward trend) with a variety of diseases of the veins, arteries, and lymphatic vessels have been admitted to the service. Available diagnostic tools include Doppler ultrasonography, vascular CW-Doppler, plethysmographic and optical pulse wave analyses, treadmill testing, ankle brachial index measurements, and specific laboratory assessment. Surgical and interventional revascularisation procedures are planned by an interdisciplinary team including specialists from the Departments of Vascular Surgery and Interventional Radiology.

Endocrinology and diabetology
(B. Allolio)

1,145 patients were treated as inpatients on the ward of the endocrinology-diabetology division in 2007. More than 5,000 patients were seen in two special outpatient clinics (endocrinology and metabolism, respectively). A total of some 900 functional diagnostic tests and more than 50,000 hormone measurements were carried out in the endocrinology laboratory. Additionally, more than 300 patients were examined using thyroid ultrasonography. Since 2003, this unit has been the reference center for adrenal carcinoma, and more than 90 patients were attended to in the year 2007 alone. Regular, structured, and evaluated education programs for patients with diabetes mellitus take place in the outpatient clinic on an individual or group basis.

Cardiology
(G. Ertl, J. Bauersachs)

- **Invasive Cardiology**
  (P. Schanzenbächer)
  In two catheterization laboratories more than 3,000 invasive coronary procedures are carried out per year, 800 of which are percutaneous coronary interventions. In 2007, 150 direct coronary interventions were performed in patients with ST-elevation myocardial infarction. Furthermore, catheter-based closure of atrial septal defects and patent foramen ovale were performed in the catheterization laboratory.

- **Electrophysiology**
  (W. Bauer)
  The electrophysiological division offers the entire spectrum of interventional and non-interventional electrophysiology. In the majority of 380 interventions a therapeutic high-frequency or Cryo ablation was performed as an ad hoc procedure. In the cardiac pacemaker outpatient clinic, the rhythm clinic, and the ICD outpatient clinic, more than 2,500 patients were registered. In cooperation with the Department of Thoracic and Cardiovascular Surgery, 150 cardiac pacemaker systems and – for the prevention of malignant rhythm disturbances – 140 ICDs were implanted.

- **Non-invasive Cardiology**
  (C. Angermann, W. Voelker)
  This diagnostic unit offers the entire range of non-invasive cardiac procedures. In 2007 a total of over 10,000 ECGs, 1,500 stress-ECGs, 850 24-hour ECGs, 8,600 2D- and Doppler-echocardiograms (also including stress and transesophageal ECGs), and 850 24-hour blood pressure measurements were performed. The 'Center of Cardiology at the Medizinische Poliklinik' serves as a vital interface between physicians in private practices and the Cardiovascular Center of the University of Wuerzburg offering unrestricted access to all cardiological and pulmonary examinations Here, clinical and health care research is closely coupled to routine outpatient clinical care. In these two outpatient clinics, more than 4,000 patients were attended to in 2007.

Center for Internal Intensive Care Medicine
(H. Langenfeld, S. Maier)

The center includes an intensive care and a critical care unit with 24 beds and an emergency room. Here, patients with diseases from the entire field of internal medicine are admitted. In 2007, 1,455 and 2,030 patients were treated in the ICU and CCU, respectively. In the ER, a total of 5,630 patients were admitted or received outpatient treatment. In order to optimize the care for patients with heart attacks, the Herzinfarktnetz Mainfranken, was established in 2007 and is coordinated by the intensive care unit.

Nephrology
(C. Wanner)

In the 5 functional units, patients were attended to as follows: (1) hemodialysis chronic-inpatient 3,500 treatments, hemodialysis acute renal failure 1,500 treatments, (2) peritoneal dialysis - IPD and CAPD - 15 patients, (3) ward with 930 patients, (4) special outpatient clinics with 2,200 pati-

ent contacts: kidney outpatient clinic 520 patients, vasculitis outpatient clinic 75 patients, transplantation postoperative care 110 patients, Fabry Center 133 patients, (5) from 2005-2007, 120 kidney transplantations were performed (including live donor program).

Pneumology
(M. Schmidt)

830 inpatients were treated (bronchial carcinoma, severe pneumonia, severe COPD or interstitial lung disease). 34 polysomnographies and 41 polygraphic screenings were performed on patients with sleeping apnea. In the special pneumology outpatient department, there were more than 2,500 patient contacts (outpatient chemotherapy with bronchial carcinoma, interstitial lung disease, sarcoidosis, tuberculosis).

Major Research Interests

Endocrinology
(B. Allolio)

One of the main focuses of the team is on translational and clinical studies on adrenal tumors (particularly adrenal carcinoma). The German Adrenocortical Carcinoma Registry and the first randomized international therapeutic study with adrenal carcinoma (FIRM-ACT-Study) are coordinated also with the support of Deutsche Krebshilfe (German Cancer Aid) and BMBF. In pre-clinical and clinical studies, new therapeutic targets for adrenal carcinoma are evaluated. In the Max-Eder research group of German Cancer Aid, headed by PD Dr. M. Fassnacht, immune-therapeutic approaches with adrenal carcinoma and – in a sub-project of the clinical research group of DFG „Tumor Microenvironment“ - the role of glucocorticoids in tumor immune response are examined. Another main focus is on projects, which have been initiated together with the Department for Nuclear Medicine, dealing with the implementation of new radioactive tracers for adrenal imaging, and which are supported by Sander-Stiftung (foundation) and IZKF (Interdisciplinary Center for Clinical Research). Moreover, several “investigator-initiated“ studies on acromegaly, hyponatremia, and adrenal insufficiency as well as studies on diabetes mellitus and osteoporosis, which have been initiated by different pharmaceutical companies, are carried out.

Cardiology
Molecular Cardiology
(J. Bauersachs, G. Ertl)

Various teams investigate molecular mechanisms of heart failure and cardiac hypertrophy using a broad array of in vitro und in vivo techniques. Among others, experimental studies on the heart itself as well as on isolated platelets and cultured cardiomyocytes, endothelial (progenitor) cells and smooth muscle cells are performed having already led to potential therapeutic approaches. Most of the research is done in interdisciplinary teams with basic scientists and clinical researchers from various departments (pharmacology, biochemistry, genetics, psychiatry, psychology, neurology (see also SFB 688). Prof. Ertl is vice spokesman of the “Kompetenznetzwerk Herzinsuffizienz”. Current projects:

- Hormonal regulation of cardiovascular healing processes (J. Bauersachs)
- Junior research group of IZKF “Wound Healing Post Myocardial Infarction“ (T. Thum)
- BMBF GoBio-1 Program: Functional antibodies against cardiac beta1-adrenergic receptors and their neutralization by cyclopeptides as an approach in heart failure treatment (R. Jahns)
- Role of innate immunity in cardiac ischemia (S. Frantz, G. Ertl)
- Calportin pharmaceuticals (O. Ritter)
- NO-synthases / oxidative stress and atherosclerosis (P. Kuhlencordt)
- Na-channel subunits of the heart (S. Maier)
- Echocardiography and rare heart diseases: strain rate imaging of regional myocardial function and the role of non-ischemic fibrosis with hypertrophic cardiomyopathy (Friedreich Ataxie and Morbus Fabry) and aortic valve stenosis in hypertrophic myocardium in clinical long-term studies after pharmacological and/or surgical therapy (F. Weidemann)

Cardiac MRT and Biophysics Team
(W. Bauer)

Basically, there are two main areas of research: 1) The development of MR-compatible pacemaker – ICD systems. This is due to the fact that the increasing number of patients with pacemakers or ICDs cannot be examined in the MR tomography apparatus due to potential interactions. This interaction is to be minimized in the systems to be developed. It is a matter of an interdisciplinary project between Hospital I, physics, and industry. There is a large-volume support by the Bavarian Research Foundation (Bayerische Forschungsstiftung). The development of electrophysiological intervention in the MR tomography apparatus is intimately connected with this project. 2) The development and application of molecular/cellular contrast agents. In this interdisciplinary research area, both platforms and specific ligands for contrast agents of different imaging modalities are to be developed. Fields of application include, among other things, the imaging of arteriosclerosis and myocardial healing. This unit is supported within the framework of SFB 688.

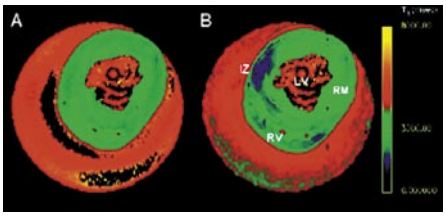

Fig. 1: Detection of apoptotic cells by specific MR contrast media in the heart of a rat after acute ischemia.

VR Simulation in Cardiology
(W. Voelker)

The Department of Medicine I is the main organizer of the interdisciplinary center for training and simulation in medicine (INTUS) at the University Hospital of Würzburg. VR-Simulation technology (supported by funding of the DFG) und several studies to evaluate simulation as tool for education in cardiology are performed.

Clinical and Health Care Research in Cardiology
(C. Angermann, S. Störk, G. Ertl)

The Unit ‚Cardiologie at the Medizinische Poliklinik' has established a clinical trial unit (in cooperation with the Center for Clinical trials in Leipzig) to facilitate high quality clinical research

- Biomaterial bank (>7000 blood samples of patients with heart failure)
- Handheld BNP trial Studie for the primary diagnosis of heart failure (BMBF Kompetenznetz Herzinsuffizienz)
- Prospective trial ‚rheuma and heart'

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- Clinical trial ‚Aldo-DHF' (BMBF Kompetenznetz Herzinsuffizienz)
- Cohort study 'Interdisciplinary network heart insufficiency' (BMBF)
- Clinical manifestation and managment of heart failure (INH-Studie/BMBF)
- MOOD-HF trial (therapy of depression in heart failure; BMBF)
- Diagnostic trial ‚BetaAk-HF trail' (Prof. R. Jahns, Corimmun GmbH)

Nephrology
(C. Wanner)

The main focus is the identification of risk factors for cardiovascular diseases in patients with diabetes type 2 with chronic renal disease. Questions are answered in huge multicenter randomized studies and cohort studies. Currently, the biobank of the completed 4D-study – Die Deutsche Diabetes Dialyse – is being updated and post-hoc analyses of the database will follow. The SHARP study (Study on Heart And Renal Protection) was started in cooperation with the university of Oxford. 1,789 patients with impaired renal function are taken care of by the coordinating center for clinical studies (ZKS). Questions about the progression of rare renal diseases (e.g. M. Fabry) are answered by prospective cohort studies. The transplantation unit with all patients is integrated into a huge multinational study. The coordinating center of KfH foundation of preventive medicine is set up and is in charge of comprehensive cohort studies. In preclinical studies, pathomechanisms of the damage and recovery of ischemic acute renal failure are examined in different mouse models with oxidative stress and regulation of eNOS being taken into consideration. Further examinations in cooperation are carried out for the regulation of transport proteins for organic anions OAT1 and OAT3.

Pneumology
(M. Schmidt)

- Recruitment of lung fibroblasts from blood fibrocytes and characterization of their homing.
- Mobilisation of fibrocytes during chronic progressive course and acute exacerbation of idiopathic interstitial lung disease.
- A controlled randomized multicentre study on simultaneous radiochemotherapy of NSCLC IIIB.
- Study on clinical benefit of erlotinib in NSCLC IIIB and IV.
- Study on clinical benefit of epoetin beta during chemotherapy of lung cancer.

Interdisciplinary projects
Interdisciplinary cooperation is of particular significance in the clinical and scientific areas of the Department of Medicine I. Such interactions are reflected in the numerous projects which are processed jointly by several teams within the university. Some examplary projects are listed here:

- Interdisciplinary training and simulation center (INTUS): multiple hospitals and institutes
- M.Fabry: nephrology, cardiology
- Cardiac insufficiency projects: cardiology, endocrinology, nephrology, human genetics, psychiatry, psychology, pharmacology, neurology
- Cardiac MR tomography: cardiology, physics, chemistry, nuclear medicine
- Development of molecular/cellular contrast agents: cardiology, chemistry, physics, nanotechnology, nuclear medicine, dept. of medicine II
- New imaging processes for adrenal tumors: endocrinology, nuclear medicine

The Department of Medicine I together with the Institute for Clinical Biochemistry supervises the special research grant SFB 688 "Cardiovascular Cell-Cell-Interaction" (see p. 127) and is involved in the DFG Clinical Research Groups KFO 124 „Tumor microenvironment" (see p. 159). In addition, clinicians and scientists of the hospital are active in the several research centers (e.g. cardiovascular center, interdisciplinary center for clinical research, interdisciplinary tumor center, center for infection research).

3.12 Department of Internal Medicine II

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Mission and Structure

The „Medizinische Klinik und Poliklinik II der Universität Würzburg“ (41 physicians, 74 nurses, technical staff comprising 44 members) is located at two sites in the city of Würzburg: „Klinikstraße/Röntgenring“ and „Luitpoldkrankenhaus“.

(1) Klinikstraße/Röntgenring:

1. Specialized outpatients’ departments (for hematology / oncology; rheumatology / immunology, and psychosomatics) as well as outpatients’ department for the therapy of haematological and oncological diseases
2. Department of sonography
3. Laboratory for routine and research analyses (clinical-chemical and immunological analyses; laboratory for experimental hematology and rheumatology)
4. Department of Molecular Internal Medicine (research laboratories; Röntgenring)

(2) Luitpoldkrankenhaus

1. Hematology / Oncology wards named Virchow and Magnus-Alsleben
2. Center for Stem Cell Transplantation
3. Interdisciplinary Oncology – Phase-I/II Unit
4. Department of Infectious Diseases (Center for Infectious Diseases DGI), comprising Infectious Disease-ward “Schottmüller” and outpatients’ department for infectious diseases
5. Rheumatology Clinical Immunology ward (Schottmüller)
6. Department of Gastroenterology including ward “Romberg” and the outpatients’ department for gastroenterologic diseases. Department for Endoscopy and Sonography
7. Infectiological laboratory/Therapeutic Drug Monitoring
8. „Auvera-Haus“ in Würzburg-Grombühl: Gastroenterologic laboratory, Metabolic suite

The hospital is divided into the following departments:

- Hematology/Oncology (Prof. Dr. R. Bargou)
- Gastroenterology (Prof. Dr. M. Scheurlen)
- Immunology/Rheumatology (Prof. Dr. H.-P. Tony)
- Infectious Diseases (Prof. Dr. H. Klinker)
- Section of Psychosomatics (Prof. Dr. H. Csef)

On an inpatient basis, our hospital is specialised in the diagnosis and therapy of all kinds of internal diseases within our focus. Moreover, we provide consiliary service for other hospitals in Würzburg and its environs. We especially focus on the following domains:

(1) Diagnosis and therapy of hematologic neoplasias (MDS, leukemia, lymphoma, myeloma), including high-dose chemotherapy and both autologous and allogeneic stem cell transplantation.
(2) Diagnosis and therapy of solid tumors, including the use of novel drugs and immunotherapy.
(3) Early Clinical Trial Unit: Use of novel cytostatics, novel antibodies, antibody constructs; immunotherapeutic treatment of lymphoma, myeloma, leukemia, and solid tumors (gastrointestinal tumors in particular)
(4) Care for and therapy of patients suffering from acute and chronic infectious diseases (with focus on HIV and chronic infectious liver diseases, evaluation of new drugs, phase II-IV studies)
5) Diagnosis and therapy of rheumatic inflammatory joint diseases, including the use of novel drugs, immunotherapy, phase II-II studies
(6) Diagnosis and therapy of systemic inflammatory diseases (vasculitis, collagenosisdes, connective tissue …)
(7) Diagnosis and therapy of immune deficiencies (CVID, drug-induced immune deficiencies)
(8) Diagnosis and therapy of patients suffering from acute and chronic, benign and malignant diseases of the gut and liver, including invasive endoscopy
(9) Therapy of patients with psychosomatic diseases (e.g. anorexia nervosa) and patients with functional or somatoform disorders. Crisis intervention and psychotherapeutic intervention in cancer patients

Major Research Interests

Hematology / Oncology

(1) Cellular (gene-modified T cells, tumor antigen-specific T cells, γδ T-lymphocytes) and humoral (antibody-based) immunotherapy of malignant diseases (groups Bargou, Kunzmann, Topp, Grigoleit, Beilhack)
(2) Function and specificity of human T-lymphocytes (group Kunzmann)

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(3) Alterations in tumor metabolism as target for therapeutic intervention in malignant diseases (group Kunzmann)
(4) Characterization of pathogene-specific immunity and its use in immunotherapeutic strategies (Topp)
(5) Characterization of signaling pathways in activated T cells and their inhibition for the treatment of GvH. (AG Stuhler/ Grigoleit)
(6) Regulation of viral T cell immunity through co-stimulation of antigen-presenting cells and soluble factors (AG Grigoleit/Stuhler)
(7) Characterization of oncogeneic signaling pathways in multiply myeloma and identification of therapeutic target structures (AG Bargou)
(8) Development of molecular and immunologic therapy approaches in non-Hodgkin lymphoma (AG Knop, Bargou)
(9) Phase-I unit for the realization of innovative therapy approaches in hemato-oncologic patients and in patients with solid tumors (Bargou).
(10) In vivo Imaging in models of graft versus host disease (GVHD) and immunologic anti-tumor response (group Beilhack)
(11) Identification of markers for the prediction of a looming graft versus host disease (GVHD) (group Beilhack)
(12) Immunoreconstitution after allogeneig stem cell transplantation (AG Grigoleit/ Stuhler)
(13) Tyrosine kinase inhibitors and their effects on different immune cells (T cells, NK cells, DCs)(AG Seggewiss)
(14) Novel strategies in allogeneic stem cell transplantation (cord blood transplantation, haploidentical stem cell transplantation)
(15) Aberrant signal transduction in tumor cells (AG Bargou)
(16) DC-vaccination against infectious and malignant diseases (AG Grigoleit)
(17) Development of vaccination strategies against HCMV infections (AG Grigoleit)
(18) Selective allodepletion of GVHD-inducing T cells as a method for optimizing therapy in allogeneic stem cell transplantation (AG Mielke)
(19) Optimization of therapy with taxans on the basis of pharmacokinetic, pharmacodynamic and pharmacogenetic knowledge in patients with solid tumors; Screening, prophylaxis, and therapy of chemotherapy-induced peripheral neuropathy (AG Mielke)

Rheumatology / Clinical Immunology

(1) Development of the B cell system in autoimmune diseases
(2) Genetic imprints of B cell receptor in autoimmune diseases
(3) Therapeutic modulation of the B cell repertoire in autoimmune diseases
(4) Immunoreconstitution in immunologic diseases
(5) TNF receptor signalling in rheumatoid arthritis
(6) Transcriptional regulation of the low-affinity receptor for IgE(CD23)
(7) Pathologic immunoregulation in lupus erythematodes (LED)

Gastroenterology

(1) Molecular diagnostics in hereditary gastroenterological tumors
(2) Cognitive, emotional, and somatic symptoms in patients with chronic hepatitis C infection and antiviral interferon therapy
(3) Computer-based subgroup analysis for quality control and data generation in gastroenterological sonography using standardized electronical patient files
(4) Molecular, cytogenetic and functional characterization of colorectal, neuroendocrine, and hepatocellular carcinoma
(5) Antimicrobial activity of human colon epithelial cells, considering in particular cathelicidin LL-37
(6) Nutritional Medicine: Investigation of novel functional carbohydrates for the prevention of inflammatory and neoplastic intestinal diseases as well as diabetes mellitus

Infectious Diseases

(1) Antiretroviral therapy in HIV-infection
(2) HIV-proteasinhibitor-plasma concentrations and resistance development
(3) Pharmacokinetic interactions of antiretroviral drugs
(4) Antiviral treatment strategies in chronic viral hepatitis B and C
(5) Pharmacokinetics of ribavirin
(6) HCV/HIV coinfection
(7) Drug monitoring of antiretroviral agents
(8) Uridine pharmacokinetics
(9) Systemic antifungal therapy of invasive fungal infections
(10) Therapeutic drug monitoring of azole-antifungal agents

Psychosomatics

(1) Psychooncology and Psychoneuroim-

munology. Palliative medicine and medical ethics.

(2) Psychosomatic diseases of the gastrointestinal tract (e.g. irritable bowel syndrome, IBS) and of the cardiovascular system (e.g. stress and myocardial infarction).

Teaching

The „Medizinische Klinik und Poliklinik II“ offers numerous courses for medical students and for postgraduate professional education. Prof. Dr. H. Einsele is certified trainer for the whole field of Internal Medicine. In addition, authorized training and education is available for the following specialties (2 years each): PD Dr. F. Weissinger (Hematology/Oncology), Prof. Dr. M. Scheurlen (Gastroenterology), Prof. Dr. H.-P. Tony (Rheumatology) and Prof. Dr. H. Klinker (Infectious Diseases). The hospital organizes numerous advanced training courses and scientific meetings for both physicians and patients. Often, patient organizations are involved in planning and realization of the events.

3.12.1 Division of Molecular Internal Medicine

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Mission and Structure

The scientific focus of the division of Molecular Internal Medicine lies on basic biomedical research and applied clinical investigations in molecular immunology and oncology. Allocation of personnel includes a scientific research position and part time secretary. Further, a transitory scientific position (Rotationsstelle) is available for clinicians of the Department of Internal Medicine II to temporarily pursue full time research that fits into the framework of the division. This initial option for scientific research is aimed to enable scientifically interested clinicians to acquire preliminary results offering a chance to achieve independent external funding. The various research projects of the division of Molecular Internal Medicine are currently funded by:

- the German Research Foundation
- the Mildred Scheel Foundation for Cancer Research
- the German José Carreras Leukaemia-Foundation e.V.
- the Federal Ministry for Education and Research
- the Wyeth company and
- the Interdisciplinary Centre for Clinical Research of the University of Würzburg

Major Research Interests

The research activities of the department are focussed on the ligands and receptors of the tumor necrosis factor (TNF) -family and TNF receptor family. The development of therapeutic useful recombinant variants of these molecules and clinically relevant aspects of TNF receptor signal transduction are investigated in three research groups:

Research group: therapeutic fusions proteins

Some ligands of the TNF family stimulate the immune system or trigger apoptosis. The potential therapeutic applications of these properties, however, are limited due to the serious side effects that are usually associated with systemic activation of TNF receptors. The research group develops fusion proteins of TNF ligands that become only robustly activated after binding to membrane-associated antigens. Utilisation of 'targeting domains' that interact with tumor specific structures facilitates the designated local activation of TNF receptors without causing systemic side effects.

Research group: death receptors
(D. Siegmund)

Death receptors, a subgroup of the TNF receptor family that includes CD95, TRAILR1 and TRAILR2, were initially studied, because of their strong apoptotic effects. Over the last years, we and others could show, however, that these receptors can also activate pro-inflammatory signaling pathways. This is especially apparent in cells, which are resistant towards death receptor-induced apoptosis. As inflammation can enhance metastasis and angiogenesis of tumor cells, it is possible that initial anti-tumoral effects of death receptors are turned into mechanisms of tumor promotion in apoptosis resistant tumor cells. Research efforts, within this group, are aimed to characterize precise conditions, when stimulation of death receptors leads to enhanced metastasis and aggressive tumor growth. Further, the molecular mechanisms of pro-inflammatory signal transduction by death receptors are also investigated.

Research group: co-operations between TNFR1-TNFR2
(F. Henkler)

TNF, the name giving cytokine of the entire ligand family, occur as a transmembrane and a soluble protein. The two TNF variants differ in their capacities to activate TNFR1 and TNFR2. Both TNF receptors can induce in a cell type-specific manner the production of their own ligand TNF and show counteracting, but also synergistic effects dependent on the cell type.The precise cellular effects of TNF depend therefore on TNF-receptor expression, cell type, extracellular setting and, importantly, on the TNF variant that was used for receptor stimulation (Fig. 1). In this research group, the regulatory principles that cause the exceptional complexity of TNF signaling are investigated at the molecular level.

Teaching

Courses, colloquia, seminaries und lectures related to the research topics of the division are offered for students of Biology and Medicine.

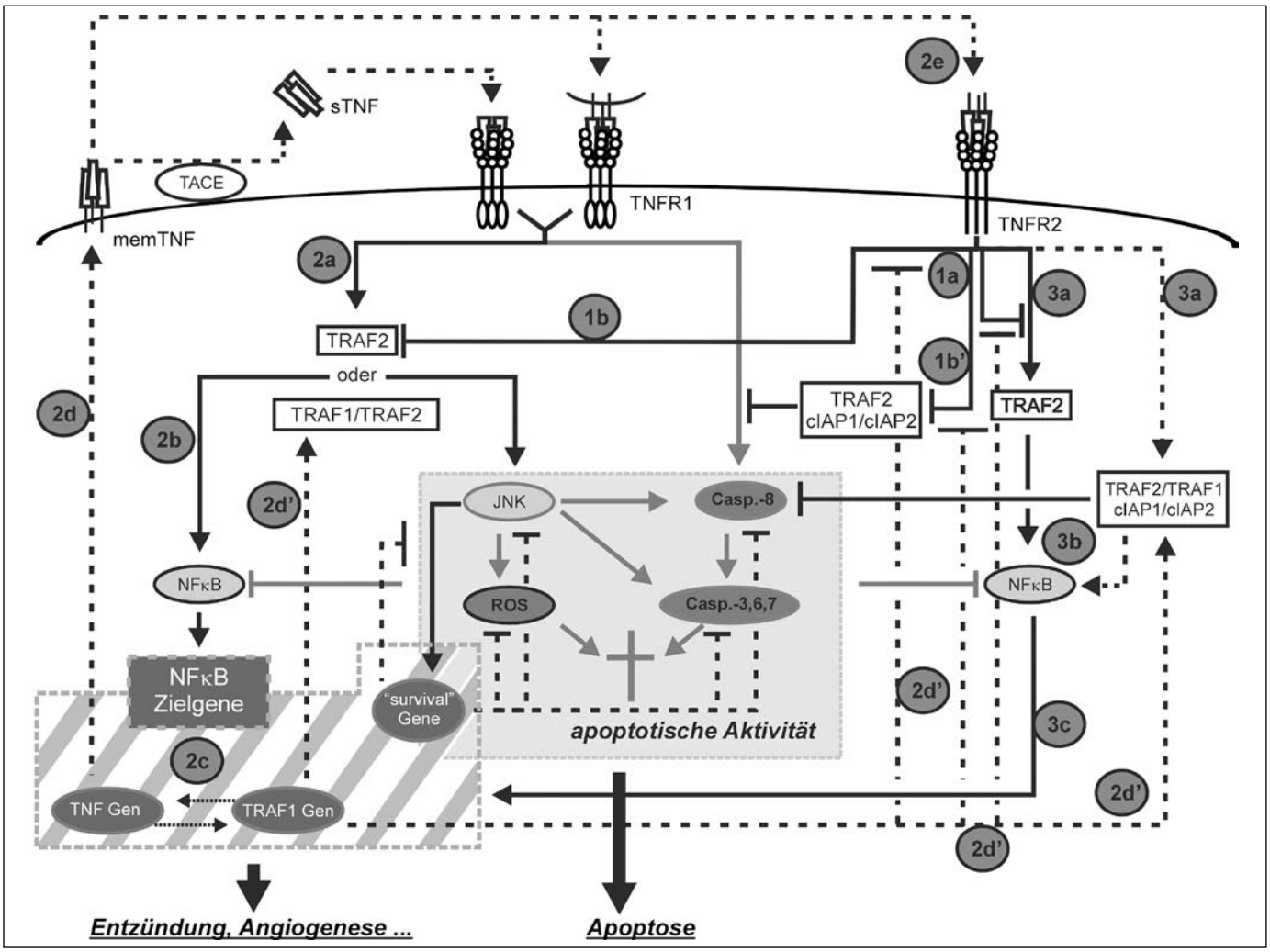

Fig.1: TNFR1 and TNFR2 are functionally linked in a highly complex manner. Activation of TNFR2 by transmembrane TNF leads to degradation of the adapter protein TRAF2 (1a,b). Because this protein is important for TNFR1-induced NFκB activation and recruitment of anti-apoptotic cIAP proteins into the TNFR1 signaling complex (2a,b'), cells are sensitized toward TNFR1-mediated cell death. Stimulation of TNFR1 by soluble TNF can induce NFκB-dependent expression of endogenous TNF (2a-2d). In its membrane-bound form, it activates TNFR2 and sensitizes cells again for TNFR1-induced apoptosis, as described above (2e). Another NFκB-target gene is TRAF1 (2a-c). TRAF1 forms hetero-complexes with TRAF2 and prevents its degradation by TNFR2 (2d'). TRAF1 can therefore disaffect TNFR2-mediated enhancement of TNFR1-induced apoptosis. Further, TRAF1 does also enhance TNFR2-induced non-apoptotic signal transduction (3a-3c), which contributes both to induction of TRAF1 and transmembrane TNF.

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3.13 Institute of Clinical Biochemistry and Pathobiochemistry – Central Laboratory (IKBZ)

CONTACT DETAILS

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Professor Dr. rer. nat. Michael Zimmer
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Mission and Structure

The institute was founded in 1995, having succeeded a DFG-funded (1989–1995) Clinical Research Unit. Later, in 2001, the institute merged with the central diagnostic laboratory (laboratory medicine) and now consits of the subdivisions

a) Clinical Chemistry & Laboratory Medicine (including an outpatient hemostasis clinic and a junior research group), and
b) Clinical Biochemistry and Pathobiochemistry (Chair & professorships of Vascular Biology and Clinical Molecular Biology

in research, teaching and patient care. With respect to clinical duties, the division of Clinical Chemistry & Laboratory Medicine (directed by Dr. U. Steigerwald) is responsible for major parts of laboratory diagnostics for hospitalized and ambulant patients of the university hospital. The diagnostic areas include clinical chemistry, hematology, hemostasis, immunology, serology, molecular diagnostics, and emergency diagnostics. Affiliated with this division is an outpatient clinic specializing in disorders of the hemostasis system.

Major Research Interests

The major aim is to elucidate pathophysiological, genetic, and diagnostic aspects of important cardiovascular diseases (thrombosis, bleeding disorders, coronary artery disease, stroke, heart failure etc.) by investigating murine and human model systems, in particular with regard to platelets and coagulation cascades. The projects are supported by the DFG, a DFG center grant SFB 688 (www.sfb688.de), and other sources including industry.

Research interest of the chairman
(U. Walter)

A central goal is to elucidate inter- and intra- cellular signal transduction pathways which are involved in the inhibition of platelets. A major focus is analysis of the NO / cGMP / PKG / VASP (Vasodilator-stimulated phosphoprotein) signal transduction pathway and its cross-talk with pathways stimulated by platelet agonists such as vWF, thrombin and ADP. Previous research established FACS-analysis of phosphorylated VASP (P-VASP) as the most specific laboratory parameter for measurement of ADP receptor inhibition by antiplatelet drugs such as Clopidogrel, Prasugrel and others. Within the SFB688 center grant, and in collaboration with Prof. A Sickmann (Rudolf-Virchow-Center) and Prof. T. Dandekar (Bioinformatics/Biocenter), a systems biology approach to platelet analysis is employed. Another group (PD Dr. E. Butt) investigates (in collaboration with the Department of Gynecology and supported by a cancer grant) the biological role of the human protein LASP-1 for growth and metastasis of breast cancers cells, also with the goal of establishing LASP-1 as a prognostic parameter for the spreading potential of these tumor cells.

The Vascular Biology Group
(joint appointment with the Rudolf Virchow Center)
(B. Nieswandt)

This group evaluates defects in platelet receptors and signaling pathways using genetically altered murine model systems. A major goal is the elucidation of molecular mechanisms which regulate adhesion, activation and aggregation of platelets. Ultimately, these studies should contribute to development of novel antithrombotic strategies.

Clinical Molecular Biology Group
(M. Zimmer)

The main focus of the group is elucidation of genetic causes of cardiac diseases and cardiomyopathies. Currently, the biological function of a novel dilative cardiomyopathy gene is being investigated. Other areas of study include laminopathies resulting from haploinsufficiency of the lamin A/C gene, and high-throughput SNP-typing using mass spectrometry.

Additional Groups
The independent Junior Research Group in Clinical Chemistry (PD Dr. rer. nat., Dr. med. T. Renné, Tel. 0931 201-36116; thomas@renne.net) supported 2002-2007 as an SFB355/SFB688 Junior Group, investigates the contact activation pathway stimulated by coagulation factor XII (Hagemann-Factor). Loss of factor XII does not increase the bleeding risk in humans or in mice. Surprisingly, FXII deficiency in mice protects against arterial thrombosis and stroke. Therefore, FXII is now an attractive target for novel antithrombotics which do not pose major bleeding risks. A further area of scientific interest entails mechanisms for the regulation of endothelial (vascular) permeability with special focus on the bradykinin-regulated NO/cGMP/cAMP/VASP signaling pathway.

An independent BayGene Professor of Vascular Genetics (Prof. Dr. med. Ute Felbor, Tel: 0931 888-4096; HYPERLINK „mailto:felbor@biozentrum.uni-wuerzburg.de“ felbor@biozentrum.uni-wuerzburg.de) holds a joint appointment with this institute and the Department of Human Genetics. Major research interests include the pathogenesis and molecular diagnostics of cerebral cavernous malformations (CCM1, CCM2, CCM3) which represent inherited forms of hemorrhagic stroke. (http://www.baygene.de/pro-dt-3_5a.htm).

Teaching

The institute offers lectures, seminars and practical courses, as well as active participation in research projects, within the area of clinical biochemistry & pathobiochemistry and laboratory medicine, to undergraduate and graduate students of medicine, biology, pharmacy, and chemistry. The institute also participates in the MD-/PhD-program and the International Graduate School of Life Sciences. The Director of the institute is also Medical Director of the Training School for Medical Assistents (www.mta-schule.uni-wuerzburg.de).

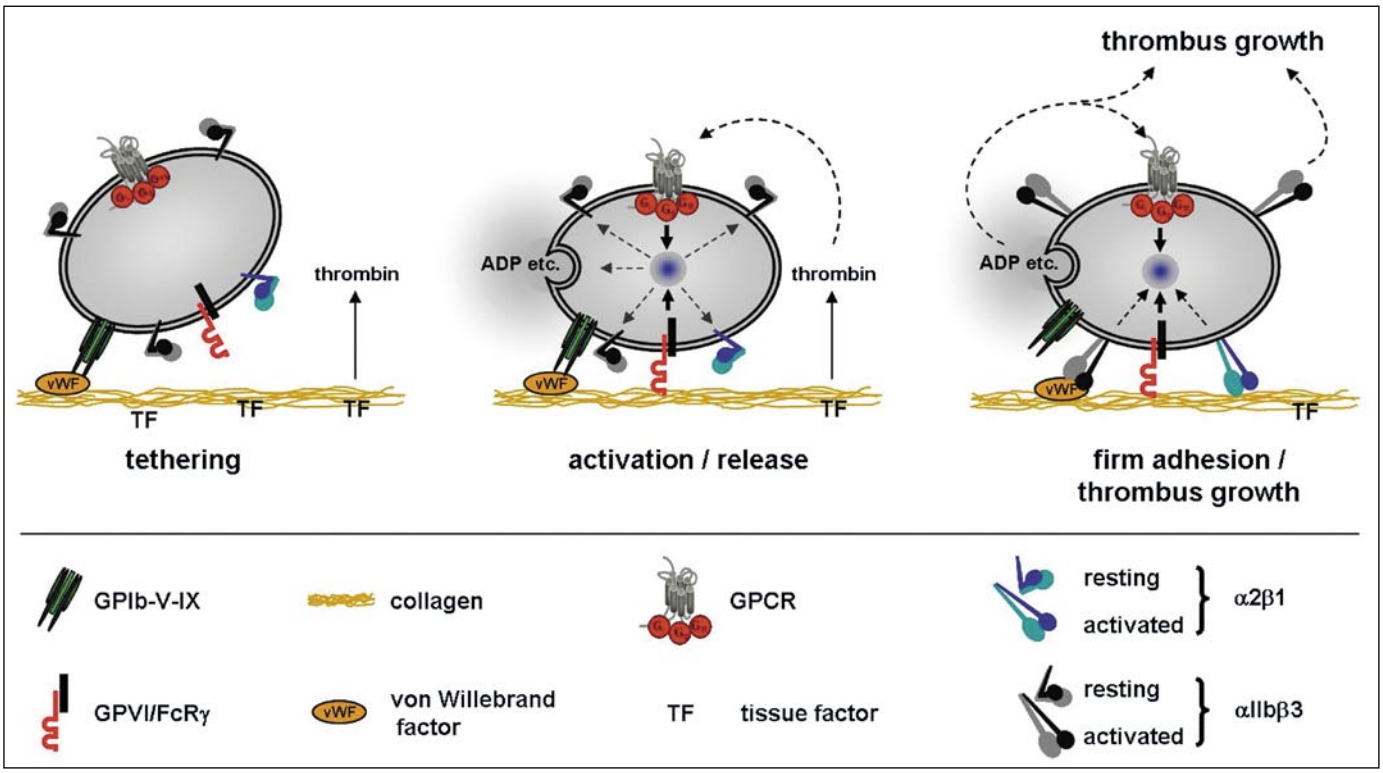

Fig. 1: Platelet adhesion to the subendothelium of the injured vessel wall [Sachs U, Nieswandt B (2007) CircRes 100:979-91].

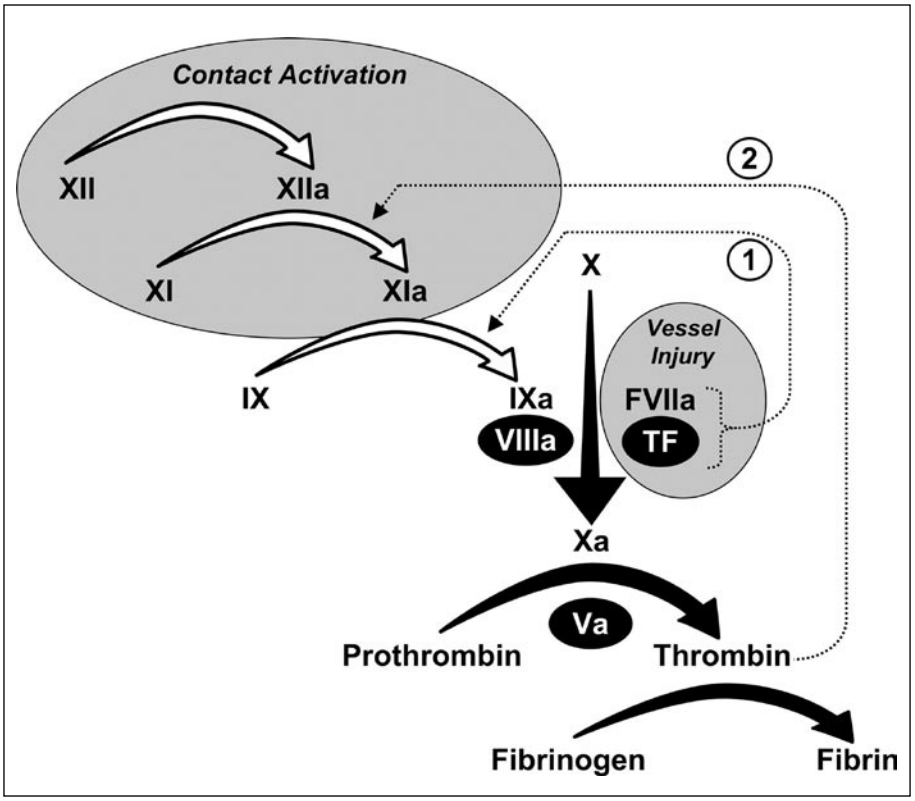

Fig. 2: Current model of plasmatic coagulation [Gailani D, Renné T (2007) Art Thromb Vasc Biol 27:2507-13].

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3.14 Department of Dermatology, Venereology and Allergology

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Professor Dr. med. Henning Hamm
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Professor Dr. med. Jürgen C. Becker
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Mission and Structure

The department offers the entire spectrum of conservative dermatology and dermatologic surgery in patient care, research and teaching. Residents can obtain a full specialisation in dermatology and venereology; additional professional qualifications include allergology, dermatohistology, medicinal tumor therapy and proctology. Apart from the head of the department, 4 professors of dermatology and 3 associate professors have been working in research and education during the period under report. The department has 9 senior physicians, 4 further specialists in dermatology and 14 assistant doctors. In research projects, 2 natural scientists are employed on regular positions and 10 research associates on third-party funds. The department comprises the following divisions:

- General outpatient clinic and consultations for specific skin diseases, outpatient clinic for private patients
- Day clinic
- Wards for conservative dermatology, dermatooncology and private patients
- Operating theatre
- Outpatient clinic for allergology
- Outpatient clinic for phototherapy
- Dermatohistology, immunofluorescence
- Laboratory for dermatologic infectiology
- Research laboratories

Focuses of clinical interest

- Dermatooncology (J.C. Becker, E.-B. Bröcker, S. Ugurel-Becker)
- Allergology and occupational dermatology (A. Trautmann)
- Autoimmune skin diseases (E.-B. Bröcker, C. Seitz, E. Schmidt)
- Hair diseases, hyperhidrosis (H. Hamm)
- Dermatologic surgery (N. Berens, H. Hamm, G. Weyandt)
- Phlebology und proctology (N. Berens, G. Weyandt)
- Pediatric dermatology (H. Hamm)
- Dermatologic infectiology (A. Kolb-Mäurer)
- Dermatohistology (E.-B. Bröcker, C. Kauczok)

Major Research Interests

Tumor biology and tumor immunology

This continuing main field of research initiated by the head of the department is conducted by Prof. Dr. J. C. Becker und addresses several aspects of the biology of cutaneous tumors within the scope of the Klinische Forschergruppe KFO 124 (http://www.tumor-microenvironment.de/index.htm) and various third-party funded projects listed as follows:

- Tumor stem cells in skin tumors (J.C. Becker, R. Houben) (see also figure)
- Signal transduction in Merkel cell carcinoma (J.C. Becker, R. Houben)
- Melanoma immunology (D. Schrama)
- Melanoma genetics, chemoresistence und preclinical testing of innovative therapies (S. Ugurel-Becker)
- Genesis and molecular diagnostics of melanoma (J.C. Becker, E.-B. Bröcker, C. Kauczok)
- Cutaneous lymphomas (J.C. Becker, C. Kauzcok)
- Resistence to therapy of malignant tumors (M.P. Schön, Ma. Schön): mechanisms of tumor metastazition, tumor-endothel interactions, resistence to apoptosis, molecular mechanisms of low-molecular substances
- Apoptotic signal pathways in epithelial cutaneous tumors (T. Giner)
- Influence of polymorphisms on melanoma prognosis (J.C. Becker, S. Ugurel-Becker, D. Schrama)
- Cell migration (P. Friedl): collective invasion of tumor cells; RAS/RAF regulation of tumor invasion; tumor invasion along vessels; multi-photon microscopy of small tumor masses; cell-based tumor therapy

Immunology and inflammation

- Interaction between T-lymphocytes and keratinocytes in dermatitis (A.Trautmann, A. Kerstan)
- Imunotherapy with wasp venom as model for therapeutic immune modulation in humans (A. Trautmann, A. Kerstan)
- Interaction of T-cells with dendritic cells and target cells (P. Friedl)
- Leukocyte recruitment in inflammatory skin diseases (Mi. Schön)
- Interaction of dendritic cells with pathogen microorganisms (A. Kolb-Mäurer)
- Signal pathways in the pathogenesis of pemphigus (E. Schmidt)

Genodermatoses
(H. Hamm)

Clinical and genetic characterization of genodermatoses in cooperation with the Ger-

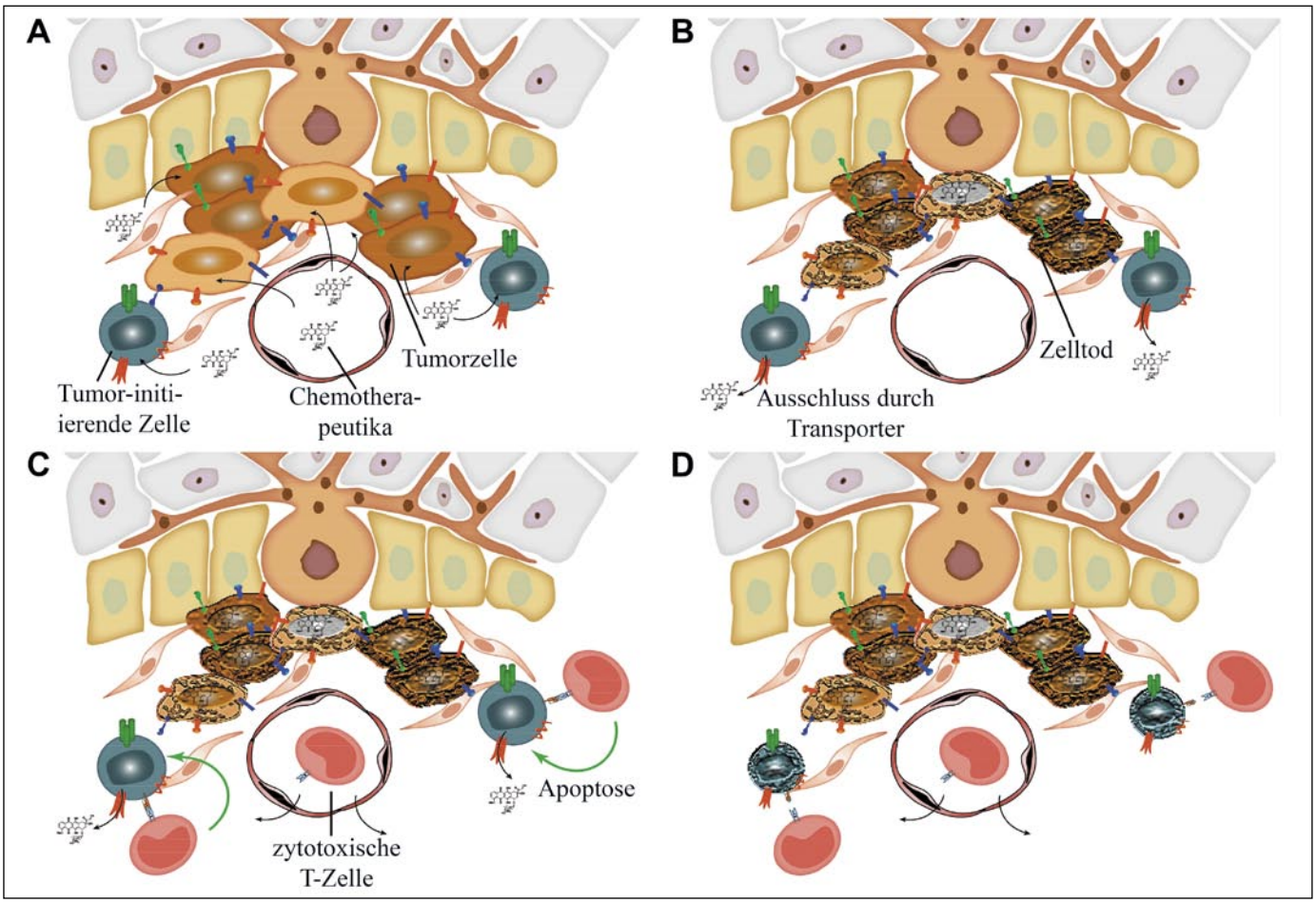

Fig. 1: Tumor initiating cells (tumor stem cells) are resistant to cytotoxic drugs. They may possibly get vulnerable by induction of a suited immune response.

man Network for Ichthyoses and Related Cornification Disorders, the German Network Epidermolysis Bullosa and the department of dermatology, University of Maastricht, the Netherlands (BMBF).

Teaching

The entire realm of dermatology, venereology, allergology and dermatooncology is taught to medical and dental students in lectures and practical courses. The department is also involved in the interdisciplinary education of medical students and in the degree program biomedicine. Main topics of doctoral theses derive from the research projects listed above.

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3.15 Institute of Radiology

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Professor Dr. med. Lásló Solymosi
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Duties and Structure

The Institute of Radiology is responsible for the entire modern radiological diagnostic at the University Hospital of Würzburg. Two professors, 13 senior staff radiologists, 20 residents and scientists as well as 53 technicians work together to ensure modern diagnostic imaging within the clinic. The Institute of Radiology includes a section of Neuroradiology and of Pediatric Radiology. With 5 Spiral-CT scanners and 4 MRI systems, which are available for emergency patients 24 hours a day, more than 60.000 people are examined each year. A main emphasis in medical diagnostics is modern sonography. Thus more than 30.000 in- and outpatients are examined at the University Hospital each year with 6 high end ultrasound systems. A further main topic in diagnostic imaging and preventive medicine is the verification of lesions of the breast, using mammography, sonography and MR-mammography. In order to exclude cancer each year about 8.000 women undergo examinations at the Institute of Radiology. A further main task in medical attention for in- and outpatients at the University Hospital is the treatment of diseases of the vascular and the bilary system. With the help of modern interventional radiology it is possible to dilate vessels with balloon catheters and metal stents in nearly every part of the body, avoiding the risks of an operation.

The section of Pediatric Radiology offers state-of-the art imaging including conventional X-rays with a strong focus on radiation protection, ultrasound and magnetic resonance imaging. Main topics of the section of Pediatric Radiology are radiation pediatric urology, oncological diagnostic, diagnostic of skeletal age and pediatric malformation.

The Institute of Radiology offers a postgraduate training in Radiology including the subspecialities Pediatric Radiology and Neuroradiology.

Major Research Focus

Basic Research and clinical investigation of the lung using MRI
(T. Pabst, H. Köstler, C. Ritter, M. Beer, M. Beissert)

Basic research and clinical investigations in the field of lung diagnosis are performed at the Institute of Radiology with the aim of introducing lung MRI in clinical routine. Special topics are the evaluation of the functional information perfusion and ventilation of the lung, the imaging of the morphological structures and the lung vasculature. The interstitial lung disease and mucoviszidosis were evaluated in several studies.

Fig.1: High resolution imaging of the pulmonary vessels

Non-invasive Cardiac Imaging
(M. Beer, C. Ritter, H. Köstler, T.Pabst)

One of the major research programs of the Institute of Radiology is the methodical and clinical development of non-invasive MR-techniques for assessment of coronary artery disease as well as of secondary non-ischemic cardiomyopathies. Besides the investigation of morphological and functional parameters, the depiction of possible metabolic alterations using MR-Spectroscopy is of upmost interest. Additionally, quantitative first pass perfusion analyses are evaluatued in several studies.

Cardiac computed tomography
(M. Beissert, M. Weininger)

The availability of high-end multi-slice CT scanners using fast rotation times of up to 0.33 seconds has the potential to allow non-invasive cardiovascular imaging. Thus, a focus of cardiovascular imaging research is the non-invasive imaging of the heart and coronary arteries, evaluating novel imaging techniques for coronary artery stenosis, assessment of myocardial infarction, diagnosis of acute chest pain, and congenital cardiovascular disorders. Ongoing research projects include quantification of coronary artery calcifications and CT coronary angiography

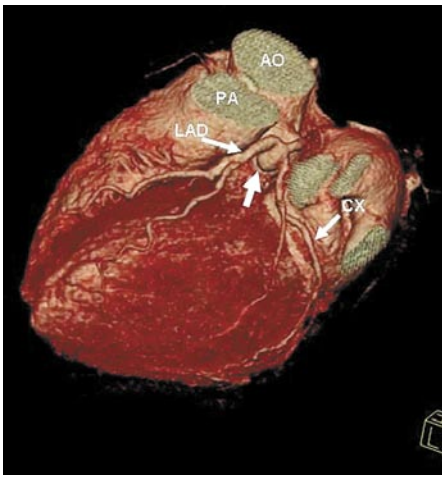

Fig. 2: 3-D reconstruction of the heart depicting the vascular anatomy of the coronary arteries and allowing the diagnosis of a coronary artery aneurysm (white arrow).

Whole-body imaging using magnetic resonance imaging and computed tomography
(M. Beissert, M. Weininger, T. Pabst)

Whole-body imaging using state-of-the art magnetic resonance imaging and computed tomography offers new diagnostic possibilities. In oncology whole-body imaging has the potential to allow a new level of flexibility, accuracy and speed to acurately stage patients. Another focus of our research includes the evaluation of available imaging methods for the diagnosis of different oncological diseases.

Pediatric Radiology
(M. Beer, M. Stenzel)

The main focus lies on the development and clinical application of high-resolution MR-techniques for the assessment of inflammatory and malignant diseases as well as for the investigation of musculoskeletal diseases. Main aims are an early and sensitive evaluation of therapeutic regimes without any radiation exposure.

New MR-acquisition strategies
(H. Köstler)

New acquisition strategies for magnetic resonance images can simultaneously reduce the image noise and improve the resolution. For this purpose density weighted magnetic resonance sequences will be developed for clinical use and investigated systematically.

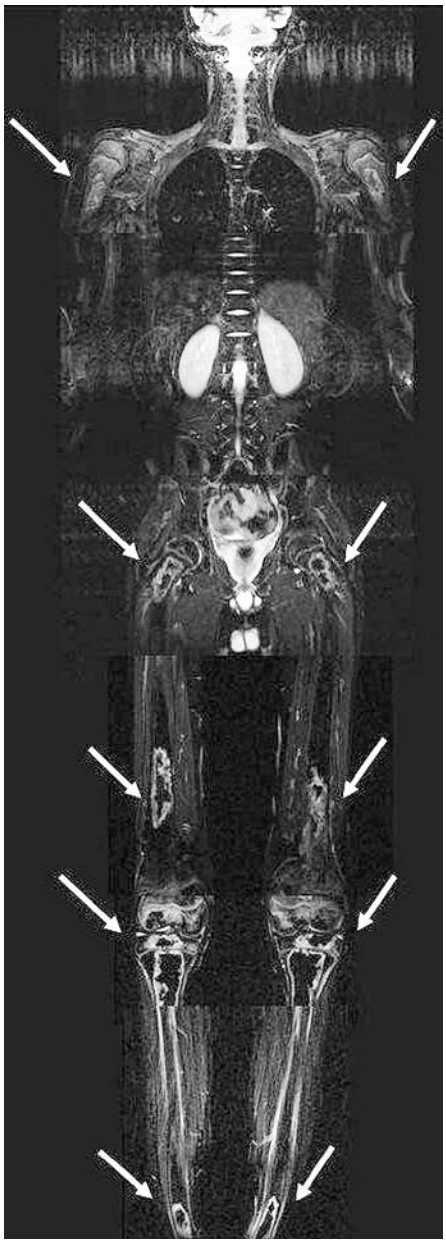

Figure 3: 16 year old boy with c-ALL. Whole body MR-imaging with T2-weighted sequences (TIRM) at the onset of clinical symptoms demonstrates typical lesions of multiple osteonecrosis in both humeri, femora and tibiae (white arrows). The conventional X-rays showed no pathologies at the same time.

Teaching

Continuing medical education is regularly offered for radiologists in private practice, senior radiologists, fellows and residents. In addition colleagues from other departments are trained in several diagnostic procedures.

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3.15.1 Division of Neuroradiology

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www.neuroradiologie.uni-wuerzburg.de

Mission and Structure

The independent Department of Neuroradiology is integrated into the Head Clinic of the University Hospital Würzburg and was founded in 1977. All modern diagnostic exams and therapeutic interventions available to the neuroradiological specialty are practiced at the technically highest standard. The following equipment is linked into the PACS: a modern digital imaging system for X-ray diagnostics, a multifunctional X-ray imaging system with fluoroscopy and DSA capability, a multislice CT scanner, a biplane digital subtraction angiography system with flat panel technology and Dyna-CT, a most up-to-date 3T magnetic resonance (MR) scanner with multi-channel und –nuclear support operated exclusively by the department and two 1.5T MR scanners operated in alternation with the radiological department.

Staff: 3 senior physicians, 4 residents, one resident of the radiological department in neuroradiological training, 9,5 medical technicians, 4 third-party funded residents and 5 research assistants (part-time).

Due to the regrettable shortage of neuroradiological departments in Germany, our institution accommodates a large and steadily increasing number of patients from far beyond the catchment area of the University Hospital per se.

Interventional neuroradiology (i.e. endovascular treatment of aneurysms, arteriovenous malformations, intracranial neoplasms as well as of stenoses and occlusions of supra-aortic vessels) constitutes a main focus of the department. The number of treated cases is among the highest in Germany. The Stroke-Unit supplies additional diagnostic and therapeutic tasks. Further emphasis is placed on neurooncology (i.e. diagnostic evaluation of CNS tumors together with the pediatric, neurosurgical and neurological specialties). Close collaboration with the Department of Pediatric Neurosurgery and of Pediatrics characterizes the second diagnostic focus of pediatric neuroradiology. A quite unique feature of the department pertains to the neuroradiological diagnostic evaluation of peripheral nerve injuries and myopathies which attracts patient referrals from all over Germany. Pre-surgical functional MR imaging is performed for surgical targeting and prior to cochlear implantaton to limit the surgical risks and to increase the predictable benefits, respectively.

Major Research Interests

Neuroimaging
(M. Bendszus)

This focus is funded by an endowed professorship assigned to Dr. Bendszus in conjunction with the Department of Neurology. Here, new innovative contrast media are investigated in inflammatory and regenerative processes of the central as well as peripheral nervous system. Furthermore, prospective studies are conducted on brain regeneration after toxic insults (such as from alcohol) and on the occurrence of specific neuropsychological deficits in the course of various procedures.

Neurooncology
(M. Warmuth-Metz)

The department acts as the neuroradiological reference site to all German multicentric, pediatric neurooncological studies. MR-examinations are evaluated to assess the therapy of experimental gliomas and novel MR contrast agents. Third-party funded.

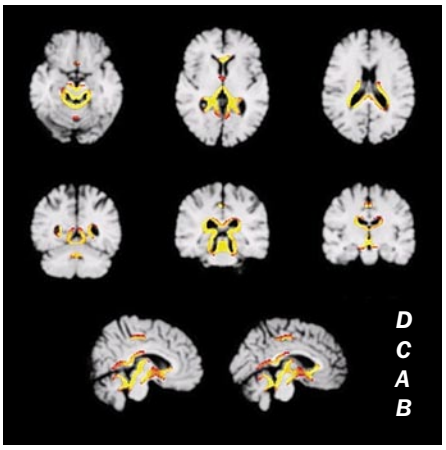

Fig. 1: Areas of brain volume gain induced by abstinence from alcoholism.

Pediatric Neuroradiology
(M. Warmuth-Metz)

Close collaboration with the Department of Pediatric Neurosurgery in the diagnosis and treatment of CNS neoplasms, spinal and vascular malformations.

MR Imaging of Neuromuscular Diseases
(M. Bendszus)

Animal experiments and clinical studies on the detection of peripheral nerve injuries and denervated muscles.

MR-Diffusion Imaging
(A. Bartsch)

Development of new analysis methods for MR-diffusion data to establish white matter integrity (e.g. Tract Based Spatial Statistics) and establishing and testing of diffusion tractography under aversive conditions.

Functional MR-Imaging
(A. Bartsch)

In cooperation with the Depts. of Neurosurgery, ENT, Neurology and Psychiatry. DFG-(German Research Council) funded subproject in the Clinical Research Group on ADHD. Characterization and quantification of neuronal resting-state networks by fMRI. Mapping prior to neurosurgical resections and coch-

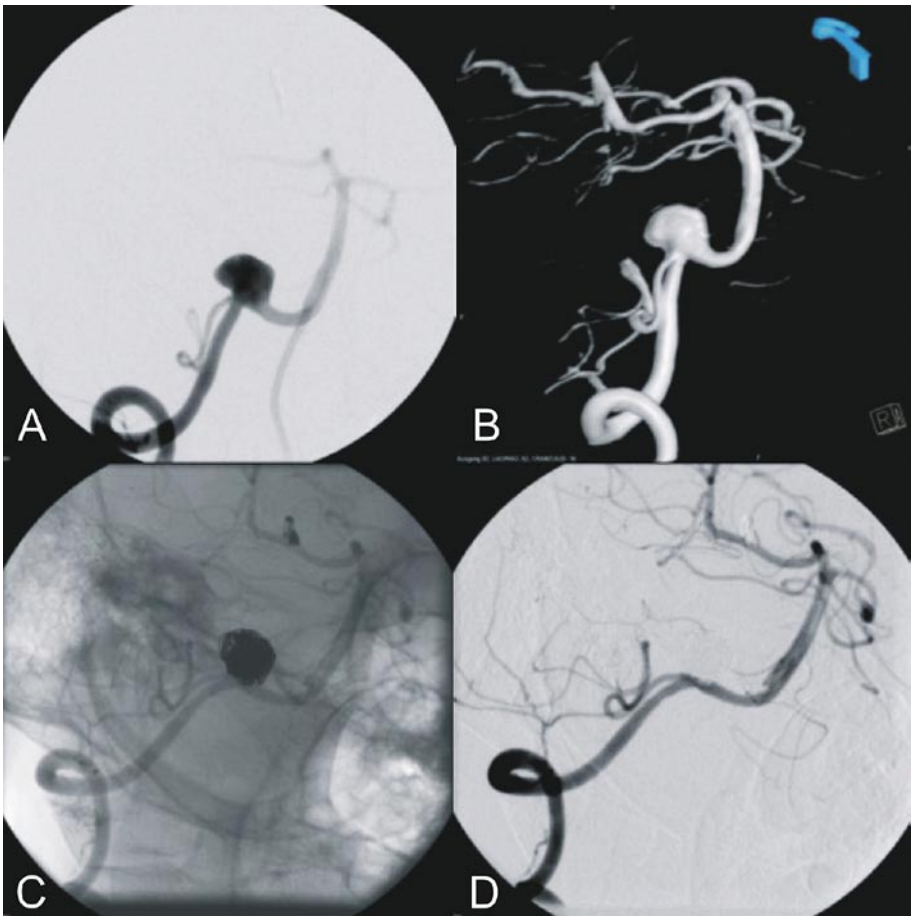

Fig. 2: Aneurysm in the posterior brain circulation before (A, B) and after (C, D) embolization by platinum coils.

lear, brainstem and midbrain implants. Examination of the effects of a series of electroconvulsive therapies and acute alcohol ingestions on the brain. FMRI and quantified perfusion in malignant brain tumors.

Interventional Neuroradiology – Vessel-occlusive Therapies
(L. Solymosi)

Endovascular treatment of vascular malformations and highly-vascularized tumors in international and national studies. Optimization of embolization materials and -techniques. Third-party funded.

Interventional Neuroradiology – Vessel-recanalizing Therapies
(L. Solymosi)

Improvement of the effectiveness of vessel recanalization. Examination of pharmacological and mechanical recanalization. Diagnostics and interventional treatment of vasospasms after subarachnoidal hemorrhages. Part of the SPACE Collaborative Group on the evaluation of treatment of carotid stenoses (SPACE).

Teaching

The department participates in the university education of students by conducting lectures and courses within the radiological and neuroradiological teaching. The head of the department is authorized to full neuroradiological training (3 years).

The department organizes regular teaching and training events with national and international neuroradiological lecturers. Its staff is constantly active in various in- and out-of-house courses (such as refresher programs at the annual Convention of German Radiologists and regular neuroradiological training for the Bavarian Medical Association) and organizes or instructs various courses at the international level (such as the FSL & Freesurfer Courses 2006 in Siena and 2007 in Cardiff or the Clinical FMRI Course on the Human Brain Mapping Conference 2007 in Chicago).

Neuroradiological reference site for all German multi-centric therapy studies of pediatric brain tumors. Various international studies on malignant brain tumors (glioblastomas, pontine gliomas). International (worldwide) therapy studies on cerebral aneurysms (detachable coils, bioactive coils, stents).

Participation on therapy studies of inflammatory CNS diseases.

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SPACE Collaborative Group; Ringleb PA, Allenberg J, Bruckmann H, Eckstein HH, Fraedrich G, Hartmann M, Hennerici M, Jansen O, Klein G, Kunze A, Marx P, Niederkorn K, Schmiedt W, Solymosi L, Stingele R, Zeumer H, Hacke W. (2006) 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. Lancet 368: 1239-1247.

3.16 Department of Nuclear Medicine

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Mission and Structure

The department of nuclear medicine is in charge of all use of open radioactive substances in humans for research, education and patient care. Within the scope of the interdisciplinary PET centre, close cooperations with many animal research groups have been established. The division of experimental nuclear medicine with radiopharmacy is headed by Prof. Dr. S. Samnick. To this end a GMP certified radiochemical/radiopharmaceutical laboratory is available. A cyclotron for radionuclide production will be installed, after the commissioning of the new Zentrum für Innere Medizin. Since 2006/2007 a micro-PET scanner has been available for preclinical research. Studies using small animal SPECT and –ultrasound are also possible.
With the equipment available for clinical routine (6 gamma cameras, 1 PET, 1 SPECT/CT-gamma camera, 1 thyroid gamma camera, 3 ultrasound, as well as, 3 bone density measuring devices and 1 whole body counter) the department performs around 15,000 examinations a year. Additionally, about 800 in-patients are treated, mainly for thyroid disorders and about 150 out-patients receive treatment for chronic inflammation of the joints or bone metastases.
In the biodosimetric laboratory, new methods are being developed to retrospectively determine the extent of an accidental radiation exposure. The laboratory for iodine analytics is an acknowledged reference laboratory for research studies, in which the amount of stable iodine has to be determined in body liquids or the thyroid gland (by means of HPLC or X-ray fluorescence analysis).
The department serves as a Regional Centre for Radiation Protection (RSZ) of the Employer's Liability Insurance Association. It is also a national Collaborating Centre of the worldwide REMPAN network (Radiation Emergency Medical Preparedness and Assistance Network) of the World Health Organization (WHO).

Major Research Interests

Diagnostics and Therapy of Thyroid Disorders
(Chr. Reiners, M. Luster, J. Biko, P. Schneider)

The main focus of scientific activities is thyroid cancer, for which in cooperation with the cancer centre, a regional incidence registry is kept. Of special interest is radiation induced thyroid carcinoma in children. A close collaboration exists with our partner institution in Minsk, Belarus, to improve the diagnosis, therapy and aftercare of radiation induced thyroid cancer in children. The department regularly participates in drug approval studies of new medications for the treatment of thyroid carcinoma (i.e. rhTSH and ZD6474).
An important focus in the field of the diagnostics of thyroid disorders is the standardization and advancement of ultrasound (i.e. fusing 3D-Ultrasound with SPECT in the scope of „hybrid thyroid imaging").
The department of nuclear medicine participates in (and is partially in charge of) several international epidemiological studies of iodine deficiency induced thyroid disorders.

Radiation Safety/Medical Physics
(M. Laßmann, H. Hänscheid, S. Schlögl)

The main point of interest is the field of internal dosimetry for radionuclide therapy. Currently, new imaging procedures like SPECT/CT and PET using non standard nuclides are being evaluated for dosimetry and are implemented into clinical practice. In this context, especially radionuclides are of interest, which can be used for pre-therapeutic dosimetry in radionuclide therapy (i.e. I-124).
Another focus of research is the methodical development of 3D-ultrasound and high resolution multi-pinhole-scintigraphy for small organs (thyroid) and small animals. In addition, the workgroup is operating a state-licensed whole body counter as an official recording point of the State of Bavaria for the incorporation monitoring workers.

Biodosimetry
(K. Hempel, M. Laßmann, R. Lorenz)

In close cooperation with the Bundeswehr Institute of Radiobiology the induction, persistence and disappearance of DNA-damages are being studied using induced gamma-H2AX-foci after radiation exposure to I-131. As a model, the in-vivo exposition of mononuclear peripheral blood cells of patients with differentiated thyroid carcinoma after ablation treatment with I-131 (activities of more than 3 GBq) is being used. In comparison with physical dosimetry, the extent and the duration of H2AX-Foci is tested to which extent it reflects the acquired radiation dose.

WHO/REMPAN-Centre
(Chr. Reiners, R. Schneider, M. Laßmann)

The WHO/REMPAN-Centre was accredited in 2005. Its key activities are the organisational improvement of the medical treatment of radiation accident patients in Germany, the administration of a radiation accident database as well as training and education in medical radiation accident management (http://www.rempan.de). As one of the Regional Centres for Radiation Protection the department is responsible for the treatment of patients exposed in occupational radiation accidents.

Neuromuscular-Skelettal System
(P. Schneider)

The quantification of bone mineral content is strongly related to force producing muscles. The densitometric measurement methods also allow assessment of bone strength, which is one of the main research focuses. In this context, methods were developed, to further assess muscular properties in humans. These methods were ceded to the university to file for patents. (PCT WO2006/005279 A1; PCT / EP2007/005847).

Experimental Nuclear Medicine – Radiochemistry/Radiopharmacy
(S. Samnick, A. Schirbel)

The work group is in charge of the development of innovative radiopharmaceuticals for imaging and therapy in nuclear medicine. The new probes are evaluated preclinically in-vitro, as well as in-vivo, by using small animal imaging (small animal PET and SPECT). The most promising tracers then are being further medically assessed in cooperation with clinical partners (please refer to subject area oncology, cardiology, neurology-psychiatry).

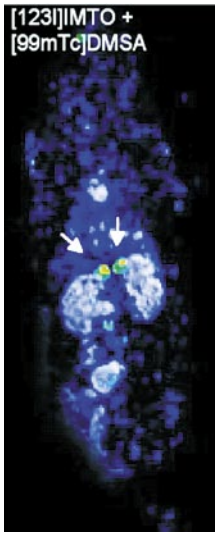

Fig. 1: Projection image: By using small animal SPECT and the adrenocortical tracer [^{123}I]Iodometomidate (IMTO) it is possible to image murine adrenal glands (arrows), which have a size of less than a millimeter in diameter. A high and specific binding of the tracer is noted. For better orientation the kidneys (depicted in blue) were also visualized using the kidney specific tracer [^{99m}Tc]DMSA.

Oncology
(R. Lorenz, M. Kreißl, M. Luster, P. Schneider, S. Samnick, A. Schirbel)

Together with the ENT-clinic, the localization of the „sentinel lymph node" in head and neck tumours was further optimized. For imaging of brain tumours, the radiochemistry/radiopharmacy group made I-123-IMT available.

In the field of PET, F-18-FDG is being used on a routine basis. For brain tumours, F-18-FET, as an analogue to I-123-IMT and for prostate carcinoma F-18-Choline, are administered. For the imaging of neuroendocrine tumours, Ga-68-DOTATOC is currently being established.
A special focus in oncology is in development; preclinical and clinical assessment of radiotracers for imaging adrenocortical cancer (together with the department of endocrinology). Here the SPECT tracer I-123-Metomidate, as well as, the PET tracer I-124-Metomidate could be successfully established. On a compassionate use basis, patients with untreatable metastatic adrenocortical cancer are treated with I-131-Metomidate.

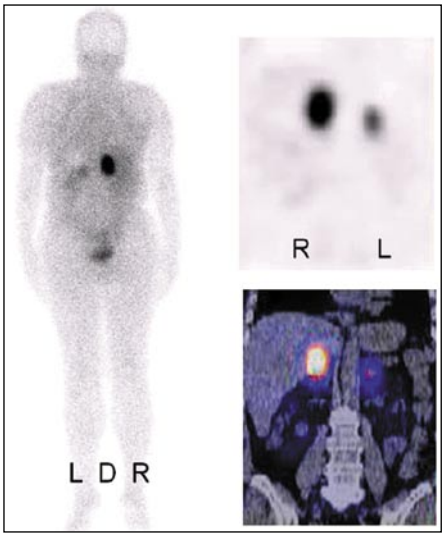

Fig. 2: 58 year old patient with right sided adrenocortical adenoma: Five hours after administration of 184 MBq [123I]Iodometomidate a strong accumulation of the radiotracer is observed in the right adrenal gland (left: planar whole body scintigraphy in a dorsal projection; right: SPECT & SPECT/CT).

Preclinical imaging
(M. Kreißl, M. Laßmann, A. Schirbel, S. Samnick)

Both, small animal PET, as well as, small animal SPECT are non-invasive imaging modalities which are being employed in-vivo to evaluate the new radiotracers developed by the radiochemistry-radiopharmacy group.
In cooperation with other research groups, studies to assess the tumour response to various chemotherapy regimens and to study the regulation of cardiac metabolism in Type-2 diabetes are being conducted.
3D-ultrasound was adapted for the use in small animals. It facilitates, after co-registration with small animal PET and –SPECT, a correlation of anatomical with functional imaging.

Cardiology
(M. Kreißl, R. Lorenz)

At the department of nuclear medicine, the influence of the normal reference database on the automated analysis of myocardial perfusion studies was systematically assessed and the process was further optimized. The effect of physical stress on cardiac function was investigated in patients with coronary artery disease (CAD). Furthermore, tracers for imaging matrixmetalloproteinases, which are known to play a crucial role in CAD and the inflammatory processes after myocardial infarction, are also being developed.

Nephrology-Urology
(R. Lorenz, O. Tiedge)

In cooperation with the children's hospital and the clinic of urology, the functional scintigraphy on children with dysfunctions of urinary transport was further optimized. For Morbus Fabry patients of the clinic of nephrology, the value of nuclear medicine assessment of renal function was determined.

Neurology/Psychiatry/Child- and Adolescent Psychiatry
(R. Lorenz, K. Nerlich, A. Schirbel)

Together with the department of neurology, transcranial ultrasound was compared with dopamine transporter scintigraphy in patients with Morbus Parkinson and atypical Parkinson syndromes. In children and adolescents with attention deficit hyperactivity disorder, the effect of medical treatment on dopamine transport was assessed. For the diagnosis of dementia, an automated parametric image analysing procedure was introduced and evaluated in corticobasal dementia.

Teaching

In a project funded by the „Virtuellen Hochschule Bayern", the department of nuclear medicine, together with the institute for Informatics IV, developed an interactive program for teaching medical students. The department of nuclear medicine is operating a CIP-Pool for students and is integrated into the interdisciplinary lecture and seminar program in oncological diagnostics.

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3.17 Department of Radiation Oncology

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Mission and Structure

The clinic for radiotherapy (17.5 physicians, 8 medical physicists, 19 radiographers, 16 nurses) uses 5 modern linear accelerators (including IGRT with an in room cone beam CT), a short distance X-ray unit and afterloading units for remote controlled radioactive inserts. Patients are treated in a policlinic department, in a ward with 20 beds in the Kopfklinikum and in a day ward with 10 treatment places. Spiral-CT, ultra sound and a user connection to the Institute of diagnostic radiology, especially related to MR-tomography for treatment planning provide the anatomical and physical basis data for a computerised treatment planning. Planning, dose calculations and the calibration of the treatment units are carried out by the section of medical physics (8 physicists, 2 technicians). About 2200 patients (mainly ambulatory) are treated annually. By means of the day ward it is possible to avoid hospitalisation also in more intensive parts of the treatment (concurrent chemotherapy, treatment of acute side effects). In addition to the typical spectrum of a modern radiation therapy special techniques are offered like intra and extracranial radio surgery, total body irradiation before stem cell transplantation, contact irradiation for tumours of the eye and interstitial brachy therapy of tumours in the head and neck, prostate, abdominal tumours, and tumours of the extremities after implantation of catheters or permanent seeds.

Major Research Interests

Development of conformal treatment techniques

The realisation of an optimal dose concentration in the tumour forms a major part of the research effort. The development of stereotactic techniques in the region of the body, the development of inverse planning techniques using intensity modulation and dynamic multi leaf collimators and integration of time dependent changes (intra- and interfractional) are part of this.

Medical physics

Research concerns image guided radiotherapy, optimisation and adaptation of dose distributions and dosimetry. Topics are: patient positioning, image registration, tracking of moving targets by means of portal images and external body markers, development of recipes for optimisation and adaptation of intensity modulated radiotherapy, dose measurement and dose calculation in inhomogeneous bodies and for small fields. The aims are effective sparing of organs at risk and increase of the tumour control rate, hence a higher accuracy and safety of treatment with ionizing radiation.

Prediction of individual radiation sensitivity

About 5% of oncology patients treated by radiation therapy develop acute or late radiotoxic effects, the molecular mechanisms of which remain poorly understood. Our radiobiological laboratory (2 scientists, 2 technicians, 6 grant positions) is appropriately equipped to carry out basic research of the biological effects of ionizing radiation in human cells. We have evaluated the potential role of the chromatin structure, genomic instability, DNA repair proteins and several other factors in the hypersensitivity of cancer patients to radiation therapy. Using the fibroblasts of hypersensitive cancer patients, neither the clonogenic survival assay nor Western blot analysis of DNA repair proteins revealed any abnormalities in the cellular radiosensitivity in vitro and in protein expression levels or migration patterns. In contrast, in vitro irradiated cells from radiosensitive patients exhibited a significantly higher number of nuclei with focally concentrated DNA repair protein Rad50 than that in control groups (see Fig. xx). The observed alteration of the distribution of radiation-induced Rad50 foci in cells derived from cancer patients with acute side reactions to radiotherapy might contribute to their radiation therapy outcome. In a recent study, we also found, using the micronucleus test, that cells from cancer patients with an adverse skin reaction to radiotherapy displayed increased frequencies of both spontaneous and radiation-induced micronuclei as compared to healthy control or the group of unselected breast cancer patients.

Clinical trials and quality assurance

The department is responsible for the conception and realisation of radiation therapy in national and international therapy studies for head and neck tumours and lung cancer.

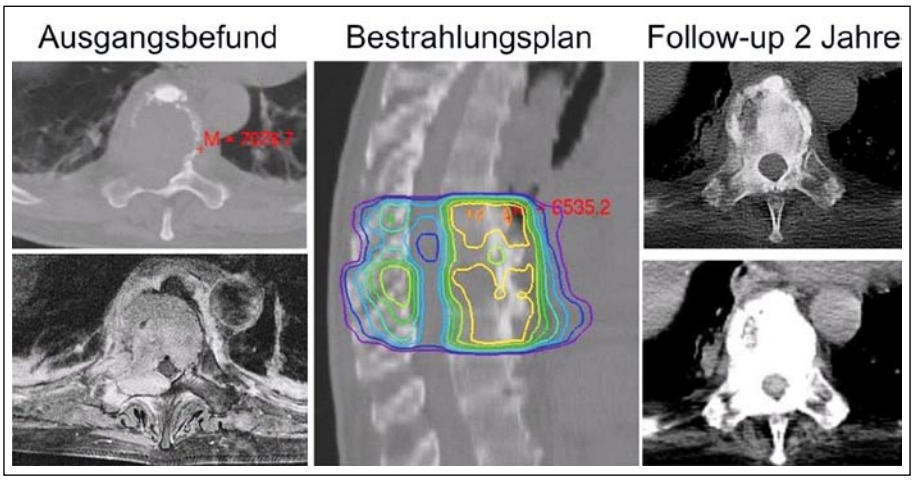

Fig. 1: Solitary metastasis of the spine (Salivary gland carcinoma). Dose distribution with chord sparing. Two years after 20 x 3 Gy image guided radiotherapy recalcification and persistent local control has been achieved. No treatment related side effects.

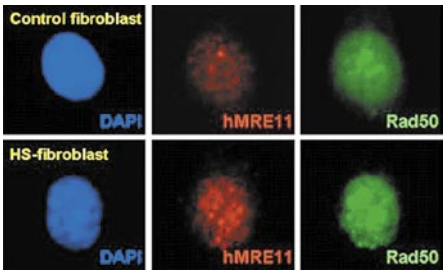

Fig. 4: Immunofluorescence analysis of nuclear hMre11 (red fluorescence) and Rad50 (green fluorescence) foci in irradiated skin fibroblasts derived from a healthy individual (top images) and from a cancer patient with increased early reaction to radiotherapy (HS fibroblast, bottom images). Cells were irradiated with 8 Gy, fixed 2 h post-irradiation and double stained with anti-hMre11 and anti-Rad50 antibodies. Left-hand images show DAPI staining of the nuclei. A protracted Rad50 foci formation was found in irradiated cells derived from cancer patients with increased early reactions to radiotherapy. Moreover, these cells displayed also an increased number of Rad50 foci per cell after irradiation (bottom images).

Major contributions concern randomized studies for organ preservation in Larynx/hypopharynx Cancer (Delos 2) and in cinciurrent radiochemotherapy in advanced lung cancer (GILT-CRT). A quality circle for Unter/Oberfranken as well as the radiation safety board (§ 83 StrSCHV) of Bavaria is chaired by the director of the department.

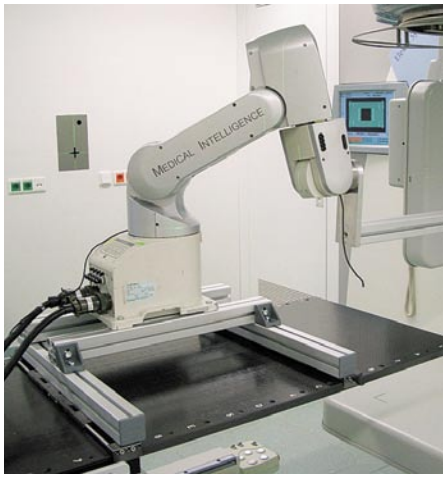

Fig. 2: Test set-up for tracking a moving object in order to keep it within the therapy beam.

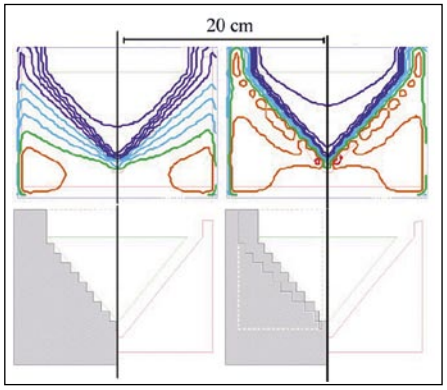

Fig. 3: Conical "organ at risk" surrounded by a target volume. Left: Rotation irradiation. Right: 2-Step Intensity modulated arc therapy. The additional 2-Step IMAT segment remarkably increases the dose homogeneity.

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3.18 Department of Oto-Rhino-Laryngology, Plastic, Aesthetic and Reconstructive Head and Neck Surgery

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Mission and Structure

The clinic of Otorhinolaryngology, plastic and aesthetic surgery (28 physicians, 5 scientists, 8 research fellows) has 113 regular beds including 4 intensive care units. Besides the complete basic care in the field of ORL there exist the following clinical specialities: device based and surgical supply of all kind of hearing disabilities by special diagnostics, conventional middle ear surgery, new active middle ear implants, implantable hearing aids as well as cochlear implantation (international reference centre), interdisciplinary skull base surgery (tumours, traumas), diagnostics and therapy of head and neck tumours with main focus on organ and function preserving and microsurgical techniques and plastic-reconstructive surgery, national reference centre for surgical treatment of pediatric sarcomas, phoniatrics (including phonosurgery), pedaudiology, allergology, sleep medicine (devices based and surgical treatment), neurootology, plastic and aesthetic interventions of the head and neck. Support of foreign ORL clinics in all continents by visitant professorships and practical education of foreign ENT doctors. National and international surgical courses with 3D-Video-Live-Transmission of surgical interventions.

Major Research Interests

Middle ear biology
(R. Mlynski, M. Schmidt, R. Hagen)

Histological morphometry and surface characteristics of middle ear implants; immunology and immunhistology of cholesteatomas for research of origin and maintenance of chronic otitis media, expression of bone morphogenetic protein-2, MMP-9 and cytokines in cells of cholesteatoma.

Biophysics of middle ear
(J. Müller, S. Brill, F. Kraus, R. Hagen)

Investigations of middle ear structures as a dynamic-mechanical system in sound transmission processes using LASER vibrometry; EDP supported documentation and evaluation of surgical and audiological outcome in patients with tympanoplasty and implantation of electronic hearing devices.

Inner ear biology
(R. Mlynski, M. Bürklein in cooperation with the institute of neurobiology, M. Sendtner, the institute of clinical biochemistry and pathobiochemistry, U. Walter, and the Univ. ORL-Department Bochum, St. Dazert)

Effects of reversible and irreversible ototoxical substances on the active cochlear amplifier system to further investigate pathophysiological processes in inner ear diseases; in vitro and in vivo investigations of neurotrophic substances (FGFs, NT-3, CNTF, LIF) on survival and growth patterns of hair cells and spiral ganglion neurite extension in the mammalian cochlea; effects of recombinant adenoviruses on cochlear cells to transducer cochlear tissues for future gene therapy, inner ear and hearing development in CNTF and LIF knockout mice, creation of transgenetic mice with a cell specific gene-knock-out in cochlear and spiral ganglion cells; investigations of function of vasodilator stimulated phosphoproteins (VASP) in terminal hair cell innervation.

Pedaudiological tests and newborn hearing screening
(W. Shehata-Dieler, C. Völter, R. Keim)

Testing of hearing in all newborns by means of complete screening, application and comparison of different objective audiological testing methods, development of new testing devices, specification of auditory neuropathy in children by special studies.

Cochlear- and brain stem implants
(J. Müller, W. Shehata-Dieler, A. Radeloff, S. Brill, S. Kaulitz in cooperation with the department for neurosurgery and the University of Innsbruck, Austria)

Investigations to improve speech intelligibility following cochlear implantation, development of new surgical techniques and innovative implant models, physiology and pathophysiology of the auditory pathway following uni- and bilateral electro stimulation considering functional anatomical correlations while stimulating different parts of the auditory pathway.

Experimental audiology
(M. Cebulla, R. Keim)

Further development of diagnostic tools for objective frequency specific measurement of the absolute threshold of hearing, standardisation of different methods of acoumetry, investigations in the fine structure of responses to click-stimuli in comparison to transit time corrected stimulation.

Hearing research
(M. Vollmer, T. Bremer in cooperation with the University of California, Prof. Beitel, and the Ludwig-Maximilians University Munic, Prof. Grothe)

Animal experiments in gerbils for investigation of central neuronal interactions in electric acoustical stimulation of the cochlea, central neuronal processing of interaural time differences (ITDs) in acoustical and electrical stimulation of the cochlea, effects of long term deafening to temporal and spatial discrimination of intracochlear electrical stimulation in the colliculus inferior and the primary auditory cortex, psychophysical and neuronal models for temporal integration of electrical stimuli, neurotrophic effects of GM1 gangliosides and electrical stimulation to spiral ganglion cells following neonatal deafening

Tumour biology and functional rehabilitation following tumour surgery
(R. Hagen, M, Schmidt, M. Scheich)

Molecular biological investigations in head and neck carcinomas (HNC), induced expression of a deletional mutant of Pseudomonas exotoxin A in cell lines of HNC, development of a new control plasmid by subcloning (pGeneA-EGFP), investigations in chemotaxis and angiogenesis of tumour cells, effects of herbal anti-tumoural extracts on paclitaxel sensitive and – resistant HNC cell lines, development of new surgical reconstructive techniques of larynx and trachea.

Functional magnetic resonance imaging
(C. Knaus, M. Unkelbach, M. Bendzus, L. Solymosi, A. Bartsch)

Development of new techniques for testing the auditory pathway in cooperation with the institute of neuroradiology

Ecological toxicology of the upper aerodigestive tract (UADT)
(N. Kleinsasser, C. Köhler, C. Ginzkey, G. Friehs)

Investigations on the toxicological effects of ecological toxins in tumour initiation testing human tissue cultures of the UADT, characterisation of genotoxical effects of tobacco smoke and environmental toxins (nitrogen dioxide) on mini organ cultures of UADT.

Tissue engineering in laryngology
(N. Kleinsasser, K. Frölich, K. Kampfinger, A. Technau)

Establishment of stabile cartilaginous structures with different scaffold materials.

Teaching

Coworkers with postdoctoral lecture qualification take part in the medical main lecture and in the clinical courses for medical students. Initiation and coaching of experimental and clinical medical dissertations. Annual german and english speaking surgical courses for microsurgery of the ear, skull base surgery, phonosurgery, reconstructive laryngeal surgery, endonasal surgery with live-3D-transmission and practical exercises for consultants. The foreign twin clinics are served by course instructors (DAAD) in all the participating countries, 4 training fellowships for practical education (actually doctors from China, Mongolia, Kasachstan, Peru). Full-time hospitations for consultants.

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Martinez R, Setien F, Voelter C, Casado S, Quesada M, Schackert G, Esteller M: (2007) CpG island promoter hypermethylation of the pro-apoptotic gene caspase-8 is a common hallmark of relapsed glioblastoma multiforme. Carcinogenesis 28:1264-1268.

Vollmer M, Beitel RE, Snyder RL, Leake PA: (2007) Spatial selectivity to intracochlear electrical stimulation in the inferior colliculus is degraded after long-term deafness in cats. J.Neurophysiol 98: 2588-2603.

3.19 Department of Ophthalmology

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Mission and Structure

A staff of 29 physicians and 76 nurses, technicians and scientists cares for 18.000 outpatients and more than 5.500 inpatients annually. In 2007, more than 6.500 surgical procedures and 1.500 laser treatments were performed. As one of the largest eye hospitals in Germany, we provide the full range of medical and surgical eye care and diagnostics. The hospital comprises a renowned glaucoma center with distinct experience in pediatric glaucoma. The retina service specializes in retinovitreal diseases and ocular trauma. Specialized teams care for eyelid affections, conjunctival, corneal and orbital diseases as well as childhood eye diseases, neuro-ophthalmological disorders or strabismus. An increasing number of patients treated for eye disease suffers from multiple systemic ailments and requires inpatient care. At the same time it is our goal to improve and expand outpatient surgery facilities to provide the best possible care for all patients.

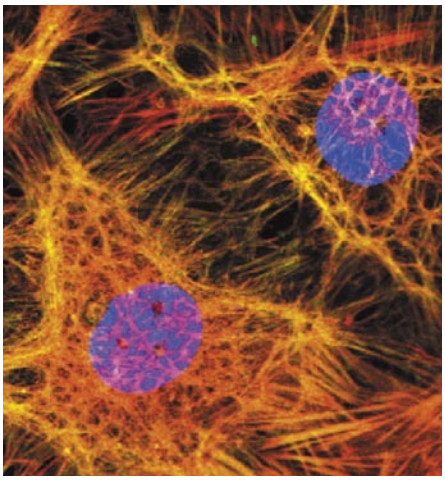

Fig. 1: Crosslinked actin cytoskeleton meshworks (CLANs) in human trabecular meshwork cells. CLANs may have a role in defective intraocular pressure regulation in glaucoma. Colocalization of F-actin (red) and smooth muscle actin (green).

Major Research Interests

Clinical Research

Research activities focus on the fields of cornea, glaucoma and retina. New strategies are developed to treat ocular surface disease, novel wound healing modulation techniques are assessed to prevent scarring following glaucoma surgery, new agents to treat age-related macular degeneration are evaluated and genetic glaucoma predisposition is studied. The glaucoma center leads the clinical assessment of innovative methods to measure intraocular pressure and develops new electronic data acquisition and management networking systems to improve national and international collaborations in patient care.

Basic Research

Electrophysiology

Minimally invasive electrophysiological methods allow for a differential examination of distinct components of the visual pathway. The electrophysiology lab develops and validates new recording methods and specializes in multifocal techniques to simultaneously detect signals from distinct areas in the visual field. Recently, these techniques were adapted to study lateral retinal interactions, to characterize genetically encoded maculopathies, to determine retinocortical transmission speed, and to study basic mechanisms in visual perception (e.g. long-term potentiation).

Biometry and Optics

The proper selection of lens implants in cataract surgery rests on an accurate determination of intraocular distances. Internationally renowned for its research and development, the biometry lab has played a crucial role in the emergence of laser interference biometry techniques as the current gold standard. Two instruments that are now widely used in clinical practice were developed in a close ongoing collaboration with Carl Zeiss Meditec AG. Another focus of the lab is the development of algorithms to validate refractive implants. These algorithms are being tested in an international network and are provided to the scientific community as an open access internet resource.

Cell Biology

Ocular wound healing, intraocular pressure regulation and ocular surface regeneration are at the focus of the cell biology lab. Central to these issues are cell-cell and cell-matrix interactions which drive cellular signal integration mechanisms to direct and coordinate cell functions. Based on these mechanisms, specific kinase inhibi-

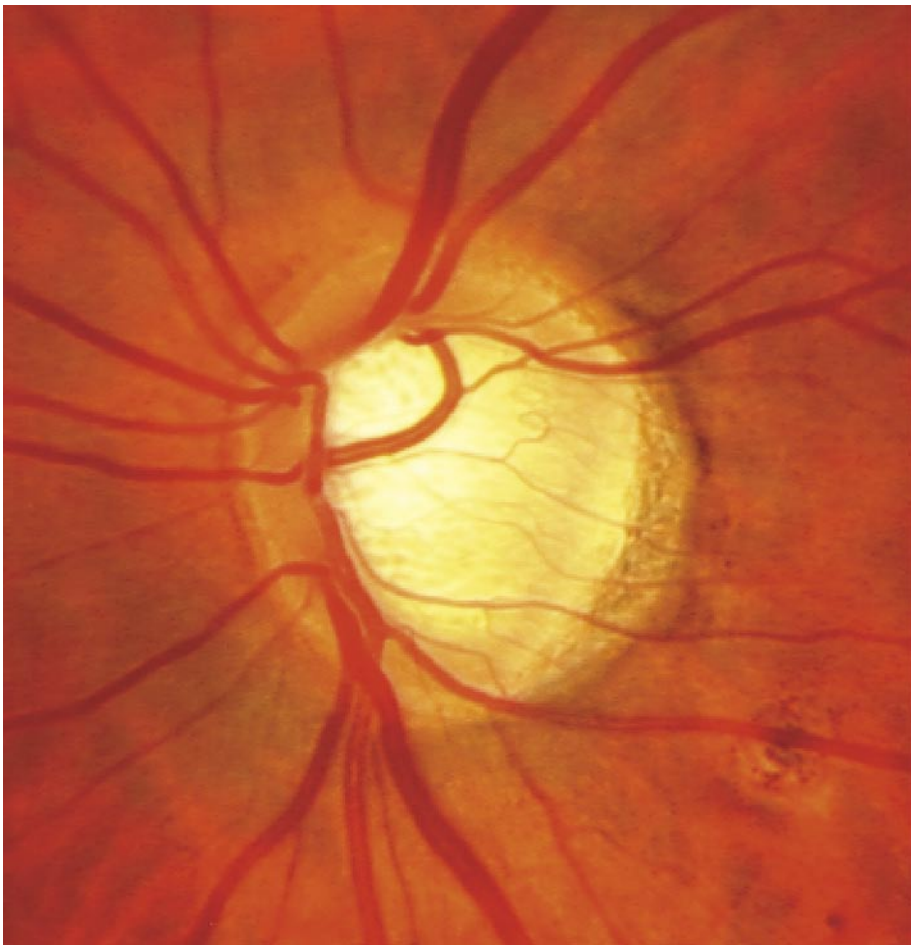

Fig. 2: Optic nerve head of a glaucoma patient with a diminished optic nerve fiber layer.

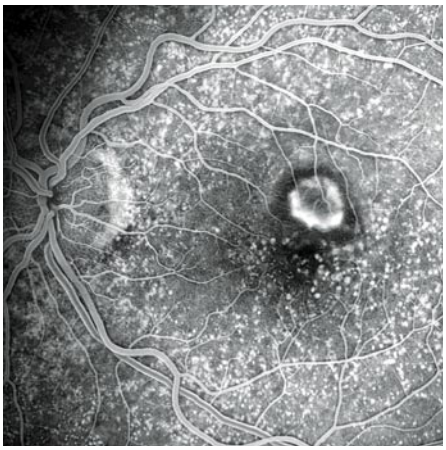

Fig. 3: Subretinal neovascularization in "wet" age-related macular degeneration. Fluid is leaking from newly formed vessels, thus leading to distorted vision and concomitant decline in visual acuity due to retinal edema. Subretinal lipid deposits (drusen) appear as white dots. Fluorscence angiogram.

tors were characterized as wound healing modulators in vitro and are currently being tested in advanced models. Similarily, the role of tissue elasticity emerges as an important determinant of trabecular meshwork cell functions with possible implications in glaucoma.

Teaching

Lectures, practical training and special interest seminars are offered to medical students. The residency program comprises daily morning rounds with case presentations and a weekly CME-certified seminar series that is also open to guest visitors. Another series of four extensive seminars per year is dedicated to update colleagues in private practice on the most recent developments in the field. In addition, the University Eye Hospital hosts regional and international ophthalmology conferences.

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3.20 Department of Neurosurgery and Division of Pediatric Neurosurgery (until October 2007)

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Mission and Structure

The Department of Neurosurgery employs 22 medical doctors, 3 scientists, 96 nurses and 4 technicians. The clinical wards are comprised of a total of 87 beds with single, double and triple patient rooms and an intensive care unit of 20 beds providing treatment for patients with cranial and spinal trauma, vascular malformations and spontaneous hemorrhage, with brain or spinal cord surgery as well as early neurological rehabilitation within a subunit for intermediate care. The operating unit consists of 4 operating theatres and one additional OR for out-patients and emergencies. Over the passed 5 years (2003-2007) 1700 to 2000 patients were treated surgically and 4000 to 4600 patients in the out-patient department. The latter offers consultation for all neurosurgical diagnoses in specialized clinics such as brain tumors, degenerative spine and disc disease, pain syndromes, peripheral nerve lesions, pituitary tumors and dysfunction, neurovascular disease, skull base tumors (jointly with Department of ENT) and movement disorders (jointly with Department of Neurology).

Infants and children with inborn malformations of the nervous system and of the skull and spine as well as children with neoplasia and trauma are taken care of by the Division of Pediatric Neurosurgery.

The whole range of neurosurgery is performed at latest technique and supported by modern technological devices such as neuronavigation, neuro-endoscopy, intraoperative ultrasound and micro-dopplersonography as well as continuous neuro-anesthesiological and neuro-physiological monitoring. Special interdisciplinary treatment protocols have been established for patients with vascular malformations (in close cooperation with the Department of Neuroradiology), furthermore for patients with brain tumours together with radiotherapists and neuro-oncologists as well as for skull base lesions, namely vestibular schwannomas and meningiomas with ENT surgeons. Spine surgery for complexe neoplastic and neurovascular lesions as well as for degenerative disease is performed at high incidence and for certain indications together with colleagues from orthopedic and trauma surgery.

Regular conferences on quality control guarantee an ongoing high standard in routine and in most sophisticated operations.

Major Research Interests

Brain injury: Neurovascular neuro-intensive medicine
(E. Kunze, T. Westermaier)

Main focus of research is on monitoring and maintenance of cerebral oxygenation and brain metabolism in acute brain disease (bleeding/ stroke/ cerebrovascular disease/ traumatic brain injury/ increased intracranial pressure). Besides invasive monitoring, transcranial dopplersonography and perfusion imaging are used for control of vascular dynamics in the clinical setting during surgery and neurosurgical intensive care as well as in the experimental setting using animal models. These approaches are combined with electrophysiological techniques in order to develop novel brain tissue saving therapeutic strategies, especially to counteract vasospasm. Further studies deal with the comparison of interventional and surgical aneurysm treatment and with dural arteriovenous fistulas.

Brain injury: Translational neurotrauma research
(A-L Sirén)

Main focus of research is on the mechanisms of neuroprotection and regeneration after brain injury and translation of this knowledge into new therapeutic approaches for human brain disease using cell culture and animal models of brain trauma. The group could recently report on brain atrophy and late cognitive deficits after experimental neurotrauma that can be prevented by early neuroprotective treatment with the anti-apoptotic and neurotrophic growth factor erythropoietin. Neuroprotective signalling cascades are being explored in cell culture and transgenic animal models. On-going animal work focuses on regeneration using growth factor and cell based therapies for brain injury and on the changes in synaptic structural plasticity and their impact on functional deterioration after brain injury using newly established in vivo 2-photon microscopy-based imaging. A proof-of-concept clinical study is aiming at better prediction of outcome using dynamic mathematical modeling of the complex pathophysiological cascades after traumatic brain injury.

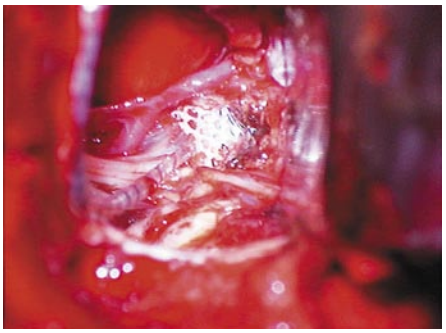

Fig. 1: Electrode array of an auditory brain stem implant placed onto the brainstem.

Functional Neurosurgery: Functional Microsurgery & Neurostimulation
(C. Matthies)

Functional microsurgery is the refined microsurgical technique guided by online information from continuous neurophysiological monitoring. This optimized method of micro-neurosurgery provides a breakthrough for achieving microsurgical cure of pathologies at the skull base, brainstem, medulla and specific functional brain areas along with functional integrity of neural structures. Prospective clinical studies are being run on improving current techniques of monitoring and adapting them to the microsurgical process. Motor evoked potentials of the cranial nerves in comparison to conventional electromyography monitoring and the improved control of the auditory pathway are main topics. Neurostimulation therapy has been established at the clinic and is scienti-

fically investigated for two clinical indications: 1. retrocochlear deafness and 2. movement disorders. 1. For retrocochlear deafness an ongoing cooperation with the Department of Otorhinolaryngology has been extended and, since 2006, has been acknowledged as a centre for "new diagnostic and treatment modalities" (NUB) in the application of auditory brainstem implants. Clinical studies on patient selection, brainstem side and site selection and on sophisticated intraoperative neurostimulation tests are been carried out along with application of latest stimulation strategies with very encouraging results. 2. In 2005, in cooperation with the Departments of Neurology, Neuroradiology and Psychiatry high frequency stimulation therapy has been started for movement disorders (tremor, dystonia and Parkinson' disease) in patients with fluctuating response to medication or medication side effects. Stereotaxy guided electrode implantation in the basal ganglia is performed for intraoperative micro-recording and micro-stimulation tests in the thalamus, pallidum or subthalamic nucleus. The established indications for deep brain stimulation are extended after careful investigation for example for patients with previous ischemic brain lesions and life threatening dystonic storms. A further newly developing topic is the combination of neuroprotective and regenerative factors (See above Siren and development of Schwann cell cultures) and neurostimulation.

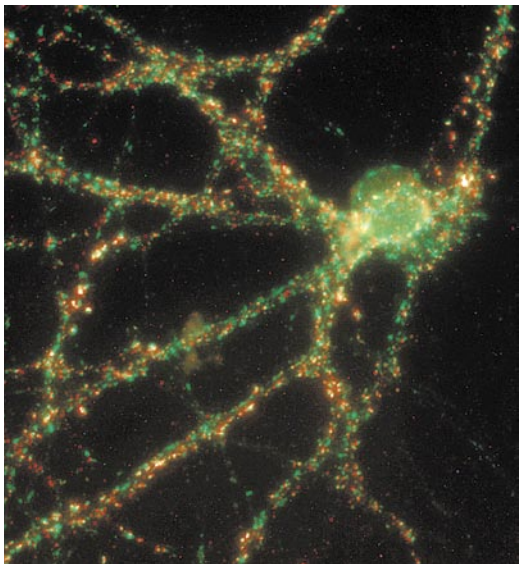

Fig. 2: Excitatory synapses in hippocampus-neuron-cultures (double-immunofluorescence for presynaptic marker synapsin-1 (green) post-synaptic density (red)).

Neuro-oncology
(G. Vince and C. Matthies)

Malignant pathologies
A large patient population is being treated neurosurgically for glioblastomas and low grade astrocytomas by the interdisciplinary team of neuro-oncologists and radiotherapists and followed long-term in longitudinal studies. They provide the base for a unique collection of tumor cell lines. In-vitro tumor cell lines and in-vivo animal models are used for investigation of tumorbiology with regard to tumor invasiveness, progression and aggressiveness. The identification of the importance of metallo-proteinases and their proteolytic activity has significantly influenced the understanding of tumor progression. Different grades of tumors and the edge between benign and malignant tumors are further focus of current interests.

Benign pathologies
For investigation of tumor biology in benign pathologies such as schwannomas and meningiomas, cooperations have been established in national and international settings. Especially, factors such as cell de-differentiation, adhesion molecules, tumor invasion, promotors of apoptosis are targets of investigation and are being compared for different clinical courses despite identical histology. A basis for these laboratory investigations are large regular outpatient clinics for patients with skull base tumors, sporadic and genetically based vestibular schwannomas and meningiomas (neurofibromatosis types 1 and 2).

Craniofacial malformations
(H. Collman, J. Krauß)

A cooperative group from neuropediatrics, neuroradiology, maxillo-facial surgery and of seven further disciplines performs the treatment of children with craniofacial malformations, especially craniosynostosis and cares long-term for over 800 children all over the country. Investigations focus on underlying causes of the disease, refinement of phenotypic classification, molecular genetic diagnostics, secondary diseases and improvement of surgical techniques. Longitudinal studies investigate problems of social integration and psychological stress.

Teaching

Weekly neurosurgical lectures and associated bedside teaching are offered to medical students of all clinical years. Third and fourth years students undergo a joint introduction to neuro-intensive medicine, neurological-neurosurgical history taking and examination in a cooperative teaching programme by the Departments of Neurology and Neurosurgery. Throughout the year medical students of the last clinical year may perform their period of choice or an elective period and are fully integrated into the clinical programme and supervised by neurosurgeons and consultants. At the Section of Experimental Neurosurgery, the Laboratory of Tumorbiology and the Neurophysiology Laboratory students from medicine and related sciences as well as postdoc students are integrated to perform their thesis or diploma within the research programmes.

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3.21 Department of Neurology

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Mission and Structure

The Department of Neurology and its associated hospital department cover the entire spectrum of neurological disorders. The clinical service includes 89 beds with a 6 bed Stroke Unit and a 10 bed specialized Neurological Intensive Care Unit with about 2800 in-patients per year. The outpatient department cares for over 8000 out-patients and 2500 through the consultation service per year. Our specialties encompass neuroimmunological diseases (multiple sclerosis, autoimmune nerve and muscle disorders), degenerative neuromuscular disorders including integrated nerve/muscle pathology, cerebrovascular disorders, movement disorders, epilepsy, neurogenic pain and neurointensive care. The Department has integrated a Division of Clinical Neurophysiology, a Clinical Research Group for Multiple Sclerosis and Neuroimmunology, a Section of Developmental Neurobiology, and numerous experimental and clinical laboratories allowing translational research from molecular basics to the bedside. The Department holds 36 full time academic members, 88 on the nursing staff, 24 technicians and 11 employees in administration and special services. Additional 11 academics are supported by extramural grants. Two endowed professorships for „Neuroimaging“ (Bayer-) Schering AG) and „Multiple Sclerosis, in particular Blood-Brain-Barrier“ (Teva und Sanofi-Aventis) and one lecturership (Merck-Serono) further support the research activities. The Department contributes to the Sonderforschungsbereiche (Program Project Center Grants) 581 und 688. An intensive cooperation is established with the Research Institute for Clinical Neurobiology (Head: Prof. Dr. Michael Sendtner; see separate section) which had been transformed out of the Neurology Department from the previous integrated Clinical Research Group for Motor Neuron Disorders in 2000.

Major Research Interests

Multiple Sclerosis and Neuroimmunology (Clinical Research Group, previously BMBF, now University of Würzburg)
(H. Wiendl, P. Rieckmann, G. Stoll, K.V. Toyka)

Pathogenesis of multiple sclerosis, polyneuritis, myasthenia gravis and myositis in humans and experimental models (experimental autoimmune encephalomyelitis (EAE) und neuritis (EAN), transgenic mouse models); studies on immune regulation, effector mechanisms of immune-mediated tissue damage and new immunotherapies; analysis of endogenous mechanisms of immune tolerance in the periphery and the CNS compartment; role of regulatory and dendritic cells; contribution of cytotoxic T-cells in neuroinflammation and of specific potassium channels in T cell activation and neuronal responses to immune-mediated injury; molecular mechanisms of breakdown of the blood-brain-barrier; development of novel MR-contrast agents for more sensitive detection of demyelinating inflammatory lesions in the CNS.

Stroke and Neuroimaging
(G. Stoll, M.Bendszus, W. Müllges)

Molecular mechanisms of thrombus formation in experimental cerebral ischemia using pharmacological and transgenic mouse models; development of novel and safer treatment options in acute stroke by blockade of platelet receptors GPIb, GPVI and the intrinsic coagulation cascade (Factor XII); functional infarct imaging by 17.6 T-high-field MRI (in cooperation with the Department of Physics V); development of novel MR contrast agents for in-vivo visualization of inflammation and nerve regeneration; participation in clinical stroke trials; studies on the aetiology of neurological complications during heart surgery.

Neuromorphology and Pain Research
(C. Sommer)

Role of pro- and anti-inflammatory cytokines in neuropathic pain; assessment in different lesion models and evaluation of underlying molecular signalling pathways; determination of cytokine profiles in patients with chronic neuropathic pain; establishment of new diagnostic procedures for small-fiber-neuropathies.

Experimental Developmental Neurobiology
(R. Martini)

Investigation of pathomechanisms underlying genetically-mediated demyelination in the central and peripheral nervous system using mouse mutants with spontaneous and genetically engineered defects of myelin and other nerve components as disease models. Morphological methods, such as confocal- and electronmicroscopy, combined with the assessment of molecular alterations are used for the analysis of neuronal and glial damage. Particular emphasis is on the role of disease-modifying mechanisms, like the

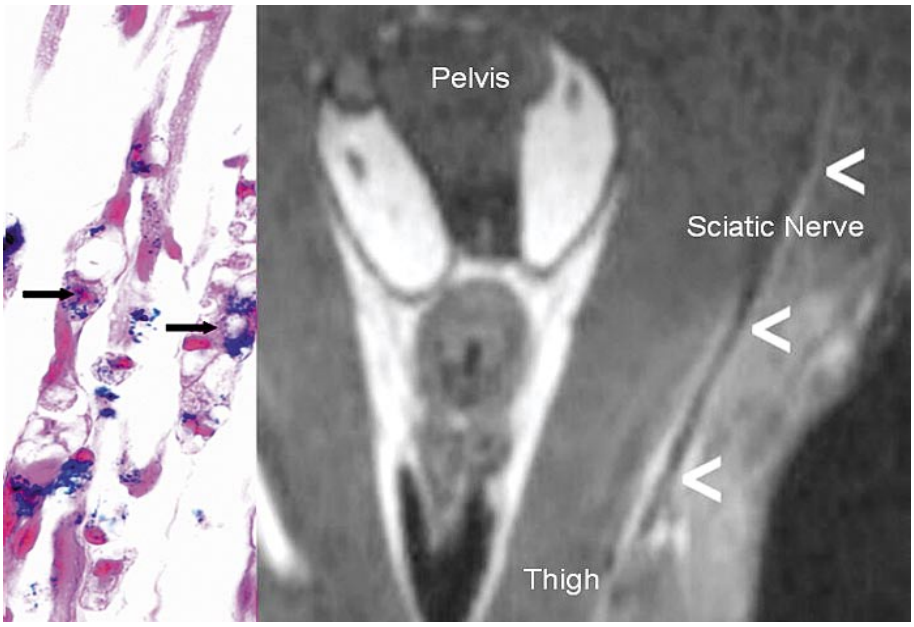

Fig. 1: In-vivo imaging of macrophage infiltration by magnetic resonance imaging (MRI). After systemic application iron particle-containing MR contrast agents are phagocytosed in the circulation by macrophages. Upon migration into injured nerve tissue, the iron-laden macrophages can be identified microscopically as blue cells (arrows; on left). Iron leads to a signal loss on T2-weighted MRI. Infiltration of iron-laden macrophages can thus be visualized in-vivo along the course of the injured sciatic nerve as dark structure marked by white arrowheads (experimental nerve trauma model on right). This MR-technique is suitable for assessment of acute macrophage infiltration into tissues in general (Source: Bendszus & Stoll (2003) J Neurosci).

impact of the immune system and emerging treatment strategies in the mouse models.

Motor Control and Movement Disorders
(J. Classen)

Human cortical physiology; development and evaluation of human models of cortical plasticity; functional significance of neuronal plasticity in inflammatory, ischemic and degenerative brain diseases; pathophysiology and treatment of disorders of motor control; deep brain stimulation in cooperation with the adjacent Department of Neurosurgery.

Clinical Neurophysiology and Neuromuscular Center (NMC)
(K. Reiners, K.V. Toyka)

Neurophysiological investigations in patients with neuromuscular problems and CNS disorders (> 25,000 investigations per year); Co-Chairman of the Interdisciplinary Neuromuscular Center together with Prof. Dr. T. Grimm, Department of Human Genetics; morphological assessment of nerve and muscle disorders by magnetic resonance imaging and correlation with neurophysiological parameters; validity of serial assessments of evoked potentials in the evaluation of multiple sclerosis and ALS.

Autoantibodies in Neuroimmunological Disorders
(K. Toyka, C. Sommer)

Studies on the functional role of humoral serum factors in immune-mediated neuropathies and on the pathophysiology of the anti-amphiphysin- and anti-GAD-associated stiff-person-syndrome; establishment of in-vivo models and cell culture systems; assessment by in-vivo- and in-vitro-electrophysiology (Patch-Clamp, reflex studies), STED-microscopy (in cooperation Institute for Clinical Neurobiology). The pathogenic role of thymus abnormalities in myasthenia gravis (in cooperation with the Institute of Pathology).

Motor Neuron Diseases
(K. Toyka, M. Beck)

Development of neurophysiological parameters for monitoring disease progression and treatment effects in amyotrophic lateral sclerosis (ALS). In 1996 an ALS data base has been established for collection of clinical data and samples; support of basic molecular and genetic investigations on disease modifying factors in sporadic and familial ALS (in cooperation with the Institute for Clinical Neurobiology).

Laboratory Medicine
(K. Toyka, A. Weishaupt)

Laboratory support of all groups and projects in neuromorphology, neurogenetics and neuroimmunology. Research focus: The role of autoreactive antibodies in the diagnosis and prognostic assessment of neurological diseases (anti-MAG-, anti-GM1, anti-aquaporin-4 antibodies, anti-acetylcholine-receptor-antibodies).

Teaching

In the lectures, seminars and mandatory courses of general neurology the basics in clinical neurology are taught accompanied by bed-side teaching in small groups of students. The Department of Neurology moreover provides special seminars in differential diagnosis of neurological disorders, neuromuscular diseases and nerve/muscle pathology and participates in numerous interdisciplinary seminars (Anatomy, Physiology, Tumour Center, Pain-Curriculum, Psychology, Neurobiology, and all classes of the International Graduate School of Life Sciences). Teaching languages are German and English.

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Mission and Structure

The Institute for Clinical Neurobiology emerged in 2000 from a clinical research group of the Deutsche Forschungsgemeinschaft ("clinical research group for Neuroregeneration"), which had been established and funded from 1994-2000 at the Department of Neurology at the University of Würzburg. It exists as an independent institute at the University Hospital since 2000 and is since then supported with substantial funding by the Herrmann und Lilly Schilling-Stiftung. The Institute for clinical neurobiology is mostly working in basic science, but it is also involved in sustaining the special health care centre for motoneuron diseases at the Department of Neurology (Director: Prof. K.V. Toyka), in order to allow and ensure the transfer of scientific knowledge into clinical applications. In the years 2005 and 2006, the spectrum of methods and scientific focuses has been expanded due to the appointment of Prof. Heckmann and Prof. Sigrist as heads of independent research groups at the Institute.

Major Research Interests

The research group headed by M. Sendtner at the Institute of Clinical Neurobiology focuses on mechanisms of neuronal cell death, the establishment and analysis of animal models for motoneuron diseases, as well as the development of therapeutic strategies for the treatment of amyotrophic lateral sclerosis and spinal muscular atrophy, the most common forms of motoneuron disease in children and adults.

One focus is the investigation of the signal transduction pathways by which neurotrophic factors influence survival and axonal growth of motoneurons. The generation and analysis of gene knockout mice allows investigating which signal molecules are involved in mediating such essential cellular effects of neurotrophic factors.

Another research focus is the analysis of the pathophysiology of spinal muscular atrophy, the most common form of motoneuron disease in children. It has been shown that this disease is not primarily caused by defects in mechanisms for motoneuron survival, but by defects in axon growth and maintenance. This disturbance is due to a disruption in β-actin mRNA transport, resulting in a depletion of actin filaments in the growth cones and presynaptic regions of neuromuscular endplates. This finding in isolated motoneurons and in animal models for spinal muscular atrophy correlates with clinical observations in patients with spinal muscular atrophy. On the basis of these experiments, new therapeutic strategies for this disease can now be developed.

The Institute for Clinical Neurobiology is also involved in the patient care of the special care centre for motoneuron diseases (Dept. of Neurology, Director Prof. K. V. Toyka), in order to ensure the transfer of basic science into clinical applications. The research results of the Institute for Clinical Neurobiology have been published in the last years in important international journals (Nature Medicine, Nature Neuroscience, Nature Genetics, Journal of Cell Biology, PNAS, and others).

Due to the appointment of Prof. Heckmann in 2005 as an independent group leader, the spectrum of methods and themes at the Institute has been expanded. This group focuses on the mechanisms of synaptic communication, the main focus next to postsynaptic receptor channels being the presynaptic exocytosis and endocytosis and the differentiation and maturation of synaptic contacts. This research group has left the Institute due to the appointment of Prof. Heckmann at the University of Leipzig, and it is planned to re-establish this group as soon as possible in 2008 by appointing a successor for Prof. Heckmann, in order to preserve this technical and thematic focus at the Institute.

The group headed by Prof. Stefan Sigrist is co-funded by the Bio-Imaging Centre of the University of Würzburg and the Institute for Clinical Neurobiology. This research group focuses on molecular, cell biological and pathophysiological mechanisms that mediate the development and activity-mediated plasticity of neuromuscular synapses at motor endplates. This research group follows a "vertical research approach", using a broad variety of molecular biology and biochemistry methods as well as electrophysiological, ultrastructural and state-of-the-art optical technology (confocal microscopy, 2-photone microscopy).

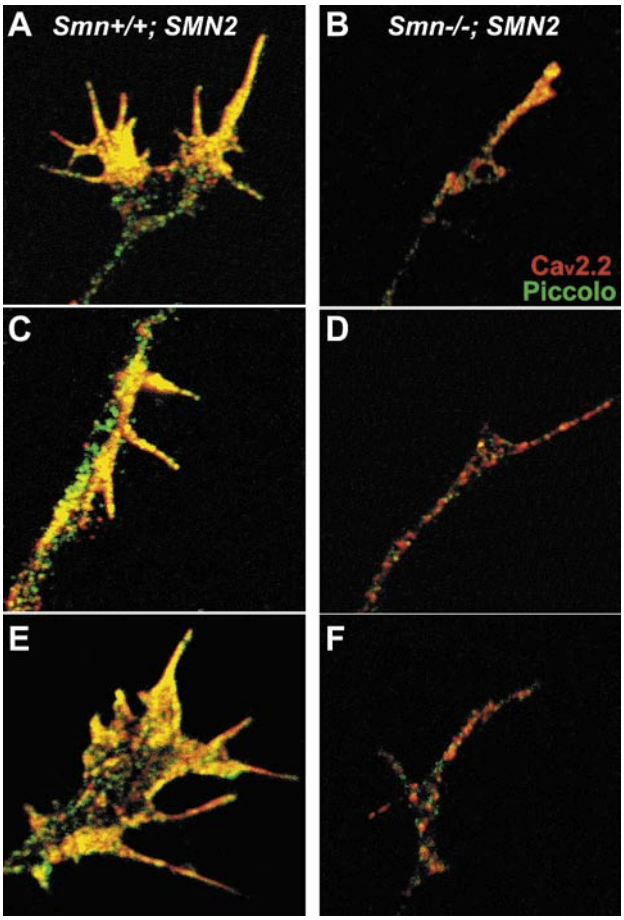

Fig. 1: Disruption of the presynaptic differentiation of the active zone of motoneurons from a mouse model of spinal muscle atrophy (B,D,F). While control motoneurons (A,C,E) form clusters of Ca2+-channels (red) with other components of the active zone (piccolo, green), this process is distorted in motoneurons from a mouse model for spinal muscular atrophy. This results in functional distortions of the signal transduction at neuromuscular synapses.

Teaching

The Institute for Clinical Neurobiology is involved in the training of students in neurology as well as the training of biology students (Diplomstudiengang, from 2008/9 Master students) with focus on neurobiology. Another focus is the training of students in the MD/PhD program. Further courses are offered for students of the course molecular medicine within the training program for MD students.

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Wiese, S., Jablonka, S., Holtmann, B., Orel, N., Rajagopal, R., Chao, M.V., Sendtner, M. (2007) Adenosine receptor A2A-R contributes to motoneuron survival by transactivating the tyrosine kinase receptor TrkB. PNAS 104, 17210-17215.

3. 23 Department of Psychiatry, Psychosomatics and Psychotherapy with Division of Forensic Psychiatry

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Mission and Structure

The clinic of Psychiatry, Psychosomatics and Psychotherapy (PPP) at the UKWürzburg (UKW) offers out-patient, day-care and in-patient diagnostic and therapeutic services for all mental (psychiatric and psychosomatic) disorders. The therapeutic focus of the clinic is on affective disorders and psychoses of the schizophrenia spectrum, but also on dementias and substance abuse disorders, as well as eating disorders, anxiety disorders and adult attention-deficit-hyperactivity disorder. Specialized out-patient services as part of the policlinic and the outpatient program as well as 16 day-care therapy slots complement the 144 in-patient therapy slots with two intensive care units and two units spezialized on substance abuse therapy and psychotherapy respectively. Specialized diagnostic and therapeutic options are provided by the laboratory on therapeutic drug monitoring and the laboratory on psychophysiology. The integrated department of forensic psychiatry provides expert opinions on legal aspects of mental disorders.

Major Research Interests

The research activities of the clinic are characterized by their interdisciplinarity with research groups of psychiatrists, psychologists, chemists and biologists as well as close cooperations at the level of the UKW in the context of the KFO 125, the SFB 581, the GKs 1156 and 1253 and the IZSF, at the national level in the context of cooperations with institutes of the Max-Planck Society and the Helmholtz Society and participation in BMBF programs for Brain Research, Depression, Panic Disorder and ADHD, and at the international level in the context of cooperations with the NIH and EMBL and participation in DAAD programs and EU programs for Brain Research and Depression, but also in the context of projects funded by foreign sponsors such as the NIH, the BBSRC and the Ludwig-Boltzmann-Foundation. Methodological approaches on the basis of differentiated clinical and neuropsychological diagnostic procedures cover a broad range from psychopysiological and modern imaging approaches such as near infrared spectroscopy and functional magnet resononance tomography (in cooperation with the Department of Neuroradiology and the research center Magnet-Resonanz-Bayern e.V. as well as the Institute of Psychology I) over modern methods of genomics and proteomics such as Highthroughput-Genotyping (Core Facility in cooperation with the Institute of Clinical Biochemistry and the IZKF, BrainNet-Reference Center in cooperation with the Department of Neuropathology) and their combination in the context of imaging genomics up to cell culture and animal models in particular knockout and transgenic mouse models (in cooperation with the Institute of Clinical Neurobiology, the ZEMM and the Biocenter). For clinical studies according to GCP-guidelines a specialiced clinical studies group was set up (J. Deckert, A. Fallgatter), which cooperates closely with the ZKS. Studies on suicide (A. Schmidtke) have already resulted in defined proposals for suicide prevention. The research environment established by Prof. Beckmann between 1985 and 2006 therefore is preserved and extended with its characteristic close interaction between translational research laboratories of the PPP such as the laboratories on Molecular Psychiatry (J Deckert, A. Reif), Clinical and Molecular Psychobiologie (K.-P. Lesch), Clinical Neurochemistry (P. Riederer), Morphological Brain Research (H. Heinsen) and Psychophysiology and Functional Imaging (A. Fallgatter, M.J. Herrmann) with the clinical research groups of the clinic on one hand and core facilities of the UKW and external research facilities on the other hand. Research topics include clinical neuroscience aspects such as the therapy of mental disorders, translational aspects such as the pathogenesis of mental disorders including the functional characterization of the identified pathomechanisms by means of modern imaging techniques and animal models as well as basic neuroscience aspects such as emotional and cognitive processes, gene-environment-interactions, neuronal plasticity and adult neurogenesis from adult stem cells.

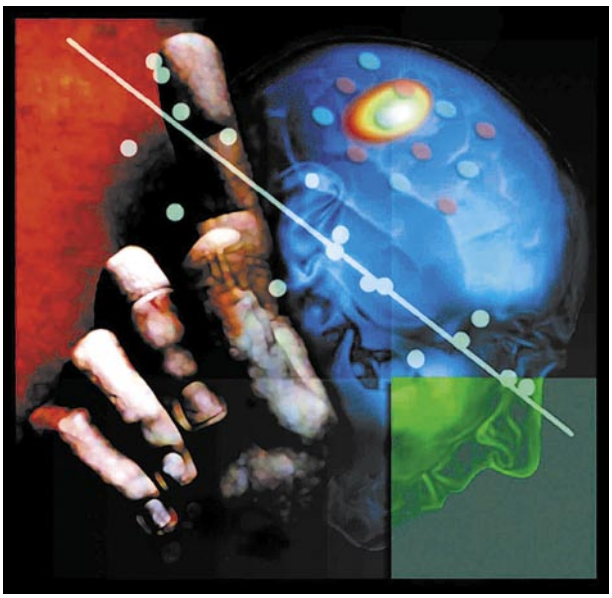

Fig.1: Cover Image of Human Brain Mapping 28/2007 (Plichta, M.M., Herrmann, M.J., Baehne, C.G., Ehlis, A.-C., Richter, M.M., Pauli, P., Fallgatter, A.J. Event-related functional near infrared spectroscopy (fNIRS) based on craniocerebral correlations: Reproducibility of activation? Human Brain Mapping 28: 733-741, 2007).

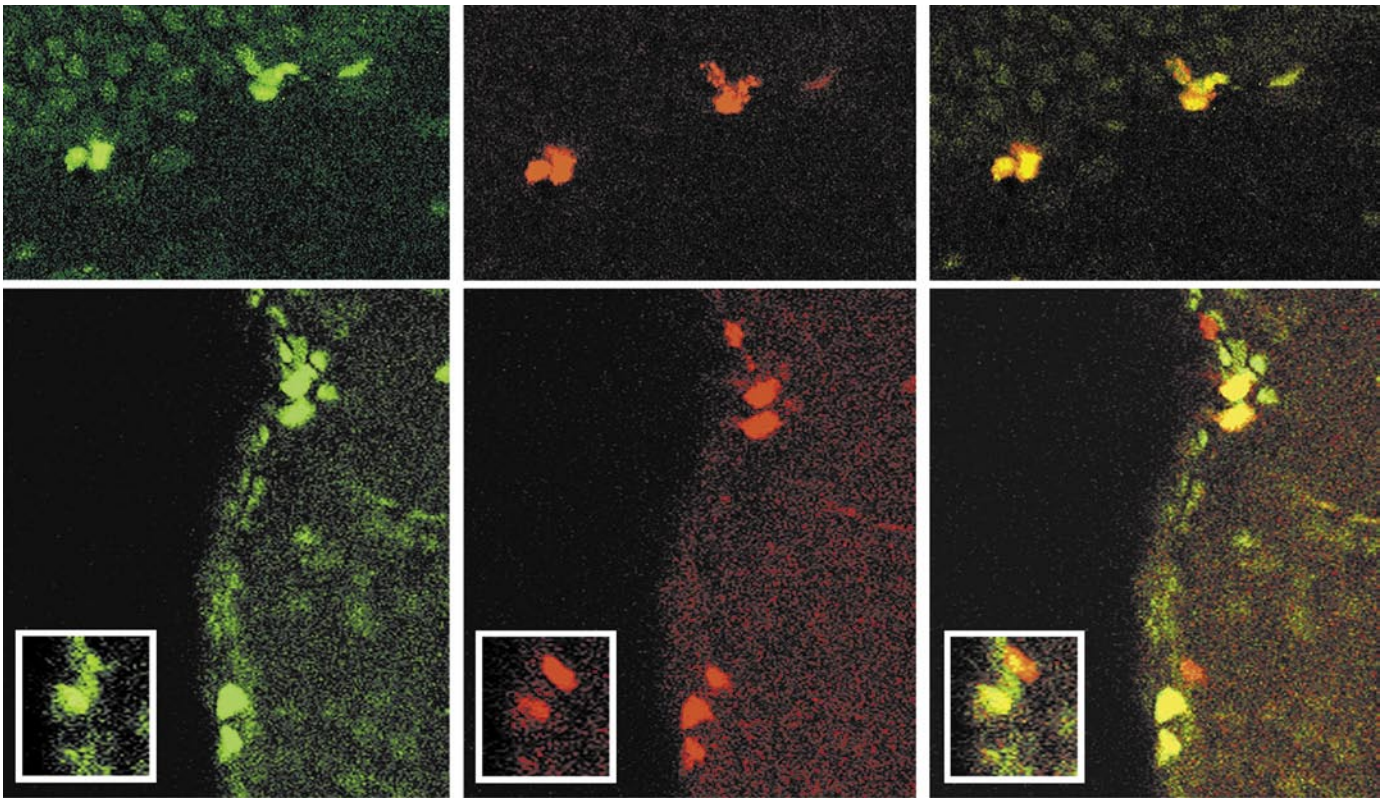

Fig. 2: Cover Image of Molecular Psychiatry 11/2006 (Reif A, Fritzen S, Finger M, Strobel A, Lauer M, Schmitt A, Lesch KP. Neural stem cell proliferation is decreased in schizophrenia, but not in depression. Mol Psychiatry 11:514-22, 2006).

The main research topics thus are:

- Markers for early diagnosis and innovative therapeutic approaches in affectiven disorders, psychoses of the schizophrenia spectrum, dementias, substance abuse disorders, anxiety disorders and adult ADHD (J. Deckert, A. Fallgatter, K.-P. Lesch, P. Riederer, A. Schmidtke, G. Stöber, B. Jabs, B. Pfuhlmann, C. Jacob, M. Lauer, A. Reif).
- Identification of morphological and neurochemical pathological processes in psychoses of the schizophrenia spectrum and neurodegenerative disorders (P. Riederer, H. Heinsen, E. Grünblatt, M. Lauer).
- Identification of genetic factors in affectiver disorders, psychoses of the schizophrenia spectrum, anxiety disorders and ADHD (J. Deckert, K.-P. Lesch, G. Stöber, A. Reif).
- Imaging of emotional and cognitive processes in adults, adolescents and children (A. Fallgatter, M. Herrmann).
- Gene-environment-interactions, neuronale plasticity and adult neurogenesis in man and in the animal model (K.-P. Lesch, J. Deckert, A. Reif, A. Schmitt).

Teaching

An integrated lecture and course on psychiatry and psychosomatics are organized and held by the PPP in cooperation with the KJPPP and other clinics and institutes. Special curricular seminars are provided for interns and students interested in special aspects of psychiatry and psychosomatics. In addition to the curricular lecture and course for medical students the PPP also provides curricular lectures and courses for students of experimental medicine, psychology and biology. Extracurricular seminars are offered to graduate students of medicine, experimental medicine, biology, psychology.

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Domschke K, Braun M, Ohrmann P, Suslow T, Kugel H, Bauer J, Hohoff C, Kersting A, Engelien A, Arolt V, Heindel W, Deckert J. (2006) Association of the functional -1019C/G 5-HT1A polymorphism with prefrontal cortex and amygdala activation measured with 3 T fMRI in panic disorder. Int J Neuropsychopharmacol. 9:349-55.

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Schmitt A, Benninghoff J, Moessner R, Rizzi M, Paizanis E, Doenitz C, Gross S, Hermann M, Gritti A, Lanfumey L, Fritzen S, Reif A, Hamon M, Murphy DL, Vescovi A, Lesch KP. (2007) Adult neurogenesis in serotonin transporter deficient mice. J Neural Transm. 114:1107-19

Grünblatt E, Löffler C, Zehetmayer S, Jungwirth S, Tragl KH, Riederer P, Fischer P. (2007) Association study of the 5-HTTLPR polymorphism and depression in 75-Year-Old nondemented subjects from the Vienna Transdanube Aging (VITA) study. J Clin Psychiatry 67:1373-8.

3.24 Department for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy

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Mission and Structure

The clinic for child and adolescent psychiatry, psychosomatics and psychotherapy is providing state-of-the-art patient care for children and adolescents aged up to 18 years offering assessment and treatment for all psychiatric and psychosomatic disorders. The clinic includes inpatient units (the locked ward is under the sponsorship of the "Bezirk Unterfranken"), a day clinic and a special school (sponsorship: "Diakonisches Werk"), a parent's pavilion (sponsorship: "Verein Menschenskinder"), a clinical research group (sponsored by the German Research Association, DFG), a neurobiological laboratory. The clinical laboratory for therapeutic drug monitoring and a lecture hall are joint facilities of this department and the department for adult psychiatry. Therapeutic units (occupational therapy, exercise therapy, music therapy, orthopedagogy including animal assisted therapy) are connected with our three inpatient units. The staffs comprise 18 physicians, 10 psychologists (including 4 psychologists attending postgraduate in-service training on psychotherapy), 22 members of the medical and technical service, 5 special therapists, 8 members of the administrative department and 50 members of the nursing and educational service. Rates of utilisation of the 38-bed inpatient unit and the 12-bed day clinic are 100 percent. Main focus of patient care – supported by special outpatient services – are the assessment and treatment of eating disorders, affective disorders (depression), anxiety disorders, psychosis, attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder, Tourette syndrome, conduct disorder, autism and specific developmental disorders, and of co-existing psychiatric disorders in non-psychiatric diseases and mental retardation.

Major Research Interests

Attention deficit-/ hyperactivity disorder (ADHD)
(M. Gerlach, T. Jans, T. Renner, M. Romanos, C. Schwenck, S. Walitza, A. Warnke)

ADHD is the most prevalent psychiatric disorder in childhood and adolescence. Pathogenesis and the impact of endophenotypes and co-morbid features are investigated using formal and molecular genetics, neuropsychological and neurophysiologic methods as well as animal models and gene expression studies. These studies are conducted in close cooperation with the Department for Adult Psychiatry and other clinics and departments of the University of Wuerzburg (Clinic for Nuclear Medicine, Department of Psychology I, Department of Radiodiagnostics). Multicentre clinical studies are carried out on the efficacy and safety of extended release methylphenidate in ADHD children and adolescents. In cooperation with the Department of Toxicology (Prof. Dr. H. Stopper) the occurrence of possible adverse reactions (e.g. chromosome aberrations) is investigated during pharmacological treatment. Within the framework of the BMBF-network on psychotherapy research in ADHD (see page 168) the efficacy of a parent training for the treatment of ADHD in children is investigated depending on the treatment of their mothers also affected by ADHD.

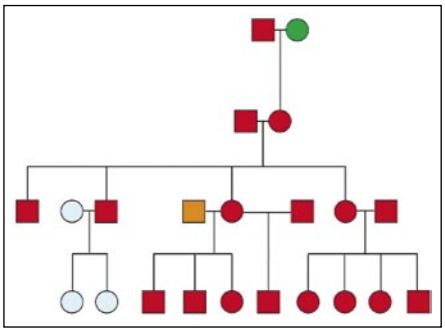

Fig. 1: Formal genetics of ADHD. Genealogical tree. Family members affected by attention deficit / hyperactivity disorder ADHD are red-coloured.

These projects are sponsored by Grants from the DFG ("Klinische Forschergruppe KFO 125", see page 161), the Federal Ministry of Education and Research BMBF (see page 168), the Interdisciplinary Centre for Clinical Trials IZKF of Wuerzburg University, the state of Bavaria, and several pharmaceutical companies.

Biomarkers
(M. Gerlach, R. Hümner-Kopf, M. Romanos, T. Renner, S. Walitza)
A biomarker (biological marker) is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenetic processes or pharmacological responses to a therapeutic intervention.The development of biomarkers is especially promising because a substantial improvement of the reliability in the diagnostic of psychiatric disorders could be achieved by this approach. Different paradigms (real-time PCR, proteomics, olfactory test) are evaluated hoping to achieve a substantial contribution to an early and reliable diagnosis of ADHD, autism and schizophrenia.

These stdies are conducted in close cooperation with other universities (Prof. Dr. Mehler-Wex, Ulm; Prof. Dr. H. Reichman, Dresden; Prof. Dr. J. Thome, Swansea, UK).

Developmental psychopharmacology
(M. Gerlach, K. Klampfl)

Off-label use, the lack of randomized controlled trials, pharmacokinetic and pharmacodynamic differences from adults and increased vulnerability towards unwanted side effects are challenging conditions of the psychopharmacotherapy in children and adolescents. Several factors of development, gender, age and individual predispositions have to be considered regarding the choice of medication and dosage finding. Since serum levels in adults suggest more intimate correlations especially with side effects, but potentially also with drug efficacy than applied dosages, therapeutic drug monitoring (TDM) is a promising tool for the improvement of dosing and drug safety also in minors. To improve the security of the patients and to establish quality standards the clinic is part of the national multicentre competence network on TDM.

Eating disorders (BMBF-project within the network „Treatment of anorexia nervosa in children and adolescents – day clinic vs. inpatient treatment")
(K. Klampfl, J. Romanos, A. Warnke)

50 percent of juvenile anorexia nervosa patients are readmitted to inpatient treatment within the first year after discharge. The study compares a day clinic and an inpatient treatment to investigate if patients partly remaining in their family have a more favourable outcome. The multicentre study is conducted at three sites (Universities of Aachen, Cologne, Wuerzburg).

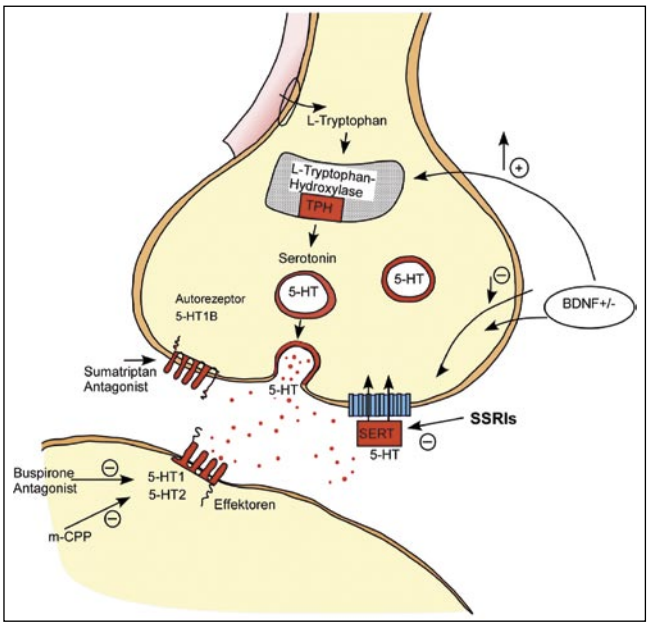

Fig. 2: Tryptophane-hydroxylase 2 is the most important enzyme in the synthesis of serotonin in the brain; gene variants are associated with ADHD.

Dyslexia – a multi-centre trial „Neurophysiological, psychometric and genetic studies on dyslexia"
(A. Warnke, Prof. Schulte-Körne, Munic, Prof. Remschmidt, Marburg)

Dyslexia as a specific developmental disorder of scholastic skills is based on specific characteristics in structural and functional brain development with a high hereditability (about 80 percent). Research on aetiology focuses on correlates of the disorder on the genetic level and on the behavioural level (reading, spelling) accounting for associations with psychological (e.g. acoustic discrimination) and neurophysiologic (e.g. EEG characteristics) endophenotypes. The DCDC2-gene which is important for the foetal brain development was identified to be associated with dyslexia. There is a correlation of the severity of dyslectic impairment and the genetic influence. Samples are recruited in Wuerzburg and Marburg. National and international cooperation have been established (Prof Dr. T. Grimm, Department of Human Genetics Wuerzburg,; Prof. Dr. P. Propping, Institute of Human Genetics Bonn; Prof. Dr. M. Nöthen, Prof. Dr. J. Schumacher, Genomics, Life & Brain Center Bonn; Department of Biosciences Karolinska Institute Stockholm; Department of Medical Genetics Helsinki; Prof.Dr Müller- Myhsok, Max- Planck-Institute of Psychiatry, Munic; Prof.Dr. Ziegler Institute of Medical Biometrics and Statistics University Lübeck).

Obsessive-compulsive disorder „A prospective study on the course of obsessive-compulsive disorder with onset in childhood and adolescence "
(M. Gerlach, U. Hemminger, T. Renner, S. Walitza, A. Warnke)

Despite recent advances there is a lack of empirical knowledge on the aetiology and course of obsessive-compulsive disorder (OCD) with onset in childhood or adolescence. In cooperation with other university clinics for Child and Adolescent Psychiatry (Prof. Dr. B. Herpertz-Dahlmann, Aachen; Prof. Dr. E. Schulz, Freiburg; Prof. Dr. Ch. Wewetzer, Köln, Prof. Dr. J. Hebebrand, Essen) and the Department for Medical Biometry and Epidemiology Marburg (Prof. Dr. H. Schäfer) and the Institute for Pharmacology of the University of Köln (Prof. Dr. E. Schömig) family studies are conducted on OCD (coordinator: PD Dr. S. Walitza). Patients and their parents are assessed by standardized diagnostic methods to allow for molecular genetic association studies. The results point to associations of gene variants in the serotonergic and dopaminergic neurotransmission. The present study is also the first prospective follow-up study of early onset OCD in a German-speaking country. Preliminary results considered the question of differences in the symptomatology, severity and course of disease of early onset OCD in dependence of comorbid disorders especially ADHD comorbidity. In our sample the persistence of symptoms is higher in the group of "OCD with ADHD" than in the group "OCD without ADHD". The studies are sponsored by the DFG.

Teaching

The obligatory lectures for students of human medicine comprising the subject matter on psychosomatics are conjointly hold by the clinic for adult psychiatry (APP), the clinic for child and adolescent psychiatry (CAPP), the clinic for neurology and other medical clinics as well as by the department for medical psychology. Obligatory lectures and examinations also refer to study courses on psychology, education and special education (diplomas, state examinations). Furthermore, lessons and trainings refer e.g. to forensic child and adolescent psychiatry, developmental psychiatry and psychodiagnostics, neurophysiological assessment, epilepsy, postgraduate and research colloquia, open lectures on clinical issues („KJPP- Nachmittage") and colloquia on neuropsychiatry conducted together with the Departments of Adult Psychiatry and the Department of Neurology. The quality of our lecture on child and adolescent psychiatry has been awarded ("Lehrpreis" of the faculty of medicine). To support university lectures and curricula a fund financed by tuition fees provides pay for a psychologist (APP) and two lecturing tutors (CAPP). In addition to scientific congresses (e.g. in 2007 the „1st International Congress on ADHD"- over 1300 participants - , and a „patient's day" - 300 attending ADHD patients and their relatives) there are annual symposia („Arzt-Lehrer-Tagung"; „Tagung Kinder-Jugendpsychiatrie und Jugendhilfe").

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Lazar A, Walitza S, Jetter A, Gerlach M, Warnke A, Herpertz-Dahlmann, Gründemann D, Grimberg G, Schulz E, Remschmidt H, Wewetzer Ch, Schömig E (2008) Novel mutations of the extraneuronal monoamine transporter gene in children and adolescents with obsessive-compulsive disorder. Int J Neuropsychopharmacol. 11:35-48.

Walitza S, Werner B, Romanos M, Warnke A, Gerlach M, Stopper H (2007) Does methylphenidate cause a cytogenetic effect in children with attention deficit hyperactivity disorder. Environ Health Perspect 115: 936-940.

4 Dental Hospital

4.1 Introduction

Five departments are integrated in the university hospital for dentistry and oral and maxillofacial surgery:

- Department of Conservative Dentistry and Periodontology
  (Head: Professor Dr. Bernd Klaiber)
- Department of Oral and Maxillofacial Surgery
  (Head: Professor Dr. Dr. Alexander Kübler)
- Department of Prosthodontics
  (Head: Professor Dr. Ernst-Jürgen Richter)
- Department of Orthodontics
  (Head: Professor Dr. Angelika Stellzig-Eisenhauer)
- Department for Functional Materials in Medicine and Dentistry
  (Head: NN)

These principals constitute the board of directors and they elect a chairman which is Professor Dr. B. Klaiber currently.

The chairman of the School of Dental Medicine is elected by the Heads of the five departments, currently Professor Dr. B. Klaiber.
The university hospital for dentistry and oral and maxillofacial surgery educates approximately 600 students, half of them in the clinical part of their studies.

For education, research and patient care 225 working places are available.

Actually, because of third-party-funds and half-time jobs 300 attendants are employed, 70 of them as scientists.

Beside education and research continuing education for dentists as well as advanced education for medical and dental specialists are major tasks.

In 2006 about 28.000 patients were treated ambulatory, 1.200 stationary.

Professor Dr. med. dent. B. Klaiber
(acting Chairman)

4.2 Department of Orthodontics

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Mission and Structure

Under the direction of Prof. Dr. Stellzig-Eisenhauer nine assistant doctors are engaged in patient care, research and teaching of students.

Health care at the Department of Orthodontics comprises all types of malocclusions, ranging from simple to extremely complex conditions. During childhood and adolescence prophylaxis of malocclusions, therapy of skeletal jaw disharmonies by using and directing bodyown growth, as well as correction of misaligned teeth are important issues. A special focus of the Department of Orthodontics is the comprehensive treatment of adult patients using specific fixed techniques with regard to the individual periodontal and prosthetic situation. Health care at the Department of Orthodontics is also characterized by interdisciplinary cooperation with the other dental disciplines.

In particular, there are very close working relationships with:
Department of Oral and Maxillofacial Surgery:

- patient with cleft lip and palate
- patients with craniofacial dysplasia
- patients with severe jaw disharmonies
- patients with mandibular condyle fractures
- patients with ectopic teeth (Fig. 1)

Department of Prosthodontics:

- pre-prosthetic uprighting or intrusion of incisors and molars
- pre-prosthetic arrangement of abutment teeth
- pre-prosthetic root extrusion

Department of Conservative Dentistry and Periodontology:

- correction of tooth alignment in patients with periodontal disease
- therapy of patients with tooth-size discrepancies

Each year approx. 1.500 patients of all ages are treated in the Department of Orthodontics with appointments every 3 to 6 weeks. About 600 patients are calling on the Department for Orthodontic consultation.

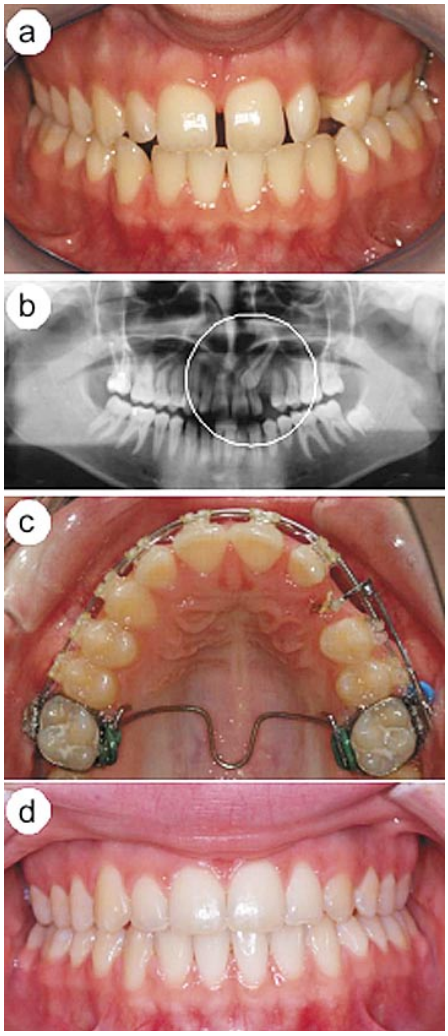

Fig. 1: A) Before orthodontic treatment. B) Dislocation of the left upper canine tooth. C) Orthodontic mobilisation of the canine tooth after maxillofacial exposure. D) After orthodontic treatment.

Major Research Interests

Establishment of 3D soft tissue analysis in orthodontics (Cooperation with the Institute of Optics, University Erlangen-Nürnberg; A. Stellzig-Eisenhauer, J. Kochel)

In orthodontics diagnostics of the soft tissues of the face are still based on the analysis of photographs. Actual methods of 3D analysis are not exact because landmarks are used to determine the facial symmetry plane. These landmarks are often located in asymmetric areas of the face or they only have low reliability. Thus, we have used a landmark-independent method for determining the facial symmetry plane, which was developed by the Institute of Optics, University Erlangen-Nürnberg. 3D data acquisition is done by using the FaceScan3D optical 3D sensor. The objective of this research project is gaining 3D mean values in a comprehensive collective. So far, 100 adult Caucasians have been analysed.

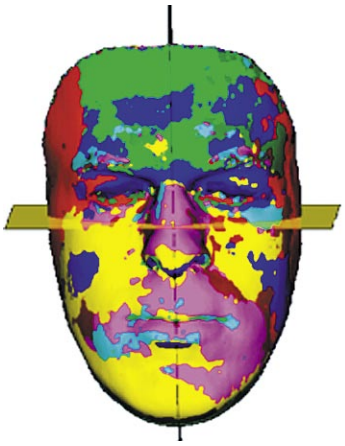

Fig. 2: Stereophotogrammetry with the optical sensor FaceScan3D (3DShape, Erlangen) to generate three-dimensional data of the facial soft parts.

3D analyses of facial asymmetries before and after orthognathic surgery.
(P. Meyer-Marcotty, A. Stellzig-Eisenhauer)

In severe skeletal jaw asymmetries combination of orthodontic and surgical treatment is required. Especially, the consideration of proportions, symmetry and harmony of the soft tissues of the face is essential for surgery planning and evaluation of the treatment results. The objective of this research project is the integration of a 3D soft tissue analysis into pre- and post-surgical diagnostics.

Eye-tracking studies on visual cognition of adult patients with unilateral cleft lip and palate.
(P. Meyer-Marcotty, A. Stellzig-Eisenhauer)

The purpose of this investigation is to answer the question whether visual cognition of adults with unilateral cleft lip and palate is different from that of a control group.

Clinical and molecular genetic investigation of patients with primary failure of eruption of permanent teeth
(Cooperation with the Institutes of Human Genetics, Universities of Würzburg and Regensburg; C. Rau, A. Stellzig-Eisenhauer)

Failure of eruption of permanent teeth without an obvious cause is rare. The correction of affected teeth by orthodontic means is limited. The underlying genetic factors of failure of eruption are not identified yet. The objective of the present investigation is the identification of genetic factors that contribute to failure of eruption of permanent teeth.

Pre-speech development and developmental disorders in patients with cleft lip and palate
(K Wermke, A Stellzig-Eisenhauer)

In the Centre for Pre-Speech Development and Developmental Disorders in patients with cleft lip and palate and craniofacial anomalies early diagnosis and characterisation of pre-speech developmental processes are investigated.

Development and testing of non-invasive orthodontic appliances for the therapy of obstructive apnoea in newborns with Pierre Robin sequenze.
(ooperation with the University Children's Hospital, University of Würzburg. Stellzig-Eisenhauer, J Kochel)

Teaching

There are orthodontic lectures and clinical courses to impart knowledge about the kind, the extent and the etiology of malalignment of teeth and jaw disharmonies. Moreover, the options of prophylaxis and treatment are to be pointed out to the students.

In the lecture "Introduction of Orthodontics" a review of the different kinds and the etiology of malocclusions is given.

The emphasis of the main lecture "Orthodontics I and II" is placed on the preparation of the students for the treatment of patients.

"Orthodontic techniques" is a course in which the students are to learn about the different kinds, the indications, the effects and the manufacturing of orthodontic appliances.

In the courses "Orthodontic treatment I and II" the knowledge of theory is promoted in small study groups and in additional seminars. In addition, diagnostic materials of patients are obtained and appliances for treatment are adapted to different patients and controlled clinically.

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4.3 Department of Functional Materials in Medicine and Dentistry

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Mission and Structure

Biologists, chemists, physicists and material scientists in cooperation with clinicians are engaged in the Department for Functional Materials in Medicine and Dentistry in tailoring functional materials for the use in medical products and application in the human body. Research is focused on analyzing the requirements for product placement depending on the location in the body. Material properties are adjusted by modification of the bulk and surface of materials to affect the interface to the biological environment. The workings were funded in the past years by the "Deutsche Forschungsgemeinschaft" with two projects within the priority program "Interface between Material and Biosystem" which was coordinated by the Department as well as in several projects as individual grants.

Major Research Interests

The main research and development focus of the Department is in the area of metallic and ceramic functional materials with applications as medical products in contact with both the oral cavity, hard and soft tissue as well as the heart / circulatory system. The aim of research is to elucidate the mechanisms of interactions between materials´ surfaces and the biological environment to redress the chain of causation between the physical properties of the solid state body and molecular biological reactions of the biosystem.

Interface Material – Biosystem

The biocompatibility of a material is determined by the surface in contact with the biological environment which is influenced by the composition, electrical end electronical properties and topography of the materials surface. Currently, the influence of nanostructured surfaces on the reaction of cells, bacteria and proteins is investigated. While structures with a correlation length in the range of 200 nm - 1 μm above all have direct influence on the cells and the biological system, nanostructures of magnitude 1 - 20 nm affect the adsorption of biomacromolecules. Changes of the potential distributions in the body electrolytes in the immediate vicinity of peaks and edges of the surface structure lead to a modified protein adsorption on the material and thus have an indirect effect on the biological system.

Research priorities of the department are in the area of metallic materials, ranging from the development of industry-processes for the production of nanostructured materials up to theoretical prediction of the expected properties. A method was developed using decomposition processes in tempered medical stainless steel to produce nano-structures (Figure 1). For a better understanding of the effects of nanomaterials on protein adsorption a software package was developed, which combines molecular dynamics calculations with the finite element method and allows a prediction of preferred adsorption sites of globular proteins on an arbitrary definable nanostructure. In the first step the prevailing electrostatic and dispersion potential distributions are calculated, followed by the simulation of the resulting protein adsorption process in the force field. The results are compared with experimental data obtained from measurements of the protein adsorption with quartz crystal microgravimetry (QCM).

Ceramic biomaterials for tissue regeneration and drug delivery

Main focus are self setting ceramic pastes derived from calcium orthophosphates for bone replacement in low load-bearing areas of the skeletal system. Research activities concern the reactivity of cement raw materials, the rheological properties of the pastes for a minimal invasive application as well as the mechanical performance of the set cement matrix. Low viscosity cement pastes are obtained by an

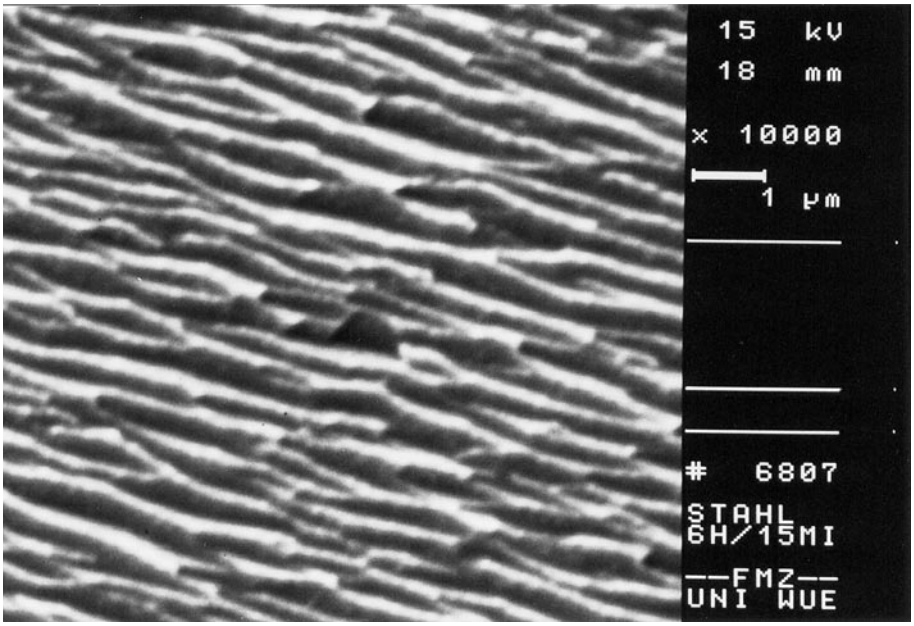

Fig. 1: Nanostructures on stainless steel surface.

electrostatic charging of the cement particles due to the adsorption of biocompatible multiple charged anions (citrates), whereas the lower water demand of these formulations results in the formation of high strength materials at room temperature with the possibility of an additional organic modification. Current developments are focused on a combination of reactive cements with 3D powder printing as generative rapid prototyping technology which enables the fabrication of patient individual degradable implants for bone replacement as well as scaffolds for tissue engineering (Figure 2). The materials are also of interest for the delivery of drugs (e.g. antibiotics or growth factors) to the hard tissue application site since they provide a controlled release of pharmaceutical active doses without systemic side effects.

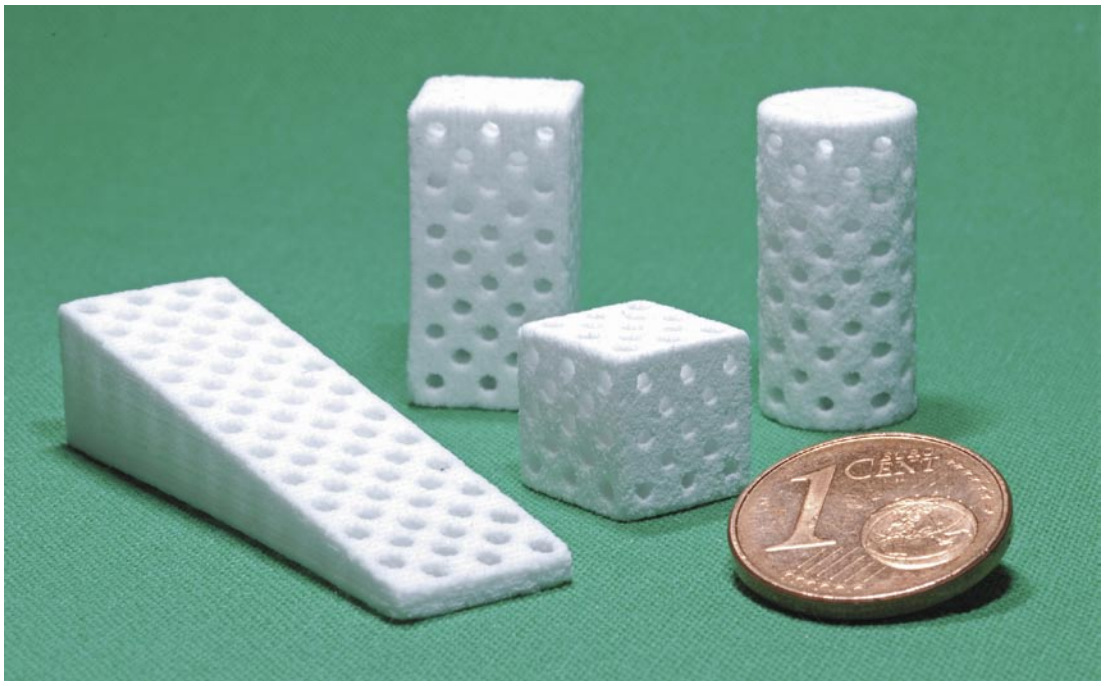

Fig. 2: Porous calcium phosphate structures prepared by 3D powder printing.

Biological properties of materials

A prerequisite for the proper integration of implant materials is an optimal contact between biosystem and implant. To improve the understanding of mechanisms occurring during tissue integration cells of different origin (e.g. fibroblasts, osteoblasts) were cultured on these surfaces. Analysed surface parameters of the materials include composition, electronic properties as well as nanostructured surfaces. Cell reaction is analysed by testing cell attachment, vitality, and proliferation rate. Tissue specific protein expression and distribution in the cell is also analysed.

Serious problems during implant integration are still caused by infections due to noscomial pathogens. Implant surfaces therefore should be designed antimicrobial. This can be achieved by integration of bacteriostatic metal ions like Ag^+ into the surface layer. Silver containing titanium surfaces developed in the department showed a clear reduction of bacterial growth. Eukaryotic culture cells were not affected by this surface modification.

Teaching

Teaching activity comprises lectures about materials designated for use in the human body and mechanisms of their interaction with the surrounding biosystem; lectures concerning quality management system and risk analysis of medical products, the application of X-rays on the human body as well as practical measurements for materials analysis. The lectures are designed for dental students, graduate students of Biomedicine and, together with the faculty of Physics and Astronomy for students of “Nanostrukturtechnik”.

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4.4 Department of Oral and Maxillofacial Plastic Surgery

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Mission and Structure

The clinic has got 20 permanent posts and a further half post which is funded externally. The clinic owns 40 permanent beds and covers the whole spectrum of oral and maxillofacial surgery. Beside the in-patient care (about 1.200 patients each year), approximately 15.000 patients are treated in the outpatient department. Further more the clinic provides a comprehensive consultant support, particularly for the paediatric clinic (craniofacial dysplasia and clefts) and within the interdisciplinary emergency treatment and intensive care of traumatised patients. Together with the adjacent specialities, especially orthodontics, neurosurgery, paediatrics and ENT, the interdisciplinary treatment of patients with complex malformations and trauma is ensured.

Within the in-patient treatment as well as the consultation hours for outpatients, we treat patients with:

- neoplasia of head and neck (therapy and functional and aesthetical reconstruction including microsurgical tissue transfer)
- trauma of jaws and viscerocranium
- craniofacial dysplasia (dysgnathic anomalies, clefts of lip, jaw and palate, craniosynostosis)
- demand on plastic-aesthetic reconstruction
- dental implants including bone augmentation methods
- dentoalveolar disorders (e.g. cysts, abscesses, osteomyelitis)
- disorders of salivary glands
- TMJ disorders
- nerv lesions in the facial area

Major Research Interests

Clinical research team for neoplasia of head and neck
(T. Reuther, U. Müller-Richter, I. Reuther, A. Kübler)

- clinical study concerning neo-adjuvant vs. adjuvant therapy of oral and oropharyngeal cancer
- in vitro study of oral mucosa exposed to carcinogens
- satisfaction survey of patients with transplants from the arm and shoulder region
- follow-up of donor-site morbidity of microvascular forearm flaps and scapular flaps
- follow-up of patients suffering from osteoradionecrosis

Differential diagnosis of oral mucosa lesions
(U. Müller-Richter, T. Reuther)

The investigations aim to establish new markers which improve the estimation of the prognosis of different oral mucosa lesions. That shall enable the assessment of the dignity and help to establish screening methods.

Research team for antigens of oral squamous cell carcinoma
(U. Müller-Richter, A. Kübler)

Focus of the research is the characterisation of the cancer/testis antigen subgroup MAGE-A in oral squamous cell carcinoma. Distinct antigens are investigated concerning their clinical relevance for prognosis and therapy.

Clinical research team for imaging methods
(U. Müller-Richter, M. Kochel, H. Grimaldi)

Different imaging methods (e.g. based on ionised radiation, ultrasound, magnetic resonance) are evaluated for their applicability in well-defined interrogations. A further topic is the fusing facility of the various methods.

Clinical research team for bisphosphonate-associated necrosis of the jaw
(A. Kübler, T. Reuther, H. Grimaldi, M. Kochel)

In collaboration with the pathologic institute the histological characterization of the affected bone as well as clinical prospective and retrospective studies concerning risk factors and concomitant diseases are conducted.

Research team for tissue regeneration of oral mucosa
(T. Reuther, U. Kriegebaum, C. Klingelhöffer, A. Kübler)

The main focus is the evaluation of various dermal equivalents, i.e. biopolymer matrices with cultivated fibroblasts on their surface. The aim is the tissue engineering of oral mucosa. The comparison of typical cocultures (dermal equivalents plus keratinocytes) with dermal equivalents alone tends to reveal insights about dermal-epithelial interaction. A further topic is the investigation of the vascularisation capability using this model. The mechanical forces affecting a transplant in the oral cavity are emulated and analyzed (mechanotransduction).

Research team for bone regeneration and bone substitution
(U. Klammert, T. Reuther, C. Jahn, A. Kübler, U. Kriegebaum)

In collaboration with the Department for Functional Materials in Medicine and Dentistry, novel bone replacement materials with calcium phosphate chemistry fabricated by the rapid prototyping technique of 3D powder printing, are investigated in vitro and in vivo. Further more, bone growth factors (BMPs) developed by the department of physiological chemistry II are used for osteoinduction at the implantation site. Another topic is the improvement of the integration of autologous bone grafts by different modifications at the recipient site. Of particular interest is the volume maintenance of the transplant. New methods of cryoconservation of autologous bone grafts are utilized in the clinical routine.

Teaching

The clinic ensures theoretical and practical educational engagements within both the medicine and the dentistry course.
For medical students the clinic provides opportunities within multidisciplinary lessons and clinical traineeships. In the context of interdisciplinary oncological lectures typical tumorous lesions of the oral cavity, jaw and face are presented, including treatment strategies and reconstructive options.

Within dentistry the fields of oral structure biology, oral pathology, oral and maxillofacial surgery as well as dental radiology are taught. That includes the local dental anaesthetic techniques. These various fields are communicated theoretical as well as in practical courses and clinical traineeships. Further more the clinic is involved in the advanced education for already approbated colleagues due to the organisation of certified meetings and courses, e.g. the Würzburger Herbst-Symposium für Zahnmedizin.

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4.5 Department of Prosthodontics

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Mission and Structure

The Department of Prosthodontics with its 37 employees is one of five Departments at the dental school of Würzburg University. Its fields consist of education of both pre-med and med dentistry students and all aspects of prosthetic and restaurative dentistry for ambulant patients, which comprise traditional treatment such as fixed and removable partial dentures to contemporary concepts using metal-free and implant-supported perioprosthethics, orofacial prosthetics, adhaesive restorations and therapy of patients with myofacial pain and TMJ-disorders.

Major Research Interests

Clinical and in-vitro studies on dental implantology are prominent subjects in the field of research with focus on improvement of implant design, e.g. special cortical threads in the neck-area of the implant and their consequences on bone-regeneration and -durability. An additional area of research is the debit of in line standing connected and unconnected implants. Furthermore, so called “index implants” and temporary implants are under development. Over the course of the past ten years strategic implants in combination with removable dentures as well as angulated implants have stood in the light of clinical interest.

Experimental studies and finite-element simulations have led to the development of the “Wuerzburg Post”, which is now available for clinical use and is being evaluated in a long term clinical study. It resets on a revolutionary approach – “inverse conicity” and an annular grove – in which the causes of hardly unavoidable longterm failures (e.g. decementation of the restoration or radicular fracture) associated with conventional post and core systems are eleminated.

The construction is designed to permit a wide-based support of the restoration on the coronal root surface while requiring only a small depth for anchorage, which is achieved by means of positve locking by a specially designed, spreadable post. The apical and middle part of the root are no longer subject to weakening, fracture of the root or decementation of the post are no longer possible. Mascatory forces are transmitted into the dentin through an annular groove and a corresponding ferrule. The Wuerzburg Post is available in two versions for FPDs or RPDs.

The clinical experience with over 95 inserted posts reflects excellent results as the survival rate is in excess of 97% within a maximum period of observation of 24 months.

An interfaculty task force (Department of Experimental Physics V) supported by the industry (Prokuro GmbH, DeguDent-Dentsply) is engaged with the forward looking technology of digital scanning of teeth as well as the production of dentures/dental restorations by avoiding the flaw-associated interaction between inpression taking and tranditional dental techniques. The digital procedures used so far are based on the optical scanning of teeth which were prepared by the dentist for in- and onlays, whereat the perpa-

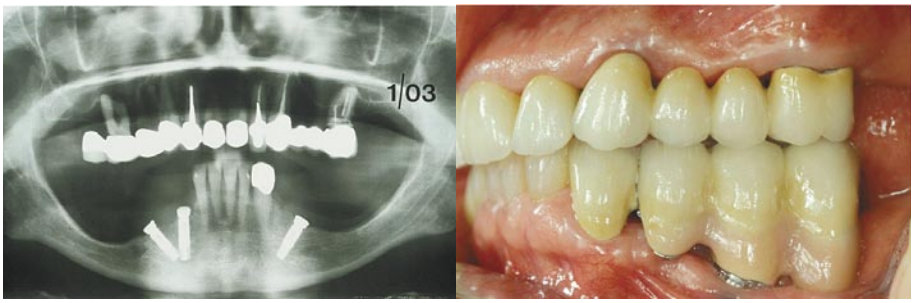

Fig. 1: (a, left) X-Ray of two angulated implants which were inserted under athrophic bone levels without augmentation. (b, right) Fixed partial denture supported by one tooth and an angular implant.

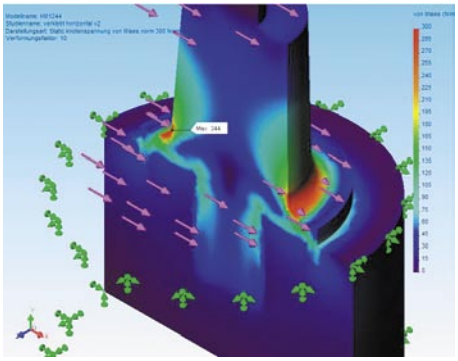

Fig. 2: (a, left) Speadable bur for the undercut cavity. (b, right) FE-Simulation, horizontal angle of attack.

ration margins lie above the gingiva in the enamel. Typically, these prodedures are limited to one tooth. The dental MRT is an alternative to conventional digital methods as it is suitable for all aspects of restorative dentistry under given circumstances, and exhibits considerable potential for the diagnostic of caries aswell as all other aspects of general dental diagnostics.

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4.6 Department of Conservative Dentistry and Periodontology

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Mission and Structure

The Department of Operative Dentistry and Periodontology (16 dentists – 4 of them in the section of periodontology-, 12,5 dental assistants -2.5 of them in the section of periodontology-, 2 dental technicians) is endued with 10 dental chairs - 3 of them in the section of periodontology-, 2 working centres for the dental technicians and facilities for taking radiographs. For the practical part of the students´ education 24 dental chairs are available, 40 workings centres for laboratory dentistry as well as 40 working centres providing phantom-puppets.

The area of responsibility of the Department of Operative Dentistry and Periodontology contains prevention, diagnostics and therapy of diseases to enamel and dentine (caries, abrasion, erosion and trauma) as well as to the pulp (pulpitis, trauma) and to the periodontal ligament (periodontitis) and their sequelae. Each year approximately 4.000 patients are treated ambulatory. In co-operation with the Department of Paediatrics, the Department of Anaesthesiology and the Department for Oral and Maxillofacial Surgery patients can be treated in general anaesthesia.

In patient-care special emphasis is based on minimal-invasive preparation and its adequate supply with adhesive techniques: Due to the micro-mechanical anchorage of the restoring materials to the conditioned enamel and dentine, the preparation of macro-mechanical cavities - with further loss of healthy tooth-substance - can be set aside. Further emphasis is based on the Aesthetic Dentistry: adjustments of contour-, colour- and position-anomalies with non-invasive or minimal-invasive techniques are made possible through the use of adhesive materials and modern resin-based composites. In the majority of cases there is no more need to prepare the teeth for veneers or crowns. The conservation of healthy tooth substance and the renunciation of lab-made restorations are obvious advantages in respect of biologic and financial interests (Fig.1).

Major Research Interests

Research at the Department of Operative Dentistry and Periodontology is focused on the evaluation of restorative materials, appliances and devices required for

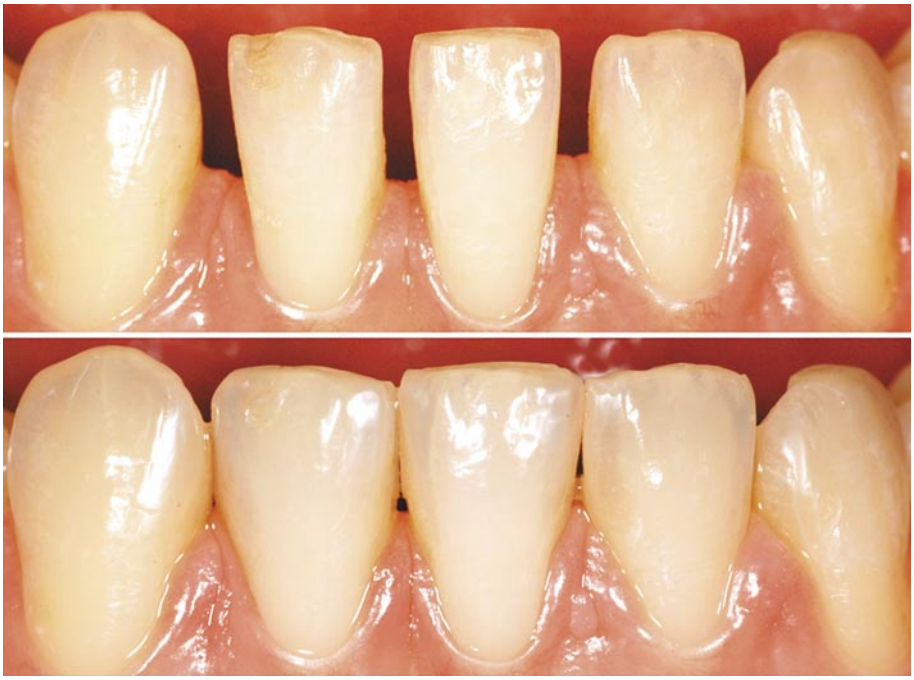

Fig. 1: Uniform interproximal spaces following traumatic loss of one lower incisor and subsequent orthodontic treatment (above). By non-invasive procedures the spaces could be closed and a natural appearance has been restored (below).

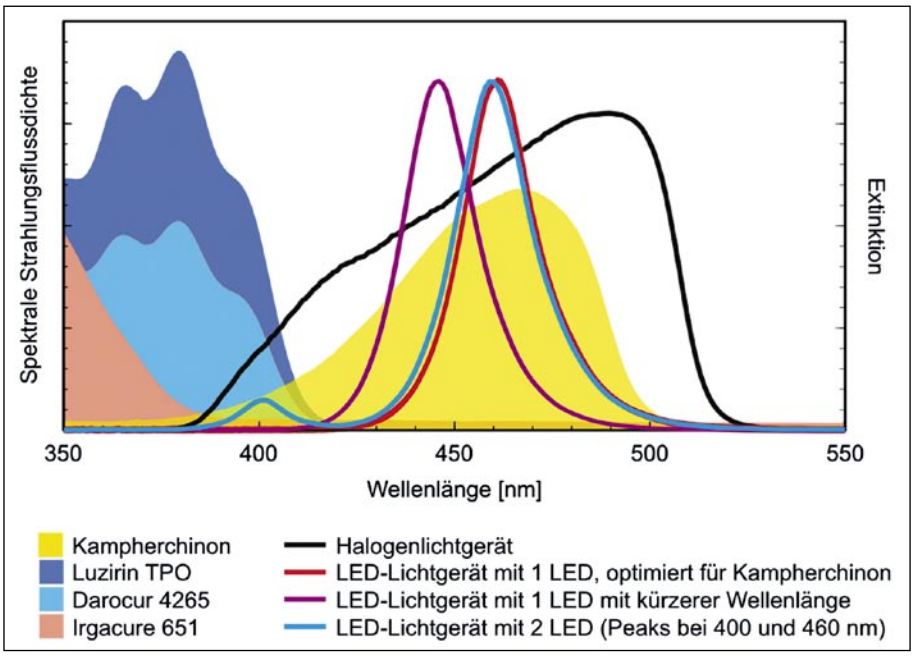

Fig. 2: Spectral absorbance of photo-initiators compared to the spectral irradiance of different light curing units.

conservative restorative therapy. In this context, the interactions between restorative materials and dental hard tissues and among different restorative materials are studied.

A universal testing machine allows the determination of mechanical properties (compressive strength, flexural strength, tensile bond strength, shear bond strength, extrusion shear bond strength). Deformation of teeth under load and during photo-activated polymerization of resin-based composite restorations can be studied using displacement transducers. Additional experimental setups allow the evaluation of the kinetics and the total amount of polymerization shrinkage of restorative resin-based composites, as well as the spectral irradiance of dental light curing units (Fig. 2).

The marginal seal of restorations is evaluated using dye penetration techniques and computer-based image analysis. The margin fidelity of restorations in vivo and in vitro is monitored morphologically by the replica technique and a scanning electron microscope, which is used together with other departments of the dental school.

An atomic force microscope is used in cooperation with the Department and Chair of Functional Materials in Medicine and Dentistry for studying the interface between dental hard tissues and restorative materials.

The purpose of the current clinical studies is to compare newly developed restorative materials and appliances with those considered to be the gold standard in the past. In some cases, undergraduate students can be involved in these studies. This lets them come to know the different tasks of a university hospital.

Currently, a newly developed restorative material is evaluated for margin fidelity in posterior cavities after four years of clinical service. Moreover, a newly developed rubber dam system (appliance for moisture control during operative procedures) will be compared to the conventional one. Until now, almost 300 patients have been included in the study.

In collaboration with the Department of Neurology, interdisciplinary research projects addressing oro-facial pain are being developed.

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4.6.1. Division of Periodontology

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Mission and Structure

Besides Prof. Schlagenhauf the staff of the department comprises further four dentists and 3 dental assistents. The Dept of Periodontology is a clinical center for referrals of patients suffering from severe periodontal disease beyond the normal scope of a practicing dentist. Especially the therapy of refractory aggressive periodontitis and gingivoperiodontal manifestations of systemic diseases is at the focus of the special competence provided by the department to referring dentists and the public. In collaboration with the Institute of Microbiology and Hygiene of the University of Wuerzburg antiinfectious strategies for the therapy of aggressive periodontitis and perimplantitis have been devised. Furthermore a therapy concept for the treatment of oral manifestations of juvenile hypophosphatasia has been developed in close contact with the Pediatric Clinic of the University of Wuerzburg. Also guided tissue regeneration of periodontal lesion using tissue-inductive enamel matrix proteins belongs to the clinical standard procedures provided by the department.

Major Research Interests

The main research projects of the Dept. of Periodontology are listed below. Some of them are joint efforts in collaboration with other institutes and clinics in Würzburg and other national or international institutions.

Microbial Recolonization and Inflammation in Aggressive Periodontitis in the Wake of Therapeutic Interventions (supported by the IZKF Wuerzburg)
(U. Schlagenhauf, U. Vogel)

In patients suffering from aggressive periodontitis the influence of adjunctive systemic antibiotic therapy on the pattern of microbial recolonization as well as on the intensity of clinical signs of inflammation following periodontal therapy was evaluated longitudinally over the course of 12 months. It was observed, that the resolution of clinically visible signs of inflammation is accompanied by a significant shift of microbial colonization patterns.

Clinical and microbiological aspects of periodontal disease in patients suffering from juvenile hypophosphatasia
(U. Schlagenhauf, H. Girschick, U. Vogel)

Premature loss of deciduous teeth is a typical early symptom of hereditary juvenile hypophosphatasia. The underlying mechanisms however are only poorly understood. The purpose of the project is to clarify whether tooth loss primarily is due to an inflammatory process driven by pathogenic microbial biofilms or due to a inherited malformation of dental cementum. First results revealed that the oral microflora of hypophosphatasia patients is not si-

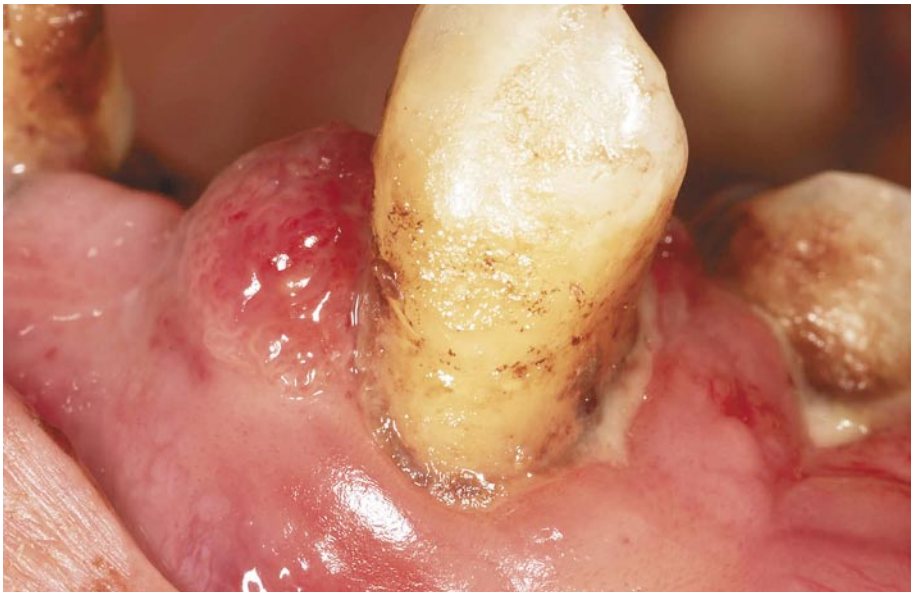

Fig. 1: Advanced chronic periodontitis in a patient suffering from angiomatosis Rendu-Osler.

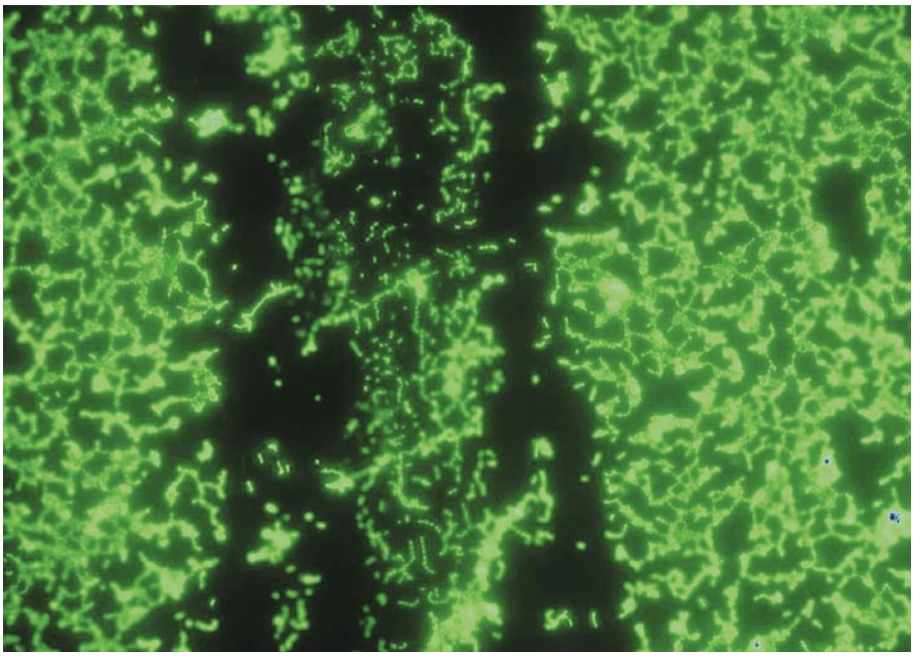

Fig. 2: Streptococcus sanguinis biofilm (fluorescence staining).

gnificantly different from healthy age-matched controls.

Long-term success of adjunctive antibiotic therapy in the treatment of aggressive periodontitis
(U. Schlagenhauf)

Periodontal lesions deeper than 8 mm are generally regarded as irrational to treat and normally lead to the extraction of the affected tooth. In clinical cases however adjunctive antibiotic therapy combined with meticolous mechanical biofilm removal resulted in a very pronounced healing even in deep defects so far regarded as untreatable. Aim of the investigations is to evaluate in a population of more than 100 patients suffering from aggressive periodontitis the effects of a adjunctive antibiotic intervention on the long-term healing success over a time period of 3-5 years.

Inhibition of bacterial biofilm formation by chemical and physical methods
(U. Schlagenhauf, A. Ewald)

Bacterial biofilms exhibit a far more sustained resistance towards antimicrobial host defense mechanisms than their planctonically growing counterparts. The efficient removal of proinflammatory microbial biofilms from the tooth surfaces and the inhibition of bacterial recolonization is at the center of of the prevention of periodontal diseases. Besides established mechanical measures which are not sufficiently efficacious in narrow inaccessible niches, bacterial biofilms may be influenced by chemotherapeutics or the physical or chemical modification of the surfaces to be colonized. In in vivo and in vitro biofilm models the biofilm inhibiting properties of diverse chemotherapeutics are evaluated as well as the inhibiting effect of some physical and electrochemical procedures.

Teaching

Dental undergraduate training comprises all aspects of periodontology. After teaching the theoretical base facts of periodontology firstly in dummy heads and subsequently in patients nonsurgical minimally invasive periodontal therapy procedures are instructed and supervised. Surgical therapy measures are practically instructed and trained in pig jaws. Postgraduate training in periodontology following the guidelines of the German Society of Periodontology is available to junior staff members of the department.

SELECTED PUBLICATIONS

Valenza, G., Burgemeister, S., Girschick, H., Schoen, C., Veihelmann, S., Moter, A., Haban, V., Vogel, U. & Schlagenhauf, U. (2006). Analysis of the periodontal microbiota in childhood-type hypophosphatasia. Int J Med Microbiol, 296, 493-500.

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5 Additional Scientific Units

In this chapter information on scientific institutions, cooperations and centers will be given which are initiated or partly organized by the Medical Faculty. The chapter comprises information on six Collaborative Research Centers (Sonderforschungsbereiche), two Transregios, five Graduate Colleges, and other joint activities which are performed together with institutions of other faculties, especially of the Biological Faculty.

Furthermore, the MD/Ph.D. program, the International Graduate School and Research Centers, Research Units and Research Alliances are described which are dealing with particular scientific problems.

5.1 Collaborative Research Centers
5.1.1 Collaborative Research Center 479, Variability of Pathogens and Host Reactions in Infectious Diseases

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General Information

After a successful review in 2006, the SFB 479 is now in its fourth and last funding period (2007-2009). This has allowed the continuous development of the unifying research topic, i.e. the interaction of infectious pathogens with host cells, but also with the intact host-organism, over the full 12 years which are the maximum life span of an SFB. The SFB 479 is composed of research groups of the medical and biological faculties. The contributing institutions are the Institute for Virology and Immunobiology, for Hygiene and Medical Microbiology, for Molecular Biology of Infectious Diseases, and for Basic Microbiology (in the faculty of Biology), the Junior Research Groups of the Centre for Research on Infectious Diseases, and the Medical Clinic and Policlinic II. By including the Medical Clinic, the SFB has realised the long-envisaged goal of building a bridge from basic to clinical research. Altogether, fourteen individual projects are funded, six of which were newly included in the current funding period.

Major Research Interests

The researchers of the SFB 479 are interested in the adaptation of pathogens to their hosts both during evolution and in the course of an infection, in the interaction of microorganisms with their target cells, and in the interplay between the host's immune system and the invaders. The research program has been structured into corresponding project areas, even though during the life of the SFB, these have, in part, been filled with new research topics:

Project area A:
Variability of Pathogens

Here, evolution and adaptation, but also regulation of pathogenicity factors in microbial pathogens are studied. Besides the bacterial systems that had been established in the SFB for some time (*E. coli*: A1 Hacker/Dobrindt; *Bordetellae*: A2 Gross; *Streptococci*: A7 Hammerschmidt; *Meningococci*: A10 Vogel), we have now included the fungus *Candida albicans* (A9 Morschhäuser), which is an important opportunistic pathogen in immune compromised patients.

Project area B:
Pathomechanisms in the interaction between microbe and host cells

How does a pathogen prepare for the invasion of a host cell, and how does the cell respond to the infection? Such questions are in the focus of project area B. While with the retirement of Werner Goebel (Microbiology), the intracellular pathogen *Listeria monocytogenes* was lost for the final funding period from the program of the SFB, we could complement the Meningococcal (B2 Frosch/Kurzai) and foamy-viral systems (B7 Rethwilm) with the parasite *Plasmodium falciparum*, the causative agent of Malaria (B8 Pradel).

Project area C:
Immune response to and immunomodulation by microbial infections

This project area has grown to be the largest one within the SFB. It deals with the immune defense against viruses and bacteria (C6 Hünig/Brombacher; C11 J. Schneider-Schaulies; C12 Topp/Einsele; C13 Lutz), but also with the complex immunomodulatory interactions between the immune system and measles virus (C4 S. Schneider-Schaulies) and the fox-tapeworm *Echinococcus multilocularis* (C10 Brehm).

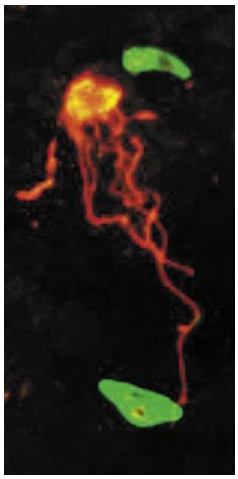

Fig. 1: Macrogamete contacting two gametocytes during fertilization in the human malaria parasite Plasmodium falciparum. The cells are connected via filamentous structures formed by the macrogamete. Labelling of the gamete-specific surface protein Pfs25 is shown in red, labelling of the gametocyte protein Pfs230 is shown in green.

Teaching

The SFB 479 interacts closely with the Graduate College 520 „Immunomodulation", the Graduate Program of the Centre for Research on Infectious Diseases, and with the Graduate School for Life Sciences (GSLS), guaranteeing a structured educational program to its graduate students.

Symposia

Every one to two years, the SFB organizes an international Symposium with varying topics derived from the themes of the SFB. Since the last research report, the following Symposia have been held:

2002	Genomics in Infectious Diseases
2003	Triggering and Modulation of Natural and Acquired Immunity by Pathogens
2005	Microbial Infection: Analysis, Prevention, and Use
2007	Host-Pathogen Co-Evolution: A Tale of Struggle and Affection

5.1.2 Collaborative Research Center 487, Regulatory Membrane Proteins: From Molecular Recognition to Drug Targets

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General Information

The SFB 487 "regulatory membrane proteins" has been founded in 2000 and is in its third period of funding. The SFB 487 consists of 15 research groups from the faculties of medicine and biology. The research is focussed on molecular mechanisms of function and regulation of membrane protein trying to extend our knowledge concerning function of receptors, channels, transporters and membrane associated regulatory proteins. Therefore a broad spectrum of methods is applied ranging from measurements on isolated proteins to investigations in living animals. Biochemical methods are used to identify interaction domains of proteins and ligand binding sites, and to determine tertiary structures of the proteins. Protein interactions and protein motion in cells are analysed using methods of cell biology, biochemistry, and genetics. Finally the physiological function of membrane proteins is investigated in intact organs and living animals after knock out or over-expression of certain genes. Thus, the SFB 487 is a methodological platform that allows access to a variety of methods for the investigation of membrane proteins. The ultimate goal of all efforts is the identification of novel pharmaceutical targets in membrane proteins. This may lead to novel therapies of diseases caused by membrane protein mal-function or mal-regulation.

Major Research Interests

The common research topic of the SFB 487 are proteins at cell surfaces that regulate cell functions. Cells are surrounded by a phospholipide bilayer membrane, which separates them from the environment. In these bilayer membrane a multitude of proteins (integral membrane proteins) are embedded. Other proteins are associated with the outer or inner leaflet of the plasma membrane (membrane associated proteins). Integral membrane proteins are parts of signal transduction pathways (receptors), involved in solute shuttling across the plasma membrane (channels, pores, transporters), or are involved in cell-cell communication (cell contact proteins). Membrane associated proteins stabilise the plasma membrane and mediate contacts of cells with extracellular (i.e. collagen fibers) or intracellular proteins (i.e. actin filaments). Membrane associated proteins regulate the amount (endocytosis, exocytosis) and the activity of integral membrane proteins in the plasma membrane. Furthermore, membrane associated proteins play a critical role in the regulation of cell metabolism, specific cell functions and mitosis because they initiate activation cascades.

Important aims of the SFB 487 are to determine structures of physiologicaly and biomedicaly relevant membrane proteins and to identify their functional epitopes. This includes binding sites for hormones, neurotransmitters, substrates and interacting proteins. The structural results will be supplemented with functional investigations to understand the physiology role of individual proteins. Functional data of membrane proteins *in vivo* are acquired from cultivated cells, intact organs or living animals. After the establishment of functional mechanisms of individual membrane proteins the acquired knowledge will be used for the development of novel therapeutic drugs.

Research area A: Proteins with several transmembrane domains

A1 Lohse (Pharmacology): Desensitization and internalization of G-protein coupled receptors

A4 Koepsell/Gorboulev (Anatomy and Cellbiology I): Investigation of the structural basis of substrate recognition, of transport mechanism, and regulation of organic cation transporters

A5 Benz (Biotechnology): Mechanism and pharmacology of toxin transport on model membranes

A9 Hedrich (Molecular Plant Physiology and Biophysics): Regulation and targeting of tandem pore channels associated with the KCO family

A10 Bünemann (Pharmacology): Kinetics and structural aspects of G-protein coupled signal transduction

Research area B: Proteins with a single transmembrane domain

B1 Sebald (Physiological Chemistry II): Molecular recognition and primary activation steps in BMP/GDF-receptor complexes

B2 Müller (Molecular Plant Physiology and Biophysics): Affinity, specificity and promiscuity of cytokine receptors

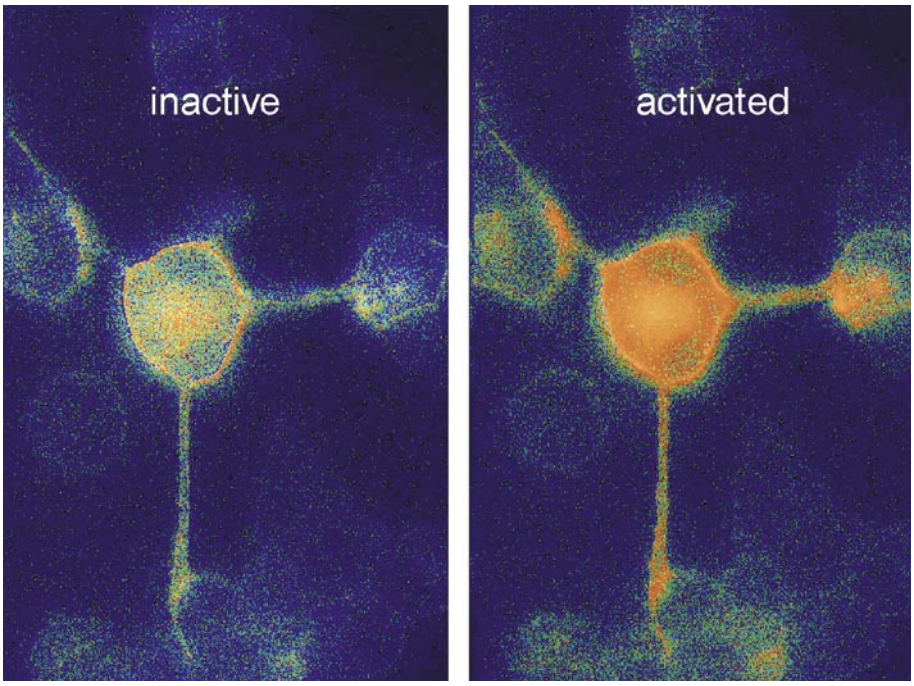

Fig. 1: Demonstration of α2-adrenergic receptor activation on neuronal differentiated PC12-cells by means of fluorescence resonance energy transfer (FRET).

B3 Schartl/Meierjohann (Physiological Chemistry I): Protein interactions at the oncogenic growth factor receptor Xmrk

B5 Drenckhahn (Anatomy and Cellbiology II): Modulation of binding of cadherins

B7 Wajant (Molekulare Innere Medizin): Mechanisms of TNF-receptor-activation

B8 Kuhn (Institute for Physiology I): Mechanisms and relevance of the desensitization of the ANP receptor, the guanylyl cyclase A (GC-A), for the cardiac hypertrophy

Research area C: Membrane-associated regulatory proteins

C1 Koepsell Anatomy and Cellbiology I): Functions of Na^+-D-glucose cotransporters and their regulation by the regulator protein RS1

C3 Rapp (Institute for Radiation Biology and Cell Research): Dynamics of the recruitment of Raf-multiprotein complexes at cellular membranes upon receptor activation: Role of scaffold proteins and lipid interactions

C4 Sendtner (Klinische Neurobiologie): Protein interactions of receptors for neurotrophic factors

C5 Raabe (Institute for Radiation Biology and Cell Research): Regulation of cell adhesion and the cytoskeleton by p21-activated kinases during neuronal differentiation

Symposia

Internal SFB-Symposia:
Oktober 2-3, 2003
Oktober 15-16, 2004
Oktober 6-7, 2006
Oktober 5-6, 2007

International Symposia:
"Mechanisms of protein activation", June 10 – 12, 2004
"Membrane proteins and diseases", June 7 - 9, 2007

5.1.3 Collaborative Research Center 567, Mechanisms of Interspecific Interactions of Organisms

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General Information

The Coordinated Research Centre (Sonderforschungsbereich) 567 "Mechanisms of Interspecific Interactions of Organisms" at the Julius-Maximilians-Universität Würzburg was established in January 2001 with the objective to provide a substantial multidisciplinary contribution to the investigation of interactions between organisms belonging to different species – symbioses in a broader sense. This is achieved by investigating interaction systems from a wide spectrum of species and over several levels of organization.

This integrative approach combining molecular and organismic biology is supposed to strengthen and intensify the technical and conceptual exchange between these two mainstream fields of modern biology represented by various disciplines within three faculties (biology, medicine, chemistry and pharmacy).

The interdisciplinary structure of the Coordinated Research Centre greatly facilitates the incorporation of multidisciplinary aspects into teaching. This helps to familiarize undergraduate and postgraduate students with current methods and techniques used in biology and adjacent fields in order to improve their qualifications to meet the requirements of the professional world.

Major Research Interests

In 16 projects scientists are engaged in approaches based on physiology, molecular biology, ecology, evolutionary biology and biophysics. A broad systematic spectrum of interaction systems is analyzed by applying techniques from infectious biology, phytopathology and analytical chemistry in order to address the following central questions:

- What are the mechanisms underlying interspecies recognition in different interaction systems?
- What kind of information flow is required for the establishment and maintenance or termination of interactions?
- What is the nature of substantial and energetic resources to be exchanged between interaction partners? How is this exchange initiated and regulated? What are the genetic and physiological predispositions required to permit interaction?
- How is the flow of information and resources generated within the interaction partners and how is it finally transmitted?
- What is the role of the phenotypic plasticity of the partners with respect to establishment and maintenance of interaction?
- What are the molecular, morphological and behavioural adaptations that can be explained as an evolutionary consequence of interaction?

Only the comparative assessment and integration of results based on a wide range of levels of complexity can elucidate common principles, characteristics and benefits of symbioses.

The Sonderforschungsbereich 567 is subdivided into three project areas: „Recognition and Reaction", „Signals in the Interaction Partners" and "Continuity and Evolution".

Recognition and Reaction

This project area focuses on signals that lead to the unilateral or mutual recognition of interaction partners and investigates mechanisms involved in the development of compatibility or incompatibility between organisms of different species. This includes the analysis of plant surface characteristics affecting the recognition of hosts and non-hosts by obligate biotrophic fungi. Other approaches investigate pathogen defense reactions in plant and animal systems on the molecular and cellular scales.

Signals in the Interaction Partners

The central objects of investigation in this project area are those signals and resulting adaptations, which are formed within organisms as a response to biotic interaction. Trans-membrane ion and metabolite flows and their functional role in the molecular response of a plant upon interaction with microorganisms are investigated. Here, the molecular basis and role of Ca^{2+} signals, expression and regulation of mass transport with respect to an infection with *Agrobacterium* or *Pseudomonas* are analyzed. In response to interactions between microbes and plants the formation of secondary plant metabolites, specific molecular patterns and the structural and functional characteristics of involved proteins are investigated.

Continuity and Evolution

This project area is concerned with the regulation and maintenance of interspecific interactions, investigating a broad spectrum of tight and obligate symbiotic systems. Regulatory aspects of even intracellular symbioses (bacteria/ants, microbes/sponges) and mutual interactions of more than two partners (plant/bee/herbivore) are analyzed. Moreover, a gynogenetic fish species serves as a model system to explore the evolutionary advantages and/or disadvantages of sexual reproduction. Within the project area „Continuity and Evolution" two projects of the Medical faculty are included, which are working on the interaction of marine sponges and microorganisms and on the interaction of fishes with their hosts:
TP C3: Hentschel/Steinert/Hacker: Analyses of the interaction of the sponge *Aplysina aerophoba* with associated microorganisms.
TP C5: Schartl: Molecular and cytogenetic mechanisms of the interaction between the gynogenetic Amazon molly (*Poecilia formosa*) and his hosts (*P. mexicana* und *P. latipinna*).

5.1.4 Collaborative Research Center 581, Molecular Models for Diseases of the Nervous system

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General Information

The "Collaborative Research Centre" SFB 581 „Molecular models of diseases of the nervous system" was established in the year 2000 at the University of Würzburg. It comprises groups from the faculties of medicine (clinical and theoretical institutes), biology and chemistry. The central goal is to investigate how gene mutations ultimatively lead to the specific phenotypes in these diseases, to identify contributions of reactive cells and neural activity in diseases of the nervous system and thus to contribute to a better understanding of the underlying disease mechanisms. For that purpose two main focuses were set: the projects of part A focus on mechanisms of inflammatory diseases, whereas the projects in part B deal with molecular mechanisms of degenerative diseases. These two project parts are supplemented by two central projects on morphology/electron microscopy and modern light microscopic techniques (confocal microscopy).

Major Research Interests

The SFB 581 has set the goal to investigate the complex course of primary and secondary pathophysiological processes in diseases of the nervous system. Diseases of the nervous system follow a complex course of primary and secondary pathophysiological processes leading from a causative cellular dysfunction to the disease phenotype. Despite the fast progress in the last two decades in uncovering gene defects, which was particularly made possible due to the genome projects for human, mouse, drosophila and other species, it is often not possible to understand the pathophysiological steps from the primary cause of these diseases, for example a gene defect, to the specific disease phenotype and from thereon to development of new therapeutic strategies. This situation calls for a cell biologically oriented neurobiology, which, in a network with clinical researchers, investigates the cell biological cascade of disease development using suitable disease models. Thus the main emphasis in the SFB 581 is

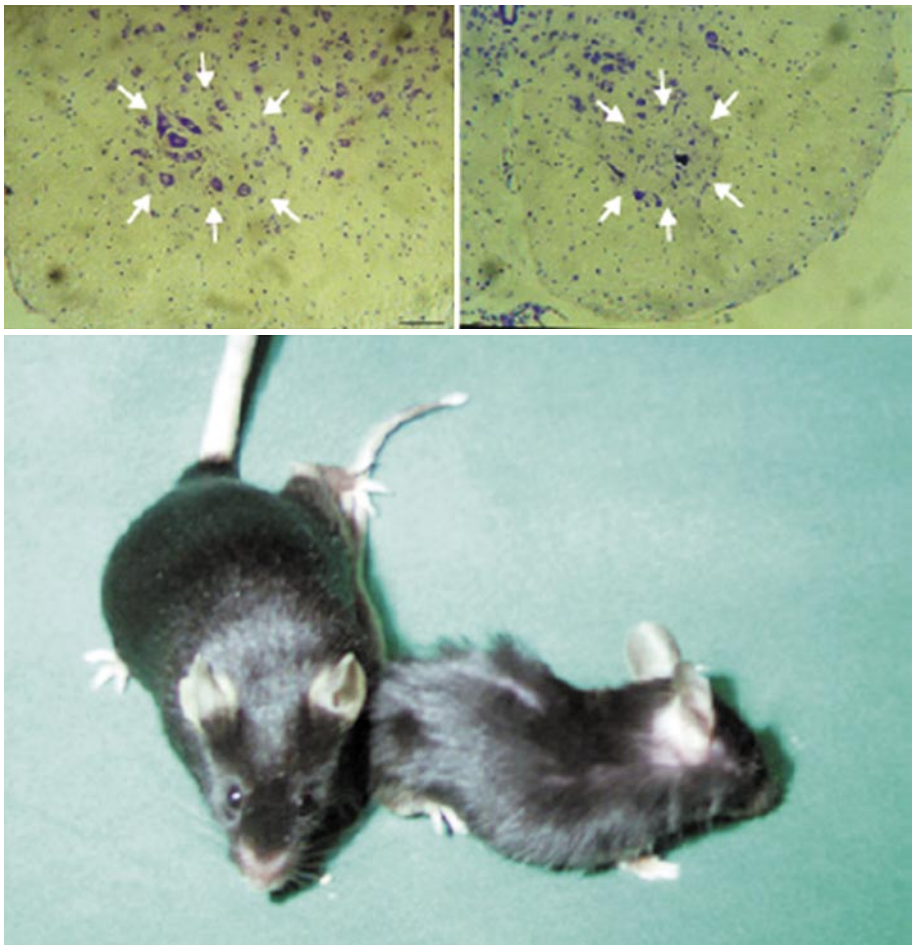

Fig. 1: Degeneration of spinal motoneurons (top) in a mouse model for spinal muscular atrophy (bottom).

put on mouse, drosophila and zebrafish models, with which not only the direct effect of signal transduction mechanisms on cellular structures and functions in the nervous system can be investigated, but also pathophysiological processes with which the interactions of different cell types can be investigated in neuroimmunological and neurodegenerative diseases.

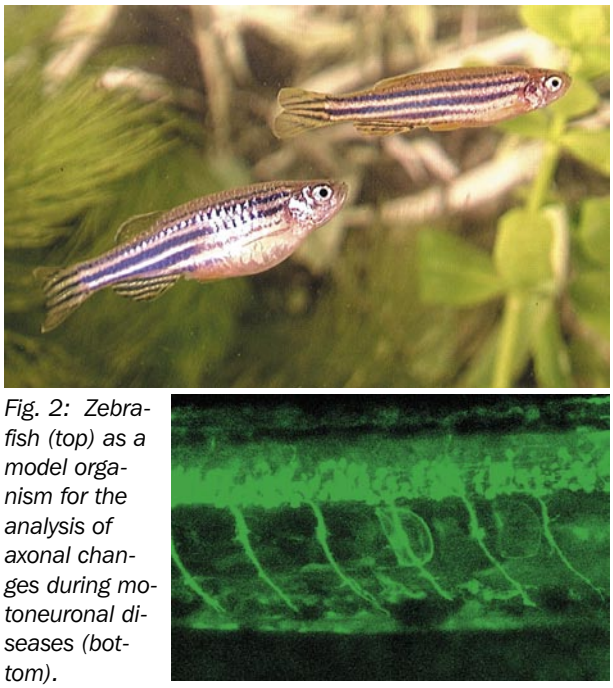

Fig. 2: Zebrafish (top) as a model organism for the analysis of axonal changes during motoneuronal diseases (bottom).

The goal of the SFB is to connect the molecular cell biologically oriented fundamental research to the understanding of the complex course of disease processes. As this can only be achieved in an interdisciplinary approach, the SFB 581 links groups working with different methods on model systems for neurodegenerative and neuroimmunological disease processes.

This collaborative research centre contributes significantly to training programs for students in the fields of Biology, Biomedicine as well as Experimental Medicine. Since the SFB was established, students that are trained in these fields are enabled to participate actively in the projects. For this purpose the Deutsche Forschungsgemeinschaft and the University are providing a considerable budget for student and graduate assistants. Members of the SFB 581 are actively involved in courses within the training programs for these students. The SFB 581 is also involved in the training of graduate students which is being coordinated in the class “Neuroscience” of the International Graduate School by the University of Würzburg. Thus the SFB plays a major role not only in promoting research in neurobiological research groups at the University of Würzburg, but also in promoting young researchers in training programs in the field of neurobiology.

5.1.5 Collaborative Research Center 630, Recognition, Preparation and Functional Analysis of Agents against Infectious Diseases

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General Information

The SFB was founded in 2003 to create an interdisciplinary platform to initiate the development of novel drugs against infectious diseases. The goal of the SFB is the identification of novel agents against infective pathogens, to characterize their mode of action and to optimise their efficiency. The complexity of this task requires interdisciplinary approaches. The 3 project divisions of the SFB consist of 17 project parts which emanate from four different faculties: the faculty of chemistry and pharmacy, of biology, of medicine and of physics and astronomy and, additionally, from the Institute of tropical medicine of the Medical Mission Clinic. The three project divisions are devoted to different duties: projects in group A prepare, characterize and optimise the compounds, which are then analysed for their activity in cellular and molecular systems in group B. The dissection of their mode of action on the molecular level as well as optimisation predictions are performed by projects in group C.

Major Research Interests

Due to the rapid spread, the faster emergence and the development of resistances, infectious diseases have an even growing impact on public health today. Efficient drugs are especially needed for tropical diseases, for which only insufficient therapies exist. Hence, the development of novel agents with novel mode of actions is of major global importance. The groups within the SFB exploit natural sources like plants, marine sponges and sponge-associated microbes as well as the versatile possibilities of combinatorial chemistry to generate small effector molecules. The inhibitory activity of these compounds is examined for a variety of clinically most relevant pathogenic bacteria, fungi and parasites. Modern technologies like transcriptomics, proteomics, metabolomics and spectroscopy as well as the bioinformatic analysis of cellular networks enable the characterization of the detailed mode of action of the active agents. The efficiency and effects in vivo are analysed by NMR imaging of the infections in well-established small animal models. Moreover in an additional approach, effector molecules are designed on a rational basis against defined well-characterized pathogenicity factors like proteases, fatty acid biosynthesis enzymes or efflux pumps. Based on the three dimensional structure of these targets, quantum mechanics, molecular modelling, docking and molecular dynamics simulations allow the design and optimisation of tailor-made inhibitors for chemical synthesis. The close collaboration of the groups with their different expertise and specialised knowledge is the basis and the driving force of the research success of the SFB.

Project division A: Preparation, characterisation and optimisation of agents

A1 U. Holzgrabe (Institute for pharmacy and food chemistry)
Small molecules for the treatment of infectious diseases

A2 G. Bringmann (Institute for organic chemistry)
A new class of active agents against infectious diseases

A3 C. Schmuck (Institute for organic chemistry)
Target-oriented combinatorial synthesis of potential new antiinfective lead structures

A4 T. Schirmeister (Institute for pharmacy and food chemistry)
Proteases as targets for agents against infectious diseases

A5 U. Hentschel (Research Center for Infectious Diseases)
Novel secondary metabolites from sponge-associated microbiota

Project division B: Interaction with cellular and molecular systems

B1 J. Hacker (Institute for infectious biology)
Prolylisomerases and serine proteases as targets for rational drug development

B2 J. Morschhäuser (Institute for infectious biology)
Inhibition of virulence and resistance mechanisms of *Candida albicans*

B3 H. Moll (Institute for infectious biology)
Analysis of the action of naphthylisoquinoline alkaloids and cysteine protease inhibitors against *Leishmania* parasites

B5 K. Ohlsen (Institute for infectious biology)
Drug-induced gene expression in staphylococci

B7 C. Kisker (Rudolf Virchow Center)
Structure-based drug design on essential enzymes from *Mycobacterium tuberculosis* and other pathogens

Project division C: Characterization of the molecular mechanism of antiinfectives and predictions for their accelerated optimisation

C1 S. Schlücker (Institute for physical chemistry)
CARS microscopy, Raman and IR spectroscopy for the localization and characterization of drugs and their interactions

C2 C. Faber (physical institute)
NMR spectroscopy and imaging for in vivo and in vitro characterisation of infections and agents against infectious disease

C3 B. Engels (Institute for organic chemistry)
Theoretical studies to characterize inhibition mechanisms and ligand-target complexes

C6 T. Dandekar (Institute for bioinformatics)
M. Unger (Institut für Pharmazie und Lebensmittelchemie)
Metabolic and bioinformatical analysis of drug effects on cellular networks exemplified in *Candida albicans*

C7 C. Sotriffer (Institute for pharmacy and food chemistry)
Computatinal structure-based drug design for the identification and characterization of new inhibitors of antimicrobial targets

Central project

Z1 T. Ölschläger (Institute for infectious biology)
A. Stich (Medical Mission Clinic, Institute for tropical medicine)
Laboratory for the central evaluation of potential antiinfective agents

Symposia

International Symposium
Novel Agents against Infectious Diseases – an Interdisciplinary Approach
12. – 15.02.2006

Joint PhD-student meetings of the SFB 630 and SFB544
New Trends in Infectious Disease Research
10. – 12.11.2004
23. – 25.11.2006

5.1.6 Collaborative Research Center 688, Mechanisms and Imaging of Cell-Cell Interactions in the Cardiovascular System

CONTACT DETAILS

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Professor Dr. med. Bernhard Nieswandt (Vice-Speaker)
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General Information

Cardio- and cerebro- vascular diseases account for most deaths worldwide. The SFB 688 center grant funded since 2006 creates a research network involving Würzburg scientists and clinicians from four faculties and eleven institutes/clinics of the University. It focuses on understanding central pathophysiological processes such as thrombosis, as well as secondary processes set in motion which lead to subsequent damage and failure of the heart, vascular system and brain. New signalling molecules which mediate cell-cell interactions are investigated in order to identifiy suitable candidate targets of innovative concepts for prevention and treatment of cardiovascular diseases.
Of special importance is the development of new magnetic resonance (MR) imaging techniques that allow in-vivo monitoring of disease progression in experimental models and patients with vascular disorders.

Major Research Interests

This integrated approach unites complementary areas of research including molecular biology, physiology, biophysics, proteomics, and bioinformatics, with clinical medicine. Molecular and pharmacological murine disease models are generated in the SFB and used by clinically-oriented groups to gain new insights into the development of thrombosis, myocardial infarction and stroke. Certain secondary complications of cardiovascular disease, such as oedema and scar formation, that strongly influence heart and brain function, are also investigated. The use of new MR contrast agents and high field MR imaging (up to 17.6 Tesla) permits better surveillance of heart and vascular function in the living organism.

Project Area A: (Fundamentals and mechanisms of vascular cell-cell interactions)

This project area investigates the initiation of pathological cell-cell interactions especially between platelets, monocytes, leukocytes, and endothelial cells in the vascular system. These cells play a central role in primary haemostasis, but also in vascular thromboses leading to organ dysfunction. Adhesion of platelets and other cells to the vascular wall, together with local activation of plasma coagulation, constitutes a complex process leading to pathological thrombus formation.

Although funded only for the last two years, the SFB 688 has already generated several outstanding results. Unexpected importance of the clotting factor XII (Hagemann factor) in stabilisation of arterial thrombi could be demonstrated. Factor XII deficient mice are protected from vascular thromboses and stroke, but not at the expense of increased bleeding risk. Blockade of the platelet glycoprotein Ib likewise prevented secondary infarct growth, without bleeding complications. The use of animal models for myocardial infarction and stroke has served to link understanding of basic cellular mechanisms to problem solving in clinical medicine. Analysis of the functional proteome, phosphoproteome and interactome of human platelets also promises to widen therapeutic options in clinical medicine.

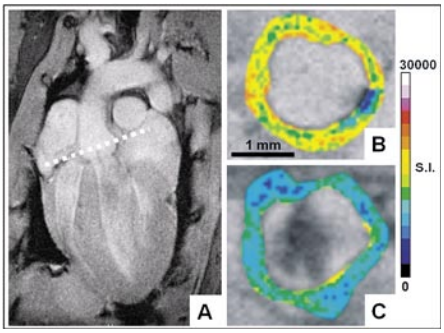

Fig. 1: Magnetic resonance imaging of a beating heart of an ApoE knock-out mouse with accelerated arteriosclerosis. (A) Heart ventricles and aortic arch are shown. (B) Cross section through the aortic root at the level of the dashed line in A. After injection of MR contrast agent containing iron-particles (C), acute infiltration of macrophages at the aortic valve can be visualized as indicated by the reduction of the signal intensity on T2-w MRI (S.I.).

Investigations in mice harbouring a deletion of the p50 subunit of the transcription factor NF-kappaB exhibited reduced cardiac ischemia-reperfusion damage. Bone marrow transplantation experiments identified attenuated activation of NF-kappaB in leukocytes as the underlying mechanism.

Also with regard to regenerative processes in the vascular wall the SFB 688 made essential advances: translational studies in mice and patients demonstrated that treatment with growth hormone via secretion of insulin-like growth factor-1 improved the age-related dysfunction of endothelial progenitor cells that are essential for vascular protection and reparation.

In general, the long-term objective of several SFB research projects is to identify more effective and safer prevention of thrombembolic events, and to characterize other targets for improving therapeutic options for patients with arteriosclerosis, myocardial infarction and stroke.

Project Area B: Molecular and functional imaging of the cardiovascular system and its cell-cell interactions

This project area encompasses imaging projects having the long-term goal of visualizing the dynamics of lesion development in murine models of vascular diseases in vivo. For this purpose, new MR techniques for imaging the vascular system, and for assessment of cellular infiltration and the expression of critical signalling molecules, are developed and applied to disease models generated in Project Area A. The effort involves generation of novel MR contrast agents and analytical sequences.
In atherosclerosis, the acute infiltration of T cells and macrophages is regarded as an important indicator of impending plaque destabilisation and increased risk for myocardial infarction or stroke. Thus, in vivo MR imaging of these processes (see Fig. 1) and the signalling molecules involved (without tissue harvesting) may help to identify plaques at risk and to monitor prevention and therapy of vascular diseases. The experimental results generated using high-field MR imaging will be transferred to clinical field strengths for the monitoring of patients with atherosclerosis and at high risk for thrombembolic events.

5.1.7 Transregio-Collaborative Research Center 17, Ras-dependent Pathways in Human Cancer

CONTACT DETAILS

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Professor Dr. rer. nat. Martin Eilers
(Speaker Marburg)

Institut für Molekularbiologie und Tumorforschung
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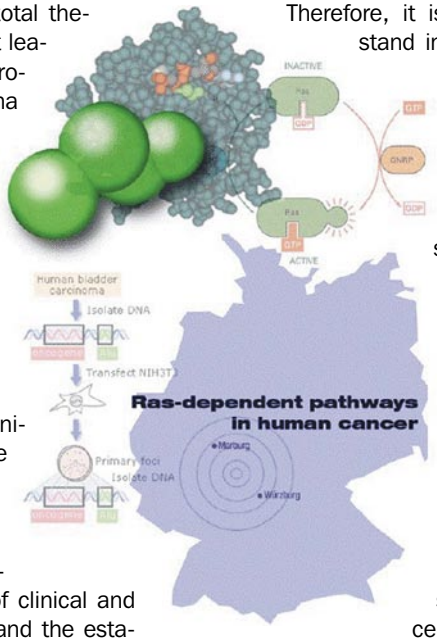
General Information

The Transregio 17 is formed by researchers at the universities of Marburg and Würzburg and is coordinated by Martin Eilers and Manfred Schartl. The Transregio started in 2004 and will continue its work for a second period after a very positive evaluation in February 2008. In total there are about 20 project leaders and within each project there are diploma and PhD students working on their theses. All PhD students are members of an integrated Graduate College, organized by the members of the Transregio. The projects are subdivided into three areas distributed over the two participating universities, however, there is a very close interaction between all areas and projects. A special focus of the Transregio is the integration of clinical and translational research and the establishment of key technologies through central facilities and specific projects.



Major Research Interests

The Transregio aims at understanding how key cellular properties of tumor cells, such as deregulated proliferation, apoptosis, chemoresistance and metastasis emerge from the interaction between deregulated signaling pathways and the genetic status of the tumor cells. Cancer is most often defined as a disease of aberrant cell signaling. While the individual molecules that constitute signal transduction pathways, their biochemical functions and the way they are mutated in human cancers are increasingly well understood, we know very little about how deregulated signal transduction translates into those cellular and clinical phenomena that ultimately dictate the course of the disease in the patient. This is particularly true for the Ras pathway, which has emerged as a key signal transduction pathway that contributes to the genesis of a wide variety of human tumors.

The striking observation underlying much of the work in this Transregio is that the outcome of deregulated signaling through the Ras pathway is not stereotype, but is dictated by the genetic status of the cell. Humans harbor protective mechanisms that prevent tumor induction by a single mutation of a proto-oncogene such as Ras. As a result, multiple mutations have to accumulate in a single cell before it develops into a tumor.

Therefore, it is necessary to understand in molecular detail how the genetic status of a cell affects the outcome of deregulated signaling through the Ras pathway. This does not solely apply to cellular phenotypes, but also to the clinical phenomena that we ultimately need to understand, like invasion, metastasis and the response to therapy.

To approach these questions, the research program concentrates on the elucidation of signal transduction through the Ras pathway (project area A), the analysis of cellular responses to Ras and their genetic control (project area B), and investigation of Ras-dependent signaling in human tumors (project area C). Key technologies supplied by members of the

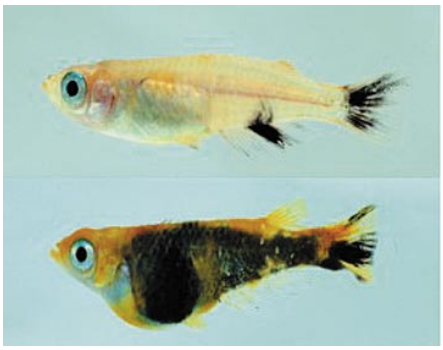


Fig. 1: Medaka fish expressing the Xmrk transgene under the control of the medaka mitf promoter. Upper: fish with a non-malignant hyperpigmentation, a large area of the tail fin is covered by melanocytes. This type of pigmentation abnormality is a precursor lesion that eventually can develop into melanoma. Lower: Fish with highly malignant melanoma showing metastasis and invasion at various sites. (by Manfred Schartl).

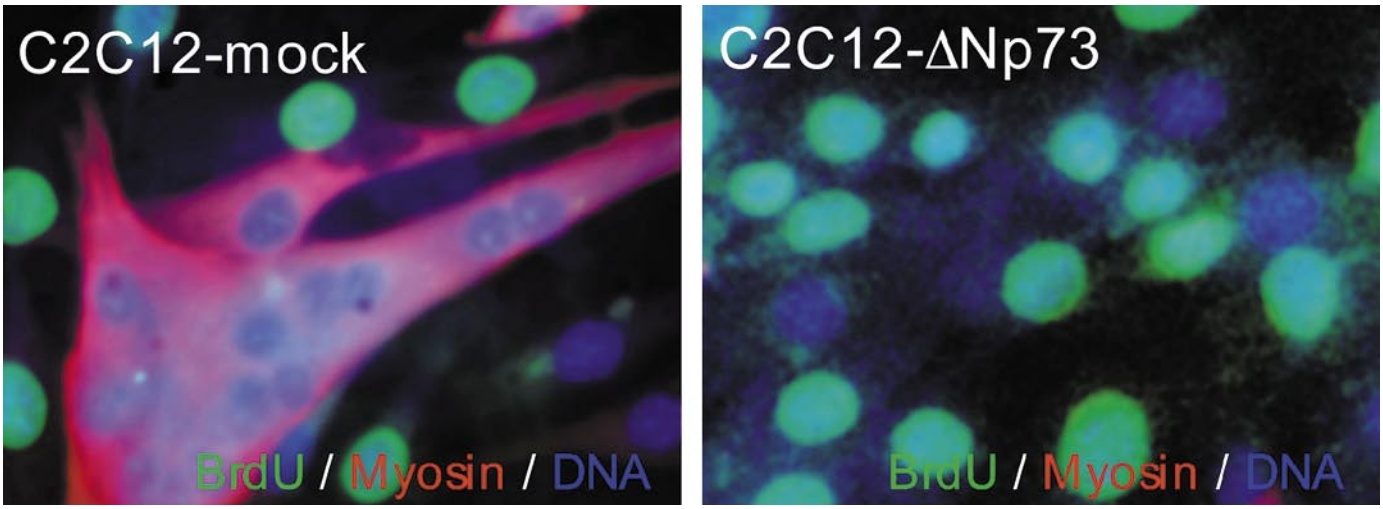


Fig. 2: DeltaNp73 as an inhibitor of the p53 family of tumor suppressors blocks the cell cycle exit and the expression of muscle marker genes when C2C12 myoblasts are induced to differentiate into mature myotubes. This differentiation block enables malignant transformation of myoblasts by Ras-activating oncogenes. Shown are immunofluorescence stainings for S-phase cells (BrdU, green), for myosin as a differentiation marker (red) and for nuclei (DAPI, blue). (by Thorsten Stiewe).

Transregio are the development of animal models for understanding Ras dependent pathways in human cancers, gene expression profiling, high-throughput RNAi screening using high-content microscopy, tissue-based pathology and mass-spectrometry assisted protein analysis.

The research teams from the Medical Faculty of Würzburg include Physiological Chemistry I (Stefan Gaubatz, Svenja Meierjohann, Manfred Schartl), Physiological Chemistry II (Martin Eilers) and Internal Medicine II (Ralf Bargou).

Symposia
2. – 4. April 2007, Rothenburg ob der Tauber, 1st Symposium of the Transregio 17: Ras-Dependent pathways in human cancer

5.1.8 Transregio-Collaborative Research Center 34, Pathophysiology of Staphylococci in the Post-genomic Era

CONTACT DETAILS

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Professor Dr. Michael Hecker
(Coordinating Speaker)

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General Information

The aim of this SFB/Transregional collaborative research center (TR34) is to take advantage of the great opportunities offered by the post-genome era to achieve a new quality of understanding of the life processes of the important human pathogen *Staphylococcus aureus*. To reach this ambitious aim the expertise of groups in Tübingen and Würzburg in cell physiology/biochemistry and infection biology of *Staphylococcus aureus* in general is combined with the established expertise in proteomics of Gram-positive bacteria in Greifswald. The research projects are grouped in three parts: in part A (5 projects), the general physiology of *S. aureus* is considered, dealing with such essential chapters as the regulation of metabolism, and the stress and starvation responses with a tight connection to its pathophysiology, a theme that has frequently been underestimated in the past. The regulation of cell-surface-bound and extracellular virulence factors constitutes the focus of part B (5 projects). Project area C (4 projects) deals with the behavior of the pathogen in the host and will provide new information on the host-pathogen interaction. Various approaches of functional genomics will be applied, such as proteomics, comparative genomics, transcriptomics, structural genomics, bioinformatics, and mathematical modelling.

Project leader Würzburg:
Dr. K.Ohlsen (A2)
Prof. Dr. T. Dandekar (A5)
PD Dr. W. Ziebuhr (B4)
Prof. Dr. Dr. h.c. mult. J. Hacker (C2, C3)
Prof. Dr. A. Szalay (C3)

Major Research Interests

Staphylococcus aureus is a human pathogen of increasing importance, mainly as a result of the spread of antibiotic resistances. The pathogenicity of this species is very complex and involves the strongly regulated synthesis of cell surface-associated and extracellular proteins forming a highly variable set of virulence factors. Due to the great variety of these proteins, *S. aureus* causes a broad spectrum of infectious diseases ranging from superficial abscesses of the skin to endocarditis, osteomyelitis, toxic shock syndrome, and sepsis. Methicillin-resistant *S. aureus* (MRSA) strains are currently predominant and dangerous nosocomial pathogens, since infections caused by these strains have become difficult to treat. In recent years, *S. aureus* and *S. epidermidis* caused more than 50% of all nosocomial infections. Vancomycin has become the drug of choice for treating MRSA infections. However, the emergence of vancomycin-resistant MRSA strains represents a great threat for humans, leading to urgent demands for alternative anti-MRSA therapies and the development of entirely new approaches for antibacterial drug research. It is generally accepted that a more holistic understanding of the cell physiology of this pathogen constitutes an essential step towards the development of new antibacterial approaches to combat *S. aureus* infections. In the SFB/TR34 projects, the great potential of functional genomics will be used to accomplish such a new quality in the comprehension of *S. aureus* physiology and infection biology, leading finally to a better understanding of the entire infection process.

The projects of the groups in Würzburg deal especially with different aspects of host-pathogen interactions. Project part A2 studies eukaryotic-type serine/threonine protein kinases (ESTPKs) and protein phosphatases that are probably involved in the regulation of several physiological pathways. The outcome of this work will open a new field in signal transduction. Comparative protein expression/mRNA profiling of the wild-type and the corresponding mutants will provide data on the physiological role of both proteins. Furthermore, mutant constructions followed by a structural analysis of the kinase will explore the structure and function of these proteins. Moreover, phosphoproteome analysis will be performed to unravel the function of the kinases and corresponding phosphatases in *S. aureus* to identify putative substrates of kinase and phosphatase activity.

In the A5 project, modern techniques of bioinformatics are applied for modelling of metabolic and cellular networks and enzyme cascades to describe the physiology of different staphylococcal strains under different growth conditions. Different functional genomics and system response data are integrated to model central metabolism (e.g. central carbon metabolism) and the stress and adaptation network during different stages of the growth cycle *in vitro*. These models will then be expanded to the metabolism of *S. aureus* in general. A new and emerging field that is becoming the increasing focus in model bacteria such as *E. coli* and *B. subtilis* is the role of small regulatory RNAs in cell physiology. These RNAs

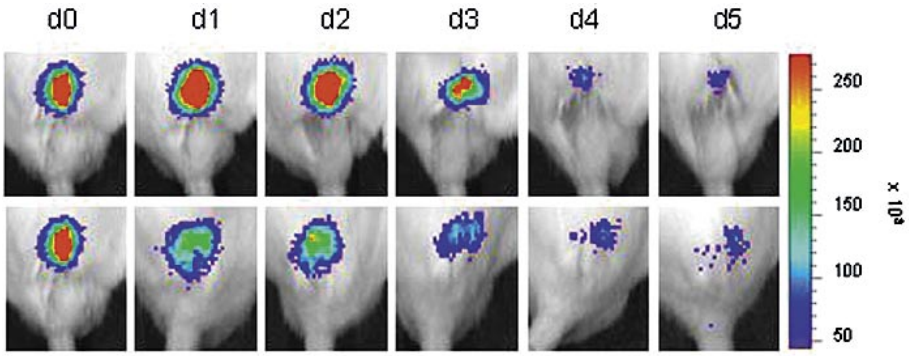

Fig. 1: Bioluminescence of Staphylococcus aureus in the subdermal infection model. The time course of bioluminescence was monitored for 5 consecutive days (d0 to d5) after subdermal infection of the lower back area of mice with 1x10^6 CFU S. aureus Xen29 (upper row) or 1x10^6 CFU S. aureus arl deletion mutant (second row). Signal intensity is indicated by a pseudocolor scale.

are significantly involved in stress adaptation of bacteria, and it can be expected that these crucial molecules also play a role in the control of virulence. This novel problem is being addressed in project part B4. Specifically, a sRNA was found that is encoded upstream of the *ica*-operon in *S. epidermidis* which is probably involved in the regulation of the *ica*-expression. This small RNA could thus influence pathogenicity via production of PIA (polysaccharide intercellular adhesin), synthesized by enzymes encoded by the *ica*-operon, and therefore constitutes a good starting point for the analysis of the role of regulatory RNAs. In addition, a bioinformatic approach that aims at the prediction of additional small RNAs will be followed. Subsequently, such new small regulatory RNAs can be analyzed for their role in cell physiology, stress adaptation, and virulence.

The analysis of the interplay between the *S. aureus* and its host environment is the focus of project C2. Transcriptional profiling using microarray technologies as well as proteomics approaches are utilized to determine the global responses of host cells and pathogens in the host-pathogen interaction. The project part C3 relies on innovative imaging procedures that should allow the real time visualization of the expression of selected genes at different locations in the host and to study the dynamics of staphylococcal infections by using non-invasive techniques. By means of bioluminescence monitoring and confocal laser microscopy, the interaction between the bacterium and the host is being studied on cellular and subcellular level. The high resolution of this technique allows a very detailed description of molecular interactions and the local recruitment of factors of the host and the bacterium, respectively. Using these techniques, the kinetics of *S. aureus* infection can be directly followed in the host providing new insights into the processes of host-pathogen interaction. The understanding of these mechanisms serves as the basis for the development of new concepts to combat infections caused by staphylococci.

Symposia

Summerschool “Pathophysiology of Staphylococci”, Vilm, 26 – 29 September 2007

5.2 Research Centers
5.2.1 Rudolf Virchow Center / DFG Research Center for Experimental Biomedicine

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Professor Dr. Dr. Stefan Engelhardt
(Cardiac Target Proteins)
Tel.: 09 31 / 201-48710

Professor Dr. Gregory Harms
(Molecular Microscopy)
Tel.: 09 31 / 201-48717

Dr. Heike Hermanns
(Cellular Signal Transduction)
Tel.: 09 31 / 201-48736

Professor Dr. Caroline Kisker
(Structural Biology: DNA-Repair and Structure-based Drug-Design)
Tel.: 09 31 / 201-48300

Dr. Stephan Kissler
(Immune Tolerance)
Tel.: 09 31 / 201-44065

Professor Dr. Bernhard Nieswandt
(Vascular Biology)
Tel.: 09 31 / 201-48996

Prof. Dr. Hermann Schindelin
(Structure Biology: Protein Folding, -Function and -Degradation)
Tel.: 09 31 / 201-48320

Professor Dr. Michael Schön
(Inflammation and Tumor Biology)
Tel.: 09 31 / 201-48977

Professor Dr. Albert Sickmann
(Functional Proteomics)
Tel.: 09 31 / 201-48730

Professor Dr. Stephan Sigrist
(Synapse Architecture)
Tel.: 09 31 / 201-44050

Professor Thorsten Stiewe (until 2007)
(Molecular Tumor Biology)

General Information

In 2001, the University of Würzburg won approval in the context of the first nationwide competition of the German Research Foundation for Research Centers. The concept of the Rudolf Virchow Center was chosen among 80 submitted concepts. After reconstruction of the temporary accommodation, the Center was founded in 2002. The center extends across several faculties and is, therefore, organized as a central institution of the University. Group leaders, if they are professors, belong to the Medical Faculty and may have a dual membership in another faculty. The Rudolf Virchow Center is composed of different elements in research and teaching (Fig. 1). Its interdisciplinary research focuses on „target proteins“, that are analyzed at several levels from molecules to disease.

Right from the beginning the Rudolf Virchow Center´s intention was to establish innovative structures at the University. An *Institute for Junior Research Groups* was established, providing junior scientists the possibility to work independently with the option of extension into temporary research professorships (tenure track) for excellent group leaders. To ensure transfer into industry one group is funded by industry and the Bavarian Ministry of Economics. The *Core Center* comprises groups that develop and utilize innovative and special research methods. Excellent established scientists have the possibility to concentrate on a five-year, high-risk project as *Research Professors* on the model of American Howard Hughes professorships. The *Bio-Imaging Center* is a new entity and comprises at present two and is planned to hold five research groups funded by the State of Bavaria and the University of Würzburg as basic funding. In order to strengthen collaborations with researchers in Würzburg the *RVZ Network* program was added. In addition to research, the Rudolf Virchow Center was also involved in conceiving and establishing the new Bachelor and Masters Program in Biomedicine, initiated in the winter term 2001/02 at the University of Würzburg and is now coordinating the program. A “Graduate School” for Biomedicine has been developed that has become the nucleus for a large-scale reform of graduate training at the University and culminated in the foundation of the “Graduate School of Life Sciences“. This school won approval in the context of the national “Excellence Initiative” in the fall of 2006. Finally, the “Public Science Center“ offers several courses for pupils.

Major Research Interests

At the time of reporting eleven research groups and seven projects within the RVZ Network are established at the Rudolf Virchow Center. Research groups work on “tar-

Fig. 1: Structure of the Rudolf Virchow Center.

get proteins". Two types of target proteins of particular biomedical importance constitute the focus of the Center: cell surface receptors and nucleic acid binding proteins. These proteins are analyzed at four levels of complexity: molecular structure and function, biochemical mechanisms, cellular response, and (patho)physiological roles.

Cardiac Target Proteins
(S. Engelhardt)

The group investigates cellular signaling mechanisms in the cardiovascular system and aims to prove their relevance *in vivo*. Its current efforts focus on transcriptional and translational control of cell growth of cardiac myocytes, β-adrenergic signaling and intercellular communication within the myocardium. The overall goal is to develop and to test novel therapeutic strategies against cardiac disease, namely heart failure. This approach necessitates a broad methodological spectrum ranging from optical studies of receptor conformational changes to analysis of cardiac function in living mice *in vivo*.

Molecular Microscopy
(G. Harms)

The research group studies molecular interactions in cell signaling of membrane proteins and cytosolic messengers like platelet adhesion through the Src kinase family, and growth and development through the Bone Morphogenetic Protein (BMP)/Smad pathway. To this end the group uses techniques like fluorescence resonance energy transfer (FRET) microscopy, single-molecule microscopy and dynamic confocal microscopy. These microscopes allow the detection of low, endogenous levels of proteins in and on living cells. Key objectives are the development of biosensors and imaging techniques.

Cellular Signal Transduction
(H. Hermanns)

Deregulated cytokine signaling is involved in the pathogenesis of a large number of diseases including chronic inflammation, autoimmunity and cancer. A large number of cytokines transduces signals via shared cell surface receptors that form multi-molecular complexes. This explains why many of the signaling cascades are common to a number of different cytokines, but leaves the question of signaling specificity open. Using the family of interleukin-6-type cytokines as a model system the laboratory investigates this question.

Structure Biology: DNA-Repair and Structure-based Drug-Design
(C. Kisker)

It has been shown that 80 to 90% of all human cancers are due to DNA damage. Among the various DNA repair mechanisms available to the cell nucleotide excision repair (NER) stands out because of its broad substrate specificity. The group aims to understand the fundamental mechanisms of the bacterial and mammalian NER machinery. Since damage can accumulate and may not be repaired prior to replication and due to the role of DNA polymerases in certain diseases, the group also analyzes different DNA polymerases and their role in genetic maintenance. A second focus is structure-based drug design to identify new therapeutics against infectious diseases.

Immune Tolerance
(S. Kissler)

While our immune system is tightly regulated and usually recognizes only harmful antigenes like pathogens, a significant number of people react to self-antigens and develop autoimmune diseases. The group seeks to understand the genetic polymorphisms that predispose individuals to autoimmunity and the regulatory pathways that fail during onset of disease. The main approach is the genetic manipulation of model organisms by RNA interference (RNAi). Therefore lentiviral transgenesis is used to generate animals in which target genes are constitutively silenced by RNAi. After pioneering this strategy in the model for type 1 diabetes, the group is now refining lentiviral technology to make its application for the study of immune tolerance more versatile and specific.

Vascular Biology
(B. Nieswandt)

At sites of vascular injury, blood platelets come into contact with the subendothelial extracellular matrix, which triggers their activation and the formation of a hemostatic plug. This process is crucial to limit post-traumatic blood loss, but may also lead to pathological thrombus formation, causing diseases such as myocardial infarction or stroke. The group uses genetically modified mouse lines in combination with disease models to identify new strategies to inhibit the thrombotic and/or pro-inflammatory ac-

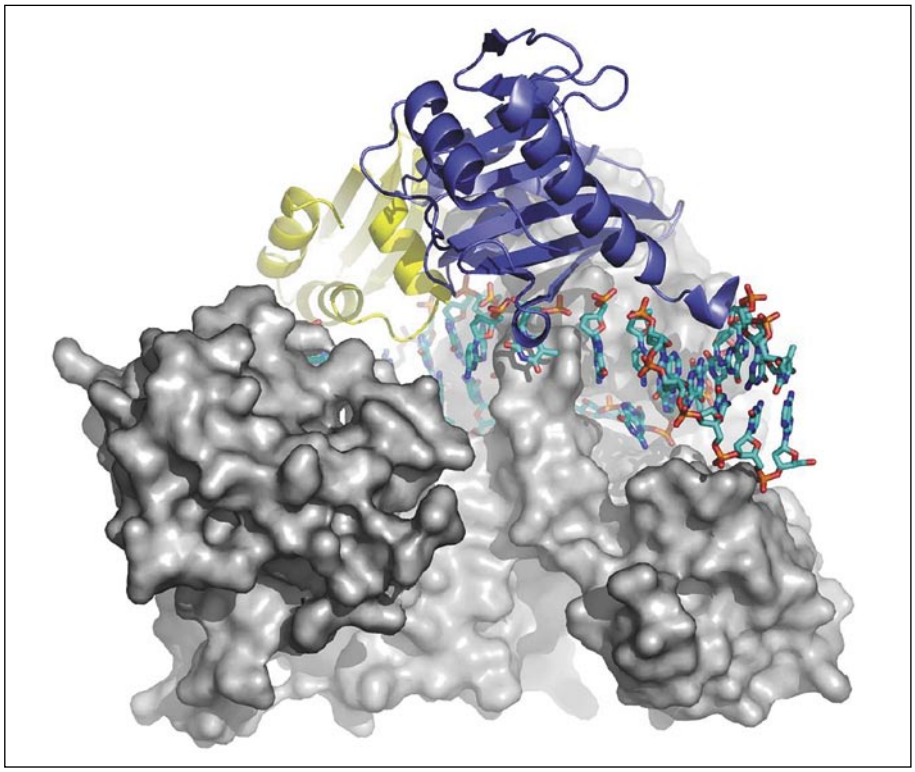

Fig. 2: DNA-Repair: Model for the interaction between UvrB (gray) and UvrC (ribbon presentation) leading to the successful incision of the damaged DNA strand.

tivity of the cells, while preserving their hemostatic function.

Structure Biology: Protein Folding, -Function and -Degradation
(H. Schindelin)

The group focuses on protein folding in the endoplasmic reticulum (ER) and degradation of mis-folded proteins via the ubiquitin-dependent protein degradation pathway. Second, they are interested in the structure and function of inhibitory neuronal receptors and the mechanism of their anchoring at the postsynaptic membrane. Therefore the group uses a combination of complementary techniques for the biochemical and biophysical characterization in addition to X-ray crystallography. Mis-folding and aggregation due to defects in the endoplasmic reticulum associated degradation (ERAD) pathway, for example, lead to a variety of pathophysiological states, such as the neurodegenerative disorders of Alzheimer's and Parkinson's disease.

Inflammation and Tumor Biology
(M. Schön)

The group is investigating the role of adhesion molecules and whether they can be exploited as therapeutic target structures in inflammatory disorders. Adhesion molecules mediate tissue-specific recruitment of leukocytes, a key step in the pathogenesis of inflammatory disorders. In addition, they focus on how tumors progress, why they are resistant to chemotherapy and how novel therapeutic compounds can overcome mechanisms of resistance.

Functional Proteomics
(A. Sickmann)

Over the last decade, mass spectrometry has not only emerged as the key technology for large scale proteomic analysis for the identification and the later functional analysis but also for the elucidation of post-translational modifications as well as relative quantification of proteins. To provide a solid basis for functional analysis in cardiovascular research, the group established an array of methods for the semi-quantitative analysis of phosphorylations and glycosylations and in addition, provided the so far largest proteomic survey of platelet plasma membrane proteins.

Synapse Architecture
(S. Sigrist)

The group studies the molecular and cellular mechanisms controlling assembly and remodeling of synapses. The predominant experimental model of their studies are glutamatergic synapses of Drosophila, which are particularly suited for combining modern molecular biology, genetics, biochemistry and advanced imaging, like the new STED technology. This approach allows an integrated view on synapse assembly and remodeling processes central for learning and memory, as well as nervous system development and disease.

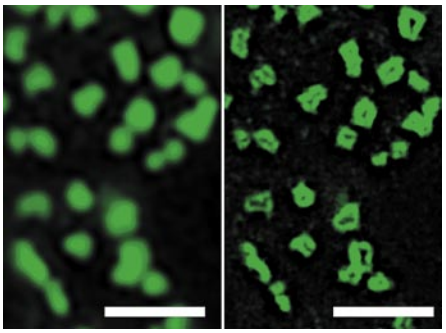

Fig. 3: STED microscopy uncovers supramolecular architectures at synaptic membranes. Conventional confocal (left) versus STED-microscopy (right) of the protein Bruchpilot (green) in synapses. Scale bar is 1 µm.

Teaching

All groups offer internships and lectures for students of the Bachelor and Masters Program in Biomedicine. Annual symposia and conferences are held for scientists from medicine and the natural sciences. Graduate students at the Center are members of the graduate program "Virchow Graduate Program" that belongs to the Section Biomedicine of the "Graduate School of Life Sciences".

SELECTED PUBLICATIONS

S. Engelhardt
Buitrago M, Lorenz K, Maass AH, Oberdorf-Maass S, Keller U, Schmitteckert EM, Ivashchenko Y, Lohse MJ, Engelhardt S (2005) The transcriptional repressor Nab1 is a specific regulator of pathological cardiac hypertrophy. Nat Med. 11, 837-44

T. Stiewe
Stiewe T (2007) The p53 family in differentiation and tumorigenesis. Nature Rev Cancer. 7, 165-168

C. Kisker
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H. Schindelin
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S. Sigrist
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5.2.2 Interdisciplinary Center for Clinical Research (IZKF)

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General Information

The IZKF Würzburg is the internal research funding instrument of the Medical Faculty. Its major goal is to strenghten clincial research on base of interdisciplinary biomedical-clinical research. The budget is fixed approximately at 5 Mill. Euro per annum.

To carry out its mission the IZKF

- supports cooperative research projects in the fields of immunology/infectiology, oncology, cardiac and vasular disease as well as neurology;
- promotes education and advancement of young researchers in medicine throughout all qualification phases;
- improves the scientific infrastructure through its core facilities. In addition it offers special flexible research funding instruments on location.

The research funding management of the IZKF based on peer review process as well as a transparent financial administration. The statutory bodies at a glance:

- General Assembly ("Zentrumskonferenz"),
- Executive Board
- External Scientific Advisory Board.

The IZKF Wuerzburg was founded in 1996 within the federal research funding programme "Health Research 2000" of the Federal Ministry of Education and Research as one of nine centers in Germany. Since 2004 it is completely funded by the Free State of Bavaria.

Major Research Interests

The IZKF devotes particular interest in offering research grants within the main research fields of the Medical Faculty. A research grant can be used to fund staff, scientific instrumentation, consumables as well as most of the other financial requirements of a research project. The declared goal of the programme is to coordinate and to improve cooperation between these main research fields. A unique feature is the concept of bringing together the expertise of basic and clinical sciences to develop novel and effective diagnostics as well as therapeutic approaches. In 2007 the IZKF supported a total of 42 research projects including three junior research groups in the following six research fields:

A: Pathological aspects of inflammation

B: Tumor-host interactions

D: Transplantation andTissue Engineering

E: Pathogenesis and therapy of vascular and myocardial diseases

F: New diagnostic and imaging techniques

N: Clinical and experimental neurobiology

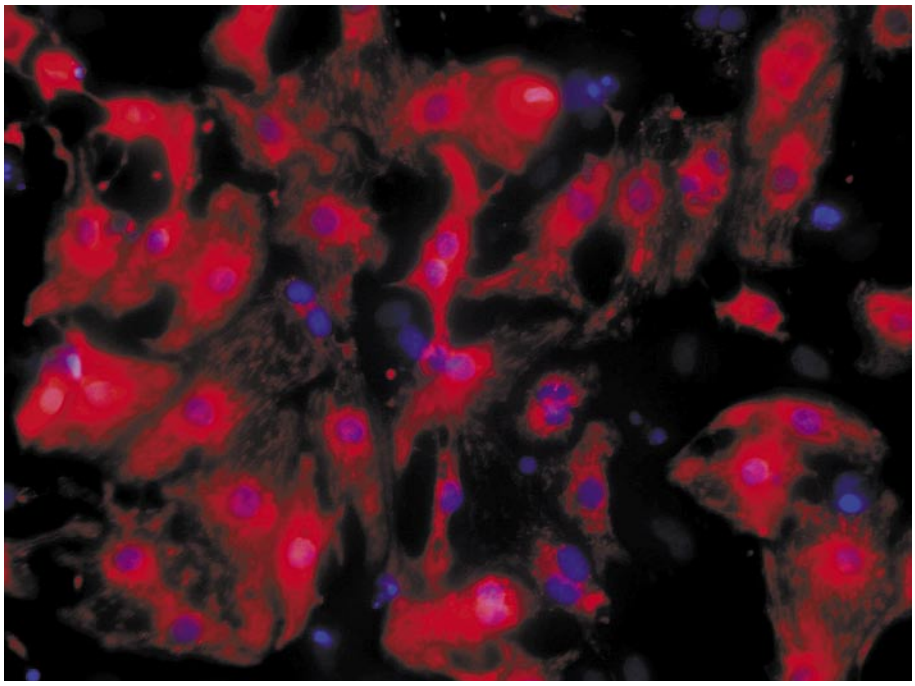

Fig.1: MicroRNA overexpression in cultured neonatal cardiomyocytes (AG T. Thum).

Teaching

Supporting young scientists in medicine is a major commitment of the IZKF that involves a wide spectrum of sponsoring activities:

- MD/PhD-Programme

is accompanied and funded by the IZKF

- Debut Grants Programme ("Erstantragsteller-Programm")

is awarded to young researchers of medicine who have completed their doctorate to carry out a clearly defined project. Supported by mentoring over a period of two years it will help these scientists to receive an external research funding, e.g. DFG.

- Rotation Positions ("Rotationsstellen")

ensure "protected" time for research of young physician scientists through providing positions for physicians who cover for seeing patients and other medical care.

- Three Junior Research Groups

are established to promote excellent young researchers in achieving independence at an early stage of their scientific careers.

Other activities

To advance the scientific infrastructure in clinical research the Center maintains the following Core Facilities:

- Microarray-Unit
- Central Office for Clinical Trial (ZKS)
- Early Clinical Trial Unit

In addition the center offers flexible research funding moduls on location in contrast to major external funding research organisations:

- Start-up financing for innovativ research ideas
- Central budget for rebursements of travel expenses
- Visiting researcher programme for scientists coming from abroad
- Organization and funding of symposia, workshops and other mettings in ordert to encourage coooperation between scientists from domestic or international universities.

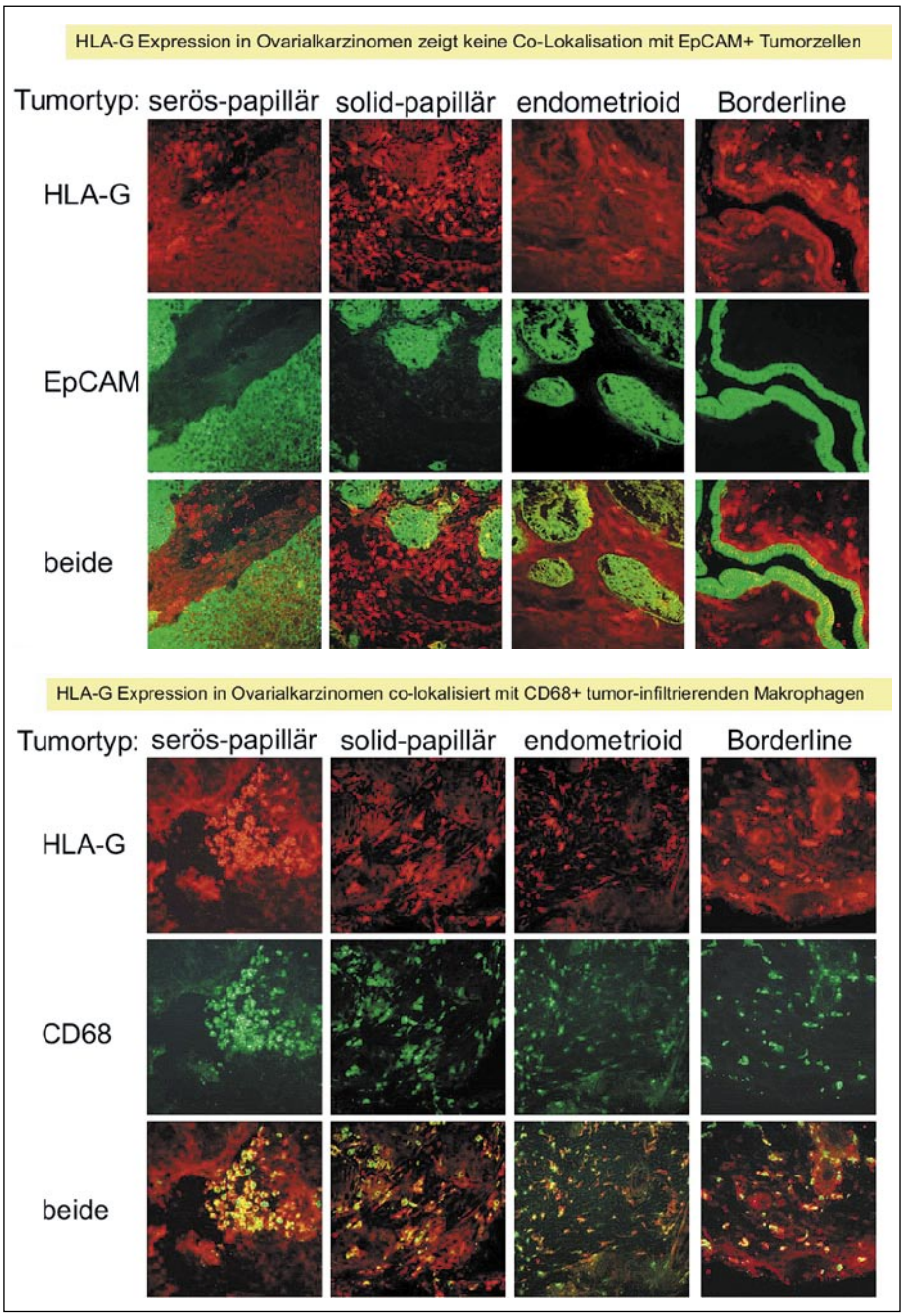

Fig. 2: A: HLA-G expression in ovary carcinomas shows no co-localisation with the tumor marker EpCAM. B: HLA-G is expressed in CD68+ cells in ovary carcinomas (AG J. Wischhusen).

SELECTED PUBLICATIONS

Annual Report (contact: Head office of the IZKF)

5.2.3 Research Center for Infectious Diseases

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General Information

Infectious diseases still cause global health problems. In this regard, the "Research Center for Infectious Diseases" (ZINF) was already established at the University of Würzburg in 1993. This interdisciplinary research centre includes young investigator groups as well as other groups of the University of Würzburg working on infectious diseases. The Research Centre belongs to the Medical Faculty and the Faculty of Biology of the University of Würzburg. One of the first objectives of the centre was to represent a link between these two faculties. An intensive scientific and organizational relationship has been built to the faculties of pharmacy, chemistry and physics. The research of the centre aims at the elucidation of fundamental aspects of infection processes. The young investigator groups are associated with the Institute for Molecular Infection Biology.

Major Research Interests of the Young Investigator Groups

Pathogen-host communication – Exploitation of cellular adhesion molecules by pathogenic bacteria
(C. Hauck, 2001-2006)

A diverse array of cell adhesion molecules is exploited by bacterial pathogens to contact their eukaryotic host cells. The investigations conducted aimed at a deeper basic understanding of the signal transduction capacity and physiologic functions of cellular adhesion molecules as well as further insights into the molecular interaction and communication between specialized microbes and their host cells. Research was focussed on integrins, the cellular receptors for extracellular matrix proteins, and carcinoembryonic antigen-related cell adhesion molecules (CEA-CAMs) that are involved in cell-cell interactions. The results of these studies not only provide insight into the sophisticated adaptations of human-specific pathogens, but also point to defense mechanisms elaborated by human host cells and tissues.

Pathogenicity of *Streptococcus pneumoniae*
(S. Hammerschmidt, 2003-2007)

Streptococcus pneumoniae (the pneumococcus) cause serious and life-threatening infections including pneumonia, septicaemia and meningitis. The function and contribution of important virulence factors, e.g. the capsular polysaccharide, the adhesin proteins PspC and PavA as well as the enolase for protection against the host immune defense and binding as well as transmigration through the extracellular matrix has been investigated.

Marine Symbioses- New Antiinfectives
(U. Hentschel, since 2004)

Marine sponges have considerable potential for drug discovery. Marine demosponges are associated with phylogenetically complex, yet highly sponge-specific microbial consortia that are responsible for the production of many important marine natural product classes, (i.e., polyketides and non-ribosomal peptides). The research goals of the group are to (i) characterize the microbial diversity associated with sponges, (ii) to investigate aspects of symbiosis and function and, (iii) to identify new antimicrobial substan-ces from sponge-associated microbiota. The overall aim of this research is to provide a basic understanding of the sponge-microbe association and to use this natural resource for small molecule discovery.

Molecular interactions during fertilization in the human malaria parasite *Plasmodium falciparum*
(G. Pradel, since 2005)

The tropical disease malaria, which is caused by the protozoan parasite *Plasmodium*, is a major health threat. Currently, there is no vaccine in circulation for the treatment of malaria, and pharmaceutical approaches are increasingly encountering parasite drug resistance. The main research focus was on proteins that are involved in sexual stage differentiation and fertilization. These proteins may represent promising candidates for transmission blocking strategies, which aim to inhibit parasite development in the mosquito vector and thereby reduce the spread of the disease.

Genetically attenuated malaria liver states as an experimental malaria vaccine
(A.-K. Müller, since 2007)

A major area of interest in the lab is the characterisation of protective immune responses to malaria induced by genetically

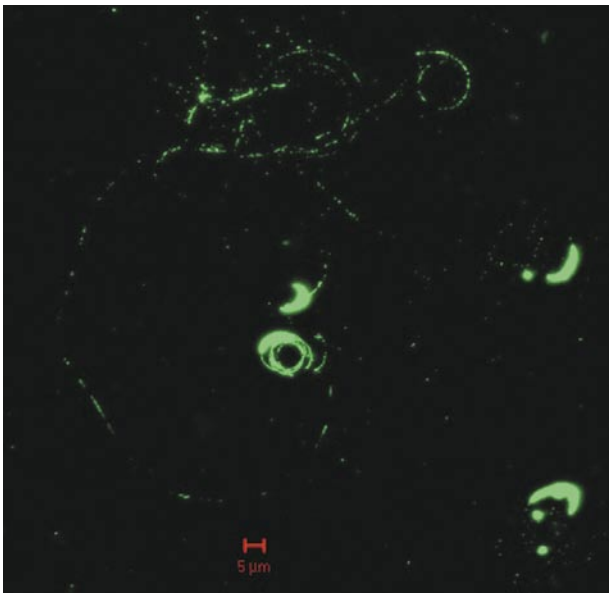

Fig. 1: Gliding motility of a Plasmodium sporozoite*. Malaria sporozoites (banana shaped) are transmitted via a blood meal of the* Anopheles *moskito. They are the infectious state and exhibit a characteristic movement pattern (gliding motility) (©A.-K. Müller).*

attenuated parasites (GAP). Genetically attenuated ***uis3(-)*** and ***uis4(-)*** parasites that constitute a reproducible and standardized source of potent live-attenuated parasites have been recently generated and characterised. Immunization with GAP elicits sterilising immunity, but so far the antigenic specificity and the effector mechanisms of this protective immune response have not been carefully characterized. The group combines molecular and cell biological research on GAP with studies aimed at understanding the immunological correlates of protection elicited by GAP.

Pathogenicity and kryptic sexuality of the human pathogenic fungus *Aspergillus fumigatus*
(S. Krappmann, since 2007)

So far uncharacterized pathogenicity determinants of the mold fungus *Aspergillus fumigatus* are within the research focus of the group. Different aspects of its saprophytic life cycle were analyzed in detail, e.g. the impact of nitrogen metabolism, the regulation of amino acid homeostasis on virulence or the function of a conserved regulator of fruiting body development. In addition, the group works on the further development of molecular biological methods for targeted manipulation of the fungal genome, in order to get insights into the *A. fumigatus* virulome by functional genomics.

Teaching

The junior groups offer lab courses and lectures for students in medicine and biology. The center organizes regularly conferences on topics of infectious diseases. Furthermore, the groups are engaged in the education of graduate students.

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(Look at the ZINF Annual Report: http://www.uni-wuerzburg.de/ueber/forschung/forschungszentren/zentrum_fuer_infektionsforschung/general_information/annual_report_2005-2006/)

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5.2.4 Interdisciplinary Cancer Center

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General Information

Plannning and carrying out of diagnostics, treatment and research of cancer diseases are objectives of the Medical Faculty of the University of Wuerzburg. To provide optimal standards of care, corresponding to the actual state of knowledge, it is required that all institutions which are involved in treatment cooperate interdisciplinary.

Bodies of the cancer centre are the members, the advisory board and the executive board with the chairman. The activities of the centre are coordinated and managed by an administrator.

The Interdisciplinary Cancer Centre was founded in 1983 within the Medical Faculty. For a long time there are scientific collaborations with the *Rudolf-Virchow Zentrum* and other scientific institutions of the University Wuerzburg. Likewise, there are close cooperations with the teaching hospitals of the University, rural hospitals and resident doctors.

To realise its aims the Cancer Centre

- periodically works out and implements standardised clinical pathways for diagnostics and treatment for different tumour entities in collaboration with the involved experts of the interdisciplinary teams
- supports the basic and clinical oncological research, and specific health service research
- collects and analyses data of tumour patients
- cares for education and training of the health care staff
- coordinates outreach programs
- informs the public about several aspects of the cancer disease

The catchment area of the University hospital, which is Lower Franconia and adjacent regions, contains about 2.5 million inhabitants. Since the passing of the federal law for cancer registries the cancer registry is of crucial importance for epidemiologicl cancer registration in Germany. In Bavaria, the law obliges the cancer centres to implement population based cancer registration.

Major Research Interests

National and international multicentre trials and study groups in pediatric brain tumors, multiple myeloma, melanoma, cutaneous lymphoma, advanced lung cancer, and thyroid cancer have been initiated and are being chaired by clinical scientists from Wuerzburg. The Institute of Pathology serves as a reference centre for many national and international studies, namely in the field of lymphatic diseases.

In Wuerzburg, basic research in oncology focuses on questions of tumour origin and molecular mechanisms of malignant transformations and their consequences for diagnostics and treatment. Another research topic is tumour immunology which aims to identify molecular targets for the development of novel therapies. The projects of these topics are notably funded by grants

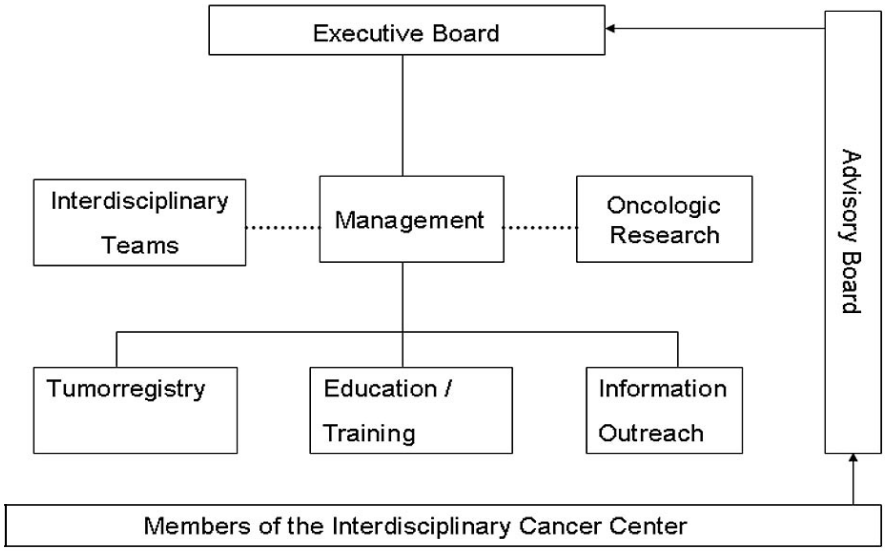

Fig. 1: Simple structure of the Interdisciplinary cancer centre.

of non public resources (DFG, BMBF, Wilhelm Sander-Stiftung, Mildred Scheel-Stiftung, Deutsche Krebshilfe).

In Wuerzburg, oncological research also benefits from several core facilities. These include the Early Clinical Development Unit (ECDU) and the clinical trial office which are set up at the University Hospital Würzburg to support the development and clinical investigation of novel compounds and therapies.

5.2.5 Interdisciplinary Centre for Addiction Research (ICAW)

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Dr. med. C. Jacob (Vice-Chair)
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General Information

ICAW has developed in 2000 from the interdisciplinary BMBF addiction research network (1996-2001) focusing neurobiological and behavioral foundations on alcohol-addiction. The objectives are enduring development and encouragement of clinical and neurobiological research on addiction. Advancement of traineeship, teaching, qualification in addiction associated topics, inpatient and outpatient interventions and political decision guidance are additional topics.

Major Research Interests

Neurophysiological assessment of cerebral cue reactivity in substance dependence
(A. Fallgatter, M.M. Richter, M. Schecklmann, Dept. of Psychiatry)

Event-related potentials (ERP), functional Magnetic Resonance Imaging (fMRI) and Near-Infrared Spectroscopy (NIRS) are used to investigate addiction memory as well as topographical aspects of emotional and cognitive processes in alcohol and tobacco dependency. Other areas of research are the reversibility of disturbances in brain function in alcohol-dependent patients and the application of repetitive Transcranial Magnetic Stimulation (rTMS) in tobacco dependent patients.

Biopsychological mechanisms of nicotine craving
(P. Pauli, R. Mucha, M. Winkler, Department of Psychology)

Within the DFG funded research group (Forschergruppe) "Emotion and Behavior" we examine the addiction specific question how emotional learning processes modulate the significance of environmental cues for craving to smoke. We expect that some environmental cues, especially those associated with the beginning of the smoking ritual, increase craving while others, especially those associated with the end of the smoking ritual, inhibit craving. An understand of the latter process seems especially important since it may help to create environments in which smokers have only little urge to smoke.

Molecular mechanisms of alcohol tolerance at Drosophila melanogaster
(A. Scholz, Institute for Genetics and Neurobiology)

With molecular genetic, genetic and anatomical methods we investigate ethanol induced behaviors in the genetic model organism Drosophila melanogaster. With our behavioral assays we analyze the influence of learned behavior and/or alcohol preference on the development of alcohol tolerance and alcoholism. We are interested in identifying networks that mediate these behaviors. In addition we try to understand how ethanol affects the brain on cellular level. Previously we have identified a new cellular mechanism that is important for the development of ethanol tolerance. This mechanism is similar to a cellular stress response. The hangover gene plays an important process in this process and the human homologue of this gene can be associated with clinical alcohol dependence (DFG-Einzelförderung und Graduiertenkolleg, Thyssen Stiftung).

Functional and structural cerebral neurodegeneration in alcohol dependency
(A. Bartsch, Department of Neuroradiology)

Chronic alcohol abuse results in morphological, metabolic, and functional brain damage which may, to some extent, be reversible with early effects upon abstinence. We investigated global and local brain volume changes in a longitudinal two-time point study with T1-weighted MRI at admission and after short-term (6-7 weeks) sobriety follow-up in 15 uncomplicated, recently detoxified alcoholics. Volumetric brain gain was related to metabolic and neuropsychological recovery. On admission and after short-term abstinence, structural image evaluation using normalization of atrophy (SIENA), its voxelwise statistical extension to multiple subjects, proton MR spectroscopy (1H-MRS), and neuropsychological tests were applied. The increase of concentration of choline was proved as a matter of a detectable increase of the brain volume. The increase of NAA, a product of the metabolism of the white matter and the neurons, is directly connected with an increased concentrativeness.

Genetic of alcohol addiction
(K.P. Lesch, Psychiatry, Psychobiology)

Neurobiological and psychobiological processes such as reward-related behavior,

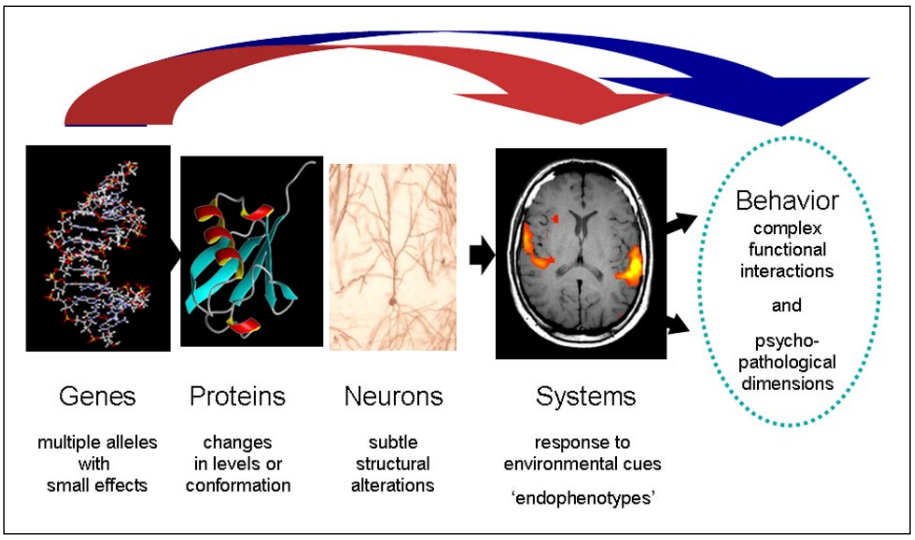

Fig. 1: Molecular imaging of complex behavior and psychopathology.

cognitive-executive dysfunction, stress coping or anxiety that are involved in the development of alcohol addiction are presumably under the influence of genetic variation. Traits, e.g. impulsivity, sensation seeking, or aggressive behavior, as well as dysfunctional cognitive styles, anxiety, emotional lability, and stress vulnerability are directly or indirectly related to morbidity. As evidenced by a plethora of research, most of these psychobiological domains are modulated by a functional serotonin transporter polymorphism. These findings demonstrate the increasing relevance of translational research and molecular-functional imaging studies in order to describe neurobiological founded endophenotypes, thereby bridging the gap between molecular variation and clinical diagnoses.

The endogenous neurotoxine TaClo
(C. Bringmann, D. Feineis, Institute for Organic Chemistry)

Chemical reactive compounds that people are in contact with due to environmental pollution, drug abuse, medical treatment or workplace conditions are suspected to be involved in the etiology of neurodegenerative processes. The investigations focus upon highly chlorinated tetrahydro-beta-carbolines such as "TaClo" that originates in man from endogenous tryptamine ("Ta") and chloral ("Clo"), e.g., after intake of the hypnotic chloral hydrate, or, due to addiction, after occupational exposure to the industrial solvent trichloroethylene (TRI), or as a consequence of solvent abuse ("sniffing").

ADHD as a risk factor of the development of addition
(J. Böning, C. Jacob, A. Schmidtke, Dept. of Psychiatry)

60%-80% of the childhood manifestations of ADHD persist into adulthood. There is a variety of co-morbid disorders including substance use disorders. The treatment of ADHD with stimulants is protective against substance use disorders. The clinical research group ADHD which is supported by the DFG performs a multilayered evaluation of the endophenotypes working memory and response inhibition.

Teaching

The seminary "neurobiology of addiction"is an advanced training for young scientists and students of medicine, psychology and biology. The annual basic and advanced training convention of addiction medicine and teaching of modules of the qualification addiction medicine are additionally activities. Research projects are presented on the annual meetings of the ICAW.

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5.2.6 Interdisciplinary Center for Familial Breast and Ovarian Cancer

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http://www.frauenklinik.uni-wuerzburg.de/brustzentrum/familiaerer_brustkrebs.htm

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General Information

Since 1996, women at risk for familial breast and ovarian cancer are offered specialized counselling in Germany. There are twelve interdisciplinary centres for familial breast and ovarian cancer (Zentren für Familiären Brust- und Eierstockkrebs - Deutsche Krebshilfe). These centres offer a structured approach by which women not only receive an answer to their concerns about personal and familial cancer risk, but also receive counselling and assistance of how to deal with an increased risk. The Würzburg centre is known as “Interdisciplinary Centre for familial breast and ovarian cancer” and includes the following institutions: Division of Medical Genetics: Prof. Dr. Grimm; University Women’s Hospital: Prof. Dr. Dietl; Department of Psychotherapy and Medical Psychology: Prof. Dr. Dr. Faller, Institute of Diagnostic Radiology: Prof. Dr. Hahn.

The results of the national pilot testing and evaluation phase were so positive that the statutory health insurance companies (in 2005) and the majority of private insurers (in 2007) agreed to include the hereditary breast cancer comprehensive care package as part of their regular coverage. The services provided are interdisciplinary – i.e. genetics, gynaecology, diagnostic radiology, and psycho oncology. Genetics includes computer-assisted risk estimates and quality-assured molecular genetic analysis of the BRCA and other susceptibility genes. Optimal use of resources and assurance of high quality care has been achieved through close cooperation within the local centre.

Breast cancer is the most common cancer for women in Germany. Approximately ten to twelve percent are affected during their lifetime, with an average age of 63 years. For the small group of women with a hereditary predisposition, risk is considerably higher: the lifetime probability of these women amounts to 80 percent for breast cancer and 20 to 50 percent for ovarian cancer. It is currently estimated that at least five percent of breast cancers and up to ten percent of ovarian cancers are due to mutations in single genes. BRCA1 and BRCA2 figure most prominently among the high-risk genes. Following the discovery of these genes 1994 and 1995, the joint project “Familial breast and ovarian cancer” was launched by the German Cancer Aid Society. Funded by the Society, twelve university hospitals developed the concept of interdisciplinary care units which includes counselling, diagnosis, follow-up, and prevention. So far, more than 10, 000 families received counselling, and over 5,000 families were included in the joint follow-up project, 574 of these families were followed in the Würzburg centre. Mutations in either BRCA1 or BRCA2 were identified in more than 1,000 families (around 100 in Würzburg). The affected women were offered a comprehensive care package. BRCA-associated breast and ovarian cancers have different characteristics such that effective prevention must be adjusted to the individual patient. As a rule, BRCA1 and BRCA2 related breast cancers are early onset cancers, with an average age of onset of around 43 years - some 20 years prior to the age of onset in the general population. Thus, primary and secondary prevention represents a major challenge. International and national data of the joint project show that mutation carriers can reduce their breast and ovarian cancer risks by prophylactic bilateral mastectomy, in combination with bilateral salpingo-oophorectomy, to below five percent. Oophorectomy alone has been shown to reduce the risk of breast cancer by at least 50%. Currently, only 1 in 10 carrier women in Germany opt for prophylactic mastectomy, but an increasing number of women undergo oophorectomy. As an alternative to radical breast removal, within the framework of the joint project 80 percent of women participate in the programme of intensive early detection. In regular intervals, these women utilize a combination of mammography, magnetic resonance imaging and sonography. The question of how successful such a conservative strategy will finally turn out to be cannot be answered at this time. In order to evaluate the performance of the twelve hereditary breast centres, a database was established at the University of Leipzig. Each centre contributes all relevant data to this anonymous database financed by the Cancer Society. The hope is that the final analysis of this dataset will permit a comparison between the different strategies of primary and secondary prevention. So far, there is a clear benefit of prophylactic mastectomy in primary prevention, but acceptance of this procedure is comparatively low. More data are needed for the evaluation of enhanced early detection using sonography, mammography and complementary magnetic resonance imaging (MRI). A major goal of early detection is to reduce mortality caused by breast and ovarian cancer.

Another focus of the work of the German consortium is on the field of molecular genetics. In about half of the families in whom breast and ovarian cancer appears to follow a monogenic pattern, no predisposing mutations in the BRCA genes are found. This could be due to undetected mutations or mutations in other genes known to be associated with breast cancer, including p53, ATM, BRIP1, etc. Some of these lower penetrance genes are studied in parallel in the Fanconi anemia research laboratory of the Division of Medical Genetics. Another possibility which needs to be explored is the interaction of several low-penetrance susceptibility genes. The differentiation between these alternatives is subject of current research efforts. Furthermore, modifying factors need to be investigated since there are obvious inter- and intrafamilial differences in the clinical presentation of BRCA1-/BRCA2-mutation families which may be caused by environmental factors and/or by modifier genes. Within the international breast cancer research consortium (CIMBA), more than 10.000-BRCA1 and 5.000 BRCA2 mutation carriers will be examined for variants in various genes in order to identify potential modifier genes.

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5.2.7 Transplant Center (TPZ)

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General Information

The Transplant Centre Würzburg (TPZ) is one of several German transplant centres. The centre was reorganized to fulfil the requirements of the new German transplantation act (Transplantationsgesetz). The new national standard waiting list for heart and liver organs has led to fewer organs from Eurotransplant (Leiden, Netherlands). Consequently, the number of liver transplantations has dropped significantly since August 2001 and there has been an increase in patients that die on waiting lists. Würzburg has been able to ease this situation slightly through interdisciplinary cooperations. Kidneys from living donors have helped to alleviate the shortage of kidney organs. So far, 63 kidneys from living donors have been transplanted. Since Würzburg started transplanting in 1984, 690 kidneys have been transplanted in the Clinic for Urology and Pediatric Urology, 71 livers in the Clinic for Surgery I, and 26 hearts in the Clinic for Heart and Thorax Surgery. One liver/kidney transplant and 13 kidney/pancreas transplantations were performed by the Clinic for Surgery I and the Clinic for Urology together. The aftercare was provided by the Medical Clinic I. Also, children and adults received stem cell transplantations and AAA facial bones were transferred to repair defects around the mouth and jaw (AAA = allogneic, autolysed, antigen extracted). The German Foundation of Organ Transplantation (DSO) educates physicians, health care workers and the general public on brain death and organ explantation. With the support of the hospitals in Aschaffenburg, Schweinfurt, Coburg and other hospitals in the region, the registration of potential organ donors has been successfully optimized and more people in the lower Franconia area are willing to donate organs. The aftercare of transplanted patients has improved greatly. Besides the university medical clinics and policlinics, the Clinic of Dermatology also contributes to aftercare by offering a dermatologic surgery for patients.

Experimental and Clinical Transplantation Research

Würzburg is one of the few places in Germany supporting experimental transplantation research, including xenotransplantation. This research is coordinated by a W2 professor for experimental transplantation immunology. Transplantation of nearly all vascularised organs in both rat and mice models can be performed in a well equipped modern laboratory for microsurgery. All departments took part in different multi-centre studies during this reporting period. The clinical and experimental working groups have had numerous dissertations and publications published. Close cooperations exist with the universities in Oxford/England, Boston/USA, Rochester/USA, Sydney/Australia and the Ludwig Maximilian University in Munich.

Further Activities

Every two years the Transplant Centre organizes a local transplantation workshop (Franconian Transplant Workshop) focusing on the operative and conservative aspects of kidney transplantation. This meeting will take place in 2008 for the 10th time. Seminars for patients and physicians also take place on a regular basis. A very successful international symposium on chronic rejection of transplanted organs was held in March 2001. In June 2002 a workshop on experimental and clinical liver transplantation and hepatology was organized.

5.2.8 Cardiovascular Center

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General Information

Cardiovascular and cerebrovascular diseases are the major cause of death in Germany. Thus, cardiovascular research is one of the most important scientific as well as clinical topics at the Medical University of Würzburg. In the cardiovascular center of Würzburg University the medical faculty and the university hospital unites the clinical and scientific competence of different institutions regarding prevention and treatment of cardiovascular diseases, its risk factors, and complications. It uses existing structures for this interdisciplinary approach of cardiovascular disease management and establishes new collaborations with local physicians and national institutes. Due to the multifactorial etiology and treatment of cardiovascular diseases this interdisciplinary approach for scientific questions is mandatory. Treatment of cardiovascular diseases also benefits from interdisciplinary networks ("comprehensive medical management"). Innovative diagnostics and therapeutics can promptly be transferred in patient care. This increases attractiveness for patients, scientists, and physicians.

Herz-Kreislaufzentrum Würzburg

The central interest of the cardiovascular center lies in the prevention and treatment of heart failure and its complications. Over 12 years mechanisms of heart failure development have been investigated in the SFB 355 "Pathophysiology of Heart Failure". Results have been transferred into clinical trials (see below). However, while mortality of coronary artery disease is decreasing, mortality of congestive heart failure is increasing. Thus, to investigate basic mechanisms and new therapeutic options for heart failure numerous projects have been funded by the DFG, IZKF, SFB 688 and by the Rudolf-Virchow-Zentrum. Molecular, genetic, as well as physical results are transferred into clinical research and practice. It is our goal to integrate basic science and clinical research (cardiology, endocrinology, nephrology, psychiatry, neurology, psychology) to improve patient care. This led to the "Interdisciplinary HeartFailure Network" as well as the "Mainfranken Heart Attack Net" fostering interdisciplinary research, teaching and patient care and the initiative for the "Integriertes Forschungs- und Behandlungszentrum (IFB) Herzinsuffizienz".

The cardiovascular center has also an important role in continuing medical education. Interdisciplinary student education and meetings have been organized including lectures for experimental medicine, cardiologic-cardiovascular surgery seminars, cardiovascular imaging seminars, cardiologic-paediatric seminars, and medical pathology conferences. Numerous meetings have taken place discussing for example acquired diseases of the aortic valve, cardiovascular healing, quality management in the cath lab, and the Mainfranken Heart Attack Net. Physician-patient-seminars have been organized in collaboration with the Deutsche Herzstiftung.

National competence net „heart failure"

Prof. Ertl is the co-chair of the national competence net „heart failure". The cardiovascular center contributes 5 out of 20 projects, as for example SP6a "New diagnostic strategies – Cardiac imaging and serum-/plasmamarkers", C. Angermann/G. Ertl, SP6b "Etiology and prognostic relevance of beta1-receptor autoantibodies in human myocardial diseases", R. Jahns/C. Angermann, SP15 „Dieases manifestation and management in chronic heart failure" (INH-Study), C. Angermann/G. Ertl. Over 2000 patients have been included in registries and studies to test effecitvity and efficiency of disease management including cardiologic as well as psycho-educative interventions to monitor and educate patients with systolic heart failure. The translation in patient care is being developed. Associated to the competence net is the Mood-HF-study (funded by the BMBF). In this study the effect of a serotonin reuptake inhibitor on morbidity and mortality of patients with heart failure and depression is tested in association with the psychiatry department. Furthermore, the connection of rheumatic and cardiac diseases is tested in collaboration with the Medizinische Klinik II.

Mainfranken Heart Attack Net

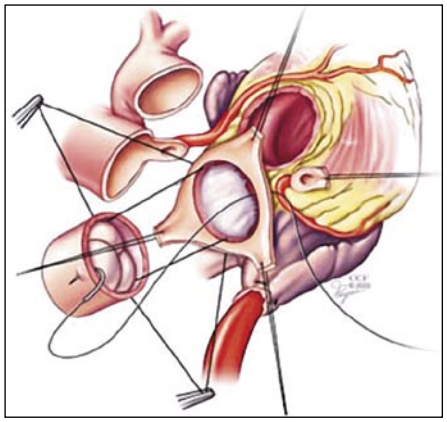
The Mainfranken Heart Attack Net was funded in 2007 to connect emergency physicians with cardiologists and cardiothoracic surgeons to minimize the time for cardiac interventional therapy. Should a coronary artery intervention not be feasible or useful

the department of thoracic and cardiovascular surgery offers emergency operations 24 hours a day. The Mainfranken Heart Attack net has diminished the time to coronary interventions within a few months and allows to collect data for quality management as well as clinical research.

SFB 688

The SFB 688 „Mechanisms of cardiovascular cell-cell interactions, and molecular and functional imaging of these interactions“ integrates cardiovascular basic with clinical science (please find more information in the according chapter). Besides the SFB there are numerous interdisciplinary collaborations demonstrated by a large number of publication. Many of them are supported by the IZKF (see separate chapter).

Department of Thoracic and Cardiovascular Surgery



Prof. Rainer G. Leyh was appointed as the new director on April 1 2007. Apart from a dramatic increase in the number of open heart cases various operative procedures have been introduced in Würzburg: Complex aortic procedures like Ross, David and Yacoub operations and emergency operations of aortic dissections. In addition, the department offers help with operative techniques e.g. for bi-ventricular pacing devices to surrounding hospitals who embark on these new procedures. In close cooperation with the departments of anesthesiology and cardiology the cardiovascular surgery department helps to transfer patients in cardiogenic shock with the life-bridge-system (a miniaturized and portable heart-lung support system).

Furthermore a cardiac transplantation program has been reinstituted. Minimally invasive surgery techniques for mitral and arotivc valve surgery are currently beeing established.

SELECTED PUBLICATIONS

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5.2.9 Center for Experimental and Molecular Medicine (ZEMM)

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General Information

The ZEMM is a facility of the Medical Faculty to provide a basis for experimental research in the field of Molecular Medicine. The labzone and the animal facility are available for defined time periods to research groups engaged in clearly defined research activities. The animal facility is in charge of the central breeding, husbandry and supply of uninfectious laboratory animals used by research institutions from the area of medicine and biomedicine.

The ZEMM is organized in two parts: the animal facility and the laboratories. Step by step, the animal facility of the ZEMM should assume the tasks of the local uninfectious animal facilities, unless special experimental approaches do not call for the housing of animals in a local facility. Upon request, well-equipped laboratories can be provided temporarily within the labzone. Furthermore, several operating rooms for small and large animals are available.

In 2001 the construction of the ZEMM building was begun and late in 2006 the building was largely finished. The laboratories covering a total of 710 square meters were taken into use in 2007 and currently harbour the Institute of Clinical Neurobiology (Prof. Dr. M. Sendtner) and two groups of the Rudolf Virchow-Center (Prof. Dr. B. Nieswandt und Dr. S. Kissler).

The animal facility offers about 1000 square meters of animal husbandry separated into three areas: the open animal facility, the breeding station and the so called SPF area for breeding and housing of transgenic animals. In total, the animal facility has a capacity to keep up to 49 000 mice. Connected to the animal facility is an extensive supply area and the facility is equipped with a complex ventilation and air conditioning system which assures the highest hygienic standards for animal husbandry. The whole animal facility is currently disinfected and animals will start to be moved into the building in the first half of 2008.

Fig. 1: The labzone from outside (Picture: Johannes Marburg, Berlin, Genf).

Major Research Interests

The animal facility of the ZEMM is in charge of the central breeding, maintenance and supply of uninfectious laboratory animals for research units from medicine and biomedicine. Being available for all interested scientists, the ZEMM does not conduct own research programmes. However, the unit “Transgenic Technology“ will provide an up-to-date facility offering modern methods for the generation of transgenic animals, the restoration of transgenic mouse strains and the cryoconservation of mouse embryos. Thus, the medical faculty expects a massive scientific support and stimulation of respective research activities.

Fig. 2: Within the animal facility – sterilisation (Picture: Johannes Marburg, Berlin, Genf).

5.3 Graduate Colleges
5.3.1 Graduate College 520, Immunomodulation

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General Information

The Graduate College gives students of medicine and biology the opportunity to perform a high level experimental research project within an interdisciplinary training programme, usually aiming at an MD or a Ph.D. The Graduate College "Immunomodulation" was initiated in January 2000, and is currently in its third and last funding period (2006-2008) after a third successful evaluation. Besides graduates funded directly by the DFG through the Graduate College, an equal number of graduate students financed through other sources have joined the programme. Since 2006, the Graduate College "Immunomodulation" is one of several training programmes which jointly form the class "Infection and Immunity" of the Graduate School for Life Sciences (GSLS) in Würzburg.

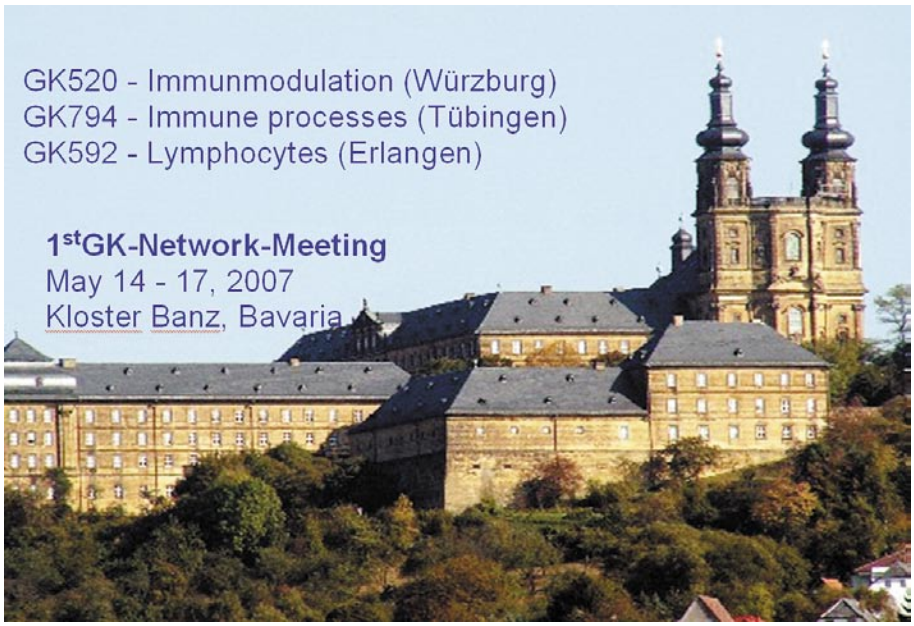
Major Research Interests

The graduates can choose a project from three research areas: "Regulation and Dysregulation of the Immune Response", "Modulation of the Immune Response by Microorganisms and Parasites", and "Experimental Approaches to the Development of Immunomodulatory Therapies". The projects offered encompass a broad range from basic research into the cell biology of the immune system to clinical-experimental studies. Accordingly, both theoretical institutes of the faculties of biology and medicine, and clinical departments participate in the graduate college.

Teaching

The most important teaching activity of the graduate college is the weekly "Jour Fixe", consisting of progress reports, special lectures and journal clubs. The programme is organized in a three year cycle, and is continuously adjusted to the progress of the current cohort of graduates. In addition, the graduates participate in the regular seminars, practical courses and lectures of the participating institutes and clinics.

The annual highlight of our scientific activities is a joint retreat with two other graduate colleges, the GRK 592 "Lymphocyte Activation" (Erlangen), and the GRK 794 "Cell Biology of immune-associated Processes" (Tübingen).



5.3.2 Graduate College 1048, Molecular Basis of Organ Development in Vertebrates

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General Information

Developmental Biology is one of the most exciting and fast moving fields of modern biology. Its research aims at understanding the principles of morphogenesis and pattern formation leading to the establishment of a fully functional, healthy organism. A similarly important goal is, by studying normal development, to contribute to the elucidation of mechanisms that lead to pathological development and disease. Transgenic mouse technology has broadened the study field for developmental biologists and serves the above-mentioned goals as do the other recently emerging study objects, the small aquarium fish models zebrafish and medaka. The coordination of research in the field of Developmental Biology with a special emphasis on organogenesis provides the crystallization point for collaborations that without this graduate college would not have taken place.

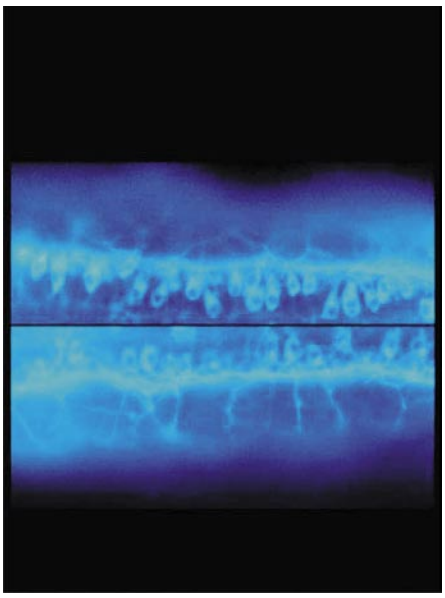

Fig. 1: Immunohistochemical visualization of sensory neurons in the neural tube of zebrafish embryos after gain (upper half) or knock down (lower half) of Midkine-b function (Published online as Liedtke et al "DD ArtPix" in Dev Dyn, Vol.237, Issue 2, 21.Jan.2008).

Major Research Interests

The focus of this initiative is on vertebrate organogenesis, which allows the use of related model organisms by all participants. The restriction to vertebrates is also of advantage for education and training as students have more closely related scientific projects, which will foster the exchange of ideas, reagents and technical protocols. The research program focuses on the role of key molecules or molecular complexes (signaling molecules, transcription factors, splicing factors, micro RNAs) in organogenesis of vertebrates. Major topics include neurogenesis, cardiovascular development and sex determination. Experiments are done in five model organisms (mouse, frog, zebrafish, medaka, and chick) and cover a wide range of techniques. An important methodological aspect of the GRK 1048 is the inclusion of modern imaging techniques such as confocal microscopy and SPIM.

Teaching

The participating research groups represent various fields ranging from stem cell biology to single molecule microscopy. This has its impact on the breadth of the teaching program, which in the past was very successful and will be further improved in the coming years by establishing novel teaching initiatives to broaden and deepen the understanding of organogenetic processes. This research training group is part of the "Graduate School of Life Science (GSLS)". Structures of supervision have been built such that each student has a Thesis Advisory Committee that mentors her/him during the entire period of his training. On an annual basis the project of each student is evaluated and restructured as necessary to guarantee a successful completion. The teaching program of this initiative comprises lectures and seminars, an annual retreat, workshops and "soft skill" training. The participants are also exposed to selected topics of clinically oriented research that is ongoing in the medical faculty of Würzburg with the aim to broaden the scope of young scientist. Together with the strong international links this program ensures that students will be well equipped for an independent and successful scientific carreer.

5.3.3 Graduate College 1141, Signal Transduction: Where Cancer and Infection Converge

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General Information

The DFG International Research Training Group 1141 (RTG 1141) started in February 2005 and will be initially funded until July 2009. Currently 12 PhD students financed by the RTG 1141 and a varying number of associated students financed by other sources are participating. The joint program between the universities of Würzburg and Nice is bringing together preeminent researchers in immunology, microbiology and cancer research and has two major goals: (1) Tear down the boundaries between the fields of oncology and infection in order to create synergies for the development of novel approaches to combat infection and cancer. (2) Educate an elite group of students under the premise that cancer and infection share many common principles, provide those students with a comprehensive scientific and technological view of both fields and enable them to perform creative research in an international spirit. The RTG 1141 also receives funds by the Franco-German University (http://www.dfh-ufa.org), which are used for exchange programs, lab visits and workshops.

Major Research Interests

Targeting the signaling machinery in eukaryotic host cells is a common denominator for the pathogenic action of bacteria and parasites during infection as well for oncogenic transformation during tumor formation. Often the same signaling molecules such as the RAF kinases or identical pathways such as those leading to apoptosis play a decisive role in both classes of diseases. Research performed by the RTG 1141 is addressing primarily three questions. (1) How is the MAP kinase pathway regulated under physiological and disease conditions? (2) How do bacterial pathogenicity factors affect signal transduction mechanisms in mammalian cells? (3) How can we exploit bacteria as Trojan horses interfering with tumor cell signaling pathways or stimulating an anti-tumor immune response? A wide range of methods including those of biochemistry, microbiology, cell biology, immunology and genetics are used to identify and characterize in detail targets and mechanisms that may be used for the development of novel therapies against infections and cancer.

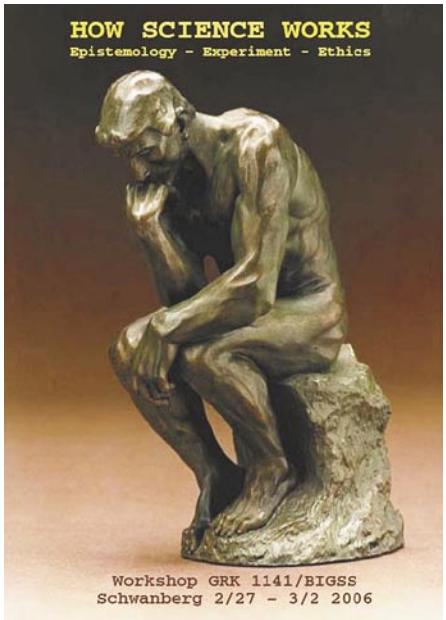

Fig. 1: Poster for the Workshop of the GRK 1141/BIGSS: How Sience Works.

Teaching

At the "Jour Fixe", which takes place each week on Tuesdays, students are presenting their research progress and novel scientific publications or textbook chapters related to the research focus of the RTG 1141. The students are also in charge to invite and take care of external scientists speaking at the Jour Fixe. Annual retreats at Nice or Würzburg are used to intensify the cooperation between the German and French scientists. The students participate in lab exchanges and have a German-French thesis committee. Additional skills are imparted by annual workshops lasting several days. Topics included so far: (1) Entrepreneurship and intellectual property management, (2) Epistemology, history and ethics of science and (3) Scientific writing. RTG 1141 students also benefit from courses and other events that are offered by the International Graduate School of Life Sciences Würzburg. Some events are also performed together with the BioMedTec International Graduate School of Science (BIGSS), which is a joint endeavor of the Universities of Bayreuth, Erlangen-Nürnberg and Würzburg and which is funded by the Bavarian Elitenetwork.

5.3.4 Graduate College 1156, From Synaptic Plasticity to Behavioural Modulation in Genetic Model Organisms

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General Information

The Graduate College 1156 was set up in 2005 as a combined interdisiplinary educational programme by the University of Würzburg, the Institute of Neuroscience, Shanghai, and the Institute of Biophysics, Beijing. Highly skilled students from both countries in the disciplines of biology and medicine will be offered an interdisciplinary educational programme aimed to study the genetic and cellular basis of synaptic plasticity using a methodologically broad approach. The Graduate College provides funding for 12 students from biology and medicine at the University of Würzburg and additional 15 students from the partner institutes in China. An integral part of the educational programme is a stay of at least 3-6 months at the respective partner institutes, allowing the students from Würzburg to become familiar with the research structures of both chinese elite institutes and to use the methods established there in their own research projects. The first round of funding will end in 2009 and the majority of the PhD-students from biology and medicine are expected to finish their theses. Since 2007, the students of this International Graduate College are also members of the class "Neuroscience" of the International Graduate School at the University of Würzburg.

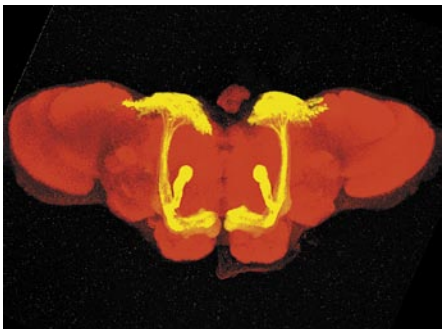

Fig. 1: Brain of an adult fly (red; in yellow the mushroom bodies, the associative center for odour learning).

Major Research Interests

Based on the research foci of the faculties of biology and medicine in the field of neuroscience which are funded and organized via the "Collaborative Research Center 554, Behavior of Arthropods" and the "Collaborative Research Center 581, Molecular Models for Diseases of the Nervous System" as well as the "Clinical Research Unit 125, Attention-Deficit/Hyperactivity Disorder - Translational Research Focus on Molecular Pathogenesis and Treatment across the Life Cycle", the students should work on basic topics concerning synaptic plasticity in the nervous system. All projects address the main question, how synaptic plasticity on the molecular, synaptic and cellular level modulates the function of the nervous system and forms behaviour. From the methodological point of view, model organisms like Drosophila and mouse models with mutations in molecules relevant for the regulation of synaptic plasticity, are in the center of interest. The analysis of the relation of structural alterations to behavioural modulations is one of the biggest challenges in current neuroscience. This challenge can only be met by a broad interdisciplinary approach going beyond faculty frontiers in Würzburg and including international cooperations with the groups at the Chinese Academy of Science.

Teaching

Central courses of the Graduate College are methodological courses to the generation and analysis of model organisms, introduction into modern microscopy (Life Immaging, confocal and STED microscopy), introduction into modern cell culture techniques, special classes and annual symposia in which the students from the groups from Würzburg and the chinese partners participate. The PhD program will extent over three years and will be adapted to the current level of education and the progress in the experimental work of the graduate students. The concomitant educational programme of the Graduate College is an integral part of the education of graduate students in the class "Neuroscience" of the International Graduate School of Life Science at the University of Würzburg.

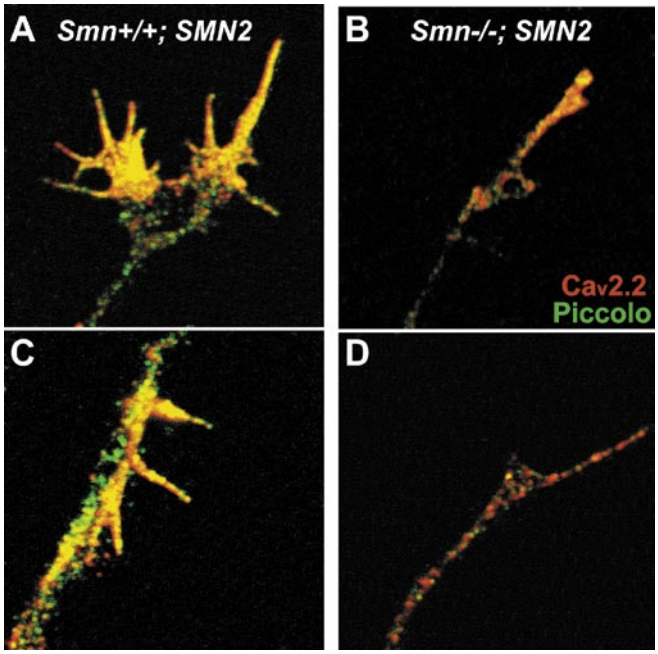

Fig. 2: Disruption of the presynaptic clustering of N-type Ca-channels in growth cones of isolated mouse motoneurons from a mouse model of spinal muscle atrophy (Smn-/-SMN2tg in contrast to controls (Smn+/+SMN2tg). While control motoneurons (A,C) form clusters of Ca-channels with other components of the active zone (piccolo), this process is distorted in motoneurons from a mouse model for the spinal muscle atrophy (B,D).

5.3.5 Graduate College 1253, Emotions

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General Information

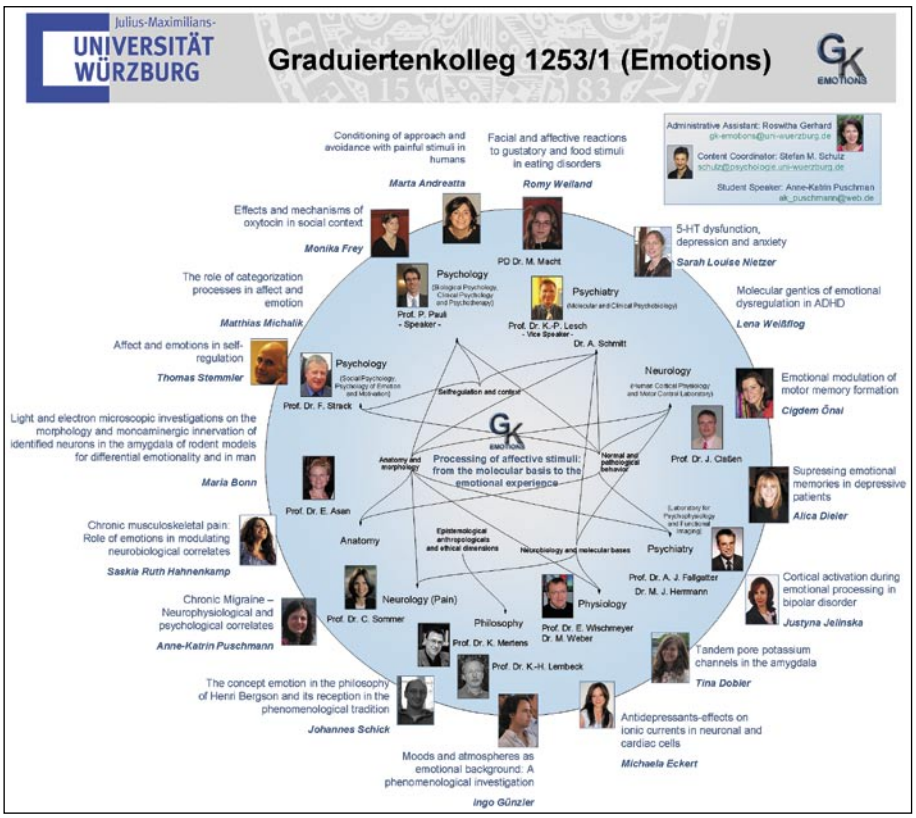
The GK is part of the International Graduate School of the University of Würzburg and follows its rules for the supervision of doctoral students. An interdisciplinary supervision is ensured by doctoral committees for each student with members from different research groups. The three year curriculum is organized to allow an intensive interdisciplinary training on theories and methods of the Affective Sciences and to provide research experiences in different laboratories. Independence of students and professional academic skills will be ensured by special workshops. The integration in international networks of scientists working in the Affective Sciences will be advanced by guest scientists, summer-schools with international scholars and the mandatory presentation of results at international meetings.

Major Research Interests

The present Graduiertenkolleg (GK) aims at identifying important mediators and moderators influencing the processing of affective stimuli. To reach this goal, nine research groups from philosophy, psychology, psychiatry, neurology, anatomy, and physiology closely collaborate in order to develop excellent and internationally visible interdisciplinary research opportunities for doctoral students within the Affective Sciences. The projects of the GK converge on four levels, each addressed by human or animal research: the neurobiological and molecular basis for the processing of affective stimuli, the morphology and anatomy of the involved neural systems, normal and pathological emotional behavior on a cognitive, behavioral and physiological level, and modulating self-regulation processes and contexts. Special interests of the GK are to evaluate the role of the serotonin system and the amygdala in the processing of affective stimuli on several work levels and to identify interactions between levels. The philosophy project provides a theoretical framework for the empirical-experimental projects, and itself focuses on the epistemological, anthropological and ethical dimension of research on emotion.

Teaching

Internet: http://www.gk-emotions.uni-wuerzburg.de/teaching/
Jour Fixe – Journal Club
Seminars and lectures
Invited Guests
Lab Rotation
Soft Skills
External Events



5.4 MD/PhD-Program

CONTACT DETAILS

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MD/PhD Committee
The Faculties of Medicine and Biology appoint one chairman to the permanent joined committee. The committee evaluates the suitability of the applicants and makes the final decision for acceptance. Chairmen of the committee are:

Professor Dr. Axel Rethwilm (Medical Faculty)
Professor Dr. Jörg Schultz (Faculty for Biology)

Purpose and Objective of the Program

The MD/PhD program is a joint training program of the Medical Faculty and the Faculty for Biology of the University of Würzburg. The MD/ PhD program is open for medical students who have finished their MD thesis and have passed successfully the "3. Staatsexamen". Goal of the program is to earn the degree of "Dr. rer. nat." (Ph.D.) according to the graduation rules of the Faculty for Biology or the International Graduate School of Life Sciences (since 2007), respectively, of the University of Würzburg. The MD/PhD program consists of lab practica, a general (specializing) study and seminar program, graduate work with thesis and a graduate defense with exam.

The MD/PhD study program includes

Lectures, seminars, and practical courses in research labs. It lasts for approx. 6 months and is followed by an oral examination. The graduate work starts after finishing the study program.

The MD/PhD program started in summer 1997 and until now 35 students were enrolled. Of these, 15 have received their PhD, 6 obtained a medical specialization ("Facharztanerkennung"), 3 are in the USA as postdocs, 4 obtained their "Habilitation" and 1 received a call for professorship. We expect 5 further PhDs to be obtained in 2008. Although not very large, the MD/ PhD-program of the Medical Faculty can be regarded to be a great success.

5.5 Research Units
5.5.1 Clinical Research Unit 103, Osteogenic Stem Cell Differentiation and Therapy of Bone Loss

CONTACT DETAILS

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General Information

The Clinical Research Unit „Osteogenic Stem Cell Differentiation and Therapy of Bone Loss“

(KFG 103) is being funded by the German Research Society DFG since 2001, to foster research at the Orthopedic Department. A full research professorship for Experimental and Clinical Osteology was established at the same time and was taken over by Prof. Franz Jakob. Presently 5 individual projects and one central project are funded within this Research Unit, two of which are externally localised. One takes place at the chair for Biophysical Chemistry of Würzburg University (Prof. em. Dr. W. Sebald), a second is run at the Charité, Berlin (Clinical Research unit 102 Prof. Dr. G. Duda). The main part of funding is performed according to the funding model of Clinical Research Units, which requires the identical amount of funding to be given from the budget for research and teaching of the state of Bavaria. The district of Unterfranken generously provides the infrastructure and overhead costs for this Clinical Research Unit (KFG). From the beginning the KFG could be built up in a 500 sq. m. environment with working and laboratory space, equipped for S1, S2 and radioactivity working procedures.
The DFG Reviewer Group strongly recommended that KFG 103 should be a seed crystal to establish a Center for Musculoskeletal Research, and should expand by associating other basic and translational science projects. It should further develop Experimental and Clinical Osteology and represent all these issues in Research and Teaching at both the national and international level. During the period under report the KFG is in its second term of funding and it will be finished by 2008. An Orthopedic Center for Musculoskeletal Research has meanwhile been successfully established and Research Capacity has been substantially developed. Based on this and other steps taken during this time the Medical Faculty has decided to advance Research on Musculoskeletal Diseases as an Emerging Field at the Research Campus Würzburg with the perspective of the development of a new research focus for this university.

Major Research Interests

KFG 103 is an interactive platform connecting basic science, translational science and clinical implementation of innovative therapeutic strategies. During the ongoing second term of funding the main topics are differentiation pathways of mesenchymal stem cells and the characterization of key transcription factors for differentiation. We focus on the phosphatonins FGF23 and sFRP4 in context with vitamin D3, on the members of the CCN family of matricellular signalling proteins and the action of bone morphogenetic proteins (BMP). We analyse subpopulations of Mesenchymal stem cells using genome wide array analysis to enhance our knowledge about the basis of regenerative therapeutic strategies. KFG 103 was tightly linked to KFG 102 at the Center for Musculoskeletal Surgery of the Charité Berlin to establish animal models for tissue engineering and bone healing and to analyse the effects of intervention using growth and differentiation factors for bone healing in small and large animal models.

Key Issues in Research

- Biology of mesenchymal stem cells, phosphatonins and osteogenic cell differentiation (F. Jakob, R. Ebert, T. Schilling, P. Benisch)
- Molecular orthopedics and cell biology, The matricellular signalling molecule CYR61/CCN1 during osteogenic differentiation (N. Schütze, T. Schilling, R. Schenk, K. Schlegelmilch)
- Physiologic BMP signals in osteogenic stem cells. Ligands, receptor cascades, modulators and signalling proteins (W. Sebald)

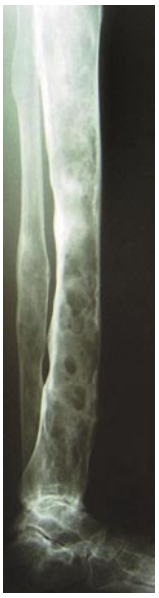

Fig. 1: Fibrous Dysplasia in McCune Albright Syndrome causing additional hypophosphatemic rickets due to FGF23 overproduction in affected osteoblast precursors.

- Regenerative Medicine/Tissue Engineering (U. Nöth, L. Rackwitz, M. Weber, A. Heymer)
- Fracture healing after trauma (KFO 103 in cooperation with KFO 102 Berlin)
- Special outpatient clinic in osteology with a focus on osteoporosis and rare metabolic bone diseases (F. Jakob, L. Seefried, S. Goebel)

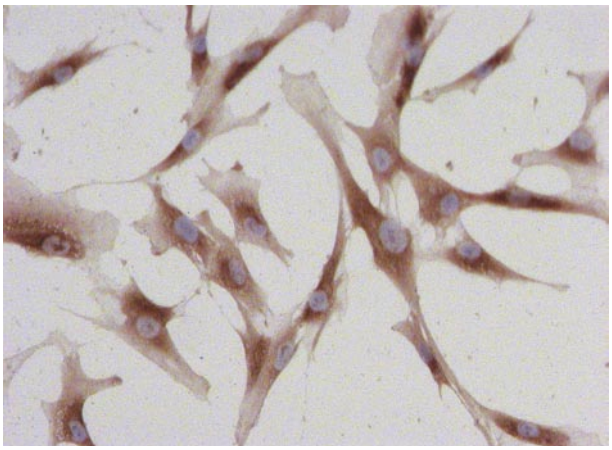

Fig. 2: Immunohistochemical staining of bone chip derived mesenchymal stem cells (antibodies against the cell membrane associated adhesion molecule L1CAM).

Teaching

- Course in clinical examination techniques for operative and conservative orthopedics
- Lectures in Basics of Orthopedics (also accompanying the practical course)
- Practical Course in Orthopedics (bedside teaching in small groups, demonstrations in physiotherapy, plaster techniques and orthopedic technical devices and corselets)
- Clinical ward Rounds, x-ray discussions, orthopedic colloquia
- Molecular Aspects of Bone Diseases – Genes and Cell Biology
- Molecular Methods for osteology in basic science
- Integrated Seminar on the Molecular Basis of Musculoskeletal Diseases

SELECTED PUBLICATIONS

Li Y, Schilling T, Benisch P, Zeck S, Meissner-Weigl J, Schneider D, Limbert C, Seufert J, Kassem M, Schutze N, Jakob F, Ebert R. (2007) Effects of high glucose on mesenchymal stem cell proliferation and differentiation. Biophys Biochem Res Comm 363: 209-15.

Nöth U, Rackwitz L, Heymer A, Weber M, Baumann B, Steinert A, Schütze N, Jakob F, Eulert J. (2007) Chondrogenic differentiation of human mesenchymal stem cells in a collagen type I hydrogel for articular cartilage repair. J Biomed Mat Res-A 83A: 626-635.

Schütze N, Wagemanns R, Fiedler J, Mattes T, Jakob F, Brenner RE. (2007) CYR61/CCN1 and WISP3/CCN6 are chemoattractive ligands for human multipotent mesenchymal stroma cells. BMC Cell Biology 2007, 8:45, (in press).

Cooper C, Jakob F, Chinn C, Martin-Mola E, Fardellone P, Adami S, Thalassinos NC, Melo-Gomes J, Torgerson D, Gibson A, Marin F. (2008) Fracture incidence and changes in quality of life in women with an inadequate clinical outcome from osteoporosis therapy: the Observational Study of Severe Osteoporosis (OSSO). Osteoporos Int. 19: 493-501.

Crockett JC, Schütze N*, Tosh D, Jatzke S, Duthie A, Jakob F, Rogers MJ. (2007) The matricellular protein CYR61 inhibits osteoclastogenesis by a mechanism independent of alphavbeta3. Endocrinology 148: 5761-8.*

5.5.2 Clinical Research Unit 124, The Tumor Microenvironment: Target Structure and Modulator of Immune Responses

CONTACT DETAILS

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General Information

The Clinical Research Group 124 (KFO124) was founded in 2004 under the guidance of Prof. Broecker and Prof. Becker at the Department of Dermatology. Other subprojects (SP) are localized at the gynecological hospital, the Medical clinic II and the Virchow Centre. In September 2007, since the prolongation of its term, 3 further subprojects at the Dermatology, Neurology, and the Medical clinic I were added to the KFO124.

The KFO124 attends to fundamental research and clinical orientated problems concerning tumor-stroma interactions. The obtained knowledge should allow to better understand immune responses in solid tumors. Subsequently, this information can be transferred to clinical aspects to improve the efficacy of immune therapies for malignant diseases and to establish new anticancer vaccines targeting the tumor micromilieu.

Major Research Interests

Malignant tumors are complex tissues composed of cellular and structural components interacting with and influencing each other. Indeed, many steps in cancerogenesis, e.g. proliferation, invasion, angiogenesis, remodeling of the extracellar matrix and metastasis depend on microenvironmental factors that are produced by stroma cells, e.g. fibroblasts, endothelial cells and infiltrating inflammatory cells. In addition, the tumor microenvironment is an important modulator of ongoing tumor-specific immune responses. The modulation is both direct, i.e. inflicting the activity of tumor infiltrating lymphocytes, as indirect, e.g. changing the function of antigen presenting cells. Interestingly, very similar mechanisms seem to be involved in several physiologic situations such as maintaining peripheral tolerance to self antigens or avoiding immune reactions to the semiallogenic fetus during pregnancy. Therefore, analyses of immune evasion mechanisms in pregnant women may help to better understand immune reactions in cancer patients and vice versa.

Within the scope of the KFO124 anti-tumor immune responses ongoing in situ in the context of the tumor microenvironment are analysed. The goal is to obtain a comprehensive understanding of the immunological relevant processes, which determine the result of immune response to solid tumors. Moreover, the tumor microenvironment may serve as an additional source for targets of therapeutic immune responses. Hence, the subprojects of the KFO 124 focus on different cell types and interaction aspects in the tumor micromilieu.

SP Becker

In this subproject stroma-associated antigens are preclinically and clinically evaluated concerning their usage in anti cancer therapy. Immunogenic peptides of tumor-stroma-associated antigens are identified. By using such peptides in a vaccination setting, an immune response should be elicited which by attacking the tumor-Stroma inhibits tumor progression.

SP Fassnacht/Reichardt

The role of tumor-induced immunosuppression in adrenocortical carcinoma is characterised in this project. In particular the effect of glycocorticoids on regulatory T cells is examined.

SP Friedl

The subproject Friedl addresses cell-cell and cell-matrix interactions in 3D collagen gels and in vivo in a mouse model. Focussed on dynamic imaging of cell-cell interactions the group analyses CTL migration, binding to target cells and killing. The aim is to identify tumor escape mechanisms that prevent CTL migration in the microenvironment and CTL-target cell interaction.

SP Kaemmerer

The placenta could be regarded as a natural model system for invasive tumours. In this project the interaction of the tumour-like invasive fetal trophoblasts with maternal immune cells are studied focussing on mechanisms which lead to the induction of tolerance and allow the cytotrophoblasts to escape the maternal immune system.

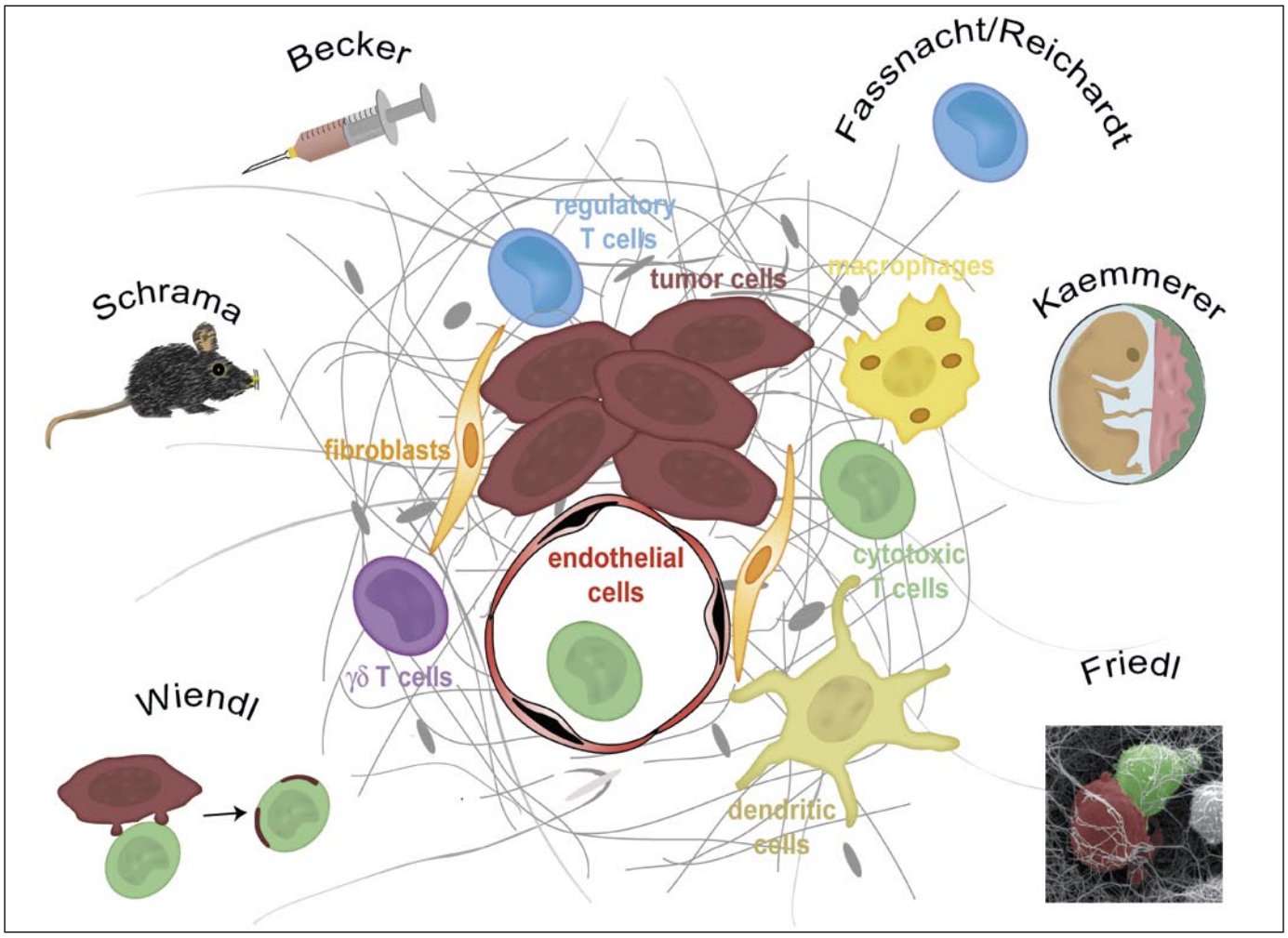

Fig. 1: Cellular components of the tumor stroma and analysis of different aspects in the KFO124 subprojects.

SP Wiendl

The main emphasis of the project is on the detailed characterization of membrane transfer of immune-tolerogenic molecules, such as the non-classical MHC molecule HLA-G or the coinhibitory B7 molecule B7-H1, using trogocytosis as a mechanism of immune-modulation in the milieu of the tumor.

SP Schrama

In this subproject the influence of the nature of the antigen on the development of effector and memory immune responses is analysed. The specific immune responses are directed against antigens which differ in their expression and regulation: a) ubiquitary b) localized, and c) after induction primarily on stroma-associated fibroblasts.

Teaching

The groups participating in the KFO124 supervise medical and biological dissertations, as well as biomedical master theses in fundamental and clinical research. The supervision of dissertations partly is done within the Graduate School of Life Sciences. In addition, the group leaders participate in lectures for the students of different specialisations (medicine, biomedicine, and biology).

SELECTED PUBLICATIONS

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Engert S., Rieger L., Kapp M., Becker J.C., Dietl J., Kammerer U. (2007). Profiling chemokines, cytokines and growth factors in human early pregnancy decidua by protein array. Am J Reprod Immunol 58, 129-137.

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Wobser M., Voigt H., Houben R., Eggert A.O., Freiwald M., Kaemmerer U., Kaempgen E., Schrama D., Becker J.C. (2007). Dendritic cell based antitumor vaccination: impact of functional indoleamine 2,3-dioxygenase expression. Cancer Immunol Immunother 56, 1017-1024.

5.5.3 Clinical Research Unit 125, Attention-Deficit/Hyperactivity Disorder – Translational Research Focus on Molecular Pathogenesis and Treatment across the Life Cycle

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General Information

The molecular pathogenesis of Attention-Deficit/Hyperactivity Disorder (ADHD) and the significance of its endophenotypes and comorbid disorders, such as substance abuse, affective disorders, and antisocial personality disorders, for the course of illness is both clinically and health politically a highly relevant but largely unsolved problem. The Clinical Research Program (KFO 125), as a joint facility of the Departments of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (KJPPP) and Psychiatry, Psychosomatics and Psychotherapy (PPP), deals with the interdependent relationships between the molecular and functional-structural mechanisms of the pathogenesis of ADHD and its significance for its long-term course using interdisciplinary and translational research strategies. The primary goals are based on the following concept: By joining preclinical and clinically oriented research groups, who work on ADHD-specific molecular mechanisms of nerve cell function as well as molecular genetic and developmental biological essentials of brain function, and on structural-functional basis of the complex behavior of ADHD, predictors and differential strategies for therapy during the long-term course of illness are being developed. Moreover, evolutionary conserved ADHD-relevant principles of structure and function of the brain as well as syndrome-typical behavior (e.g., hyperactivity, attention-deficit, impulsivity, aggression, substance use) are being defined by comparative investigations of different species (humans, nonhuman primates, mice). Finally, the preexisting areas of convergence between the fields of neuropsychology, psychobiology as well as child and adolescent, and adult psychiatry will strengthen the connections between the individual disciplines by establishing new research groups, who will investigate common topics. In that, new opportunities for the study of the molecular foundations in the etiopathogenesis and long-term course of ADHD have been put into practice.

Major Research Interests

ADHD (MIM 143465) is the most common behavioral disorder in childhood with a prevalence of 4-8% and with substantial heritability which is likely due to multiple genes of small effect size. Longitudinal studies demonstrated persistence into adulthood with a lifetime prevalence estimated at approximately 2-4%. Epidemiological studies suggested high co-morbidity with other psychiatric disorders; lifetime prevalence rates of anxiety disorders in adult ADHD approach 50%. Affective disorders and alcohol/drug dependence also display a remarkable frequency (Fig. 1). A co-morbidity with antisocial personality disorder was reported to be increased in several clinical cohorts. The burden of disease cannot be overestimated by accounts of social and economic problems as well as impaired academic achievement and work performance. Particularly, disruptive family environment may harm offspring development.

Fig. 1: ADHD subtypes and co-morbidity.

By integrating the concepts of molecular genetics, neurobiology, and cognitive psychology, the psychiatric neurosciences have witnessed remarkable progress in the understanding of the relationship between neurodevelopment, neural function, and behavior related to ADHD. In this context particularly animal models such as genetically modified mice or nonhuman primates contributed important insight. On the other hand improvement of methodological tools in psychology and psychiatry permitted the accumulation of new information on the psycho- and neurobiological basis of behavior and its alteration in ADHD. The human genome project and the sequencing of mouse and rhesus macaque genomes shifted the focus also to investigations of gene function in psychiatry. This development will allow better understanding of both the molecular and cellular foundation of ADHD and the relevance of genetic variation for disease-related behavior such as hyperactivity, attentional and cognitive deficits, emotional dysregulation, and drug use. Finally, the design of novel therapeutic strategies requires translational approaches with interdisciplinary cooperation of basic research and clinical medicine.

The KFO 125 is divided into ten tightly interconnected subprojects (Fig. 2): Two subprojects (SP 1 and 2) focus on clinical aspects including diagnostic evaluation of ADHD and co-morbid disorders across the life cycle as well as ascertainment of patients and their families for genetic study. In addition, these two subprojects assess etiological heterogeneity, clinical symptoms of subtypes and outcome, as well as psychosocial impact of ADHD within the framework of a family-centered outpatient unit. In contrast to previous longitudinal studies, a multi-layer analysis facilitates a novel

approach in follow-up research which is likely to provide a more profound understanding of the interaction between genetic disposition and environmental influences on the course of juvenile and adult ADHD. In synergy to SP 1 and 2 a BMBF-supported study entitled "Effects and Mechanisms of Psychotherapy in the Treatment of ADHD in Children and Adults – The First Randomized Multicentre Study" exclusively focuses on the treatment of ADHD across the life cycle.

Three subprojects (SP 3-5) represent an integrated approach toward elucidation of specific molecular genetic and neurobiological mechanisms of complex behavior related to ADHD. Genome-wide linkage scans using 50K SNP arrays are being performed on extended multigenerational families with high density of ADHD and a sample of affected sib pairs. In addition, application of a 500K SNP array in genome-wide association (GWA) studies will provide a profound basis for subsequent studies on genetically modified mouse models of ADHD. Furthermore, three subprojects (SP 6-8) attempt to define endophenotypes of ADHD by electrophysiological and neuropsychological paradigms as well as functional magnetic resonance imaging (fMRI). Finally, all aspects of the clinical and neurobiological research program are integrated by a subproject on genetic epidemiology/biostatistics (SP 9) and by a junior research group on imaging of genetic variation (SP 10 - JRG). The primary goal of the JRG is the elucidation of the effects of genetic variation on the functional neuroanatomy of attention, impulsivity as well as emotion and its relevance for ADHD using different brain imaging techniques like EEG, NIRS, fMRI and PET.

The basis for the pursuit of these concepts and goals is the interdisciplinary composition of KFO 125 and its integration into the research structures of the University of Wuerzburg (e.g. SFB 581, GRK 1156, GRK 1263, GSLS, IZKF) as well as into a wide spectrum of national (e.g. BMBF Multicentre Study, Nationales Schwerpunktnetzwerk ADHS, MPI für Molekulare Genetik) and international collaborations (e.g. EU Newmood Network, NIMH, NHGRI, NIDA, NIAAA, Tgen Research Institute). This resulted in a specific and long-term configuration of competence at the Clinical Institute of the University of Wuerzburg with focus on future-oriented translational research of etiopathogenetic mechanisms and novel therapeutic options of ADHD.

Teaching

The unique configuration of competence for translational research of the KFO 125 together with the SFB 581 and Graduate Programs within the International Graduate School of Life Sciences (GSLS) provides an excellent platform for competent education and training of a wide variety of junior researchers including Bachelor and Master students, M.D. and Ph.D. students as well as Postdocs from the Faculties of Medicine, Biology, Physics, and Humanities. The enhancement of the interdisciplinarity of teaching in the psychiatric neurosciences is therefore an ultimate goal of the KFO 125. Complex approaches to neurobiological questions and the joint use of techniques and methods derived from molecular biology, genetics, and imaging are the hallmarks of modern psychobiological research, making psychiatric neurosciences interdisciplinary by definition.

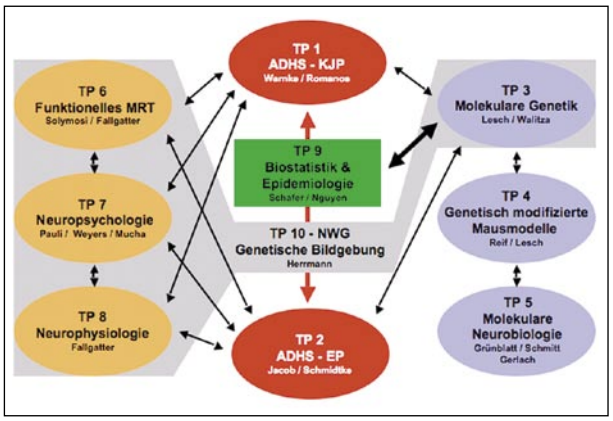

Fig. 2: Overview of KFO 125 subproject interactions indicating the respective main research focus and principle investigators.

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Jacob CP, Romanos J, Dempfle A, Heine M, Windemuth-Kieselbach C, Kruse A, Reif A, Walitza S, Romanos M, Strobel A, Brocke B, Schäfer H, Schmidtke A, Böning J, Lesch KP (2007) Co-morbidity of adult attention-deficit/hyperactivity disorder with focus on personality traits and related disorders in a tertiary referral center. Eur Arch Psychiatry Clin Neurosci 257:309-317.

Canli T, Lesch KP (2007) Long story short: the serotonin transporter in emotion regulation and social cognition. Nature Neurosci 10:1103-1109.

Herrmann MJ, Huter T, Müller F, Mühlberger A, Pauli P, Reif A, Canli T, Fallgatter A, Lesch KP (2007) Additive effects of serotonin transporter and tryptophan hydroxylase-2 gene variation on emotional processing. Cerebral Cortex 17:1160-1163.

Romanos M, Freitag C, Jacob CP, Craig DW, Dempfle A, Nguyen T, Halperin R, Walitza S, Renner TJ, Seitz C, Romanos J, Palmason H, Reif A, Heine M, Windemuth-Kieselbach C, Vogler C, Sigmund J, Warnke A, Schäfer H, Meyer J, Stephan DA, Lesch KP (2008) Genome-wide linkage analysis of ADHD using high-density SNP arrays: novel loci at 5q13.1 and 14q12. Molecular Psychiatry (13:522-530.

5.6 Research Alliances
5.6.1 Rehabilitation Research Network of Bavaria

CONTACT DETAILS

Professor Dr. med. Dr. phil. Hermann Faller (Speaker)

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General Information

The Rehabilitation Research Network of Bavaria (RFB) was founded in 1998 with funding from the "Rehabilitation Sciences" program of the German Ministry of Education and Research and the German Statutory Pension Insurance. As chronic disorders have gained increasing medical and economical importance, medical rehabilitation should be more scientifically oriented. The RFB provides well-coordinated and high-quality rehabilitation research, contributes to the transfer of research results into practice, and improves the regional research infrastructure on a long-term basis. The central institutions, such as the coordination center, methods counseling center (Prof. Dr. Dr. H. Faller, Würzburg), and health economics counseling center (Prof. Dr. G. Stucki, Munich), provide support for research methods and coordinate the 25 network projects. A close cooperation of university departments, rehabilitation clinics, and regional pension insurance institutes characterizes the network structure.

Major Research Interests

The theme of the network is "Patients in Rehabilitation: Disease-specific and Overlapping Approaches to Motivation, Coping, Intervention and Evaluation". During two separate stages of funding, research questions organized into three topics were examined with a patient-oriented perspective (see below). Transfer projects are currently being executed in the areas of patient education and occupational rehabilitation.

Project Area A – Diagnostic and Predictor Studies

In a multi-center study, several patient-based questionnaires for the assessment of rehabilitation effects (SF-36, IRES, SCL-90-R) were examined regarding their sensitivity to change (Prof. Dr. Dr. H. Faller). The German version of the Short Musculoskeletal Function Assessment Questionnaire (SMFA-D), which is suitable for the assessment of functional capacity during routine orthopedic care, was developed and validated (Prof. Dr. A. König). The subjective illness theories of patients with chronic back pain were explored regarding their role as facilitating or inhibiting factors in the rehabilitation process (Prof. Dr. R. F. Wagner). Several studies that were performed outside the University of Würzburg provided information for the development of a questionnaire for the fear of progressive disease, ICF-Core-Sets for selected disorders, and a concept for the monetary evaluation of health outcomes in rehabilitation. Furthermore, gender-specific predictors of rehabilitation successes in patients with myocardial infarction were identified.

Project Area B – Evaluation of Treatment Programs

Patient education programs are a central feature of medical rehabilitation. Their successes depend, among others, on the patients' own motivational factors. In a multi-center study, interventions for the enhancement of motivation in developing healthy lifestyles were evaluated (Prof. Dr. H. Ellgring). In a multi-network project, in-depth analyses of the predictors of successes in patient education were identified and recommendations for the evaluation of patient education were published (Dr. H. Vogel, A. Reusch). Several other projects of rehabilitation clinics aimed to develop and evaluate disease-specific interventions of chronic back pain, kidney diseases, chronic obstructive pulmonary disease, somatoform disorders, and lesions of the brain. Based on studies of Area A, both a treatment program for the fear of progressive disease and a gender-specific intervention for cardiological rehabilitation were also developed and evaluated.

Project Area C – Interface Problems in Rehabilitative Care

In two successive projects, the social medicine evaluation process and the selection of patients for medical rehabilitation were explored in cooperation with the statutory pension insurance. Different strategies for evaluating rehabilitation needs were examined regarding their prognostic validity, and an algorithm for a systematic, stepwise decision-making strategy in social medicine was developed and assessed (Dr. H. Vogel, Dr. A. Holderied). Two other consecutive studies were designed to evaluate working-capacity tests in psychosomatic rehabilitation and to optimize work-related treatment measures. A model project aimed to improve the care of diabetes mellitus patients in a specific region by es-

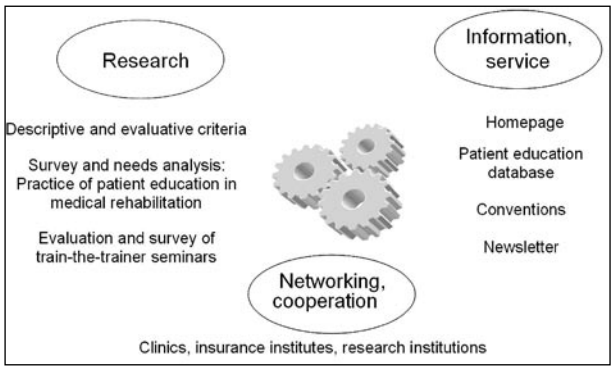

Fig. 1: Aims and roles of the Center of Patient Education.

tablishing a network between a diabetes center and general practitioners. Lastly, a project that combined both philosophical reasoning and empirical research attempted to answer questions of efficiency and justice in the rehabilitation system.

Transfer Projects

The goals of the project "Center for Patient Education" (Prof. Dr. Dr. H. Faller, A. Reusch, Dr. H. Vogel) include the optimization of patient education and the dissemination of research results into rehabilitation clinics (see Fig. 1). Criteria for describing and evaluating patient education programs that may be applied to a wide range of diseases were developed. Existing educational programs were surveyed on a nation-wide basis, and this information was systematically assessed and presented in an online database. In a successive project, one of the focuses will be on quality assurance (training of trainers, among others). The focus of another transfer project is on occupational rehabilitation. A generic screening instrument for the identification of occupational problems and the assessment of job-related rehabilitation needs is currently being developed (Dr. H. Vogel). A second project performs a survey of all occupational interventions currently being applied in rehabilitation clinics in order to determine which interventions are most appropriate (Dr. S. Neuderth). An education module covering occupational rehabilitation topics suitable for various disorders and easily accessible is developed and evaluated as part of a multi-center cooperation project.

In the recent funding program, "Patient Orientation and Chronic Diseases" (BMBF, among others), five additional rehabilitation research projects have been accepted.

Consolidating and extending the departmental section of Rehabilitation Sciences at the above-mentioned institute has improved the research infrastructure. A major input was a professorship for rehabilitation sciences (Prof. Dr. Dr. H. Faller), which was initially granted by third-party payers and is now implemented into the university budget. Additionally, the Network of Rehabilitation Research of Bavaria (NRFB) aims to sustain the regional cooperation of research, clinics, and insurance institutes.

Teaching

The institute's departmental section of Rehabilitation Sciences is responsible for the education in the cross-sectional subject area 12, "Rehabilitation, Physical Medicine, Naturopathy", and offers an optional seminar on Rehabilitation Science. In addition, it contributes to the cross-sectional areas 3, "Health Economy, Health Care System, Public Health", and 10, "Prevention, Health Promotion".

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Wollmerstedt N, Kirschner S, Faller H, König A (2006) Reliability, validity and responsiveness of the German Short Musculoskeletal Function Assessment Questionnaire in patients undergoing surgical or conservative inpatient treatment. Qual Life Res 15:1233-1241.

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5.6.2 BMBF-Network PathoGenoMik-Plus

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General Information

The „PathoGenoMik-Plus“ network is part of the funding and research initiative “Genome research on microorganisms” which was initiated by the German Federal Ministery of Education and Research (Bundesministerium für Bildung und Forschung, BMBF).

During the funding period from 2006 to 2009 the participating groups of the “PathoGenoMik-Plus” network focus on human pathogenic bacteria that are of high socioeconomic relevance for the public health system in Germany due to their wide dissemination in, e. g., hospitals or that pose a particular threat for the health system due to their high rate of antibiotic resistance or their high virulence potential.

While the “PathoGenoMik” initiative (2001-2006) focused on the sequencing of entire genomes from a number of medically important bacterial pathogens the functional analysis of the sequenced genomes with respect to potential applications in the diagnosis, therapy as well as prophylaxis of infectious diseases is the main focus of the “PathoGenoMik-Plus” funding initiative.

The PathoGenoMik-Plus network is coordinated by Prof. Dr. M. Frosch from the Institute for Hygiene and Microbiology from the University of Würzburg. Besides several research groups of the University of Würzburg further German research groups from eight different Universities, the Max-Planck-Institute of Infection Biology (Berlin), the Robert-Koch Institute and the Research Center Borstel are members of the network (Fig. 1).

Fig. 1: Locations of the research groups of the “PathoGenoMik-Plus” network.

Major Research Interests

According to the wide spectrum of infectious diseases investigated in the network the reasearch groups collaborate in four clusters.

Cluster 1 is coordinated by Prof. Dr. Dr. h.c. J. Hacker from the Institute for Moleculare Infection Biology at the University of Würzburg and is focussed on nosocomial infections with special emphasis on the hospital-acquired bacterial species Staphylococcus aureus, Staphylococcus epidermidis and Pseudomonas aeruginosa.

Cluster 2 is coordinated by Prof. Dr. M. Frosch and works on Neisseria meningitidis (the meningococcus) and Streptococcus pneumoniae (the pneumococcus) which are both responsible for the vast majority of cases of acute bacterial meningitis worldwide, especially in young children.

The research activities of the other two clusters focus on the causative agent of tuberculosis in humans Mycobacterium tuberculosis and on periodontitis as a model for polymicrobial disease.

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Batzilla CF, Rachid S, Engelmann S, Hecker M, Hacker J, Ziebuhr W. 2006. Impact of the Accessory Gene Regulatory System (Agr) on Extracellular Proteins, codY Expression and Amino Acid Metabolism in Staphylococcus epidermidis. Proteomics 6(12): 3602-13

A detailed overview about the projects of the former “PathoGenoMik” network (2001-2006) is given in the special issue of the International Journal of Medical Microbiology; Volume 297; November 2007; pp. 479-642; ISSN 1438-4221.

5.6.3 Network of Excellence EuroPathoGenomics

CONTACT DETAILS

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Dr. rer. nat. Andreas Demuth (Office)
Dr. rer. nat. Gabriele Blum-Oehler (Office)
Tel.: 09 31 / 31-2126

General Information

Bacterial infections remain a major cause of disease and mortality in humans and animals throughout the world. Only the detailed understanding of their pathogenic processes will provide us with innovative tools for their prevention and treatment. The study of infectious disease needs a multidisciplinary approach that brings together the different disciplines of molecular biology, immunology, cell biology and structural biology. Although scientific collaborations within Europe have been established to some extent, there is a pressing need for more permanent links and structures between the different disciplines.

This task is accomplished by the Network of Excellence "EuroPathoGenomics" (NoE EPG) that is supported by the European Union with 6.7 million Euro for the duration of five years (July 2005 – June 2010). The NoE EPG, comprising 38 top level laboratories from 13 different nations, is co-ordinated by the University of Würzburg under the direction of Professor Jörg Hacker.

Major Research Interests

One of the major objectives in the field of research is to organise the mass of genomic information that has become available, regarding both microorganisms and their hosts, into schemes allowing one to decipher the cross talks between pathogens and commensals and their host cell and tissue targets. Innovation in diagnostic techniques and therapy, as well as the development of vaccines against pathogenic microorganisms, are expected to come out of the joint research activities of these top-level European research groups in the field of genomic research.

Accordingly, several topics are in the focus of the EPG project:

Comparative genomics/Biodiversity

Comparative genomics has been used to contribute to a better understanding of genome content and evolution of bacterial pathogens. Therefore, DNA-DNA hybridizations, sequencing as well as analysis of genes and complete genomes of different bacteria (e.g. *Vibrio, Rickettsia, Chlamydia, Listeria, Salmonella, Legionella, Bartonella, Escherichia, Staphylococcus, Helicobacter*) were performed in the NoE EPG. Broad comparative genome analysis of different *Vibrio* genomes for example allowed the establishment of a map of the overall genome plasticity in this bacterial group. Furthermore, preliminary results of the comparison of pathogenic *Legionella* species indicate major differences in the virulence gene repertoire and in secretion systems. Moreover, the genome sequence of *Staphylococcus carnosus*, a non-pathogenic *Staphylococcus* species has been completed and the genome has been annotated. Comparative genome analysis with the pathogenic *S. aureus* will give new insight into the core-genome of the species and new accessory genes that might contribute to the virulence of *S. aureus*. These data provide the basis for the application of new genomic approaches allowing the specific combat of pathogenic bacteria.

Antibiotic resistance

Lateral gene transfer through its implication in the development and spread of antibiotic resistance genes among bacterial pathogens is also a topic of major concern in the EPG network. Using Gram-negative and Gram-positive model systems, different aspects of the evolution and spread of antibiotic resistances were analysed by comparative genomics and functional studies. Furthermore, bacterial gene expression in response to exposure to antibiotics was investigated in order to get a deeper insight into the effect of antibiotics on gene regulation. These approaches will result in an improved understanding of the molecular mechanisms contributing to the development and spread of antibiotic resistances and

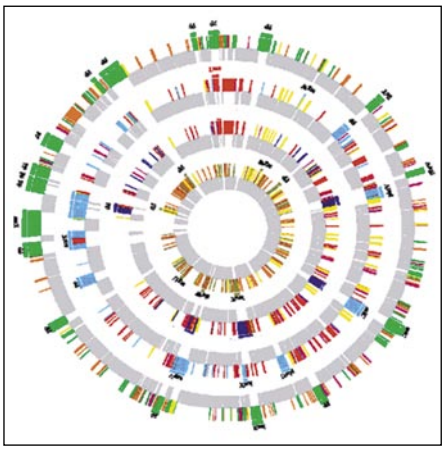

Fig.1: Comparison of different E. coli genomes. Circles represent complete E. coli genomes. From inside to outside: E. coli K-12 strain MG1655, uropathogenic E. coli strain 536, uropathogenic E. coli strain CFT073, enterohemorrhagic E. coli strain EDL 933.

to the discovery of novel anti-infectious agents and their targets.

Cellular microbiology

The analysis of factors influencing the virulence of bacterial pathogens is one of the cornerstones of experimental infection biology. Therefore, extensive analysis of regulatory networks involved in the production of virulence factors and survival of pathogens (e.g. *Mycobacteria, Pseudomonas, Listeria, Legionella, Salmonella, Neisseria*) in vitro and within the host was carried out in the EPG project. Whole genome expression and comparative gene profiling were performed to allow the identification and quantitative analysis of network components that are parts of signalling pathways.

Microbe-microbe interaction

Microbial communities such as biofilms are involved in many infections in humans often resulting in chronic states that are very difficult to combat. Therefore, to develop new strategies for diagnosis, prevention and control of microbial infections it is aimed to identify specific factors expressed within biofilms (e.g. *Escherichia, Legionella, Pseudomonas, Staphylococcus*). The collaboration of some EPG network partners already showed that the presence of specific genes (e.g. *cupB/cupC* and *flp/tad/rcp* gene cluster) and surface proteins is important for biofilm formation of *Pseudomonas aeruginosa*.

Pathogen-host cell interactions

Microbial diseases are the result of the interaction of the parasite and its host. Therefore, analysis of the interactions between bacterial pathogens and eukaryotic cells were accomplished in various cell culture and animal models and corresponding adhesion assays as well as screening tests were established. For example, a library of small organic molecules was screened for their inhibitory capacities on microbial specific structures that induce Toll-like receptor activated signal transduction cascades. This screen resulted in 20 substances classified as inhibitors that could not only help to understand the stimulation of cascades but also serve as therapeutic agents.

Teaching

One of the main activities of the EPG project is related to the education and training of students in the field of pathogenomics. Therefore, the so-called "EuroPathoGenomics Graduate Academy" (EGA) has been established. The EGA provides young scientists a broad-based interdisciplinary study programme with a wide range of seminars, summer schools and practical workshops. Furthermore, participants of the implemented exchange programme have the opportunity to visit the laboratory of project partners in order to exchange expertise and to gain new insights into particular areas of interest.

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5.6.4 Research Program of the BMBF: Effects and Mechanisms of Psychotherapy in the Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in Children and Adults

CONTACT DETAILS

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www.klinik.uni-wuerzburg.de/kjp
www-i.klinik.uni-wuerzburg.de/deutsch/einrichtungen/kliniken/kjp/forschung/ADHD/ForschungsverbundPsychotherapieADHS/content.html

General Information

This national network is part of a research program on psychotherapy in the treatment of psychiatric disorders founded by the German Ministry of Education and Research. The need for a more intense study of psychotherapy in Germany had been stressed by the advisory committee for evidence based psychotherapy (Wissenschaftlicher Beirat Psychotherapie) of the German Psychotherapeutic Association (Bundespsychotherapeutenkammer) and the German Medical Association (Bundesärztekammer). Our network focuses on the treatment of ADHD. ADHD in adults has long been unrecognized and underestimated. Randomized controlled clinical trials including morphological and genetic variables are still missing worldwide.

The aims of the present network are:

- to evaluate the effects of a structured disorder specific psychotherapy (group setting) in adult ADHD in a randomized, placebo-controlled multi-centre study;
- to compare the efficacy of this psychotherapeutic program to pharmacological treatment (methylphenidate) alone and a combination of both;
- to analyse whether the developed psychotherapy manual can be successfully transferred to the setting of child and adolescent psychiatry: does ADHD parent (i.e. adult) treatment reinforce parent (i.e. mother) training outcome in the treatment of ADHD children;
- to examine whether there are specific neurobiological markers (e.g. cerebral morphology, neurochemistry and genetic variations), which can differentially predict therapeutic response to pharmacotherapy, psychotherapy or a combination of both.

The structure of the national network is interdisciplinary and multicentre. 4 projects are established in 10 study centres: recruiting and manualized therapy are provided by Departments for Adult Psychiatry and Psychotherapy (APP) and Department for Child and Adolescent Psychiatry and Psychotherapy (CAPP) in Würzburg (APP, CAPP), in Freiburg (APP, CAPP), Mannheim Central Institute (APP, CAPP), Homburg (forensic psychiatry, CAPP) and Berlin (APP). The multimodal imaging studies will be conducted by the recently established South German Brain Imaging Center (APP Freiburg). Genetic data will be collected and analyzed in Würzburg (EPP). Data management, statistical analysis and monitoring will be provided by the Centre for Clinical Trials in Freiburg. An advisory board is supervising the projects. Treatment integrity is assured by randomized videotaping and external supervision. The consideration of scientific and ethical criteria based on the GCP document of the International Conference on Harmonization (ICH) is supervised by a Data Monitoring Committee (DMC). Our research program is strengthened by the cooperation with the Clinical Research Group ADHD (KFG 125, funded by the German Research Association, DFG) in Würzburg and international cooperations.

In cooperation with the Clinical Research Group ADHD (KFG 125) the “1st International Congress on ADHD” was held in Würzburg. More than 1300 experts and among them the representatives of all leading research groups on ADHD out of 5 continents participated in the congress. Within this framework the „World Association on ADHD“ (president: Prof. Dr. Warnke) and the „International Journal ADHD“ (chief editor: Prof. Dr. Gerlach) had been founded. More than 300 patients and relatives participated in a “patient’s day” and had the opportunity to be informed on new developments in ADHD research and treatment.

Major Research Interests

Main issue of the child psychiatric study groups (principal investigator: Prof. Dr. A. Warnke, CAPP Würzburg) is the project **“Does the treatment of maternal ADHD enhance the effectiveness of parent management training for children’s ADHD?”.** (M. Gerlach, T. Jans, T. Renner, M. Romanos, A. Warnke) The therapy of mothers includes a structured group-psychotherapy-program for adult ADHD in combination with medication (methylphenidate). The control intervention is psychiatric counselling without the implementation of specific therapeutic strategies (randomized trial). After 13 weeks all mothers and children receive parent management training for children’s ADHD carried out on a one-to-one basis. Each of the 4 study centres is going to screen 40 mother-child-pairs for eligibility, 36 will be randomized. Other research questions to be addressed by the study are: To what extent do treatment effects generalize on co-morbid symptoms, family functioning and quality of life areas? Are the differences between the ratings of child, mo-

ther or therapist? Does the sole treatment of maternal ADHD already have influences on the child's symptoms? Are the effects of treatment stable over settings (school, family environment) and time? Is there an association between the child's co-morbidity and treatment outcome?

The project **"Evaluation of the efficacy and effectiveness of a structured disorder specific psychotherapy in ADHD in adults"** (principal investigator: Dr. A. Philipsen, APP Freiburg) is a randomized controlled multicentre clinical trial including 4 conditions: "group psychotherapy + placebo", "group psychotherapy + medication (methylphenidate)", "clinical management + medication" and "clinical management + placebo".

Both of these clinical studies are linked with other projects. The project **"Molecular imaging might predict therapeutic response in adult patients with ADHD. A pilot multimodal neuroimaging study"** (principal investigator: Prof. Dr. L. Tebarzt van Elst, APP Freiburg) is designed to investigate morphological and functional biological brain markers of treatment response using MR spectroscopy.

The moleculargenetic project is entitled **"The association of genetic variation with molecular imaging and the efficacy of cognitive behavioural therapy in adult ADHS"** (principal investigator: Prof. Dr. K. P. Lesch, APP Würzburg). Main study questions are: Which genetic variations are risk factors for the persistence of ADHD in adulthood and which different allele distributions are present in treatment non-responders as compared to responders and allow for a prediction of treatment response? Which specific morphological or neurochemical abnormalities are associated with specific genetic variants? Genotyping and statistical analysis will be performed in national (Institute of Human Genetics, Würzburg; Institute of Medical Biometry and Epidemiology, University of Marburg) and international (amongst others the National Human Genome Research Institute, NIH, Bethesda) cooperation.

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5.7. International Graduate School – Graduate School of Life Sciences

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General Information

For many years the Faculties of Biology and Medicine have offered high-level structured graduate training. Early experiences with structured graduate training at the University of Würzburg were achieved most notably in the context of several DFG-funded graduate programs (Graduiertenkollegs). A prime example of graduate training is also the MD/PhD-program, which was initiated by the Faculties of Biology and of Medicine in 1996/7 as the first such program in Germany. These programs with several generations of basic and clinical scientists have shown the effectiveness of such structured training programs and came together to found the Section Biomedicine in the International Graduate School in 2003. This section has not only built up new structures and developed key elements but also served as a nucleus for the foundation of the "Graduate School of Life Sciences". The last years, and in particular 2006, have seen major steps towards this goal, in particular the foundation of separate graduate schools and the funding of the "Graduate School for Life Sciences" in the "Excellence Initiative of the Federal and State Governments".

Foundation of the International Graduate School (2003-2005)

Discussions in the entire university on modern forms of graduate training culminated in the foundation of the "International Graduate School" (IGS) by the University Senate in December 2003. This "International Graduate School" was initiated to encompass the whole university, with separate sections ("Klassen") to cover the specific scientific and training needs and cultures of their diverse disciplines.

Section of Biomedicine

As a first step, a Section of Biomedicine was formed in the IGS in 2003 by unifying several programs and their graduate students:

- The graduate program "Target Proteins" of the Rudolf Virchow Center
- The graduate program of the Research Center for Infectious Diseases
- The MD/PhD-program of the Interdisciplinary Center for Clinical Research
- Four DFG-funded graduate programs (GK520 "Immunomodulation", international GK587 "Gene regulation in and by microbial pathogens", GK639 "Molecular and structural basis of tumor instability", and GK1048 "Molecular basis of organ development in vertebrates")

These programs came together to find and develop common structures and curricula, to share activities and to set common standards (see box). In 2006, the first graduate students received their PhD from this common program.

The growing Graduate School

Increases in size and scope resulting from the progressive integration of further programs and the discussions in the context of the national "Excellence Initiative" called for a number of changes within the International Graduate School in 2006. These changes concerned both the internal structure and the formal status. The IGS transformed into a holding structure of the independent Graduate Schools by 2006. These Graduate Schools now cater for the needs of different broad fields of science, uniting research in the Life Sciences, the Humanities and Natural Sciences (see Fig. 1). A fourth School in the area of Social Sciences is under way. Each of these schools will independently handle their specific affairs.

The holding, the IGS, assures adherence to, and development along common rules. It also provides general services to the individual schools. In this context, graduation regulations ("Promotionsordnung") were developed and passed by the University Senate in 2006. These regulations contain a set of common articles along with specific regulations of the individual schools. The core principles laid down in the graduation regulations remain those that were originally established in the Section of Biomedicine, including a mentoring system as well as rules for admissions and formal standards (see box). A common charter for the IGS and all the individual Graduate Schools was passed by the Senate in August 2007, regulating issues of membership and operating procedures. The IGS has also developed a standard regulation for doctoral study programs that is easily adaptable to the needs of the individual Graduate Schools. The Study programs "Life Science" and "Humanities" were approved by the Bavarian State Ministry of Sciences at the end of 2007.

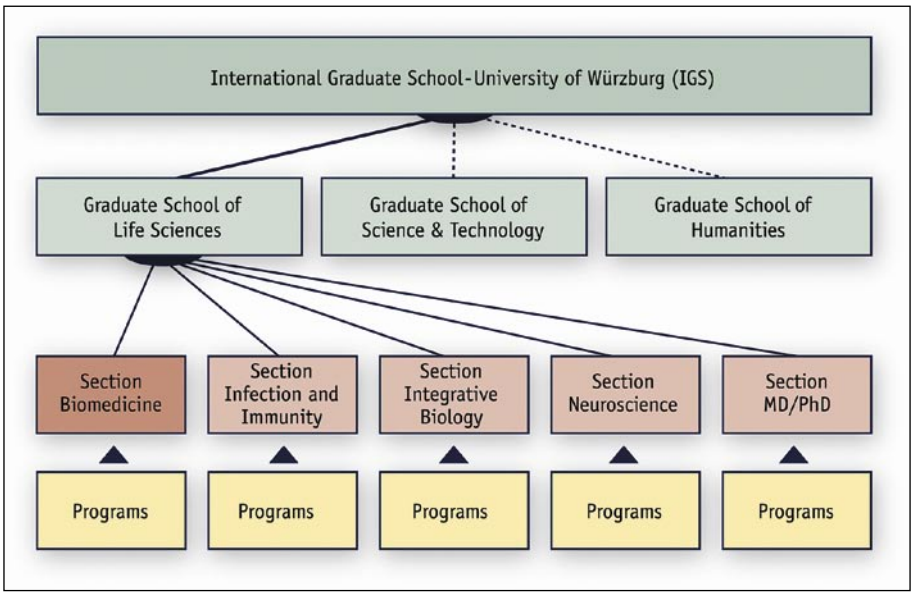

Fig. 1: Structure of the International Graduate School.

During 2007, the number of formal members of the GSLS rose to 103 principal investigators from all participating faculties. 127 young researchers were enrolled in the newly established doctoral study program "Life Sciences".

Recent developments in the Graduate School of Life Sciences

The Graduate School of Life Sciences (GSLS) is now the most advanced Graduate School in Würzburg. It is putting to work the plans that were set forth in the successful application within the Excellence Initiative.

The GSLS now houses graduate students of all collaborative research programs – such as the DFG-funded collaborative research centers ("Sonderforschungsbereiche"), research training groups ("Graduiertenkollegs") and clinical research groups (Klinische Forschergruppen), as well as also other collaborative programs funded by the Federal Ministry of Education and Research (BMBF), the European Union and other sources. This will be a total of more than 300 graduate students. The school is therefore currently divided into five separate Sections. In addition to the Section "Biomedicine", the Sections "Infection and Immunity", "Neurosciences" and "Integrative Biology" were established in addition to the MD/PhD-program. A section usually comprises different programs of about 15 to 25 graduate students. These programs are the scientific as well as social "home" of the graduate students.

A special fellowship program of the GSLS is the core element of funding by the Excellence Initiative. The third round of international recruitment was already underway at the end of 2007. More than 1000 standardized written applications have been evaluated so far in a newly developed process, and interviews with more than 150 candidates were performed by the admission board or are currently scheduled in Würzburg, abroad and by means of video conferencing. Sixteen of the 27 fellows that started their thesis in 2007 are from 9 different countries, underscoring the international character of the GSLS.

Key elements of training in the Graduate Schools

- The traditional single advisor ("Doktorvater") is replaced by a three-person committee.
- A panel of training activities is offered, from which an individual program is tailored to each graduate student.
- Graduate students actively participate in the program by offering and organizing courses and symposia.
- A set of requirements has to be met to warrant a common quality standard.

Mentoring System

Each student has an individual supervisory committee, which meets with the doctoral student at regular intervals to monitor progress and adjust the research and training activities. Additionally, the graduate students report the status of their project within the research groups and programs, exchanging ideas and obtaining feedback within their peer-group.

Training activities

The training activities total a minimum of 150 hours per year and consist of laboratory seminars, journal clubs, program-seminars, methods courses and transferable skills workshops as well as retreats and international conferences.

Common Graduation Commission

The participating faculties form a new common Graduation Commission within the Graduate School. The Commission is responsible for the conferral of all doctoral degrees within the Graduate School. This enforces common standards across disciplines and fosters interdisciplinary cooperation in graduate training.

6. The Medical Faculty: Basic Data

1. Collaborative Research Centers, Graduate Colleges, Clinical Research Units (in 2007)

Collaborative Research Centers:

Collaborative Research Center 479, Variability of Pathogens and Host Reactions in Infectious Diseases

Collaborative Research Center 487, Regulatory Membrane Proteins: From Molecular Recognition to Drug Targets

Collaborative Research Center 567, Mechanisms of Interspecific Interactions of Organisms

Collaborative Research Center 581, Molecular Models for Diseases of the Nervous system

Collaborative Research Center 630, Recognition, Preparation and Functional Analysis of Agents against Infectious Diseases

Collaborative Research Center 688, Mechanisms and Imaging of Cell-Cell Interactions in the Cardiovascular System

Transregio-Collaborative Research Center 17, Ras-dependent Pathways in Human Cancer

Transregio-Collaborative Research Center 34, Pathophysiology of Staphylococci in the Post-genomic Era

Graduate Colleges:

Graduate College 520, Immunomodulation

Graduate College 1048, Molecular Basis of Organ Development in Vertebrates

Graduate College 1141, Signal Transduction: Where Cancer and Infection Converge

Graduate College 1156, From Synaptic Plasticity to Behavioural Modulation in Genetic Model Organisms

Graduate College 1253, Emotions

Clinical Research Units:

Clinical Research Unit 103, Osteogenic Stem Cell Differentiation and Therapy of Bone Loss

Clinical Research Unit 124, Clinical Research Group 124, The Tumor Microenvironment: Target Structure and Modulator of Immune Responses

Clinical Research Unit 125, Attention-Deficit/Hyperactivity Disorder - Translational Research Focus on Molecular Pathogenesis and Treatment across the Life Cycle

2. Honorary doctorates awarded by the medical faculty

1948 Dr. Albert Knoll
Ludwigshafen
1952 Professor Dr. Georg Hohmann
München
1956 Dr. G. Wahl
Würzburg
1961 Professor Dr. Ernst Freudenberger
Basel, Schweiz
1963 Professor Dr. Franz Büchner
Freiburg
1982 Dr. Johannes von Elmenau
München
1982 Professor Dr. Wilhelm Feldberg
London, England
1991 Professor Dr. Arno G. Motulsky
Seattle, USA
1995 Professor Dr. Peter Vogt
La Jolla, USA
1995 Professor Alan E.H. Emery
Budleigh Salterton, England
1997 Professor Dr. Hans Thoenen
München
2000 Professor Dr. Hermann Bujard
Heidelberg
2001 Professor Dr. Hermann Wagner
München
2005 Professor Dr. Volkmar Braun
Tübingen
2007 Professor Dr. G. Fritz Melchers
Basel/Berlin

3. Rinecker- Medals awarded by the medical faculty

1890 Professor Dr. Robert Koch*
Berlin
1891 Professor Dr. Camillo Golgi*
Pavia, Italien
1994 Professor Dr. Emil von Behring*
Marburg
1897 Professor Dr. Johannes von Kries
Freiburg i. B.
1900 Professor Dr. Karl Schleich
Charlottenburg
1903 Dr. Ernst Overton
Würzburg
1909 Professor Dr. Clemens von Pirquet
Breslau
1912 Geheimrat Dr. Max Rubner
Berlin
1917 Professor Dr. Heinrich Albers-Schönberg
Hamburg
1922 Professor Dr. Franz Hofmeister
Würzburg
1929 Professor Dr. Ludolf von Krehl
Heidelberg
1936 Professor Dr. Adolf Butenandt*
Danzig
1943 Professor Dr. Bernhard Bavink
Bielefeld
1950 Professor Dr. Georg Sticker
Zell a. Main
1956 Professor Dr. Erich Grafe
Garmisch-Partenkirchen
1965 Professor Dr. Hans Rietschel
Würzburg
1973 Professor Dr. Dr. Viktor Emil
Freiherr v. Gebsattel
Würzburg/Bamberg
1977 Professor Dr. Georges Schaltenbrand
Würzburg
1982 Professor Dr. Loris Premuda
Padua, Italien
1986 Professor Dr. Shaul G. Massry
Los Angeles, USA
1993 Professor Dr. Miklos Palkovits
Budapest, Ungarn
1995 Professor Dr. Ernst J.M. Helmreich
Würzburg

(*Nobel laureates)

4. Virchow-Lectures

1997 Professor Dr. Melitta Schachner
Hamburg
1997 Professor Dr. Donald Metcalf
Melbourne, Australien
1997 Professor Dr. Carlo Croce
Philadelphia, USA
1997 Professor Dr. Ralph Steinmann
New York, USA
1998 Professor Dr. Salvador Moncada
London, England
1998 Professor Dr. Max Perutz*
Maryland, USA
1999 Professor Dr. Heiner Westphal
Cambridge, USA
2000 Professor Dr. Harald zur Hausen
Heidelberg
2000 Professor Dr. Rudolf Jänisch
Cambridge, USA
2001 Professor Dr. Manfred Eigen*
Göttingen
2002 Professor Dr. Axel Ullrich
Martinsried
2002 Professor Dr. Alfred Wittinghofer
Dortmund
2002 Professor Dr. Dieter Gallwitz
Göttingen
2003 Professor Dr. Peter Gruss
München
2004 Professor Dr. Kai Simons
Dresden
2004 Professor Dr. Peter Walter
San Francisco, USA
2005 Professor Dr. Hartmut Michel*
Frankfurt
2005 Professor Dr. Svante Pääbo
Leipzig
2006 Professor Dr. Günter Blobel*
New York, USA
2007 Professor Dr. Oliver Smithies*
Chapel Hill, USA
2007 Professor Dr. Klaus Rajewsky
Boston, USA

(*Nobel laureates)

5. Winners of the Albert Koelliker-Award for excellent teaching

Semester	Winners
Autumn 2003	Doctors of the Department of Anaesthesia and Critical Care and students of the AGN (Arbeitsgemeinschaft Notfallmedizin): PD Dr. F. Kehl, Dr. A. Schoefinius, cand. med. T. Plappert, cand. med. U. Rohsbach
Spring 2004	Professor Dr. K. Wilms, Director of Department of Internal Medicine II
Autumn 2004	Professor Dr. D. Patzelt, Head of the Institute of Forensic Medicine
Spring 2005	Professor Dr. A. Warnke, Director of the Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy
Autumn 2005	University lecturers of the Institute for Anatomy and Cell Biology II: Professor Dr. D. Drenckhahn, Professor Dr. E. Asan, Professor Dr. P. Kugler, Dr. J. Waschke
Spring 2006	Professor Dr. M. Gekle, Institute of Physiology
Autumn 2006	Professor Dr. M. Frosch, Head of the Institute for Hygiene and Microbiology
Spring 2007	Professor Dr. M. Böck, Director of the Institute for Transfusion Medicine and Haemotherapy
Autumn 2007	University lecturers and tutors of the Skills Lab: Professor Dr. W. Voelker (Med. Clinic I), Professor Dr. M. Schmidt (Med. Clinic I), PD Dr. R. Jahns (Med. Clinic I), Dr. J. Schönberger (Med. Clinic I), Dr. W. Burghardt (Med. Clinik II), PD Dr. Dr. U. Dietz (Surgery), PD Dr. T. Meyer (Surgery), PD Dr. E. Gerharz (Urology), S. Böning (Urology), cand. med. S. Beck, cand. med. J. Filser, cand. med. J. Jahn, cand. med. P. Jahn, cand. med. S. Koerdt

6. Habilitations

2005

Clinical

Dr. Ulrich Oppitz	Radiation Therapy
Dr. Peter Flachenecker	Neurology
Dr. Jürgen Zielasek	Neurology
Dr. Christiane Schneider-Gold,	Neurology
Dr. Richard Kellersmann	Surgery
Dr. August Stich	Internal Medicine
Dr. Kay Double	Neurochemistry
Dr. Norbert Hofmann	Dental-, Oral- and Maxillofacial Medicine, especially Operative Dentistry and Periodontology
Dr. Volker Kunzmann	Internal Medicine
Dr. Frank Weidemann	Internal Medicine
Dr. Peter Reimer	Internal Medicine
Dr. Sebastian Maier	Internal Medicine
Dr. Wolf Bertram Illert	Surgery
Dr. Dominik Brors	Otorhinolaryngology
Dr. Sibylle Jablonka	Neurogenetics
Dr. Uwe Gbureck	Experimental Dentistry
Dr. Thomas Meigen	Biophysics of Visual Perception
Dr. Christiane Völter	Otorhinolaryngology
Dr. Burkhard Jabs	Psychiatry and Psychotherapy
Dr. Oliver Ritter	Internal Medicine
Dr. Kai Schuh	Clinical Biochemistry, focus Molecular Biology
Dr. Christiane Waller	Internal Medicine
Dr. Brigitte Buchwald-Lancaster	Neurology
Dr. Herbert Kuhnigk	Anaesthesiology and Intensive Care
Dr. Thomas Dirk Böhm	Orthopedics

Preclinical

Dr. Andreas Rosenwald	Pathology
Dr. Gerald Schwerdt	Physiology
Dr. Stefan Engelhardt	Pharmacology
Dr. Philipp Ströbel	Pathology and Pathological Anatomy
Dr. Wolfram Brune	Virology
Dr. Carsten Scheller	Virology

2006

Clinical

Dr. Annette Kolb-Mäurer	Dermatology and Venerology
Dr. Axel Larena-Avellaneda	Surgery
Dr. Claudia Mehler-Wex	Child and Adolescent Psychiatry and Psychotherapy
Dr. Markus Luster	Nuclear Medicine
Dr. Christian Wunder	Anaesthesiology
Dr. Boris Kramer	Pediatrics
Dr. Stefan Frantz	Internal Medicine
Dr. Lorenz Rieger	Obstetrics and Gynecology
Dr. Matthias Eyrich	Pediatrics
Dr. Enno Schmidt	Dermatology and Venerology
Dr. Martin Gasser	Surgery
Dr. Hans-Thomas Renné	Clinical Biochemistry
Dr. Anil Martin Sinha	Internal Medicine
Dr. Thorsten Stiewe	Biochemistry and Molecular Biology

Preclinical

Dr. Wolfgang Völkel	Toxikology and Pharmakology
Dr. Christoph Sauvant	Physiology
Dr. Jean-Nicolas Volff	Biochemistry and Molecular Genetics
Dr. Bernhard Schmitt,	Anatomy and Cell Biology
Dr. Moritz Bünemann	Pharmacology

2007

Clinical

Dr. Andreas Eggert	Dermatology and Venerology
Dr. Marcus Koller	Internal Medicine
Dr. Stefan Rutkowski	Pediatrics
Dr. Arnd Hönig	Obstetrics and Gynecology
Dr. Ulrich Dietz	Surgery
Dr. Oliver Al-Taie	Internal Medicine
Dr. Jochen Weber	Neurosurgery
Dr. Ulrich Schwemmer	Anaesthesiology
Dr. Jonas Gehr	Surgery
Dr. Susanne Grunewald	Dermatology and Venerology
Dr. Susanne Schwedler	Internal Medicine
Dr. Thomas Meyer	Surgery
Dr. Susanne Walitza	Child and Adolescent Psychiatry and Psychotherapy
Dr. Jörg Bederlau	Anaesthesiology and Intensive Care
Dr. Winfried Göbel	Ophthalmology
Dr. Anna Tycholpon Djuzenova	Clinical Radiation Biology
Dr. Steffen Kunzmann	Pediatrics
Dr. Thomas Bohrer	Surgery
Dr. Martin Fassnacht-Capeller	Internal Medicine
Dr. Dr. Tobias Reuther	Dental-, Oral- and Maxillofacial Medicine, especially Oral and Maxillofacial Surgery
Dr. Thomas Klink	Ophthalmology
Dr. Stefan Störk	Internal Medicine
Dr. Stefan Radke	Orthopedics
Dr. Ulrich Nöth	Orthopedics
Dr. Bernd Baumann	Orthopedics

Preclinical

Dr. Andreas Zettel	Pathology and Pathological Anatomy
Dr. Jens Waschke	Anatomy and Cell Biology
Dr. Carola Förster	Histology and Cell Biology

7. Statistics

Registration numbers

Year	human medicine / thereof female	dentistry / thereof female	biomedicine Bc. / thereof female	biomedicine Ma. / thereof female
WS 2004/05	135 / 79	50 / 32	26 / 18	16 / 14
SS 2005	139 / 71	52 / 29	-	-
WS 2005/06	139 / 85	50 / 29	33 /28	13 / 10
SS 2006	144 / 65	53 / 25	2 / 2	-
WS 2006/07	150 / 108	61 / 41	27 / 25	25 / 16
SS 2007	162 / 87	63 / 39	-	-
WS 2007/08	154 / 83	60 / 40	34 / 27	12 / 6

Graduations (Abschlüsse)

Year	human medicine / thereof female	dentistry / thereof female	biomedicine Bc. / thereof female	biomedicine Ma. / thereof female
Spring 2005	144 / 76	32 / k. A.	-	-
Autumn 2005	133 / 64	42 / k. A.	17 / 12	-
Spring 2006	146 / 81	34 / k. A.	-	-
Autumn 2006	142 / 83	34 / k. A.	28 / 19	14 / 12
Spring 2007	138 / 76	38 / k. A.	-	-
Autumn 2007	96 / 64	40 / k. A.	21 / 12	14 / 11

Doctorates (without doctorates in natural sciences)

Year	preclinical	clinical	total
2005	54	179	233
2006	58	214	272
2007	57	202	259

Habilitations

Year	preclinical	clinical	total
2005	6	25	31
2006	5	14	19
2007	3	25	28

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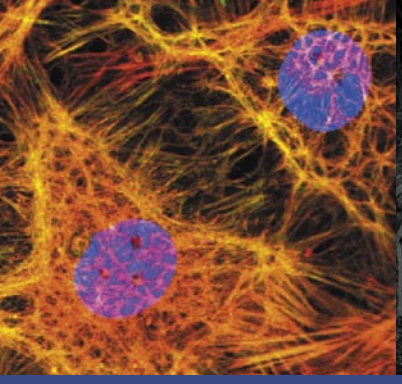
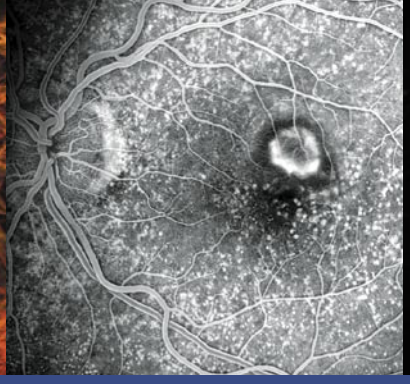

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