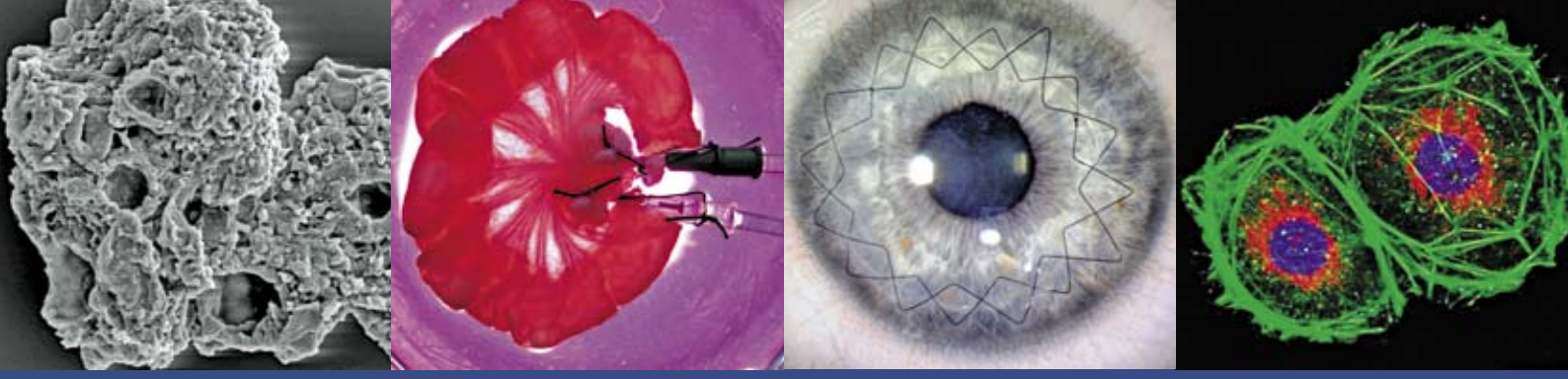

# University of Würzburg
# Medical Faculty

# Research Report 2010

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# Medical Faculty




# Research Report 2010

# Content

**5 Additional Scientific Units**

# 1 General Part
## 1.1 Preface

After having published the Research Report 2008 a number of important developments have taken place in quick succession between 2008 and 2009 at the Faculty of Medicine of the Julius-Maximilians-Universität Würzburg. It has therefore become necessary to again present a report documenting the personnel and structural progress and to highlight the thereof resulting perspectives in a timely manner.

A generation break is taking place at the Faculty of Medicine evidenced by the huge number of new appointments on the theoretical and clinical chairs. During the past years the chairs at the theoretical and clinical institutes have been restocked as follows: Physiology – core theme neuroyphysiology (Professor Dr. Manfred Heckmann), Physiological Chemistry II (Professor Dr. Martin Eilers), Molecular Infection Biology (Professor Dr. Jörg Vogel), Forensic Medicine (Professor Dr. Christoph Meißner), Pathology (Professor Dr. Andreas Rosenwald) and Human Genetics (Professor Dr. Thomas Haaf). In the clinical section Professor Dr. Christoph-Thomas Germer has taken the chair for Surgery, Professor Dr. Ralf-Ingo Ernestus for Neurosurgery and Professor Dr. Maximilian Rudert the chair for Orthopaedics. New chairs have been established for Anatomy III (Professor Dr. Jens Waschke), Developmental Biochemistry (Professor Dr. Manfred Gessler), Experimental Biomedicine with focus on Vascular Medicine (Professor Dr. Bernhard Nieswandt) and Tissue Engineering and Regenerative Medicine (Professor Dr. Heike Walles). With the mentioned appointments the Faculty of Medicine has perfectly succeeded to reinforce and extend the scientific and clinical core themes. In addition, six W2-professor positions have been filled in the clinical and the preclinical/clinical-theoretical area.

In the year 2000 the Bavarian Parliament has accepted the building and structural concept for the Faculty of Medicine which, for example, implies new buildings for the surgical fields and for Internal Medicine, and which aims at joining institutes on the Campus in the Grombühl city district in the process of re-use of the ancient medical and surgical clinics. The start-up and solemn inauguration of the ZIM (Zentrum für Innere Medizin / Center for Internal Medicine) has taken place on the 11th December 2009 in the presence of Prime Minister of Bavaria Horst Seehofer. This central project of the Faculty of Medicine's construction and structural concept has made possible an economically optimized medical care which has become more attractive for patients. It also offers improved conditions for teaching and will give new impulses to research.

The ZIM building has been directly annexed to the ZOM building which has been occupied in 2005. 22,600 square meters of effective area have been constructed with a 157 million € budget. The surface is being shared by the Departments of Internal Medicine I and II, the Department of Nuclear Medicine, the Institute of Clinical Biochemistry and Pathobiochemistry with the central laboratory, the Institute for Transfusion Medicine and Haemotherapy and the Institute of Radiology.

A few weeks before inaugurating the Center for Internal Medicine (ZIM) the Faculty of Medicine celebrated the delivery of the new DFG-Research Center for Experimental Biomedicine (Rudolf-Virchow Center) building and the building of the Research Center for Infectious Diseases (with the Institute for Molecular Infection Biology and four Junior Research Groups). A modern research building of 10,000 $m^2$ effective area has emerged replacing the ancient surgical clinic. Both research centers are united under this roof and thus decisively chracterize the biomedical research profile the University of Würzburg. The total cost for the mentioned construction project has amounted to 78 million €.

With these two construction projects the Faculty of Medicine's declared scientific focuses have received significantly improved conditions for research for meeting the international competition challenges. The Bavarian state government has decided to stabilize the Rudolf-Virchow Center after the DFG support expiry. The basis for the above mentioned far-sighted decision has been laid by the DFG's external assessment of the Rudolf-Virchow Center which has attested international importance and scientific quality on a supreme international level. The supreme scientific performance of the researching staff at the Rudolf-Virchow Center is not only being documented by numerous publications in the most important professional journals but also by the fact that during the past years a number of Rudolf-Virchow Center junior scientists have been appointed for professorships and chairs in Germany and abroad. The DFG has again very positively assessed the Rudolf-Virchow Center in 2009 and conceded a last four-year funding period. In 2013 the Federal State of Bavaria will take over the financial responsibility for this central scientific institution of the University of Würzburg.

A glance at the most recent ranking values makes evident that the huge investment sums resulting from the building projects and the permanency process of the Rudolf-Virchow Center are to be considered as perfectly invested capital: The University of Würzburg holds the 4th rank in the sector of life sciences in the ranking of the German universities with the highest DFG support volumes in 2005 and 2007. Among the Bavarian universities only Munich (LMU) is topping Würzburg: Taking into account the relativised numbers regarding third third-party funding per professorship, however, Würzburg holds indeed the leading position in Bavaria with 505,000 €, and, within the national competence, it shares rank 6 with the universities of Hannover, Ulm, Cologne, Freiburg and Heidelberg. Würzburg holds one of the top places among the competent research universities in medicine also according to the present CHE-ranking.

Starting with this year the clinical research will receive numerous important impulses, and it will complement the defined profile of the University of Würzburg and the Faculty of Medicine in the biomedical basic research in the clinical epidemiologic area. With the Federal Ministry of Education and Research's successful concept appraisal for an integral research and a treatment Center (Comprehensive Heart Failure Center) in 2009 and the announced start of this affirmative measures, the Faculty of Medicine has successfully won a very competitive selection process and has acquired subsidies in the amount of 50 million € for the coming 10 years. By focussing on heart failures the Faculty of Medicine addresses the most frequent cause for referrals to hospitals, which is showing a higher mortality rate than most of the cancer occurrences. The heart failure syndrome is having an increasing relevance for the health policy due to the ageing population. Innovative concepts in research and treatment are meeting this challenge. For this purpose, new and permanent cooperative structures are being established for the interdisciplinary research and teaching in heart failure. For this purpose appointments for several new chairs have been made and a specific study course "Clinical Epidemiology and Biometry" has been conceived for the training of students and clinical researchers.

The Bavarian State has concluded an expansion program in 2008 which will create 38,000 new study places in preparation of the double Abitur (school leaving examination) age group. Although the study places in human and dental medicine are exempted from this extension program, the Faculty of Medicine will make a contribution for the young generation and offer new study courses across faculties. Together with the Faculty for Chemistry and Pharmacy the new study course "Biochemistry B.Sc." has been introduced in the winter semester 2009/2010. The Bachelor study

**Tabelle 1: Forschungsprofil forschungsstarker Hochschulen in Medizin**

| Hochschule | Zahl Spitzenplätze (von max. 9) | Vergleich zu 2006 | absolut | | | | relativ | | | | | Reputation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Drittmittel | Publikationen | Promotionen | Erfindungen | Drittmittel | Publikationen | Zitationen | Promotionen | Erfindungen | |
| Charité Berlin | 6 | ++ | ● | ● | ● | ● | ● | | | | ● | ● |
| Uni Freiburg | 6 | ++ | | | ● | ● | ● | | ● | ● | ● | ● |
| Uni Heidelberg | 5 | ++ | ● | ● | ● | | ● | | ● | | | ● |
| Uni Köln | 7 | + | ● | ● | ● | | ● | ● | | ● | ● | |
| Uni Mainz | 5 | + | ● | | ● | ● | | | | ● | ● | |
| LMU München | 7 | ++ | ● | ● | ● | ● | ● | ● | | ● | | ● |
| TU München | 6 | + | | ● | | | ● | ● | ● | ● | ● | ● |
| Uni Tübingen | 8 | ++ | ● | ● | ● | ● | ● | ● | | ● | ● | ● |
| Uni Würzburg | 5 | ++ | ● | | ● | ● | ● | | ● | | | |

*Medizinische Fakultät in Heidelberg

*Fig. 1: CHE-Ranking from 9th December 2009 / Medicine.*

course “Technology of Functional Materials”, introduced by the Faculties for Physics and Chemistry/Pharmacy in 2006, will be topped up to 60 study places; a respective master study course has been introduced in the 2009/2010 winter semester. The offer of these study courses, which are being complemented by meanwhile established further study courses “Biomedicine” and “Experimental Medicine” makes evident that the Faculty of Medicine feels obliged to junior scientists training in the biomedical basic disciplines. The medical graduates from Würzburg regularly return top results; this shows that a huge importance is being attributed to the core tasks: teaching and training of junior specialists in human and dental medicine. The fact that Würzburg has attained the best results in Germany with the best 2nd state examination past autumn gives prove of the high quality of the medical training at the Faculty of Medicine and the big commitment of the teachers, who are continually improving their teaching with innovative teaching concepts.

On the following pages, the clinical departments and institutes are presenting themselves with their profiles and results. The results and the positive developments to which I have been alluding in this preface would not have been possible without manifold support.

Finally, I am very grateful for the huge support from the Bavarian state government and the Bavarian Parliament which the Faculty of Medicine has received during the implementation of the construction concept and which it is still receiving. I want to specially thank H. Dierl from the Bavarian Ministry for Sciences, Research and the Arts as well the ancient member of the Bavarian Parliament, Mr. M. Ach, who have rendered outstanding services to the Faculty of Medicine. I am grateful for the valuable advice of externs. I thank the expert witnesses from our research centers and research units. With their critical and constructive advice they have essentially contributed to the positive development of our faculty. I also thank the donors of external funds who give essential support to our faculty. Finally, I thank all my colleagues of the Faculty of Medicine, who are notably contributing to the reputation and further development of the faculty with their engagement and creativity.

Würzburg, February 2010
Professor Dr. Matthias Frosch
Dean

# Inauguration of the new Building for the Rudolf Virchow Center and the Research Center for Infectious Diseases on October, 8, 2009

*Fig. 1: Handing over of keys for the new Research Center. From left to right: D. Maußner, building authority Würzburg, F. W. Rothenpieler, head of the office, Bavarian Ministry of Science , the President of the University A. Forchel, M. Lohse from the Rudolf Virchow Center and M. Frosch (Research Center for Infectious Diseases).*

*Fig. 2: The new lecture hall for the Rudolf Virchow Center and the Research Center for Infectious Diseases at the commemorative event for the inauguration during the address by M. Lohse.*

*Fig. 3: The foyer with the historical front of the old lecture hall.*

*Fig. 4: The historical staircase.*

*Fig. 5: The historical south front of the former Departments of Surgery.*

*Fig. 6: The new laboratory building with the main entrance.*

# Inauguration of the Center for Internal Medicine (ZIM) on December, 12, 2009

*Fig. 1: Aerial view of the ZOM/ZIM complex.*

*Fig. 2: The Dean M. Frosch (right) and the Managing Medical Director C. Reiners (2nd from right) guide District President P. Beinhofer (left) and Prime Minister of Bavaria H. Seehofer (2nd from left) through the main thoroughfare of the ZOM/ZIM.*

*Fig. 3: During the commemorative event for the inauguration of the ZIM. First row from left: Managing Medical Director C. Reiners, President of Parliament B. Stamm, Prime Minister of Bavaria H. Seehofer and President of the University A. Forchel.*

*Fig. 4: View form the terrace of the ZIM towards one of the bed-houses.*

*Fig. 5: Interior view of the main thoroughfare of the ZIM.*

*Fig. 6: View of the bed-houses and the illuminated main thoroughfare.*

*Fig. 7: One of the inner courtyards between the bed-houses.*

*Fig. 8: A look inside the central laboratory.*

# Honors awarded by the Medical Faculty

*Fig. 1: Awarding of the honorary doctorate to* ***Professor Dr. Harald zur Hausen*** *during the graduation ceremony on May, 31, 2008 in the Neubaukirche through the Dean Professor Dr. M. Frosch (right). Professor H. zur Hausen was faculty member at the Institute of Virology and Immunobiology of the University of Würzburg from 1969 to 1972 prior to accepting a chair in Erlangen. The Medical Faculty honored his outstanding scientific achievements in the field of virology and especially his contributions leading to the identification of the human papilloma virus as the causative agent of cervix-carcinoma. With Professor Dr. H. zur Hausen the Medical Faculty not only honored an internationally regarded scientist, but also appreciated his long-lasting connections to the Medical Faculty of the University of Würzburg.*

*Fig. 2: For his long standing achievements in the Medical Faculty of the University of Würzburg, the Rinecker-Medal in gold was awarded to* ***Professor Dr. Volker ter Meulen*** *(right) on May, 23, 2009 during the graduation ceremony of the faculty in the Neubaukirche. The medal and the certificate were handed over by the Dean Professor Dr. M. Frosch (left). In his laudation, Vice-dean Professor Dr. M. Lohse appreciated, besides the scientific achievements of the virologist who was born in Osnabrück in 1933, especially his contributions to the development of a scientific strategy of the Medical Faculty.*

*Fig. 3: The Siebold-Medal honors people, who rendered outstanding services to the Medical Faculty and the University Hospital. On May, 8, 2009* ***Manfred Ach****, Member of Parliament, off duty (2nd from left) and* ***Professor Dr. Walter Eykmann****, Member of Parliament, off duty (3rd from left) were honored by the Dean Professor Dr. M. Frosch (left) and the Managing Medical Director Professor C. Reiners (right) with the newly created Siebold-Medal.*

# 1.2. Medical Education

The Faculty of Medicine continuously improves medical education. Comprehensive teaching evaluations, also for the practical year, are being performed since many years. They reveal areas for improvements; positively evaluated teaching models may also be transferred to other areas. The Albert-Koelliker teaching price amounting to 10,000 Euro is being awarded twice a year for extraordinary teaching achievements. The Dean for Student Affairs' Office is closely and successfully cooperating with the students' representatives, so that constructive improvement suggestions may be quickly set into action.

Würzburg's medical students regularly achieve first places at the state examinations which are identical all over Germany (ranking among 35 faculties of medicine). The Würzburg students have reached the first place in the 2nd state examination in autumn 2009. The Faculty of Medicine's main aim in medical education is to offer to students an excellent theoretical training and a comprehensive training in practical medical skills as well as in a qualified scientific education.

**Teaching clinic**

Since 2009 the previous Skills Lab is being expanded to a teaching clinic which will occupy 1,500 $m^2$ with a fully functioning operating theatre. After a comprehensive renovation, the teaching clinic, as integral part of clinical training of medical students, will concentrate the practical courses in a conceptive and spatial way and at the same time integrate preclinical and clinical subjects. A division into operative section, ward section, skills training rooms with phantoms for e.g. blood sampling, auscultation ultrsound, lumbal puncture, and seminar rooms reflects the training concept. The earlier compulsory courses for the 5th semester are complemented by compulsory courses with higher clinical demands for the 7th and 10th semesters. Students will also have to pass an OSCE (objective structured clinical examination) for these courses. A unit with standardized patients to simulate clinical settings is financed by tuition fees and is integrated as inherent part into the teaching clinic's concept. Study rooms and lounges will be at the students' disposal. The use of the new seminar rooms shall be open to many clinics and institutes. The medical administration of the teaching clinic has been transformed from a honorary to a part-time occupation.

**E-Learning, Wue-Campus**

Patient case training plays a central role

*Fig. 1: Student training with a simulation patient.*

in medical education. Although the treatment of virtual patients cannot substitute the real patient contact it constitutes a perfect means for the preparation since notably the theoretical basis of the patient treatment can be trained in a case-oriented way. Numerous studies are proving that dealing with didactically prepared cases considerably increases the learning success. At the same time the cases' complexity may be adapted to the students' progress.

Didactically prepared cases are successfully being employed and evaluated since a few years at Würzburg's Faculty of Medicine, notably in rheumatology[1] and haematology[2]. Due to the successful results the university is aiming at a systematic application by means of the university-wide Blended Learning Project which is being financed by study fees since 2007. Case-training cases have been developed for the following subjects: Internal Medicine (cardiovascular diseases, pneumology, haemato-oncology, endocrinology, nephrology, gastroenterology), infectiology, clinical immunology/rheumatology, geriatrics, surgery, dermatology, neurology, medical terminology, clinical chemistry, ophthalmology, psychiatry and psychosomatics, neurosurgery, gynaecology, nuclear medicine, urology.

The university-wide e-learning platform WueCampus is a further improvement made possible by tuition fees. In Wue-Campus e-learning materials all are being centrally administered and are made accessible to students by a single-sign-on. Two semesters ago, electronically supported examinations have been introduced in some areas. The aim of this project is to perform electronic examinations in the near future.

Since April 2008 the Faculty of Medicine Würzburg has been appointed to be the e-learning competence center within the project "Teaching in Medicine in Bavaria" financed by the Bavarian State Government. Seven project applications of the Faculty of Medicine have been approved by the vhb (virtual Bavarian university) in 2009.

**Promotion of junior scientists**

The Faculty of Medicine not only teaches the transfer of medical skills, but also claims that the medical education shall convey the scientific basics of medicine and introduce the student into the current biomedical research. In order to ensure the students' intensive education in the biomedical basic research, the additional study course "Experimental Medicine" has been introduced in the 2005/2006 winter semester.

The additional study course "Experimental Medicine" is performed with a research orientation and shall convey current scientific issues in the area of life sciences as well as the experimental procedures and methodical principles at the intercept points of medicine, biology, chemistry and physics. The interdisciplinary education is being reflected by the participation of further faculties – biology, chemistry, physics – besides medicine. The student's intensive support is guaranteed by limiting the number of students to 5 per semester.

With the 2009/2010 winter semester the master study course Experimental Medicine has been developed out of the additional study course. The 'state exam medicine' qualifies for application. Course achievements of the additional course can be credited, so that the graduation can be obtained with the master thesis already after one semester. By this means, an additional final degree can be obtained besides a qualification. Also students from other universities with a final degree are allowed to follow the master study course in Würzburg.

In addition to the MDPhD program, financed by the IZKF, the Faculty of Medicine grants 30 scholarships for experimental doctorates and thus improves the quality of the medical doctor for students, who spent an additional semester to write an outstanding doctoral thesis.

**Mentoring**

A mentoring program for female students, financed by tuition fees, has been introduced in the 2008/2009 winter semester. Even though the majority of medical stu-

[1] Reimer S, Hörnlein A, Tony, HP, Krämer D, Oberück S, Betz C, Puppe F, Kneitz C (2006). Assessment of a case-based training system (d3web.Train) in rheumatology. Rheumatology International 26 (10), 942-948,

[2] Krämer D, Reimer S, Hörnlein A, Betz C, Puppe F, Kneitz C (2005). Evaluation of a novel case-based Training Program (d3web.Train) in Hematology. Annals of Haematology 84 (12), 823-829.

*Fig. 2: A medical student from Würzburg (r.) in the operating room of the Bugando Hospital Mwanza, Tanzania, during his last year elective third.*

dents and graduates are women, only 10 % of them, or even less, finally occupy leading positions (senior physicians, chief physician, professors). Studies reveal that different career goals and career tracks of men and women become evident already few years (1-3) after graduation. Therefore it is our aim to give our female students the possibility to reflect their situation, to become aware of their career goals and to pursue these goals already during their studies. The students are accompanied during their lectures, workshops and seminars by female and male mentors who give them professional career advice and support.

The current mentoring program design for female students is now being adapted and also opened for male students. In addition, foreign students are supported in a mentoring program which has been especially adapted to their needs and to overcome their language barriers.

**Internationalization**

A part-time employee, financed by study fees, supports the international student exchange. Apart from the faculty partnership agreements with the University of Rochester/USA and the University of Nagasaki new cooperation agreements have been signed in the meantime with the Weill Bugando University College of Health Sciences in Mwanza, Tanzania, and the University of Sao Paulo, Brazil.

A number of new ERASMUS partnerships have been contracted with European universities, which offers more students better facilities to pass part of their studies abroad.

**Dental Medicine**

At present, 600 dental students are enrolled at the University of Würzburg, 300 of them in the preclinical, 300 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 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 26,600 out-patients and more than 1,300 in-patients have been treated in 2008.

All departments are equipped according to the newest technical standard (exception: conservative dentistry). State-of-the-art equipment necessary for a modern dentist training is available. In diverse departments, interactive training concepts and problem-based learning integrated in the clinical training are now offered. With the new Medical Licensure Act for dentistry students the teaching concept will pass through further modifications. Students have access to an extensive library with numerous computer work stations with internet connection for their private studies. 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 the student courses. A part of the financial

***Tab. 1: ERASMUS partners of the Faculty of Medicine Würzburg***

| Land | Stadt | Universität |
|---|---|---|
| Belgium | Antwerp | Universiteit Antwerpen |
| Finland | Turku | Turun Yliopisto, Turku |
| France | Caen | Université de Caen |
| | Grenoble | Université Joseph Fourier |
| | Limoges | Université de Limoges |
| | Strasbourg | Université Louis Pasteur Strasbourg |
| Greece | Salonika | Aristoteleio Panepistimio Thessalonikis |
| Italy | Ferrara | Università degli Studi di Ferrara |
| | Rome | Università Campus Bio-Medico di Roma |
| | Rome | Università degli Studi di Roma "La Sapienza" |
| Poland | Wroclaw | Uniwersytet Wrocławski |
| | Cracow | Uniwersitet Jagiellonski w Krakowie |
| Portugal | Coimbra | Universidade do Porto |
| | Porto | Universidade do Porto |
| Schweden | Umeå | Umeå Universitet |
| Slowenia | Maribor | Univerza v Mariboru |
| Spain | Barcelona | Universitat Internacional de Catalunya |
| | Granada | Universidad de Granada |
| | Salamanca | Universidad de Salamanca |
| Turkey | Bursa | Uludağ Üniversitesi, Bursa |
| | Izmir | Ege Üniveritesi |
| Hungary | Budapest | Semmelweis Egyetern, Budapest |

burden, which dental students have to bear today, is thus taken off.

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

Prof. Dr. med. J. Deckert, Dean of Student Affairs Human Medicine
Prof. Dr. med. Dr. med. dent. A. Kübler, Dean of Student Affairs Dental Medicine
Dr. E. Lüneberg, Dean of Student Affairs' Office

# 1.3 Students' Representatives

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**97080 Würzburg**

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**E-mail: fachschaft.medizin@uni-wuerzburg.de**
**www.fi-med.de**

The student council is a group of students who advocate on the interests of the medical students at the University of Würzburg Medical Faculty. It is our objective to enhance the conditions for studying and teaching by our student engagement in cooperation with the academics at our faculty. To solve conflicts, develop new concepts and ideas, we beat bridges between academics and studying.

We mainly work on two major aspects: On one hand we represent the medical students in a various number of committees: in the faculty council, in the committee of study affairs, in the student council and in the appointment board of the faculty.
Since tuition fees had been implemented, we are engaged in the fee commission and we are working for a wise and efficient use of the money.
The second working field complies of different tasks around consultation and support of the students, e.g. organisation of informative meetings, office work and improve social life by organizing parties and various other meetings.

At the beginning of the studies we welcome the freshers in the context of the first semester days. We give them the opportunity here to get to know better their new fellow students, the city of Würzburg and the university. At the beginning of the clinical part of their medical studies, we take the new clinical semester on a guided tour of the hospital and introduce them to the different clinical complexes and institutes. For the two events we publish an information booklet which informs the students about the faculty, lectures, courses, examinations, books, events and many broader topics. In addition, we offer information on our redesigned home page. During the lecture time our office serves as a contact point for questions and problems of the students. Here, we offer further study and informative material around the study of medicine.

The Segmed, a nationwide association of medical students, which offers favourable medical equipment (e.g. stethoscopes) as well as the bvmd which among other things cares about international exchange programs for medical students, find a room in our premises for their consultation hours.

The group of MSV is an interactive prevention project of medical students for pupils. The MSV informs about save and tolerant dealing with sexuality and contraception. The teddy bear clinic, which shall easily lead children up to the situation with the doctor and in the clinic, enlarges the supply around the student engagement.

Our students' council meeting takes place weekly. This serves the exchange of information and offers room for discussion about current requests and for the planning of new projects.

Among other things, results of our engagement are the AG teaching co-ordinators which represent a close cooperation with the teaching coordinators financed from tuition fees to initiate innovative teaching strategies and the PromoMed convention which supports students when finding a medical dissertation.

We organize film- and cinema evenings, live assignments of the soccer European championships and World Cups and numerous parties, to the better social networking of the medical students.

Within the next semesters, furthermore we want to commit ourselves to the improvement in the teaching; this is yet concretely comprehensible at the idea and conception of the teaching clinic with library, practical-clinical examination courses, recreation, study, and conference rooms, whose opening lies ahead soon. We look forward to a furthermore active and constructive cooperation within the faculty.

The students' representatives
of the medical faculty

# 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 is not clear, however, to what degree formal medical teaching was inaugurated at the time. Certainly, any regular teaching activities must have come to an end within a few decades, due to 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, a 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 paradigm, 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. Adriaan 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 witness 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 word 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 reconstruction work created space for about 200 curable patients and thus markedly improved the conditions for 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 on 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 Wilhelm Schelling who sought to put medicine on new, philosophical foundations. At the height of his fame in Würzburg, 270 medical students immatriculated 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 improved 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 called for 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 also came from researchers outside of the Medical Faculty, from the biologists Julius Sachs and Theodor Boveri, for example, and 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. Werner Heyse, who was appointed professor of psychiatry in Würzburg in 1939, played a leading role in the so-called „Aktion T4", the organized mass murder of 10.000s of psychiatric patients and handicapped men, women and children between 1939 und 1941. Based on the „Gesetz zur Verhütung erbkranken Nachwuchses" (1933) 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 that diseases, in order to examine 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 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 outpatient 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 "Graduate School of Life Sciences". 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 the creation of a "Zentrum Operative Medizin" (ZOM), a "Zentrum Experimentelle Molekulare Medizin" (ZEMM) and a "Zentrum Innere Medizin" (ZIM).

Professor Dr. med. Dr. phil.
Michael Stolberg
Institute for the History of Medicine

# 2. Research Institutes
# 2.1 Institute of Anatomy and Cell Biology, Chair of Anatomy 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. One Post-Doc and four 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 physiologically 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. 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 and organic anions. 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 (Fig.1). Using fluorescent labeling of single amino acids of OCT1 we could demonstrate motion of the 11th transmembrane domain during transport of organic cations. 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.

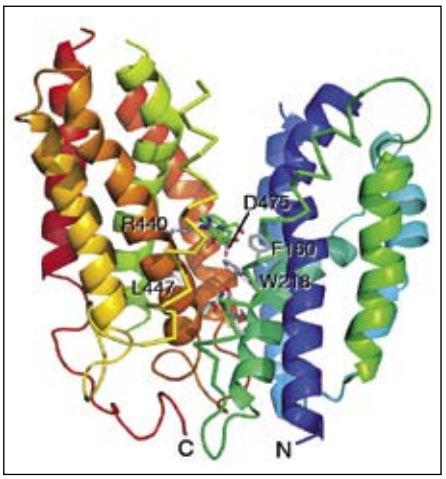


*Fig. 1: Model of the interaction of corticosterone with the outward-facing substrate binding pocket of the organic cation transporter rOCT1. For the indicated amino acids an interaction with corticosterone has been shown experimentally.*

**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 differen-

tiated 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. We identified two RS1 domains, which are responsible for the post-transcriptional inhibition of SGLT1. Tripeptides derived from these domains inhibited SGLT1 function at nanomolar 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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*Gorbunov D, Gorboulev V, Shatskaya N, Mueller T, Bamberg E, Friedrich T, Koepsell H (2008) High-affinity cation binding to organic cation transporter 1 induces movement of helix 11 and blocks transport after mutations in a modeled interaction domain between two helices. Mol. Pharmacol. 73, 50-61.*

*Keller T, Schwarz D, Bernhard F, Dötsch V, Hunte C, Gorboulev V, Koepsell H (2008) Cell free expression and functional reconstitution of eukaryotic drug transporters. Biochemistry 47, 4552-4564.*

*Volk C, Gorboulev V, Kotzsch A, Müller TD, Koepsell H (2009) Five amino acids in the innermost cavity of the substrate binding cleft of organic cation transporter 1 interact with extracellular and intracellular corticosterone. Mol. Pharmacol. 76, 1-15.*

*Filatova A., Leyerer M, Gorboulev V, Chintalapati C, Reinders Y, Müller TD, Srinivasan A, Hübner S, Koepsell H (2009) Novel shuttling domain in a regulator (RSC1A1) of transporter SGLT1 steers cell cycle-dependent nuclear location. Traffic 10, 1599-1618.*

# 2.2 Institute of Anatomy and Cell Biology, Chair of Anatomy II

CONTACT DETAILS

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**Professor Dr. med. Peter Kugler**
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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 and epithelial 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 and a new technique to measure vascular permeability in rats in vivo (single-microvessel perfusion technique) was established.

## Main research focus

**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 (desmo¬cadherins). 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 neuro¬transmitter 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 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.

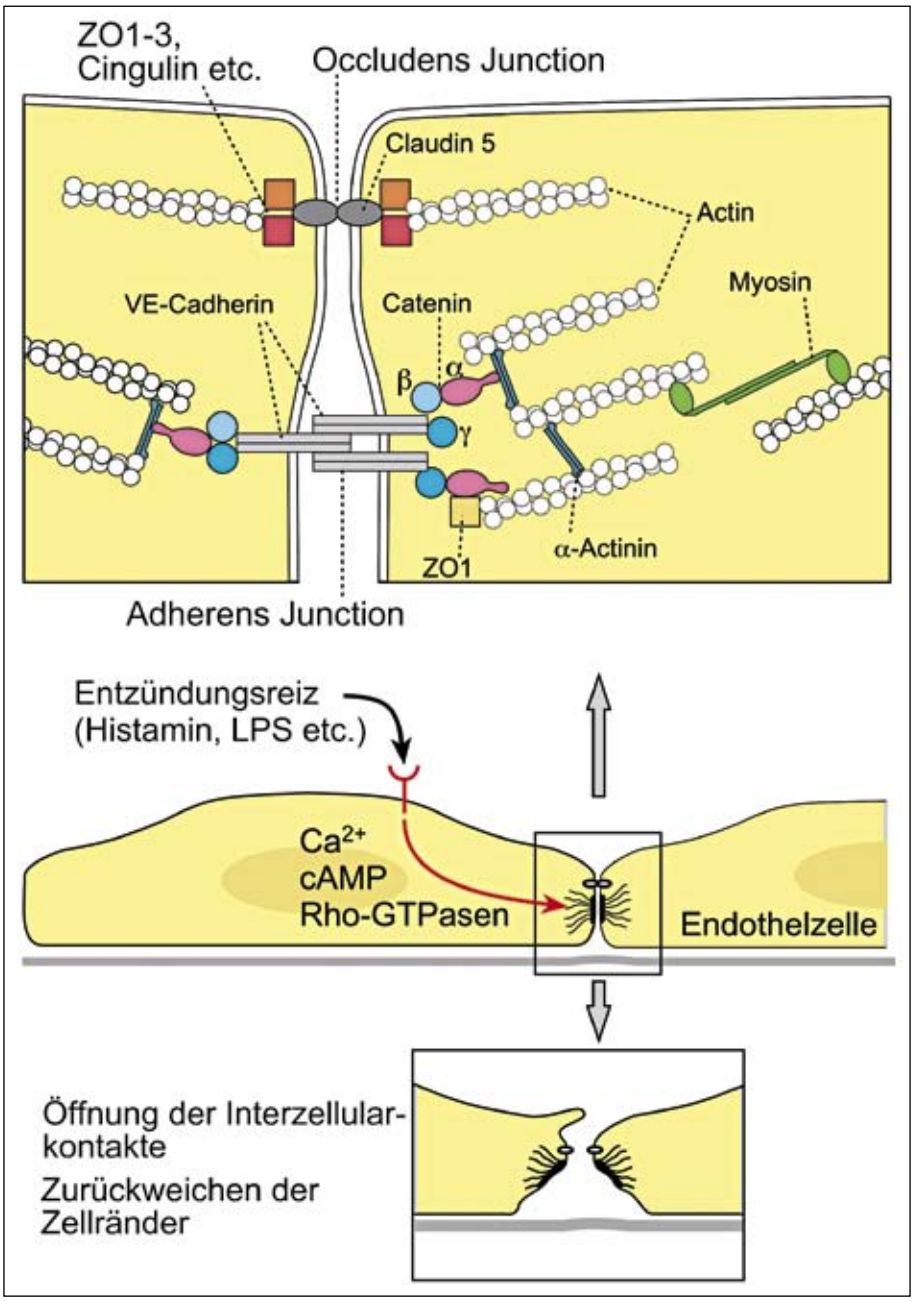


*Fig. 1: Cytoskeleton and adhesion molecules (cadherins) control the barrier between blood and tissue (endothelial layer). How inflammatory stimuli modify the barrier is one aspect investigated by the group.*

**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 both of changes in the nervous system which may be the cause of neuropsychiatric disorders, and of regeneration processes. 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 activity

Courses in microscopic and macroscopic anatomy, neuroanatomy and cell biology are held for medical, biomedical 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

*Förster C, Burek M, Romero IA, Weksler B, Couraud PO, Drenckhahn D (2008) Differential effects of hydrocortisone and TNF alpha on tight junction proteins in an in vitro model of the human blood-brain barrier. J. Physiol. 586:1937-1949.*

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*Busch A, Kiel T, Heupel WM, Wehnert M, Hübner S. (2009) Nuclear import is reduced in cells expressing nuclear envelopathy-causing lamin A mutants. Exp. Cell Res. 315: 2373-2385.*

*Heupel WM, Efthymiadis A, Schlegel A, Baumer Y, Baumgartner W, Drenckhahn D, Waschke J (2009) Endothelial barrier stabilization by a cyclic tandem peptide targeting VE-cadherin transinteraction in vitro and in vivo. J. Cell Sci. 122:1616-1625.*

*Heupel WM, Zillikens D, Drenckhahn D, Waschke J (2009) Pemphigus vulgaris IgG directly inhibit desmoglein 3-mediated transinteraction. J. Immunol.181:1825-1834.*

# 2.3 Institute of Anatomy and Cell Biology, Chair of Anatomy III

CONTACT DETAILS

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## Mission and Structure

At department III (PI: Prof. Dr. med. J. Waschke), which was newly established in 2008, research is focussed on three major research interests. Research is carried out by scientists Dr. med. N. Schlegel who since 4/2009 joins the Department for Surgery (Director: Prof. Dr. med. Ch. Germer) and now is an external member of our group as well as by Dr. med. V. Spindler. Further experiments are performed by 7 MD and Ph.D. students as well as 4 technicians.

## Major Research Interests

**Endothelial barrier regulation by Rho GTPases *in vivo* and *in vitro***
(N. Schlegel, V. Spindler, D. Drenckhahn, J. Waschke)

The project is funded in SFB 688 (Project leader: Prof. Dr. med. J. Waschke and Prof. Dr. med. D. Drenckhahn) and characterizes the mechanisms by which cAMP and the GTPase Rac1 stabilize endothelial barrier functions. This signaling pathway apparently is compromised in inflammation and sepsis leading to fluid extravasation from blood vessels into surrounding tissues.

**Pemphigus pathogenesis**
(V. Spindler, D. Drenckhahn, J. Waschke)

We are interested how skin blister formation is induced by autoantibodies in the severe autoimmune blistering skin disease pemphigus. Pemphigus serves as a good model because it is well established that autoantibodies against adhesion molecules of specialized cell contacts (desmosomes), i.e. desmogleins, are pathogenic. Besides new therapeutical approaches these studies are sought to gain basic insights into the regulation of desmosomal adhesion.

**Adhesion mediated by desmosomal cadherins**
(V. Spindler, D. Drenckhahn, J. Waschke)

Stratified epithelia such as the epidermis of the skin rely on specialized adhesion contacts (desmosomes) to provide efficient barrier properties against the environment. Desmosomal adhesion proteins belong to the cadherin superfamily. In this project, which is funded in SFB 487 (Project leader: Prof. Dr. med. J. Waschke and Prof. Dr. med. D. Drenckhahn), we use biophysical approaches to characterize the molecular binding properties of different cadherin family members and study ways to modulate their interaction.

## Teaching

Courses in microscopic and macroscopic anatomy, neuroanatomy and cell biology are held for medical and dentistry students (a total of 450 students per year). Additionally, interdisciplinary lectures are given together with Prof. Dr. med. Ch. Germer (Department for Surgery).

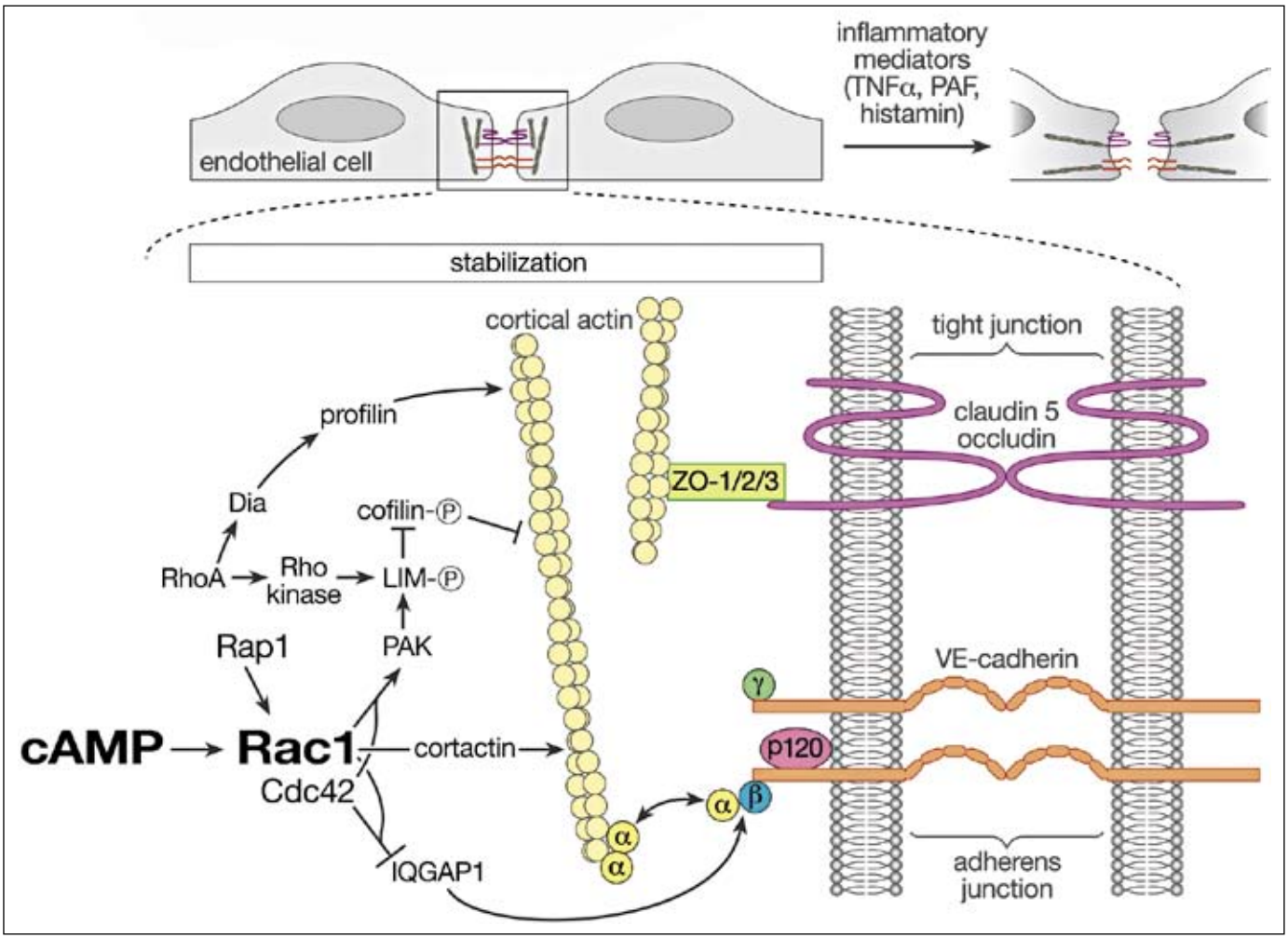


*Fig. 1: cAMP and the GTPase Rac1 are crucial for maintenance of endothelial barrier functions. We investigate how inflammatory mediators interfere with this signaling pathway.*

## SELECTED PUBLICATIONS


*Schlegel N, Waschke J (2009) VASP is involved in cAMP-mediated Rac 1 activation in microvascular endothelial cells. AJP Cell Physiology, 296(3): C453-462*

*Heupel WM, Efthymiadis A, Müller T, Schlegel N, Baumer Y, Baumgartner W, Drenckhahn D, Waschke J (2009) Endothelial barrier stabilization via a cyclic peptide targeting VE-cadherin transinteraction. J. Cell Sci., 122:1616-1625*

*Schlegel N, Baumer Y, Drenckhahn D, Waschke J (2009) LPS-induced endothelial barrier breakdown is cAMP-dependent in vivo and in vitro. Crit. Care Med., 37(5): 1735-43*

*Heupel WM, Engerer P, Schmidt E, Waschke J (2009) Pemphigus vulgaris IgG cause loss of desmoglein-mediated adhesion and keratinocyte dissociation independent of epidermal growth factor receptor. Am. J. Pathol., 174(2): 475-485*

*Spindler V, Heupel WM, Efthymiadis A, Schmidt E, Eming R, Rankl C, Hinterdorfer P, Müller TD, Drenckhahn D, Waschke J (2009) Desmocollin 3-mediated binding is crucial for keratinocyte cohesion and impaired in pemphigus. J. Biol. Chem., 284(44):30556-30564*

# 2.4 Institute of Physiology, Chair of Vegetative Physiology

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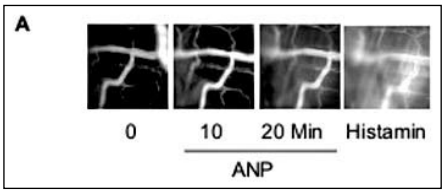
## Mission and Structure

The Institute of Physiology comprises Chairs for Vegetative Physiology and for Neurophysiology (Prof. Heckmann). The building accomodates the research laboratories and offices, a lecture hall seating 200 students, course laboratories, seminar rooms, and a library. Facilities for animal husbandry, for work with radioactive isotopes and a repair shop are also available. The research at Vegetative Physiology is focused on Cardiovascular Physiology and three research groups are led by the University Professors Dr. Michaela Kuhn (Head since 2005), Dr. Andreas Friebe and Dr. Kai Schuh.

## Major Research Interest

Our research focuses on elucidating the regulation and physiological functions of guanylyl cyclase (GC) receptors and their second messenger cGMP. This receptor family comprises transmembrane receptors for cardiac and intestinal natriuretic peptides (e.g. GC-A for ANP and BNP; GC-C for guanylin) and the intracellular nitric oxide (NO)-sensitive GC. We investigate whether these different GC-receptors mediate the formation of cGMP in separate intracellular compartments to regulate different third messengers and cell functions. A second research focus is the role of SPRED (Sprouty-related protein with an EVH1 domain) in cell proliferation and differentiation. Our projects are funded by grants from the DFG, in particular the SFB 487 and 688, and the IZKF Würzburg.

**Regulation and functions of Guanylyl Cyclase-A (GC-A), the receptor for the cardiac hormones ANP and BNP**
(M. Kuhn, K. Völker, B. Gaßner, M. Hartmann, M. Klaiber, W. Chen, M. Hünerberg, J. Schröter, A. Gazinski, B. Dankworth, C. Siegl)



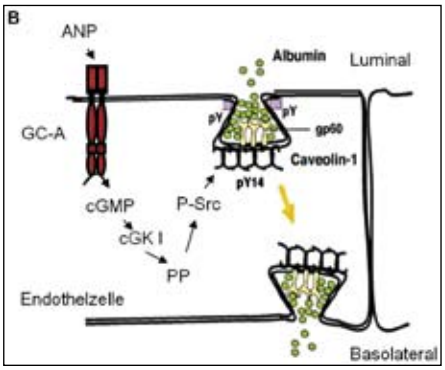




*Fig. 1: The figure shows (A) that ANP stimulates the extravasation of FITC-albumin in the microcirculation, as observed by intravital microscopy; and (B) a model for the participating endothelial signaling pathways.*

Atrial natriuretic peptide (ANP) regulates arterial blood pressure and intravascular volume as well as metabolism. To dissect the cell-specific actions of ANP in vivo, we generated genetic mouse models with cell-restricted GC-A-deletion in vascular endothelial or smooth muscle cells, cardiac myocytes and pancreatic ß-cells. Our observations demonstrate that concerted renal and endothelial actions of ANP maintain intravascular volume homeostasis. ANP, via endothelial GC-A and cGMP-dependent activation of a specific Protein Kinase (cGKI), modulates transendothelial, caveolae-mediated transport of albumin (Fig. 1). This shifts the balance of hydrostatic and colloid osmotic forces across capillary walls in favor of moving protein-free fluid from the plasma into interstitial pools of the skin and skeletal muscle and thereby adjusts intravascular fluid volume.

Pathophysiological conditions such as hypoxia induce the cardiac and extracardiac formation of B-type natriuretic peptide (BNP), a second specific ligand for GC-A. Local BNP, via GC-A/cGMP signaling, stimulates pathways involved in microvascular endothelial proliferation (such as the p38 MAPK) and migration (i.e. VASP) and thereby acts as a stress-responsive regulator of angiogenesis.

In patients with cardiac hypertrophy and insufficiency, ANP plasma levels are markedly enhanced, but the cardiovascular effects are diminished, indicating GC-A dysfunction. In collaboration with Prof. Albert Sickmann (Leibnitz-Institut für Analytische Wissenschaften) we applied mass spectrometry to characterize the phosphorylation of GC-A and its changes during ANP-provoked desensitization. Together with site-directed mutagenesis the results indicate that ANP-provoked phosphorylation at Ser487 induces the dephosphorylation of neighboring residues. In addition, we observed that alternative splicing of the GC-A gene results in the formation of a silent GC-A-mutant, which forms inactivating dimers with the

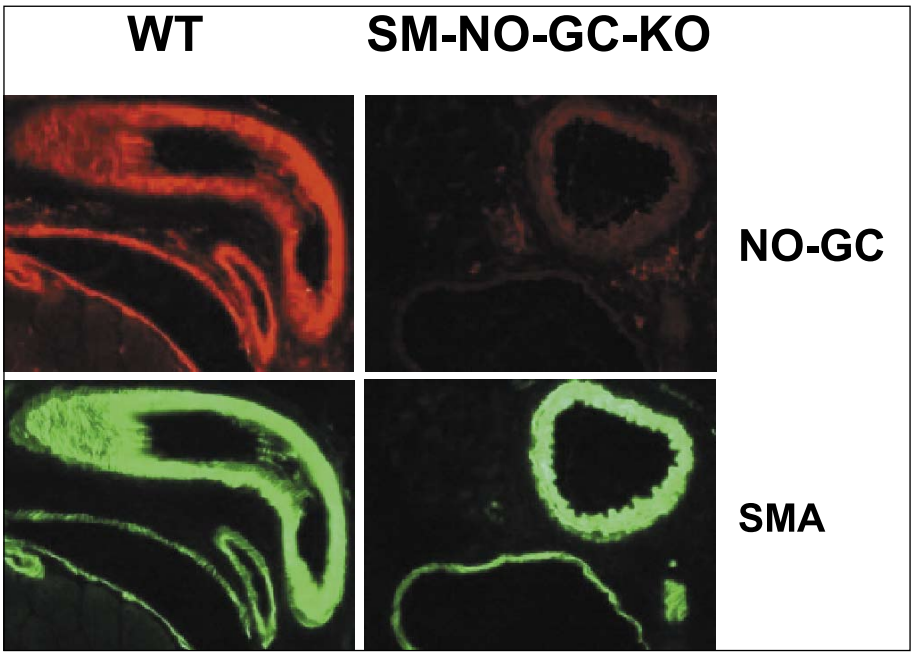



*Fig. 2: Immunohistochemical analysis of NO-GC deletion in vascular smooth muscle. Tissue sections from femoral vessels from WT and smooth muscle-specific knock out mice (SM-NO-GC-KO) were stained with specific antibodies against NO-GC (red) and α-smooth muscle actin (SMA; green).*

wildtype receptor. We are currently investigating whether these processes contribute to inhibition of the NP/GC-A system in patients with chronic heart failure.

**The significance of NO/cGMP signaling in the cardiovascular and gastrointestinal system**

(A. Friebe, D. Groneberg, R. Jäger, M. Kümmel)

The nitric oxide (NO)-sensitive intracellular guanylyl cyclase (NO-GC) is also involved in many physiological processes. We have generated mice with global deletion of NO-GC. These mice show increased blood pressure, gastrointestinal dysmotility, early postnatal lethality and shortened bleeding time. To identify the specific cell types mediating the effects of NO on blood pressure and gastrointestinal peristalsis, we generated mice in which NO-GC is specifically deleted in smooth muscle cells (Fig. 2) or interstitial cells of Cajal. A third project characterizes the role of NO-GC in endothelial cells. Although a fundamental role of NO in angiogenesis has been described, the function of NO-GC in endothelium remains unclear. To clarify the role of NO-GC in angiogenesis we plan to generate mice with endothelium-restricted deletion of this receptor. By comparing the phenotype of these different genetic mouse lines we hope to gain new insights into the cell-specific functions of the NO/GC/cGMP signaling system.

**Physiological functions of SPRED and ATIP1**

(K. Schuh, M. Ullrich, D. Fetting, T. Fischer, M. Abeßer, P. Benz)

Gene trapping is an elegant tool to combine ablation of a specific gene with parallel analyses of promoter activity of this trapped gene in mice. Trapping of the ubiquitous MAPK signalling pathway inhibitor SPRED2 resulted in a complex phenotype, with dwarfism, renal failure and severe alterations in the production of hormones of the hypothalamic-pituitary-adrenal axis. Our observations in this new mouse model emphasize that SPRED2 is critically involved in the regulation of cell proliferation and differentiation in various organs.

We applied the same strategy to delete the murine gene encoding the Angiotensin receptor interacting protein 1 (ATIP1). ATIP1 interacts with the AT2-receptor for Angiotensin II, but the functional implications remain unclear. Interestingly, ATIP-1-deficient mice exhibit blood pressure-independent cardiac hypertrophy. We are currently investigating the molecular mechanisms accounting for these different phenotypes and overall the (patho)physiological roles of SPRED and ATIP1.

## Teaching

The chairs of Vegetative Physiology and Neurophysiology offer a broad spectrum of lectures, integrative seminars and practical courses for students of Medicine, Dentistry, Pharmacy, Biology and Biomedicine. A major focus is the intensive teaching of Vegetative Physiology and Pathophysiology to students of Medicine (3th - 4th term).

## SELECTED PUBLICATIONS

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# 2.5 Institute of Physiology, Chair of Neurophysiology

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## Mission and Structure

Our research focusses on synaptic transmission, synaptogenesis and neuronal excitability from the molecular to the cellular and systems levels. We use the mouse and the fruitfly *Drosophila melanogaster* as prime model organisms and combine electrophysiological methods, molecular biological and genetic tools, with high-end microscopy.

## Major Research Interests

**Latrophilins - the molecular bridge between neuronal organization and synaptic function**
(T. Langenhan)

Latrophilins are ancient surface receptors, which are found on neuronal and epidermal cell types from earliest developmental stages onwards. Latrophilins are involved in coordinating the distribution of polarity information within an epithelium, a process described as planar cell polarity. Planar cell polarity is required to shape the proper architecture of epithelial structures such as the lamination of the mammalian cortex. At the same time, latrophilins appear to control key events during synaptic vesicle exocytosis through unknown mechanisms, and can thereby partake in synaptic transmission. We investigate, which properties of latrophilin receptor molecules allow for these widely differing tasks using the fruitfly and the nematode *C. elegans* as model systems.

**Drosophila MAN1 regulates BMP signaling at the neuromuscular junction**
(N. Wagner)

Bone morphogenic proteins (BMPs) regulate a variety of cellular processes, including cell differentiation, developmental processes and tissue homeostasis. BMP signaling responses are refined by distinct secreted and intracellular antagonists in different cellular and temporal contexts. We could show that the inner nuclear protein MAN1 is a tissue-specific antagonist of BMP signaling in *Drosophila*. MAN1 mutants show reduced locomotor activity and electrophysiology recordings uncovered a new presynaptic role of MAN1 at the neuromuscular junction. We found that synaptic transmission is severely impaired and short-term synaptic plasticity is altered in MAN1 mutants. Reduction of a BMP-ligand Gbb ameliorates these defects, indicating that the phenotype in MAN1 mutants reflect changes in BMP signaling at the neuromuscular junction.

**Functional characterization of $K_{2P}$ channels from mouse and fly**
(F. Döring)

Two-pore domain $K^+$ ($K_{2P}$) channels give rise to time- and voltage- independent background currents that substantially control cellular excitability and $K^+$ homeostasis. The activity of $K_{2P}$ channels is modulated by various physical and chemical stimuli as well as by G-protein coupled receptors. Molecular mechanisms underlying such regulation and processes of membrane targeting were analyzed in detail for pH-sensitive $K_{2P}$ channels (TASK, TRESK). Knockout mice deficient in these channels were used to discover their physiological role in different organs. As we previously analyzed the elementary properties of K2P channel orthologs from *Drosophila*, the genetic advantages of this model organism are currently used to reveal the physiological function of *Drosophila* TASK channels by imaging techniques and behavioral studies.

**Antidepressants interact with potassium background currents**
(E. Wischmeyer)

Several members of the $K_{2P}$ channel family are expressed in brain as well as in the heart and are directly influenced by antidepressants like fluoxetine (‚Prozac'). Closure of these channels leads to an augmented excitability in neurones and cardiac cells, hence to wanted antidepressive effects as well as unwanted cardiac arrhythmias. Unraveling the mechanism of the interaction between antidepressants and $K_{2P}$-channels might elucidate our understanding of the correlation betweeen neuronal and cardiac effects.

**Serotonergic regulation of fear behaviour by potassium channels**
(M. Weber)

The modulation of neuronal excitability by TASK-3 channels is mediated by serotonin receptor (e.g. 5-$HT_{2C}$) coupling. We could show that this mechanism is active in medial amygdala neurones and thereby reduces innate fear behaviour. Serotonin modulates in a similar way brainstem neurones that mediate the startle response (PnC gi-

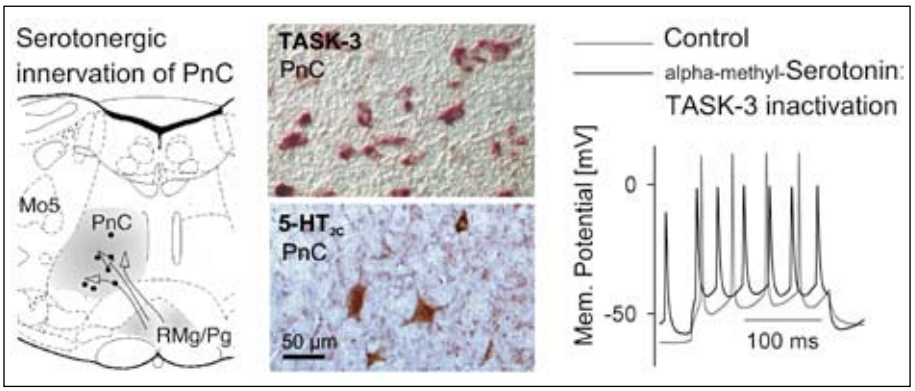


*Fig. 1: Caudal pontine reticular formation (PnC) brain stem neurones express TASK-3 (in situ hybridisation) as well as 5-HT2C receptors (immunohistochemistry) and receive serotonergic input from Raphe (RMg/Pg) neurones. Inactivation of TASK-3 potassium channels by α-met.-Serotonin enhances excitability of these neurones.*

ant neurones, see figure). This finding may explain the enhanced startle response in anxious and depressive patients.

**Physiology and plasticity of the active zone in vivo**
(R. J. Kittel, DFG Emmy-Noether research group leader)

Synapses are specialised intercellular contact sites, which serve as the communication link between neurons and their partner cells. At chemical synapses, calcium-ion influx triggers the fusion of transmitter-laden vesicles with the presynaptic membrane at a specific sub-cellular region termed the active zone. Transmitter substances released by this process then diffuse across the synaptic cleft and are sensed by postsynaptic receptors to convey signal transduction. A hallmark of synaptic transmission is its plasticity, which enables synapses to regulate complex brain processes by filtering, modifying, or integrating information. The details of active zone physiology and how its modulation contributes to synaptic plasticity are, however, barely understood. By combining genetics with high resolution opto- and electrophysiological methods in Drosophila melanogaster, this project tests the hypothesis that active zone physiology is modified during activity-induced plasticity *in vivo*.

## Teaching

We teach physiology and pathophysiology to undergraduates enrolled in medicine, dentistry, biomedicine, pharmacy, psychology and neurobiology (lectures, practical and comprehensive courses, seminars). The clinical aspect of human physiology is conveyed in integrated seminar series, which are held in collaboration with clinicians, which co-lecture on physiological topics.

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*Weber M, Schmitt A, Wischmeyer E, Döring F (2008). Excitability of pontine startle processing neurones is regulated by the two-pore domain K+ channel TASK-3 coupled to 5-HT2C receptors. Eur J Neurosci 28: 931-940.*

# 2.6 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 questions, which concern the development of the total organs and its interactions with the environment. All research groups at this unit use molecular methods to understand problems in Biology and Medicine on all levels of the biological organization. The multi-faceted approach is well reflected in the fact that the scientists of the department are biologists, chemists and physicians and that the head of the institute is a member of the Medical Faculty as well as of the Biological Faculty. The research focus is the molecular understanding of developmental processes and the pathobiochemistry of cancer.

## 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 invivo 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 to the clinical important, but still unsolved question whether nevi are benign, precancerous state of the malignant melanoma.
The intracellular signaling network is critically involved in bringing about the neoplastic phenotype of tumor cells. The changes that occur on this level during tumor formation from the first transformed cell to final malignant stage are therefore the key for a better understanding of cancerous disease. Consequently, components of the signaling network are intensively scrutinized for diagnostic markers and therapeutic targets.
In the Xiphophorus melanoma model system, on the molecular level, the primary signal transduction events induced by the receptor tyrosine kinase Xmrk are reasonably well understood. Importantly, similar events occur during the generation of human melanoma, such as the activation of the MAP kinase pathway by BRAFV600E and NRASQ61K or the activation of the PI3 kinase pathway by NRASQ61K or by PTEN deletion. The “division of labor“ between the MAP kinase and the PI3 kinase pathway in human melanoma is one subject of our studies.

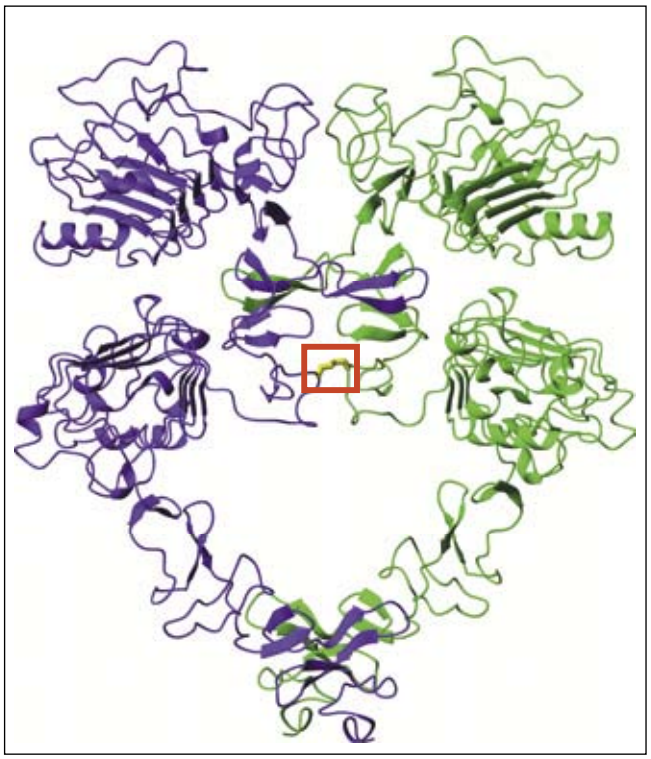

Fig. 1: Structure model of the extracellular domain of the melanoma-inducing EGF receptor variant Xmrk. Red box highlights an intermolecular cystein bridge generating covalent dimers, which are constitutively active receptors . Permanent signaling of this receptor leads to pigment cell transformation.

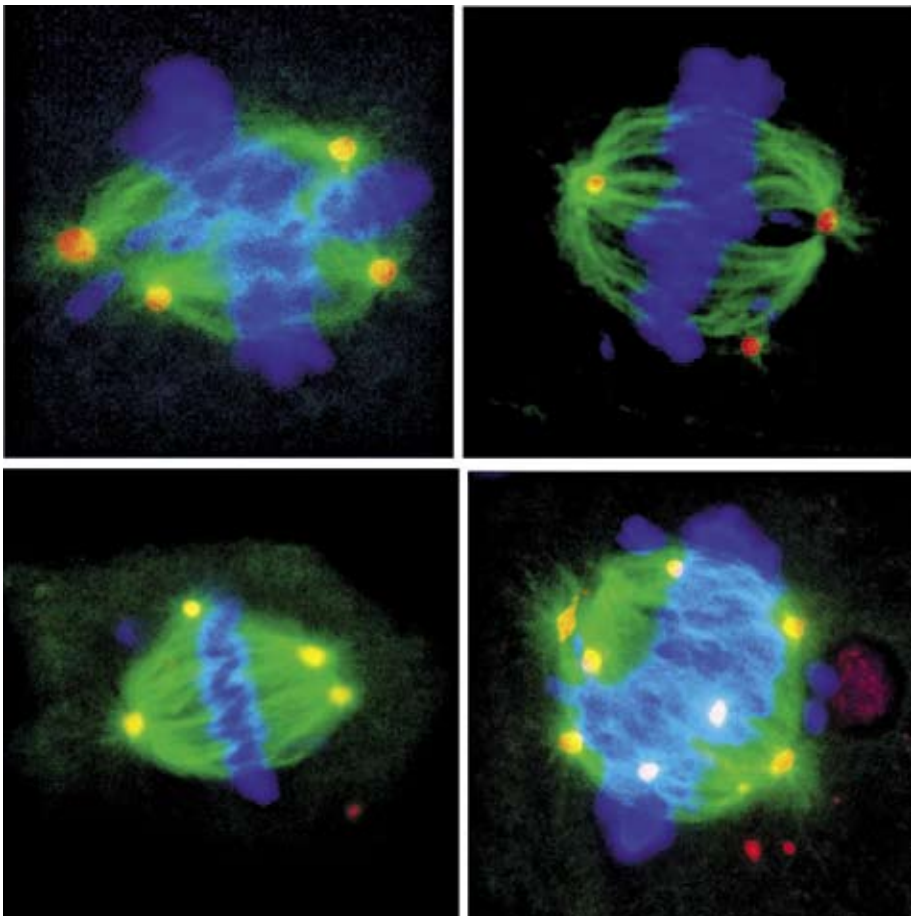

*Fig. 2: Inactivation of the mammalian DREAM complex in conditional LIN9 knockout MEFs results in formation of chaotic multipolar mitotic spindles. Red: gamma-tubulin; green: alpha-tubulin; blue: DNA.*

Many additional melanoma-relevant pathways are simultaneously activated by the oncogenic Xmrk receptor, which offers the possibility to use this oncogene to search for new molecular players relevant for melanoma in general. By high-throughput methods revealed a large number of genes and proteins that are regulated in response to Xmrk activation were identified. These include several transcription factors, but also antioxidant proteins such as peroxiredoxins. We have observed that peroxiredoxins are also upregulated by the endogenous oncogenes of many human melanoma cell lines. An efficient antioxidant capacity is particularly important to counteract melanoma oncogenes. Those can generate high amounts of reactive oxygen species. We have shown that this leads to high levels of DNA damage and the generation of multinucleated senescent melanocytes. The characterization of the senescence process and its effect on the melanocytes are subject of our ongoing studies.

The role of tumor modifiers is studied in the fish medaka, which offer the possibility of genetic alterations, whole genome mutagenesis and high throughput drug screens. We have generated a transgenic line, which produces spontaneously pigment cell tumors due to overexpression of xmrk under control of the mitf promoter. Candidate tumor modifier genes are functionally analyzed in double transgenics. To identify novel modifiers, a whole genome mutagenesis screen on the mitf::Xmrk transgenic background is performed. Genes that enhance or ameliorate the malignant process will be identified by their phenotypic effect after outcrossing, mapped and isolated by reverse genetic approaches.

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

Our 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 a novel E2F/ pocket protein complex in human cells that is related to similar complexes in invertebrates. We found that this complex, called human DREAM or LINC, regulates the expression of mitotic genes and is essential for entry into mitosis. Inactivation of the LIN9 subunit of DREAM 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 inhibition of LIN9 promotes tumorigenesis by weakening the mitotic spindle checkpoint and increasing genomic instability. We are also interested the function of B-MYB, another subunit of DREAM. B-MYB is an oncogenic transcription factor that is highly expressed in different human cancers. We found that B-MYB is required for recovery from the DNA-damage induced G2 checkpoint in p53-negative cells. High levels of B-MYB are also consistently associated with mutated p53 and with a poor prognosis in human cancers. These observations suggest B-MYB overexpression contributes to tumor progression in a p53-negative background and that B-MYB could be a future target for therapy.

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# 2.7 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 preclinical students in Medicine and Dentistry and for the Bachelor students in Biomedical sciences. Seven research groups work at PCII, two of which are headed by junior investigators (Dr. Nikita Popov and Dr. Daniel Murphy). The aim of PCII is to contribute to therapy and diagnosis of human cancer by the establishment of biological model systems and the setup of chemical/biochemical methodology.

## Major Research Interests

**Function and Regulation of the Human Myc Proto-oncogene**
(M. Eilers)

The *c-myc* proto-oncogene participates in the genesis of the majority of all human tumors. The gene encodes a nuclear protein (Myc) that is a central regulator of cell growth and cell proliferation. Myc exerts this control at least in part by binding to specific DNA sequences and affecting the transcription of multiple genes involved in protein synthesis, metabolism and cell proliferation. Many central questions about the basic function of Myc and the regulation of its multiple activities remain unanswered. Our research tries to unravel how Myc functions and to devise strategies to use this knowledge for the treatment of human disease. The junior group of Nikita Popov studies ubiquitination of Myc and its functional consequences; the group of Dan Murphy develops novel mouse models to study the role of Myc in tumor progression.

**Control of Cell Growth in Drosophila**
(P. Gallant)

The fruit fly Drosophila melanogaster offers a unique model system that allows the genetic analysis of pathways controlling cellular growth, and of their effects on organismal growth and on cell proliferation. We use several strategies to identify novel growth regulators that act either in a cell autonomous or a systemic manner.

**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.e. 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 murine caspase-12**
(J. Hoppe)

Caspase-12 was originally described as initiator caspase, which is activated in a $[Ca^{2+}]$ 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.

**Structure, mechanism and cellular functions of growth and differentiation factors**
(W. Sebald)

We are focussing on Interleukins involved in generation and maintenance of allergic diseases and asthma, as well as on BMP´s/

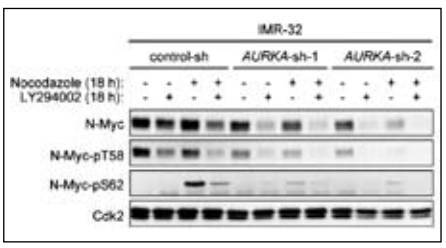


*Fig. 1: Depletion of the Aurora-A kinase leads to loss of the N-Myc protein in MYCN-amplified neuroblastoma cells. The panels shows immunoblots documenting the amount of N-Myc in IMR32 cells after treatment with nocodazole in combination with a PI3-kinase inhibitor either in control cells or in cells that were depleted of Aurora-A. The figure documents that Aurora-A is required to stabilize N-Myc in these cells (from Otto et al., Cancer Cell 2009).*

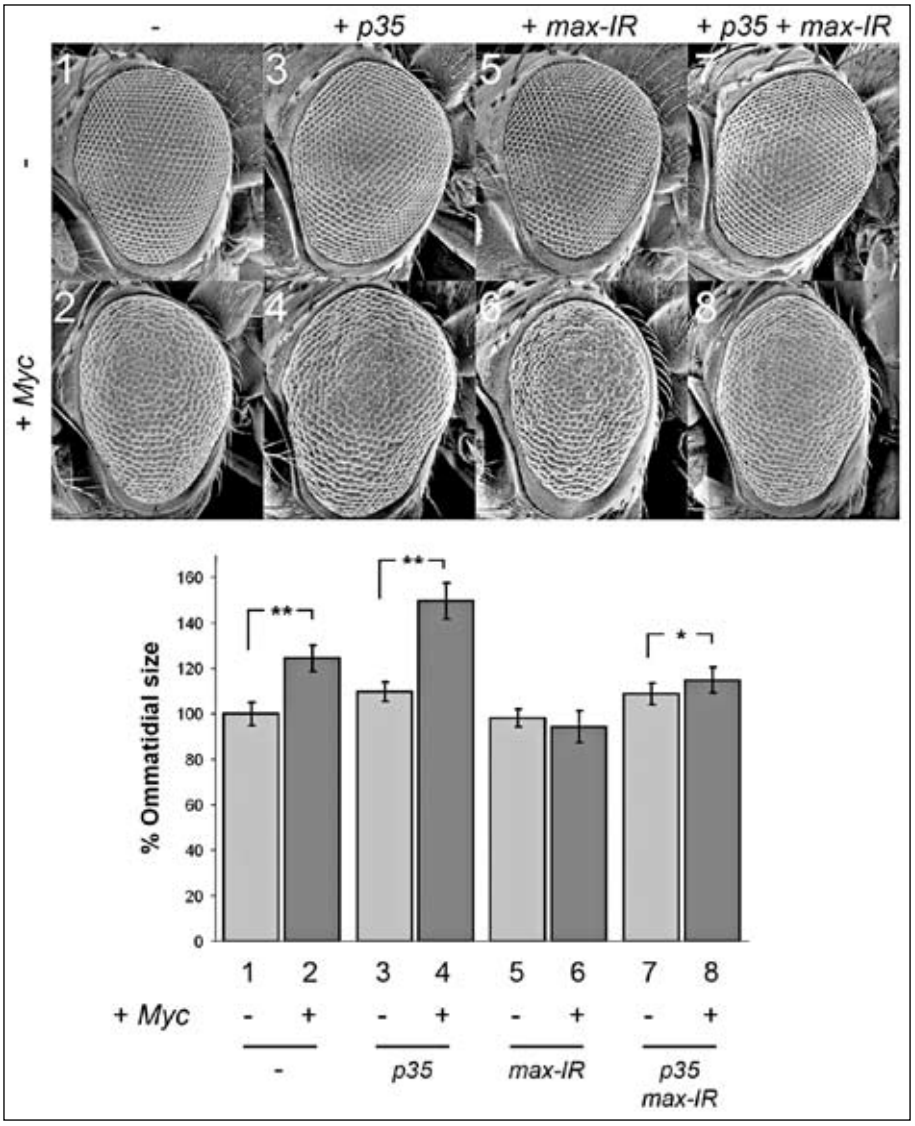


*Fig. 2: Drosophila Myc overexpression in the eye induces growth (as revealed by increased ommatidial size) and apoptosis (as revealed by disturbed eye morphology, i.e. roughness) in a largely Max-dependent and -independent manner, respectively. The panels show scanning electron micrographs of adult eyes overexpressing the indicated transgenes (top), and the average ommatidial sizes for the corresponding genotypes (lower); note that „p35" blocks apoptosis and „max-IR" indicates knockdown of Max. This figure illustrates one facet of Myc's activities that do not require association with Max (from Steiger et al., Nature Genetics 2008).*

TGF-betas, which regulate the development and regeneration of tissues and organs. Our ongoing projects concern the molecular recognition and primary activation steps in BMP/GDF-receptor complexes as well as the analysis of interleukin-4 antagonists.

## Teaching

The chair of Physiological Chemistry II in conjunction with the Chair of Physiological Chemistry I and with the Chair of Developmental Biochemistry teaches Biochemistry and Molecular Biology to the more than 400 annual students of Medicine and Dentistry. We also teach Biochemistry to the 24 annual students of Biomedicine (B.Sc./M.Sc.).

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# 2.8 Biocenter Würzburg, Chair of Developmental Biochemistry

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## Mission and Structure

The Chair of Developmental Biochemistry was newly established in 2008. Its scientific interests range from elucidation of the molecular control of development and differentiation processes to uncovering of disease mechanisms that are caused by deregulation of these pathways. The current focus is on the development of the kidneys and the cardiovascular system as well as on childhood kidney cancers, i.e. nephroblastomas. These projects are funded by the DFG (individual grants, GK and SFB), the BMBF and the Wilhelm-Sander-Foundation. The chair participates in the training of students of Medicine and Dentistry, Biology, Chemistry and Biomedicine. Since fall 2009 the teaching spectrum has been expanded to include the newly established study program in Biochemistry.

## Major Research Interests

**Analysis of Hey gene functions**
In their function as central transducers of Delta/Notch signals, Hey genes control the embryonic development of the cardiovascular and other organ systems. In the developing heart Hey1, Hey2 and HeyL are critical for epithelial-mesenchymal transformation (EMT). This is a prerequisite for the formation of precursor cells that are in turn needed to form the cardiac septum and valves. This could be demonstrated convincingly through high resolution magnetic resonance microscopy and in vitro time-lapse monitoring of knockout mouse embryos. It could be shown that Hey2 as well as Hey1/HeyL exert similar functions and they exhibit partial redundancy. Hey1 and Hey2 also appear to participate in the positioning of the atrio-ventricular canal as an organizing center.

The target genes of Hey factors in these processes are still largely unknown. Current efforts are directed towards their identification through gene expression analyses and sequencing of binding sites in the genome of genetically engineered cardiomyocytes. These are generated from embryonic stem cells that are differentiated in vitro.

Hey genes are also important for embryonal angiogenetic remodeling and for arterialization of blood vessels. They repress expression of the venous regulator Coup-TFII (NR2F2) in the context of the hypoxia response. A lack of Hey1 and Hey2 results in a lethal angiogenesis defect. Again, in vitro differentiation systems are employed to recapitulate these processes and to identify or to modulate corresponding target genes.

Besides these cardiovascular functions we could identify first hints for a role of Hey2 in the development of the organ of Corti and for Hey1 in the activation macrophages and the control of their cytokine production. While Hey2 functions in the inner ear appear to be independent of Notch signaling, the latter is essential in macrophages. This underscores that Hey genes can be activated by different stimuli and they likely regulate a multitude of physiological functions, as has been expected from their complex expression patterns in numerous organs.

With the fjx1 ligand that is part of the planar cell polarity signaling (PCP), another signaling pathway critical of embryonic development was analyzed. Fjx1 could be shown to regulate dendrite growth and extension in the CNS, but also PCP processes in other organs. As an example, fjx1 appears to be causally involved in the formation of kidney cysts.

**Nephroblastomas / Wilms tumors**
Wilms tumors are early childhood kidney cancers that originate from a failure of em-

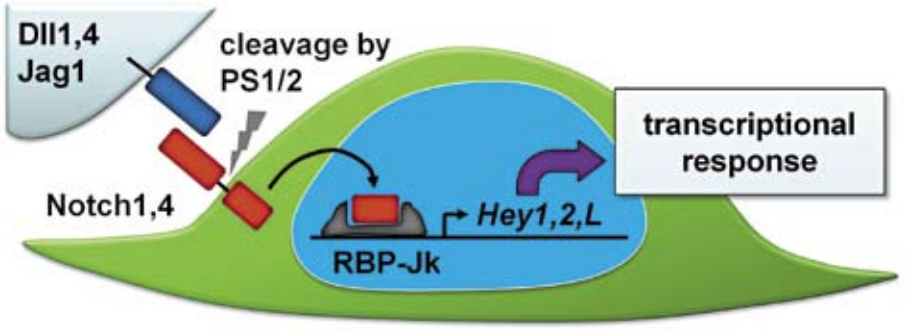


*Fig. 1: The Delta/Notch signaling pathway activates transcription of the Hey genes.*

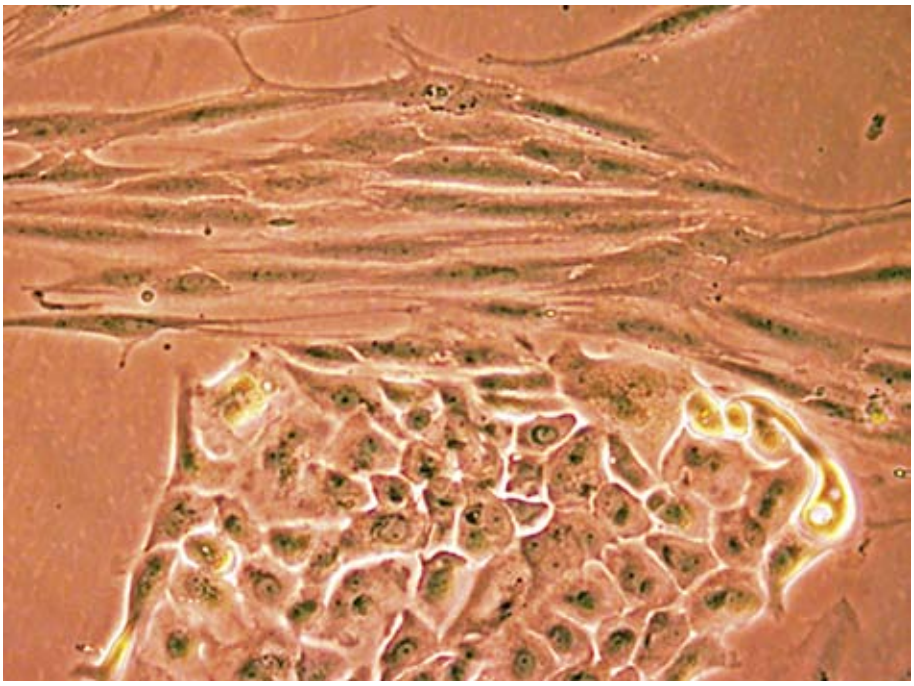

*Fig. 2: Wilms tumors are often comprised of different cell types and these can initially be seen in cell culture as well.*

bryonic precursor cells to fully differentiate. Within the framework of the German Wilms tumor study we have established a tumor bank that by now includes more than 800 tumors and corresponding control tissues. These are routinely screened for chromosomal alterations and mutations in known tumor genes like WT1 or CTNNB1 and they are used to identify novel markers and target structures for improved diagnosis and treatment.

Gene expression analyses led to the identification of promising and novel tumor markers. All known or proposed candidate genes were systematically reevaluated in a large cohort of more than 200 Wilms tumors. A number of genes could be identified, whose expression correlates with the prognosis of tumors. Moreover, the nature and relevance of changes in WTX were systematically analyzed in a large tumor collection. However, these data showed that WTX alterations poorly correlate with clinical data and they appear to occur rather late in the course of tumor development.
Microarray analysis revealed that tumors which poorly respond to chemotherapy treatment are characterized by a decreased activity of the retinoic acid signaling pathway. This finding could be substantiated in experiments with primary tumor cell cultures. First therapeutic trials of individual cases have already been initiated based on these results. Our current efforts to establish and validate a larger set of primary tumor cell cultures will help to create an in vitro system for preclinical assessment of tumor response to new therapeutics such as retinoic acid derivatives.

## Teaching

The Chairs of Physiological Chemistry I and II and the Chair of Developmental Biochemistry 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 in Biochemistry, Molecular Biology and Developmental Biology. For Biology students advanced modules with a focus on biochemistry and developmental biology are offered. Further course units will be offered for the new B.Sc./M.Sc. study program in Biochemistry, which was initiated by the Chairs of Biochemistry (Faculty of Chemistry and Pharmacy) and Developmental Biochemistry, starting with the winter term 2009/10. Additional training courses for PhD students are offered within the framework of the research training group 1048 (Graduiertenkolleg Organogenese) and the Graduate School of Life Sciences (GSLS).

## SELECTED PUBLICATIONS


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*Hu, X., Chung, A.Y., Wu, I., Foldi, J., Chen, J., Ji, J.D., Tateya, T., Kang, Y.J., Han, J., Gessler, M., Kageyama, R. and Ivashkiv, L.B. (2008). Integrated regulation of Toll-like receptor responses by Notch and interferon-gamma pathways. Immunity 29, 691-703.*

*Saburi, S., Hester, I., Fischer, E., Pontoglio, M., Eremina, V., Gessler, M., Quaggin, S.E., Harrison, R., Mount, R., and McNeill, H. (2008). Loss of Fat4 disrupts PCP signaling and oriented cell division and leads to cystic kidney disease. Nat Genet 40, 1010-1015.*

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*Wittmann, S., Wunder, C., Zirn, B., Furtwangler, R., Wegert, J., Graf, N., and Gessler, M. (2008). New prognostic markers revealed by evaluation of genes correlated with clinical parameters in Wilms tumors. Genes Chromosomes Cancer 47, 386-395.*

# 2.9 Institute for the History of Medicine

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## Mission and Structure

The origins of the Institute for the History of Medicine date back to the 19th century when medical history became an established part of the medical curriculum in Würzburg. In the 1920s the University boasted of one of the first institutes for medical history in Germany under Georg Sticker. The Institute was closed under National-Socialist rule but revived after 1945. The Institute is housed in a former ONT-clinic generously donated for the purpose by the late Würzburg professor Horst Wullstein and his wife Sabina. It occupies additional rooms 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 and palliative care 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.

**Early modern physicians' correspondence**
(M. Stolberg, S. Gröne, S. Herde, U. Schlegelmilch, T. Walter)

Under the auspices of the Bayerische Akademie der Wissenschaften, a work group for the study of early modern physicians' correspondences was established in early 2009. Over the next 15 years, the group will undertake a systematic survey of the thousands of letters written by and to 16th- and 17th-century physicians in the German speaking area which have come down to us in libraries and archives all over Europe. These letters are valuable sources for the study of wide range of topics. They reflect, for example, professional networks and the dissemination of new medical findings and theories but they also provide manifold insights into the mentalities, the professional lives and the domestic affairs of the early modern upper classes in general. From 2011, detailed summaries of the letters' contents and, if possible, digital reproductions of the original letters will be made accessible to the international research community via OPAC.

**Out-Patient Medical Care 1600-1850**
(M. Stolberg, K. Nolte, S. Schlegelmilch, F. Wiesendanner)

In two projects which are part of a German-Swiss-Austrian research network funded by the Deutsche Forschungsgemeinschaft (DFG) and coordinated by M. Stolberg a physician*s medical practice around 1650 and domestic out-patient care provided by the policlinics in Würzburg and Göttingen around 1800 are studied. Work focuses, in particular, on the organization of ordinary medical practice, the class, age and gender of the patients and the way in which the medical theories of the time informed ordinary diagnostic and therapeutic practice at the bed-side.

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

The long pre-history of modern palliative medicine is virtually unknown. In this DFG-funded project we pursue for the period from the 16th to the 20th centuries how physicians and nurses dealt with incurable and dying patients and analyze the changing role of hospitals, poor-houses and similar institutions in the care of such patients.

**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 and 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-to-day basis. Work on this project which was orignally funded by the Fritz Thyssen-Stiftung has changed established historical knowledge in crucial respects. It has shown, for example, that various means to achieve active euthanasia were widely accepted among the population across Europe and that individual physicians already around 1800 publicly endorsed active euthanasia on dying patients, a century earlier than had hitherto been assumed. Analysis of the changing attitudes towards truth-telling in the case of fatal prognosis and towards informed consent to painful and risky operations has shown the crucial importance of changing roles and patterns of interaction among patients, relatives, physicians, nurses and priests.

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

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

Based on printed and manuscript medical writing, court records and letters and autobiographies written by physicians and patients as well as 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.

**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 to preserve this historical knowledge and make it accessible to modern medical practitioners.

## Teaching

The Institute offers 16 compulsory courses in Medical Terminology and Professional Orientation every term, for students of medicine and of dentistry, as well as two medico-historical seminars. In addition, with funding from the "Virtuelle Hochschule Bayern", online-courses in medical terminology are currently being developed. The Institute is also responsible for the course in "History, Theory and Ethics" for medical students in their third year. Furthermore, a wide variety of elective courses and seminars is offered, ranging from Medical English and courses in bibliography and paleography 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 and individual staff members and collaborators support teaching activities at the Historical Faculty in Würzburg.

## SELECTED PUBLICATIONS


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*Nolte, K. (2006) Wege zu einer „Patientengeschichte des Sterbens" 19. Jahrhundert. In: BIOS 19/2006, Heft 1, 36-51.*

*Stolberg, M. (2007) Active euthanasia in early modern society. Learned debates and popular practices. In: Social history of medicine 20: 205-221.*

*Stolberg, M. (2007) „Cura palliativa". Begriff und Diskussion der palliativen Krankheitsbehandlung in der vormodernen Medizin (ca. 1500-1850). In: Medizinhistorisches Journal 42: 7-29.*

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# 2.10 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 research topics comprise both psychosocial factors of somatic diseases and processes involved in coping with illness and rehabilitation. In the area of medical education, the institute is responsible for the subjects Medical Psychology and Sociology in the pre-clinical study section and Psychotherapy and Psychosomatic Medicine as well as Rehabilitation in the clinical section. For the area of patient care, a psychotherapeutic out-patient department and consultation-liaison services for the University Hospital are provided.

Currently, 4.5 researchers are financed through the institute's budget and another 16 through third-party payers. 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)

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 with chronic heart failure at risk for depression and whether depression itself is a risk factor for heightened mortality (Fig. 1). Moreover, we evaluate an intervention for optimizing disease management, including telephone-based patient education, in regards to mortality, morbidity, re-hospitalization, and quality of life (INH Study). In another study, the efficacy of pharmacotherapy for depression in reference to mortality of chronic heart failure is examined (MOOD-HF Study).

**Psychooncology**
(H. Faller)

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 and in various treatment stages (acute care, rehabilitation) and settings (in-patient and out-patient care) are included.

**Psychonephrology**
(S. Neuderth)

In cooperation with the Department of Internal Medicine I (Nephrology), both donors and recipients who had been psychologically evaluated before a kidney transplantation are followed up with. 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 developed. We evaluate both the success of this after-care program and the short and long-term psychosocial outcomes of the surgical treatment.

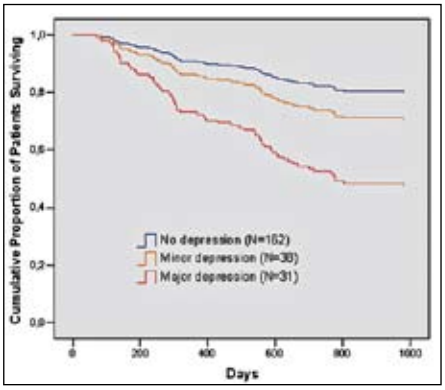


*Fig. 1: Depression and survival rate of patients with chronic heart failure according to degree of depression.*

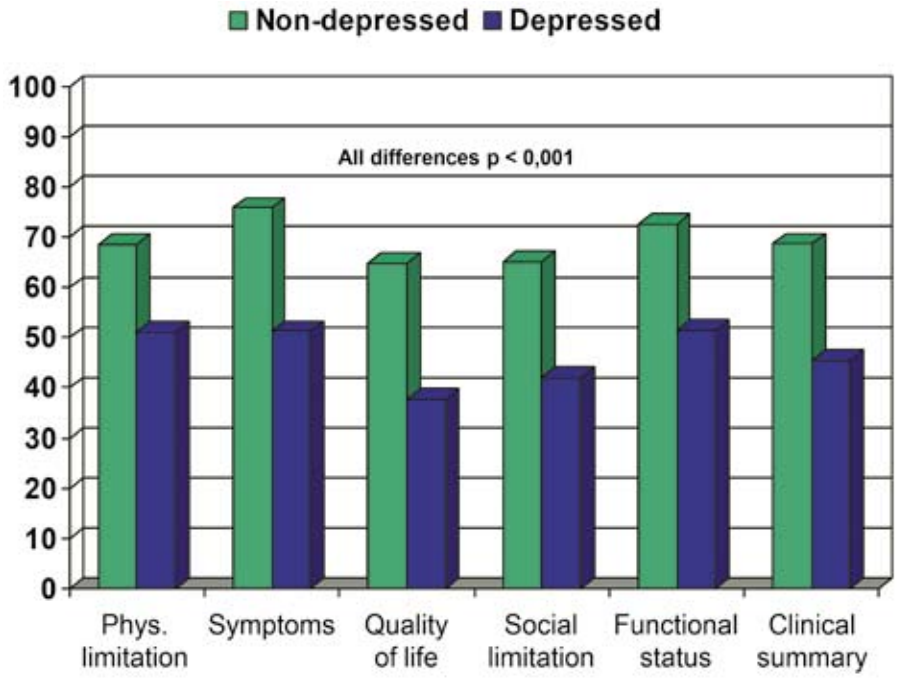


*Fig. 2: Impact of depression on disease-specific quality of life in chronic heart failure patients (Kansas City Cardiomyopathy Questionnaire).*

**Patient Education**
(H. Faller, H. Vogel, K. Meng, A. Reusch)

Several research projects aim to advance the concepts of education for patients with chronic diseases, to enhance patient orientation, to perform a survey on the present state of educational practice, to develop a patient education database, and to evaluate the effectiveness of educational programs for various disorders. Specific strategies are implemented to increase the sustainability of education effects and to transfer newly learned skills to everyday life situations. Examples include behavioral planning and after-care using modern media (see also RFB, Ch. 5.6 Research Networks).

**Occupational Rehabilitation**
(S. Neuderth, H. Vogel)

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 to develop screening instruments for occupational impediments, to create a survey of the present state of work-related treatments in rehabilitation and to foster 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 quality management concepts for medical rehabilitation carried out by the German Statutory Accident Insurance and for prevention and rehabilitation in mother-child-clinics. Another method of quality assurance is the development of therapy standards 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.

**Quality of Life Measurement**
(H. Faller)

A final research focus is on the development and psychometric evaluation of self-assessment instruments for health-related quality of life. In collaboration with the Department of Internal Medicine I, an innovative tool for the assessment of disease-specific quality of life in chronic heart failure patients has been psychometrically validated (Kansas City Cardiomyopathy Questionnaire; Fig. 2). In a multi-center study, the Health Education Impact Questionnaire (heiQ) is being translated and psychometrically evaluated in collaboration with the Medical University of Hannover.

## Teaching

As part of the subjects Medical Psychology and Medical Sociology, the following 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, Steinbüchel T, Störk S, Schowalter M, Ertl G, Angermann CE (2009) Impact of depression on quality of life assessment in heart failure. International Journal of Cardiology (epub a head of print)*

*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*

# 2.11 Institute for Hygiene and Microbiology

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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 Robert-Koch-Institute established the national reference centre for meningococci (NRZM). The activities of the NRZM include the 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 "European Monitoring Group on Meningococci". In cooperation with the European Center for Disease Control (ECDC) the "Laboratory surveillance and external quality assurance of invasive bacterial diseases in EU" (IBD-labnet) project is coordinated by the Institue for Hygiene and Microbiology which focuses on the establishment of an Eurpean laboratory network for the surveillance of invasive infections caused by *Neisseria meningitidis, Streptococcus pneumoniae* und *Haemophilus influenzae*. 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**
(A. Schubert-Unkmeir, O. Kurzai, M. Frosch)

Meningococci, an important cause of septicemia and meningitis in infants and adolescents, are in the focus of research on infection biology. The molecular basis of transmission across specialized endothelial cells underlining the blood-brain barrier is a major point of interest in our research. The

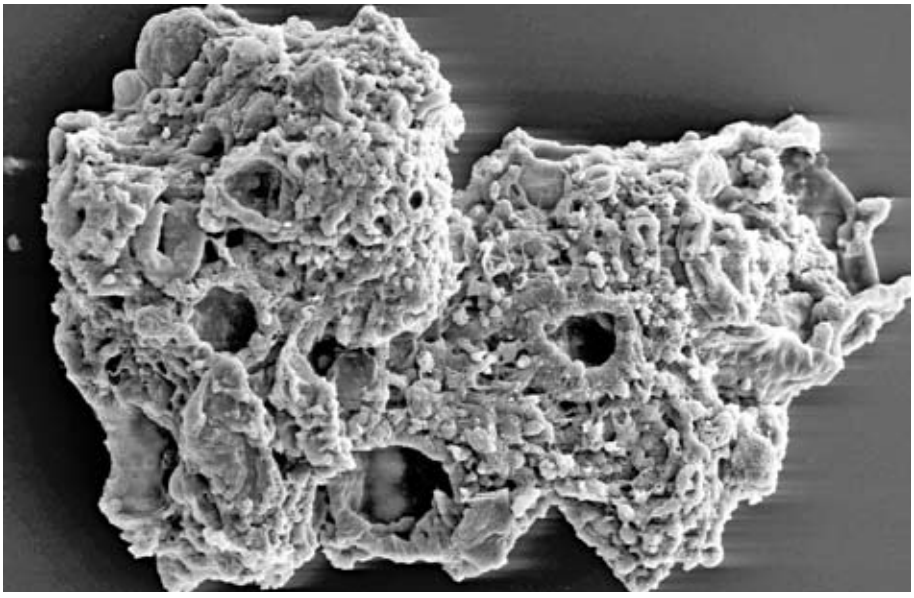

*Fig. 1: Aggregate of Echinococcus multilocularis totipotent stem cells forming a parasite liver vesicle in vitro.*

group works on the analyses of bacterial factors as well as host cell receptors, which determine the interaction, and the characterization of a transcriptional regulator involved in bacterial cell interaction.

**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 meningococci is another main research focus of the institute. The comparison of the genomes from pathogenic as well as from non-pathogenic strains provides insights into the genetic basis of the observed differences in the pathogenic phenotypes and the evolution of pathogenic strains. 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.

**Host cell interaction with 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. In addition, the response of *S. aureus* to contact with biocides and detergents is analyzed.

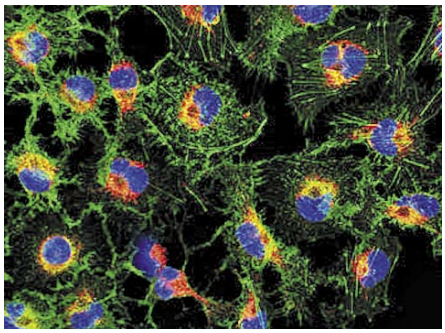

*Fig. 2: Human brain microvascular endothelial cells incubated with MitoTracker Red CMXRos to label the mitochondria. After fixation and permeabilization, the cells were stained with Alexa Fluor 488 phalloidin to label the filamentous actin (F-actin) and finally counterstained with DAPI to label the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

**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.

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*Schielke, S., Huebner, Spatz, C., Nägele, V., Ackermann, N., Frosch, M., Kurzai, O., and Schubert-Unkmeir, A. (2009). Expression of the meningococcal adhesion NadA is controlled by a transcriptional regulator of the MarR-familiy. Mol. Microbiol., 72:1054-1067,*

*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.*

# 2.12 Institute of Virology and Immunobiology, Chair of Virology

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## Mission and Structure

Research within the Chair of Virology is focused 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. In addition, Axel Rethwilm is speaker of the International Research Training Group 1522 that was established by the DFG as a joint research and educational project between Würzburg University and Universities in Cape Town (South Africa).

## Major Research Interests

**Molecular mechanism of measles virus (MV) induced immunosuppression**
(S. Schneider-Schaulies)

A generalised suppression of cellular immunity is induced in the course of the acute disease and almost exclusively accounts for the continuously high rates of measles associated morbidity and mortality. Most likely, the virus accesses secondary lymphatic tissues by using dendritic cells (DCs) as Trojan horses. Infection of which is mediated by surface expression of the MV entry receptor CD150 and DC-SIGN. It appears that MV impairs DC function to stimulate T-cells via action of their glycoprotein using a complex signaling pathway.

**Neuroimmunology and Neurodegeneration of Prion Diseases**
(M. Klein)

Prion diseases are infectious neurodegenerative diseases, which affect both animals and humans. During disease progression, PrPSc, an abnormal, detergent-insoluble isoform of the host encoded cellular prion protein (PrPC) accumulates within infected tissues. The exact mechanisms of neuroinvasion into the brain from the lymphoid system, the role and function of PrPC, and the molecular aspects of axonal transport of the infectious agent and the resulting prion-induced neurodegeneration are analyzed within various projects

**Pathogenesis of Pneumoviruses**
(C. Krempl)

Respiratory Syncytial virus (RSV) is a major viral cause of serious lower respiratory tract disease in the pediatric world, in the elderly and in severely immunocompromised patients. However, our understanding of the pathogenicity mechanisms of RSV-infection is still fragmentory. We use infection of mice with molecular cloned and closely related pneumonia virus of mice (PVM) that causes symptoms similar to those induced by RSV-infection of humans, as surrogate model. The goal is to contribute to a better understanding of the mechanism of RSV-induced disease and to develop rationally-designed molecules.

**Model systems for virus uptake and mechanisms of virus spread**
(J. Schneider-Schaulies)

We investigate the mechanisms of virus spread and the possibilities of blocking the spread in various model systems. In the focus of interest are uptake and spread of measles virus, which is accompanied by a persisting CNS infection. We have developed a mouse model with molecularly cloned MV to test antiviral strategies including siRNA technology. Similar test systems to identify inhibitors of virus uptake and spread are being developed for Nipah- and Dengueviruses.

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

Retroviruses are divided into the orthoretroviruses and the foamyviruses. Major differences in the replication strategies of both subfamilies were responsible for this distinction. We investigate these differences on the transcriptional, post-transcriptional, and translational level

**Development of Foamy Virus Vectors for Gene Therapy**
(C. Scheller, T. Wiktorowicz, 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 ther-

apy. Such vectors for efficient transduction of mesenchymal and haematopoietic stem cells are under development and are being applied in an animal model for rheumatoid arthritis.

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

M. Alzheimer and M. Parkinson are in the center of our interest. AAV-vectors and siRNA technology (M. Alzheimer) as well as foamy virus-vectors (M. Parkinson) are being used to develop genetic strategies against these diseases.

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

HIV dementia is probably a result of an initial microglial activation in CNS, production of inflammatory mediators with subsequent direct cytocidal effect on non-infected neurons. The pathogenesis of the disease is studied in HIV patients from Germany and Africa. Several factors that might be associated with pathogenesis of HIV dementia are studied in greater detail, such as NMDA-Receptor architecture, immune activation and the subtype of the underlying HIV-infection.

**Pathogenesis of HIV-AIDS**
(C. Scheller, E. Koutsilieri, A. Rethwilm)

The pathogenesis of AIDS is driven by a chronic immune activation that eventually leads to the exhaustion of the regenerative capacities of the immune system. In this project the effects of low-dose immunosuppressives on disease progression are studied in a German HIV cohort and in patients who participate in a clinical study in Tanzania.

**Lentiviral reportergen vectors for the detection and isolation of tumor stem cells**
(M. Kirschner, A. Rethwilm)

Using lentiviral-vectors and a histone-based fusion protein, we developed a reporter to detect and isolate slow cycling, label retaining cells with stem cell properties. With this system we will be able to detect and isolate label-retaining cells (LRC) with stem cell properties (tumor stem cells) *in vivo* as well as *in vitro*.

**Development of new screening platforms to identify antiviral compounds**
(M. Kirschner, A. Rethwilm)

Inhibiting the interaction of the human cytidin-deaminase Apobec3G (hA3G) with the HIV-1 specific viral infectivity factor (Vif) represents a novel therapeutic approach where a cellular factor with potent antiviral activity (hA3G) plays a key role. In HIV-infected cells the interaction of Vif with hA3G leads to the subsequent degradation of hA3G. We engineered a double transgenic cell line constitutively expressing an EYFP-hA3G fusion as well as Tet-Off controllable Vif protein as a stable and convenient cellular testing platform for a high throughput screening of antiviral compound libraries.

**Clinical Virology**
(B. Weißbrich, J. Schubert)

30-35 thousand clinical samples are processed in our Clinical Unit each year. Furthermore, a variety of clinical virological questions are being addressed. For instance, in cooperation with the children's hospital of the university clinic, recently discovered respiratory viruses, such as the 2005 discovered human bocavirus, are being studied.

## Teaching

The Chair of Virology teaches students in Medicine, Biomedicine and Biology.

SELECTED PUBLICATIONS


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# 2.13 Institute of Virology and Immunobiology, Chair of Immunology

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**Professor Dr. rer. nat. Manfred Lutz**
**Tel.: 0931/201-49957**

## Mission and Structure

The individual research groups are interested in basic and applied immunological topics. These include the regulation of B cell apoptosis, suppressor mechanisms of regulatory T cells and myeloid-derived suppressor cells, antigen recognition by NKT cells and tolerance induction by dendritic cells. Many of the results from basic research are then translated into preclinical therapy models for allergies, autoimmune diseases, transplant rejection and graft-versus-host-disease. Our research is supported by local and international funding and supported by various cooperations within Germany and abroad. The institute also provides immunodiagnostic analyses for autoantibodies from patients from the University Clinic (head PD Dr. T. Kerkau).

## Major Research Interests

**Function of the costimulatory receptor CD28**
(T. Hünig)

CD28 is a central regulator of T-cell responses. Using conditionally CD28 deleting mice and blocking as well as stimulating CD28-specific monoclonal antibodies, we study the contribution of this receptor to the function of the immune system.

**The response of human T-cells to the CD28 superagonist TGN1412**
(T. Hünig)

Stimulatory CD28-specific monoclonal antibodies had proven therapeutically effective in animal models against autoimmunity and inflammation. In contrast, the first-inman study of the human CD28 superagonist TGN1412 led to a life-threatening release of inflammatory cytokines. We are investigating why animal and tissue culture experiments did not predict this and work on the establishment of new preclinical test systems.

**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 of axons, we can selectively destroy these cells with „killer" CD8 T-cells in mice, in using MS-like lesions. We are using this system to explore novel therapeutic approaches.

**The role of CD28 for the development and persistence of Multiple Myeloma**
(I. Berberich and T. Hünig)

CD28, which normally is expressed by T-lymphocytes, is also found in the final stage of B-cell differentiation, the plasma cell, and on the malignant myeloma cells derived from this cell type. Since in humans, this expression correlates with an unfavourable prognosis, we are studying the role of CD28 expression on myeloma cells in vitro and in a mouse model.

**T-cell activation by non-conventional T-cells**
(T. Herrmann)

Most T cells recognize with their antigen receptor complexes of MHC molecules and peptide-antigens. Moreover, „non-conventional antigens" such as glycolipids and „phosphoantigens" exist. The Herrmann group studies - preferentially in the rat – the glycolipid-presenting molecule CD1d, CD1d-restricted NKT cells and a „new" MHC class II molecule (RT1Db2). Moreover, human Vγ9Vδ2 T cells are investigated. These cells recognize so called „phosphoantigens" and shall be used to fight tumors.

**Tolerance induction by dendritic cells**
(M. Lutz)

The generation of dendritic cells (DC) from bone marrow progenitor cells and the activation of their tolerogenic functions represent the major topics investigated with this cell type. Recent data showed that the expression of so-called co-inhibitory molecules by DC plays an important role for their tolerogenicity. The expression of the co-inhibitor B7-H1 on tolerogenic DC is required to control conventional T cells but also unconventional type II NKT cells that recognize glycolipid antigens on CD1d molecules.

**Immunosuppression by myeloid suppressor cells**
(M. Lutz)

Our latest investigations with myeloid-derived suppressor cells (MDSC) in the murine system show that myeloid progenitor cells

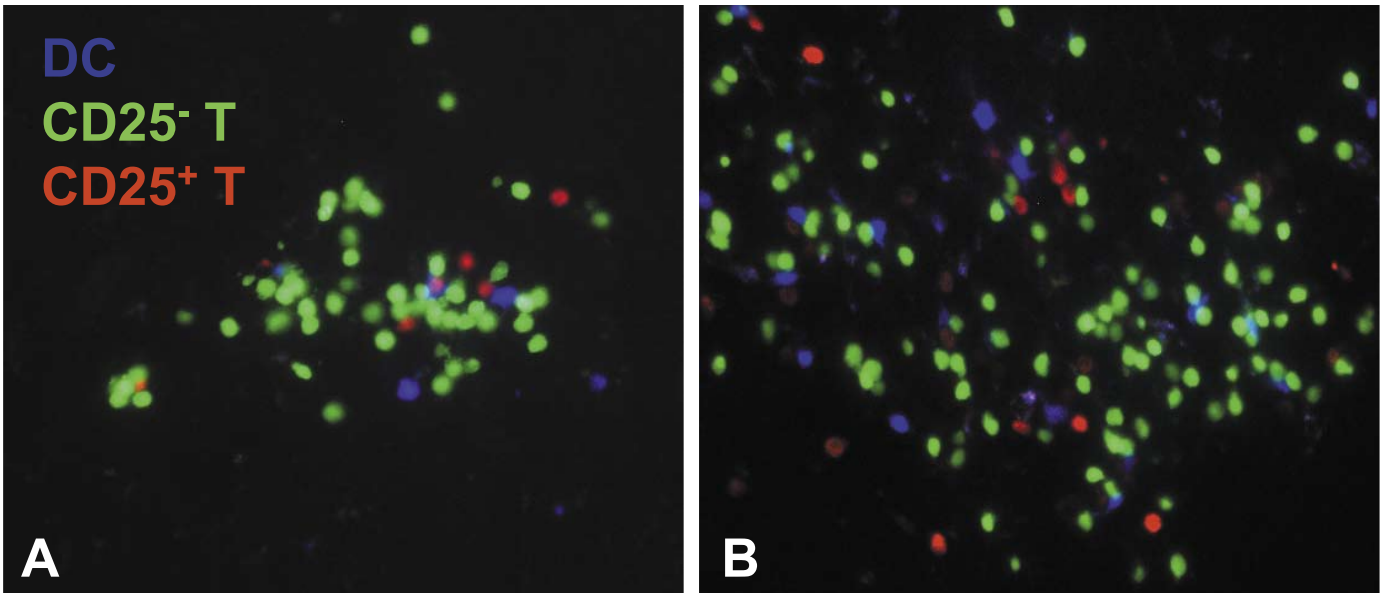


*Fig. 1: Suppression of immune responses by regulatory T cells in vivo. Different fluorescence-marked cell types were injected intravenously into mice and the development of cell clusters in the spleen was analysed. Antigen-loaded mature dendritic cells (blue) form clusters with CD4⁺ CD25- effector-T-cells (green) as a sign of their activationa and proliferation in the presence of CD4⁺ CD25⁺ resting regulatory T cells (red) (A). In contrast, activated regulatory T-cells inhibit clustering of dendritic ells with effector T-cells as a sign of their suppressor activity (B). Photographs Dr. Jens Hänig.*

can differentiate under steady state conditions to neutrophils, macrophages and dendritic cells or after activation by bacterial pathogenic factors (LPS) plus interferon-γ into suppressive MDSC. As a typical marker for MDSC the Gr-1 antibody is used. Detailed analyses with it showed that the antibody can mediate apoptosis of differentiated neutrophils but also via phosphorylation of STAT molecules the myelopoiesis into macrophages.

**B cell maturation**
(I. Berberich)

B cells recognize microbes and foreign substances (antigens) invading an organism. After contact with antigens, B cells proliferate and differentiate to antibody-producing „factories". The proteins Blimp-1 and C/EBPβ drive the maturation. So-called Bcl-2 proteins allow the cells to survive this process. Currently, we analyse the function of C/EBPβ and of the Bcl-2 protein A1/Bfl1 in B cells in vivo and in vitro.

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

The team is working on the significance and therapeutic manipulation of regulatory T cells in the context of pathological immune reactions. In addition to animal models of multiple sclerosis, we are particularly interested in the development of novel strategies for the treatment of Graft-versus-host-disease, a major complication after allogeneic bone marrow transplantation. In case of GvHD, regulatory T cells have been shown to modulate disease activity, but in most cases they are not powerful enough to prevent the disease. Therefore, novel monoclonal antibodies, which are able to activate regulatory T cells and/or to make pathogenic T cells more susceptible to suppression by regulatory T cells are now being assessed for their potential to keep GvHD in check.

## Teaching

Various theoretical and practical courses are provided to students. These include basic immunology lectures for medical, biomedical and biology students, which are complemented by a series of seminars for advanced students together with practical courses of 8 weeks per year.

## SELECTED PUBLICATIONS

*Beyersdorf, N., Ding, X., Hunig, T. and Kerkau, T. Superagonistic CD28 stimulation of allogeneic T cells protects from acute graft versus host disease. Blood 2009.*

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*Li, J., M.J. Herold, B. Kimmel, I. Müller, B. Rincon-Orozco, V. Kunzmann, T. Herrmann (2009) Reduced expression of the mevalonate pathway enzyme farnesyl pyrophosphate synthase unveils recognition of tumor cells by Vgamma9Vdelta2 T cells. J Immunol 182:8118-24.*

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# 2.14 Institute for Molecular Infection Biology

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**Professor Dr. rer. nat. Dr. med. habil.**
**Heidrun Moll**
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**Professor Dr. rer. nat. Joachim Morschhäuser**
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## Mission and Structure

The Institute for Molecular Infection Biology (IMIB) was founded in 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". Traditionally, the chairman is also a member of the Faculty of Biology, thus IMIB constitutes a link between the Faculties of Medicine and Biology. 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. We study molecular aspects of infections caused by a variety of bacteria, parasites and fungi, and the biological function of small non-coding RNAs in pro- and eukaryotes. Additionally, the interactions between parasitic pathogens and the host immune system are investigated.

## Main 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 host immune response to pathogens is studied. In addition to bioinformatics, microbiological, molecular and cell biological methods, genomic (genome analysis) and proteomic (protein expression analysis) approaches are applied within the following projects:

**RNA biology**
(J. Vogel)

Small, noncoding RNAs (sRNAs) as regulators of gene expression in both prokaryotes and eukaryotes have attracted much attention over the last few years. We use biochemical, genetic and biocomputational approaches to characterize bacterial sRNA functions, particularly with respect to host-pathogen interactions of *Salmonella* and *Helicobacter* species. Furthermore, we study the biological role of small RNAs induced in eukaryotes in response to a bacterial infection.

**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 adhesin-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)

*Leishmania* cause a spectrum of different diseases, depending on the parasite species and the type of the host's immune response. This model allows the analysis of the mechanisms involved in host resistance or susceptibility to a microbial pathogen. The development of new strategies for immunotherapy and vaccination based on the use of dendritic cells and the identification and characterization of leishmanicidal compounds are the major research topics of this group.

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

The group studies virulence mechanisms of the pathogenic yeast *Candida albicans* and the molecular basis of antimycotic drug resistance in this fungus. For this purpose, the signals, signal transduction pathways and transcription factors that control morphogenesis, virulence gene expression and antifungal drug resistance in C. albicans are analyzed.

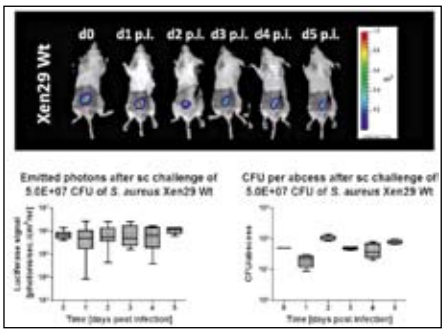


*Fig. 1: Bioluminescent Staphylococcus aureus strain Xen29 in an abscess infection model (top) and quantification of bioluminescent signals and determination of colony forming units (CFU) (bottom center).*

**Virulence- and resistance mechanisms of pathogenic staphylococci**
(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.

## Teaching activity

A considerable part of the teaching activities contribute to the training of biology students 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.

## SELECTED PUBLICATIONS

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*Putze J, Hennequin C, Nougayrède JP, Zhang W, Homburg S, Karch H, Bringer MA, Fayolle C, Carniel E, Rabsch W, Oelschlaeger TA, Oswald E, Forestier C, Hacker J, Dobrindt U. (2009) Genetic structure and distribution of the colibactin genomic island among members of the family Enterobacteriaceae. Infect Immun. 77:4696-4703.*

# 2.15 Institute of Pharmacology and Toxicology, Chair of Toxicology

CONTACT DETAILS

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**Professor Dr. sc. techn. Werner Lutz**
**(Head until 31. 3. 2009)**

**Professor Dr. med. Gilbert Schönfelder**
**Tel.: 0931/201-48777**

## 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. Helga Stopper, Dr. Gilbert Schönfelder, the Associate Professors Dr. Erwin Eder and Dr. Wolfgang Dekant, the Research Associates PD Dr. Angela Mally and Dr. Nicole Schupp and the former head of toxicology Prof. Dr. Werner K. Lutz (until spring 2009). Three postdocs and on average 18 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 on a top position among the Bavarian Toxicological Departments in this respect. This is also reflected by the number of publications in refereed journals reaching on average 20 per year.

### Chemical Carcinogenesis

Our research focuses on elucidating the first-line interactions of mutagenic and carcinogenic chemicals with biological targets, 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. We study genotoxicity by analyzing 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 are biomarkers in both animals and humans. Biomarkers of exposure are based mainly on the analysis of metabolites in urine and on cytogenetic alterations, for example in peripheral lymphocytes and buccal mucosa cells in humans. In animal models, early cytological alterations are also investigated in the search of early biomarkers of toxicity and carcinogenicity in kidney and liver, including idiosyncratic reactions. 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.

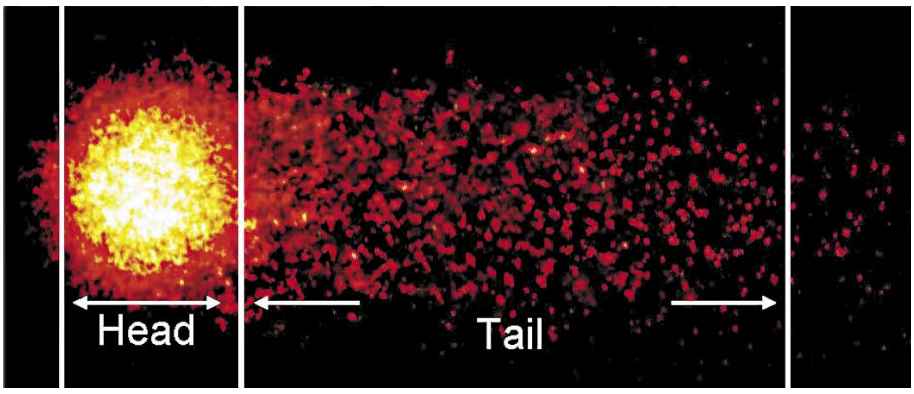


*Fig. 1: "The Comet Assay": DNA fragments induced by a genotoxic agent migrate in an electric field out of the cell nucleus (Head) into a Tail.*

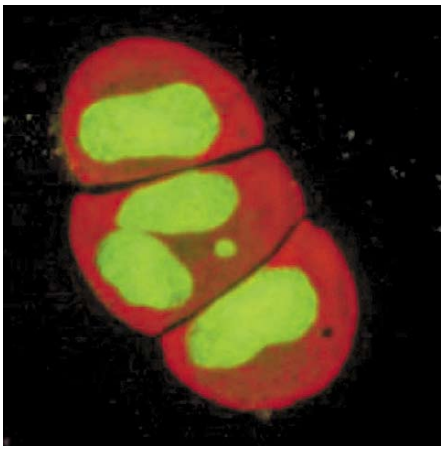

*Fig. 2: "The Micronucleus Test": Chromosome damage is indicated by the presence of a DNA-containing fragment in the cytoplasm of the bi-nucleated cell in the middle of the three cells.*

**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, fumonisin B1), 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 differences 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. Stopper is speaker of the class "Biomedicine" of the Graduate School of the University. The working group leaders contribute to the postgraduate courses organized by the Society of Toxicology of the DGPT to register as DGPT and EUROTOX-certified Toxicologist. The institute offers advanced education for the degree of Pharmacist for Toxicology and Ecology. 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.

SELECTED PUBLICATIONS


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# 2.16 Institute of Pharmacology and Toxicology, Chair of Pharmacology

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**Professor Dr. rer. nat. Moritz Bünemann**

**Professor Dr. Dr. Stefan Engelhardt**

## Mission and Structure

The Institute of Pharmacology and Toxicology comprises Chairs for Pharmacology (Prof. Lohse) and for Toxicology (Prof. Lutz). The institute also houses research groups of the Rudolf Virchow Center that was funded in 2001 and 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 models as well as equipment for rapid microscopic imaging, for confocal, 2-photon and TIRF microscopy, for electrophysiology and for cardiovascular physiology and histology.
The chair also provides a drug information service for the university hospital and accomodates the faculty's ethics committee.

## 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, D. Calebiro 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. 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. We have shown extremely rapid (50 ms) activation of receptors and their direct cross-talk at the cell surface. Another discovery concerns signaling by internalized receptors from intracellular sites.

**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.

**Phosphatases and Cellular Motility**
(A. Gohla; joint appointment with Rudolf Virchow Center)

The cytoskeleton plays a fundamental role for cell adhesion and motility, and is an important drug target for cancer and cardiovascular disease. We have discovered a novel class of human phosphatases that regulate cytoskeletal dynamics. Employing primarily biochemical and cell biological methods, we study phosphatase interaction partners and substrates, and investigate the signalling pathways that determine phosphatase activities downstream of extracellular cues.

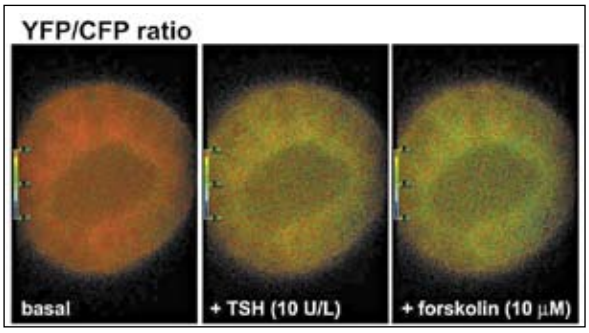


*Fig. 1: Visualizing receptor function: thyroid follicles from a transgenic mouse expressing a fluorescent sensor for cAMP change their fluorescence upon stimulation with thyroid stimulating hormone, TSH. Changes in color reflect the increase in intracellular cAMP.*

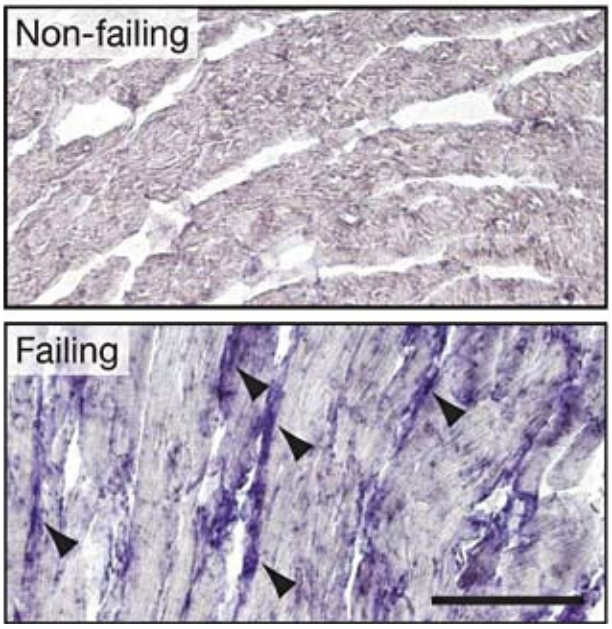


*Fig. 2: MicroRNAs in the heart – demonstration of micro RNA21 in failing but not in non-failing heart.*

**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, joint appointment with Rudolf Virchow Center; K. Lorenz, J. Schmitt)

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. We have discovered a number of pathways that can lead to heart failure (β-adrenergic receptors, the sodium/proton exchanger NHE1, the interleukin converting enzyme ICE, the transcriptional regulator NAB1, the protein kinase inhibitor RKIP, a newly discovered activation pathway for the protein kinases ERK1/2 as well as mutations in signaling and contractile proteins. We have also established a contribution of newly discovered micro RNAs in heart failure.

**Receptor-Antiodies in Heart Failure**
(R. Jahns, in collaboration with the Department of Medicine and Rudolf Virchow Center)

Over many years we have demonstrated the presence of antibodies against β1-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.

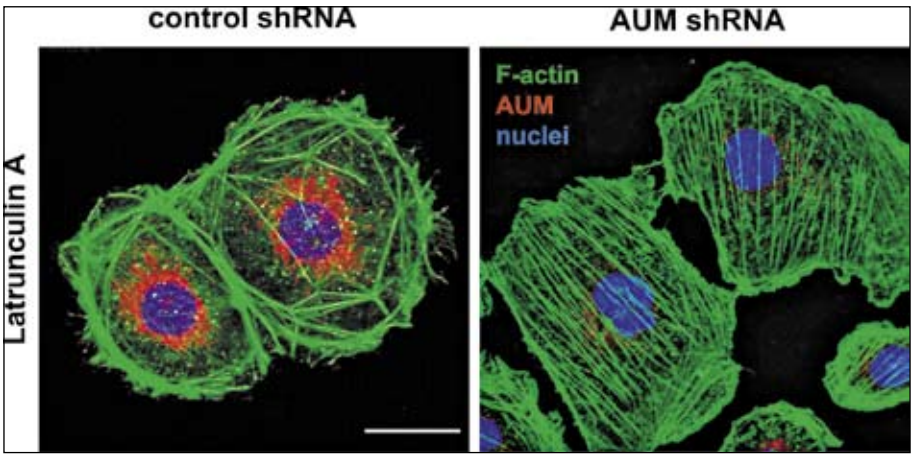


*Fig. 3: Demonstration of phosphatase action on cytoskeletal dynamics. The depletion of the phosphatase (AUM) by RNA interference stabilizes actin fibres (shown in green).*

## 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 offer the full curriculum for the medical specialties of pharmacology and clinical pharmacology.

SELECTED PUBLICATIONS

*Calebiro D, Nikolaev VO, Gagliani MC, de Filippis T, Dees C, Tacchetti C, Persani L, Lohse MJ (2009) Persistent cAMP-signals triggered by internalized G-protein-coupled receptors. PLoS Biol. 7:e1000172*

*Dorsch S, Klotz KN, Engelhardt S, Lohse MJ, Bünemann M (2009) Analysis of receptor oligomerization by FRAP microscopy. Nature Methods 6, 225-30*

*Lorenz K, Schmitt JP, Schmitteckert EM, Lohse MJ (2009) A new type of ERK1/2-autophosphorylation causes cardiac hypertrophy. Nature Medicine 15, 75-83.*

*Thum T, Gross C, Fiedler J, Fischer T, Kissler S, Bussen M, Galuppo P, Just S, Rottbauer W, Frantz S, Castoldi M, Soutschek J, Koteliansky V, Rosenwald A, Basson MA, Licht JD, Pena JT, Rouhanifard SH, Muckenthaler MU, Tuschl T, Martin GR, Bauersachs J, Engelhardt S (2008) MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. Nature 456, 980-4*

*Vilardaga JP, Nikolaev VO, Lorenz K, Zhuang Z, Lohse MJ (2008) Direct inhibition of G protein signaling by cross-conformational switches between a2-adrenergic and m-opioid receptors. Nature Chemical Biology 4, 126-131.*

# 2.17 Institute of Forensic Medicine

CONTACT DETAILS

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## Mission and structure

In 2008, the academic staff of the Institute of Forensic Medicine at Würzburg University consisted of two physicians and one toxicologist as well as the head of the intsitute. Temporarily there was only one senior physician (Oberarzt), due to maternity leave of one physician. With the change in leadership, under the new conditions of an attending physician (Chefarzt) contract, another physician and a molecular biologist were employed. Two of these academic staff, as well as two more technicians and a secretary are being financed through third-party means of the institute. The remaining job capacity is oriented at the discipline's tasks of research, teaching and privileged services of forensic medicine.

Forensic medicine services for the region Unterfranken (as well as bordering parts of Oberfranken and Baden-Württemberg) are done at the request of courts, district prosecutors and police stations. The main tasks are the resolution of causes of death, clinical forensic medicine including examination of the living and victims of physical violence, forensic analysis of traces, paternity analyses, and forensic-toxicologic analysis to determine causes of death and solve traffic accidents.

## Major Research Interests

Research in forensic medicine is to be developed in a bipartite manner. On the one hand, it is essentially required to improve analytical methods and possibilities, in order to provide the authorities with material evidence for the solution of cases. On the other hand, a focus on research is imperative; this can represent an important mosaic piece within the faculty, in order to undertake interdisciplinary research in times of scarce resources. Over the years, an expertise has grown in forensic medicine such that useable results can be extracted from very little and heavily degraded starting material – an expertise that can benefit other disciplines.

Preliminary experiments towards the improvement of forensic methods have been performed, where, employing miniSTRs, even with degraded DNA and telogenic hair (i.e. shed hair) results can be obtained. Telogenic hair usually contains either no roots or only rudimentary roots and frequently does not allow routine DNA analysis work.

Another research focus is forensic neuropathology. Based on a method which is in routine use at the department of neuroanatomy (Prof. Dr. H. Heinsen) at the Clinic and Polyclinic for Psychiatry, Psychosomatics and Psychotherapy, it is possible to assemble 3D images from gallocyanin-stained sections and to gain detailed insights which thus far have been impossible to image. The targeted use of this method in certain nuclear regions of Alzheimer brains, in sudden infant death syndrome (SIDS) and sudden unexpected death in epilepsy (SUDEP) is in the pipeline.

In collaboration with the department of neuropathology (Dr. C. Monoranu) and the Clinic and Polyclinic for Psychiatry, Psychosomatics and Psychotherapy (Prof. A.J. Fallgatter), a project combining clinical data with basic science in an ideal fashion has been developed. Since a diagnosis of Alzheimer's disease can presently only be ascertained when the aetiology is well advanced, better diagnostic options must be found. In the Polyclinic for Psychiatry, Psychosomatics and Psychotherapy the method of vagus-evoked potentials has been developed and validated for early diagnosis on Alzheimer patients. Based on these clinical data, the project is aiming for examination of the brainstem of these patients, in particular morphological and molecular biological changes associated with oxidative stress. Evidence of cell-specific deletions of mitochondrial DNA due to oxidative stress and altered patterns of gene expression in these regions could then serve as the starting point for innovative strategies in diagnostics and therapy.

## Teaching

Teaching forensic medicine to medical students involves a lecture series, laboratories and seminars. In the lectures, topics include thanotology, various forms of violence, forensic/molecular biology aspects, forensic toxicology, as well as ethical and medical-legal aspects. Students also learn how to perform autopsies; here an expansion of the practice-oriented teaching in small groups seems desirable. The practical skills that students can acquire for their later work in general practice are particularly emphasised in teaching. The distinction between self-harm and external harm as well as the clinical analysis of domestic violence are taught through a multitude of case studies with extensive imagery.
External teachings include a well-attend-

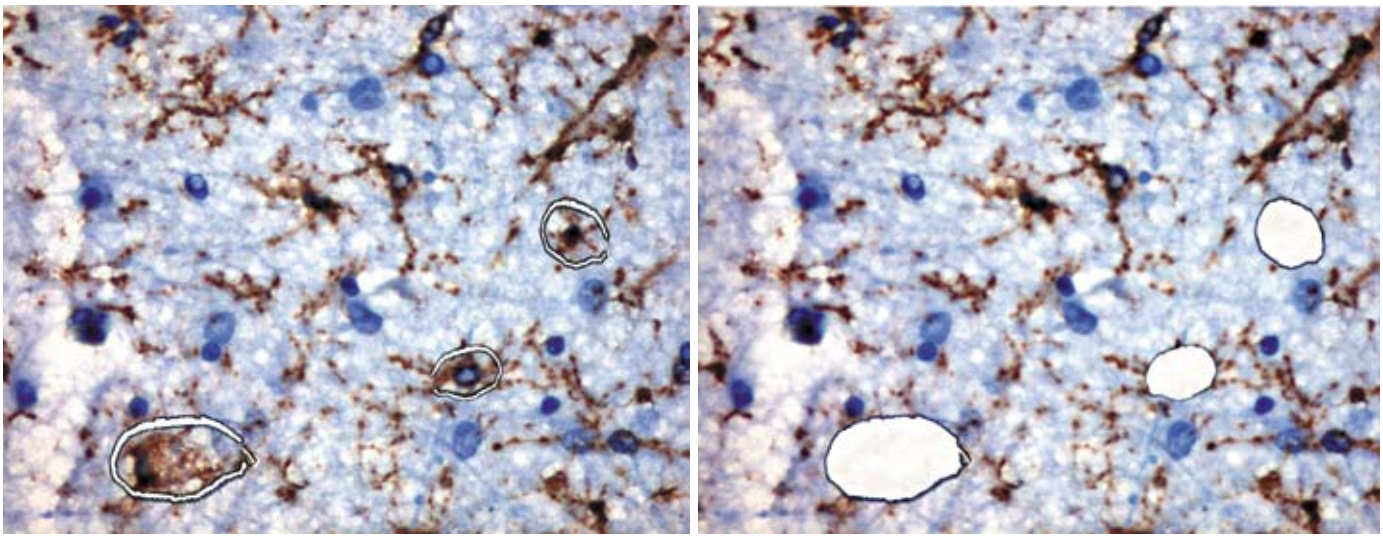

*Fig. 1: Isolation of immunohistochemically labelled single cells by means of a laser dissection microscope for molecular biological analysis of certain cell entities in Alzheimer's disease.*

ed class for law students entitled "Forensic medicine for lawyers". For legal interns (Rechtsreferendare), instructions on the effects of alcohol and drugs in traffic are also on offer, with a monitored drinking experiment. Furthermore, biology students can take the class "Forensic medicine for biologists".

## SELECTED PUBLICATIONS


*Bauer M, Patzelt D (2008) Identification of menstrual blood by real time RT-PCR: technical improvements and the practical value of negative test results. Forensic Sci Int 174:55-59.*

*Michel TM, Frangou S, Camara S, Thiemeyer D, Jecel J, Tatschner T, Zoechling R, Grünblatt E. (2008) Altered glial cell line-derived neurotrophic factor (GDNF) concentrations in the brain of patients with depressive disorder: a comparative post-mortem study. Eur Psychiatry 23:413-20.*

*Oehmichen M, Wötzel F, Meissner C (2009) Hypoxic-ischemic changes in SIDS brains as demonstrated by a reduction in MAP2-reactive neurons. Acta Neuropathol (Berl) 117:267-274.*

*Walter T, Meissner C, Oehmichen M (2009) Pathomorphological staging of subdural hemorrhages: statistical analysis of posttraumatic histomorphological alterations. Leg Med (Tokyo) 11 Suppl 1: S56-62.*

*Oehmichen M, Gronki T, Meissner C, Anlauf M, Schwark T (2009) Mast cell reactivity at the margin of human skin wounds: an early cell marker of wound survival? Forensic Sci Int 191: 1-5.*

# 2.18 Institute of Pathology

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**Professor Dr. med. Dr. h.c. Hans-Konrad Müller-Hermelink**
**(Head until 30. 9. 2008)**

**Professor Dr. med. Stefan Gattenlöhner**
**Tel.: 0931/201-47420**

**Professor Dr. med. Wolfgang Roggendorf**
**Tel.: 0931/201-47429**

**Professor Dr. rer. nat. Dr. sc. nat. Edgar Serfling**
**Tel.: 0931/201-47431**

## Mission and Structure

The Institute of Pathology is an academic center with more than 90 employees including 15 pathologists. The institute delivers clinical care including histological and cytological diagnostic assessments of biopsies and other materials, as well as autopsies. Specialized departments, e.g. for Neuropathology or Molecular Pathology, concentrate on specific diagnostic and scientific topics. The Institute of Pathology has a particular focus on diagnostic and scientific aspects of hematopathology and constitutes one of six German reference centers for lymph node pathology. The diagnostic expertise in this field and the scientific achievements are internationally visible.

## Major Research Interests

**Research in Hematopathology and Consultation Center for Lymph Node Pathology**
(A. Rosenwald)

The Reference Center for Lymph Node Pathology operates as a national consultation center and coordinates research activities associated with prospective clinical lymphoma trials including trials of the 'German study group for high-grade non-Hodgkin lymphomas (DSHNHL)'. Professor Rosenwald's group has a major research focus on the molecular pathogenesis of malignant B- and T-cell lymphomas. Specifically, high-throughput technologies including gene expression profiling and high-resolution genomics approaches are used to decipher molecular alterations in lymphoid neoplasms. Recently, major studies were performed in mantle cell lymphomas and diffuse large B-cell lymphomas. In follicular lymphomas, new molecular and clinical subgroups could be identified.

Dr. Geissinger's group is interested in the molecular and immunophenotypic characterization of peripheral T-cell lymphomas (PTCL). Recent projects identified a disturbed expression of the T-cell receptor/CD3 complex and associated signalling molecules in primary cutaneous, but also in systemic CD30-positive lymphoproliferations.

Dr. Haralambieva and coworkers analyzed the biological and genetic heterogeneity of multiple myeloma by using a fluorescence in situ hybridization (FISH) approach that was specifically developed to detect various chromosomal translocations in paraffin embedded tumor tissue.

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

In the framework of this research area it was shown that the cell adhesion molecule and signal transducer CD56 induces apoptosis and inhibits the calcium transport in human heart cells and reduces contractility in cardiac myocytes, whereas it functions anti-apoptotic and pro-proliferative in malignant hematopoietic neoplasms via the NFκB pathway.

**Immunotherapy for Rhabdomyosarcoma and Rhabdoid Differentiated Tumors**
(S. Gattenlöhner)

Rhabdomyosarcomas (RMS) are the most common malignant soft tissue tumors in children that show a 5-year survival rate of 5% in advanced stages. After identification of the fetal acetylcholine receptor (fAChR) as a tumor-specific antigen in RMS, we established an anti-fAChR-based immunotherapy. In future investigations, a fully human immunotoxin shall be generated and tested in Phase I clinical trials.

**Transcriptional Control in T-Lymphocytes**
(E. Serfling)

The Department of Molecular Pathology contributed to the establishment of a new SFB/Transregio (Collaborative Research Center), TRR52, of the German Research Association (DFG) which started its work in July 2008 with the topic 'Transcriptional programming of individual T-cell populations'. Professor Serfling's research is focused on the role of calcium/calcineurin inducible nuclear factor of activated T-cell (NFAT) transcription factors in lymphocyte function and their proliferation and apoptosis. Main topics are the creation of mouse lines for the conditional inactivation of the murine Nfatc1 gene, post-transcriptional modifications of NFAT factors and the transcriptional inactivation (and repression) of the murine Nfatc1 gene.

**Human Immunity to Cancer**
(H.P. Vollmers)

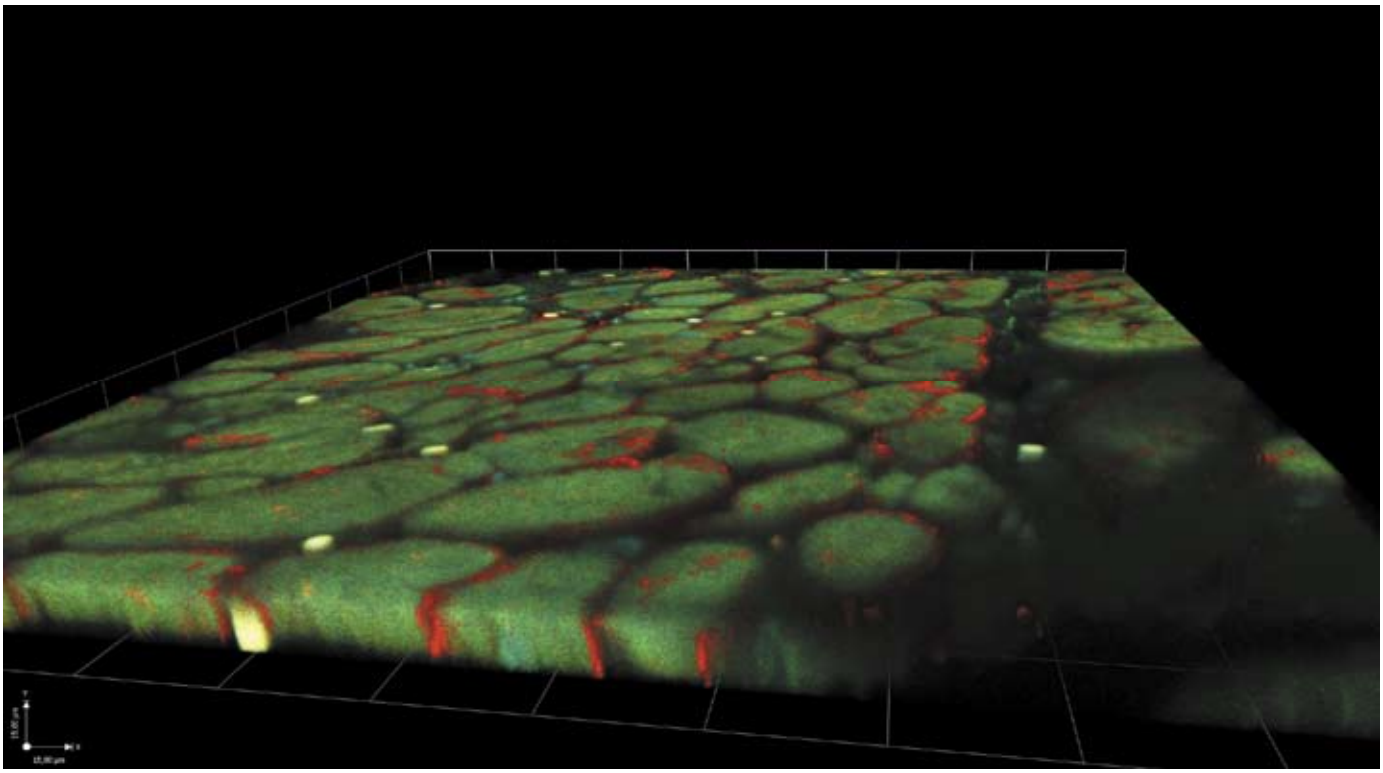

*Fig. 1: Three-dimensional presentation of the overexpression of CD56 (rot) in human heart muscle cells.*

The experimental work of this research group is focused on human innate immunity to cancer in which antibodies play an important role. Several tumor-specific natural antibodies could already be identified and characterized. The antibodies are coded by distinct germ line genes, their targets being post-transcriptionally modified carbohydrate epitopes on tumor cell surface receptors. Such tumor-specific modified epitopes could be found on proteins such as CD55, CFR-1, GRP78 and TAF15. All tested antibodies remove malignant cells in vitro and in vivo by inducing apoptosis. In collaboration with an Australian company, some of the identified antibodies are scheduled to enter clinical trials in 2010. The ongoing scientific work is concentrated on the characterization of the antibody epitopes and the apoptotic pathways.

**Neurooncology and neurodegeneration**
(W. Roggendorf)

The neurooncological focus of Professor Roggendorf's research group is on ependymomas, a primary tumor of the central nervous system that often occurs in childhood. The clinical prognosis is very variable. Using molecular analyses on the gene expression and genetic levels, characteristic genetic alterations and gene expression profiles could be identified. In the field of neurodegeneration, the role of microcirculation and its impairment is being investigated in Alzheimer's disease.

## Teaching

The institute of pathology is responsible for teaching pathology as part of the medical curriculum of the Wuerzburg Medical School. Specifically, 6 professors and additional teaching staff conduct 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 clinical departments.

## SELECTED PUBLICATIONS


*Leich E, Salaverria I, Bea S, Zettl A, Wright G, Moreno V, Gascoyne RD, Chan WC, Braziel RM, Rimsza LM, Weisenburger DD, Delabie J, Jaffe ES, Lister A, Fitzgibbon J, Staudt LM, Hartmann EM, Mueller-Hermelink HK, Campo E, Ott G, Rosenwald A (2009). Follicular lymphomas with and without translocation t(14;18) differ in gene expression profiles and genetic alterations. Blood 114(4): 826-34.*

*Nayak A, Glöckner-Pagel J, Vaeth M, Schumann JE, Buttmann M, Bopp T, Schmitt E, Serfling E, Berberich-Siebelt F (2009). Sumoylation of the transcription factor NFATc1 leads to its subnuclear relocalization and interleukin-2 repression by histone deacetylase. J Biol Chem 284(16): 10935-46.*

*Gattenlöhner S, Stühmer T, Leich E, Reinhard M, Etschmann B, Völker HU, Rosenwald A, Serfling E, Bargou RC, Ertl G, Einsele H, Müller-Hermelink HK (2009). Specific detection of CD56(NCAM) isoforms by novel qRT-PCRs and antibodies identifies aggressive malignant neoplasias with tumor progression. Am J Pathol. 174(4):1160-71.*

# 2.19 Institute for Medical Radiation and Cell Research (MSZ)

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**Professor Dr. med. Ulf R. Rapp**
**(Head until 31. 3. 2009)**

**Professor Dr. rer. nat. Thomas Raabe**
**Tel.: 0931/201-45841**

## Mission and Structure

The objective of the MSZ under the aegis of Prof. Ulf Rapp was to better understand cancer with special emphasis on signaling pathways known to be disrupted in tumors. In addition, in cooperation with pharmaceutical companies the MSZ was involved in the development of small molecule inhibitors and therapeutic vaccines. With the retirement of Prof. Rapp the MSZ has seen a major change, which touched the scientific direction of the Institute as a whole. The focus shifted towards understanding various aspects of regenerative stem cell biology. Two groups which were organized as part of the department earlier because of the intimate relationship between cancer and regenerative stem cells are currently carrying the scientific program. Prof. Müllers group is analyzing gene expression programs in mammalian embryonic and adult stem cells with a special emphasis on chromatin regulation. Prof. Raabes group is studying signal transduction within the progenitor compartment of the developing *Drosophila* brain. The MSZ is working together with several institutes of the faculties of medicine and biology and is integrated in local and national collaborative research centers.

## Major Research Interests

**Tumor Genetics**
(U. Rapp)

We have successfully used an in house developed mouse model system for non-small cell lung cancer (NSCLC) to study various aspects of cancer related genes in the past. The system is based on the expression of an oncogenic form of the RAF kinase, termed C-RAF BXB in specific cells of the lung which leads to the development of adenomas within two weeks after birth of transgenic animals. No progression of these tumors to metastasis has ever been observed. As NSCLC is the most lethal human cancer due to its high rate of metastasis the dissemination of cancer cells from the primary tumor and the contribution of cancer associated genes to this process has been in the focus of our studies. Our most recent work employing the C-RAF BXB NSCLC system has led to the generation of the first conditional model for metastasis of NSCLC and identified a gene, c-MYC that is able to orchestrate all steps of this process (Rapp UR et al., PLoS One. 2009; 4(6): e6029.). A second project identified the cancer stem cell related factor Bmi1 as crucial for the growth of NSCLC (Becker et al., PLOS One 2009; 4(1):e4230).

**Biochemistry**
(U. Rapp)

The mitogenic cascade RAF/MEK/ERK plays a central role in the regulation of cell proliferation, differentiation, transformation and apoptosis. Over the past years we have focused our research effort on the elucidation of molecular mechanisms involved in RAF activation. In detail, our team provided new insight into regulation of C-RAF kinase by scaffold proteins 14-3-3 and prohibitin. (Fischer et al., J. Biol. Chem. 2009, 284:3183). Additionally, our team uncovered new aspects in isoform specific regulation and cellular function of A-RAF kinase. Using mass spectrometry we identified and characterized a number of new phosphorylation sites in A-RAF (Baljuls et al., J. Biol. Chem. 2008, 283:27239). Moreover, we were able to establish a new function of A-RAF in endocytosis and internalization of the cell receptors, which has been unknown so far (Nekhoroshkova et al., PLOS One 2009; 4(2):e4647). Of particular importance are the new data on the interplay between RAF kinases and the apoptosis regulatory proteins IAP and BAD, which advance our understanding of the mechanisms involved in the regulation of apoptosis (Dogan et al., Nature Cell Biol. 2008,10:1447; Polzien et al., J. Biol. Chem 2009, 284:28004).

**Bacterial Tumor Therapy**
(U. Rapp, B. Bergmann)

The state of knowledge in tumor immunology indicates that previous approaches can barely stimulate the innate immunity. Furthermore, they cannot bypass anti-immunological mechanisms located within the tumor. Apparently, both aspects are important for the efficacy of a tumor vaccine.
The research group deals with the potential of attenuated intracellular bacteria as carrier for specific tumour antigens. The immune response against the tumor is enhanced by bacterial components thereby breaking the immune tolerance of the tumor. In a transgenic lung tumor model in mice vaccination with recombinant attenuated Salmonella has been proven successfully to act therapeutically. In addition, the fusion of a part of a bacterial toxin to the tumor antigen could further improve the efficacy of the orally applied live Salmonella based vaccine. A prostate cancer vaccine based on the latter ap-

*Fig. 1: The MSZ building.*

proach showed significant therapeutic effects in the mouse model (Fensterle et al., Cancer Gene Ther. 2008, 15:85). In parallel, the platform technology could further be improved by increasing the level of tumor antigen secretion (Hotz et al., Int. J. Med. Microbiol. 2009, 299:109). In cooperation with Æterna Zentaris a Salmonella-based vaccine against prostate carcinoma is now in preparation for clinical study.

**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 unraveled. The stem cell biology group focuses on embryonic, hematopoietic and mesenchymal stem cells and asks how global chromatin states guide stem cell behavior (Dinger et al., Stem Cells 2008, 26:119; Obier & Müller, CTO 2009, DOI: *10.1159/000240247*). 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 of the* BMBF-consortium: CB-HERMES (Cord Blood-Hematopoietic Stem Cells: Reliable Methods for ex-vivo ExpanSion) and he is member of the bioethics committee of the Bavarian state government.

**Molecular Genetics**
(T. Raabe)

In our group we take advantage of the genetic model organism Drosophila in combination with molecular and cell biological approaches to elucidate mechanisms that control generation and differentiation of neuronal cells. Despite great anatomical differences, vertebrates and invertebrates share a number of highly conserved signalling pathways that control developmental processes. Thus studies in model organisms can contribute to a better understanding of human diseases of the central nervous system. We are investigating a number of mutations, which cause an altered proliferation pattern of neural progenitor cells (Hovhanyan & Raabe, J. Neurogen. 2009, 23:42). A further focus of our research lies on proteins of the p21-activated kinase family and their involvement in morphogenetic processes during eye development (Menzel et al., Biochem. J. 2008, 416:231). In collaboration with clinical research groups we are analysing the function of the kinase RSK in synaptic plasticity. Mutations of the human RSK homologue are associated with mental retardation.

## Teaching

With the renovation and equipment of our practical room, which was also paid in part from tuition fees, a significant improvement for hands-on training for medical, biomedical and biological students was achieved.

SELECTED PUBLICATIONS


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*Dogan T, Harms GS, Hekman M, Karreman C, Oberoi TK, Alnemri ES, Rapp UR, Rajalingam K. X-linked and cellular IAPs modulate the stability of C-RAF kinase and cell motility. Nat Cell Biol. 2008 Dec;10(12):1447-55.*

*Fensterle J, Bergmann B, Yone CL, Hotz C, Meyer SR, Spreng S, Goebel W, Rapp UR, Gentschev I. Cancer immunotherapy based on recombinant Salmonella enterica serovar Typhimurium aroA strains secreting prostate-specific antigen and cholera toxin subunit B. Cancer Gene Ther. 2008 Feb;15(2):85-93.*

*Hovhanyan A, Raabe T. Structural brain mutants: mushroom body defect (mud): a case study. J Neurogenet. 2009;23(1-2):42-7.*

*Dinger TC, Eckardt S, Choi SW, Camarero G, Kurosaka S, Hornich V, McLaughlin KJ, Müller AM. Androgenetic embryonic stem cells form neural progenitor cells in vivo and in vitro. Stem Cells. 2008 Jun;26(6):1474-83.*

# 2.20 Institute of Human Genetics

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**Professor Dr. med. Holger Höhn**
**(Head until 31. 3. 2008)**

**Professor Dr. rer. nat. Clemens R. Müller-Reible**
**Tel.: 0931/31-84063**

## 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. Haaf) 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 Institute belongs to the University of Würzburg School of Medicine.

## Major Research Interests

**Epigenetics**
(T. Haaf)

Epigenetic information is not encoded by the DNA sequence itself but by reversible modifications of DNA (methylation of CpG dinucleotides) and/or histones. In mammals, the paternal and maternal genomes undergo parent-specific methylation reprogramming in the germ line and early embryogenesis. Stochastic and/or environmentally induced errors (epimutations) in this highly coordinated process may contribute to human disease. We analyze the effects of assisted reproductive technologies on epigenetic reprogramming in murine and bovine germ cells/embryos as well as in human miscarriages and newborns.
In another project we search for epigenetic differences in the regulation of gene expression in human and non-human primate brains. DNA sequence variations alone cannot account for the enormous differences between human and primate brain structure/function and their cognitive abilities. Epigenetic factors may form a main source of phenotypic variation between individuals and between species.

**Molecular human genetics**
(C. R. Muller-Reible)

Using a positional cloning approach and collaborating with Johannes Oldenburg (Institute of Experimental Hematology, Bonn), 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. A knock-out of *VKORC1* in mice causes lethal spontaneous bleedings which can be prevented by oral substitution of vitamin K.
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)

Genes that ensure genomic stability of somatic cells and thus safeguard against neoplasia and premature ageing are of key interest to this group. These so-called caretaker genes are involved in the recognition and reversal of DNA damage. They include, among others, *ATM, NBN, RAD50, LIG4, NEHJ1, WRN, MCPH1* and the Fanconi anemia (FA) family of genes. Most recently, the group participated in the identification of three novel FA genes (*FANCJ, FANCN* and *FANCI*). As a partner and interactor of one of the high-penetrance breast and ovarian cancer genes, *BRCA2*, biallelic mutations in *FANCN* play a significant role in the emergence of certain types of early childhood tumors, apart from the predisposition of monoallelic mutations for breast or ovarian cancer. Collaborating with groups from Germany and abroad, the Schindler laboratory has made major contributions to cell genetic, epidemiological and functional aspects of FA and other caretaker gene syndromes including ataxia telangiectasia, the Nijmegen breakage syndrome and related disorders. The group investigates protein complexes (MRN complex, FA core complex, and histone-fold complex) and pathways (FA/BRC pathway for genomic maintenance, non-homologous end joining and homologous recombination repair) in which caretaker genes exert their functions. Impairments of these genes result in cell cycle arrest, chromosome breakage, increased cell death rates, cancer predisposition, and features of premature aging. Current efforts are directed at identifying new members of the genomic maintenance gene networks, elucidating their function, and studying their phenotypic effects in zebrafish models.

**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 (Institute 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 methods (including FISH, SKY and CGH) to a variety of other groups within the biocenter and the medical school. Michael Schmid serves as editor or co-editor of a number of genetics journals and book series (*Cytogenetic and Genome Research, Sexual Development, Molecular Syndromology, Genome Dynamics, and Monographs in Human Genetics*).

## Teaching

The medical school curriculum includes a lecture course entitled "Clinical Human Genetics" which is taught in the 6th semester, together with a 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 Institute 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 the major subjects. Graduate students can obtain their M.S. or Ph.D. degrees within one of the research groups of the Department.

## SELECTED PUBLICATIONS


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# 2.20.1 Division of Medical Genetics

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## Mission and structure

As a subspecialty and application of human genetics, medical genetics involves the transfer of scientific insights from basic human genetics research into the clinic. In addition of genetic diagnostics and genetic counselling, hallmark features of medical genetics are aspects of preventive and predictive medicine. Medical genetics deals with a large spectrum of inherited disorders, with focus on affected individuals, entire families, and the population at large. Interaction with patients and their families is established during the genetic counseling sessions. This includes the exploration of family history, the physical exam of affected individuals, the collection of medical information concerning the individual and family members, knowledge of syndromology and congenital disorders, expertise in formal genetics and psychological aspects of disease in order to arrive at a correct genetic diagnosis and provide adequate counselling. In addition, medical genetics assures access to genetic testing for an ever increasing number of inherited disorders and disease susceptibilities. The genetic counsellor is responsible for the correct communication and interpretation of genetic test results. Overall guiding principles are patient autonomy and ethical concerns. Diagnostic and predictive genetic testing are embedded in the counseling process. Comprehensive genetic services are provided by the Würzburg Center of Medical Genetics. The center includes the Department of Human Genetics (Chair: Prof. Dr. med. T. Haaf), the Division of Medical Genetics (Head: Prof. Dr. med. T. Grimm), and a private practice located and operated within the Department of Human and Medical Genetics (PD. Dr. med. E. Kunstmann). As a general practicioner of human genetics, Dr. Kunstmann is fully accredited with the public insurance system.

The Division of Medical Genetics includes the following sections:

**Center for muscular disorders of the German Society of Muscular Diseases**
(Speakers: Prof. Dr. K. Reiners, Neurology, and Prof. Dr. T. Grimm, Medical Genetics; Coordinator: Dipl. Soz. Päd. Angelika Eiler)
The Center for muscular disorders provides diagnostic, counseling and social services for patients and families affected by or at risk of muscle disease. It is operated in close cooperations with the Department of Neurology of the Würzburg University Hospital (cf. contribution 3.21).

**Center for Familial Breast and Ovary Carcinoma (FBOC)**
(Speakers: Prof. Dr. T. Grimm, Medical Genetics, and Prof. Dr. J. Dietl, Department of Obstetrics and Gynecology, University Hospital)
The Center is a cooperative venture between the Department of Human and Medical Genetics and the Department of Obstetrics and Gynecology and the Department of Radiology of the University Hospital. It takes care of patients and families affected by or at risk of familial cancer of the breast and ovary. Services provides by the center include genetic counselling, genetic testing, and provision of medical as well as preventive care (e.g. mammography screenings) (cf. contribution.5.2.6). The Würzburg FBOC center serves the entire region of northern Bavaria and is supported in part by the German Cancer Aid.

## Major Research Interests

In terms of research activities, the Division of Medical Genetics focusses on three main topics: (1) phenotypic, statistical and population genetic aspects of inherited neuromuscular diseases, (2) epidemiology, patterns of inheritance and molecular genetics of dyslexia, and (3) fundamental aspects of formal and statistical genetics as they relate to monogenic and polygenic diseases.

**Statistical and formal genetics of inherited neuromuscular disorders**
(T. Grimm)

Risk calculations in medical genetics require precision of genetic models underlying the inheritance patterns of the respective disorders. For example, mutation rates for X-linked disorders (such as muscular dystrophies Duchenne / Becker) were shown to vary as a function of gender and mutation type. Another research focus is on risk calculations within the context of counseling implications of somatic and germ cell mosaicism.
Another example is the elaboration of a specialized genetic model for spinal muscular atrophy (SMA) which allows for reasonably precise risk calculations despite unclear or problematic molecular genetic testing results.

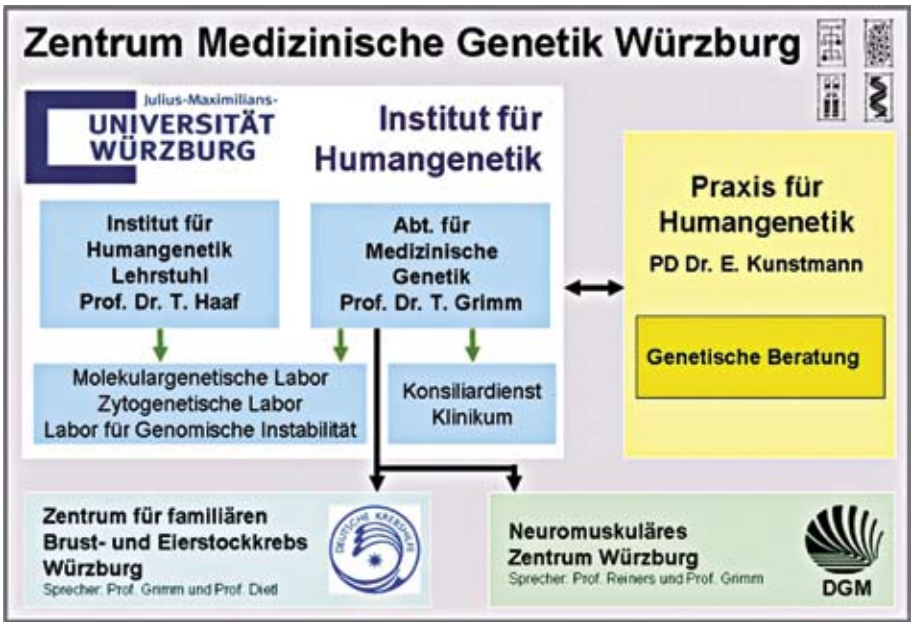


*Fig. 1: Organisational structure of the Würzburg Center of Medical Genetics.*

**Genetics of dyslexia**
(T. Grimm)

Dyslexia affects an estimated 5% of german primary and secondary school students. Extensive family studies provide evidence for familial clustering, including rare pedigrees suggestive of monogenic inheritance. Whole genome mapping (collaboration with the Max Planck Institute of Molecular Genetics, Berlin) in a family with a clear autosomal dominant inheritance pattern of the dyslexia trait revealed a novel dyslexia locus on human chromosome 4. Using a large series of dyslexia families in whom linkage to chromosome 4 has not been excluded we currently attempt to replicate these findings. If successful, candidate gene approaches will be used to identify the putative novel dyslexia gene.

**Disorders of premature closure of cranial sutures (craniosynostoses)**
(W. Kress)

Around 20 % of patients with premature closure of cranial sutures belong to the category of complex autosomal dominant craniosynostoses which include additional malformations of the distal extremities. Underlying genetic alterations involve mutations in a variety of fibroblast growth factor receptors and transcription factors. Major efforts are directed at establishing genotype-phenotype correlations, and at defining nosologic subgroups by way of molecular analysis.

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

Rapid developments in the area of prenatal and predictive genetic testing, including the medical applications of genetic technology (e.g. gene therapy; therapeutic cloning, regenerative medicine, etc.) mandate ethical guidlines. What shall we expect from, and how shall we interpret the results of the 1.000 Dollar genome which is on the horizon? What is the role and what are the implications of human genetics within the emerging field of personalized medicine? These and other questions are discussed and dealt with on a national and european level in order to arrive at clinically useful recommendations, guidelines and critical evaluations.

## Teaching

The Division of Medical Genetics provides lectures, hands-on courses and discussion rounds for medical students, students of biomedicine, and students of biology. In addition, the Division provides clerkships and internships during the clinical part of the medical curriculum. Students acquire theoretical and practical knowledge in establishing a genetic diagnosis, including aspects of dysmorphology, syndromology, pre- and postnatal genetic testing using cytogenetic, cell genetic and molecular methods, and they acquire practical knowledge in genetic counselling.

## SELECTED PUBLICATIONS


*Rudnik-Schöneborn S, Berg C, Zerres K, Betzler C, Grimm T, Eggermann T, Eggermann K, Wirth R, Wirth B, Heller R (2009). Genotype-phenotype studies in infantile spinal muscular atrophy (SMA) type I in Germany: implications for clinical trials and genetic counselling. Clin Genet. 76:168-178.*

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# 3 University Hospital
# 3.1 Introduction

The University Hospital Würzburg comprises 19 Clinics (for inpatients), 22 Policlinics (for outpatients), 4 Clinical Institutes as well as 2 independent Chairs. Furthermore there are 6 affiliated Training Colleges of Health Care, which together offer more than 500 apprenticeship training positions.

The University Hospital employs a total of 4.237 full-time employees, among them 740 physicians, 1.210 nurses, 359 employees working as ancillary staff and 1.023 medical-technical employees.

Interdisciplinary – and partially outreach collaboration is the focus of 16 **Clinical Centers**: Comprehensive Cancer Center, Center for Stem Cell Therapy, Breast Center, Colon Center, Thorax Center, Cardiovascular Center, Comprehensive Heart Failure Center, Infarct Network, Trauma Center, Musculo-Scelettal Center, Center for Rheumatism, Transplant Center, Comprehensive Hearing Center, Center for Cleft, Lip and Palate, Perinatal Center, Interdisciplinary Center of Palliative Care. The Center for Interdisciplinary Clinical Research (IZKF) builds the bridge between clinical theoretical research and clinical research.

According to the official plan 2008, the University Hospital provides 1,461 hospital beds; the utilization rate of the 1,414 beds having been set up was 97.4% with an average resting time of 8.2 days. In the year 2008, 50,248 patients received inpatient treatment and a total amount of 411,046 care days were performed; additionally a total of 183,535 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% of all patients come from the adjacent Baden-Wuerttemberg, the remaining 7% from the rest of Germany or from abroad.

The modern **Health Care Center ZOM | ZIM**, build up from the Centers of Operative Medicine and Internal Medicine, combines the following institutions under one roof: Department of Anesthesiology, General-, Visceral-, Vascular- and Pediatric Surgery (Surgical Clinic I), Department of Traumatology, Hand-, Plastical- and Reconstructive Surgery (Surgical Clinic II), Department of Thorax-, Heart- and Thoracic Vascular Surgery as well as the Department of Urology and Paediatric Urology in building A1/A2 and on the other hand Department of Internal Medicine I, Department of Internal Medicine II, Department of Nuclear Medicine, Institute of Radiology, Institute of Clinical Transfusion Medicine and Hematotherapy as well as Institute for Clinical Biochemistry and Pathobiochemistry with Central Laboratory in building A3/A4.

The other locations of the University Hospital are closely interlocked: "**Kopfklinik**" (Departments of Neurology, Neurosurgery, Neuroradiology, Ophthalmology, Ear-, Nose- and Throat-Surgery and Radiation Oncology in building B1/B2), "**Nervenkliniken**" (Departments of Psychiatry, Psychosomatic and Psychotherapy for Adults as well as Children and Adolescents in area F), the **Center of Dentistry, Oral- and Maxillofacial Surgery** in area G and the **Departments of Pediatrics, Obstetrics and Gynecology** as well as **Dermatology and Venerology** in area C and D.

Among the constructional activities in the future are the reconstruction of the "Kopfklinik", and the construction of a „Mother-Child-Center". With the existing infrastructure, which has to be improved continuously, the University Hospital will be prepared to fulfill the challenges of a changing healthcare market and simultaneously will be able to ensure a prosperous working environment for research and teaching.

Professor Dr. med. Chr. Reiners
Managing Medical Director

*Fig. 1: Entrance hall of the Center of Internal Medicine (ZIM).*

# 3.2 Department of Anaesthesia and Critical Care

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**Professor Dr. med. Peter Kranke**
**Tel.: 0931/201-30116**

## Mission and Structure

The Department of Anaesthesiology annually performs anaesthesia for approximately 26.000 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 9.000 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.

The section "Scientific anaesthesiology" (chair: Mrs. Prof. Dr. rer. nat. C. Förster) allows the handling of scientific and clinical approaches in close collaboration with scientists and modern fundamental research techniques.

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**
(H. Rittner, A. Brack, G. Sprotte)

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

**Organ-Protection**
(M. Lange)

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 post-conditioning and to characterize their complex intracellular interaction in the heart and the brain.

**Acute lung injury**
(R. Muellenbach)

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.

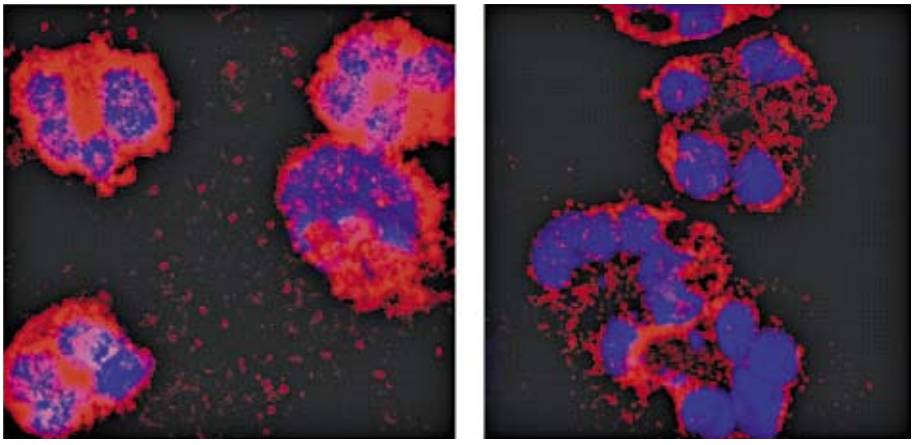

*Abb. 1: Translocation of opiod receptors to the cell membrane in neutrophils before (left) and after (right) stimulation.*

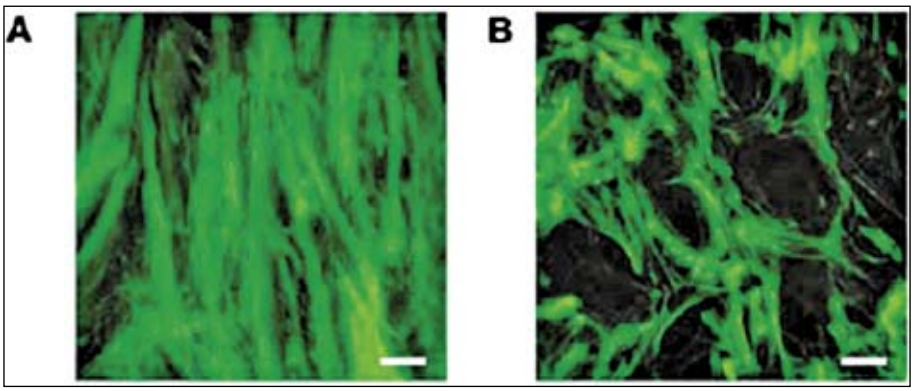


*Abb. 2: Morphological changes of the F-actin cytosceleton in microvascular brain endothelial cells without (A) and with (B) glucocorticoid treatment.*

**Blood-Brain-Barrier**
(C. Förster)

Brain capillaries generate a tight barrier between the blood and the neurons in the central nervous system (CNS). The so called blood-brain-barrier (BBB) consists of endothelial cells lining the brain capillaries. The endothelial cells perform inter-cellular tight-junctions composed of members of the claudin family. Several diseases of the CNS derange the BBB and result in diminished expression of the claudin proteins. The scientific aim is the identification of molecular targets of steroids in the BBB and the underlying signal transduction pathways. Additional the molecular functions of different tight junction proteins of the BBB during the CNS development are investigated.

**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. 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.

## SELECTED PUBLICATIONS

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# 3.3 Department of General, Visceral, Vascular and Pediatric Surgery (Surgery I)


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## Mission and Structure

The Department of General, Visceral, Vascular and Pediatric Surgery covers the whole spectrum of services in all these surgical fields. The department has 132 beds, including intermediate and intensive care units. Six thousand surgical procedures are performed every year. Specialized consultations hours are available to patients:

- interdisciplinary tumour surgery
- oesophagus and gastric diseases
- liver, gallbladder, and pancreas
- endocrine diseases
- gastrointestinal diagnosis
- endoscopy, proctology and endosonography
- vascular and pediatric surgery

## Clinical Services

Oncological surgery is one of the major fields in the department. Centre of Intestinal Medicine, a certified, interdisciplinary centre, was established two years ago. Patients are treated according to the therapy guidelines of the tumour board. Special expertise exists in the care of gastric, pancreas and rectal cancer, primary and secondary liver cancer, and thyroid cancer.

The endocrinology unit treats the dysfunction of parathyroid and adrenal glands with minimally invasive thyroid surgery and monitoring of the recurrent laryngeal nerve.

The coloproctology unit offers therapies for hemorrhoids, incontinence, constipation, and complicated anal fistulas. Special expertise also exists for the treatment 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 births, treatment of birth defects, basic pediatric urology, and pediatric traumatology.

The vascular surgery unit treats abdominal aortic aneurysms with aorta-iliac bifurcation prostheses. Aorta and iliac vascular diseases are treated with endovascular procedures. Our surgeons are well experienced in femur crural artery bypass surgery and carotid artery surgery.

## Major Research Interests

New points of focus include some very interesting areas of surgical research. Projects examine clinically relevant questions in close cooperation with the fundamental research department. In addition to a modern repertoire of analyses in cell and molecular biology, protein chemistry and immunology, the projects are equipped with relevant animal models. For example, the anti-tumour effect of antibodies on human tumours is being investigated in vivo in pre-clinical xenograft models. Last year the Society of Bavarian Surgeons (Vereinigung der Bayerischen Chirurgen) honoured the achievements in this field with the Otto-Götze Prize.

Some of the project heads are also members of the Excellence Academy, a cooperation of the German Society of Surgery (Deutsche Gesellschaft für Chirurgie) and the German Research Foundation (DFG) that promotes young scientists. The projects network within the university and also with many national and international groups. One example is the joint project with the Institute for Molecular Infection Biology. This project, funded by the Federal Ministry of Education and Research (BMBF), investigates the special complex of problems of hospital infections. Another example is a cooperation on oncology with the Biocenter Würzburg, Chair of Physiological Chemistry II (Prof. Dr. M. Eilers). Projects are also integrated in research centres of the university, such as the Interdisciplinary Centre for Clinical Research (IZKF) and the graduate schools (Graduiertenkollegs). The success of these projects can be seen in the third party funding, patents, prizes, awards, and scholarships attained. Further information on the following projects is available on the web site of the department:

**Clinical Studies**
(U. Dietz, Th. Meyer, J. Pelz, A. Thalheimer)

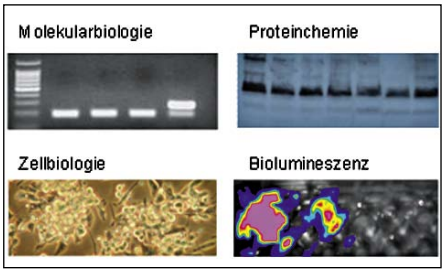


*Fig.1: Many different in vitro and in vivo tests are part of a modern repertoire of analyses.*

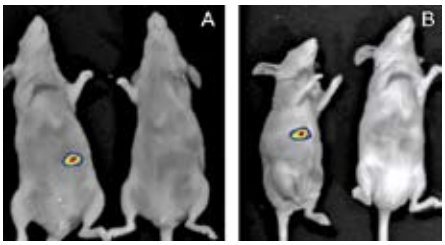


*Fig. 2: Minimally invasive evidence of human tumours in bowel (A) and liver (B) in xenograft models using bioluminescence imaging.*

Studies in oncology (peritoneal carcinosis, rectal cancer), pediatric surgery (compression therapy for burns and scalds of children), and tissue engineering (two-component nets) are currently in progress.

**Infection / Inflammation**
(U. Lorenz, N. Schlegel)

Surgical implant materials are being tested for their resistance to staphylococcus aureus infections. The project "Pathophysiology of the intestinal barrier in the case of acute inflammation" examines the intercellular signalling pathway following the breakdown of the intestinal barrier. This might lead to new pharmacological approaches to stabilize the intestinal barrier.

**Oncology**
(C. Otto, J. Pelz, U. Steger, A. Thalheimer, B. v. Rahden, A. M. Waaga-Gasser)

The development of tumours in the gastrointestinal tract is being examined. Pre-clinical experimental models should lead to new therapy concepts for cancer of the colon, colorectal liver metastases, and peritoneal carcinosis. We are working in cooperation with Prof. Dr. G. Schönfelder, Institute of Pharmacology and Toxicology. Further points of focus are the interaction between cancer cells and immune cells on a cellular and molecular level, and the metabolism of cancer cells.

**Metabolic Disorders**
(M. Bueter, C. Jurowich)

Type 2 diabetes mellitus is a common concomitant disease in patients with adiposity. Conservative therapies to treat morbid adiposity are seldom successful. In contrast, different methods of bariatric surgery lead to a marked improvement, and sometimes total recovery from type 2 diabetes. We are presently working on joint projects on this topic with the Chair of Anatomy and Cell Biology I (Prof. Dr. H. Koepsell) and the Department of Investigative Medicine, Hammersmith Hospital, Imperial College London, UK (Prof. CW le Roux).

**Tissue Engineering**
(U. Dietz, Th. Meyer)

Biocompatible materials are being tested to determine if they could replace the artificial materials presently used for treating large congenital defects of the abdominal wall. The project "Adhesion of tumour cells on surgical sutures" examines modifications of sutures to prevent the adhesion of tumour cells.

**Transplantation-Immunology**
(I. Klein, C. Otto, U. Steger, K. Ulrichs)

Different projects examine regulatory immune cells in vitro and in vivo in several established animal models and how they inhibit immune responses. They play a very important role in transplantation medicine because they are involved in the formation of graft-specific tolerance. They prevent the patient's immune cells from destroying the essential but foreign organ or graft. Several projects deal with liver immunology because inhibitory responses often occur in the liver.

## Teaching

All aspects of modern surgery are covered in lectures and seminars in the advanced education programme. The medical faculty awarded the department the Albert-Kölliker teaching prize for its outstanding teaching commitment. Bedside teaching has been optimized to ensure a qualified practical training. An Interdisciplinary Training and Simulation Centre (INTUS) was established in the SkillsLab to give students more opportunities to improve their operating skills on training simulators under realistic conditions. Training courses for thyroid 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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## General Information

In the department of Trauma, Hand, Plastic and Reconstructive surgery 18 medical doctors are occupied. For the treatment of patients, 52 beds are available on our wards. Additional beds are available on the Intensive Care Unit and the Intermediate Care unit

There is a close cooperation inbetween the department of genereal surgery, the department of anaesthesiology and the institute of radiology in regard to the interdisciplinary treatment of patients.

Polytraumatized patients are first examined and treated in the modern shock room with spiral CT. Other functional facilities as the central sterilisation, the operating theatres, the intensive care units and the physiotherapy facilities are of highest standard. Moreover, angiography, CT and MRI are available.

### Care

The different focuses of the department of Trauma, Hand, Plastic and Reconstructive surgery are represented in different consultation hours. These are nect to the general consultation hour, one for spinal fractures, pelvic fractures and problem fractures, Berufsgenossenschaft, for hand, for arthroscopy of the knee and shoulder as well as for joint replacement and for injuries of the foot. Besides, there are consultation hours for asthetic and plastic surgery.

The main focuses of our department are reflected in the statistics of more than 3000 operations per annum. These include about 180 interventions of the spine. About 60 interventions in the pelvic ring, 150 osteosynthesis of long long bones and about 300 complicated joint injuries. We perform about 500 surgeries on the hand and 300 in plastic surgery. Within the scope of trauma network we treat about 100 polytraumatized patients interdisciplinary.

## Major Research Interests

Our current clinical studies include a prospective randomerised study for the treatment of fractures of the clavicle, a retrospective study of complications of locking plates in the treatment of proximal humerus fractures. Additionally, we analyze the clinical outcome of subtalar joint dislocations as well as the outcome after operative treatment of distal radius fractures. In addition, there is a multi center study II of the spine group of the German society of traumatolgy. Moreover, we additionally examine the outcome of thoracal and lumbar spine fractures. Another prospective study deals with different surgical treatments of incomplete burst fractures of the thoracal and lumbar spine and the influence of hydroxylapatit for the biological fusion in the treatment of ventral monosegmental spondylodesis of unstable fractures of the thoraco-lumbar. Besides, the use of DBM versus autologous tricortical bone chips is examined.

The focus of the experimental research was also extended. Two of our research groups are supported by the IZKF now. One of these groups examines the influence of VEGF165 on the experimentally induced musculoskeletal trauma. Because of very promising results they now also examine the influence of another proangiogenic growth factor (CYR61) in coorperation with Prof. Schütze of the Department of Orthopaedics. Besides, the influence of CYR61 on skeletal muscle cells is examined. After approval by the local ethics commitee muscle cells of patient´s are generated and cultured. Besides, the biocompatibility of silicone coated implants are examined. Since 2007 we have a set up for biomechanical testings. Projects enclose biomechanical testings of implants in hand surgery and e.g. for ankle fractures with special respect to osteoporotic bones. In addition, different locking plates for fractures of the metacarpal bones are tested.

*Fig. 1: Biomechanical testing of a newly developed angle-stable external ankle plate.*

*Fig. 2: Experimental fracture model to test angle-stable mini implants at the metacarpals.*

## Teaching

Education is divided into eduation of students as well as into teaching for our doctors on daily rounds and discussions. Since this semester the number of the weekly main lectures for students was doubled. At the end of the semester we have got a repititorium in which students are able to repeat the content of the semester with the help of patient related cases.
In addition, there are two grand rounds every week. Twice per day indications are discussed. For students we offer a great variety of hospitations. Besides, we continously have foreign students visiting. The extensive teaching offer for the students also integrates clinical investigation courses, training periods with ‚bedside-teaching', weekly block training periods as well as different consultation hours.
Every three months we organise an interdisciplinary polytrauma conference which is well accepted. Inhere, everybody can present their own subject related cases to be discussed.

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# 3.5 Institute of 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

## Clinica 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 immuno-haematological 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 Interest

**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.

## Teaching

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

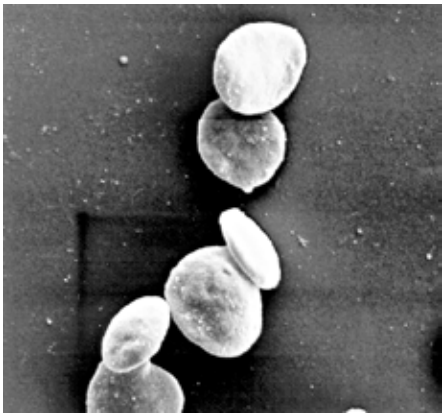

*Fig. 1: Platelets from a stored platelet concentrate.*

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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 its own 14 bed intensive care/intermediate care unit. At present 20 physicians and 1 psychologist are working in this department.

Approximately 2000 procedures are performed annually covering the entire field of adult heart and thoracic surgery. 950 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 provide 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, reconstructive valve surgery including DAVID-, YACOUB-procedures. In 2009 transapical/transfermoral minimally-invasive aortic valve replacements were introduced into routine clinical practice. This is a joint project with the Department of Cardiology. In selected patients we also offer the ROSS procedure.

A mobile heart-lung-machine (Lifebridge) is available for improved 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 the 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 procedures for the 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 responsible 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**

Over the last two years Drs. Sommer and Prof. Sinha have established a rat model for the induction of pulmonary ischemia-reperfusion-injury (IR). Susceptability to infecetion and function of pulmonary mitochondria during IR are determined. The influence of mitochondrial function on IR is unknown. Utilizing single-lung-transplantation the function of AMs, mitochondria and surfactant during IR is examined. Isolated AMs will be examined regarding their function ( phagocytosis, cytokine-secretion, NO-synthesis). Resveratrol will be used to modify these functions. The results are expected to improve the outcome after lung-transplantation. The project is partly funded by the interdisciplinary center for clinical research Würzburg (IZKF).
In addition the impact of volatile anesthetics on myocardial infarction in a mouse model is examined in cooperation with the department of anaesthesiology (Dres. Lange and Stumpner). Another cooperation with PD Dr. Otto from experimental tumorimmunology (ETI) will examine mitochondrial function of isolated tumor cells and the dependency of different tumors from glykolysis and oxidative phosphorylation.

**Quality of life of surgeons**

This project is a cooperation with the German Society for Surgery (DGCh; Prof. Bauer and PD Dr. Bohrer)

**Neuropsychological studies and cardiac surgery**

Studies on neuropsychological abilities with the computer-based test “TAP” have been cmpleted and the results presented. In the

near future, the TAP will be compared with the standard "paper and pencil" tests. We expect the TAP-data to be more reliable and robust. It would enable us to routinely examine cardiac surgical patients in a neuropsychological manner. Similar studies with patients undergoing transapical aortic valve replacements are under way (Dr. Krannich)

**Prevention and therapy of deep sternal wound infections (DSWI)**

At present we are conducting a double-blind, randomized study with antibiotics-releasing felts (Gentacoll) regarding the incidence of DSWI. We are leading the inauguration of a working group ("wound management") of the German society of Thoracic and Cardiovascular Surgery (DGTHG). We plan to establish a nationwide registry on DSWI and hope to deduct scientific guidelines for the prevention and therapy of DSWI (Dr. Schimmer)

**Thoracic surgery**

Predictive markers of non-small cell lung cancers and stem cells (Dr. M. Lazariotou).
Establishment of a nationwide registry "malignant mesothelioma" (PD Dr. Bohrer),
History of thoracic surgery at the University Hospital Würzburg since 1945 (PD Dr. Bohrer)
Outocme of patients with empyema (Dr. Hamouda)

Surgery for pulmonary nodules an established therapeutic approach. However, the psychological benefit of these procedures in patients with underlying benign or malignant disease has not been investigated at all yet. Therefore, the quality of life after thoracic surgery needs to be examined (Dr. Krannich, Dr. Bohrer, Dr. Neukam).

## 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 two weeks in the department as part of a mandatory surgical rotation. Final year medical students spend a 16 week rotation in our department.

A new weekly cardiology/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 is 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 2010 we are planning to host two clinical fellows from Serbia and Tadjikistan, 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 surgery of renal cell cancer; polychemotherapy); paediatric urology (correction of complex congenital malformations), reconstructive urology (all types of urinary diversion and conversion, reconstruction of the whole urinary tract, ureteral replacement, open urethral reconstruction, complex fistula repair) including implantation of artificial urinary sphincters and penile prosthesis, urogynaecology and renal transplantationen (cadaver and living related transplantation).

## Major Research Interests

**Translational Prosatate Carcinoma Research**
**Treatment of patients with high risk prostate cancer**
(M. Spahn, B. Kneitz)

The percentage of patients with high risk prostate cancer (PCa) (>T2c or PSA >20 ng/ml or Gleason score >8) is still significant (2003: 22%). In this group of patients the risk of biochemical progression within a 5-year period is approximately 40%.
We evaluate the outcome of surgical techniques in high risk PCa in an european multicenter study.

**Identification of tumor supressors or onco- microRNAs in prostate cancer**
(B. Kneitz, M. Possner, M. Spahn)

The aim of our studies is to analyse the role of miRNAs for the development and progression of prostate cancer. Tumor tissue from a European multicenter database is used for the analysis. Using microarrays and qRT-PCR miRNA analysis we detected specific miRNA signatures for prostate 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.

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

To understand the role of aberrant expression of mitotic spindle checkpoint (MSC) genes for the development of PCa we analysed the expression of two MSC genes. 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 PCAs. Our results suggest that the expression of MSC genes may be helpful biomarkers and might be involved

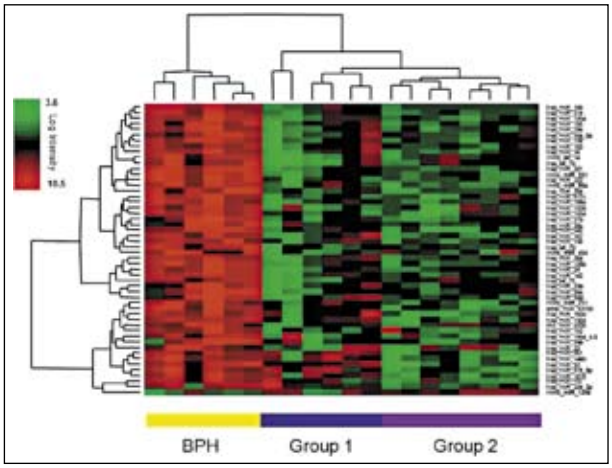


*Fig. 1: MiRNA expression signature of Prostate cancer.*

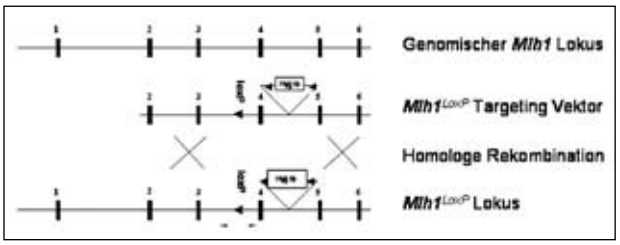


*Fig. 2: Generation of a transgenic mouse model to inactivate mismatch repair activity in the prostate using the Cre-loxP system.*

in malignant progression of PCAs and failure of treatment using cytotoxic agents.

**Impact of mismatch repair defects on pathogenesis and prognosis of prostate cancer**
(B. Kneitz, M. Spahn)

To answer the question what impact mismatch repair (MMR) defects play for PCa development we generated novel mouse models based on a prostate specific inactivation of the MMR system using the Cre-LoxP. This model will provide the opportunity to study the molecular and genetic mechanisms of the early development, progression and eventually metastasis of PCa and will allow to functionally explore different therapies in vivo.

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

Intravesical immunotherapy with Mycobacterium bovis Bacillus Calmette-Guerin (BCG) is the current standard of care against superficial high-grade transitional cell carcinoma of the urinary bladder (carcinoma in situ, pT1G3). However, individual patient outcome is hardly predictable due to the lack of serum markers. As a result, progression to muscle-invasive bladder cancer and critical delay of treatments (such as neoadjuvant combination chemotherapy and/or radical cystectomy) often occur.

We identified a biomarker capable of measuring immune response induced by BCG and therefore predicting the outcome of this therapy: Antibody production against M. bovis BCG HSP-65 can serve as a serological marker for the predictive outcome of BCG-immunotherapy. Subsequent studies will determine the value of this candidate marker to modify BCG-mediated treatment for individual bladder cancer patients.

**Identification of tumor-suppressor- und onco-microRNAs in bladder- and renal cell carcinoma.**
(B. Kneitz, A. Kocot, D. Vergho)

The aim of our studies is to analyse the role of miRNAs for the development and progression of bladder and renal cell cancer. Using microarrays and qRT-PCR miRNA analysis we detected specific miRNA signatures for both cancer entities. 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.

## 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. Hos-pitation in the operating theatre and outpatient clinic is possible throughout the en-tire academic year.

## SELECTED PUBLICATIONS

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# 3.8 Department of Orthopaedics

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## Mission and Structure

The Orthopaedic Department König-Ludwig-Haus is a top level hospital for the treatment of musculoskeletal diseases and injuries. The hospital is operated by the district of Unterfranken. Integrated are the Chair of Orthopaedics and the Outpatient Clinic for Orthopaedics of the University Hospital, as well as the Orthopaedic Center for Musculoskeletal Research. The Chairman of the Department, one full Professor of Osteology, 6 Associated Professors and 22 Residents are taking care of the patients and teaching. The hospital has 140 beds and in 4 operating theatres more than 4.100 surgical procedures are performed each year. The University Outpatient Clinic provides care for about 13.500 patients a year. The König-Ludwig-Haus also runs its own x-ray department and physiotherapy.

Specialities in the treatment of orthopaedic patients are

- Arthroplasty of the Hip, Knee, Shoulder, Elbow and Tumor Prostheses
- Shoulder and Elbow Surgery
- Sports Medicine
- Ankle and Foot Surgery
- Pediatric Orthopaedic Surgery
- Spine Surgery
- Tumor Surgery
- Orthopaedic Rheumatology
- Arthroscopy of the Knee, Shoulder, Elbow and Ankle
- Osteology (metabolic and degenerative diseases with a special focus in osteoporosis and malignant bone disease)

Orthopaedic consulting is offered for several other hospitals and centers for disabled.

The Orthopaedic Center for Musculoskeletal Research is an interactive platform between basic science, translational research and clinical implementation of innovative therapeutic strategies. The main research topics are mesenchymal stem cell biology and the development of cell-based therapeutic strategies for the regeneration of mesenchymal tissues, such as bone, cartilage, tendons and ligaments. The Center supports the representation of the chair in the field of Orthopaedic Surgery concerning research and teaching. The Head of the Center, Prof. Dr. Franz Jakob, is also the speaker of the Interdisciplinary Musculoskeletal Center Würzburg MCW, which plays an important role in the development of a new research branch at the university.

## Major Research Interests

The Orthopaedic Center for Musculoskeletal Research is located in a 600 sq. m laboratory space (S1, S2, radioactivity) with one location at Brettreichstrasse 11 and another at Röntgenring 11. 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), the German Ministry of Research BMBF (BMBF-Konsortium Osteopath, BMBF-Verbundprojekt Präeklampsie), the Ministry of Economy (EXIST Phase I), the European Union (EU-Konsortien ADIPOA und VASCUBONE), the IZKF of the University of Würzburg, the Arthrose Hilfe e. V. and the Research Fund of the State of Bavaria (Research consortium cell-based regeneration of the musculoskeletal system and age, FORZEBRA), as well as several industrial cooperation. The number of positions funded is 25 (as of 2009).

**Key Issues in Research**

- Biology of Mesenchymal Stem Cells (F. Jakob, R. Ebert, B. Mentrup, P. Benisch, B. Klotz, N. Raijmaakers, S. Müller-Deubert, L. Seefried)
- Molecular Orthopaedics and Cell Biology (N. Schütze, T. Schilling, R. Laug, Simone Hilpert, A. Noll, K. Schlegelmilch)
- Tissue Engineering, Regenerative Medicine, Translation in Cell Therapy (U. Nöth, L. Rackwitz, R. Hallinger, M. Weber, M. Rudert)
- Gene Therapy in Musculoskeletal Diseases (A. Steinert, P. Prager, N. Armbruster, C. Weber)
- Molecular and Classical Biomechanics (F. Jakob, L. Seefried, S. Müller-Deubert, A. Steinert, M. Hoberg)
- Fracture Healing in Trauma and Osteoporosis (KFO 103 in Cooperation with KFO 102 Berlin; FOR 793)

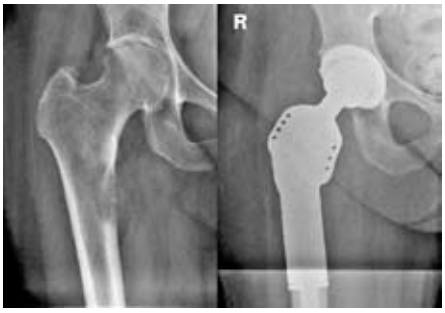


*Fig. 1: Tumor prostheses of the hip after resection of a metastasis of the proximal femur due to a bronchial carcinoma.*

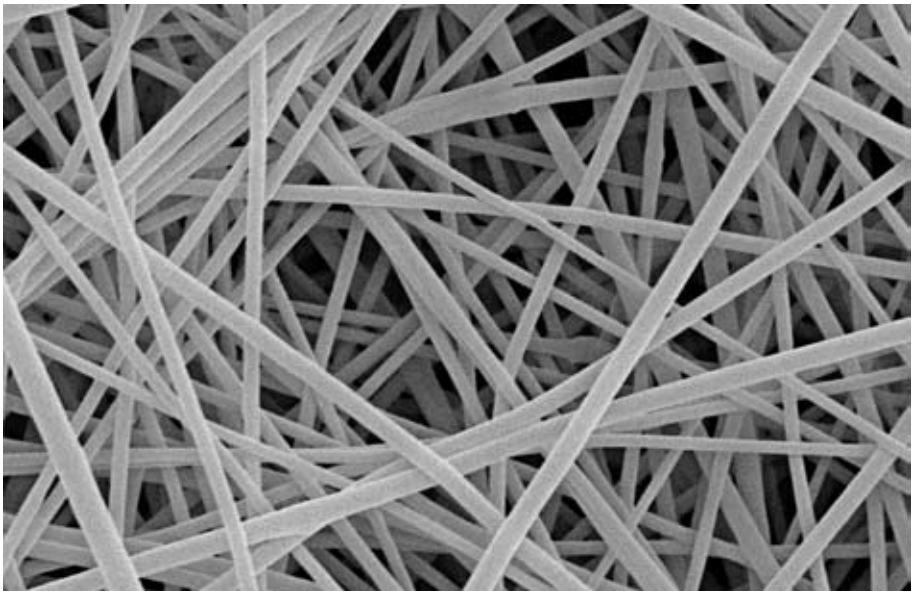

*Fig. 2: Electrospinning of collagen type I fibers for tendon and ligament replacement.*

- Particle Disease and Infektion of Prostheses (B. Baumann, N. Schütze)
- Tumor Surgery and Modern Brachytherapy (M. Rudert, P. Raab, M. Lüdemann)
- Special Techniques in Shoulder Joint Reconstruction (S. Goebel)
- Tissue Engineering of the Meniscus (M. Rudert, M. Hoberg, A. Steinert)
- Nanofiber Technology and Electrospinning (L. Rackwitz)
- Autologous Chondrocyte Transplantation ( U. Nöth, L. Rackwitz, A. Steinert, M. Rudert, T. Barthel)
- Application of mesenchymal stem cells for the therapy of Femoral Head Necrosis and Osteoarthritis (M. Rudert, L. Rackwitz, U. Nöth)
- Endoprosthesis of Hip and the Knee (U. Nöth, M. Hoberg, M. Lüdemann, M. Rudert)
- Special Orthopaedic Pediatric Surgery, Spine and Foot Surgery (P. Raab, V. Ettl)
- Clinical Studies on Osteoporosis (F. Jakob, L. Seefried, S. Goebel)
- Pain Research in Orthopaedics (S. Goebel)

## Teaching

- Course in clinical examination techniques for operative and conservative orthopaedics
- Lectures in Basics of Orthopaedics (also accompanying the practical course)
- Practical Course in Orthopaedics (bedside teaching in small groups, demonstrations in physiotherapy, plaster techniques and orthopaedic technical devices and corselets
- Clinical ward Rounds, x-ray discussions, orthopaedic 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
- TecFun Technology of Operation Materials

Fellowships

The ortopaedic department König-Ludwig-Haus hosts fellows from all over the world. Dedicated fellowshops are the SICOT (Societé Internationale de Chirurgie Orthopédique et de Traumatologie) Wuerzburg Travelling Fellowship (3 Month) and the Wuerzburg-Assiut SICOT Fellowship (6 Month). Each year also fellows from the ASG (Austrian-Suisse-German) Fellowship and the German Travelling Fellowship visit Würzburg for one week.

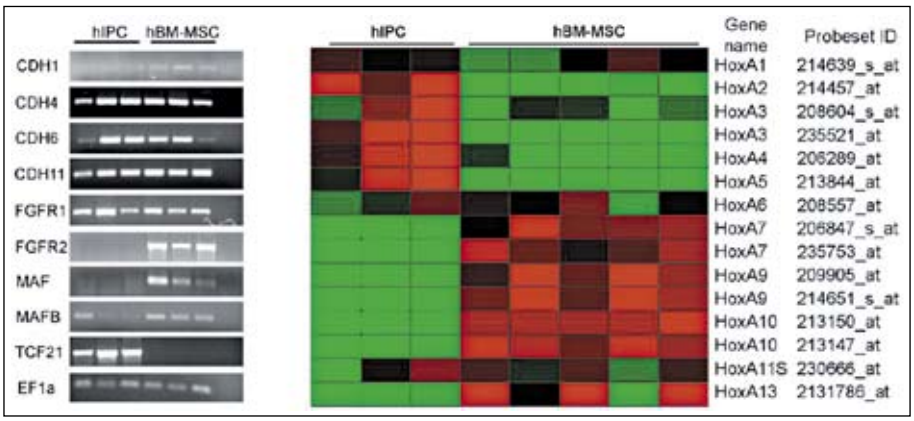


*Fig. 3: Signatur of different mesenchymal stem cells from bone marrow stroma of the femoral head (hBM-MSC) in contrast to mesenchymal Progenitors associated with pancreatic islets (hIPC). Besides the differential expression of different key receptors and transcription factors the cells show a „positionell memory" based on their HoxA-expression (from Limbert et al. 2009).*

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*Schilling T, Küffner R, Klein-Hitpass L, Zimmer R, Jakob F, Schütze N. (2008) Microarray analyses of transdifferentiated mesenchymal stem cells. J Cell Biochem. 103: 413-433.*

*Nöth U, Steinert AF, Tuan RS. (2008) Technology insight: adult mesenchymal stem cells for osteoarthritis therapy. Nat Clin Pract Rheumatol 4:371-380.*

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# 3.9 Department of Obstetrics and Gynaecology

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## Mission and Structure

The Woman's Hospital (bed capacity of 84, 33 doctors, 102 nurses, 14,5 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).

Per annum, approximately 2,200 operations, 1,500 deliveries, 5400 DRG cases, 22,000 outpatient therapies (of which 3500 were 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)

Haemochorial placentation in humans still represents an unique situation: the fetus, which can be considered as a semiallogenic transplant is not rejected, even though fetal trophoblast cells are found in close contact to maternal immune cells. Factors providing this adequate microenvironment for the establishment of peripheral tolerance are cytokines, growth factors and hormones.

**Investigation of impact and function of thrombopoietin (TPO) in human pregnancy decidua**
(S. Segerer, U. Kämmerer, J. Dietl)

A new "first applicant" programme by the IZKF Wuerzburg promotes the investigation of the role of the growth factor thrombopoietin on the fetomaternal interface. Thus, analysis of interactions between fetal and maternal cells at the feto-maternal interface should further elucidate the physiologic control of the invasive growth of the placenta by the maternal immune system.

Cooperating as a clinical research group (KFO 124, cooperation with the department of dermatology, J. Becker), we investigate placentation as a tumor model. In project 4 of KFO 124 the interaction of invasive fetal trophoblast cells with maternal uterine immune cell populations are investigated. The function of the immune cells under the influence of mediators specific for pregnancy is evaluated and the trophoblast cells are investigated with regard to their features similar to tumor cells (with focus on matrix metalloproteases).

**Research Project „Tumour immune escape"**
(J. Wischhusen, S. Häusler, A. Chandran, M. Junker, A. Seida, M. Ossadnik)

With funding from the IZKF, a junior research group could be established on the field of tumour immunology. Particular attention is paid to members of the TGF-β superfamily (M. Junker), as TGF-β promotes migration, invasion and angiogenesis and contributes to "immune escape". In a GSLS-funded collaborative project with the Max-Planck-Institute in Munich, immunoregulatory functions of TGF-β-inducible miRNAs are investigated (A. Chandran).

In close association with the junior research group, another project investigates the immunomodulatory function of the ectonucleotidases CD39 and CD73 in the tumor microenvironment (S. Häusler).

A further focus is placed on the exploration of the immunogenic properties of cancer stem cells (joint DFG-funded project BE 1394/9-1 together with Prof. Jürgen Becker from the Department of Dermatology). This lead to the discovery of a new „immune escape" mechanism which could be highly relevant for the treatment of HER2-positive breast cancer with Trastuzumab (F. Reim, J. Wischhusen).

In order to screen for better tumour markers, miRNA profiles are investigated in peripheral blood from ovarian cancer patients and age- and sex-matched healthy controls. This project i spart of a cooperation with the newly founded Heidelberg-based biotech company Febit and is sponsored by funds for the promotion of the biotech area (S.Häusler. J. Wischhusen).

**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).

*Fig. 1: Developement of the embryo from the oocyte to the blastocyst. a) intracytoplasmatic sperm injection (ICSI) of a spermatozoa in metaphase II oocyte. b) fertilized oocyte, c-f) early stages of the developement of the embryo.*

**New GnRH antagonists in the treatment of gynaecological malignancies and triple negative breast cancer**
(J. Engel, A. Hönig)

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

**The AKT-pathway as a therapeutic target in gynecological and breast cancers**
(J. Engel, A. Hönig)

The AKT-pathway is overactivatedin various and seems to hold a key position in malignant transformation by regulating a multitude of actions, such as proliferation, resistance to apoptosis and chemotherapy and cell metabolism. Thus, proteins such as AKT in PI3K, which are in different positions in that pathway are highly promising targets in cancer therapy. In endometrial cancerrs for instance AKT is frequently overactivated by loss of its suppressor PTEN. In ovarian cancers overactivation of AKT is associated with resistance to chemotherapy. It could be demonstrated, that AKT-inhbitor perifosine displays substantial anti-tumor activity in models of human ovarian and endometrial cancers and shows additive effects with platinum derivatives. These results have been the basis for project which is funde by IZKF from January 2010, aiming at investigating the AKT-pathway in ovarian cancers with special regard to immunemodulatory effects (B-131-N).

**Molecular analysis of gamete interaction and the influence of uropathogenic microbes on fertility**
(C. Rennemeier, C. Albert)

Infertility in men and women is frequently associated with genital contaminations caused by various microorganisms. The molecular basis of this correlation remains still elusive, and little attention has been paid on potential direct influences of commensal or uropathogenic microbes on human gametes. Since many microorganisms are known to release distinct communication signalling molecules in substantial amounts, we raised the question whether such molecules can directly affect human gametes. Our studies revealed that signalling molecules employed by the opportunistic human pathogens Candida albicans and Pseudomonas aeruginosa elicit multiple detrimental effects on human spermatozoa. In a beginning project we investigated the interaction of uterine dendritic cells (DCs) with human spermatozoa and the influence of seminal plasma on this interaction.

## 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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*Reim F, Dombrowski Y, Ritter C, Buttmann M, Häusler S, Ossadnik M, Krockenberger M, Beier D, Beier CP, Dietl J, Becker JC, Hönig A, Wischhusen J. Immunoselection of breast and ovarian cancer cells with trastuzumab and NK cells: Selective escape of CD44high/ CD24low/HER2low breast cancer stem cells. Cancer Res. 69(20):8058-66, 2009.*

*Rennemeier C, Frambach T, Hennicke F, Dietl J, Staib P. Microbial quorum-sensing molecules induce acrosome loss and cell death in human spermatozoa. Infect Immun 2009, 77: 4490-4497.*

*Schally AV, Varga JL, Engel JE. Antagonists of growth-hormone-releasing hormone: an emerging new therapy for cancer. Nat Clin Pract Endocrinol Metab 2008, 4: 33-43.*

*Segerer SE, Müller N, van den Brandt J, Kapp M, Dietl J, Reichardt HM, Rieger L, Kämmerer U. Impact of female sex hormones on the maturation and function of human dendritic cells. Am J Reprod Immunol. 2009 Sep;62(3):165-73.*

# 3.10 Department of Pediatrics

CONTACT DETAILS

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**Professor Dr. med. Paul-Gerhard Schlegel**
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**Professor Dr. med. Hans-Michael Straßburg**
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## Mission and Structure

The Children's Hospital of the University of Würzburg (staff: 59.45 MD`s, 163.5 nurses, 34.75 technicians / administrative staff) comprises 115 beds including a pediatric-neonatal intensive care unit (12 beds) and a neonatal intensive care unit (12 beds) in the perinatal centre (obstetrics and gynecology). The Children's Hospital is divided into the following functional sections: neonatology (Prof. Dr. C. P. Speer, Dr. E. Frieauff, PD Dr. S. Kunzmann, Dr. W. Thomas, Dr. J. Wirbelauer, Dr. R. Wössner), pediatric intensive care (Prof. Dr. C. P. Speer, Dr. E. Frieauff, PD Dr. S. Kunzmann, Dr. W. Thomas, Dr. J. Wirbelauer), oncology / haematology / stem cell therapy (Prof. Dr. P.-G. Schlegel, Dr. F. Deinlein, PD Dr. M. Eyrich, Dr. B. Winkler), cardiology (Dr. J. Wirbelauer), pulmonology / cystic fibrosis / sports medicine (Prof. Dr. H. Hebestreit), gastroenterology (Dr. A. Dick), nephrology (Dr. A Beissert, Dr. B. Wiewrodt), endocrinology (Dr. K. Ergezinger), diabetes (Dr. R. Wössner), neuropediatrics / social pediatrics (Prof. Dr. H.-M. Straßburg), immunology / infectiology (Prof. Dr. J. Liese, MSc), rheumatology (Prof. Dr. J. Liese, MSc), and others. Patients of all pediatric age groups ranging from premature infants up to adolescents are treated for the entire spectrum of pediatric diseases on the wards as well as in outpatient clinics. The Children's Hospital is in close cooperation with pediatric neurosurgery, pediatric surgery, urology / pediatric urology, and the hospitals for dental, oral, and facial therapy. Every year, around 6500 patients are treated as inpatients and 15000 as outpatients.

## Major Research Interests

**Inflammation in acute and chronic lung disease of premature infants and newborns.**

The aim of this long-term project is to analyze pathophysiological mechanisms in order to establish new strategies for prevention and therapy for this disease. Among other projects, studies are conducted to analyze the influence of prenatal inflammation on the development of regulatory T-lymphocytes in the fetal thymus, to evaluate the interaction between surfactant protein A and transforming growth factor ß as a novel mechanism to regulate inflammatory and fibrosing reactions in the lungs, and to characterize the effects of steroids and interleukin 6 on the gen expression of surfactant protein B and the Jak/Stat signal pathway.

**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. Specifically, this project studies the inverse gene regulation of transforming growth factor ß and connective tissue growth factor as potential new mechanism in the pathogenesis of BPD.

**Reconstitution of the immune system after stem cell therapy**

After the start of the stem cell transplantation unit in 2005, the reconstitution of the immune system after transplantation of highly purified hematopoietic stem cells beyond HLA-barriers has been 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. Another aspect of the studies related to the reconstitution of the immune system is the interaction of human peripheral blood stem cells with notch-ligands and the resulting differentiation of lymphoid cells. The great importance of this scientific focus is underlined by the installation of an endowed professorship for experimental and clinical cellular therapy financed by the "Elterninitiative für leukämie- und tumorkranke Kinder Würzburg e.V.". Prof. Dr. Matthias Eyrich has been appointed for this position in December 2009.

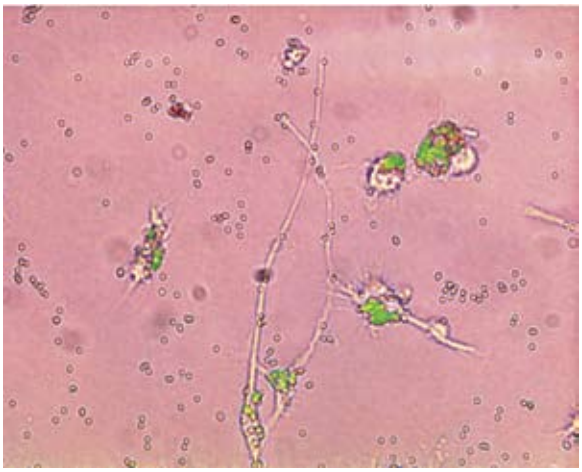

*Fig. 1: Following 5 days of differentiation in the presence of the cytokines GM-CSF and IL-4, dendritic cells phagocyte fluorescence-labelled synthetic particles. Maturation is achieved with TNFα and IL-1ß. The particles are used to visualize the ability of the cells to phagocyte. In clinical application, tumor antigens are used instead of the synthetic particles which will be presented by the dendritic cells to the immune system of patients with brain tumors.*

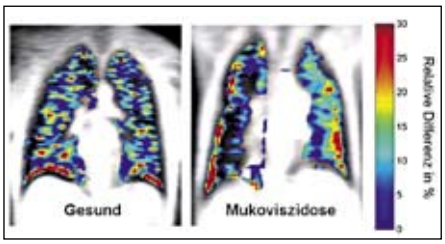


*Fig. 2: Ventilation of the lungs visualized by magnetic resonance spectroscopy using oxygen as contrast medium. The images are generated by subtracting maps acquired during breathing of room air and pure oxygen. Left panel: normal homogenous ventilation in a healthy individual; right panel: inhomogeneous ventilation with ventilation defects in the right lung in a female patient with cystic fibrosis.*

**New cellular therapeutic concepts for brain tumors**

Within a newly founded European network, innovative cellular therapeutic concepts to treat malignant brain tumors are tested and refined for the use in patients. One of these approaches, for example, is based on the combined application of patient-specific dendritic cells (loaded with patient´s tumor antigens) and tumor-specific cytotoxic T cells. To set the stage for clinical studies, extensive validation procedures for the manufacturing of dendritic cells and tumor-specific T-cells in our own GMP-facility following all legal demands are under way (see Figure 1). These new techniques strengthen the established neurooncological focus of the Children´s Hospital, which has hosted the German center of the pediatric brain tumor study for many years. In this study, the primary therapy for children with medulloblastomas, ependymomas and supratentorial primitive neuroectodermal tumor is evaluated and refined.

**Epidemiology and prevention of pediatric infectious diseases**

In several studies, the effects of vaccination programs on the epidemiology of infectious diseases such as varicella, influenza, pneumococcal infections and pertussis and their acceptance are evaluated in children and adolescents. Regional surveillance programs which have been established in close cooperation with pediatricians in private practices and pediatric hospitals such as the "Bavarian Varicella Project" (BaVariPro) provide valid epidemiological data to evaluate the impact and success of vaccination programs. In clinical studies, data on safety, immunogenity and effectiveness of vaccines are gathered in cooperation with pediatricians.

**Pathogenesis of rheumatoid diseases and immunodeficiency**

Several research projects entailing basic research and clinical studies investigate pathomechanisms of inflammatory processes in rheumatological diseases (juvenile rheumatism, chronic non-bacterial osteomyelitis) and hypophosphatemia, and evaluate therapeutic options. Furthermore, patients with compromised defense against infections are studied to identify the pathophysiological defects in immunity.

**Magnetic resonance imaging techniques for examination of the lungs**

This interdisciplinary project in cooperation with Prof. Dr. M. Beer (Institute of Radiology) and Prof. Dr. P. Jakob (Biophysics) 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 (figure 2).

**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 underlying a reduced exercise capacity and involved in the basics for the beneficial effects of exercise are investigated. The validity of exercise testing for diagnosis and 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 MDs in pediatrics, as well as in neonatology and pediatric intensive care. The heads of the sections for pediatric haematology and oncology, neuropediatrics, pediatric pulmonology 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 50 nations. Outside of the United States of America this symposium represents the largest scientific forum for neonatology.

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# 3.11 Department of Internal Medicine I

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## Mission and Structure

The Department of Internal Medicine I (DIM I) includes six divisions of internal medicine in research, teaching, and patient care: Endocrinology, Emergency- and Intensive Care, Cardiology / Angiology, Nephrology, and Pneumology.
Excellent conditions for clinical research, teaching, and patient care through closest interdisciplinary contact have emerged from the move of the Department to the Centre of Internal Medicine (Zentrum Innere Medizin, ZIM) mid-year 2009.

The Division of Endocrinology is in charge of the ward specialized in endocrinology/diabetology and cares for more than 5000 outpatients. Since 2003 the Division of Endocrinology has become the international reference centre for the adrenal carcinoma; in 2008/2009 more than 170 patients were cared for this very rare disease. An interdisciplinary centre for obesity was established in cooperation with the Department of Surgery.

Nephrology does more than 5000 hemodialysis and peritoneal dialysis treatments per year. Beside the care for hospitalized patients in a core unit, there are several outpatient clinics including the (1) low clearance clinic, (2) the vasculitis clinic, (3) the Fabry disease clinic (a national reference center) and the (4) transplant clinic for post kidney transplantation care. In 2008/9, more than 60 transplants (including living donors) could be realized.

The Division of Pneumology cares for inpatients with bronchial carcinoma, severe pneumonia, severe COPD or interstitial lunge disease. In the special pneumology outpatient clinic chemotherapies are performed in patients with bronchial carcinoma and patients are cared for with interstitial lunge diseases, sarcoidosis, severe asthma and alpha-1-antitrypsin-deficiency. A centre for pulmonary hypertension was recently established. The Pneumology is a central part of the interdisciplinary Thorax-Centre Mainfranken.

The Division of Cardiology performed more than 3000 invasive procedures in 3 catheterization laboratories, including 1000 percutaneous coronary interventions. In addition, catheter based implantations of closure devices in patients with atrial septal defects and persistently open foramen ovale are performed. In cooperation with the Department of Cardiac Surgery the minimally invasive stent-based implantation of aortic valves was established. More than 300 high frequency- or cryo-ablations are performed per year. In cooporation with the Department of Cardiac Surgery more than 150 cardiac pace maker systems and 110 ICDs were implanted. Several specialized outpatient clinics cover the whole spectrum of cardiology: general cardiology, aortic valve disease, heart failure, adults with congenital heart disease, psycho-cardiology, arrhythmias, ICD and pacemaker.
The DIM I runs a state of the art intensive care ward with 24 beds and an emergency ward with 12 beds in addition to the emergency room. The intensive care ward coordinates the Infarct Network Mainfranken - founded in 2007 - which manages 600 patients with acute coronary syndrome per year.

## Major Research Interests

**Endocrinology**
(B. Allolio, M. Fassnacht)

A major research focus of the team consists of translational and clinical studies in adrenal tumors (particularly adrenocortical carcinoma). The German Adrenocortical Carcinoma Registry and the first randomized international therapeutic study in advanced adrenal carcinoma (FIRM-ACT-Study) are coordinated by Prof. Allolio and PD Dr. Fassnacht with the support of Deutsche Krebshilfe (German Cancer Aid) and BMBF. In basic and clinical studies, new diagnostic and therapeutic targets as well as targeted therapies for adrenal carcinoma are evaluated. In a Max-Eder research group of the German Cancer Aid, headed by PD Dr. M. Fassnacht, immune-therapeutic approaches in adrenal tumors and – in a sub-project of the clinical DFG research group „Tumor Microenvironment“ - the role of glucocorticoids for tumor immune response are examined.

A second focus, initiated by Prof. Allolio and Dr. Hahner jointly with the Department of Nuclear Medicine, aims at developing and implementing new radioactive tracers for adrenal imaging. This research is supported by both the Sander-Stiftung (foundation) and the IZKF (Interdisciplinary Center for Clinical Research).

Moreover, several “investigator-initiated“ studies on acromegaly, hyponatremia and adrenal insufficiency are currently carried out. As part of an initiative for a German

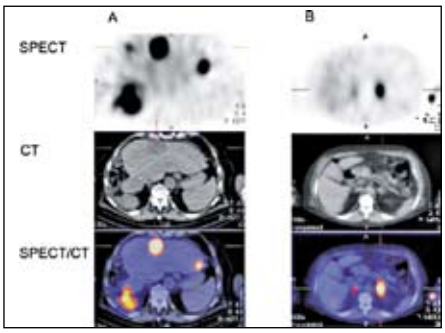


*Fig. 1: 123I-Iodmetomidat SPECT in a 68 year old patient with adrenocortical carcinoma with metastasis of kidney and liver (A) and a 55 year old patient with an endocrine inactive adrencortical carcinoma (B).*

Conn Registry, patients with primary aldosteronism are prospectively evaluated to assess long-term outcome. Our Interdisciplinary Obesity Center has become the basis for a number of preclinical and clinical studies. Finally a number of multicenter studies initiated by different pharmaceutical companies in the field of diabetes mellitus, hyponatremia, thyroid cancer, osteoporosis, and neuroendocrine tumors are carried out.

**Cardiology/Angiology**
(G. Ertl, J. Bauersachs)

Various teams investigate molecular mechanisms, imaging and treatment of heart failure and hypertrophy of the heart using a broad array of in vitro and in vivo techniques: Among others, experimental studies of the heart, cultured cardiomyocytes and endothelial progenitor cells, isolated platelets and vessels are performed. These investigations already yielded potential new therapeutic approaches. Results from experimental studies are transferred into clinical studies and patient care. Professor Ertl is vice spokesman of the "Kompetenznetz Herzinsuffizienz" and the special research program SFB 688 as well as speaker of the Review Board (Fachkollegium) "Medicine" and of the Section "Heart and Circulation" of the DFG. He holds main responsibility for the integrated research and treatment centre (IFB) "Prevention of heart failure and its complications" which will be established in 2010 in Würzburg and is supported by the ministry of research and education.

Current research projects in basic science: Electrophysiology of the heart on several levels, especially cardiac sodium channels (S. Maier). MRI-Imaging of the heart and cardiac biophysics (W. Bauer) in rodents and humans, modelling of cardiac microcirculation, cellular and molecular processes in the vascular system. Heart failure: healing and remodelling after myocardial infarction in animal models and using imaging techniques. Several aspects are investigated: platelet function, clotting system (A. Schäfer); oxidative stress (J. Widder), micro RNAs, ischemia perfusion injury (J. Bauersachs, S. Frantz), role of receptor antibodies during development of heart failure (R. Jahns); role of calcineurin (O. Ritter); vascular activity (J. Bauersachs, A. Schäfer, J. Widder); platelets/coagulation and their influence on cardiovascular function (A. Schäfer, J. Bauersachs); pulmonary hypertension together with the Division of Pulmology (H. T. Pelzer).

Current translational projects (R. Jahns): therapeutic cyclopeptides in autoimmune mediated heart failure; BMBF program (Gründungsoffensive Biotechnologie, Go Bio), 2007 founding of the company Corimmun; 2009 completion of preclinical study and current phase I study in humans.

Current clinical projects (only investigator initiated studies): biomaterial bank (R. Jahns, S. Störk), 3D- and tissue doppler echocardiography, storage heart diseases (Morbus Fabry together with nephrology, Morbus Friedreich together with Neurology) and aortic stenosis (F. Weidemann, W. Voelker); heart failure – study selection with principal investigator at DIM I (S. Störk, C. Angermann, R. Jahns, G. Ertl): handheld BNP-study: echocardiography and BNP testing in primary care. INH-interdisciplinary network heartfailure) – intervention study of nurse based disease management. MOOD-HF study: serotonin reuptake inhibition with escitalopram in patients with chronic heart failure and depression as a comorbidity. Prospective cohort-study rheumatism and heart. Ethics HF: etiology/pathogenesis, prevalence and pathophysiological importance of B1 auto-antibodies in heart failure, acute myocardial infarction and myocarditis. Pacemaker-ICDs (W. Bauer, O. Ritter): role of new sensors; development of new MRI-suitable pacemaker probes. Platelets (A. Schäfer, J. Bauersachs) role of platelets in acute coronary syndrome, predictors of clopidogrel non-responsiveness, vascular activity, endothelial progenitor cells (J. Bauersachs, T. Thum): in patients with coronary arterial disease and other cardiac diseases endothelial function and circulating progenitor cells are investigated. Angiology (J. Baulmann): several multicenter studies regarding vascular stiffness were initiated and coordinated from Würzburg.

Taking together the cardiovascular research in Würzburg is characterised by interdisciplinary basic science, translational and clinical projects with the focus on heart failure and cell-cell-interactions.

**Research in Nephrology**
(C. Wanner)

The clinical topic is the identification of predictors for sudden cardiac death and risk factors for cardiac and vascular disease in Type 2 diabetics with chronic kidney disease. The questions are answered in large multicenter randomized trials and cohort studies. Currently, the biobank of the completed 4D study – Die Deutsche Diabetes Dialyse Studie – is delivering useful results in that respect. The SHARP study (Study on Heart And Renal Protection) will come to an end in 2010 and is managed in cooperation with the University of Oxford. 1,789 patients with impaired kidney function are taken care of by the coordinating centre for clinical studies (ZKS). Research questions about the progression of rare renal diseases (e.g. M. Fabry) are being approached by prospective cohort studies. The transplantation unit with their patients is integrated into a large multinational observational study (PORT study). The coordinating centre of the KfH foundation of preventive medicine is being set up and is in charge of comprehensive cohort studies. A randomized controlled trial has been initiated by investigators of the academic hospital of Coburg and has offered co-chair function to Würzburg in the EPIC-CKD trial. In preclinical studies, pathomechanisms of the damage and recovery of ischemic acute renal failure are studied 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.

**Pneumonology Working Group**
(M. Schmidt, H.-T. Pelzer)

Basic research: Investigation of recruitment and homing of blood fibrocytes to lung, and the role of fibroblasts and myofibroblasts in the exacerbation of idiopathic lung fibrosis. Animal model of chronic thromboembolic pulmonary hypertension in cooperation with the institute of physiology (K. Schuh).

Clinical research: Radiochemotherapy of non-small-cell lung cancer, molecular targeted therapy of lung cancer. Palliative

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treatment of terminal lung disease. Development of the Würzburg Lung Embolism Registry. Multicenter vasodilative treatment study of chronic thromboembolic pulmonary hypertension (CTEPH).

**Interdisciplinary projects**

Interdisciplinary research 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 Department and the University Hospital, but also within the University together with research groups of other faculties. Some exemplary projects are listed here:

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

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. 140) and is involved in the DFG Clinical Research Group KFO 124 „Tumor microenvironment" (see p. 189). In addition, clinicians and scientists of the department are active in the several research centers (e.g. cardiovascular centre, interdisciplinary centre for clinical research, interdisciplinary tumor centre, centre for infection research). With the support of the ministry of research and education in 2010 the integrated research and treatment centre (IFB) "Prevention of heart failure and its complications" will be established in 2010 in Würzburg. This centre brings together several interdisciplinary research projects within the faculty of medicine and beyond, and will play a central role for cardiovascular research in Würzburg.

## Teaching

About 850 undergraduate clinical students participate in courses in Internal Medicine each semester. In the 5th Semester, students train in the basics of history taking and physical examination in the Skills Lab with simulators and real patients. The students´ skills are then tested in a standardized clinical situation in a so-called OSCE (Objective Structured Clinical Examination). In the 6th and 7th Semester, the main lecture and the clinical course in internal medicine take place. In the 10th Semester, students join a "14day-on-the-ward-training", followed by a one year internship ("Praktisches Jahr") during the 11th and 12th Semester. With about 3,000 hours of teaching per semester, internal medicine is a major subject in the medical curriculum. The results in the nationwide exams are excellent: Würzburg ranks first among all 36 medical schools. Teaching for both medical departments is organized by a teaching coordinator and a secretary. The teaching coordinator's tasks are also to improve and test the quality of teaching, to further develop active teaching techniques, to increase the validity and reliability of students´ tests, the improvement of students´ basic skills in physical examination and history taking, faculty development and the promotion of e-learning. The teaching coordinator is also in charge of students counselling und cooperation with students` representatives.

# 3.12 Department of Internal Medicine II

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**Professor Dr. med. Michael Scheurlen**
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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 in the city of Würzburg: ZIM (Center for Internal Medicine) and „Luitpoldkrankenhaus“.

**Zentrum für Innere Medizin (ZIM)**

1. Center for Stem Cell Transplantation
1. Interdisciplinary Oncology – Phase-I/II Unit
2. Department of Infectious Diseases (Center for Infectious Diseases DGI), comprising Infectious Disease-ward “Schottmüller” and outpatients’ department for infectious diseases
3. Rheumatology ward (Behring)
4. Department of Gastroenterology including ward “Romberg” and the outpatients’ department for gastroenterologic diseases

**Department for Endoscopy and Sonography**

5. Laboratories for immunology and Infectiology/Therapeutic Drug Monitoring

**Luitpoldkrankenhaus**

6. Outpatients’ department for the therapy of haematological and oncological diseases (from January 2010)

**Day Clinic for Psychosomatic Medicine (building C2)**

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. 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. – Interdisciplinary tumorboards, interdisciplinary tumorsurgery, interdisciplinary ambulatory Unit for tumortherapy.
(3) Innovative stem cell transplantation programme (2nd large programme in Germany) with new transplantation procedures (cord blood programme, haploidentical stem cell transplantation) and optimized control of complications (immunotherapy of infections, T cell therapy, bispecific antibodies, immunotherapy of residual tumor cells)

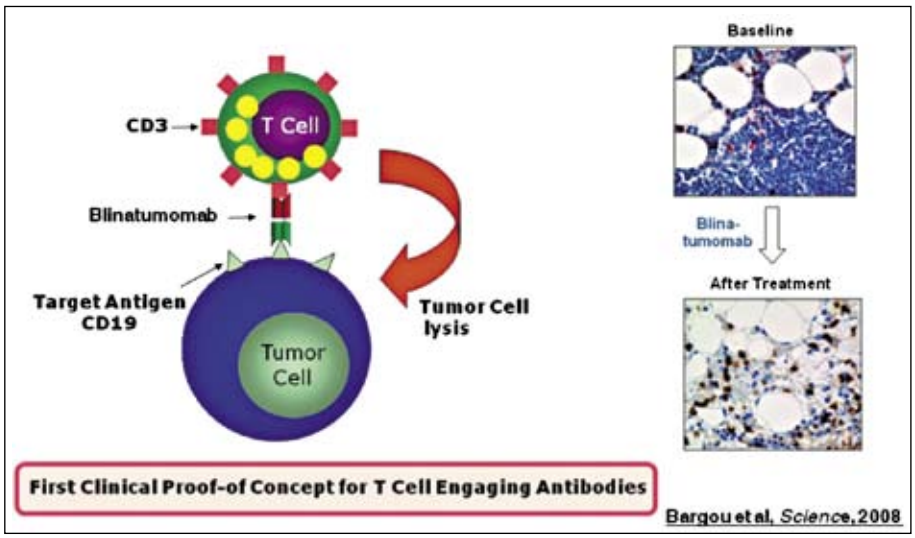


*Fig. 1: Phase I study in NHL.*

(4) 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)
(5) 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)
(6) Diagnosis and therapy of rheumatic inflammatory joint diseases, including the use of novel drugs, immunotherapy, phase II-II studies
(7) Diagnosis and therapy of systemic inflammatory diseases (vasculitis, collagenosis…)
(8) Diagnosis and therapy of immune deficiencies (CVID, drug-induced immune deficiencies)
(9) Diagnosis and therapy of patients suffering from acute and chronic, benign and malignant diseases of the gut and liver, including invasive endoscopy
(10) Diagnostic and therapeutic gastrointestinal and biliary endoscopy
(11) 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 γδ T-lymphocytes (group Kunzmann)
(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 (AG 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 artificial antigen-presenting cells and soluble factors (AG Grigoleit/Stuhler)

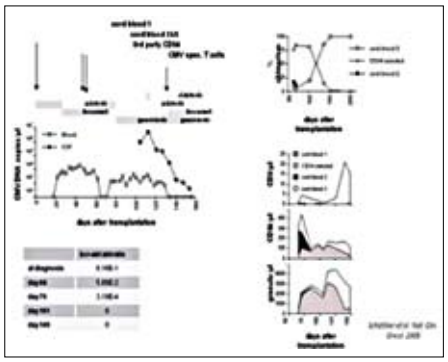

*Fig.2: Combined CBT/Haplo-SCT + Third Party T-Celltherapy.*

(7) DFG CRU 216: Characterization of oncogeneic signaling pathways in multiply myeloma and identification of therapeutic target structures (Einsele/Bargou)
(8) EU FP6 MANASP: Development of novel management strategies for invasive aspergillosis (Koordinator: Einsele)
(9) EU FP7 NanoII: Nanoscopically-guided induction and expansion of regulatory hematopietic cells to treat autoimmune and inflammatory processes (Einsele)
(10) Development of molecular and immunologic therapy approaches in non-Hodgkin lymphoma (AG Knop, Bargou)
(11) Phase-I unit for the realization of innovative therapy approaches in hemato-oncologic patients and in patients with solid tumors.
(12) In vivo Imaging in models of graft versus host disease (GVHD) and immunologic anti-tumor response (group Beilhack)
(13) Identification of markers for the prediction of a looming graft versus host disease (GVHD) (group Beilhack)
(14) Immunoreconstitution after allogeneig stem cell transplantation (AG Seggewiss)
(15) Tyrosine kinase inhibitors and their effects on different immune cells (T cells, NK cells, DCs)(AG Seggewiss)
(16) Novel strategies in allogeneic stem cell transplantation (cord blood transplantation, haploidentical stem cell transplantation) (Einsele/Stuhler/Mielke)
(17) DC-vaccination and T cell therapy against infectious and malignant diseases (AG Grigoleit/Einsele)
(18) Development of vaccination strategies against HCMV infections (AG Grigoleit)
(19) Selective allodepletion of GVHD-inducing T cells as a method for opti-

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mizing therapy in allogeneic stem cell transplantation (AG Mielke)
(20) 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) Modulation of the B cell repertoire in autoimmune diseases
(2) Immunoreconstitution in immunologic diseases
(3) Development of the B cell system in autuimmune diseases
(4) Transcriptional regulation of the low-affinity receptor for IgE(CD23)
(5) 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
(4) gastroenterological sonography using standardized electronical patient files
(5) Molecular, cytogenetic and functional characterization of colorectal, neuroendocrine, and hepatocellular carcinoma
(6) Antimicrobial activity of human colon epithelial cells, considering in particular cathelicidin
(7) LL-37
(8) 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 Psychoneuroimmunology. 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).
(3) Psychological state, psychosocial factors and quality of life in longterm-survivors after stemcell transplantation

## 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): Prof. Dr. H. Einsele (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.

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# 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.
- Wilhelm Sander-Stiftung
- the Wyeth company and
- the Interdisciplinary Centre for Clinical Research of the University of Würzburg

## Major Research Interests

The research activities of the division are focused on ligands of the tumor necrosis factor (TNF) family and their corresponding receptors. Ligands and receptors of the TNF family are of central importance for immunoregulation and also control programmed cell death (apoptosis) in a variety of physiological and pathophysiological situations. The development of therapeutic useful recombinant TNF ligand variants 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. Utilization 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 that 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 basic molecular mechanisms of pro-inflammatory signal transduction by death receptors are also investigated.

### Research Group: Co-operation of TNFR1 and TNFR2

TNF, the name giving cytokine of the entire ligand family, occur as a transmembrane and a soluble protein. The two forms of TNF 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 conditions and, importantly, on the form of TNF 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.

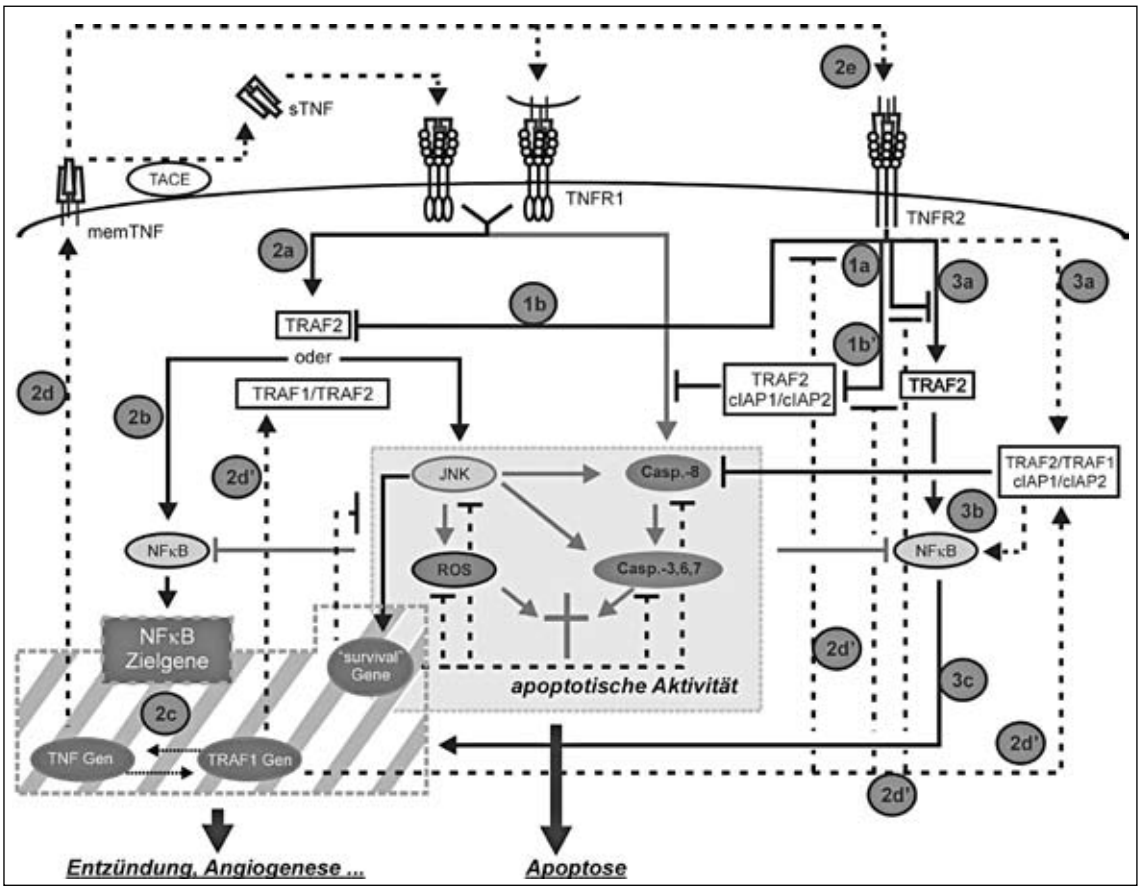


*Fig.1: TNFR1 and TNFR2 are functionally linked in a highly complex manner. Activation of TNFR2 by transmembrane TNF leads to degradation of the adapter protein TRAF2 (1a,b). Because this protein is important for TNFR1-induced activation of the proinflammatory transcription factor NF-kappaB and recruitment 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 NF-kappaB-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 NF-kappaB target gene is TRAF1 (2a-c). TRAF1 forms heteromeric 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.*

## SELECTED PUBLICATIONS


*Wyzgol A, Müller N, Fick A, Munkel S, Grigoleit GU, Pfizenmaier K, Wajant H. (2009) Trimer stabilization, oligomerization, and antibody-mediated cell surface immobilization improve the activity of soluble trimers of CD27L, CD40L, 41BBL, and glucocorticoid-induced TNF receptor ligand. J. Immunol. 183:1851-1861.*

*Wicovsky A, Salzmann S, Roos C, Ehrenschwender M, Rosenthal T, Siegmund D, Henkler F, Gohlke F, Kneitz C, Wajant H. (2009) TNF-like weak inducer of apoptosis inhibits proinflammatory TNF receptor-1 signaling. Cell Death Differ. 16:1445-1459.*

*Wicovsky A, Henkler F, Salzmann S, Scheurich P, Kneitz C, Wajant H. (2009) Tumor necrosis factor receptor-associated factor-1 enhances proinflammatory TNF receptor-2 signaling and modifies TNFR1-TNFR2 cooperation. Oncogene 28:1769-1781.*

*Berg D, Stühmer T, Siegmund D, Müller N, Giner T, Dittrich-Breiholz O, Kracht M, Bargou R, Wajant H. (2009) Oligomerized tumor necrosis factor-related apoptosis inducing ligand strongly induces cell death in myeloma cells, but also activates proinflammatory signaling pathways. FEBS J. [Epub ahead of print].*

*Egberts JH, Cloosters V, Noack A, Schniewind B, Thon L, Klose S, Kettler B, von Forstner C, Kneitz C, Tepel J, Adam D, Wajant H, Kalthoff H, Trauzold A. (2008) Anti-tumor necrosis factor therapy inhibits pancreatic tumor growth and metastasis. Cancer Res. 68:1443-1450.*

# 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 at the conclusion of a DFG-funded (1989–1995) Clinical Research Unit, was later merged in 2001 with the Central Diagnostic Laboratory, and now consists of the:

a) Department of Clinical Chemistry / Laboratory Medicine and Hemostaseology including an outpatient hemostasis clinic and the
b) Department of Clinical Biochemistry and Pathobiochemistry (Chair, Professorship of Clinical Molecular Biology and additional groups),

which conduct research, teaching and patient care. With respect to clinical duties, the division of Clinical Chemistry & Laboratory Medicine (directed by Dr. med. U. Steigerwald) is responsible for the major laboratory diagnostics of hospitalized and ambulatory patients of the university medical center (ca. 4 million patient laboratory analyses/year). Affiliated with this division is an outpatient clinic specialized in disorders of the hemostasis system.

## Major Research Interests

The major objective is elucidation of pathophysiological, genetic, and diagnostic aspects of important cardiovascular diseases (thrombosis, bleeding disorders, coronary artery disease, stroke, heart failure etc.) by investigating platelet and coagulation cascades in murine and human model systems, also using systems biological approaches. Research projects are supported by the DFG/SFB 688 (www.sfb688.de), BMBF, foundations, and industry.

**Departments of Clinical Biochemistry and Laboratory Medicine**
(U. Walter)

The central research focus is the investigation of inter- and intra- cellular signal transduction pathways that are involved in the inhibition of platelets, especially 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. This project (guided by Drs. Stepan Gambaryan and Sabine Herterich) is part of the SFB688 (Director: Prof. Dr. med. U. Walter) and was prolonged by the DFG in July 2009 for another 4 years (see also SFB 688 report). In cooperation with vasopharm biotech, the status of VASP phosphorylation was established as the most specific laboratory parameter for measuring of ADP receptor (P2Y12) inhibition by antiplatelet drugs such as Clopidogrel and Prasugrel.

In 2009, the BMBF network project SARA (Systems biology of prostaglandin and ADP P2Y12 receptor signaling pathways) was funded within the framework of the BMBF research initiative “Systems biology in medicine” (coordinator: Prof. Albert Sickmann, Dortmund; project leaders of the medical subproject C ”Functional analysis of thrombocytes”: Dr. Jörg Geiger and Prof. Ulrich Walter). The goal of the BMBF project (see report of the SARA project) is to obtain a comprehensive understanding of platelet function regulation in healthy as well as diseased states.

An additional group in the institute (PD Dr. Elke Butt) investigates the biological role of the human protein LASP-1 in growth and metastasis of different cancers, with the prospect of establishing LASP-1 as a prognostic marker for the metastatic potential of tumour cells. The work is supported by the German Cancer Foundation. An additional research domain is the characterization of cyclic nucleotides and their effector proteins.

**Clinical Molecular Biology Group**
(M. Zimmer)

This group is interested in the genetics of cardiac diseases and cardiomyopathies. Currently, it investigates the pathogenesis of a dilative cardiomyopathy caused by a novel disease gene. Other research areas focus on laminopathies which result from haploinsufficiency of the lamin A/C gene, mutational diagnostics of DCM genes, and

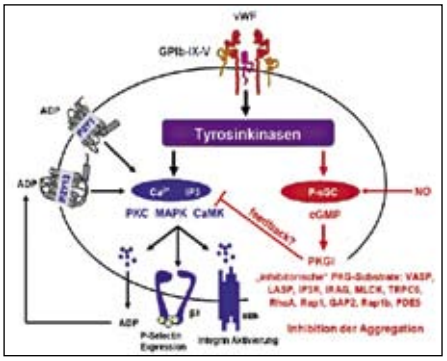


*Fig. 1: Activating (ADP, vWF) and inhibitory (NO/cGMP/PKG/VASP) pathways in platelets (SFB 688, TP A2).*

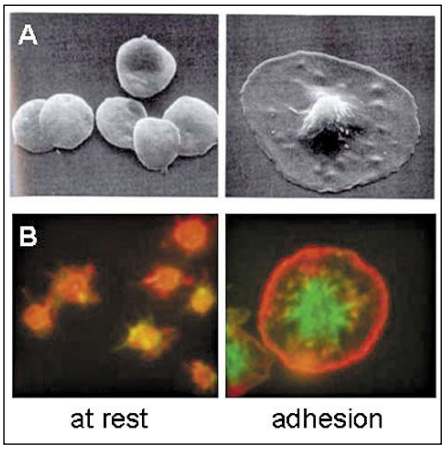


*Fig. 2: (A) Electron microscopy of resting and adherent platelets. (B) Immunofluorescence images of LASP (red) and F-actin (green) in resting and adherent human platelets [Traenka, Butt et al. (2009) Thromb. Haemostasis 102:520-528].*

the development of high-throughput SNP-typing using mass spectrometry.

**Metabolic Syndromes and Vascular Diseases**
(J. Schneider)

In October 2009, Dr. Jochen Schneider (diabetologist and endocrinologist) joined the institute after returning from Washington University, St. Louis Mo., USA. His research focuses on non-traditional risk factors for the metabolic syndrome, vascular disease and chronic inflammation, in particular cell-specific (dys)function of the ß3-integrin adhesion molecule.

**In 2009, three leaders of research groups left the institute after receiving professorships:**
**DFG/SFB Junior Research Group** (T. Renné) The DFG-funded junior research group investigated the contact activation pathway stimulated by coagulation factor XII (Hagemann-Factor) as an attractive target for novel antithrombotics, as well as the molecular regulatory mechanisms of endothelial barrier function. Dr. Thomas Renné is now Professor of Clinical Chemistry in the Department of Molecular Medicine and Surgery at the Karolinska Institute in Stockholm (www.ki.se).

**BayGene Program "Vascular Genetics"** (U. Felbor) The independent BayGene professorship of vascular genetics held by Prof. Ute Felbor focused on the pathogenesis and molecular diagnostics of cerebral cavernous malformations (CCM1, CCM2, CCM3) which are a predispositon for inherited forms of hemorrhagic stroke. Dr. Felbor is now professor in the Institute of Human Genetics, University of Greifswald (www.medizin.uni-greifswald.de/humangen).

**Vascular Biology Group** (B. Nieswandt) This group evaluated defects in platelet receptors and signalling pathways using genetically altered murine model systems with the goal of developing novel antithrombotic strategies. In December 2008, Prof. Bernhard Nieswandt became chairman of the Department of Experimental Biomedicine at the University of Wuerzburg (www.virchow.uni-wuerzburg.de/forschung).

## Teaching

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

## SELECTED PUBLICATIONS

*Poppe H; Rybalkin SD; Rehmann H, Hinds TR, Tang X-B, Christensen AE, Schwede F, Genieser HG, Bos JL, Doskeland SO, Beavo JA, Butt E (2008) Cyclic nucleotide analogs as probes of signaling pathways. Nat. Methods 5, 277-278.*

*Gambaryan S, Kobsar A, Hartmann S, Birschmann I, Kuhlencordt PJ, Müller-Esterl W, Lohmann SM, Walter U. (2008) NO-synthase-/NO-independent regulation of human and murine platelet soluble guanylyl cyclase activity. J. Thromb. Haemost. 6:1376-1384.*

*Benz P.M., Blume C., Moebius J., Oschatz C., Schuh K., Sickmann A., Walter U., Feller S.M., Renné T. (2008) Cytoskeleton assembly at endothelial cell-cell contacts is regulated by II-spectrin-VASP complexes. J Cell Biol, 180,205-19.*

*Lewandrowski U, Wortelkamp S, Lohrig K, Zahedi RP, Wolters DA, Walter U, Sickmann A (2009). Platelet membrane proteomics: a novel repository for functional research. Blood. 114, E10-E19.*

*van der Meijden PEJ, Munnix ICA, Auger JM, Govers-Riemslag JWP, Cosemans J, Kuijpers MJE, Spronk HM, Watson SP, Renne T, Heemskerk JWM (2009) Dual role of collagen in factor XII-dependent thrombus formation. Blood. 114: 881-890.*

# 3.14 Department of Dermatology, Venereology and Allergology

CONTACT DETAILS

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**Professor Dr. med. Henning Hamm**
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**Professor Dr. med. PhD 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 1 associate professor have been working in research and education during the period under report. The department has 9 senior physicians, 2 further specialists in dermatology and 19 assistant doctors. In research projects, 7 natural scientists are employed on regular positions or 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 general dermatology, dermatooncology , dermatosurgery and private patients
- Operation 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, A. Gesierich, S. Ugurel-Becker)
- Allergology and eczematous skin diseases (A. Trautmann, J. Stoevesandt, A. Kerstan)
- Autoimmune skin diseases (E.-B. Bröcker, S. Benoit, J. Stoevesandt)
- Hair diseases (H. Hamm, A. Kerstan), hyperhidrosis (H. Hamm)
- Dermatologic surgery (G. Weyandt, A. Gesierich)
- Phlebology und proctology (G. Weyandt)
- Pediatric dermatology (H. Hamm)
- Dermatologic infectiology (A. Kolb-Mäurer)
- Dermatohistology (E.-B. Bröcker, H. Kneitz, A. Kerstan)

## Major Research Interests

**Tumor biology and tumor immunology**

This continuing main field of research addresses several aspects of the biology of cutaneous tumors within the scope of the Clinical Research Group 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)
- Molecular pathogenesis of 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, S. Ugurel-Becker, E.-B. Bröcker)
- Apoptotic signal pathways in epithelial cutaneous tumors (T. Giner)
- Influence of polymorphisms on melanoma prognosis (J. C. Becker, S. Ugurel-Becker, D. Schrama, E.-B. Bröcker)
- Cell migration (P. Friedl, J. Storim)
- Stroma of Basal Cell Carcinoma (E.-B. Bröcker, H. Kneitz)
- Aberrant signal transduction in Merkel Cell Carcinoma ( J.C.Becker, R.Houben)

**Immunology and inflammation**

- Interaction between T-lymphocytes and keratinocytes in dermatitis (A. Trautmann, A. Kerstan)
- Immunotherapy 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)

**Genodermatoses**
(H. Hamm)

Clinical and genetic characterization of genodermatoses in cooperation with the German Network for Ichthyoses and Related Cornification Disorders, the German Network Epidermolysis Bullosa and the department of dermatology, University of Maastricht, the Netherlands (BMBF).

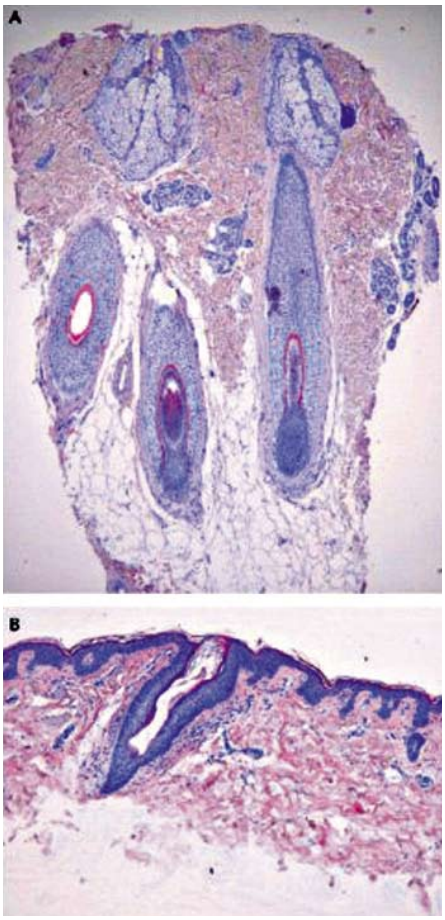

*Fig. 1: Donor site (A) and split-skin graft of the scalp with 0.3 mm thickness (B).*

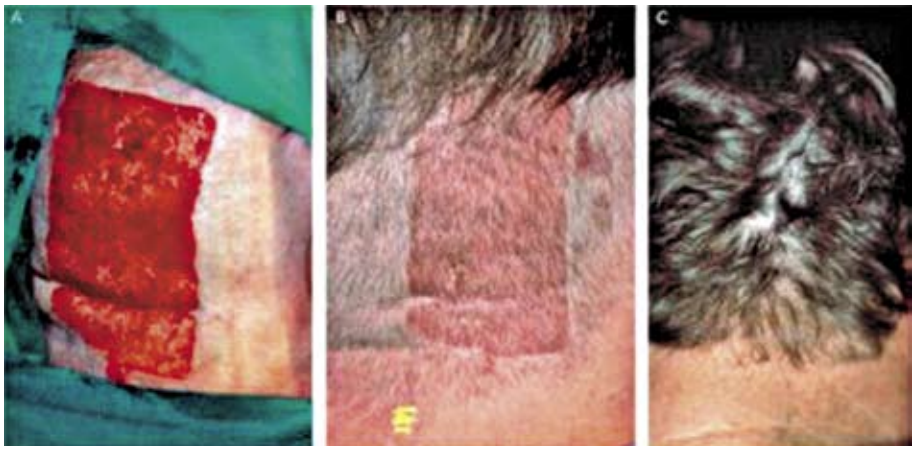

*Fig. 2: Appearance of the same patient's scalp after harvesting (A), 6 days later (B), and 12 weeks later (C).*

## Teaching

The entire field 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.

## SELECTED PUBLICATIONS


*Armbruster N, Trautmann A, Bröcker EB, Leverkus M, Kerstan A. (2009) Suprabasal spongiosis in acute eczematous dermatitis: cFLIP maintains resistance of basal keratinocytes to T-cell-mediated apoptosis. J. Invest Dermatol. 129:1696-702.*

*Hofmann UB, Voigt H, Andersen MH, Straten PT, Becker JC, Eggert AO. (2009) Identification and characterization of survivin-derived H-2Kb-restricted CTL epitopes. Eur J Immunol. 29:1419-1424.*

*Houben R, Schrama D, Becker JC. (2009) Molecular pathogenesis of Merkel cell carcinoma. Exp Dermatol. 18:193-198.*

*Hofmeister-Mueller V, Vetter-Kauczok CS, Ullrich R, Meder K, Lukanidin E, Broecker EB, Straten P, Andersen MH, Schrama D, Becker JC. (2009) Immunogenecity of HLA-A1-restricted peptides derived from S100A4 (metastasin 1) in melanoma patients. Cancer Immunol Immunother. 58:1265-1273.*

*Weyandt GH, Bauer B. Berens N, Hamm H, Broecker EB (2009). Split-skin grafting from the scalp: the hidden advantage. Dermatol Surg. 35:1873-1879.*

# 3.15 Institute of Radiology

CONTACT DETAILS

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**Professor Dr. med. Meinrad Beer**
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## Mission 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 4 Spiral-CT scanners and 7 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 Interests

**Basic Research and clinical investigation of abdominal organs using MRI**
(F. Wendel, H. Neubauer, T. Pabst)

Basic research and clinical investigations in the field of abdominal organ diagnosis are performed at the Institute of Radiology with the aim of introducing diffusion weighted imaging (DWI) in clinical routine. Special topics are the evaluation of the liver, kidney and gastrointestinal tract. The characterisation of masses in the liver and the kidney, as well as functional aspects are investigated in several studies. Special topics are the evaluation of DWI in M. Crohn and colorectal cancer.

**Basic Research and clinical investigation of pathologics of facial skull and neck using MRI**
(F. Wendel, T. Pabst)

Basic research and clinical investigations in the field of diagnosing pathologics of facial skull and neck are performed at the Institute of Radiology with the aim of introducing diffusion weighted imaging (DWI) in clinical routine. Special topics are the evaluation of the clinical value of DWI for investigation of neoplastic masses in the oropharynx, head and neck region.

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

The availability of high-end multi-slice CT scanners using fast rotation times of up 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.

**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.

**MRI of the human lung**
(M. Beer, M. Beissert, H. Köstler, T. Pabst, M. Oechsner, C. Ritter, A. Stäb, C. Wirth)

Techniques for morphological (under free breathing) and functional (with and without contrast agents) assessment of lung parenchyma are developed with a main focus on techniques for oxygen enhanced ventilation imaging. Patients with acquired interstitial as well as congenital diffuse lung diseases are studied. Moreover, diffusion-weighted (DWI) and late enhancement (LE) imaging is tested for a possible characterization of pulmonary macro- and micro anatomic structure.

**Cardiac MR-Imaging**
(M. Beer, H. Köstler, W. Machann, C. Ritter, D. Stäb, A. Weng)

Main focus is the development of new imaging strategies for non-invasive primary diagnosis of coronary artery disease (CAD) and for the detection/exclusion of secundary cardiomyopathy. Besides the acquisition of morphologic and functional parameters our special interest is the detection of metabolic changes with 31P-MR-Spectroscopy (fig. 1). Supported by a DFG-grant, main research in functional imaging is based on

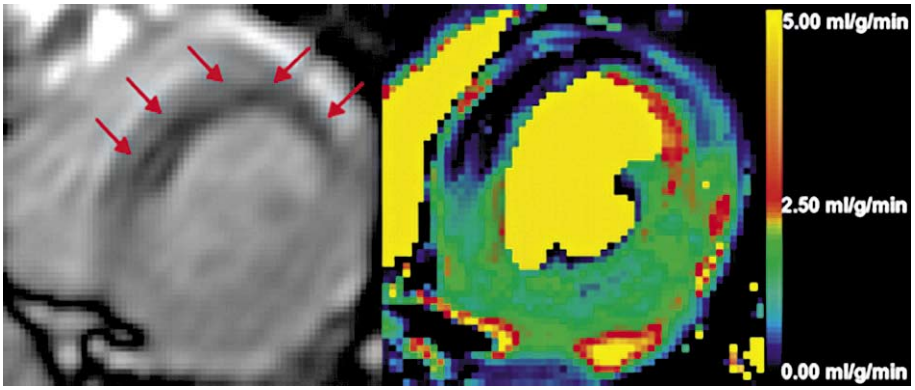


*Fig. 1: Short axis slice of a rest perfusion examination of the heart (left) and corresponding perfusion map (right) with absolute quantification of perfusion showing a 75% transmural perfusion defect of the anterior wall (arrows) in a high grade LAD stenosis.*

the development of high-resolution imaging techniques for the determination and absolute quantification of cardiac perfusion (fig. 2). In this context, we advance MR techniques for the quantitative examination of endothelium-derived vasoreaction. Furthermore, innovative MR contrast agents are applied. In addition, we focus on functional cardiac real-time and free-breathing MR imaging.

**Pediatric Radiologie**
(M. Beer, C. Wirth)

Aims are development and clinical application of high-resolution whole body MR techniques for assessment of inflammatory and oncologic diseases as well as inborn errors of musculo-skeletal metabolism. Non-invasive determination of renal function is another research topic in collaboration with the Children´s Hospital of Philadelphia (Prof. Darge). The role of high-resolution ultrasound is evaluated for assessment of neonates. Also for neonates and for young infants, interactive teaching programs for optimal X-ray applications are developed in co-operation with another hospital (PD Langen). Supported by a grant, possible interactions between pulmonary and musculoskeletal symptoms are investigated using a special designed MR-compatible ergometer for assessment of muscular metabolism.

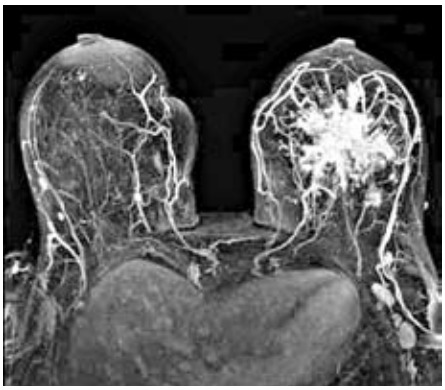

*Fig. 2: MRI of breast cancer of the left side using a 3T whole body system.*

**MR Mammography**
(H. Köstler, A. Roth)

One of the major aims of our work on the 3T-MR-machine is the non-invasive evaluation of different breast-diseases with the MR-mammographie. The main focus lies on the developement of high-resolution MR-techniques to detect smallest carcinomas/ DCIS at the earliest possible stage without any exposure to radiation. New acquisition strategies for magnetic resonance images like the diffusion weighted sequences have been developed and investigated systematically. All these techniques are being developed for clinical use (fig. 3).

**New MR acquisition methods**
(H. Köstler, M. Beer, M. Gutberlet, C. Ritter, A. Roth)

By developing of density weighted MR acquisition in a project funded by the Deutsche Forschungsgemeinschaft the MR image quality (resolution, signal to noise ratio) of MR can be improved. Density weighted MR imaging is applied to MR real time imaging of cardiac function and perfusion as well as to 3D MR mammography for detection of carcinomas and therapy control.

**Interventional Radiology**
(R. Kickuth, C. Ritter, J. P. Goltz)

The main investigational topics of the subdivision of Interventional Radiology are the Misago-II-Registry (SFA stenting), the evaluation of the technical and clinical outcome of port catheter systems of the forearm, the evaluation of the causalities for the explantation of port catheter systems of the forearm, and a feasibility study with regard to I-Guide-Kappa supported punctures, drainages, and fluid collection aspirations.

## 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.

## SELECTED PUBLICATIONS

*Beer M, Wagner D, Myers J, Sandstede J, Köstler H, Hahn D, Neubauer S, Dubach P, J. Effects of exercise training on myocardial energy metabolism and ventricular function assessed by quantitative phosphorus-31 magnetic resonance spectroscopy and magnetic resonance imaging in dilated cardiomyopathy. Am. Coll. Cardiol. 51, 1883-1891 (2008).*

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# 3.15.1 Division of Neuroradiology

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## Mission and Structure

The independent Division 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, "large display" 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, 5.5 residents, 9.5 medical technicians, 3 third-party funded residents and 4 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 Pediatric Neurosurgery and the Department 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**
(A. Biller, C. Várallyay)

This focus is funded by an endowed professorship assigned to Dr. Várallyay 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, C. Várallyay)

The division acts as the neuroradiological reference site to all German multi-centric, pediatric neurooncological studies. Staging according to the different stages of disease is the basis for treatment recommendations. Reference staging is an inclusion criterion in most of the pediatric brain tumor studies. New international treatment concepts are discussed together with the reference centers. In this context internationally agreed guidelines for the imaging in children with brain tumors have been developed and agreed upon. MR-examinations are evaluated to assess the therapy of experimental gliomas and novel MR contrast agents. Third-party funded.

**Pediatric Neuroradiology**
(M. Warmuth-Metz)

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

**MR Imaging of Neuromuscular Diseases**
(C. Várallyay)

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

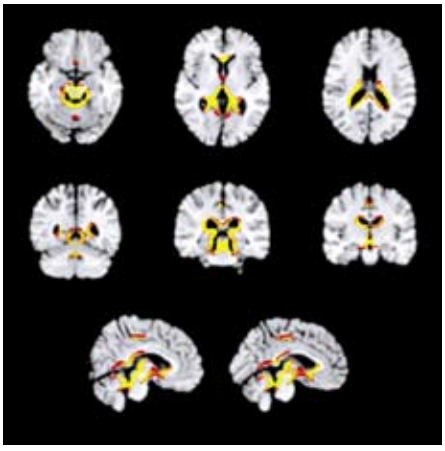

*Fig. 1: Areas of brain volume gain induced by abstinence from alcoholism.*

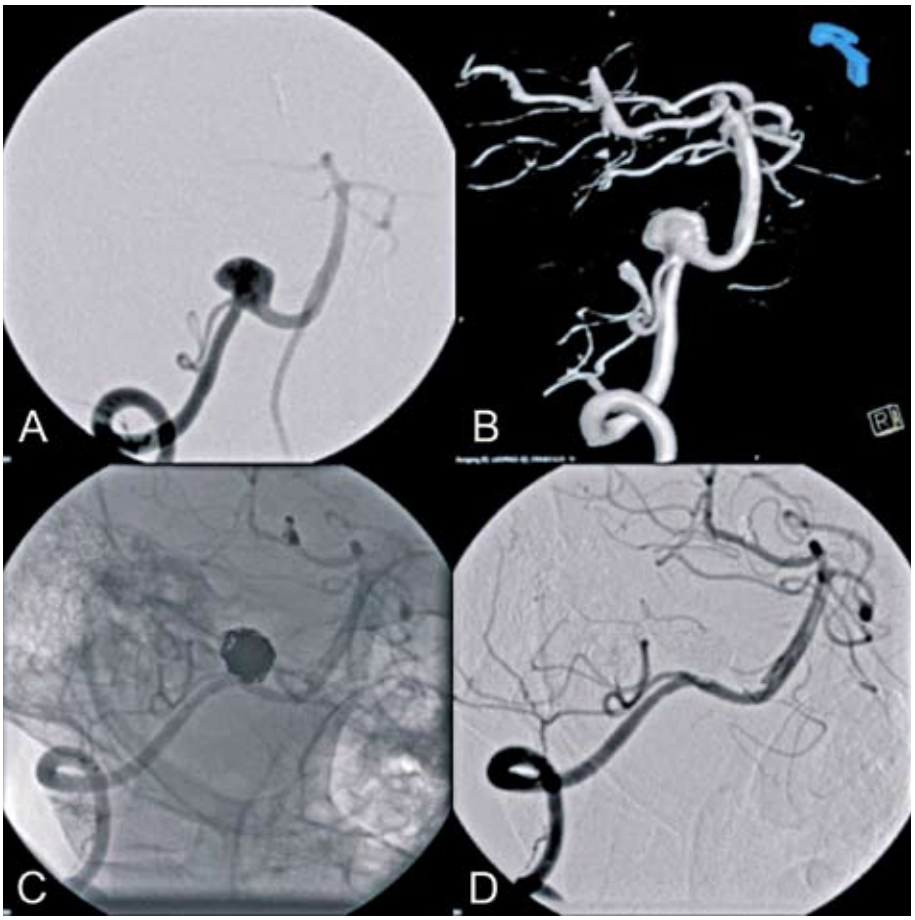


*Fig. 2: Aneurysm in the posterior brain circulation before (A, B) and after (C, D) embolization by platinum coils and stent.*

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 cochlear, 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.

## Teaching

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

The division 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 or the Clinical FMRI Course on the Human Brain Mapping Conference).

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, “flow diverter”).

Participation on therapy studies of inflammatory CNS diseases.

## SELECTED PUBLICATIONS

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# 3.16 Department of Nuclear Medicine

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## Major Research Interests

**Experimental Nuclear medicine - Radiochemistry/Radiopharmacy**
(S. Samnick, A. Schirbel)

The research group is in charge of the development of innovative radiopharmaceuticals for imaging and therapy in nuclear medicine. Probes are evaluated pre-clinically in-vitro (e.g. in primary human cell-cultures), 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 areas oncology, cardiology and neurology-psychiatry). IZKF, Deutsche Krebshilfe, BMBF as well as DFG sponsor the radiopharmaceutical developments and the clinical evaluation of new radiopharmaceuticals in the framework of SFB 688.

**Pre-clinical imaging**
(M. Kreißl, M. Laßmann, A. Schirbel, S. Samnick)

Small animal PET, as well as animal SPECT are both 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 groups from IFB or SFB 688 and IZKF. Subjects of study are tumor response to different chemotherapy regimens, regulation of cardiac metabolism in type II diabetes, remodelling after myocardial infarction as well as the role of transmembranprotease fibroblast-activation-protein α for wound healing and the fibrose reaction after infarction in animal models. In addition, small animal PET studies are performed in stroke and neurotrauma-models.

In addition, 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.

**Diagnosis and Therapy of Thyroid Disorders**
(Chr. Reiners, J. Biko, F. Verburg, P. Schneider)

The main focus of the clinical research is thyroid cancer, for which in, cooperation with the Comprehensive Cancer Center, a regional incidence registry is kept. A close collaboration exists with partner institution in Minsk, Belarus, and Nagasaki, Japan, 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, ZD6474, XL184, E7080 and Sorafenib). The department of nuclear medicine participates in (and is partially in charge of) several international epidemiological studies of iodine deficiency induced thyroid disorders. In addition, a cooperation with Su Yat-Sen University of Guangzhou, China, exists concerning longitudinal studies for optimization of radioiodine therapy in thyrotoxic patients.

**Medical Physics/Radiation Safety**
(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 nonstandard radionuclides are being evaluated for dosimetry and are implemented into clinical practice. In this context, particularly radionuclides are of interest, which can be used for dosimetry in radionuclide therapy (i.e. I-124, Y-90, Lu-177).

A further focus of research is the methodological development of 3D-ultrasound and high resolution multi-pinhole-scintigraphy for small organs (thyroid) and small animals. Additionally, the research group is operating a whole body counter as an official recording point of the State of Bavaria for the incorporation monitoring in persons who are occupationally exposed to radiation.

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

In the field of PET-diagnostics, F-18-FDG is routinely used for patient care and clinical studies; for diagnosis of brain tumors and prostate cancers, F-18-Fluorethyltyrosine and F-18-Fluorethylcholine respectively are available. For non-invasive diagnosis of neuro-endocrine tumors, Ga-68-DOTATOC has been established as somatostatin-receptor-ligand for PET.

A special focus in oncology is development, pre-clinical 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 in the framework of a study sponsored by Wilhelm-Sander-Stiftung in more than 100 patients. On a compassionate use basis, patients with untreatable metastatic adrenocortical cancer are treated with I-131-Metomidate (Fig. 2). In parallel, the spectrum of radiopharmaceuticals for radionuclide therapy has been actually broadened. For patients with neuroendocrine tumors and other neoplasias with over expression of hormone receptors, the receptor directed radionuclide therapy with Y-90 DOTATOC and Lu-177-DOTATATE are effective treatment options.

**Cardiology**
(M. Kreißl, R. Lorenz)

At the department of nuclear medicine, the influence of the normal reference data base 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 has been 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.

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

Together with the department of neurology, transcranial ultrasound was compared with dopamine transporter scintigraphy in patients with Parkinson's disease and atypical Parkinson syndromes. In children and adolescents with attention deficit hyperactivity disorder, the effect of medical treatment on

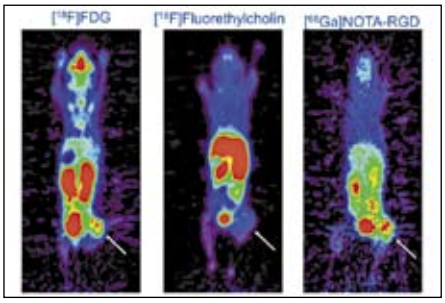


*Fig. 1: Coronal small animal PET images of a mouse implanted with prostate carcinoma cells (arrows). The tumor shows a increased glucose metabolism as visualized by a strong accumulation of [18F]-Fluorodesoxyglucose whereas choline uptake imaged with [18F]-Fluoroethylcholine is lower. Tumor angioneogenesis may be assessed using [68Ga]-NOTA-RGD.*

dopamine transport was assessed. For the diagnosis of dementia, an automated parametric image analysing procedure was introduced and evaluated in corticobasal dementia.

**Neuromuscular-Skeletal System**
(P. Schneider, H. Hänscheid)

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 the properties of the neuromuscular system in humans. These methods were ceded to the university to file for patents. In addition, field studies have been carried out to test these methods as predictive parameters of fall risk.

**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 data base 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.

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

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 to physical dosimetry, thhe induction, persistence and the disappearance of radiatin-induced gamma-H2AX and 53BP1 foci I-131 therapy of patients with differentiated thyroid carcinoma is studied as a model for protracted, continuous, internal whole-body irradiation.

## Teaching

In a project funded by the „Virtuelle Hochschule Bayern“, the department of nuclear medicine - together with the institute for Informatics IV – optimizes an interactive program for teaching medical students.

## SELECTED PUBLICATIONS

*Kobe C, Dietlein M, Franklin J, Markova J, Lohri A, Amthauer H, Klutmann S, Knapp WH, Zijlstra JM, Bockisch A, Weckesser M, Lorenz R, Schreckenberger M, Bares R, Eich HT, Mueller RP, Fuchs M, Borchmann P, Schicha H, Diehl V, Engert A Positron emission tomography has a high negative predictive value for progression or early relapse for patients with residual disease after first-line chemotherapy in advanced-stage Hodgkin lymphoma. Blood. 2008 Nov 15;112(10):3989-94.*

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*Samnick S, Romeike BF, Lehmann T, Israel I, Rübe C, Mautes A, Reiners C, Kirsch CM. (2009) Efficacy of systemic radionuclide therapy with p-131I-iodo-L-phenylalanine combined with external beam photon irradiation in treating malignant gliomas. J Nucl Med 50: 2025-32.*

# 3.17 Department of Radiation Oncology

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## Mission and Structure

The clinic for radiotherapy (18 physicians, 9 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. Over that, the ward for palliative care of the university hospital is linked to our department. 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. 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 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 brachytherapy 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 highly 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 and movement compensation, dose calculation on image data sets from cone-beam-CT, calculation of the accumulated dose in the presence of tumour movements, 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.

**Preclinical testing of DNA Topoisomerasel-targeted radiotherapy of different human glioblastoma cell lines**

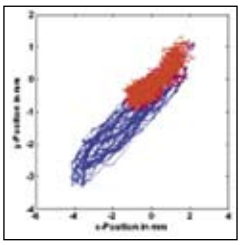

*Fig. 1. Example for the respiratory movement of a lung tumour during radiation (blue line). By means of tracking and respective countermeasures the movement was reduced significantly (red curve).*

Glioblastoma multiforme is the most aggressive primary brain tumor in adults. Standard therapy consists of surgical resection followed by radiotherapy (RT) which significantly prolongs survival. Chemotherapy added to RT is used as concurrent or adjuvant treatment. Although more long-term survivors have been reported after combined chemoradiotherapy, its success is limited in patients who develop chemoresistance.

A number of anticancer agents are known to synergistically enhance the cytotoxicity of ionizing radiation (IR). Among them are several camptothecin (CPT) derivatives, a novel class of anticancer drugs directed against DNA topoisomerase I (topoI). CPT, a plant alkaloid isolated from Camptotheca acuminata, is a potent antitumor drug with a broad spectrum of antitumor activity. CPT, however, failed through brief phase I/II clinical trials in the early 1970s because of its excessive toxicity. Nevertheless renewed interest in CPT has come from the identification of its only known molecular target, DNA topoI, and the elucidation of the mechanism of its action.

Our radiobiological laboratory (2 scientists, 2 technicians, 2 grant positions) is appropriately equipped to carry out basic research of the biological effects of ionizing radiation in human cells.

In order to enhance the cytotoxicity of radiation, CPT, an inhibitor of DNA topoisomerase I, was added to the cultured glioma cell lines before irradiation (IR). We found that CPT enhanced the radiotoxicity in U87-MG and SNB-19 cell lines if cell and colony counts were used as the end-points (Fig. 3). In contrast, pre-treatment with CPT of U373-MG, GHE and GaMG cell lines did not enhance cytotoxicity of IR in terms of cell and colony counts but accelerated DNA damage repair assessed by Rad50 foci. CPT treated glioma cells revealed at least two subpopulations with respect to the expression of histone H2AX, a marker of DNA double-strand breaks. Combined CPT-IR treatment followed by 30 min repair exert-

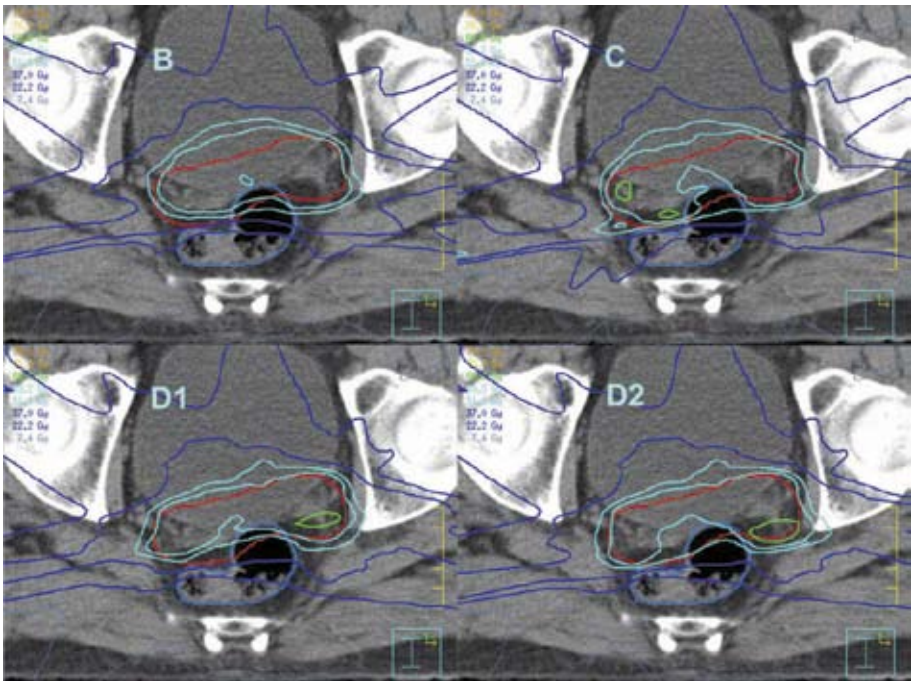


*Fig. 2: Dose distribution for a prostate case achieved with IMRT technique: B: Adaptation to anatomical changes with translations only, C: complete re-planning, D2: controlled adaptation of the original technique.*

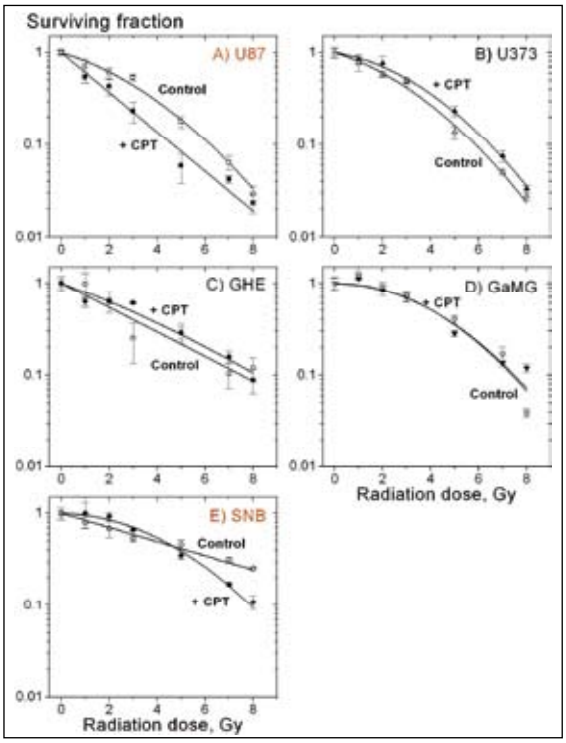


*Fig. 3: Clonogenic abilities of glioblastoma cell lines as functions of radiation dose and CPT exposure. Untreated and CPT-treated cells (empty and filled symbols, respectively) were irradiated with single IR doses ranging between 1 and 8 Gy. After irradiation, cells were plated in CGM and incubated under standard conditions. Two weeks later, colonies containing at least 50 cells were scored as survivors. Note that CPT enhanced the radiotoxicity in U87 and SNB19 cell lines (marked red).*

ed stronger effects on γH2AX expression in the case of U87 and SNB cells than either treatment alone. Because of the importance of topoI for the cytotoxicity of CPT, we additionally analyzed the expression levels of topoI in exponentially growing glioblastoma cell cultures by flow-cytometry. We found that the untreated U87 cells showed the highest expression of topoI (mean ≈ 460 a.u.), followed by SNB cells (337 a.u.). The other three lines (U373, GHE and GaMG) showed much lower background levels of topoI ranging between 160-180 a.u. The failure of CPT to enhance the radiotoxicity of glioma U373-MG, GHE and GaMG cell lines in terms of cell and colony counts was found to correlate with accelerated DNA damage repair, and with low expression of topoisomerase I, a target of CPT.

**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. Major contributions concern randomized studies for organ preservation in Larynx/hypopharynx Cancer (Delos 2) and in concurrent 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.

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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 92 regular beds including 6 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.

## Main Research Interests

**Middle ear biology**
(R. Mlynski, M. Schmidt, A. Radeloff, 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. Development of coated electrode carriers for medicamentous treatment of middle and inner ear.

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

LASER-vibrometrical measures of middle ear mechanics in petrous bones. Clinical and experimental investigations of middle ear implants and transplants using EDP supported documentation. Intraoperative monitoring of transmission function in active middle ear prostheses.

**Inner ear biology**
(R. Mlynski, K. Rak, N. v. Wasielewski in cooperation with the institute of neurobiology, M. Sendtner)

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.

**Impact of stem cells in auditory pathway**
(A. Radeloff, K. Rak, R. Mlynski)

Detection of adult stem cell populations in inner ear and central auditory pathway. In-vivo application of cultured stem cells to damaged inner ear in animals (guinea pigs).

**Pedaudiological tests and newborn hearing screening**
(W. Shehata-Dieler, D. Ehrmann, R. Keim in cooperation with the center of pre-speech development and developmental disorders, K. Wermke)

Development of new objective test procedures for frequency specific examination of newborns. Investigation of pre-speech sounds in infants as a new tool for pedaudiological testing.

**Cochlear- and brain stem implants**
(J. Müller, W. Shehata-Dieler, A. Radeloff, S. Brill, S. Kaulitz in cooperation with the department of neurosurgery, C. Matthies, and Univ. of Innsbruck, P. Nopp)

Evaluation of new stimulation strategies for further improvement of speech intelligibility following cochlear and brain stem implantation. Advancement of intraoperative telemetry and monitoring systems.

**Experimental audiology**
(M. Cebulla, R. Keim, W. Harnisch in cooperation with the department of psychiatry, psychosomatics and psychotherapy, A. Fallgatter)

Further development of diagnostic tools for objective frequency specific measurement of the absolute threshold of hearing. Objectification of binaural hearing in normal hearing and hearing impaired persons.

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

Electrophysiological basic research on central-neuronal processing of acoustic and electric stimulation of auditory pathway in an animal model.

**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.

**Ecological toxicology of the upper aerodigestive tract (UADT)**
(N. Kleinsasser, C. Köhler, C. Ginskey, S. Hackenberg, 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, A.Scherzed, M. Burghartz, A. Technau in cooperation with the department of orthopaedics, U. Nöth)

Establishment of stable cartilaginous structures with different scaffold materials. Investigations on the functionality of stem cell engineered tissue in an animal model.

**Functional Electrostimulation of the larynx**
(R. Hagen, W. Harnisch in cooperation with the university departments Innsbruck and Jena and the ENT department Gera, C. Pototschnig, O. Guntinas-Lichius, A. Müller)

Development of a larygeal pacemaker for treatment of uni- and bilateral recurrent nerve paralysis.

## 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, Syria, Argentina, Albania). Full-time hospitations for consultants.

## SELECTED PUBLICATIONS


*Ginzkey C, Kampfinger K, Friehs G, Köhler C, Hagen R, Richter E, Kleinsasser N (2009) Nicotine induces DNA damages in human salivary glands. Toxicol Lett 184:1-4.*

*Schmidt M, Polednik C, Grünsfelder P, Roller J, Hagen R (2009) The effects of PC-Spes on chemosensitive and chemoresistant head and neck cancer cells and primary keratinocytes. Oncol Rep 21:1297-1305.*

*Tolsdorff B, Petersik A, Pflesser B, Pommert A, Tiede U, Leuwer R, Höhne KH (2009) Individual models for virtual bone drilling in mastoid surgery. Computer Aided Surgery 14:21-27.*

*Radeloff A, Unkelbach MH, Mack MG, Settevendemie C, Helbig S, Mueller J, Hagen R, Mlynski R (2009) A coated electrode carrier for cochlear implantation reduces insertion forces. The Laryngoscope 119:959-963.*

*Brill S, Müller J, Hagen R, Möltner A, Brockmeier S, Stark T et al (2009) Site of cochlear stimulation and its effect on electrically evoked compound action potentials using the MED-EL standard electrode array. BioMedical Engineering On-Line 8:40-49.*

# 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 approx. 20.000 outpatients and more than 5.000 inpatients annually. In 2008, 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, neuroophthalmological disorders or strabismus. To supplement our services, a cornea bank meeting recent and future regulatory requirements is being established. 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.

## Main Research Interests

### Clinical Research

Research activities focus on the fields of cornea, glaucoma and retina. New strategies are developed to treat ocular surface disease, recent methods of cornea transplantation are studied, 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

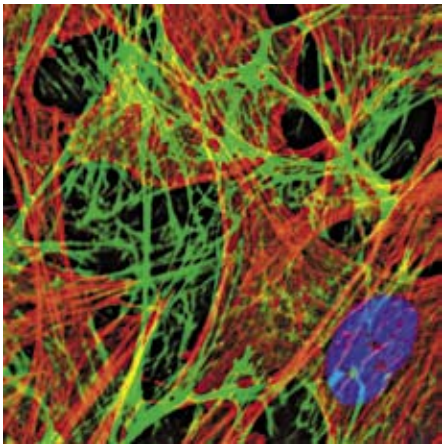

*Fig. 1: Human trabecular meshwork cells deposit extracellular matrix proteins (fibronectin, green) and process them to form extracellular network structures. An increased matrix deposition appears to have a role in glaucoma pathophysiology. The actin cytoskeleton (red) and the cell nucleus (blue) are depicted as well.*

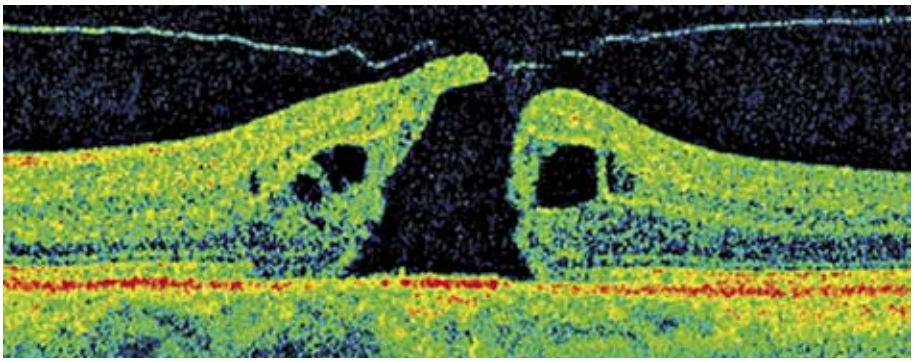

*Fig. 2: A tissue gap in the central retina (macular hole) due to membraneous traction leads to distorted vision and reduced visual acuity. At the stage depicted, retinal microsurgery allows for recovery in 90% of all patients. Optic coherence tomogram depicting retinal layers and intraretinal cysts.*

mechanisms, specific kinase inhibitors 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.

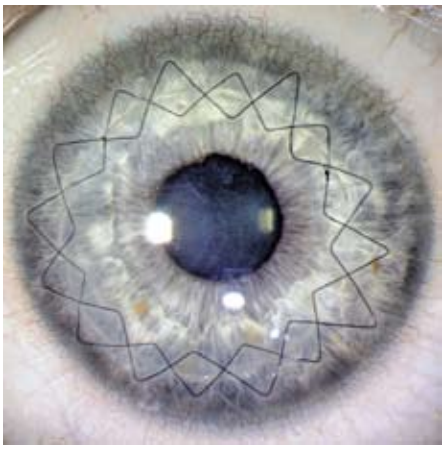

*Fig 3: Clear implant several days after full-thickness corneal transplantation. Two sutures secure the implant.*

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*Fritsche LG, Loenhardt T, Janssen A, Fisher SA, Rivera A, Keilhauer CN, Weber BH: Age-related macular degeneration is associated with an unstable ARMS2 (LOC387715) mRNA. Nat Genet. 40(7):892-6, 2008.*

*Geerling G, Garrett J, Paterson K, Sieg P, Collin J, Carpenter G, Hakim S, Lauer I, Proctor G: Innervation and secretory function of transplanted human submandibular salivary glands. Transplantation. 85:135-140, 2008.*

*Haigis W: IOL calculation after refractive surgery for myopia: the Haigis-L formula. J Cataract Refract Surg. 34(10): 1658-1663, 2008.*

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

*Schlunck G, Han H, Wecker T, Kampik D, Meyer-ter-Vehn T, Grehn F: Substrate rigidity modulates cell matrix interactions and protein expression in human trabecular meshwork cells. Invest Ophthalmol Vis Sci. 49(19): 262-9, 2008.*

# 3.20 Department of Neurosurgery

CONTACT DETAILS

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## Duties and Structure

The Department of Neurosurgery employs 22 medical doctors, 3 scientists, 96 nurses and 7 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 17 beds providing treatment for patients with cranial and spinal trauma, vascular malformations and spontaneous haemorrhage, 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 2 years (2008-2009) 1900 to 2000 patients were treated surgically and 4900 to 5300 patients in the out-patient department, resulting in an increase in activity of the department by 5 to 8%. The outpatient clinic 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 complex neoplastic and neurovascular lesions as well as for degenerative disease is performed at high incidence and for certain indications together with orthopedic and trauma surgery. Regular quality control conferences guarantee an ongoing high standard in routine and in most sophisticated operations.

The Division of Experimental Neurosurgery performs studies on neurotrauma, neurodegeneration and –regeneration, neurovascular pathophysiology and neuro-oncology and holds established collaborations with other basic science and clinical departments.

## Main Research Focus

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

Main focus of research is on development of novel therapies for and a better understanding of mechanisms of early brain injury after subarachnoid hemorrhage as well as 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 Doppler sonography 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 vasospasms. Further studies deal with the comparison of interventional and surgical aneurysm treatment and with dural arteriovenous fistulas.

**Translational neurotrauma research**
(A.-L. Sirén)

Main focus of research is on the mechanisms of neuroprotection and regeneration after brain injury and on translation of this knowledge into new therapeutic approaches for human brain disease using cell culture, transgenic animals and experimental models of brain trauma. On-going work focuses on regeneration using growth factor and stem cell based therapies for brain injury and on the changes in synaptic structural plasticity and their impact on functional deterioration after brain injury. 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.

**Functional Microsurgery & Neurostimulation**
(C. Matthies)

Functional microsurgery is the refined microsurgical technique guided by online information from continuous neurophysiological monitoring 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. A prospective study on motor evoked potentials of the cranial nerves has shown an increase in monitoring safety and improved prognosis of functional outcome in tumor surgery. A further study on continuous monitoring on the ICU after surgery has detected functional changes in this early period and has prompted new intensive medication protocols, among those the application of rheologicly active substances.

Neurostimulation therapy has been established for retrocochlear deafness and a centre for “new diagnostic and treatment modalities” (NUB) has been set up for the application of auditory brainstem implants in cooperation with the Department of ENT. The current study shows – different to previous international reports – that also in patients with large tumors or with previous implant trials – very satisfactory results can be obtained. The technique applied here by the interdisciplinary team and the modern stimulation processors provide useful auditory perception in the majority of patients.

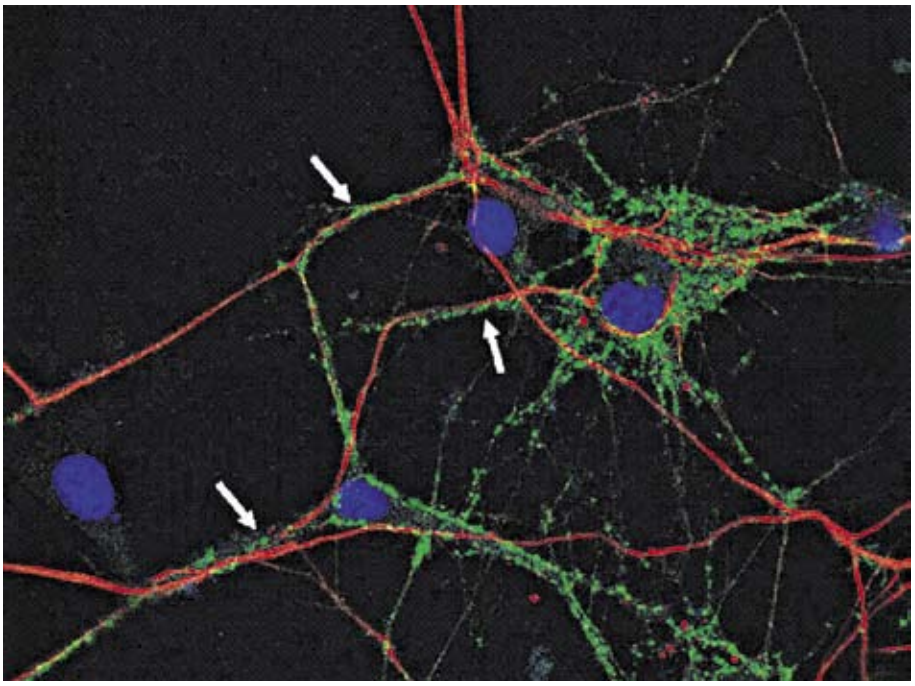

*Fig. 1: Hippocampus neurons (green) establish synaptic contacts with neural progenitor cells derived from embryonal stem cells (red).*

A cooperation with the Departments of Neurology, Neuroradiology and Psychiatry has been started for high frequency stimulation therapy in movement disorders (tremor, dystonia and Parkinson' disease). Stereotaxy guided electrode implantation is performed for intra-operative 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 patients with previous ischemic brain lesions and life threatening dystonic storms. A further developing topic is the combination of neuroprotective and regenerative factors.

**Neuro-oncology**
(G. Vince, C. Matthies)

A large patient population is being treated neurosurgically for glioblastomas and low grade astrocytomas and 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 investigations on invasiveness, progression and aggressiveness of brain tumors. 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.

Tumor biology and mutation analysis in benign pathologies such as schwannomas and meningiomas, are investigated in established national and international cooperations. Cell de-differentiation, adhesion molecules, tumor invasion, promotors of apoptosis are targets of investigation in benign tumor cell cultures and shall be 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**
(T. Schweitzer, J. Krauß)

An interdisciplinary team of pediatric neurosurgeons, neuropediatricians, neuroradiologists, maxillo-facial surgeons and specialists from seven further disciplines treats 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 morphometrics and development of infants with craniosynostosis and positional deformations.

## Teaching

Weekly 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. Doctoral and diploma students from medicine and related sciences as well as for post-doctoral fellows are working in projects at the Section of Experimental Neurosurgery, the Laboratory of Tumorbiology and the Neurophysiology Laboratory.

## SELECTED PUBLICATIONS


*Ammoun S, Ristic N, Matthies C, Hilton DA, Hanemann CO: Targeting ERK1/2 activation and proliferation in human primary schwannoma cells with MEK1/2 inhibitor AZD6244. Neurobiol of Dis, Epub Oct 2009.*

*Byts N, Samoylenko A, Fasshauer T, Ivanisevic M, Henninghausen L, Ehrenreich H, Sirén A-L: Essential role of Stat5 in the neurotrophic but not in the neuroprotective effect of erythropoietin. Cell Death Differ 15: 783-792, 2008.*

*Lee J-Y, Huang D-L, Keep R, Sagher O: Effect of electrical stimulation of the cervical cord on blood flow after subarachnoid hemorrhage. J Neurosurg 109: 1148-1154, 2008.*

*Stojic J, Hagemann C, Haas S, Herbold C, Kühnel S, Gerngras S, Roggendorf W, Roosen K, Vince GH: Expression of matrix metalloproteinases MMP-1, MMP-11 and MMP-19 is correlated with the WHO-grading of human malignant gliomas. Neurosci Res 60(1):40-9. 2008.*

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# 3.21 Department of Neurology

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Professor Dr. med. Heinz Wiendl
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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 an 8 bed Stroke Unit and a 10 bed Neurological Intensive Care Unit with over 2800 in-patients per year. The outpatient department cares for over 9000 out-patients per year including the hospital consultation service. The special expertise includes neuroimmunological diseases (multiple sclerosis, autoimmune nerve and muscle disorders), degenerative neuromuscular disorders including an integrated nerve/muscle pathology service, cerebrovascular disorders, movement disorders, epilepsy, neurogenic pain and neurointensive care. The Department has integrated a Division of Clinical Neurophysiology and a Clinical Research Group for Multiple Sclerosis and Neuroimmunology 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 in administration and special services. In addition 11 academics are supported by extramural grants. Two endowed professorships for „Neuroimaging“ (Bayer-) Schering AG) and „Multiple Sclerosis and Blood-Brain-Barrier“ (Teva und Sanofi-Aventis) and one lecturership (Merck-Serono) have been transferred into project grants. The Department contributes to the Sonderforschungsbereiche (Cooperative 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 entry) which had been outsourced from the Neurology Department and its integrated Clinical Research Group for Motor Neuron Disorders in 2000; and the Institute of Physiology II (Head: Prof. Dr. Manfred Heckmann).

## Major Research Interests

**Multiple Sclerosis and Neuroimmunology (Clinical Research Group, previously BMFT, now University of Würzburg)**
(H. Wiendl, G. Stoll, K.V. Toyka, A. Weishaupt, C. Sommer)

Pathogenesis of multiple sclerosis, polyneuritis, myasthenia gravis and myositis in humans and experimental rat and mouse models (experimental autoimmune encephalomyelitis (EAE) und neuritis (EAN), transgenic mouse models); studies on immune regulation, effector mechanisms of immune-mediated tissue damage and new immunotherapy; 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 damage; 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. Pathogenesis of antibody-mediated PNS and CNS disorders. International treatment trials.

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

Molecular mechanisms of thrombus formation in experimental cerebral ischemia (e.g. von Willebrand-Faktor, STIM-1) and development of novel and safer treatment options; mechanisms of brain edema formation and neuroprotection; role of immune cells in stroke; imaging of lesion evolution by 17 TESLA-high-field MRI (in cooperation with Dept of Physics V); novel MR contrast agents for in-vivo visualization of inflammation; cognitive decline and MRI abnormalities as a consequence of microangiopathy, chronic heart failure and after heart surgery. International treatment trials.

**Neuromorphology and Pain Research**
(C. Sommer)

Role of pro- and anti-inflammatory cytokines in neuropathic pain, utilizing different lesion models and evaluation of underlying molecular signalling pathways; assessment of cytokine profiles in patients with chronic neuropathic pain; establishment of new diagnostic procedures for small-fiber neuropathies. International pain treatment trials. Standardization and diagnostic validation of peripheral nerve pathology. (Intramural cooperation with K.V. Toyka)

**Experimental Developmental Neurobiology**
(R. Martini)

In the focus is the investigation of pathogenic mechanisms underlying genetically-mediated demyelination in the central and

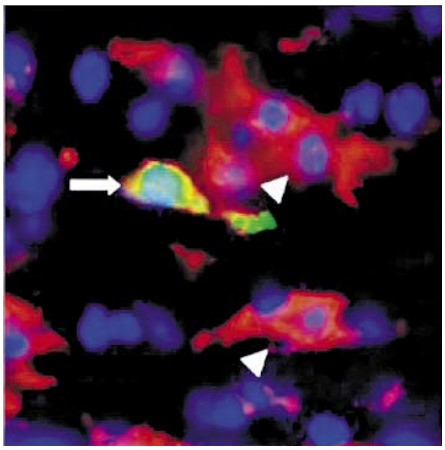

*Fig. 1: Identification of macrophage-like cells (arrowheads, red colour) using antibodies to CD11b in the optic nerve of a CNS myelin mutant mouse. The majority of these pathogenic cells are resident cells and only few cells are of hematogeneous origin, as revealed by bone marrow transfer experiments using mice transgenically expressing green fluorescent protein (GFP) as bone marrow donors. The arrow points to a rare immigrated green cell, which is additionally labelled by the macrophage marker CD11b. The intrinsic origin of pathogenic macrophage-like cells behind a preserved blood brain barrier may have consequences for possible treatment strategies of the corresponding myelin disorders in humans. The bue colour identifies cell nuclei. (from: Mol Cell Neurosci 38:489-494; 2008).*

peripheral nervous system using mouse mutants with spontaneous and genetically engineered defects in myelinating glial cells and other neural cells. Particular emphasis is on the role of disease-modifying mechanisms, like the impact of the immune system and emerging treatment strategies in the mouse models. Morphological methods, such as confocal and electron microscopy, combined with the assessment of molecular alterations are used for the analysis of glial damage, impaired axonal transport and synaptic alterations. (Intramural cooperation with H. Wiendl, K.V. Toyka, C. Sommer)

**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 Department of Neurosurgery. (Intramural cooperation with K. Reiners, G. Stoll, K.V. Toyka)

**Clinical Neurophysiology und Neuromuscular Disease Center; Motor Neuron Disorders**
(K. Reiners, M. Beck, C. Wessig)

Neurophysiological examinations in patients with neuromuscular and CNS disorders (> 25,000 examinations per year); development of tools for the assessment of disease severity and progression in MS and ALS, and correlation with molecular diagnostic probes (Institute of Clinical Neurob iology);coordination 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. International treatment trials in ALS. (Intramural cooperation with M. Sendtner; K.V. Toyka)

**Autoantibodies and Disease Models in Neuroimmunological Disorders**
(K. Toyka, C. Sommer)

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

**Specialized Laboratory Medicine**
(K. Toyka, A. Weishaupt)

Laboratory support of all groups and projects in neuromorphology, neurogenetics and neuroimmunology. Research focus: The role of serum autoantibodies in the diagnosis and prognostic assessment of neurological diseases (anti-MAG-, anti-GM1, anti-aquaporin-4 antibodies, anti-acetylcholine-receptor-antibodies). Serum and CSF biomarkers in dementia and other degenerative CNS disorders.

## Teaching

In the lectures, seminars and curricular 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, Oncology Center, Pain-Curriculum, Psychology, Neurobiology, and all classes of the Würzburg International Graduate School of Life Sciences). Teaching languages are German and English.

## SELECTED PUBLICATIONS


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# 3.22 Institute for Clinical Neurobiology

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## Mission and Structure

The Institute of 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. Since 2000, it is 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. It will receive new laboratories in 2010 after its move to the former MSZ.

## Major Research Interests

Central research focus are studies on the 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 laterals sclerosis and spinal muscular atrophy, the most common forms of motoneuron disease in children and adults.

Further lines of research focus on the mechanisms how neural stem cells differentiate into neurons and functional neural circuits. Investigation of the signal transduction pathways by which neurotrophic factors influence differentiation, survival and axonal growth of neurons are of central interest. 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. This disease is characterized by axonal defects and defects of neurotransmission at neuromuscular synapses. These defects are due to reduced β-actin mRNA transport in axons of motoneurons, resulting in functional deficits in the presynaptic parts 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.

Central technologies, beside the generation of mouse models are modern microscopic techniques, including confocal microscopy, 2-photone microscopy and life imaging, in order to study defects in structure and function in neurons from models of neurodegenerative diseases.

## Teaching

The Institute for Clinical Neurobiology is involved in the training of students in Neurology as well as the training of biology students (Bachelor and MSc Courses) with focus on neurobiology. Another focus is the training of students in the MD/PhD program and participation in training programs for the class Neuroscience of the Graduate School Life Science at the University of Wuerzburg. Further courses are offered for students of the course molecular medicine within the training program for MD students.

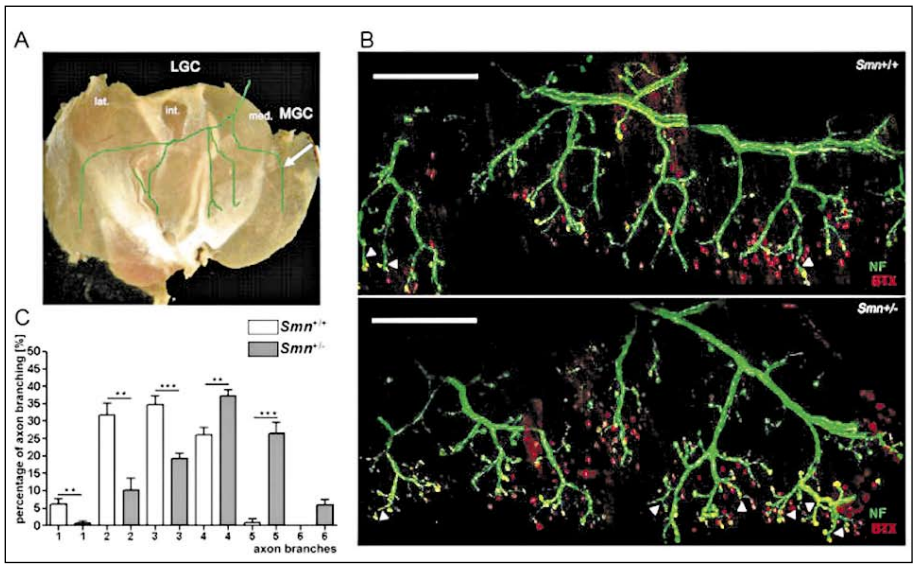


*Fig. 1: Alterations in axonal branching in the gastrocnemic muscle from a mouse model of spinal muscular atrophy (Smn+/-). The number of terminal sprouts is increased, a sign that compensatory mechanisms take place in the disease process.*

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*Poesen, K., Lambrechts, DE., Van Damme, P., Dhondt, J., Bender, F., Frank, N., Bogaert, E., Claes, B., Heylen, L., Verheyen, A., Raes, K., Tjwa, M., Eriksson, U., Shibuya, M., Nuydens, R., Van Den Bosch, L., Meert, T., D'Hooge, R., Sendtner, M., Robberecht, W. and P. Carmeliet. Novel Role for VEGF-Receptor-1 and its Ligand VEGF-B in Motor Neuron Degeneration. J. Neurosci. 28, 10451-10459, 2008.*

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*Trimbuch, T., Beed, P., Vogt, J., Schuchmann, S., Maier, N., Kintscher, M., Breustedt, J., Schuelke, M., Streu, N., Kieselmann, O., Brunk, I., Laube, G., Strauss, U., Battefeld, A., Wende, H., Birchmeier, C., Wiese, S., Sendtner, M., Kawabe, H., Kishimoto-Suga, M., Brose, N., Baumgart, J., Geist, B., Aoki, J., Savaskan, N.E., Bräuer. A.U., Chun, J., Ninnemann, O., Schmitz, D. and R. Nitsch. Synaptic PRG-1 modulates excitatory transmission via lipid phosphate-mediated signaling. Cell 138,1222-35, 2009.*

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# 3.23 Department of Psychiatry, Psychosomatics and Psychotherapy with Division of Forensic Psychiatry


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**Professor Dr. med. Klaus-Peter Lesch**
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## Mission and Structure

The clinic of Psychiatry, Psychosomatics and Psychotherapy (PPP) at the UKWürzburg (UKW) offers comprehensive 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 outpatient department as well as 36 day-care therapy slots for psychiatric and psychosomatic disorders complement the 144 in-patient therapy slots with two intensive care units and units specialized on affective disorders (bipolar depression and treatment-resistant depression), substance abuse therapy and psychotherapy. Specialized diagnostic and therapeutic options are provided by the laboratory of therapeutic drug monitoring and the laboratory of 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, the GSLS and the IZSF, at the national level in the context of cooperations with institutes of the Max-Planck Society, the Helmholtz Society and participation in BMBF programs for Brain Research, Depression, Panic Disorder and ADHD, the SHIP study and the recently founded TRR SFB 58. At the international level, the PPP participates in cooperations with the NIH and EMBL and takes part in DAAD programs and EU programs for Brain Research and Depression, but also international research collaborations such as IMpACT, IMAGE2, the ADHD Molecular Genetics Network, PANIC, ANGST, ConLiGen, and the Psychiatric GWAS Consortium. Funding agencies include the DFG, the BMBF, EU and the NIH.

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 magnetic resonance 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 high throughput genotyping (Core Facility Genetics 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 specialized clinical studies group was established (J. Deckert, A. Fallgatter), which cooperates closely with the ZKS. Studies on suicide (A. Schmidtke, B. Pfuhlmann) have already resulted in defined proposals for suicide prevention. The signature of the department is the close interaction between translational research laboratories of the PPP, such as the laboratories on Clinical Neurochemistry, Psychiatric Neurobiology, and Psychobiology (J. Deckert, K.-P. Lesch, A. Reif, P. Riederer, A. Schmitt), 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.

**The main research topics thus are:**

- Markers for early diagnosis and innovative therapeutic approaches in affective 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. Pfuhlmann, C. Jacob, 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 affective 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, neuronal plasticity and adult neurogenesis in humans and in rodent models (K.-P. Lesch, J. Deckert, A. Reif, A. Schmitt).

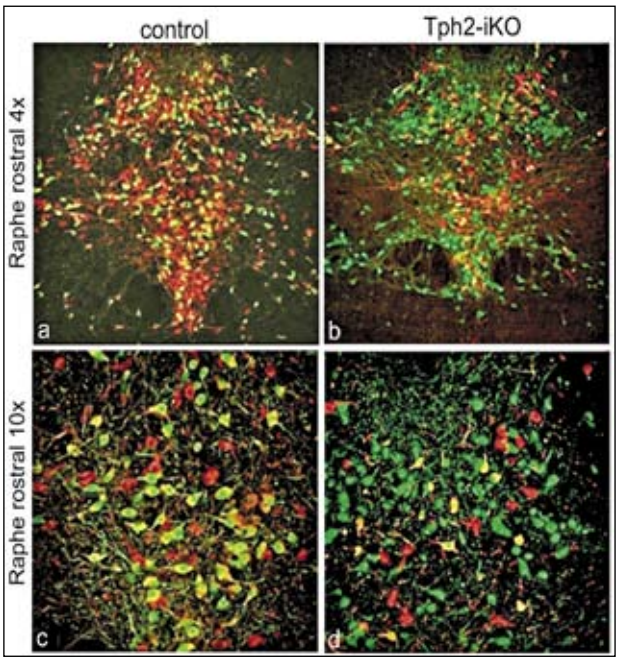


*Fig .1: ß-Galactosidase (green) and Tph2 (red) double immunostaining in rostral raphe of Tph2 inducible knockout. Tph2 tamoxifen-inducible KOs (TPH2-iKO) and Pet1-creER mice (control) were crossbred with the ROSA26 cre reporter strain; detection of green cells shows effective cre recombination of Tph2 floxed in the typical pattern of serotonergic cells of the raphe nuclei (a, b). Thus, double labelled cells demonstrate effective cre recombination for ß-galactosidase but not for Tph2 floxed in cells which still express Tph2-protein. Very low amount of double labelled cells was detected in inducible Tph2 knockout mice (b, d) demonstrating the effective functioning of cre recombination in combination with Tph2 deletion (from C. Kriegebaum et al., unpublished).*

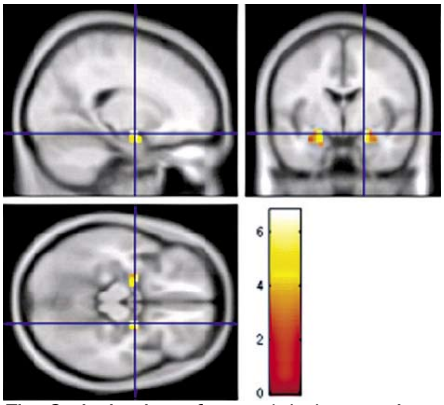


*Fig. 2: Activation of amygdala by emotional faces (from Hahn et al. unpublished).*

## 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 biomedicine, psychology and biology. Extracurricular seminars are offered to graduate students of medicine, experimental medicine, biology, and psychology.

## SELECTED PUBLICATIONS


*Baehne CG, Ehlis AC, Plichta MM, Conzelmann A, Pauli P, Jacob C, Gutknecht L, Lesch KP, Fallgatter AJ. Tph2 gene variants modulate response control processes in adult ADHD patients and healthy individuals. Mol Psychiatry. 2009 Nov;14(11):1032-9.*

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*Grünblatt E, Monoranu CM, Apfelbacher M, Keller D, Michel TM, Alafuzoff I, Ferrer I, Al-Saraj S, Keyvani K, Schmitt A, Falkai P, Schittenhelm J, McLean C, Halliday GM, Harper C, Deckert J, Roggendorf W, Riederer P. Tryptophan is a marker of human postmortem brain tissue quality. J Neurochem. 2009 Sep;110(5):1400-8.*

*Murphy DL, Lesch KP. Targeting the murine serotonin transporter: insights into human neurobiology. Nat Rev Neurosci. 2008 Feb;9(2):85-96.*

*Reif A, Jacob CP, Rujescu D, Herterich S, Lang S, Gutknecht L, Baehne CG, Strobel A, Freitag CM, Giegling I, Romanos M, Hartmann A, Rösler M, Renner TJ, Fallgatter AJ, Retz W, Ehlis AC, Lesch KP. Influence of functional variant of neuronal nitric oxide synthase on impulsive behaviors in humans. Arch Gen Psychiatry. 2009 Jan;66(1):41-50.*

# 3.24 Department for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy

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## Mission and Structure

The department 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 responsible body for the locked ward is the "Bezirk Unterfranken"), a day clinic and a special school (responsible body: "Diakonisches Werk"), a parent's pavilion (responsible body: "Verein Menschenskinder e.V."), a clinical research group (sponsored by the German Research Association, DFG) and 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 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. Main focus of patient care are the assessment and treatment of eating-, affective-, anxiety disorders, psychosis, attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder, Tourette syndrome, conduct disorder, autism spectrum disorders, 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. Romanus, A. Warnke)

Pathogenesis, endophenotypes and comorbid features are investigated using formal and molecular genetics, neuropsychological and neurophysiologic methods as well as animal models and gene expression studies. There are many cooperations with local and national departments and international research networks on ADHD (DFG: KFO 125; see page 191). 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 (The Interdisciplinary Centre for Clinical Trials IZKF of Wuerzburg University). Within the framework of the BMBF-network on psychotherapy research in ADHD 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 (BMBF; see page 200).

**Biomarkers**
(M. Gerlach, M. Romanos, R. Taurines)

Different paradigms (real-time PCR, proteomics, olfactory test) are evaluated in the effort to achieve a substantial contribution to an early and reliable diagnosis of ADHD, autism spectrum disorders and schizophrenia. Alterations in mRNA expression of mitochondrial genes could be identified as potential biomarkers for early onset schizophrenia. In a proteomic approach, patients with autism spectrum disorders showed differences in the serum proteome compared to controls; a characteristic that might be used as a peripheral biomarker. These studies were done in cooperation with the University of Ulm (Prof. Dr. C. Mehler-Wex), the University of Bochum (Prof. Dr. K. Marcus), the University of Leipzig (Prof. Dr. J. Claßen) and the University of Swansea, United Kingdom (Prof. Dr. J. Thome).

**Developmental psychopharmacology**
(M. Gerlach, K. Klampfl, A. Warnke)

To improve the security of the patients and to establish quality standards the clinic is part of the international multicentre competence network on TDM. Data internet

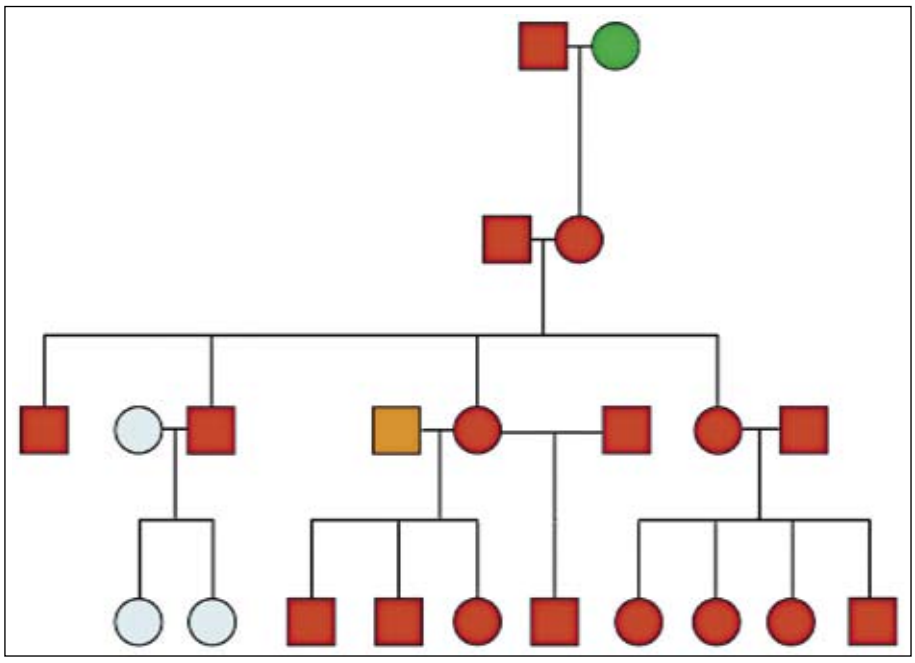

*Fig. 1: Formal genetics of ADHD. Genealogical tree. Family members affected by attention deficit / hyperactivity disorder ADHD are red-coloured.*

recruitment is standardised. Blood levels, conditions of medication, effectiveness and undesirable side-effects are documented at the course of the treatment (www.tdm-kjp.com).

**Eating disorders**

**Treatment of anorexia nervosa in children and adolescents (BMBF: ANDI):** The multicentre study compares a day clinic and an inpatient treatment to investigate if patients partly remaining in their family have a more favourable outcome.
**Katamnese study on anorexia nervosa (BMBF):** In this study those patients of the ANDI sample are reexamened 1,5 years after the first treatment period. Study on the long-term course of very early onset anorexia nervosa: Patients who were treated in the years 2002-2006 and were younger than 13 years old are re-examined.

**Dyslexia**
(A. Warnke)

Research (DFG) on aetiology focuses on correlates of the disorder on the genetic level and on the behavioural level (reading, spelling) accounting for associations with psychological and neurophysiologic endophenotypes. The DCDC2-gene which is important for the foetal brain development was identified to be associated with dyslexia. National and international cooperations have been established.

**Obsessive-compulsive disorder**
(T. Renner, A. Warnke)

In a multicentre project (DFG) family studies are conducted on OCD. Patients and their parents are assessed by standardized diagnostic methods before inclusion into molecular genetic association studies. The results indicate associations of genes involved in the serotonergic and dopaminergic neurotransmission with early onset OCD. Further, the present study design includes also the first prospective follow-up study of early onset OCD in Germany. The genetic research is strengthened by cooperation with international research networks on OCD and the Centre of Child and Adolescent Psychiatry of the University of Zürich, Switzerland (Prof. Dr. S. Walitza).

## Teaching

The obligatory lectures for students of human medicine comprising the subject matter on psychosomatics are conjointly held by the clinic for child and adolescent psychiatry (CAPP), the clinics for adult psychiatry (APP), neurology, general medicine and the department for medical psychology. Obligatory lectures and examinations also refer to study courses on psychology, education and special education (diplomas, state examinations). Further lessons and trainings refer e.g. to forensic child and adolescent psychiatry, developmental psychiatry and psychodiagnostics, neurophysiological assessment, postgraduate and research colloquia, open lectures on clinical issues 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). In 2009 the 2nd International Congress on ADHD" (Vienna) with over 1800 participants from over 70 countries was organised by the department.

## SELECTED PUBLICATIONS


*Walitza S, Kämpf K, Artamonov N, Romanos M, Gnana Oli R, Wirth S, Warnke A, Gerlach M, Stopper H (2009). No elevated genomic damage in children and adolescents with attention deficit/hyperactivity disorder after methylphenidate therapy. Toxicology Letters 184, 38-43.*

*Klampfl K, Taurines R, Preuss A, Burger R, Rothenhöfer S, Wewetzer Ch, Pfuhlmann B, Fegert J, Gerlach M, Mehler-Wex C (2010) Serum concentrations, therapeutic response and side effects in children and adolescents with impulsive-aggressive symptoms during risperidone therapy. Pharmacopsychiatry 43: 58-65*

*Reif A, Jacob CP, Rujescu D, Herterich S, Lang S, Gutknecht L, Baehne CG, Strobel A, Freitag CM, Giegling I, Romanos M, Hartmann A, Rösler M, Renner TJ, Fallgatter AJ, Retz W, Ehlis AC, Lesch KP (2009) Influence of functional variant of neuronal nitric oxide synthase on impulsive behaviors in humans. Arch Gen Psychiatry 66: 41-50.*

*Schimmelmann BG, Friedel S, Nguyen TT, Sauer S, Vogel CI, Konrad K, Wilhelm C, Sinzig J, Renner TJ, Romanos M, Palmason H, Dempfle A, Walitza S, Freitag C, Meyer J, Linder M, Schäfer H, Warnke A, Lesch KP, Herpertz-Dahlman B, Hinney A, Hebebrand J (2009). Exploring the genetic link between RLS and ADHD. J Psychiatr Res. 43(10), 941-945.*

*Schmitt J, Romanos M, Schmitt NM, Meurer M, Kirch W (2009), Atopic eczema and attention-deficit/hyperactivity disorder in a population-based sample of children and adolescents. JAMA 301(7), 724-726.*

# 3.25 Chair of Experimental Biomedicine - Vascular Medicine

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## Mission and Structure

The Chair of Experimental Biomedicine / Vascular Medicine was established in 2008 and is part of the Rudolf Virchow Center (RVZ), DFG Research Center for Experimental Biomedicine (see page 150), and is co-funded by the University Hospital Würzburg. It emerged from the Research group "Vascular Biology" that was jointly appointed at the RVZ (from 2002) and the Institute of Clinical Biochemistry (2004 – 2008; see page 86). The chair focuses on basic research in the field of cardiovascular diseases and is actively engaged in the education of Bachelor and Master students of Biomedicine. Most of the research projects are integrated into Collaborative Research Centers (SFB 688, page 140 and SFB 487 page 132) at the University of Würzburg.

## Major Research Interests

Our scientifc work focuses on the mechanisms of platelet and immune cell activation in physiological and pathological processes.
Damage of the endothelial layer of blood vessels results in rapid adhesion and activation of platelets at the site of injury, followed by coagulant activity and subsequently the formation of fibrin-rich thrombi that seal the wound. These processes are crucial for wound healing (hemostasis), however, in diseased vessels they can lead to complete occlusion and thus to ischemic infarction of vital organs. Our main scientific interest lies on the function of platelet surface receptors and their intracellular signaling pathways in hemostasis as well as thrombotic and inflammatory events. By use of genetically modified mouse lines that display defined defects in platelet receptors or signaling pathways we aim to investigate the molecular mechanisms that regulate platelet adhesion, activation and aggregation. These experiments serve as a basis for the development of novel anti-thrombotic therapeutical strategies which are subsequently tested using in vivo models of ischemic and inflammatory diseases. Furthermore, signal transduction processes in T-cells and macrophages in the context of autoimmune-inflammatory diseases are studied in vitro and in vivo.

### Mechanisms of $Ca^{2+}$-Signaling

Changes in the intracellular $Ca^{2+}$ concentration regulate fundamental processes in virtually all cell types. In platelets, the mechanisms of agonist-induced $Ca^{2+}$ entry have remained elusive. Recently, STIM1 has been identified as the $Ca^{2+}$ sensor in the endoplasmic reticulum (ER) which activates *store-operated calcium* (SOC) channels (Orai1) in T-cells, however, its general physiological relevance remained unclear. By use of different knock-out mice generated in our laboratory we could show that STIM1 represents the $Ca^{2+}$ sensor also in patelets which subsequently induces $Ca^{2+}$ entry by activating Orai1. Importantly, STIM1-, as well as Orai1-deficient mice were protect-

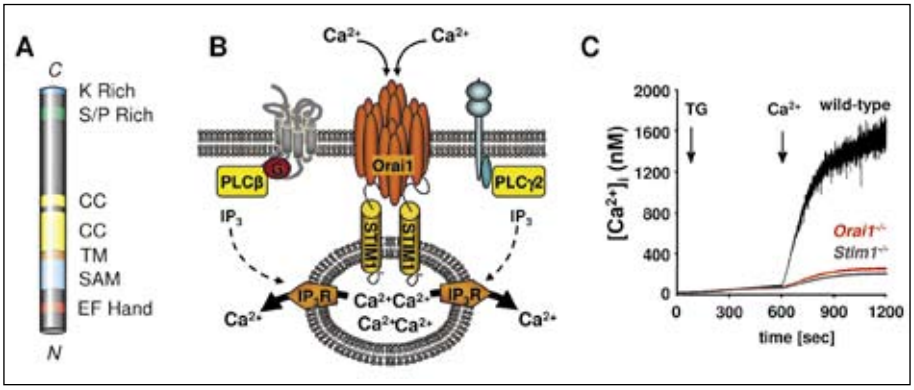


*Fig. 1: STIM1 and Orai1 are essential for store-operated Ca2+ entry (SOCE) in platelets. A. Structure of STIM1. SAM, sterile α-motif; TM, transmembrane domain; CC, coiled-coil domain. B. Platelet receptors induce activation of PLCβ and PLCγ leading to $Ca^{2+}$ store release through inositol-1,4,5-trisphosphate receptors ($IP_3$-R) in the endoplasmic reticulum (ER) membrane. The decrease in ER $Ca^{2+}$ concentration is detected by STIM1 which translocates to the plasma membrane and activates the SOC channel Orai1 that induces $Ca^{2+}$ influx into the cell. C. Measurement of store release and SOCE in platelets. The store content was estimated by addition of the SERCA inhibitor thapsigargin and SOCE was measured by subsequent addition of extracellular $Ca^{2+}$.*

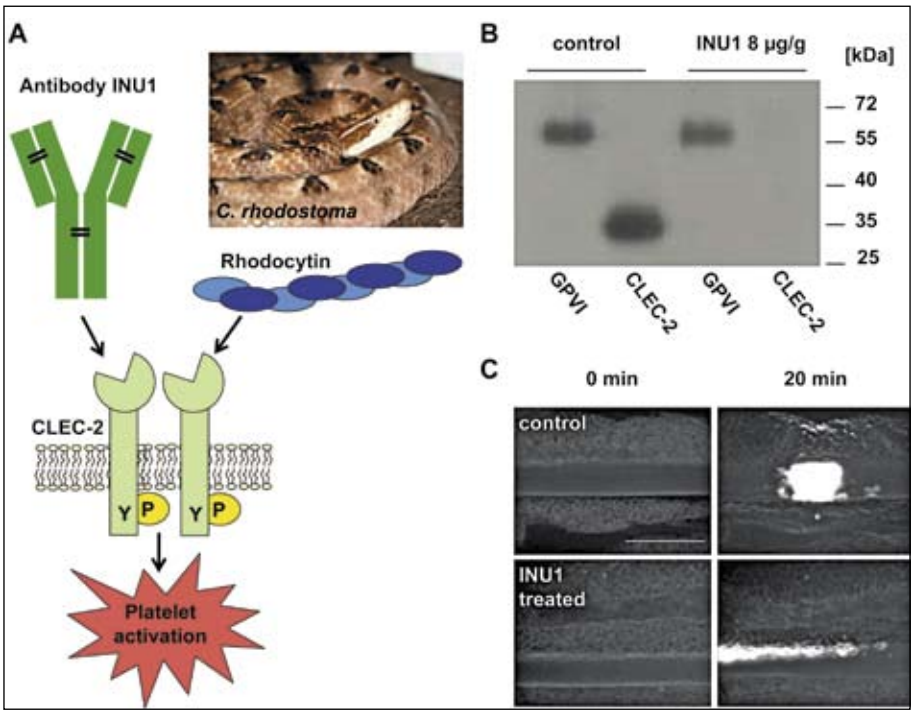


*Fig. 2. CLEC-2 is an essential platelet-activating receptor in hemostasis and thrombosis. A. Scheme of CLEC-2 activation in platelets by the snake venom toxin rhodocytin and INU1. B. Immunoprecipitation of CLEC-2 and GPVI from surface-biotinylated platelets from control and INU1-treated mice. C. Representative images of thrombus formation in $FeCl_3$ injured arterioles of control and CLEC-2-deficient mice. The asterisk indicates vessel occlusion.*

ed from arterial thrombosis and ischemic brain infarction whereas hemostasis was only slightly affected. Furthermore, it could be demonstrated that STIM1 is essential for Fcγ receptor activation and phagocytosis in macrophages and that STIM1 deficiency resulted in protection from IgG-mediated auto-inflammatory diseases.
By analyzing recently generated STIM2-deficient mice we were able to demonstrate for the first time that STIM2, but not STIM1, is essential for $Ca^{2+}$ entry in neurons and that STIM2 deficiency protected neurons from cell death under hypoxic conditions.

**Platelet membrane receptors and cytoskeletal dynamics in platelet function and formation**

The process of platelet activation, aggregation and thrombus formation is complex and involves the activation of various membrane receptors and their downstream signaling pathways. Due to their easy accessibility, platelet receptors represent attractive targets for the development of new antithrombotic therapy strategies. We have generated an antibody against CLEC-2, an activating receptor recently identified to be expressed in platelets. We could show that that treatment of mice with INU1 led to the loss of CLEC-2 from the platelet surface for several days and thus resulted in a knock-out-like phenotype. CLEC-2-deficient platelets displayed unaltered adhesion under flow *in vitro* and *in vivo*, however, subsequent platelet aggregation was markedly reduced. *In vivo*, CLEC-2 deficiency resulted in protection from arterial thrombosis and prolonged bleeding. Thus, CLEC-2 was identified as a new platelet-activating receptor in the growing thrombus.

Cytoskeletal rearrangements not only play a key role for receptor-mediated platelet activation, but also for the formation of new platelets from their precursor cells, the megakaryocytes (MK). By using different genetically modified mouse lines with MK- and platelet-specific deficiencies for regulatory proteins of the actin cytoskeleton we study the impact of cytoskeletal rearrangements for differentiation, maturation and platelet formation from MKs, as well as for platelet function.

## Teaching

We are engaged in the education of students in the Bachelor and Master Program in Biomedicine, where we offer lectures, seminars and practical lab courses. All doctoral students are members of the section "Biomedicine" of the "Graduate School of Life Sciences" at the University of Würzburg. The chair regularly participates in the organization of symposia and conferences for medical and natural scientists.

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*Braun, A., Gessner, J.E., Varga-Szabo, D., Syed, S.N., Konrad, S., Stegner, D., Vögtle, T., Schmidt, R.E., Nieswandt, B. (2009) STIM1 is essential for Fcgamma receptor activation and autoimmune inflammation. Blood 113(5), 1097-1104.*

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# 3.26 Chair of Tissue Engineering and Regenerative Medicine

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## Mission and Structure

The Chair Tissue Engineering und Regenerative Medicine has been established 2009 at the University of Würzburg. Since August it is headed by Prof. Heike Walles.

The discrepancy between necessary transplants and donor organs increases steadily. Additionally, there are problems like rejection reactions and lifelong immune suppressions. By means of tissue engineering, damaged, affected or even missing tissues and organs can be replaced by biological compatible and functional implants generated from primary cells. All concepts in Regenerative Medicine have the proliferation necessity of capable human cells in common. After isolation, the relevant primary cells will be increased by cell-culture techniques until sufficient cells are available for the culture on 3D scaffolds (matrix) or even for the cell therapeutically application.

New drugs and substances have to be tested before market authorization regarding their quality, safety and efficacy. For lack of equivalent alternative methods, animal experiments are an important standard instrument in drug research. Due to species-specific differences, however, animal experiments are not in every case suitable for the authorization of new substances or the adaptation of new therapies to humans. Therefore, Prof. Walles group has been increasingly engaged in the development of alternative human tissue models (test systems) that reflect the complex characteristics of the body and permit the investigation according to the ADMET criteria (absorption, distribution, metabolism, excretion and toxicity). These test systems are based on *in vitro* cultivated human primary cells. In order to ensure the functionality of these cells *in vitro*, culture conditions must be created that are similar to the natural microenvironment of the cell in the body. This requires, in addition to the sufficient supply of the cells, co-culture with other cell types as well as the provision of a suitable biomaterials as carrier structures.

The core competences of the chair are based on the following technologies: biomaterials, 3D co-culture of primary cells, and bioreactor technology. By applying these technologies human tissue models will be developed to study *in vitro* mechanisms of diseases and infections as a prerequisite for the development of regenerative therapies.

In addition to the establishment of the Chair Tissue Engineering and Regenerative Medicine a Fraunhofer Projektgruppe »Regenerative Technologies in Oncology« was founded at the Röntgenring 11. In proof of concept experiments Prof. Walles has shown, that it is possible to engineer human vascularised solid tumour tissue on the vascularised scaffold BioVaSc® (figure). In cooperation with different faculties of the University Würzburg vascularised human tumour models will be used to develop new methods for Diagnosis and individual therapies.

## Major Research Interests

**Bioreactor technology**
(T. Schwarz, H. Walles)

As a prerequisite of the *in vitro* generation of functional 3D human tissue models the construction of near-natural cellular and organ-like functional units will be established, based on (I) computer simulation of structural arrangements and interactions in human tissues and (II) the development of computer-controlled tissue specific bioreactor.

**Vascularised human tissue and disease models**
(A. Heymer, H. Walles)

In 2010, the EU project VascuBone (FP7-Gesundheitsprogramm) coordinated by Prof. Walles will start. The goal of VascuBone is to develop a “tool box” for bone regeneration, which on one hand fulfils basic requirements and on the other hand is freely combinable with what is needed in the respective patient’s situation. The tool box will include a variation of biocompatible biomaterials and cell types, FDA approved growth factors, biomaterial modification technologies, simulation and analytical tools. This tool box will be used to develop translational approaches for regenerative therapies of different types of bone defects, e.g. avascular necrosis of the hip (FHN), therapy of large defects in jaw and long bone.

**Biomaterial**
(A. Appelt, H. Walles)

Every implantation of alloplastic materials causes a reaction based on the material-tissue-interaction resulting in limited or annihilated implant efficiency. Spider silk could have an essential effect on the function of the medicinal implants. In an IZKF founded

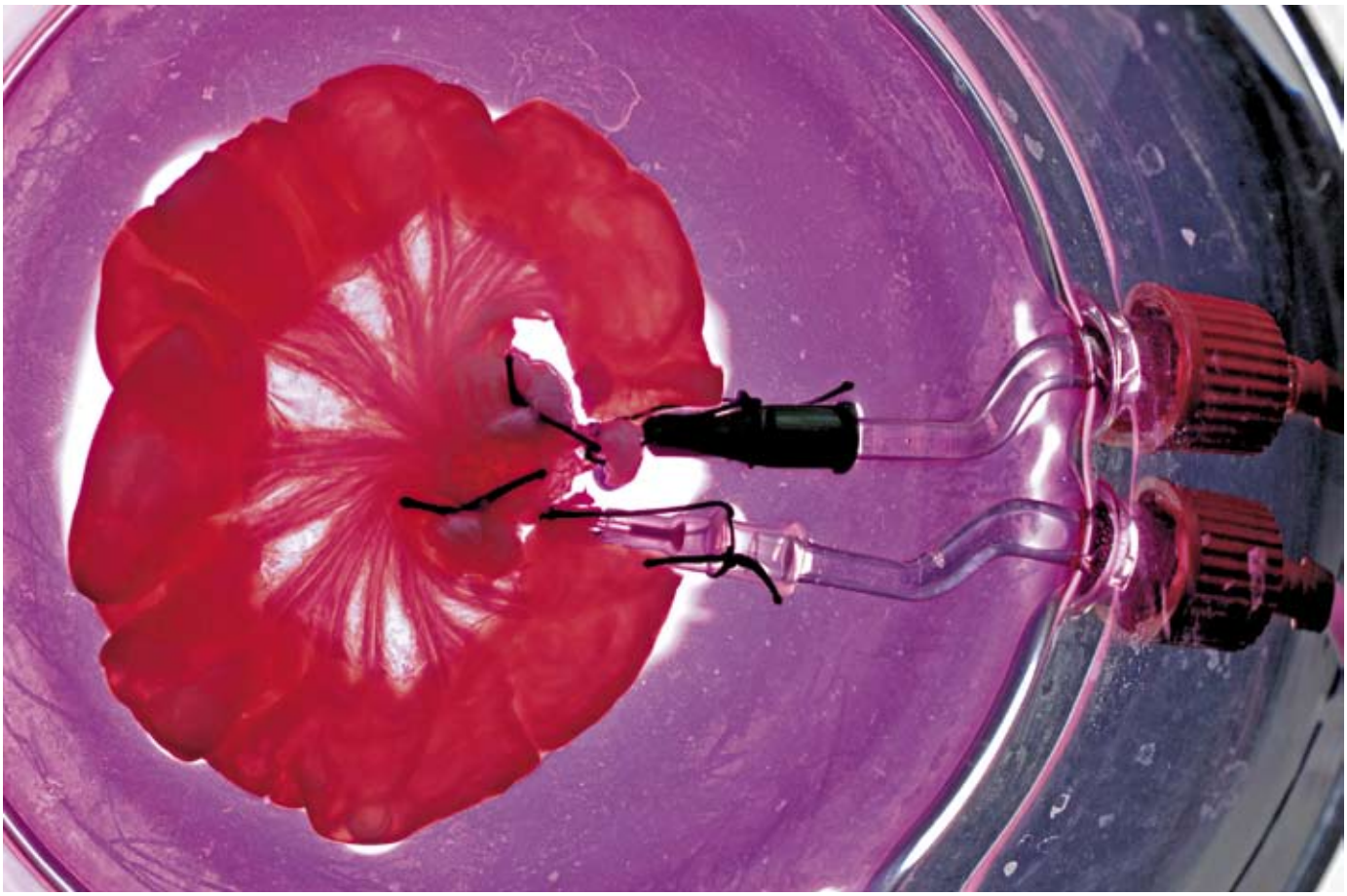

*Fig. 1: In this figure the biological vascularised scaffold BioVaSc® is shown. The BioVaSc® is used as matrix for the generation of autologous transplants, human tissue and tumour models.*

project *in vitro* und *in vivo* studies will be performed to enhance the biocompatibility of alloplastic implants by surface modification using recombinant spider silk.

**Transplants**
(A. Heymer, H. Walles)

Tears of the avascular zone of the meniscus do not heal, have to be removed surgically and inevitably lead to premature osteoarthritis of the knee joint. To date, implants as well as tissue engineering constructs for meniscus regeneration failed, due to their limited integration capacities. Therefore, we will generate vascularised neo-meniscus tissue by using a multi-stage approach. Vascularised fibrocartilage constructs will be generated by seeding collagen matrices and the BioVaSc with mesenchymal and endothelial progenitor cells. This project will be performed in cooperation with the König-Ludwig-Haus and the Muskuloskelettales Centrum Würzburg (MCW) founded by the IZKF.

**Project group »Regenerative Technologies in Oncology«**
(H. Walles)

Human vascularised tumour models will be established to develop new methods for individualised diagnosis and therapies.

## Teaching

The Degree program Technologie der Funktionswerkstoffe (Technology of functional materials) (TEC-FUN) is an interdisciplinary engineering study course. It includes education in the chemical synthesis of materials, physical characterisation of these materials and the development of biomaterials for clinical applications as medicinal product and in the field regenerative medicine. The program of study is organised by the faculty of Chemistry and Pharmacy, Physics, Medicine (Prof. Dr. Walles, Prof. Dr. Jakob), the technical college Würzburg-Schweinfurt, the Fraunhofer Institute for "Silicatforschung", the "Zentrum angewandte Energieforschung (ZAE)", and the "Süddeutschen Kunststoffzentrum" (SKZ).

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*Heymer A, Haddad D, Weber M, Gbureck U, Jakob PM, Eulert J, Nöth U (2008) Iron oxide labelling of human mesenchymal stem cells in collagen hydrogels for articular cartilage repair. Biomaterials. 29,1473-1483.*

# 4 Dental Hospital

# 4.1 Introduction

There are four separate departments or clinics, which are comprised under the name of 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. Dipl.-Ing. Ernst-Jürgen Richter)
- Department of Orthodontics
  (Head: Professor Dr. Angelika Stellzig-Eisenhauer)

Part of our hospital is furthermore the Department for Functional Materials in Medicine and Dentistry (acting Head: Professor Dr. Bernd Klaiber) and the Division of Periodontology (Head: Professor Dr. Ulrich Schlagenhauf)

All the different heads of the departments form the Board of Directors of the "University Dental Hospital", headed by the acting chairman (at present: Professor Dr. Dipl-Ing. Ernst-Jürgen Richter).

At this Hospital there are scarcely 600 students of dental medicine, approximately half of them working in the clinical section. As far as formation and research is concerned, as well as medical specialist care of sick people we have 224 positions at our disposal.

By means of Extra-budgetary Funds and half-time employment however, the number of employees is around 300, seventy of which are scientists.

Apart from the instruction of students, research and care for sick persons our hospital is occupied with the post-graduate education of dentists, as well as with further training for medical and dental specialists. In 2008 about 26600 persons got outpatient treatment and about 1250 were treated as in-patients.

Professor Dr. Dipl-Ing. Ernst-Jürgen Richter
(acting Chairman)

# 4.2 Department of Orthodontics

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## General Information

In the Department of Orthodontics under the directorship of Professor Stellzig-Eisenhauer, nine research assistants work in patient care, research and student teaching.

Patient care in the Department of Orthodontics covers the whole range of orthodontic anomalies. These include in childhood and adolescence (1) the prevention of misalignment of teeth and jaws, (2) the treatment of malpositions of the jaws by wear and control of endogenous growth and (3) the correction of misaligned teeth. A special focus of the Department of Orthodontics is the treatment of adult patients using specific fixed treatment techniques based on the particular periodontal and prosthetic situation.

In addition, patient care in the Department of Orthodontics is characterized by interdisciplinary cooperation with specialties associated with dentistry. In particular, there is a close clinical collaboration with the Oral, Maxillary and Plastic Facial Surgery in the treatment of patients with complex craniofacial deformities (cleft lip and palate, syndromes), pronounced malocclusions (dysgnathia) and condylar neck fractures.

Reorientation of the teeth is performed in collaboration with Dental Prosthetics and Restorative Dentistry/Periodontology. This therapeutic measure is indicated as preparation prior to restorative rehabilitation of the entire stomatognathic system.

In the Department of Orthodontics, around 1500 patients from all age groups are treated annually, with check-ups every 3 to 6 weeks. Approximately 600 patients a year attend the department for an orthodontic consultation.

## Major Research Interests

Three-dimensional stereophotogrammetric diagnostics of the skull and progress analysis in children with positional plagiocephaly or sagittal suture synostosis taking into account psychomotor development.

**Establishing and 3D evaluation of a non-invasive dynamic treatment method by means of individually adjusted head orthosis.**
(P. Meyer-Marcotty (Orthodontics), H. Böhm (Oral, Maxillary and Plastic Facial Surgery), T. Schweitzer (Neurosurgery)

In a clinical research project involving the Department of Neurosurgery, the Department of Oral, Maxillary and Plastic Facial Surgery and the Department of Orthodontics, a valid, non-invasive method is to be developed in order to record and analyze the form and development of children's skulls three-dimensionally. The results are expected to help resolve unanswered questions about the treatment of children with cranial deformities (with/without surgery or with/without helmet therapy).

The contribution of the Department of Orthodontics is: Longitudinal 3D data acquisition from the neurocranium and viscerocranium of healthy children and children with cranial deformities.

To date there are no standardized longitudinally recorded 3D standard values for babies' cranial shape. The objective is to build up a database of three-dimensional, morphometric, longitudinally recorded data from baby and infant skulls with and without premature sagittal suture synostosis.

**Recording prespeech or early speech development in children with and without cranial deformities**
(K. Wermke in cooperation with the Pediatric Clinic and the Department of Educational Psychology )

**Development of a 3D soft tissue analysis in orthodontics**
(J. Kochel, P. Meyer-Marcotty, A. Stellzig-Eisenhauer)

In a pilot study by the Department of Orthodontics in collaboration with the Institute

*Fig. 1: Visualization of 3d-Data.*

of Optics, Information and Photonics of Erlangen-Nürnberg University, three-dimensional soft tissue imaging was successfully integrated into orthodontic diagnostics and treatment (see 2008 Research Report).

The aim of further research projects is: to expand conventional two-dimensional orthodontic imaging of the facial soft tissues to include 3D analysis

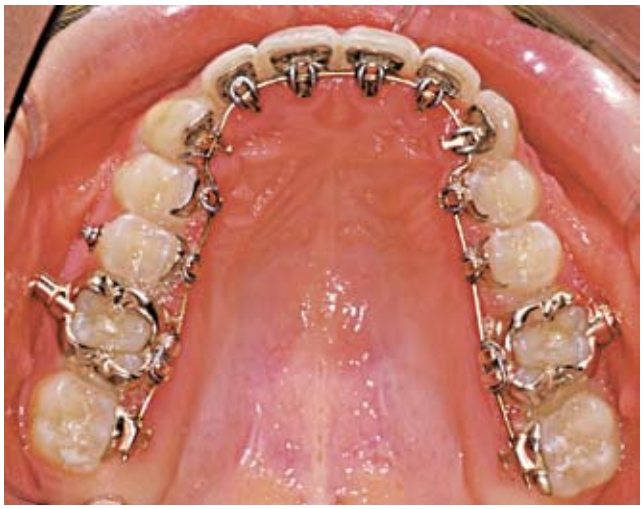

*Fig. 2: Lingual fixed appliance for the upper jaw.*

**Primary Failure of Eruption (PFE) – clinical and molecular genetic analysis**
(A. Stellzig-Eisenhauer in cooperation with the Institute of Human Genetics)

The molecular basis of a disturbance in the eruption mechanism of primary, non-ankylosed teeth is so far unknown. Three heterozygous mutations in the PTHR1 gene in diseased patients were first described in an interdisciplinary clinical and molecular genetic study. In a proposed future study in collaboration with the Physiology Institute and the Department of Oral, Maxillary and Plastic Facial Surgery, it is planned to analyze the underlying pathogenesis of failure of eruption.

## Teaching

The orthodontic courses aim to convey knowledge about the nature, extent and pathogenesis of positional defects of the teeth and jaws and to present possible preventive methods and orthodontic treatment options.

The lecture “Introduction to Orthodontics” is intended to provide an overview of the nature, extent and pathogenesis of various jaw anomalies.

The principal lecture “Orthodontics I and II” focuses on preparing students to perform treatment on patients.

The “Course on Orthodontic Technology” aims to provide knowledge about the type, indications, mode of action and fabrication of orthodontic appliances.

The “Course on Orthodontic Treatment I and II” explores theoretical knowledge in depth in small groups and accompanying seminars. In addition, students draw up diagnostic records on patients and learn to use and check therapeutic equipment.

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*Meyer-Marcotty P, Gerdes ABM, Stellzig-Eisenhauer A, Alpers GW. Biased to asymmetry – face perception of adults with cleft lip and palate - an eye tracking study. Cleft Palate Craniofac J 2009; accepted.*

*Kochel J, Meyer-Marcotty P, Kochel M, Stellzig-Eisenhauer A. 3D-soft tissue analysis – Part 1: sagittal parameters. J Orofac Orthop 71:40-52 ,2010.*

# 4.3 Department of Functional Materials in Medicine and Dentistry

CONTACT DETAILS

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## Mission and Structure

Biologists, chemists, physicists and material scientists in cooperation with clinicians are engaged in the Department of 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 of material properties depending on the location in the body. Material properties are adjusted by modification of the bulk and surface of materials to influence the interface to the biological environment. The workings were funded in the past years by the „Deutsche Forschungsgemeinschaft“ with two projects as individual grants.

## Major Research Interests

### Surface modification of functional materials

The biocompatibility of a functional material emanates from the surface and is influenced by its composition, its topography, and its electric and electronic properties. Current work is focused on the surface modification of refractory metal implants with low-crystalline calcium and magnesium phosphate layers, produced by electrochemical deposition. One aim of these studies is the development of novel multi-phase coatings combining antimicrobial with biocompatible properties, thus lowering the risk of inflammation after surgery as well as supporting the ingrowth of the implant. Another surface modification is based on anodic oxidation of the metal surface in fluoride-containing electrolytes leading to tube-like structures, which may be utilized as reservoirs for the inclusion of antibiotics.

### Rapid-Prototyping of patient specific implants

The combination of reactive cement systems with 3D powder printing allows the fabrication of patient specific implants and porous scaffolds for tissue regeneration from bioactive and degradable bone replacement materials, mainly calcium and magnesium phosphates. The scaffolds made by this method consist of a micro porous structure, which contributes to the bioactivity. Furthermore, the printing method at room temperature offers the possibility to introduce organic modifications into the material. Antibiotics or growth factors can be printed directly into the structure, thus enabling the controlled release of pharmacologically effective doses at the application site without systemic side effects. Besides the application of protein based growth factors, the use of bioactive metal ions like $Sr^{2+}$ or $Cu^{2+}$ is being investigated, which would have the advantage of better availability and manageability.

### Biological testing of materials

One crucial precondition for a good tissue attachment to the implant material is an optimal contact between the biological system and the material surface. Improvements of this contact can be achieved either by the modification of the metallic implant surfaces or by the application of calcium or magnesium phosphate cements, which are similar to biological minerals and thus can be converted in the body and replaced by natural material. The differentiation of osteoclasts on the surfaces and the degradation of those is being analyzed by means of cell vitality and proliferation rate as well as tissue specific protein expression and distribution in the cell. Also the interaction of cells of different origin (fibroblasts, osteoblasts etc.) with variably modified surfaces and cements is investigated. Antimicrobial implant surfaces are being developed to avoid infections, which still cause problems during implant osseointegration and wound healing. Here an important role is played by antimicrobial metal ions like $Ag^{+}$ as well as by calcium hydroxide compounds or antibiotic loaded cements. These materials, which were developed by the department, showed significant bactericidity combined with good tolerance by eukaryotic culture cells.

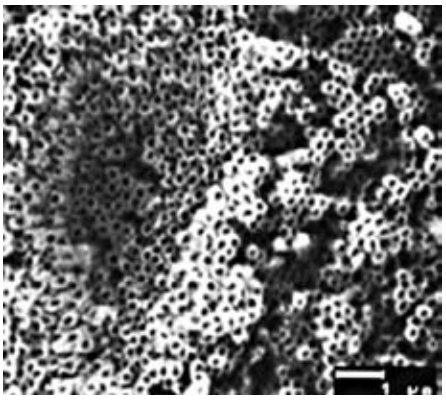

*Fig. 1: Electron-microscopical image of a titanium surface after anodisation in an electrolyte based on ethylen glycol. The nanotubes consist of titanium dioxide and have a diameter of about 160 nm.*

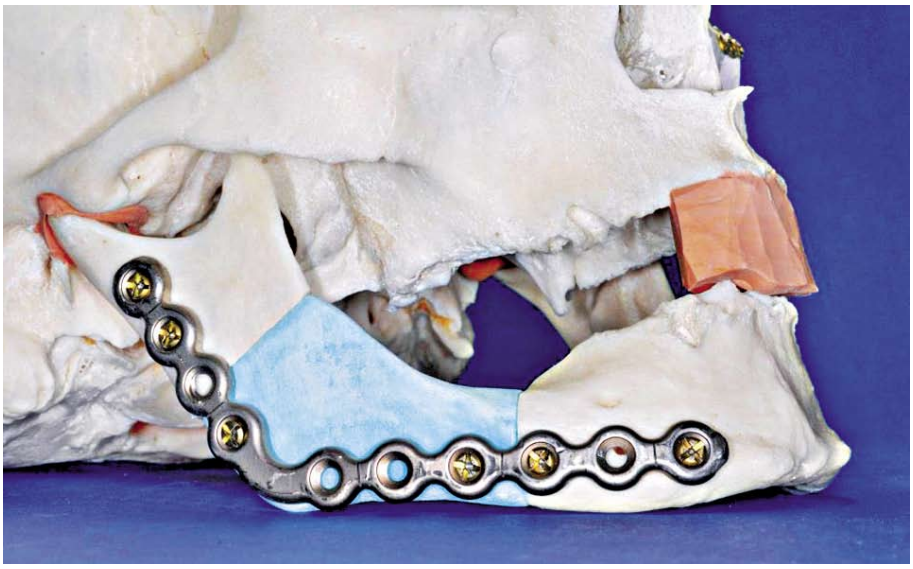

*Fig. 2: Calcium phosphate based mandibular implant (blue) made by 3D powder printing.*

## Teaching

The teaching activity contains lessons about functional materials for clinical applications and their interaction mechanisms with the biological system, courses about quality management systems and risk analysis of medical devices, medical application of x-rays, as well as practical measuring techniques for material 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“ and with the faculty for Chemistry and Pharmacy for students of „Technologie der Funktionswerkstoffe“.

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*E. Vorndran, M. Klarner, U. Klammert, L.M. Grover, S. Patel, J.E. Barralet, U. Gbureck: 3D Powder Printing of ß-Tricalcium Phosphate Ceramics using different Strategies, Advanced Biomaterials 2008; 10: B67-B71.*

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# 4.4 Department of Oral and Maxillofacial Surgery

CONTACT DETAILS

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## Mission and Structure

The clinic has got 20 permanent staff positions and a further half post which is funded externally. The clinic provides 40 permanent beds and covers the whole spectrum of oral and maxillofacial plastic surgery. Beside the in-patient care (about 1.200 patients each year), approximately 15.000 patients are treated in the outpatient clinic. Further more the clinic provides a comprehensive consultant support, particularly for the paediatric clinic (craniofacial dysplasia and cleft-lip-palate patients) 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:

- tumors of the head and neck (treatment and functional and aesthetical reconstruction including microsurgical tissue transfer)
- trauma of jaws and face
- craniofacial dysplasia (orthognathic malformations, clefts of lip and palate, craniosynostoses)
- plastic-aesthetic reconstruction
- dental implants including bone augmentation
- oral surgery (e.g. cysts, abscesses, osteomyelitis)
- diseases of salivary glands
- TMJ disorders
- atypical facial pain and nerve lesions

## 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 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)

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. New 3D-Methods like cone beam computed tomography and 3D-surface imaging are examined to predict the outcome of aesthetic and orthognathic surgery.

**Clinical research team for bisphosphonate-associated necrosis of the jaw**
(A. Kübler, T. Reuther, T. Bittner)

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 co-cultures (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. These implants are examined to be used as individual Skull substitutes. Furthermore different agents (e.g. growing factors) are tested to enhance their properties. 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.

**Three dimensional stereophotogrammetric diagnosis and treatment evaluation of children with craniofacial anomalies**
(H. Böhm, in cooperation with P. Meyer-Marcotty (department of orthodontics) T. Schweitzer (department of neurosurgery)

This study examines children with premature closure of the cranial sutures or positional plagiocephaly.
The aim of this project is: First, to establish a three dimensional stereophotogrammetry as a non invasive imaging technique in diagnostics and follow up of infantile skull deformities; second, comparing different therapeutical strategies (surgical or conservative approach in children with a sagittal craniosynostosis, and molding therapy in positional plagiocephaly (with an individual CAD/CAM manufactured orthesis) versus positioning and physiotherapy alone) in regard to morphologic skull changes and neuropsychological development. Documentation and analysis of early language skills as well as individual evolution of neuropsychology parameters are monitored at different defined time-points. Predictive parameters for counseling and disease progress under different therapeutical strategies will be defined.

## 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.

SELECTED PUBLICATIONS


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*Klammert U, Reuther T, Blank M, Reske I, Barralet JE, Grover LM, Kübler AC, Gbureck U. Phase composition, mechanical performance and in vitro biocompatibility of hydraulic setting calcium magnesium phosphate cement. Acta Biomater 2010, 6:1529-1535.*

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*Müller-Richter UDA, Dowejko A, Driemel O, Reuther T, Reichert TE, Kübler AC Impact of MAGE-A antigens on taxane response in oral squamous cell carcinoma Oncology Letters 2009 [in press].*

*Müller-Richter UDA, Dowejko A, Peters S, Rauthe S, Reuther T, Gattenlöhner S, Reichert TE, Driemel O, Kübler AC. MAGE-A antigens in patients with primary oral squamous cell carcinoma Clinical Oral Investigations [EPub 2009].*

# 4.5 Department of Prosthodontics

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## Mission and Structure

The Department of Prosthodontics (currently 46 employees) is one of five departments in the Dental University Clinic. Its main mission is to provide theoretical and hands-on education to students in material sciences as well as medial fields. The ambulatory care comprises all fields with a main focus on prosthetic-restorative dentistry. Classic restorations like crowns, bridges or removables are supported as are current techniques, such as metal-free-, implant-, perioprosthodontics and facial prostheses, in addition to which treatment of cranio-mandibular dysfunctions and myofacial pain syndromes is offered.

## Major Research Interests

Clinical field studies and experimental research in the field of dental implantology are prominent research topics, spanning evaluation of temporary index-implants as stabilizers for surgical guides and biodynamic analysis of implant superstructure loading. For 12 years, research has also been focussed on the concept of „strategic“ and angulated implants in conjunction with removable dentures.

The „Wuerzburg Post“, which was developed by the Department of Prosthodontics and has been commercially available since 2006, is undergoing clinical testing as part of a long-term study. Since May of 2005 almost 150 of these cores have been placed in fractured teeth. At that point the survival rate amounted to over 90%, underlining the competitiveness of this system versus „classic“ post-and-cores.

On the basis of this concept‘s good results a successor version is under development, offering a broader spectrum of indications at improved usability and aesthetics, grace to new materials.

A cooperation with other faculties (Department of Experimental Physics V) and an industry-sponsored (Prokuro GmbH, Degu-Dent-Dentsply) workgroup are working on implementation of magnetic resonance tomography into dental medicine (dMRT). The long-term goal is to eliminate diagnostic routines which make use of X-rays from dentistry. For example, information about anatomy of teeth and the alveolar processus as well as the amount and density of alveolar bone can be used in surgical planning, while precise information on size and localization of caries is of importance for conserving therapy.

In regards to therapy of cranio-mandibular dysfunctions special sampling methods were developed which, for the first time, enable real-time visualization of the temporomandibular joint under different load situations (Figure 1).

On the other hand, dMRT data can be used to fabricate fixed partial dentures, eliminating the need for displeasing and error-prone impressions of prepared teeth. For this purpose, a proprietary HF-receiver coil was conceived and developed which allows high resolution images of prepared teeth. The proof of principle has been provided by a bridge which was modelled and milled (CAD/CAM) based on dMRT data, which could be permanently placed (Figure 2).

## Teaching

The premed curriculum comprises two classes (technical propaedeutics, 66 students and Phantom I, 65 students). The six week Phantom II course (128 students)

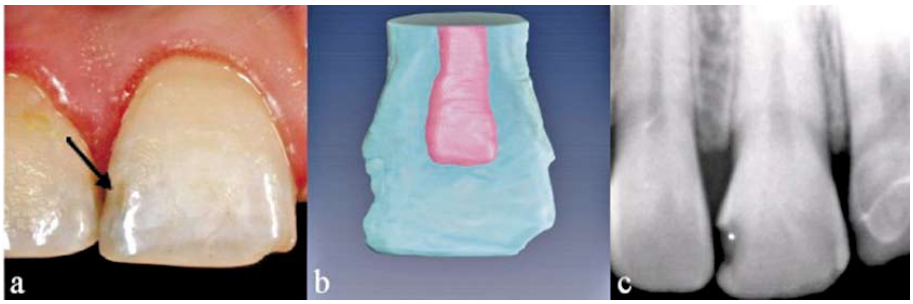


*Fig. 1: a: Clinical situation: there is a visible discoloration on the upper right incisor which suggest the presence of a carious lesion (arrow). b: dMRT image of the same tooth. The significant site of the lesion is visible, as is the dental pulp (pink). c: X-ray of said tooth: By contrast, the lesion is more difficult to make out.*

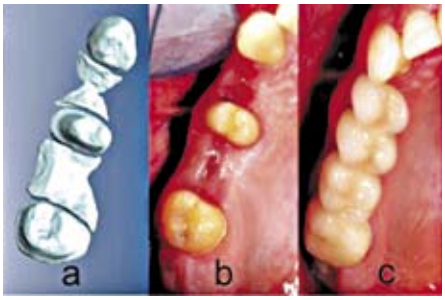


*Fig. 2: a: Segmented dMRT dataset of two prepared upper teeth as well as the adjacent canine. b: intra-oral image of the clinical situation. c: definitively placed restoration which was modelled and manufactured based on the dMRT dataset.*

takes place annually during the summer offterm. A total of 257 students participated in the medical courses of 2009, aided by 8 instructional videos, 4 written instructional booklets and two scripts for material sciences. Material science classes span two semesters. All materials are also made available as digital downloads. As of summer 2010, an eLearning project will be instituted in cooperation with the VHB.

Two clinical courses are being offered as part of the medical curriculum for fourth and fifth year students, during which the trainees treat own patients under close supervision of professors and assistant doctors. 56 students are trained per class. The lecture on prosthodontics covers general fields of prosthetic dentistry, wherease the lecture on special prosthodontics aims at CMD and geriatric dentistry. Both lectures span two semesters.

On average, each student performs three restorations which are subject to individual grades. Accordingly, there were 672 restorations in both courses and 448 in the 10-day biannual state examinations which had to be monitored and graded. In each course there are two written tests, summing up to roughly 300 corrections and gradings!

## SELECTED PUBLICATIONS

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*Tymofiyeva O, Rottner K, Jakob PM, Richter EJ, Proff P.: Three-dimensional localization of impacted teeth using magnetic resonance imaging. Clin Oral Investig. 2009 Apr 28. [Epub ahead of print].*

*Boldt J., Richter E.-J., Schilling K.-U. et al.: Failure analysis of a new post-and-core restoration system using the finite element method. Biomed Tech (Berl) 2008, 53 (5): 251-4.*

*Proff P., Bayerlein T., Rottner K. et al.: Effect of bone conditioning on primary stability of FRIALIT-2 implants. Clin Oral Implants Res 2008, 19 (1): 42-7.*

# 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 working 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.

## 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 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, ten-

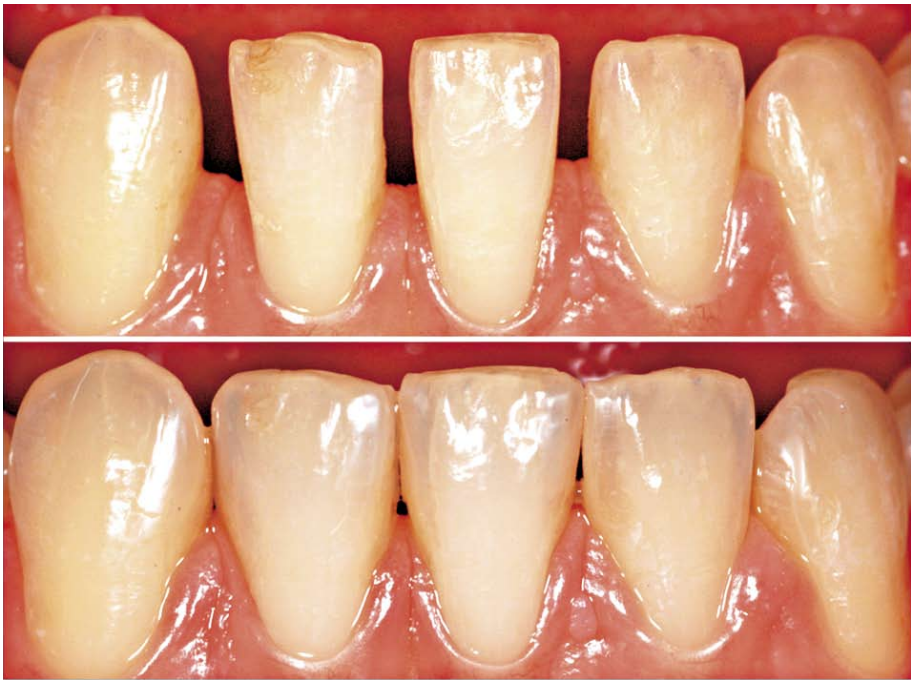

*Fig.1: Uniform interproximal spaces following traumatic loss of one lower incisor and subsequent orthodontic treatment (above). By non-invasive procedures the spaces could be closed and a natural appearance has been restored (below).*

sile 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.

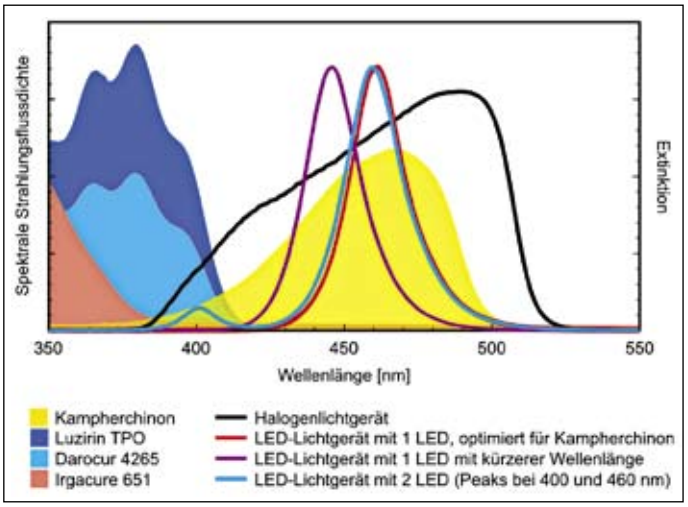


*Fig. 2: Spectral absorbance of photo-initiators compared to the spectral irradiance of different light curing units.*

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, endodontic treatments, performed during the students' courses 10 years ago, are clinically and radiographically examined. An investigation of this kind is nationwide unique so far. Moreover, a newly developed rubber dam system (appliance for moisture control during operative procedures) was compared to the conventional one. The general acceptance among both clinicians and patients was good, which is in contrast to most of the published data up to now.

Another clinical study investigates a further developed composite, which will be mainly used in the anterior region. The duration of this study will be four years.

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*Feierabend S, Klaiber B (2008) Atypische Odontalgie und protrahierte psychische Reaktion auf diese Erkrankung nach inkonsequenter zahnärztlicher Behandlung. Quintessenz 59(3):289-297.*

*Eichelsbacher F, Denner W, Klaiber B, Schlagenhauf U (2009) Periodontal status of teeth with crown-root fractures: results two years after adhesive fragment reattachement. J Clin Periodontol 36(10): 905-911.*

*Klaiber B (2009) Inlays und Teilkronen aus Gold – wann noch und dann Wie? Quintessenz 60(10):1163-1174.*

*Feierabend S, Gerhardt-Szep S (2010) Evidence based Dentistry – Tipps für die Praxis. Fall 1: Avulsion bleibender Zähne. Dtsch Zahnärztl Z 65(1): 94-98.*

# 4.6.1 Division of Periodontology

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## Mission and Structure

Besides Prof. Schlagenhauf the staff of the division comprises further four dentists and 3 dental assistents. The Division of Periodontology forms part of the Department of Conservative Dentistry and Periodontology and is a clinical center for referrals of patients suffering from severe periodontal disease beyond the scope of an average 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 division to referring dentists and the public in the region of Unterfranken and beyond. 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 surgical interventions for the minimally invasive correction or regeneration of periodontal lesion belongs to the clinical standard procedures provided by the division.

## Major Research Interests

The main research projects of the Division. 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.

**Adjunctive use of systemic antibiotics in the therapy of chronic and aggressive periodontal disease**
(U. Schlagenhauf, Y. Jockel, M. Bechtold)

In preceding clinical trials realized in collaboration with the Institute of Hygiene and Microbiology the adjunctive use of systemic antibiotics subsequent to the mechanical removal of microbial biofilms for exposed root surfaces resulted in a marked enhancement of periodontal healing even in severly compromised teeth. The extended periodontal healing made it possible to maintain severly compromised teeth in function long-term, which, previously had to be removed already at the beginning of the initial phase of periodontal therapy. In order to further verify the scientific validity of this tooth-saving therapy concept, the Division. of Periodontology participates in a multicenter clinical trial supported by the Deutsche Forschungsgemeinschaft (DFG) and is contributing more than 100 own study patients..

**Periodontal diseases and cardiovascular health**
(Y. Jockel, J. Baulmann, G. Ertl, U. Schlagenhauf)

Recent investigations performed in collaboration with the Clinic for Internal Medicine I revealed, that patientes suffering from peri-

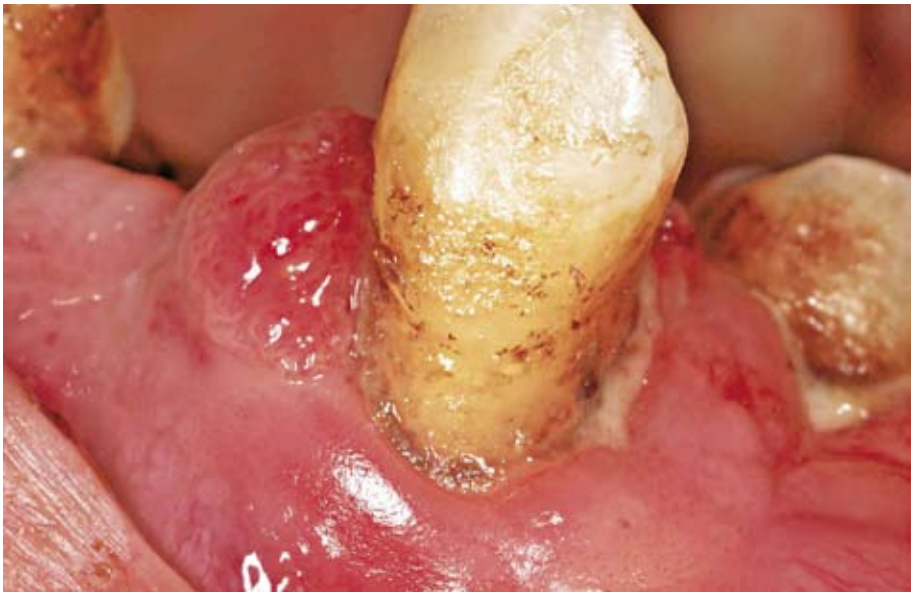

*Fig. 1: Advanced chronic periodontitis in a patient suffering from angiomatosis Rendu-Osler.*

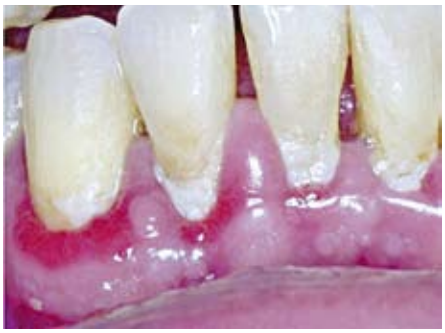

*Fig. 2: Pronounced plaque-induced gingival inflammation in a patient with insufficiently controlled diabetes type I.*

odontal disease frequently display a significantly elevated vascular augmentation when compared to age-matched periodontally healthy controls. Whether successful periodontal therapy has a significant impact on the status of cardivovascular health is subject to an ongoing clinical trial which also is realized in collaboration with the Clinic for Internal Medicine I and supported by the DFG.

**Socket preservation after tooth extraction**
(S. Fickl, U. Schlagenhauf)

Subsequent to the extraction of a tooth the neighbouring alveolar bone tends to be resorbed to an extent, which frequently endangers a functionally and esthetically inconspicuous rehabilitation of the defect by a fixed bridge or a dental implant without additional surgical augmentative interventions. Preliminary clinical studies proved that a preferably tight seal of the alveolar bone defect by the placement of a mucosal connective tissue graft significantly reduced the exent of aveolar bone resorption. The identification of further co-factors is subject of current investigations.

## Teaching

Dental undergraduate training comprises the clinically most relevant aspects of periodontal diagnosis and therapy. Subsequent to the intensive teaching of the basic principles of periodontology firstly in dummy heads and subsequently in real patients nonsurgical minimally invasive periodontal therapy procedures are instructed and trained under the close supervision of experienced clinicians. The basic facts of periodontal surgergy are also demonstrated and practically instructed in a pig jaw model. Junior staff members of the Division of Periodontology are given the opportunity to acquire a formal postgraduate specialization in periodontology by following a formal 3 year postgraduate training program according to the guidelines of the German Society of Periodontology.

SELECTED PUBLICATIONS


*Eichelsbacher, F., Denner, W., Klaiber, B. & Schlagenhauf, U. (2009). Periodontal status of teeth with crown-root fractures: results two years after adhesive fragment reattachment. J Clin Periodontol, 36, 905-911.*

*Fickl, S. Zuhr, O. Wachtel, H. Kebschull, M. & Hürzeler, M. B. (2009). Hard tissue alterations after socket preservation with additional buccal overbuilding: a study in the beagle dog. J Clin Periodontol 36, 898-904.*

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*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.*

# 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), four Transregios, six 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

With the year 2009, the SFB 479 completed its life cycle of four three year funding periods. During those 12 years, microbiologists, infection biologists and immunologists have intensively interacted to create a truly interdisciplinary network and research programme. Boundaries between faculties played no role, and the recruitment of new professors in the faculties of biology and medicine was used to further strengthen our infection biology focus. Participation of the juniour research groups of the Center for Research on Infectious Diseases was an important tool to promote young researchers within the SFB, and with the inclusion of the Medical Clinic II, a firm bridge from basic to clinical research was established.

## Major Research Interests

Over the 12 years of DFG funding, the researchers of the SFB 479 have been 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. Accordingly, the SFB was structured into three project areas: the variability of pathogens (A), pathomechanisms in the interaction between microbe and host cells (B), and immune response to and immunomodulation by microbial infections (C).

It will be the specific aspects of microbial adaptation to the host environment, and of the study and instrumentalisation of the host's immune response to pathogens which will provide the basis for future research networks.

## Teaching

The Ph.D. students of the SFB 479 were associated with the various training programmes of the class "Infection and Immunity" within the Graduate School for Life Sciences. These are the Graduate College "Immunomodulation" (GRK 520) (now continued as Graduate Training Programme "Immunomodulation"), the graduate programme of the Center for Research on Infectious Diseases, and the International Research Training Group (IRTG 1522) "HIV and Related Diseases in Southern Africa", thereby providing a structured scientific education.

### Symposia

The biannual symposia held by the SFB throughout its twelve year life cycle culminated in a final international symposium in July 2009 with the heading "Living with Pathogens: Never Lose Control". This meeting provided an optimal opportunity to summarize the SFB's achievements, and to discuss new roads to be taken with our international guests.

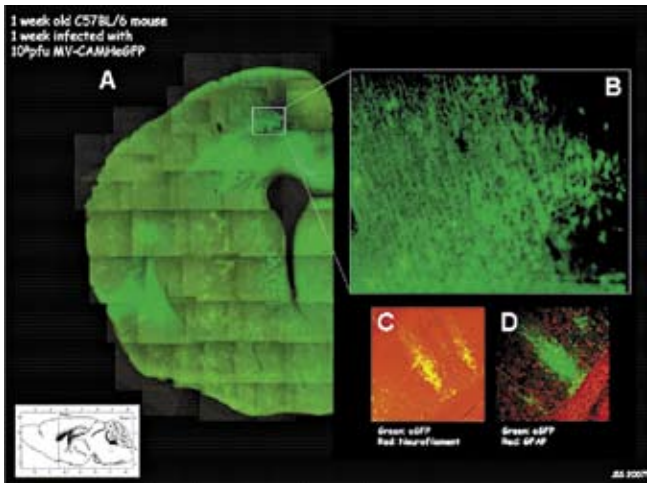


*Fig. 1: GFP expression in a brain of a 2 week-old mouse infected with recombinant measles virus MV-eGFP-CAMH. The overview (coronal section) of the left hemisphere (A), enlargement (B), and GFP/marker colocalizations with neurofilament in neurons (red) (C) and absence of colocalization with GFAP in astrocytes (red) (D) demonstrates the exclusive infection of neurons. (TP C11 Jürgen Schneider-Schaulies).*

# 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 fourth period of funding. The SFB 487 consists of 18 research groups from the faculties of medicine and biology. The research is focussed on molecular mechanisms of function and regulation of membrane proteins 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 topics 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 (see for example Fig.1). 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/Hoffmann (Pharmacology): Activation, desensitization and internalization of G-protein coupled receptors

A4 Koepsell/Gorboulev (Anatomy and Cell Biology I): Structure-function-relationships of substrate recognition and transport mechanism of polyspecific transporters of the SLC22 family

A5 Benz (Biotechnology): Mechanism and pharmacology of toxin transport across model membranes

A9 Hedrich (Molecular Plant Physiology and Biophysics): Regulation and Targeting of Arabidopsis Tandem-Pore-$K^+$ (TPK) channels

A10 Bünemann (Pharmacology): Kinetics and structural aspects of G-protein coupled signal transduction

A12 Nagel (Molecular Plant Physiology and Biophysics): Characterization and mutagenesis of channelrhodopsins

**Research area B: Proteins with a single transmembrane domain**

B2 Müller (Molecular Plant Physiology and Biophysics): Affinity, specificity and promiscuity of cytokine and BMP receptors

B3 Schartl/Meierjohann (Physiological

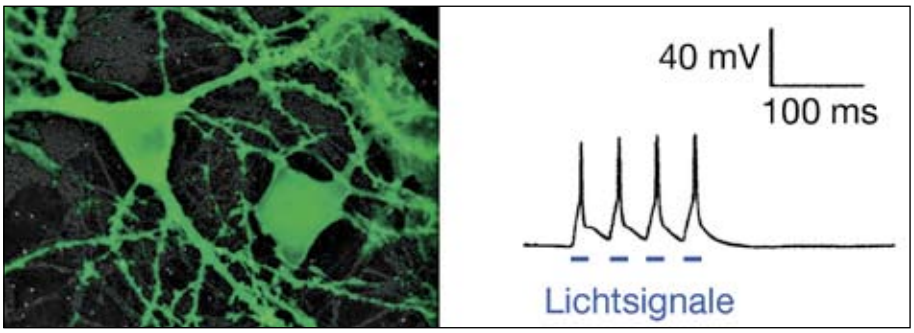


*Fig. 1: Generation of neuronal activity by light. A fluorescence labelled cation channel was expressed in neurons of rat brain (left). A member of SFB 487 detected that this channel (channelrhodopsin) opens after illumination. Short applications of light impulses lead to short depolarization signals in neurons (right).*

Chemistry I): Protein interactions at the oncogenic growth factor receptor Xmrk

B5 Waschke/Drenckhahn (Anatomy and Cell Biology II): Modulation of the Cadherin-Binding

B7 Wajant (Molecular Internal Medicine): Mechanisms of TNF-receptor-activation

B8 Kuhn (Institute for Physiology) Cardiac function and dysfunction of the guanylyl cyclase-A receptor for ANP: lessons from genetic mouse models

B9 Hermanns (Rudolf-Virchow-Zentrum, DFG Research Center for Experimental Biomedicine): „Structural requirements for cytokine receptor-mediated activation of the JAK/STAT and MAPK signaling pathways“

**Research area C: Membrane-associated regulatory proteins**

C1 Koepsell (Anatomy and Cell Biology I): Functions of $Na^+$-D-glucose cotransporters and their regulation by the regulator protein RS1

C3 Rapp (Institute for Radiation Biology and Cell Research): Mechanisms of isoform-specific regulation of membrane-integrating protein kinases of the RAF family

C4 Sendtner (Klinische Neurobiologie): Protein interactions at receptors for neurotrophic factors

C5 Raabe (Institute for Radiation Biology and Cell Research): Regulation of cell adhesion and the cytoskeleton by „p21-activated kinases“ (PAK) during neuronal cell differentiation

C6 Nieswandt (Rudolf-Virchow-Zentrum, DFG Research Center for Experimental Biomedicine): Mechanisms of agonist-induced $Ca^{2+}$-entry in platelets in vitro und in vivo

C7 Schindelin (Rudolf-Virchow-Zentrum, DFG Research Center for Experimental Biomedicine): Structural and functional basis of gephyrin-induced clustering of neurotransmitter receptors

**Zentrale Verwaltung**

Z1 Service Koepsell/Müller (Anatomy and Cell Biology/Molecular Plant Physiology and Biophysics): Analysis of protein-protein interactions employing surface plasmon resonance

Z2 Administration Koepsell (Anatomy and Cell Biology)

**Symposia**

Internal SFB-Symposia:
October 6 - 7, 2000, Bad Brückenau
September 28 - 29, 2001, Pommersfelden
October 11 – 12, 2002, Bad Brückenau
October 2 - 3, 2003, Bad Brückenau
October 15 - 16, 2004, Staffelstein
October 6 - 7, 2006, Bad Brückenau
October 5 - 6, 2007, Bad Brückenau
July 24 – 25, 2009, Pommersfelden

**International Symposia:**

“Molecular Physiology of the Synapse”, June 14 -16, 2001
“Mechanisms of protein activation”, June 10 – 12, 2004
“Membrane proteins and diseases”, June

# 5.1.3 Collaborative Research Center 567, Mechanisms of Interspecific Interactions of Organisms

CONTACT DETAILS

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**Professor Dr. rer. nat. Rainer Hedrich (Vice-Speaker)**
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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 13 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 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

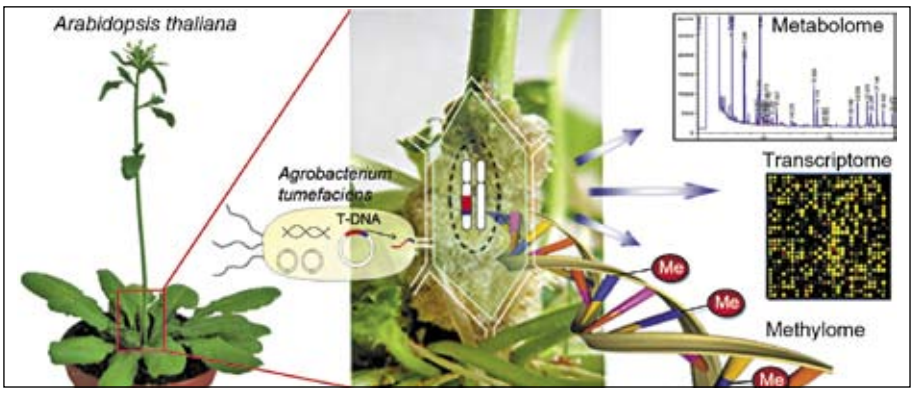


*Fig. 1: Molecular Mechanisms controlling the interaction between Arabidopsis thaliana and Agrobacterium tumefaciens (TP B5).*

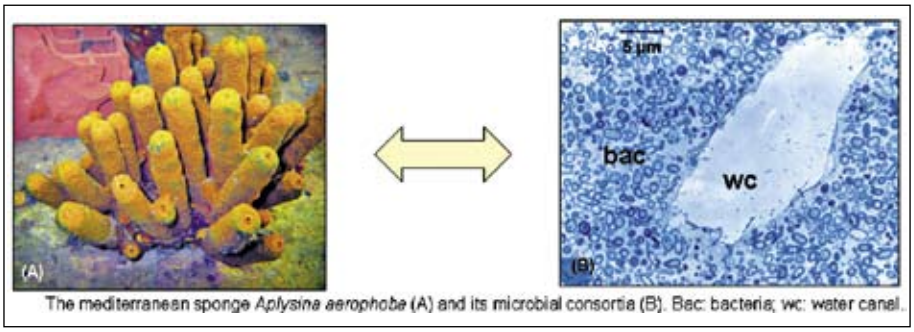


*Fig. 2: Interactions between the marine sponge Aplysina aerophoba and its symbiotic microbial consortia (TP C3).*

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“ one project whose principal investigator is member of the Medical Faculty is included, which is working on the “Interactions of the gynogenetic Amazon molly Poecilia formosa and its hosts”.

# 5.1.4 Collaborative Research Center 581, Molecular Models for Diseases of the Nervous System


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**Steering committee:**

**Professor Dr. Esther Asan**
**Institut für Anatomie und Zellbiologie**

**Professor Dr. Klaus.V. Toyka**
**Neurologische Klinik**

**Professor Dr. Manfred Heckmann**
**Physiologisches Institut**

**Professor Dr. Rudolf Martini**
**Neurologische Klinik**

**Professor Dr. Utz Fischer**
**Institut für Biochemie**

**Professor Dr. Klaus-Peter Lesch**
**Klinik für Psychiatrie**

**Frau Urveen Oberoi-Lehrieder (Office)**
**Tel.: 0931/201-49787**


## General Information

The "Collaborative Research Centre" SFB 581 „Molecular models of diseases of the nervous system" has been established in the year 2000 at the University of Würzburg. In 2009, it was reviewed and now will be funded for a final round of support until June 2012. 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 put on mouse and drosophila 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.

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 (GSLS) 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.

**Projects supported within the collaborative research center 581:**

Projects Section A:

*A3 Martini (Neurologie):* Immunpathologische Mechanismen bei Tiermodellen für erbliche Neuropathien

*A5 Hünig (Virologie und Immunbiologie):* Auslösung und Therapie einer Ovalbumin-spezifischen experimentellen autoimmunen Enzephalomyelitis

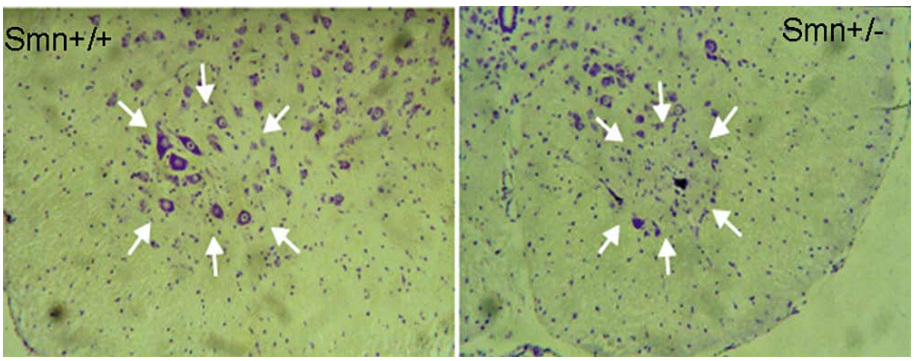


*Fig. 1: Degeneration of spinal motoneurons in a mouse model for spinal muscular atrophy (Smn+/- right side). The area where motoneurons degenerate is labelled with white arrows.*

*A7 Toyka/Sommer (Neurologie):* Immunpathogenese des Stiff-Person-Syndroms

*A8 Wiendl (Neurologie):* Pathogene Mechanismen neuroinflammatorischer Erkrankungen: Rolle koinhibitorischer Signale für die parenchymale Immunregulation

*A9 Lutz (Virologie und Immunbiologie):* Präsentation cerebraler Glycolipide durch dendritische Zellen an NKT-Zellen und persistierende ZNS-Virus-Infektionen bei der Auslösung der EAE

*A10 Meuth (Neurologie):* Pathophysiologische Relevanz von Zwei-Poren-Kalziumkanälen (K2P) für Inflammation und Neurodegeneration in T-Zell-vermittelten Autoimmun-erkrankungen des zentralen Nervensystems

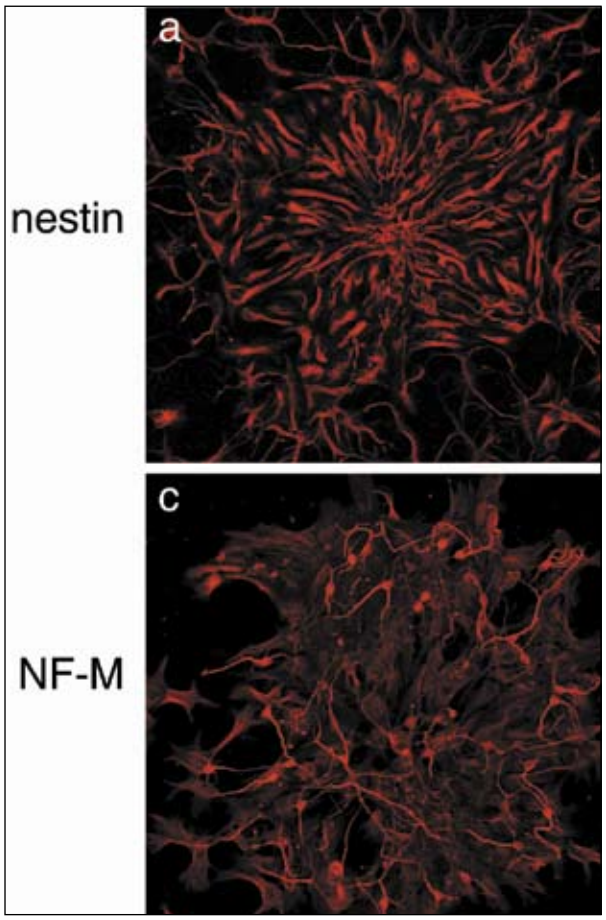


*Fig. 2: Differentiation of neural stem cells in cell culture. Immature stem cells are labelled with an antibody against Nestin (panel a), 24 hrs after plating on Laminin, differentiated neurons that grow long neurites can be identified by labelling with antibodies against Neurofilament-N (lower panel).*

**Projects Section B:**

*B1 Sendtner (Klinische Neurobiologie):* Pathogenese der Spinalen Muskelatrophie (SMA): Charakterisierung von Zellkulturen und Tiermodellen zur Analyse der axonalen Pathologie bei der SMA

*B4 Sendtner (Klinische Neurobiologie):* Die Rolle neurotropher Faktoren bei der Pathogenese von Motoneuronerkrankungen: Untersuchungen an Gen-Knockout-Mäusen

*B5 Rapp (Medizinische Strahlenkunde und Zellforschung):* Molekulare Mechanismen des Überlebens, der Migration und der Axonregeneration von Nervenzellen bei Mausmutanten mit Fehlsteuerung der Raf-Wirkung

*B9 Lesch (Psychiatrie):* Multiple molekulare Defekte des zentralen Serotoninsystems und ihre Rolle in der Pathophysiologie neuropsychiatrischer Erkrankungen

*B14 Raabe (Medizinische Strahlenkunde und Zellforschung):* Drosophila als Modellsystem zur Untersuchung der Rolle von RhoGTPasen regulierten Kinasen aus der PAK-Familie sowie der Kinasen CK2 und RSK in neurologischen Erkrankungsprozessen

*B18 Fischer (Biochemie):* Defekte im RNA-Metabolismus als Ursache von neuronaler Degeneration: Molekulare Analyse der spinalen Muskelatrophie und der Retinitis Pigmentosa

*B24 Jablonka (Klinische Neurobiologie):* Untersuchung von Krankheitsmechanismen an Motoneuronen eines Mausmodells für spinale Muskelatrophie mit Ateminsuffizienz (SMARD)

*B26 Eilers (Physiologische Chemie):* Rolle von Myc und Miz1 in der Neurogenese im Zentralnervensystem

B27 Heckmann (Physiologie): Molekulare Mechanismen der Plastizität präsynaptischer aktiver Zonen

**Core projects:**

*V1 Sendtner (Klinische Neurobiologie):* Sprecher, Sekretariat und Verwaltung des SFB

*Z3 Asan (Anatomie und Zellbiologie):* Zentrales Serviceprojekt für Morphologie, insbesondere Elektronenmikroskopie

*Z4 Sendtner (Klinische Neurobiologie):* Konfokale Mikroskopie

**Scientific meetings organized by the collaborative research centre 581:**

July 3-4, 2009: International symposium, CRC 581 in Würzburg

December 1st, 2009: International symposium “Latrophilin-2”

## SELECTED PUBLICATIONS

*Chari,A., Golas,M.M., Klingenhager,M., Neuenkirchen,N., Sander,B., Englbrecht,C., Sickmann,A., Stark,H., and Fischer,U. (2008). An assembly chaperone collaborates with the SMN complex to generate spliceosomal SnRNPs. Cell 135, 497-509.*

*Jablonka,S., Beck,M., Lechner,B.D., Mayer,C., and Sendtner,M. (2007). Defective Ca2+ channel clustering in axon terminals disturbs excitability in motoneurons in spinal muscular atrophy. J. Cell Biol. 179, 139-149.*

*Kroner,A., Schwab,N., Ip,C.W., Ortler,S., Gobel,K., Nave,K.A., Maurer,M., Martini,R., and Wiendl,H. (2009). Accelerated course of experimental autoimmune encephalomyelitis in PD-1-deficient central nervous system myelin mutants. Am. J. Pathol. 174, 2290-2299.*

*Schmid,A., Hallermann,S., Kittel,R.J., Khorramshahi,O., Frolich,A.M., Quentin,C., Rasse,T.M., Mertel,S., Heckmann,M., and Sigrist,S.J. (2008). Activity-dependent site-specific changes of glutamate receptor composition in vivo. Nat. Neurosci. 11, 659-666.*

# 5.1.5 Collaborative Research Center 630, Recognition, Preparation and Functional Analysis of Agents against Infectious Diseases

CONTACT DETAILS


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## Goals and Structure

Researchers of four faculties of the University of Würzburg together with the Medical Mission Clinic founded the SFB 630 in 2003 driven by their common vision to identify and to develop novel agents against infectious diseases. The extraordinarily high level of interdisciplinary exchange of the presently 15 individual projects belonging to Organic Chemistry, Pharmacy, Microbiology, Theoretical Chemistry, Bioinformatics, Physics, and Medicine accounts for the success of the concept. The SFB is divided in three Project Areas: Project Area A is responsible for the preparation and characterization of the compounds, which are then analyzed for their interaction with several clinically relevant pathogens and pathogenicity factors at the cellular and molecular level in Project Area B. The determination of the mode of action of the agents and also predictions for their further structural optimization are implemented in Project Area C.

## Major Research Interests

In spite of the efforts of modern medicine, infectious diseases are still the major cause of deaths worldwide. The rapid development of resistances against common antimicrobials and the expeditious distribution of novel pathogens by technical means due to enhanced geographical mobility and tourism impede the fight against the pathogens. In addition, economical factors prevent the development of novel therapeutics especially for tropical diseases. Therefore, the search for novel agents against infectious diseases with novel modes of action integrated in a state-aided research environment is of pivotal importance. The researchers of the SFB make use of natural sources like plants and marine microorganisms to isolate active compounds as lead structures for synthetic analogs and derivatives. Furthermore, the versatile potential of combinatory chemistry is used to generate novel chemical entities. The antimicrobial activity of these compounds is routinely analyzed against several clinically important bacteria, fungi, and parasites. Up to now, out of more than 1500 screened compounds, 109 showed activities in the same range as conventional antimicrobial agents or are even superior to them. A network of modern technologies like proteomics, transcriptomics, metabolomics and spectroscopic and bioinformatic analysis is utilized to reveal the effective mechanism of their activities. Based on the three-dimensional structure of the target proteins, quantum mechanical calculations and docking allow the design of optimized structures for the subsequent chemical synthesis. The next stage is the examination of the pharmacokinetic and toxicologic effects in vitro and in vivo.

**Project Area A: Preparation, characterization and optimization 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

A4 T. Schirmeister (Institute for Pharmacy and Food Chemistry)
Proteases as targets for agents against infectious diseases

A5 U. Hentschel (Julius-von-Sachs Institute for Biological Sciences)
Novel secondary metabolites from sponge-associated microbiota

**Project Area B: Interaction with cellular and molecular systems**

B1 J. Hacker (Institute for Molecular Infection Biology / Robert-Koch-Institute, Berlin)
Prolylisomerases and serine proteases as targets for rational drug development

B2 J. Morschhäuser (Institute for Molecular Infection biology)
Inhibition of virulence and resistance mechanisms of Candida albicans

B3 H. Moll (Institute for Molecular Infection Biology)
Analysis of the action of naphthylisoquinoline alkaloids and cysteine protease inhibitors against Leishmania parasites

B5 K. Ohlsen (Institute for Molecular Infection Biology)
Drug-induced gene expression in staphylococci

B7 C. Kisker (Rudolf-Virchow Center)
Structure-based drug design on essen-

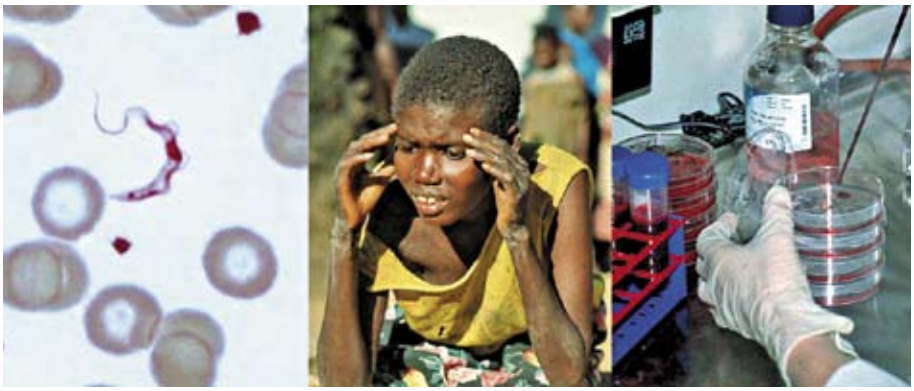

*Fig. 1: After crossing the blood-brain barrier, the parasite Trypanosoma brucei causes the typical symptoms of sleeping sickness, which is fatal without treatment. Novel anti-trypanosomal agents developed in the SFB 830 are examined in cell cultures for their activity.*

tial enzymes from Mycobacterium tuberculosis and other pathogens

**Project Area C: Characterization of the molecular mechanism of antiinfectives and predictions for their accelerated optimization**

C1 T. Hertel (Institute for Physical and Theoretical Chemistry)
CARS microscopy, Raman and IR spectroscopy for the localization and characterization of drugs and their interactions

C2 P. Jakob (Physical Institute)
NMR spectroscopy and imaging for in vivo and in vitro characterization 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 (Institute for Pharmacy and Food chemistry)
Metabolic and bioinformatical analysis of drug effects on cellular networks exemplified in Candida albicans

C7 C. Sotriffer (Institute for Pharmacy and Food Chemistry)
Computational structure-based drug design for the identification and characterization of new inhibitors of antimicrobial targets

**Central Project**

Z1 T. Ölschläger (Institute for Molecular Infection Biology)
A. Stich (Medical Mission Clinic)
Laboratory for the central evaluation of potential antiinfective agents

**Quality Management**
QM H. Bruhn

**Symposia since 2008**
2nd International Symposium
Novel Agents against Infectious Diseases – An Interdisciplinary Approach
7. – 10.10.2009

**Joint PhD-student meetings of the SFB 630, SFB 544 and SFB 766**
New Trends in Infectious Disease Research
10. – 12.11.2004, Würzburg
23. – 25.11.2006, Heidelberg
28. – 29.06.2007, Benediktushöhe Retzbach
20. – 22.11.2008, Kloster Bronnbach
19. – 21.11.2009, Heidelberg

# 5.1.6 Collaborative Research Center 688, Mechanisms and Imaging of Cell-Cell Interactions in the Cardiovascular System

CONTACT DETAILS

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## General Information

Cardio- and cerebrovascular diseases account for most deaths worldwide. The SFB 688 centre grant founded in 2006 and recently extended until 2013 creates a research network involving Würzburg scientists and clinicians from four faculties and eleven institutes/clinics of the University. Its aim is the understanding of central pathophysiological processes in vascular disorders such as thrombus formation and of secondary processes leading to damage and failure of heart, vascular system and brain. New signalling molecules for cell-cell interactions are aimed to be identified to create innovative concepts for prevention and treatment of cardio- and cerebrovascular 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 that allow clinically orientated groups to gain new insights into the development of thrombosis, myocardial infarction and stroke. Additional emphasis lies on secondary complications such as oedema and scar formation that strongly influence heart and brain function. The use of new MR contrast agents and high field MR imaging (up to 17.6 Tesla) in animal models for myocardial infarction and stroke shall allow the better surveillance of heart and vascular function in the living organism and provides a further link to clinical medicine.

**Project Area A (Fundamentals and mechanisms of vascular cell-cell interactions)**

This project area investigates the initiation of pathological cell-cell interactions especially of platelets, monocytes, leukocytes and endothelial cells within the vascular system. These cells play a central role for primary haemostasis, but also for vascular thromboses leading to organ dysfunction. The adhesion and activation of platelets and other cells to the vascular wall, and the local activation of the plasmatic coagulation is a complex process leading to pathological thrombus formation. During the last two years again important new insights have been obtained:

By generating transgenic mice the central role of the calcium sensor STIM-1 for platelet activation and intravascular thrombus formation could first be shown. Importantly, STIM-1 deficient mice were protected from cerebral ischemia without bleeding complications pointing to a new therapeutic target in cardio- and cerebrovascular diseases. Moreover, it could be shown that polyphosphates released from human platelets display proinflammatory and procoagulant properties. Functional proteome and phosphoproteome analysis of human platelets revealed a novel molecular interaction between activating (von Willebrand factor/GPIb) and inhibitory signaling pathways (soluble guanylyl cylcase) that might regulate the fine balance between thrombus formation and bleeding.

The heart hormones ANP and BNP exert an endocrine function by regulating blood pressure and volume. The corresponding guanylyl cylclase receptor-A (GC-A-R) is expressed by the microvascular endothelium. Studies in transgenic mice with an endothelial specific knock-out of their GC-A-R showed that the modulation of endothelial permeability by ANP is decisive for systemic volume homeostasis. Novel insights have also been obtained into the regulation of the endothelial barrier function via cAMP-mediated Rac1 activation and VE-cadherin as well as on the effects of glucocorticosteroids and estrogens at the blood brain barrier.

The heart is often affected by vascular dysfunction. Recently, the expression of the microRNA miR-21 could be identified as a novel and predominant mechanism leading to myocardial fibrosis, hypertrophy and insufficiency. Accordingly, antagonizing miR-21 led to a better functional outcome in a mouse model of heart failure. In another approach it could be shown that the activation of NF-κB in immune cells led to deterioration of heart function after myocardial infarction.

The long-term objective of this combined research efforts are better therapeutic options for patients with atherosclerosis, myocardial infarction and stroke, among others a more effective and safer prevention of thromboembolic events.

**Project Area B (Molecular and functional imaging of the cardiovascular system and its cell-cell interactions)**

This project area encompasses imaging projects with 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 the imaging of the vascular system, assessment of cellular infiltration and expression of critical signalling molecules are developed and applied to the disease models generated in Area A. During the last 2 years perfusion and diffusion weighted MR imaging was established in the mouse brain and used to follow study stroke development under antithrombotic treatments. In addition, a novel contrast agent allowed more sensitive detection of blood-brain barrier disturbances. To assess early stages of atherosclerosis in-vivo a technique was developed allowing measurement of pulse wave velocities in the mouse aorta. Thereby it will be possible to compare functional parameters and inflammation within the vessel wall as revealed by iron particle enhanced MRI. Furthermore, mathematical models were developed that allow quantification of cellular and vascular structures by field inhomogeneities and of their influence on MR signals.

SELECTED PUBLICATIONS


*Dittrich M, Birschmann I, Mietner S, Sickmann A, Walter U, Dandekar T (2008) Platelet protein interactions: map, signaling components, and phosphorylation groundstate. Arterioscler Thromb Vasc Biol 28:1326-31.*

*Kuhn M, Völker K, Schwarz K, Carbajo-Lozoya J, Flögel U, Jacoby C, Stypmann J, van Eickels M, Gambaryan S, Hartmann M, Werner M, Wieland T, Schrader J, Baba HA (2009) The natriuretic peptide/guanylyl cyclase - A system functions as a stress-responsive regulator of angiogenesis in mice. J Clin Invest 119:2019-30.*

*Pham M, Kleinschnitz C, Helluy X, Bartsch AJ, Austinat M, Behr VC, Renné T, Nieswandt B, Stoll G, Bendszus M (2009) Enhanced cortical reperfusion protects coagulation factor XII-deficient mice from ischemic stroke as revealed by high-field MRI. Neuroimage [Epub ahead of print]*

*Thum T, Gross C, Fiedler J, Fischer T, Kissler S, Bussen M, Galuppo P, Just S, Rottbauer W, Frantz S, Castoldi M, Soutschek J, Koteliansky V, Rosenwald A, Basson MA, Licht JD, Pena JT, Rouhanifard SH, Muckenthaler MU, Tuschl T, Martin GR, Bauersachs J, Engelhardt S (2008) MicroRNA-21 contributes to myocardial disease by stimulating MAP kinase signalling in fibroblasts. Nature 456:980-4.*

*Varga-Szabo D, Braun A, Kleinschnitz C, Bender M, Pleines I, Pham M, Renné T, Stoll G, Nieswandt B (2008) The calcium sensor STIM1 is an essential mediator of arterial thrombosis and ischemic brain infarction. J Exp Med 205:1583-91.*

# 5.1.7 Transregio-Collaborative Research Center 17, Ras-Dependent Pathways in Human Cancer

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## General Information

The Transregio 17 is formed by researchers at the universities of Marburg and Würzburg and is co-ordinated by Martin Eilers and Andreas Neubauer. The Transregio started in 2004 and has continued 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.

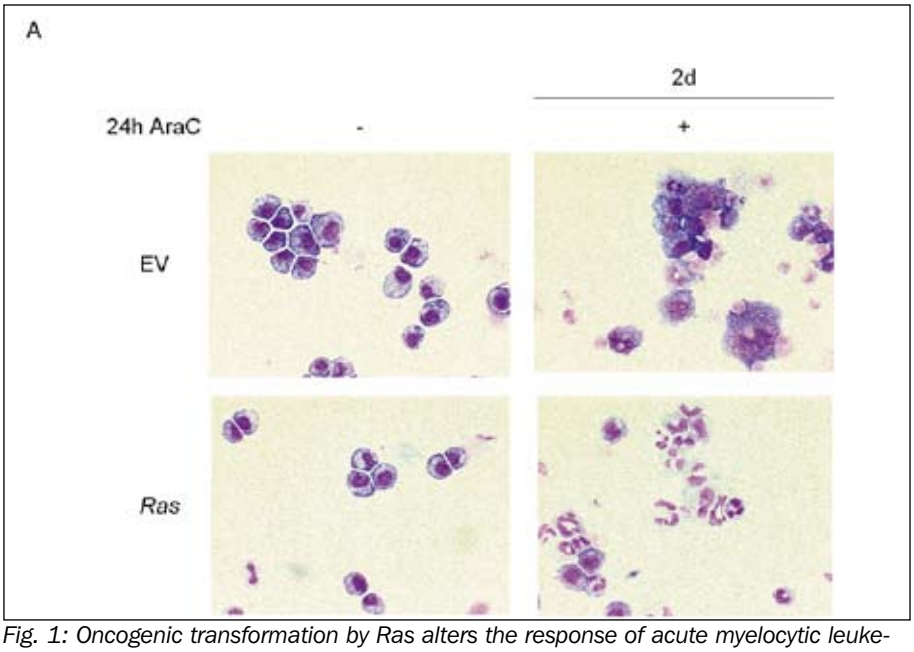


*Fig. 1: Oncogenic transformation by Ras alters the response of acute myelocytic leukemia cells to a cytostatic drug. Control and Ras-transformed cells were treated with cytarabine for 24 hours. Ras-transformed cells stained with May-Grunwald/Giemsa show morphological features of differentiation upon treatment of with cytarabine (Meyer et al., PLOS One 2009).*

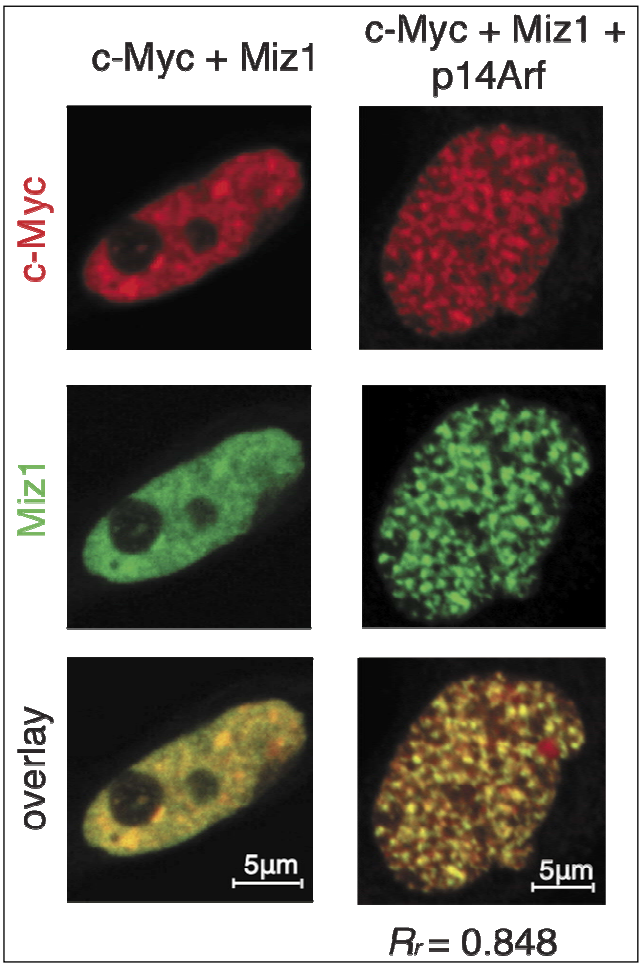


*Fig. 2: Complexes of the Myc-proteins. The immunofluorescence pictures show the distribution of the Myc-oncoproteins and one of their partner proteins, Miz1 in a growing cell (left) and in a cell expressing the Arf tumor suppressor protein and undergoing apoptosis under the influence of Arf (right). The changes in the localization arise from an Arf-induced modification of Miz1 (Herkert et al., Journal of Cell Biology, 2010).*

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 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, Peter Gallant) and Internal Medicine II (Ralf Bargou).

**Symposia**

Meeting of the Graduate College of the Transregio
Location: Würzburg Residenz
Date: 06.10.2010 - 08.10.2010
Organizer: Graduate Students

3rd Transregio Meeting
Location: Schloss Hirschberg, Beilngries
Date: 02.04.2009 - 04.04.2009
Organizer: Martin Eilers, Würzburg; Andreas Neubauer, Marburg

# 5.1.8 Transregio-Collaborative Research Center 34, Pathophysiology of Staphylococci in the Post-genomic Era

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Professor Dr. rer. nat. Michael Hecker
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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 (5 projects) deals with the behavior of the pathogen in the host and will provide new information on the host-pathogen interaction.

**Project leader Würzburg:**
PD 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)
Prof. Dr. Dr. B. Sinha (C6)

## 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. 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 (Fig. 1).

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 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 addi-

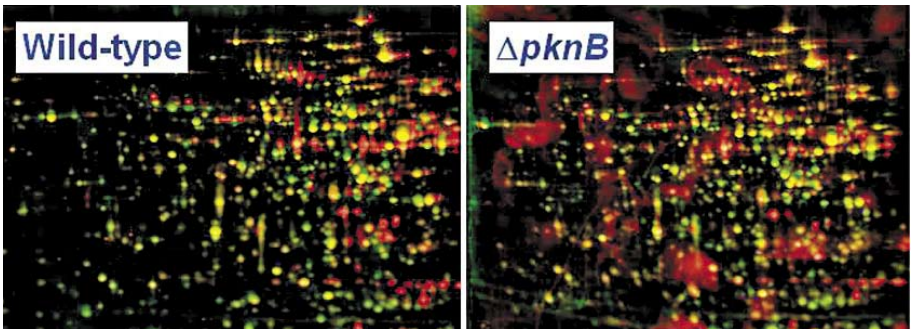


*Fig. 1: Phophoproteome analysis of Staphylococcus aureus wild-type strain 8325 and isogenic ser/thr kinase ΔpknB. Phospoproteins were visualized with proQ dye (red spots).*

tion, 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. The C3 project deals with the fate of the *S. aureus*–containing phagosomal compartment after invasion of host cells. The fate of this compartment and delineate virulence factors involved in phagosomal modulation/escape is studied. In addition, the fate of *S. aureus* residing in this compartment and its adaptive response to this environment is investigated using a combination of functional genomics and cellular microbiology.

**Symposia**

Internationales Symposium “Pathophysiology of Staphylococci”, Kloster Banz 28. – 31. October 2008

# 5.1.9 Transregio-Collaborative Research Center 52, Transcriptional Programming of Individual T-Cell Subsets


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**Professor Dr. Richard Kroczek (Speaker Berlin)**
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## Structure

**Project group A:** Transcriptional Programing of Regulatory T-Cells

**Project group B:** Transcriptional Programing of Effector T-Cells by T-Cell Receptor and Co-Receptor Signals

**Project Group C:** Animal Models for the Analysis of Defective Transcription in T-Cells

**Z projects:**

## Major Research Interest

The Transregional Collaborative Research Center (Transregio, TR) TR52 – Wuerzburg/Mainz/Berlin - has been established in 2008 by the DFG and started its scientific activities on July 01, 2008.

The long term research aim of this newly founded TR52 is to gain new scientific insights into the function of T-lymphocytes. This shall be achieved through the intensification and concentration of scientific research on the transcriptional control of gene expression in this vital population of lymphoid cells. Thereby, it is the aim to merge the different fields of expertise of laboratories in Würzburg, Mainz and Berlin, each of whose work is devoted to different aspects of T-cell biology. The expected findings are intended to significantly broaden our insight into the regulation of transcription, one of the fundamental steps in the control of the immune system. They will contribute to rendering the development of causal therapeutic approaches to frequent diseases of the immune system, above all auto-immune disorders and allergies, in future.

## Major Research Activities

T- and B-lymphocytes are at the heart of the adaptive immune system of vertebrates, which was formed with these during evolution approximately 400 million years ago. These cells are equipped with the unique capability to identify antigens as foreign with the help of their immune receptors and thereby to initiate the immune response which protects the organism from infections. The functional genes for immune receptors, i.e. T- and B-cell receptors, only emerge during the somatic development of lymphocytes by assembly of DNA segments that are separated in the germ line genome as well as by somatic mutations. These manifold genetic changes occur during the complex process of differentiation of haematopoietic stem cells to lymphocytes, which primarily takes place in the bone marrow and, in the case of T-lymphocytes, in the thymus. The differentiation of lymphocytes is regulated by finely tuned transcriptional control mechanisms which, in the case of defects such as the deficiency in certain transcription factors, can lead to the loss of further differentiation.

## Research Interest

Through complex interactions, the cells of the immune system initiate and uphold an "adaptive" immune response until invading pathogens have been destroyed. However, the effector cells in the immune system can also get out of control and thus become the cause for life threatening diseases themselves. This is the case in autoimmune disorders and severe allergies. In the case of autoimmune diseases, the immune system erroneously attacks the body's own tissue. When we lose the capability to differentiate between harmless antigens and hazardous pathogens, allergies can occur, which represent "excessive" reactions to otherwise harmless substances in the environment. The basis of both disease forms is a loss of balance in our immune system to be ready to defend us against infectious agents, while at the same time being tolerant towards harmless environmental antigens and structures of our own bodies. In the case of T-lymphocytes, this tolerance is achieved mainly through positive and negative selection of thymocytes. In the thymus, double-positive thymocytes with „correct" T-cell receptors are propagated, while those with dysfunctional or auto-aggressive receptors are deleted through apoptosis.

At present, allergies such as asthma, rhinitis and allergic skin reactions are among the most common disorders in western industrialized nations and their importance is constantly increasing. They are based upon imbalances and hyper reactivity of peripheral T-lymphocytes. An increased number of Th2-cells, which secrete large amounts of IL-4, IL-5 and IL-13 are a typical trait of these diseases. Although much has been learned concerning the molecular mechanisms of Th1/Th2-cell differentiation, very little is still known concerning the signals

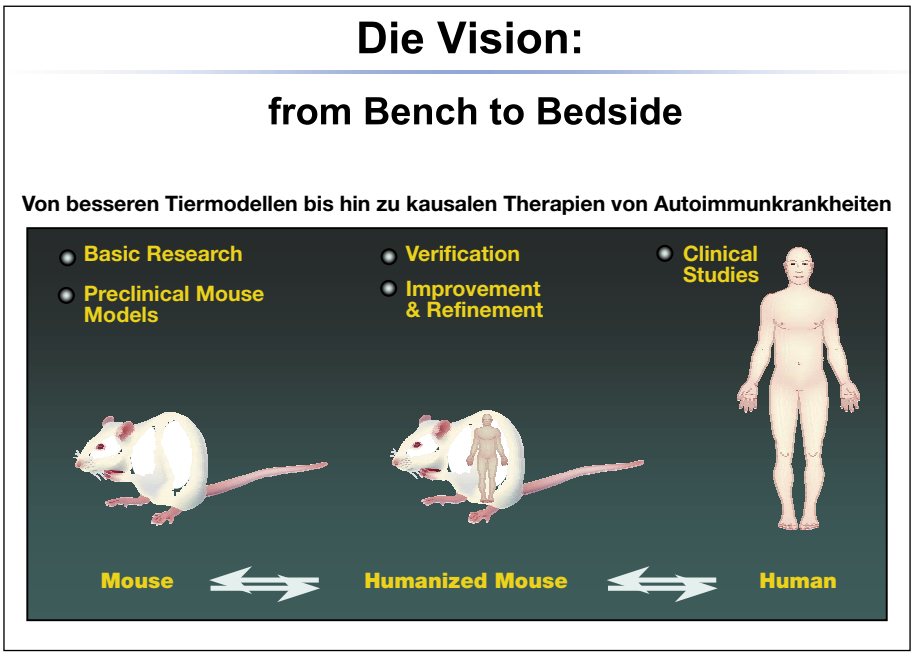


*Fig. 1: The vision of the Transregio TR52: The generation of scientific knowledge, mainly by establishing new animal models for human diseases, should lay the ground for new rational therapies. Autoimmune diseases like inflammatory gastro-intestinal diseases (eg Morbus Crohn) and asthma are major areas of interest.*

that lead to the frequently fatal consequences of these atopic reactions via STAT6 and, above all, GATA-3.

These examples show that the transcriptional control of differential gene expression determines cellular differentiation, which is expressed in the differentiation of naïve T-cells into effector T-cells and memory T-cells. However, the underlying molecular mechanisms and their effects on the development and activity of the adaptive immune system are largely unknown. This is based in part on the complexity of the transcription process as well as on the complexity of the adaptive immune system itself. As is the case in protein biosynthesis, more than fifty, more probably hundreds of proteins are involved in the transcription of a single gene, which together form the general transcription machinery, the transcription complex, and the chromatin proteins. The activity of many of these (nuclear) proteins is controlled by receptor-mediated signals and is responsible for the differentiation of haematopoietic precursor cells into effector T-cells, which in turn control the immune system. One of the significant goals of this TR is to unravel the complexity of these processes. A further aim is to introduce the findings achieved into the causal treatment of human autoimmune and allergic disorders.

## Research Activities in Würzburg

This TR52 is based on long-standing experimetal collaborations that started more than 10 years ago between research laboratories of Universities of Würzburg (Dept. of Molecular Pathology) and Mainz (Institute of Immunology). One result of these collaborations are more than 10 manuscripts which were published in (or have been submitted to) excellent scientific journals.

The experimental work of Department of Molecular Pathology (Head: E. Serfling) at the Institute of Pathology of University Würzburg 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 led to a detailed analysis of NFAT transcription factors whose induction - by increasing elevated $Ca^{++}$ levels and calcineurin-mediated signals – appears to be unique for the activation of lymphocytes. In the TR, the experimental work shall be extended by (1.) studies on the expression and function of individual NFATc1 isoforms (TPC5; E.S. & Andris Avots) and the characterisation of DNA sequence elements and TFs controling NFATc1 expression in vivo (B2; Andris Avots & E.S.) and (2.) the analysis of interaction of NFATc factors with further transcription factors, such as GATA-3, STAT6, Foxp3 and Runx factors (TPA3 [Friederike Berberich-Siebelt] and TPA8 [Stefan Gattenlöhner]). This shall be achieved in collaboration with further laboratories. These are the Proteomics facility at the Rudolf-Virchow-Center of Experimental Biomedicine guided by Albert Sickmann and the Institute of Immunology, Mainz (head: E. Schmitt). By using the TAP technology and protein sequencing facilities in A. Sickmann`s team, in TPA3 multi-protein complexes formed with selected TFs will be isolated and characterized.

The close scientific contacts between the Department of Molecular Pathology and the Institute of Virology and Immunobiology of Univ. Würzburg (Head: Thomas Hünig) are reflected in the participation of two immunological research laboratories directed by Thomas Hünig and Manfred Lutz. While the scientific work in Thomas Hünig`s team is devoted to various aspects of CD28 structure, expression and function, the project proposed here (TPA5) deals with the stimulatory role which CD28 signals play in the generation, homeostasis and function of regulatory T cells. Manfred Lutz` major interest summarized in his project application (TPB7) is devoted to the role of programming Th2 effector cells by differentially matured dendritic cells.

Numerous projects of TR52 will profit from the participation of Andreas Beilhack (Medical Clinic and Policlinic II, Univ. Würzburg), a young expert in bioluminescence imaging, who leads the Central core project Z2, In vivo imaging.

# 5.1.10 Transregio-Collaborative Research Center 58, Fear, Anxiety, Anxiety Disorders


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**Professor Dr. Christian Büchel**
**(Speaker Hamburg)**


## Mission and Structure

The Transregio-SFB 58 was initiated in July 2008 and comprises work groups of the Universities of Hamburg, Münster and Würzburg. The speakers are C. Büchel (Hamburg, deputy speaker), H.-C. Pape (Münster, speaker) and J. Deckert in Würzburg (deputy speaker). Altogether, over 40 scientists collaborate in 13 subprojects of the SFB-TRR 58 in an interdisciplinary way and numerous graduates and Ph.D. students undergo research training in a structured Ph.D. program, at Würzburg in the context of the GSLS and the GK1156.

Fear and anxiety, the two phylogenetic oldest emotions, are in the focus of research. These emotions may emerge in pathological anxiety states in humans and as anxiety disorders are important precursors of depressive disorders, both being the two most common mental disorders. Together with colleagues from the other two universities, the scientists in Würzburg want to explore the development of anxiety in its physiological as well as pathological form on a comprehensive and integrative basis from the gene over the single cell and complex cell networks to human behaviour and back. Obtaining a better understanding of the underlying complex molecular and psychological mechanisms of the development and remission of pathological anxiety will hopefully lead to innovative and individualized treatment strategies.

## Research topics

Aim of the Transregio-SFB is to explore the pathogenesis of physiological and pathological anxiety from the gene level to humans suffering from panic disorder in a translational approach. To do so, molecular biologists and neurophysiologists, physicists and psychologists, neurologists and psychiatrists closely work together in an interdisciplinary manner (Figure 1). Results from model organisms like knock-out mice and drosophila will be validated in humans by innovative experimental approaches (*imaging genomics, pharmacogenomics*). Genetic findings in humans will in turn be experimentally verified in animal models (*reverse genetics*). To achieve these aims, the TRR-SFB 58 consists of three closely connected areas of research:

Research area A - **basic science** - explores the molecular mechanisms of the development of fear in animal models. Studies of serotonin-transporter knock-out mice as best-established animal model of fear with regard to the impact of pre- and postnatal stress on subsequent behaviour and epigenetic programming (Lesch, Schmitt, Seidenbecher, Sachser) are complemented by studies of neuronal plasticity of amygdaloid networks and the role of synchronized neuronal activity with a special focus on the GABA-A and the endocannabinoid system (Pape, Lutz). The mechanisms of safety learning as a process of relevance for therapy is studied in drosophila mutants (Gerber).

In research area B – **behavioural science** - healthy subjects are investigated on multiple levels with experimental psychophysiological paradigms for fear and anxiety –relevant processes such as perception, conditioning and extinction. In each experiment, the genetic modulation (e.g. by variations in the NPS receptor gene or in the endocannabinoid system) of the behavioural response is scrutinized. Startle studies on cue versus context fear conditioning in virtual reality (Pauli, Mühlberger) are applied as well as functional magnetic resonance imaging studies to display neuronal correlates of fear-relevant prediction errors (Büchel). An alternative approach is pursued by the last project of this area (Engel, Büchel) which explores the impact of cerebral coherence on emotional and cognitive modulation of stimulus salience using magnetoencephalography.

Research area C – **translational science** - focuses on the investigation of pathomechanisms relevant for anxiety disorders. Using again magnetencephalography, fast neuronal processes in multimodal fear conditioning and extinction and their modulation by transcranial magnetic stimulation are investigated (Junghöfer, Pantev and Zwanzger). In the second project, the emotional perception of fear-relevant stimuli and their modulation by dopamine or caffeine is investigated (Domschke, Deckert). The function of the prefrontal cortex and its modulation by transcranial magnetic stimulation. as a possible innovative therapy approach is explored by fMRI and fNIRS in patients suffering from panic disorder (Figure 2) in the third project (Fallgatter, Ehlis). The role of genetic variants is again under investigation in all three projects.

A large (n=1500) cohort with ex ante phenotypically and genetically well defined control subjects for the studies of areas B and C is made available by the **central proj-**

International Symposium on Fear, Anxiety, Anxiety Disorders; Münster, 10.-12.12.2009

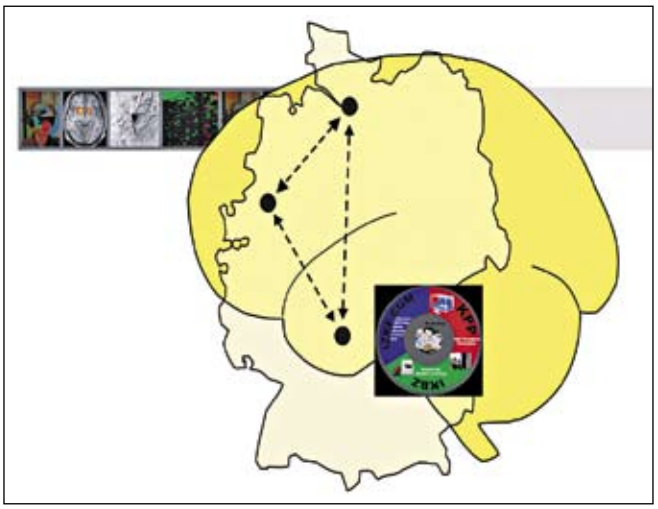

*Fig. 1: From mice to men and back: Combining basic, behavioural and translational science at three university sites (Hamburg, Münster and Würzburg) as exemplified by the central project Z2 (Deckert, Reif and Pauli).*

**ect Z2** (Deckert, Reif, Pauli). In addition, this project deals with the complex genetics of fear-and anxiety-relevant behaviours and thus provides new candidate molecules for research area A.

At the University of Würzburg, the following institutions are involved:
Medical Faculty, Department of Psychiatry, Psychosomatics and Psychotherapy (project leaders: J. Deckert, A.-C. Ehlis. A.J. Fallgatter, K.P. Lesch, A. Reif, A. Schmitt);
Faculty of Philosophy, Institute of Psychology I (project leaders: A. Mühlberger, P. Pauli); Faculty of Biology, Chair of Genetics and Neurobiology (project leader: B. Gerber).

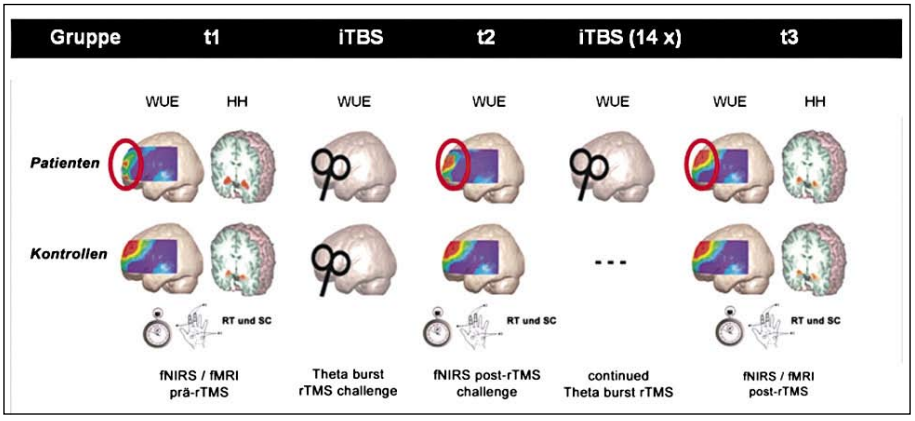


*Fig. 2: Effects of NIRS-guided facilitating rTMS treatment in patients with panic disorder: Protocol of project C4 (Fallgatter and Ehlis).*

# 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 (until 2008)**
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**Professor Dr. Manfred Heckmann (since 2008)**
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**Dr. Asparouh Iliev**
**(Membrane/Cytoskeleton Interactions)**
**Tel.: 0931/201-48997**

**Professor Dr. Caroline Kisker**
**(Structural Biology: DNA-Repair and Structure-Based Drug-Design)**
**Tel.: 0931/31-80381**

**Dr. Stephan Kissler**
**(Immune Tolerance)**
**Tel.: 0931/31-80367**

**Professor Dr. Bernhard Nieswandt**
**(Vascular Biology)**
**Tel.: 0931/31-80406**

**Professor Dr. Hermann Schindelin**
**(Structural Biology: Protein Folding, Function and Degradation)**
**Tel.: 0931/31-80382**

**Professor Dr. Michael Schön (until 2008)**
**(Inflammation and Tumor Biology)**

**Professor Dr. Albert Sickmann (until 2008)**
**(Functional Proteomics)**

**Professor Dr. Stephan Sigrist (until 2008)**
**(Synapse Architecture)**

**Dr. Alma Zernecke (since 2009)**
**(Immunopathogenesis of Arteriosclerosis)**
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## 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. In July 2009, researchers of the Rudolf Virchow Center and the Center for Infectious Disease Research moved together into a new building, the former surgical hospital. Almost 10.000 m2 of space with excellent facilities are now open for research, teaching and training, as well as events for the public. The overall cost of the building was 78 million Euro, covered by the Federal Government and Bavarian Government.

The center spans multiple faculties and was therefore established as a central institution of the University. Group leaders, if they are professors, belong to the Medical Faculty or 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 diseases.

Right from the beginning the Rudolf Virchow Center´s intention was to create innovative structures within a 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 the 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 three and is planned to hold four 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 was 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 five projects within the RVZ Network are established at the Rudolf Virchow Center. Research groups work on “target proteins“. The research pursued at the Center can therefore be grouped into four Research Fields: (1) Protein Structure and Function, (2) Proteins in Cellular Signaling, (3) Nucleic Acid Binding Proteins, and (4) Proteins in Cell-Cell Interactions and Motility. The main projects reflect the focus on cell surface proteins and their signaling proteins, and on nucleic acid binding proteins.

**Biology of Cytoskeleton**
(A. Gohla)

Failure of cells to migrate, or migration of

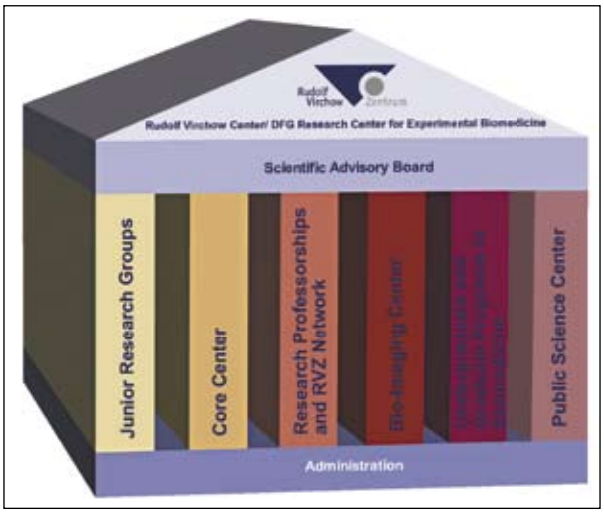


*Fig. 1: Structure of the Rudolf Virchow Center.*

cells to aberrant locations, is intricately involved in pathologies including vascular and inflammatory diseases as well as in tumor formation and metastasis. Effective cell adhesion and migration are based on the precise integration of localized, transient signaling events with changes in the cytoskeleton and appropriate cell-cell and cell-matrix interactions. The goal is to understand the physiological and pathological functions of the newly identified phosphatases Chronophin and AUM, which emerge as major regulators of Rho-GTPase-dependent cytoskeletal dynamics.

**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. Therefore 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.

**Synapse Architecture**
(M. Heckmann)

The birth of synaptic connections between nerve cells is an intriguing developmental period that paves the way for the complex functions executed by nervous systems. If the intricate network between neurons is improperly formed during embryogenesis or is subsequently injured, network malfunctions cause severe disability. How synapses are established during embryogenesis and by which molecular means their highly specialized properties are maintained throughout a lifetime is studied in this group (see also 2.5, page 24).

**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.

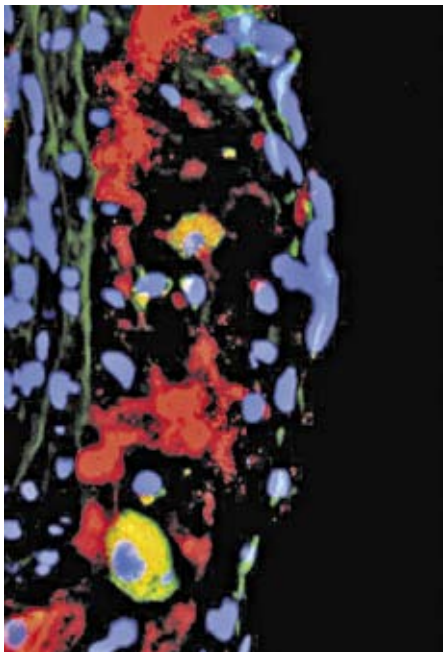

*Fig. 2: Molecular mechanisms are linked to cardiovascu¬lar diseases: Lipid deposits stained by Oil-red-O in an atherosclerotic lesion in the aortic root of an apolipoprotein E-deficient mouse transplanted with cx3cr1+/gfp bone marrow and fed on a high fat diet (left panel); immunfluorescence staining was performed for monocytes/macrophages (using the marker MOMA-2, red) in co-localization with gfp+ cells (green), cell nuclei were counterstained with DAPI (blue, right panel).*

**Membrane/Cytoskeleton Interactions**
(A. Iliev)

Streptococcus pneumoniae is a common pathogen causing the most frequent form of bacterial meningitis. A major virulence factor of S. pneumoniae is the pore-forming toxin pneumolysin. It induces rapid cell lysis or apoptosis in a concentration-dependent manner. The serious outcome and prognosis of pneumococcal meningitis contrast with the limited presence of cell death. The aim of the project is to clarify the molecular steps leading to the small GTPase activation, to redistribution of the cytoskeleton and to changes in cell signaling of neuronal target cells after pneumolysin challenge.

**Structural 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

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*M. Heckmann*
*Meuth, S.G., Herrmann, A.M., Simon, O.J., Siffrin, V., Melzer, N., Bittner, S., Meuth, P., Langer, H.F., Hallermann, S., Boldakowa, N., Herz, J., Munsch, T., Landgraf, P., Aktas, O., Heckmann, M., Lessmann, V., Budde, T., Kieseier, B.C., Zipp, F., Wiendl, H. (2009) Cytotoxic CD8+ T cell-neuron interactions: perforin-dependent electrical silencing precedes but is not causally linked to neuronal cell death. J Neurosci, 29(49):15397-409.*

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*H. Hermanns*
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*A. Iliev*
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*C. Kisker*
*Wolski, S.C., Kuper, J., Hänzelmann, P., Truglio, J.J., Croteau, D.L., Van Houten, B., Kisker, C. (2008) Crystal structure of the FeS cluster-containing nucleotide excision repair helicase XPD. PLoS Biol. 6(6):e149. PMID: 18578568.*

*S. Kissler*
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*B. Nieswandt*
*Berna-Erro, A., Braun, A., Kraft, R., Kleinschnitz, C., Schuhmann, M.K., Stegner, D., Wultsch, T., Eilers, J., Meuth, S.G., Stoll, G., Nieswandt, B. (2009) STIM2 regulates capacitive Ca2+ entry in neurons and plays a key role in hypoxic neuronal cell death. Sci Signal, 2(93):ra67.*

*H. Schindelin*
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*A. Zernecke*
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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.

**Signalling Processes of Receptors**
(M. Lohse)

Cyclic nucleotides – cyclic AMP (cAMP) and cyclic GMP (cGMP) – belong to the most ubiquitous intracellular messengers. Both are produced in response to multiple stimuli, act on several intracellular targets, and regulate a vast array of biological functions. However, in spite of the fundamental importance of these signaling systems, very little is known about the temporal and spatial patterns of their production and action. To gain an insight into these dimensions, the group develops methods to create images of these second messengers in intact cells, and to resolve these intracellular signals in space and in time (see also 2.16, page 46).

**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 activity of the cells, while preserving their hemostatic function (see also 3.25, page 112).

**Structural 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.

**Immunopathogenesis of Arteriosclerosis**
(A. Zernecke)

Atherosclerosis is imminently becoming the leading cause of death worldwide. Importantly, immune responses are described to participate in all phases of atherosclerosis. The exact functions of immune cells in controlling the development of atherosclerosis, however, remain elusive to date. By targeting specific chemokines/ cytokines and their receptors the group addresses the role of different immune cell subpopulations in atherosclerosis. The focus is to study cellular constituents and understanding the complex equilibrium and interplay between immune-cell subpopulations.

## 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 in the graduate program "Virchow Graduate Program „ that belongs to the Section Biomedicine of the "Graduate School of Life Sciences".

# 5.2.2 Interdisziplinary Center for Clinical Research (IZKF)

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## General Information

The IZKF Würzburg organizes the internal research funding of the Medical Faculty. Its major goal is to strenghten clincial research based on interdisciplinary cooperations between clinical research groups and groups of the biomedical sciences. The budget is fixed at approximately 5 millions Euro per annum.

To carry out its mission the IZKF uses particulary three instruments:

- Supporting cooperative research grants in the fields of immunology/infectiology, oncology, cardiac and vasular disorders as well as neurosciences;
- Promoting education and advancement of young researchers in medicine throughout all qualification phases;
- Improving scientific infrastructure by centrally funded core facilities and local research funding programmes.

The IZKF promotes research after internal and external peer review. In this way, the IZKF guarantees quality-based differentiation in the research funding of the Medical Faculty.

- The General Assembly ("Zentrumskonferenz"),
- The Executive Board
- The External Scientific Advisory Board.

The IZKF Wuerzburg was founded in 1996 within the federal advancement program "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.

## Main Research Interests

One major task of the IZKF is to select and finance research projects in the main research fields of the Medical Faculty. A unique feature of this research grant programme of the center is the concept of bringing together the expertise of basic and clinical sciences to develop novel and effective diagnostics as well as therapeutic approaches. 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. In 2009 the IZKF supported 33 research projects and three junior research groups in the following research fields:

**A: Pathological Aspects of Inflammation**

**B: Tumor/Host-Interactions**

**D: Transplantation and Tissue Engineering**

**E: Cardiac and Vascular Disorders**

**F: Imaging**

**N: Clinical and Experimental Neurobiology**

## Junior Career Programmes

Supporting young scientists in medicine is the second major commitment of the IZKF that involves a wide spectrum of sponsoring activities:

- **MD/PhD-Programme**

Is funded by the IZKF since 1997. The MD/PhD-Programme is integrated in the Graduate School of Life Sciences of the University (GSLS). Currently 15 doctoral candidates are enrolled in this programme.

- **Erstantragsteller-Programm (The First Application)**

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 gaining access to external research funding. Currently 8 young scientists are supported in this programme.

- **Rotation Positions ("Rotationsstellen")**

ensures "protected" time for young physician scientists. The IZKF provides five rotation positions. This support proved a successful measure to extempt these researchers from daily clinical duties. The rotation positions are granted for six to twelve months.

- **Junior Research Groups**

The implementation of junior groups is an integral part of the junior career programme of the IZKF. Excellent young scientists are selected and supported over a period of five years including a substantial running budget. In this time they are expected to establish their scientific reputation and to qualify for academic positions. Within the year 2009 two IZKF junior group leaders have

completed the programme successfully. So, at the beginning of 2010 one group is currently active in the IZKF.
The following groups have been funded:

1. Prof. Dr. Andreas Rosenwald, Gene Expression Profiling of Non-Hodgkin-Lymphomas (2004-2009) – In September 2009 Andreas Rosenwald accepted the offer to become director of the department of pathology at the University Würzburg.

2. Prof. Dr. Dr. Thomas Thum, Cardiac Wounding and Healing, (2006-2009) – Since October 2009 Thomas Thum directs the Institute of Molecular and Translational Therapeutic Strategies at the Hannover Medical School.

3. PD Dr. Jörg Wischhusen, TGF beta as a key mediator of the immune escape of invasively growing tumors (2005-2010)

## Other activities

To improve the scientific infrastructure in clinical research the Center maintains the following Core Facilities:

- Microarray-Unit
- Early Clinical Trial Unit

Finally the center offers flexible funding moduls which are not available from to major external funding research organisations.

- Start-up financing for innovative research ideas
- Central budget for reimbursements of travel expenses
- Visiting researcher programme for scientists coming from abroad
- Organization and funding of symposia, workshops and other meetings in order to encourage coooperation between scientists from domestic or international universities.

In 2010 the Center will offer consulting service for scientists, particulary young scientists and groups of scientists, in applying external research funding.

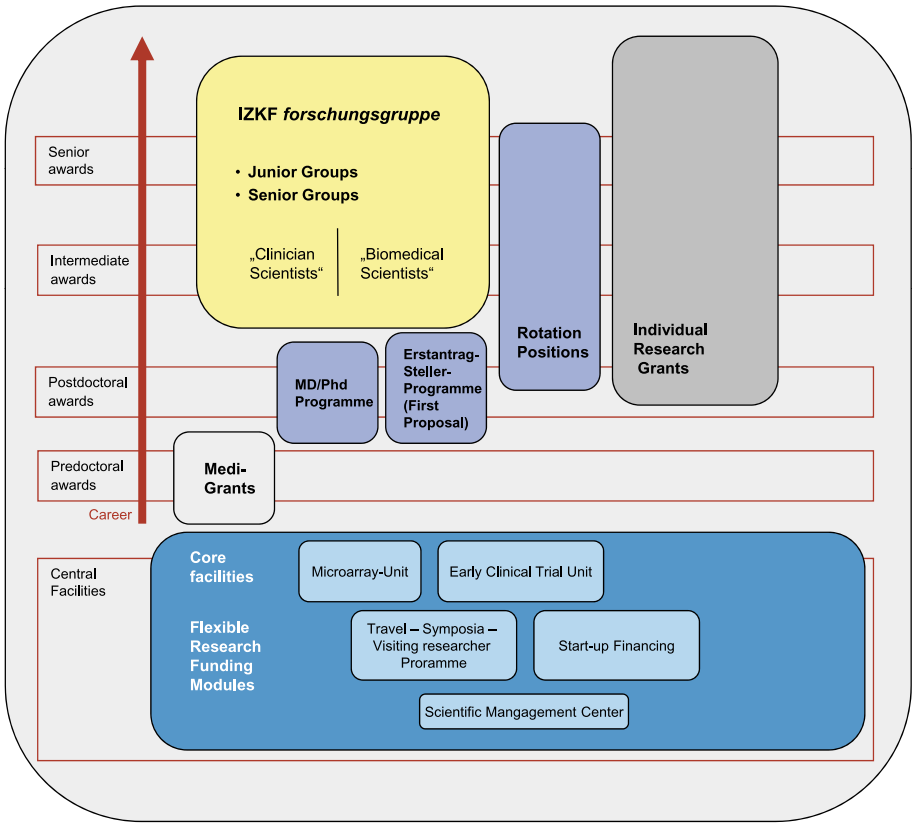


*Fig.1: Research support via the IZKF in 2010.*

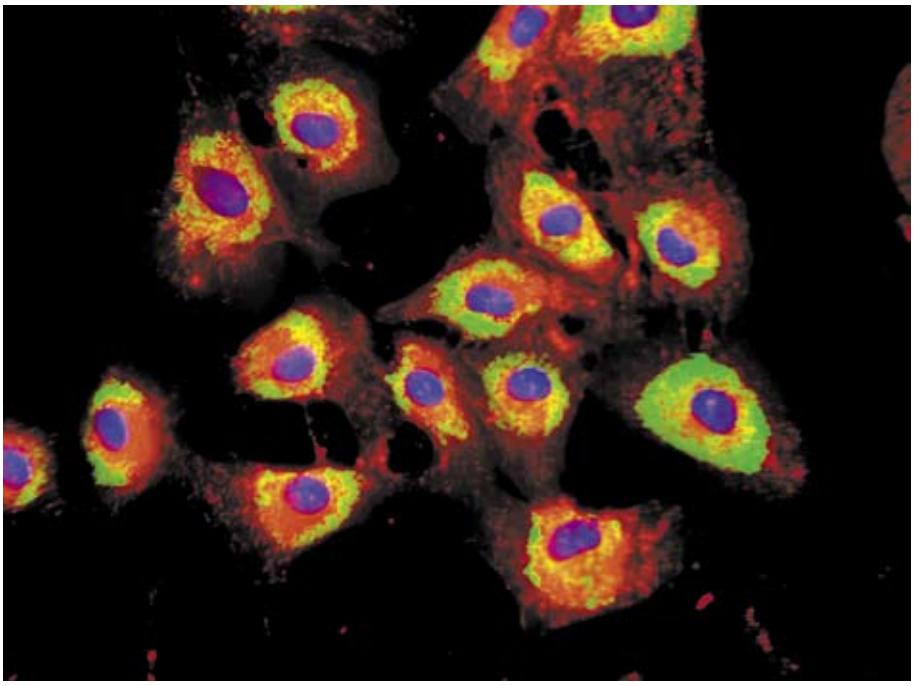

*Fig. 2: Internalized antagomirs (microRNA-antagonists; red) in cardiac fibroblasts (in green; nuclei in blue) (from: T. Thum, Nature. 2008).*

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*For the Annual Progress Report: Please contact: IZKF-Office*

*Thum T, Gross C, Fiedler J, Fischer T, Kissler S, Just S, Rottbauer W, Bussen M, Galuppo P, Frantz S, Castoldi M, Muckenthaler M, Soutschek J, Koteliansky, Rosenwald A, Pena JT, Tuschl T, Martin GR, Bauersachs J, Engelhardt S. (2008) MiR-21 derepresses fibroblast MAPkinase signalling and contributes to myocardial disease. Nature. 2008;456:980-4.*

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# 5.2.3 Research Center for Infectious Diseases

CONTACT DETAILS

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**(Speaker)**

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## General information and structure

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

**Marine Symbioses- New Antiinfectives**
(U. Hentschel, 2004-2009)

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 substances 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 mechanisms of malaria transmission**
(G. Pradel, since 2005)

The tropical disease malaria, which is caused by the protozoan parasite *Plasmodium*, is a major health threat and one of the most important infectious diseases worldwide. Currently, there is no vaccine in circulation for the treatment of malaria, and pharmaceutical approaches are increasingly encountering parasite drug resistance. It is the main research goal of the Pradel group to gain deeper insight into the molecular mechanisms underlying reproduction of the malaria parasite, which takes places in the midgut of the blood-feeding mosquito and which plays a major role for disease transmission. Sexual stage 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, 2007-2008)

A major area of interest in the lab is the characterisation of protective immune responses to malaria induced by genetically 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 characterised. The group combines molecular and cell biological research on GAP with studies aimed at understanding the immunological correlates of protection elicited by GAP.

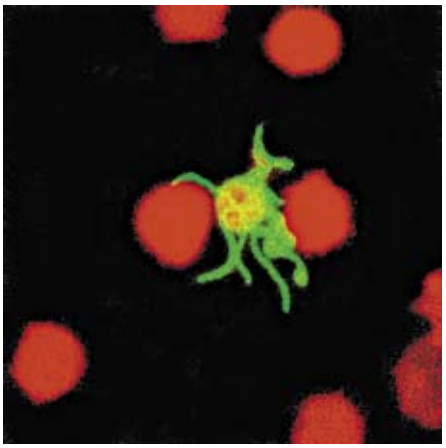

*Fig. 1: Exflagellating male Plasmodium microgametocyte with microgametes, depicted by fluorescence-labelling of protein alpha-tubulin II (shown green). During exflagellation the motile microgametes stick to human erythrocytes (in red).*

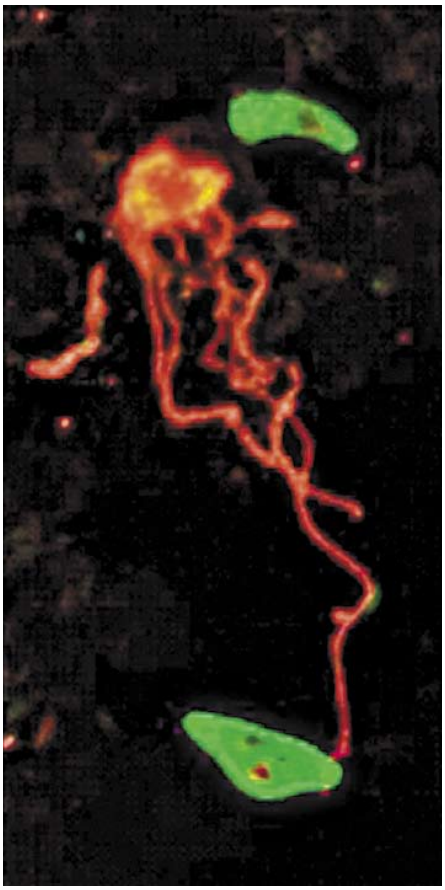

*Fig. 2: Filamentous cell protrusions of a Plasmodium macrogamete (shown in red via fluorescence-labelling of protein Pfs25), mediating contact to gametocytes (shown in green via fluorescence-labelling of protein Pfs230).*

a severe and often life threatening complication for the immunocompromised individual, with knowledge of factors that support fungal growth inside the host being scarce. Research activities are focussed on specific aspects of nitrogen metabolism, such as regulation of extracellular proteolysis or transport of breakdown products from the surrounding proteinaceous matrix. This is complemented by studies on hematogenous dissemination of the fungus as well as its impact on hemostasis. Furthermore, we investigate the differentiation of sexual fruiting bodies using improved methods of molecular biology for gene targeting in *A. fumigatus*.

## 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 contribute to the education of graduate students.

**Virulence determinants of the human pathogen *Aspergillus fumigatus***
(S. Krappmann, since 2007)

Major research goal is the identification of novel factors that support pathogenicity of *Aspergillus*. Infection with this saprophyte is


*Fig. 3: Marine sponges (A) and associated microbiota (B) are rich sources of secondary metabolites, such as the novel macrolactam cebulactam A1 (C).*

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# 5.2.4 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 platform for experimental research in the field of Molecular Medicine. The *ZEMM* comprises two parts: an animal unit and a research unit. The building was completed in 2008. In the research unit, well-equipped laboratories are temporarily provided to research groups in biomedicine upon request. The animal facility is in charge of the central breeding, husbandry and supply of non-infectious laboratory animals used by research institutions in the area of medicine and biomedicine. In addition, the animal unit has the tasks to provide clean animal holding areas and to generate gene-modified animals. Furthermore, several operating rooms for small and large animals are available. The lab-zone and the animal facility are available for defined time periods to research groups engaged in clearly defined biomedical research activities.

## Major Research Interests

The animal facility of the *ZEMM* is in charge of the central breeding, maintenance and supply of clean laboratory animals for research units from medicine and biomedicine.

The unit Transgenic Technology supports interdisciplinary research by providing a wide range of services associated with the generation of genetically modified mice, embryo-cryopreservation and rederivation of mouse lines by embryo transfer for the entire network of biomedical research at the University of Würzburg.

For the generation of genetically modified mice conventional transgenic (DNA pronuclear microinjection) and knock-out (blastocyst injection of genetically modified ES cells) technologies are provided.

The production of transgenic mice is currently performed in the Institute of Pharmacology and Toxicology. A total of 15 projects have passed through our lab in 2009 and a total of 30 transgenic founder mice could be generated. The blastocyst injection technology (gene- targeting) is currently being established in the animal facility of the ZEMM.

Cryopreservation provides a less expensive and efficient alternative for maintaining nucleus colonies that are currently not in use and protects against loss due to colony contamination (health or genetic). A mouse embryo bank will therefore be developed which provides a collection and storage service to researchers.

*Fig. 1: DNA pronuclear microinjection.*

Also, sperm freezing and in vitro fertilization procedures are currently being developed.

The rederivation of mouse lines by embryo transfer has started in 2009. To ensure the microbiological security of the SPF area embryo transfers are performed under sterile conditions in laminar flow benches while preparation of embryos is performed within a separated small animal operating room.

A total of 166 requests for embryo rederivation from clinical (90.2%) and non-clinical (9.2%) institutions has been submitted and 113 mouse lines could successfully be transferred into the clean area. Breeding colonies under specific pathogen- free (SPF) conditions could be established and maintained from all these mouse lines. In summary, the Transgenic Technology unit provides a platform of advanced technologies to successfully support and perform biomedical research programs.

*Fig. 2: Mice in the open area of the animal facility.*

*Fig. 3: Blastocyst injection in a small animal operating room.*

# 5.2.5 Interdisciplinary Center for Addiction Research (ICAW)

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## General Information

ICAW has developed in 2000 from the interdisciplinary BMBF addiction research network (1996-2001) focusing on neurobiological and behavioral foundations of 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. For this purpose an outpatient and consultation-liaison program for the treatment of alcohol and nicotine addiction has been established at the department of psychiatry, psychosomatics and psychotherapy in 2008 in connection with the reestablishment of a full professor position in psychiatry focusing on addiction medicine (Prof. Fallgatter). Additionally, the Dept. of Psychology I established a full professorship for Interventional Psychology (Prof. A. Kübler) with a focus on addiction research.

## Major Research Interests

**Neurophysiological assessment of cerebral cue reactivity in substance dependence**
(A. J. Fallgatter, M.M. Schecklmann, L. Ernst, A. Dieler, 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 understanding 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 in 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 the 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).

**Genetics of alcohol addiction**
(K.P. Lesch, Psychiatry, Psychobiology)

Neurobiological and psychobiological processes such as reward-related behavior, 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 for the development of addiction**
(C. Jacob, 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.

**Addiction and Mental Disorders**
(J. Deckert, Dept. of Psychiatry, Psychosomatics and Psychotherapy)

The relevance of substance abuse and dependence other than alcohol (caffeine, nicotine, amphetamine and cannabis) and its neurobiology for the pathogenesis and therapy of mental disorders has developed as an additional research topic, partly within the context of the SFB-TRR58 on "Fear, Anxiety and Anxiety Disorders". It focuses on the modulation of mental disorders by substance abuse– related genetic factors and the consequences of substance abuse for the therapy of mental disorders employing drug monitoring as well as genetic and imaging techniques.

**Substance and behavioural addiction: executive function and learning**
(Kübler, A. Meule, Y. Paelecke-Habermann, Dept. of Psychology I)

**a) Addiction as automatic behavior and failure of executive control**
Although the concept of automaticity is not sufficient to explain the emergence and maintenance of addiction, there is no doubt that addictive behavior shows components of automaticity. Addiction could be seen as a failure to instantiate executive control to overcome cue-induced automatic behavior. To investigate this hypothesis, we developed a visual search task that allows us to investigate automatization, automaticity and re-establishment of executive control within few training sessions. In cocaine addicts we could show, that dorsolateral prefrontal cortex is less activated than in healthy subjects when executive control is required after automatization. We are currently adapting the visual search task to specific addictions and eating disorder. (DFG Graduiertenkolleg)

**b) Deficits in reward learning as a component of addiction**
In addicted subjects positive reinforces such as food, sex, or other pleasurable activities lose their rewarding qualities; the brain reward centres such as the Nucleus accumbens remain silent when confronted with such stimuli. It could thus be hypothesized that a deficit in reward learning could be a component of addiction. In a group of smokers such deficits in implicit and explicit learning could be shown. We are currently investigating whether such deficits can be shown in non-addicted social drinkers, women with restrained eating behavior, addicted smokers, non-smokers and smokers in the state of withdrawal.

## 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 is an additional teaching activity. 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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## General Information

Since 1996, women at risk for familial breast and ovarian cancer are offered specialized counselling in Germany. Currently, 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; University Women‘s Hospital; Department of Psychotherapy and Medical Psychology, and Institute of Diagnostic Radiology.

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 agreed to include a “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 prinicipal 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 onset 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. Over 800 of these families were followed in the Würzburg centre. Mutations in either BRCA1 or BRCA2 were identified in many of these families. 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 overall breast and ovarian cancer risks to less than 5% via prophylactic bilateral mastectomy, in combination with bilateral salpingo-oophorectomy. 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 German 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 concerns 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 two BRCA genes are found. This could be due to undetected mutations or mutations in other genes known to be associated with breast cancer, including ATM, BRIP1, PALB2, and others. Some of these lower penetrance genes are studied in parallel in the Fanconi anemia research laboratory of the Department of Human Genetics. Recently, rare pathogenic mutations in RAD51C were identified in families with breast and ovarian cancer. Another possibil-

ity 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.

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# 5.2.7 Transplant Center (TPZ)

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## Clinical Transplantation

The Transplant Centre Würzburg (TPZ) is one of several German transplant centres. Since the ratification of the German Transplant Act between 35 and 45 transplantations per year could be achieved in the kidney transplant program. The number of transplantations is thereby depending on the size of the waiting list. Due to the ever increasing discrepancy between organ demand and supply the living donation program was enforced on the one hand, furthermore far more organs with expanded donor criteria were accepted (for example in the Eurotransplant Senior program). Fluctuations are mostly due to the number of acceptable living donors, until the end of 2009 68 living kidney-transplants of related and unrelated donors were performed. Altogether 817 kidneys were transplanted in close cooperation of the Division of Nephrology and the Department of Urology since the start of the program in 1984. Furthermore 13 combined kidney-pancreas-transplantations and one combined kidney-liver-transplantation were performed together with the Department of Surgery I. Actually 213 patients are waiting for a kidney graft in Wuerzburg.

Since 1989 also 30 heart transplantations, two of them in 2009, were conducted by the Department of Thoracic and Cardiovascular Surgery in collaboration with the Department of Internal Medicine I. At present 7 patients are admitted to the waiting list.

Between 1992 and 2007 71 liver transplants had been performed by the colleagues of the Department of Surgery and the Department of Internal Medicine II (Divisions of Hepatology and Gastroenterology). It is planned to reactivate the liver program in 2010. In 2009 225 stem cell transplant were performed at the Universitätsklinikum Würzburg for adult patients. Thus the stem cell transplantation programme in Würzburg is the second largest in Germany. Our SCT programme includes novel approachies like cord blood transplantation, haploidentical stem cell transplantation and adoptive T cell therapy.

All patients of the programs mentioned above are served by the outpatient departments of the involved sections, most of them together with resident practitioners in the vicinity. Also involved is the Department of Dermatology with a special out-patient clinic for patients transplanted with a solid organ.

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.

### Clinical and Experimental Transplantation Research

All specialities mentioned above are involved in multiple multicenter studies, either investigator-driven or with industrial sponsoring. Diverse dissertations and publications originate from this work. Wuerzburg 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. Close cooperations exist with the universities in Oxford / UK, 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, the next meeting will take place in autumn 2010 for the 11th time. In regular yearly intervals seminars for patients and resident (“fit for transplantation”) physicians are arranged with great success, in 2009 more than 250 participants attended.

## SELECTED PUBLICATIONS


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# 5.2.8 Comprehensive Cancer Center Mainfranken

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## General Information

The Comprehensive Cancer Center Mainfranken developed from the 1983 founded „Interdisciplinary Tumour Center at the University Wuerzburg". The CCC Mainfranken is a multidisciplinary cancer therapy and cancer research centre with the primary function to treat patients with tumour diseases in an optimal way and accordingly to the most recent level of medical knowledge. All involved disciplines like prevention, diagnostics and therapy cooperate in the treatment of oncologic diseases. The medical specialists work closely together with biologists and other scientists to perform cancer research on an international and competitive level.

The University Hospital Würzburg, the clinical-theoretical and the theoretical institutes of the medical faculty are part of the CCC Mainfranken. Research cooperation is maintained also with other faculties of the University.

Members of the CCC Mainfranken are also the Academic Teaching Hospitals (Julius-Spital and Medical Mission Hospital in Würzburg as well as the Hospitals in Aschaffenburg and Schweinfurt), additional hospitals and specialists in private practices of the region Mainfranken.

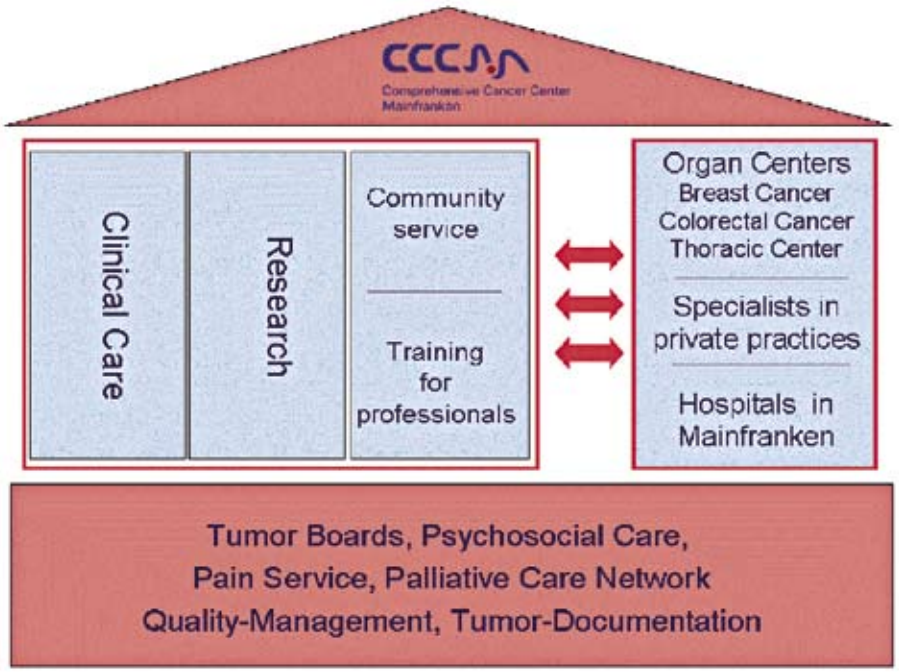
**The medical care** of patients suffering from cancer is provided at the University Hospital and its affiliates on an interdisciplinary basis. The CCC Mainfranken offers the structural framework for an efficient cooperation. Experts from all involved departments participate in weekly interdisciplinary tumour conferences. They discuss and decide therapy concepts based on most recent guidelines reflecting the evidence based knowledge for a successful treatment.

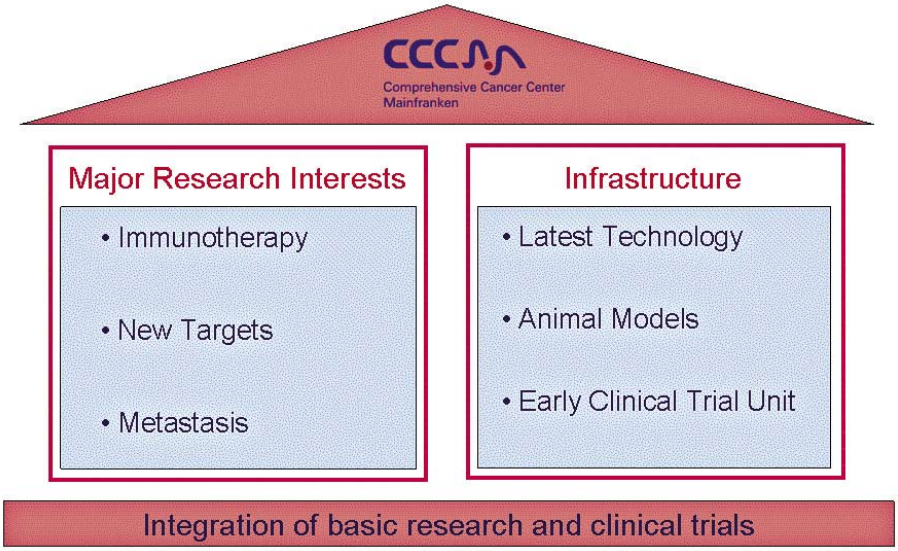
**Further offers for** patients and the community:

- Psychological support during all phases of disease by qualified psycho-oncologists
- Social service
- Information about self-help groups
- Palliative care network
- Information about different tumour diseases

**The clinical cancer registry** collects long term follow-up data and mortality information of tumour diseases. This is an important tool to monitor the quality of treatment. The cancer registry is also entrusted with the epidemiological cancer registration for the bavarian population based cancer registry (www.krebsregister-bayern.de). This registry aims to discover regional and temporal differences of cancer incidences and provides useful data for cause studies and healthcare research.

## Major Research Interests and Research Infrastructure






At the CCC Mainfranken, the oncologic research is intensively carried out on three levels - basic research, translational and clinical research - in order to be able to offer patients the most recent knowledge and advances of medicine as soon as possible. Main research interests are therapies of malignant diseases by using defence mechanisms of the immune system, the description of new targets to control tumour diseases and investigation of the molecular mechanisms of metastasis. The latest technology and special animal models are used for research.

A special facility of CCC Mainfranken is the Early Clinical Trial Unit where clinical trials of phases I and II a/b are offered for patients with advanced tumour diseases. Since establishing this trial unit in 2007, 15 phase I/II studies testing several novel compounds could be initiated. This unit aims on the development of targeted molecular and immunological therapies.

The clinical and laboratory research of several departments embedded in the CCC Mainfranken were and are substantially funded through third-party grants.

Several EU projects of the Department of Internal Medicine II focus on further development of immunotherapy for cancer diseases and fighting infections in affected patients. (Euro Net Leukämie, MANASP. AlloStem, NANO II). Additional projects of this Department, funded by DFG, the German Krebshilfe, Mildred Scheel Foundation, Carreras Foundation, International Myeloma Foundation and by Sanderstiftung are working on the induction of tumour-specific immune response and the improved treatment of myeloma patients. The scientists focus on new concepts of a better GvHD prophylaxis and B-cell-reconstitution following allogeneic stem cell transplantation, as well as improving diagnostics and therapy of fungal infections in immune-compromised patients. Aspects of umbilical cord blood transplantation are examined of a project supported by the Carreras foundation.

KFO 216 (Characterisation of the Oncogenic Signalling Network of the Multiple Myeloma: Development of Targeted Therapies) is one of the clinical research groups (scientific leadership: Prof. Dr. med. R. Bargou) supported by the DFG who are working on oncological subjects. Twenty scientists of six different departments of the University of Wuerzburg are participating. Apart from the Dept. of Internal Medicine II the following institutes are cooperating: the Institute for Pharmacy and Food Chemistry, the Institute for Organic Chemistry, the Institute for Virology and Immunobiology, the Institute for Pathology and the Dept. of Physiological Chemistry. In addition there is a close cooperation with scientists and clinicians of the Dept. of Internal Medicine II at the University of Ulm.

Six interdisciplinary teams of the clinical research group KFO 124 (The Tumor Microenvironment: Target and Immune Modulator of the Immune Response; scientific leadership: Prof. Dr. med. J. Becker) are dedicated to analyse ongoing anti-tumor immune responses in situ in the context of the tumor microenvironment. The results can be applied to clinical aspects in order to improve the efficacy of immune therapy for malignant disease and to establish new anti-cancer vaccines directed at the tumor micromilieu.

# 5.2.9 Comprehensive Hearing Center Würzburg

CONTACT DETAILS

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## Mission and Structure

The Comprehensive Hearing Center Würzburg (CHC) is an interdisciplinary, integrative center for diagnosis, counselling and research regarding all aspects of hearing. It is spatialized to the Department of Oto-Rhino-Laryngology, Plastic, Aesthetic and Reconstructive Head and Neck Surgery. Patients with hearing disorders and their relatives a comprehensive counselling on all possible diagnostic measures and therapeutical options is offered.

The combination of different diagnostic and therapeutic institutes comprising hearing research, care units, supporting companies and rehabilitation institutes allows for a comprehensive expertise on all aspects of hearing.

Patient´s care takes place in an interdisciplinary setting, according to the latest developments in science and medical techniques. Postclinical treatment is adjusted individually with all cooperating rehabilitation partners.

### Hearing Research

Experimental and applied research provides the latest information in all aspects of hearing, which is integrated into treatment strategies. Networking with local as well as international research groups allows for the actual state of knowledge, being integrated into patient´s care. In order to intensify the interdisciplinary research concepts, a foundation professorship on "Experimental hearing research" shall be established. The Wuerzburg CHC concept lead to a worldwide network of cochlea implant centers, which are in close cooperation under the roof of "Hearring" (www.hearring.com).

### Development of innovative instruments

Together with partners of the biomedical industry new instruments are developed with a special focus on a practical design at the CHC. This further development comprises diagnostical instruments as well as improved implant systems. The possibilities of intense testing of new devices and instruments in an optimized clinical setting keep the CHC attractive for new co-operation partners.

### Interdisciplinary Treatment

Hearing disorders often have a difficult pathophysiological background, which necessitates an interdisciplinary diagnosis and treatment. Starting with the first hearing tests in newborn babies, developmental aspects are included as well as non-medical support. Furthermore direct involvement of companies offering specialized supplying service is part of the treatment concept.

### Follow-up Care and Rehabilitation

In many cases surgical therapy has to be followed by a highly specialized support service, especially in hearing implants. First fitting of the implant processor normally takes place in the implanting clinic, for further after-care and rehabilitation CHC has close contact to all important rehab institutes in Germany. This guarantees an optimal and individualized support with the necessary feed-back to the hearing center.

## Major Research Interests

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

Histological morphometry and surface characteristics of middle ear implants; immunology and immunohistology 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. Development of coated electrode carriers for medicamentous treatment of middle and inner ear.

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

LASER-vibrometrical measures of middle ear mechanics in petrous bones. Clinical and experimental investigations of middle ear implants and transplants using EDP supported documentation. Intraoperative monitoring of transmission function in active middle ear prostheses.

**Inner ear biology**
(R. Mlynski, K. Rak, N. v. Wasielewski in cooperation with the Institute of Neurobiology, M. Sendtner)

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

*Fig. 1: Neuronal differentiation of adult stem cells for application in the inner ear (guinea pigs).*

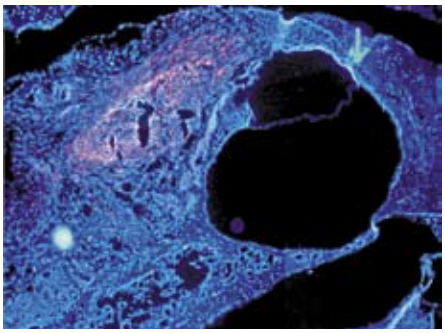

*Fig. 2: Active migration of stained stem cells (pink) from basal cochlear turn (guinea pigs).*

cells; investigations of function of vasodilator stimulated phosphoproteins (VASP) in terminal hair cell innervation.

**Impact of stem cells in auditory pathway**
(A. Radeloff, K. Rak, R. Mlynski)

Detection of adult stem cell populations in inner ear and central auditory pathway. In-vivo application of cultured stem cells to damaged inner ear in animals (guinea pigs).

**Pedaudiological tests and newborn hearing screening**
(W. Shehata-Dieler, D. Ehrmann, R. Keim in cooperation with the Center of Pre-speech Development and Developmental Disorders, K. Wermke)

Development of new objective test procedures for frequency specific examination of newborns. Investigation of pre-speech sounds in infants as a new tool for pedaudiological testing.

**Cochlear- and brain stem implants**
(J. Müller, W. Shehata-Dieler, A. Radeloff, S. Brill, S. Kaulitz in cooperation with the Department of Neurosurgery, C.Matthies, and Univ. of Innsbruck, P. Nopp)

Evaluation of new stimulation strategies for further improvement of speech intelligibility following cochlear and brain stem implantation. Advancement of intraoperative telemetry and monitoring systems.

**Experimental audiology**
(M. Cebulla, R. Keim, W. Harnisch in cooperation with the Department of Psychiatry, Psychosomatics and Psychotherapy, A. Fallgatter)

Further development of diagnostic tools for objective frequency specific measurement of the absolute threshold of hearing. Objectification of binaural hearing in normal hearing and hearing impaired persons.

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

Electrophysiological basic research on central-neuronal processing of acoustic and electric stimulation of auditory pathway in an animal model.

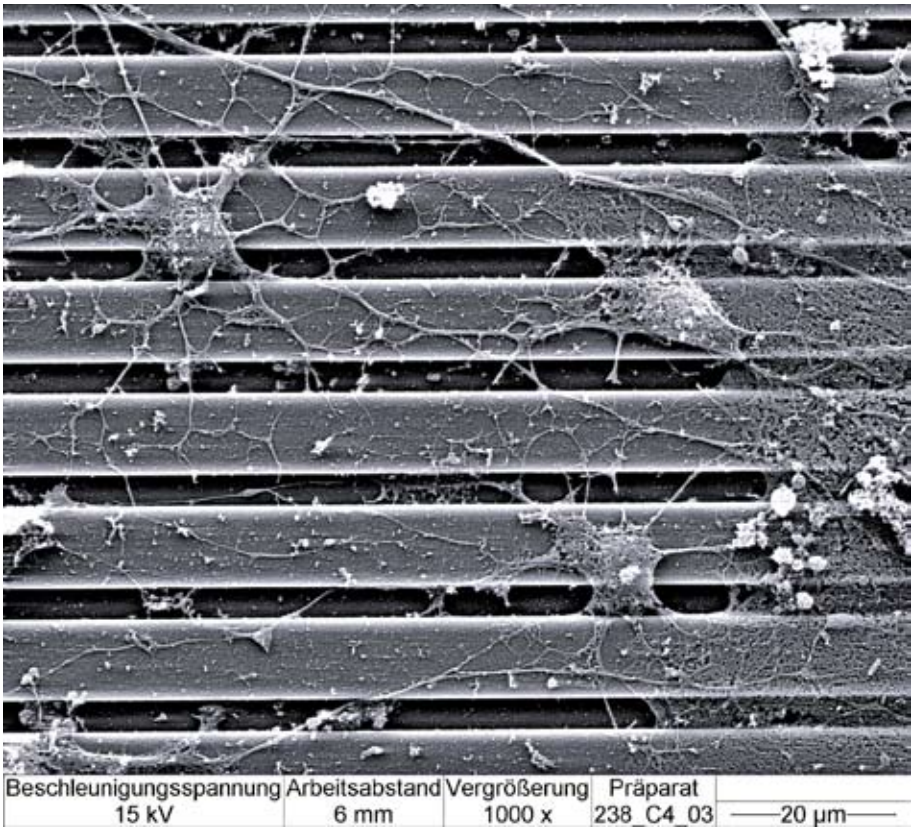


*Fig. 3: Collateral sprouting of neuronal cells on semiconductor-material.*

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# 5.2.10 Center for Intestinal Medicine

CONTACT DETAILS

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**Professor Dr. med. Christoph-Thomas Germer**
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The University of Würzburg's Center for Intestinal Medicine was first certified by the German Cancer Society and the Southern Technical Inspection Authority in September 2008.

Since then, the number of patients has increased by 40%. Our aim is to provide the highest quality of therapy for each individual patient. Different clinics and departments work together to ensure the best possible care. We provide medical care in cooperation with the patients' physicians, nutrition counselling and psychological and social services. Individual therapy plans are developed in the weekly tumour board meetings. The high quality of care is also a result of the proximity of the doctors and care givers involved in the Centre for Intestinal Medicine. Physicians in private practice and other partners in the region perform the outpatient examinations wherever possible and, when necessary, refer patients to the Centre for Intestinal Medicine. Here they benefit from having all their therapies in one place. We offer several cancer therapies along with specialty services in prevention and rehabilitation. An effective pain therapy and counselling for patients with a colostomy are other important services available.

Because we are certified, we have an increasing number of patients involved in clinical studies.

The Center for Intestinal Medicine passed the reassessment for certification with flying colours in August 2009. This seal of quality, based on strict guidelines of the German Cancer Society, acknowledges the high quality of our care for patients with colon cancer.

**Participating Clinics and Institutes:**

- Clinic for General, Visceral, Vascular and Pediatric Surgery (Surgery I)
- Clinic for Radiation Therapy
- Institute for Diagnostic Radiology
- Medical Policlinic II (Hematology and Oncology)
- Institute of Pathology
- Institute for Psychotherapy and Clinical Psychology???

Appointments for prevention and therapy of colon cancer can be made through the central patient management unit (ZPM) in Surgery I, Tel. (0931) 201-39999.

# 5.2.11 Center for Rheumatic Diseases

CONTACT DETAILS


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## General Information

The diagnosis and treatment of immune mediated diseases is one topic at the medical faculty of the university of Wuerzburg. The Center of Rheumatic Diseases founded in 2003 is an association of different institutes and clinical centers that are dedicated to rheumatic diseases. In addition to members of different medical, surgical, diagnostic or research specialities of the university hospital also hospitals and physicians in private practice outside the university are integral parts. The aim of the Center of Rheumatic Diseases is to improve the health care of patients suffering from rheumatic diseases in the greater area surrounding the university hospital of Wuerzburg. Particularly the interdisciplinary cooperation in teaching, science and clinical care will be improved. The Center of Rheumatic Diseases is a member of the working group of Centers for Rheumatic Diseases within the German society of rheumatology.

## Major Research Interests

The Center for Rheumatic Diseases by itself does not institute scientific projects. However it promotes scientific interactions and cooperation programs of its members and sustains scientific projects dealing with rheumatic diseases. For that purpose the center organises interdisciplinary meetings and regular informal scientific workshops. At national level the Center for Rheumatic Diseases contributes regularly to the German epidemiological register for rheumatic diseases.

## Teaching

The Center for Rheumatic Diseases is particularly involved in teaching. It coordinates the lectures, seminars and internships for clinical immunology/ rheumatology in the graduate program. In addition it commissions relevant continuing education for doctors in training and rheumatology specialists.

# 5.2.12 Center for Stem Cell Therapy

CONTACT DETAILS


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**Professor Dr. med. Matthias Eyrich**
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**Activities**

The stem cell therapy unit was established in 2005. In 2009, we offered a graft to 239 adult and paediatric patients. 154 received an autologous and 85 an allogeneic transplant. To accomplish this program, the „Gemeinsame Stammzell-Labor“, which means a high end stem cell processing unit joined by the Medizinischen Klinik II and the Universitätskinderklinik, is of paramount importance. Here, most elaborated techniques are utilized to visualize, isolate and cryopreserve discrete cell populations in order to create the optimal cellular composition of the graft. The production process is performed under good manufacturing practice. Based on these competences, the major focus of the joined research program lies in modular cellular therapy and accompanying translational research.

**Immune reconstitution after allogeneic stem cell transplantation**

After launching the allogeneic stem cell transplantation program in 2005, analysis of immune reconstitution after stem cell transplantation over HLA-barriers has been one of our major research activities. Aim of the project is to increase safety and efficacy of established immunotherapeutic approaches like donor-lymphocyte infusions (DLIs) as well as augmenting the anti-leukemic potential of the graft. Another important subproject of the „Immune reconstitution-program“ are the multifacetted interactions between human hematopoietic stem cells and Notch-ligand expressing stroma cells. Emphasis of the investigations are the lymphoid differentation pathways resulting from these interactions under various conditions.

**Novel cellular therapies for malignant brain tumors**

Under the umbrella of a newly established, EU-wide network innovative cellular therapies for patients with malign brain tumors are developed, validated and finally tested in clinical trials. One of these approaches includes the vaccination of glioblastoma patients with autologous, tumor-lysate pulsed dendritic cells (DCs) with subsequent application of in vitro generated, tumor-specific T cells. In preparation of a phase I/II clinical trial, comprehensive validation experiments for clinical grade and scale production of DCs and antigen-specific T cells are currently carried out. The implementation of production procedures compatible with regulatory constraints in a GMP-facility represent a particular challenge of these concepts. Once established, these clinical trials will underline the dedicated immunotherapeutic emphasis of our stem cell transplantation program.

*Fig.1: The building D30 hosts the Center for Stem Cell Therapy.*

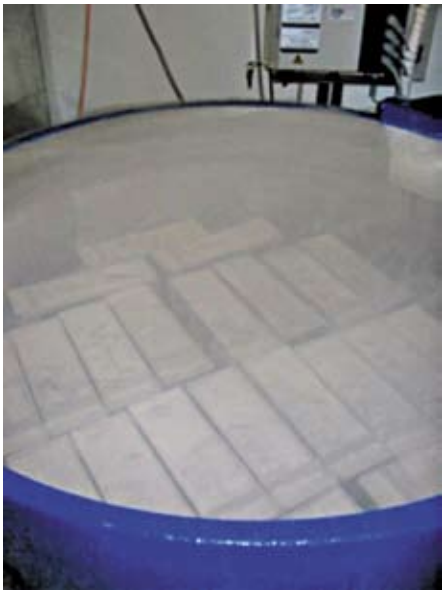

*Fig. 2: The stem cells are stored in liquid nitrogen at minus 196 °C.*

**Immune therapy of chronic CMV infection**

In the first DC vaccination trial after allogeneic SCT, we treated 24 patients suffering from chronic CMV infection. The DC vaccination was tolerated without any relevant toxicities. Vaccination led to a significant benefit compared to a historic control group.

**Adoptive immune transfer of streptamer selected T cells**

We are chairing a national multicenter trial investigating the safety and efficacy of streptamer selected CMV specific T cells in chronic CMV infection after allogeneic SCT. The CMV specific T cells are selected from an unstimulated leukapheresis of the stem cell donor or, in case of a seronegative stem cell donor, from a CMV seropositive third party donor.

**Cord blood transplantation**

Cord blood transplantation is an alternative option for patients who urgently need an allogeneic stem cell graft but lack a suitable donor. Well established in the paediatric setting, cord blood grafts are increasingly employed for adults. Central fort the broad applicability of cord blood is the finding that cord blood derived T lymphocytes are highly active against leukemia without inducing an overt risk for graft versus host reactions despite HLA discrepancies.

In cooperation with researchers from Heidelberg and Düsseldorf, we carefully investigate the hematological and immunological reconstitution of bone marrow function after cord blood transplantation. To this end and supported by the Deutsche Jose Carreras Leukemia Foundation, we successfully established a clinical and scientific protocol within a multicenter phase I/II study.

**Haploidentical stem cell transplant program**

Our haploidentical stem cell transplant program focuses clearly on the reduction of transplantation related mortality (TRM). We are chairing an international multicenter trial (Study Chair Europe and Wuerzburg: S. Mielke; Sponsor Kiadis Pharma, The Netherlands) on the use of selectively allodepleted donor lymphocytes as a novel method of an adoptive immune transfer after T cell depleted haploidentical blood stem cell transplantations to cut down on TRM. In a first step donor lymphocytes are ex vivo co-cultured with irradiated patient-derived peripheral blood mononuclear cells. In a second step patient-reactive donor-derived lymphocytes are eliminated by the photodepletion pocess. This trial is associated with respective translational scientific program studying the specific immune reconstitution following haploidentical transplantation.

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# 5.2.13 Cleft Lip and Palate Center

CONTACT DETAILS

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## General Information

In the Cleft Lip and Palate Center of the University of Wuerzburg patients were treated with congenital anomalies and syndomes in the maxillo-facial region. The treatment sequence is characterized by interdisciplinary cooperation with the Maxillo-Facial Surgery, the Otorhinolaryngology, the Pediatric Clinic, the Gynecology and the Institut for Human Genetics. The treatment starts immediately after birth and continues to adulthood.

A nationwide unique Center for Prespeech Development & Developmental Disorders (Prof. K. Wemke) is integrated in the Cleft Lip and Palate Center. Approximately 40 newborns a year with a cleft lip palate were newly attended for treatment in the Center for an orthodontic consultation.

## Major Research Interests

**Three-dimensional stereophotogrammetric diagnostics of the face of babies with congenital cleft lip and palate**
**Establishing and three-dimensional evaluation of a non-invasive dynamic treatment method for presurgical nasoalveolar orthopedic molding**
(P. Meyer-Marcotty, U. Bareis, A. Stellzig-Eisenhauer)

Three-dimensional data for the facial soft tissues of babies and infants with cleft lip and palate will be generated during the course of this research project. The objective is to analyze three-dimensionally the presurgical molding of the external nose with orthodontic pads and to assess longitudinal progress.

**Development and testing of non-invasive orthodontic plate appliances to treat obstructive apnea in neonates with Pierre Robin sequence.**
(U. Bareis, A. Stellzig-Eisenhauer in cooperation with the Pediatric Clinic)

**Identification of early indicators of later speech and language disorders in babies with cleft lip and palate**
(K. Wermke)

Research activity at the Center for Prespeech Development & Developmental Disorders (ZVES), Department of Orthodontics, University of Würzburg aims to identify early indicators from early baby sounds that might be used to detect specific risks of speech development disorders. Based on the results of an interdisciplinary longitudinal project, the German Speech Development Study, which was sponsored by the DFG (German Research Foundation) and the Max Planck Institute of Cognitive and Brain Sciences, Leipzig, we were able to identify suitable risk markers in the 2nd and 4th month of life (incl. Wermke et al., 2007; Denner, 2008; Wermke et al., submitted). We are currently in the process of testing these risk markers in babies with orofacial clefts for their suitability in clinical practice.

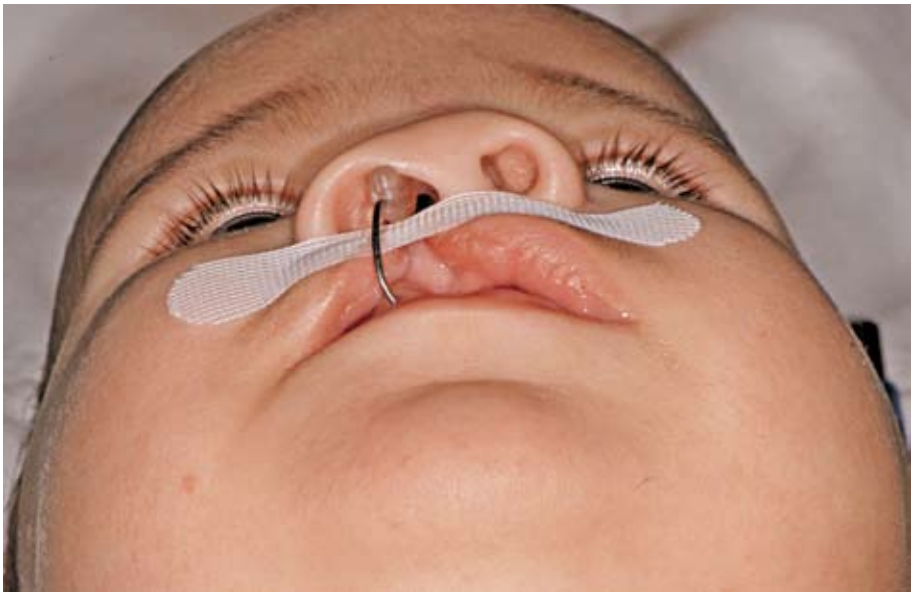

*Fig. 1: Preoperative nasoalveolar molding with an orthopedic plate in a newborn with a cleft lip and palate.*

*Fig. 2: Orthopedic appliance with a nasal stent.*

**Language development disorders in children with congenital cleft lip and palate**
(Longitudinal study in cooperation with D. M. Hansen and A. Jurkutat, University of Würzburg, Philosophy Faculty III, Department of Special Needs Education III, Speech Therapy Education and the Department of Ear, Nose and Throat Diseases, Plastic and Cosmetic Surgery)

Children with congenital cleft lip and palate, owing to their complex damage in the oronasopharyngeal area, display physiological functional impairment which results in secondary developmental disabilities. These include impairment of articulation, phonation and respiration in the children concerned. The causal connection between organic defect and the resulting speech characteristics is obvious. However, the question of whether language-systematic development abnormalities additionally exist in children with cleft deformities has not yet been adequately resolved. In view of the heterogeneity of the research results on language development in children with cleft lip and palate, starting with a doctoral thesis project based on selected models for language acquisition, various hypotheses about the etiology of language development disorders are being put forward and empirically tested. Suitable test methods for evaluating the language skills of children with cleft lip and palate aged 4–5 years will be deduced from the results and applied in subsequent longitudinal studies.

**Interdiciplinary consultation-hours cleft lip and palate:**
Tuesdays, 2:00 to 4:00 PM, contact: 0931/201-73330 or –73320, Department of Orthodontics, Professor Dr. med. dent. Angelika Stellzig-Eisenhauer, Pleicherwall 2, 97070 Würzburg

SELECTED PUBLICATIONS


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*Wermke, K., Robb, M. Fundamental Frequency of Neonatal Crying: Does Body Size Matter? J Voice. 2009 Aug 5.[Epub ahead of print].*

# 5.2.14 Level I Perinatal Center

CONTACT DETAILS

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## Mission and structure

The Mother- and Children-Centre (Level I Perinatal Centre) is a joint institution of the departments of Obstetrics and Gynecology and of Pediatric comprising two obstetrical wards, 5 labour and delivery rooms, an operating room for caesarean sections and outpatient clinics for obstetrics, reproductive medicine and prenatal diagnostics. For healthy newborns there exit a nursery room. Furthermore, the Perinatal Centre has a special care unit for moderately premature infants and newborns, who must be observed, and a neonatal intensive care unit for extremely preterm baby's und critically ill newborns. On the neonatal intensive care unit preterm infants and newborn with severe disorders and congenital malformations are treated on state of the art technology and by highly qualified staff. This is done in close cooperation with the departments of Pediatric Neurosurgery, Pediatric Surgery, Urology with Pediatric Urology, Ophthalmology, Oto-Rhino-Laryngology, Thoracic and Cardiovascular Surgery, Orthopaedics and Orthodontics. In 2009 there were 1482 births with 51 very low birth weight infants with a birth weight below 1500 g.

## Major Research Interests

**Possible role of imbalance of angiopoietin-1 and endostatin in the pathogenesis of bronchopulmonary dysplasie (BPD)**

Chorioamnionitis and funisitis have been shown associated with preterm labor and postnatal pulmonary morbidity of preterm infants. A systemic inflammatory response of the fetus is a risk factor for BPD. Impaired pulmonary angiogenesis accompanied by simplification and rarification of alveoli is a histological hallmark of BPD. Angiopoietin-1 mediates vascular development, maturation, and stabilization. Endostatin mainly acts as an angiostatic factor. In a cohort of extremely premature infants funisitis was associated with decreased concentrations of endostatin and angiopoietin-1 in airways during the very early phase of premature life. Infants, who developed BPD, had a decreased ratio between angiopoietin-1 and endostatin suggesting an imbalance toward inhibition of pulmonary angiogenesis.

**Long time effect of BPD on physical activity and exercise capacity in children**

In this current study the long time effects of BPD on lung function, physical activity and exercise capacity of school age children are analysed.

**Serum and glucocorticoid-inducible kinase (SGK1) in pulmonary tissue of preterm fetuses exposed to chorioamnionitis.**

The purpose of this set of studies was to analyse if the expression of SGK1 is influenced by chorioamnionitis by studying lung tissue sections of stillborn fetuses with or without chorioamnionitis. SGK1 stimulates epithelial Na(+) channel ENaC and the Na(+)/K(+)-ATPase activity, an effect presumably participating in the regulation of transepithelial Na(+) transport. It could be shown that exposure to chorioamnionitis is associated with a downregulation of SGK1 in fetal lung tissue. The possible consequences of a decreased rate of SGK1 could be an impaired ability to clear the lungs from excessive fluid immediately after preterm birth.

**Antenatal inflammation induced TGF-β1 but suppressed CTGF in preterm lungs**

TGF-β1 and CTGF are key regulators of lung development, airway- and vascular-remodeling. We asked whether chorioamnionitis-associated antenatal inflammation would regulate TGF-β1and CTGF expression in preterm lamb lungs. It could be shown that antenatal inflammation-induced TGF-β1, but decreased CTGF expression in preterm lung. This dysregulation may inhibit vascular development or remodeling and limit lung fibrosis during remodeling. These effects may contribute to the impaired alveolar and pulmonary vascular development that is a hallmark of BPD.

**Thymic changes after chorioamnionitis induced by intraamniotic LPS in fetal sheep**

Regulatory T-cells (Treg) mediate homeostasis of the immune system and differentiate under the control of the transcription factor FoxP3 in the fetal thymus. Using an animal model of chorioamnionitis we assessed if fetal inflammation caused by chorioamnionitis would modulate thymus development. Results show that antenatal inflammation during fetal life induces thymus changes and influences Treg development. Possible consequences of these temporary changes in the immune system in postnatal life remain to be studied, but accumulating evidence suggests an important role for antenatal inflammation in fetal programming and subsequent disease development.

**Fetomaternal interface**

The interactions between the maternal immune system and the placenta that lead to tolerance of the fetus are 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.

**Therapeutic strategies for the treatment of premature labour**

Tocolytic drugs have different mechanisms

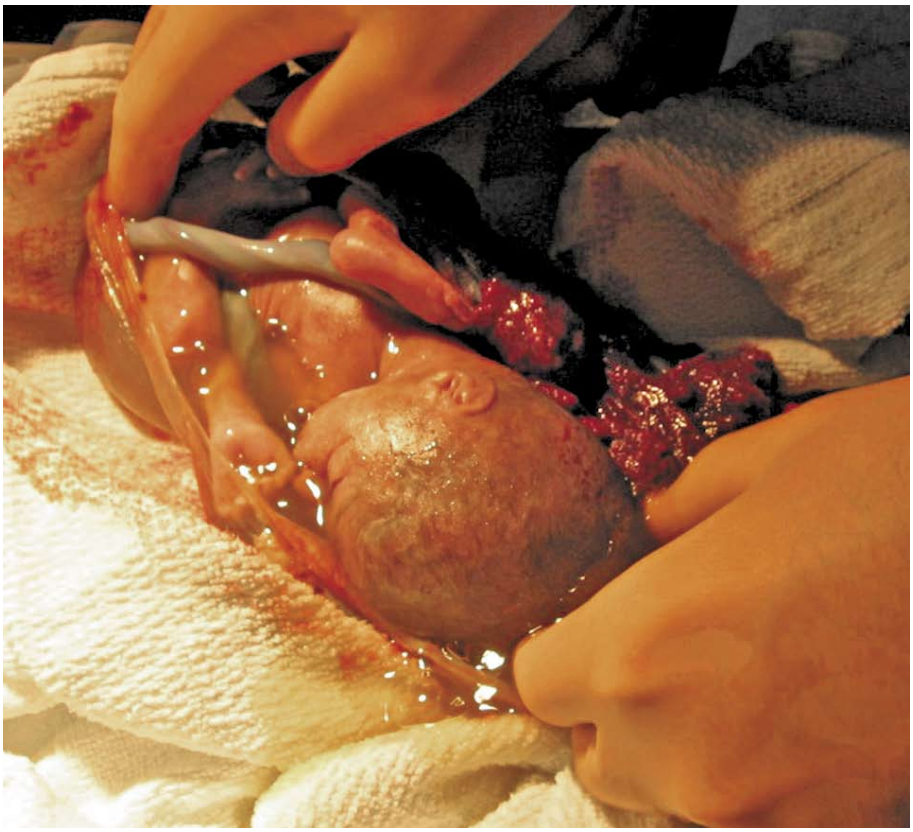

*Fig. 1: Extremely low birth weight preterm infant with a birth weight of 450 g.*

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, 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.

## Teaching

The Mother- and Children-Centre offers several courses for medical students. In a "skill`s lab" students have the opportunity to train clinical situations and to handle diagnostic equipment. Once a week, there is an interdisciplinary conference between the department of Obstetric and Pediatric as part of the Perinatal Centre. In addition, regular 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.

## SELECTED PUBLICATIONS


*Thomas W, Seidenspinner S, Kramer BW, Kawczynska-Leda N, Chmielnicka-Kopaczyk M, Marx A, Wirbelauer J, Szymankiewicz M, and Speer CP. Airway concentrations of angiopoietin-1 and endostatin in ventilated extremely premature infants are decreased after funisitis and unbalanced with bronchopulmonary dysplasia/death. Pediatr Res 65: 468-473, 2009.*

*Wirbelauer J, Schmidt B, Klingel K, Cao L, Lang F, and Speer CP. Serum and glucocorticoid-inducible kinase in pulmonary tissue of preterm fetuses exposed to chorioamnionitis. Neonatology 93: 257-262, 2008.*

*Kunzmann S, Speer CP, Jobe AH, and Kramer BW. Antenatal inflammation induced TGF-beta1 but suppressed CTGF in preterm lungs. Am J Physiol Lung Cell Mol Physiol 292: L223-231, 2007.*

*Rieger L, Segerer S, Bernar T, Kapp M, Majic M, Morr AK, Dietl J, and Kammerer U. Specific subsets of immune cells in human decidua differ between normal pregnancy and preeclampsia--a prospective observational study. Reprod Biol Endocrinol 7: 132, 2009.*

*Segerer SE, Muller N, van den Brandt J, Kapp M, Dietl J, Reichardt HM, Rieger L, and Kammerer U. Impact of female sex hormones on the maturation and function of human dendritic cells. Am J Reprod Immunol 62: 165-173, 2009.*

# 5.2.15 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 unite the clinical and scientific competence of different institutions regarding prevention and treatment of cardiovascular diseases, their 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 to science 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.

The central interest of the cardiovascular center lies in the prevention and treatment of heart failure and its complications. However, while mortality from coronary artery disease is decreasing, mortality from 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. Results from molecular biology, genetics and physics 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 Heart Failure Network" (supported by funds of the BMBF) as well as the "Mainfranken Heart Attack Net" (see below) fostering interdisciplinary research, teaching and patient care, and the initiative for an "Integrated Centre for Research and Treatment Heart Failure". The latter has proposed a Comprehensive Heart Failure Center (CHFC), which has been positively evaluated in three rounds (final vote pending). The principal research objective at the CHFC will be the comprehensive advancement of care for patients with heart failure thus improving their quality of life and life expectancy. The CHFC aims to pursue preventive strategies on all levels of disease development – from the clarification of basic mechanisms leading to heart failure to the advanced and terminal stages of heart failure and its complications and comorbidities. The spectrum of research objectives will include diagnostics, treatment and health care strategies. The following themes for research into diagnostic, therapeutic and management strategies of heart failure have been defined: 1. Advancement of Diagnostics and Management; 2. Healing, Remodeling, Protection; 3. Rare Heart Diseases and Genetic Principles; 4. Endocrince System and Metabolism; 5. Cardiorenal Cross-talk; 6. Heart Failure: Emotion, Cognition, Cerebral Dysfunction; 7. Advanced/End-stage Heart Failure, Tissue Engineering and Regenerative Medicine.

The cardiovascular center has also an important role in continuing medical education. Interdisciplinary student education and meetings have been organized including a corollary course of 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 continue to be organized in collaboration with the Deutsche Herzstiftung.

### Interdisciplinary Network Heart Failure and National Competence Net Heart Failure

Prof. Ertl is co-chair of the national competence net heart failure. The cardiovascular center contributes 5 out of 20 projects and has collaborations with several others, as for example *SP6a* "New diagnostic strategies – Cardiac imaging and serum-/plasma-markers", C. Angermann/G. Ertl, SP6b "Etiology and prognostic relevance of beta1-receptor autoantibodies in human myocardial diseases", R. Jahns/C. Angermann, SP15 Disease manifestation and management in chronic heart failure (Randomized INH Study), C. Angermann/G. Ertl. More than 3,000 patients have been included in registries, cohort studies and trials of the local Interdisciplinary Network Heart Failure in order to test the efficacy and effectiveness of disease management programmes including cardiologic as well as psycho-educative interventions to monitor and educate patients with heart failure. The translation into patient care is being developed. Associat-

ed 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 in patients with heart failure and depression is tested in association with the department of psychiatry. Furthermore, the connection of rheumatic and cardiac diseases is tested in collaboration with the Medizinische Klinik II. Another large project has been launched in March 2010: The ETiCS study (R. Jahns/G. Ertl) will investigate the role of activating autoantibodies directed against the cardiac beta-adrenergic receptor in a series of cross-sectional and longitudinal studies. ETiCS is a collaborative effort of the competence net, also involving several other European universitary centers investigating the biomaterials and clinical data sets of more than 1,300 patients and healthy subjects. The main aim is to elucidate the pathogenetic role of these antibodies in human heart disease also utilizing high-end diagnostic tools that were developed at the University of Würzburg.

**Mainfranken Heart Attack Net**

The Mainfranken Heart Attack Net was funded in 2007 to connect emergency physicians with cardiologists and cardiothoracic surgeons in order to minimize the time for cardiac interventional therapy. If coronary artery intervention appears not to 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.

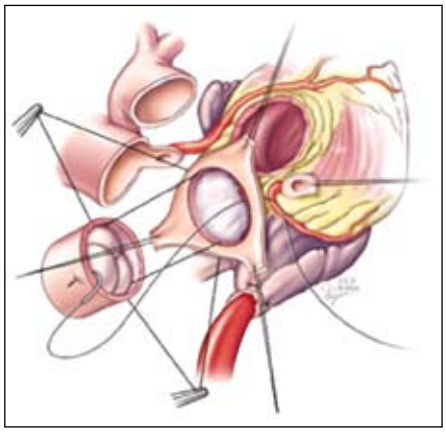
**SFB 688**

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 chapter 5.1.6, page 140). Besides the SFB there are numerous interdisciplinary collaborations as demonstrated by a large number of publication. Many of them are supported by the IZKF (see separate chapter 5.2.2, page 153).

**Department of Thoracic and Cardiovascular Surgery**

Prof. Rainer G. Leyh was appointed new director of the department on April 1 2007. Apart from a dramatic increase in the case load for open heart surgery various operative procedures have been introduced in Würzburg: Complex aortic procedures like Ross, David and Yacoub operations and emergency operations of aortic dissections have been established on a large scale. 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 internal medicine I the cardiovascular surgery department facilitates transferral of patients in cardiogenic shock with the life-bridge-system (a miniaturized and portable heart-lung support system). This measure will continue to strengthen the impact of the Mainfrank Heart Attack Net and the clinical management of these high risk patients.

Furthermore, the cardiac transplantation program has been reinstituted, supporting interdisciplinary research in the field of heart failure and strengthening the cooperation with the Interdisciplinary Network Heart Failure. Scientific interest is centered around improvement of donor acceptance criteria for heart and lung transplantations and basic and clinical research into transplant vasculopathy. Selected patients with end-stage heart failure benefit from ventricular mechanic support system (assist devices) and/or complex cardiosurgical procedures as, e.g., reconstruction of the left ventricle. Finally, minimally invasive surgery techniques for mitral and aortivc valve surgery are currently beeing established. Thus, thoracic and cardiovascular surgery has become a decisive contributor for the research focus Heart Failure.



# 5.3 Research Training Groups
# 5.3.1 Research Training Group 520, Immunomodulation

CONTACT DETAILS

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## General Information

The DFG funded Graduate College Immunomodulation completed a full term of three times three years at the end of 2008, and received funding for a limited number of graduates for an additional year. In the meantime, the popularity of this graduate college led to an increase in associated members, allowing its continuation as a graduate training programme within the class "Infection and Immunity" of the Graduate School for Life Sciences with more than 30 participants.

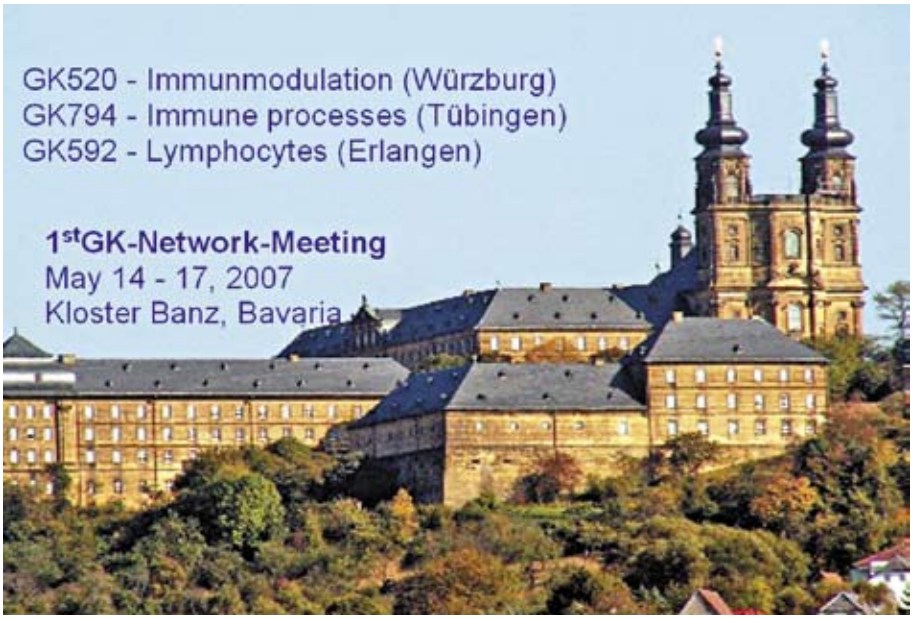
## Major Research Interests

Graduates from all research groups at the University of Würzburg working on immunological topics are welcome in the graduate training programme. Basic immunology performed in rodent models is complemented by infection biology, tumor immunology and clinical immunology.

## Teaching

The wide spectrum of research within the framework of immunology provides the training programme with specialist teachers who guarantee a comprehensive education. During the period of the DFG funded graduate college, a versatile training programme has been developed in which teaching modules vary each semester. These include the joint study of a modern immunology textbook, miniprojects to learn new techniques, journal clubs, and progress reports.

2009 saw the 4th joint retreat with two other graduate colleges, GRK 592 "Lymphocyte Activation" (Erlangen) and the GRK 794 "Cell Biology of immune-associated processes" (Tübingen), and we plan to continue this fruitful tradition. Funding for this retreat is now provided by the GSLS, and a limited number of GSLS graduates from other training programmes is offered free participation.



# 5.3.2 Research Training Group 1048, Molecular Basis of Organ Development in Vertebrates

CONTACT DETAILS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## General Information

The aim of the research training group GRK 1048 is to provide a structured PhD research and training environment in Developmental Biology. The scientific goal is to contribute to a better understanding of the molecular mechanisms of morphogenesis, patterning, cell specification and cell differentiation as the basis for the establishment of a fully functional, healthy organism. Under the paradigm that normal and pathological development often uses the same molecules and pathways, the topic of the GRK 1048 is of immediate relevance to medicine. Consequently several projects address questions that are directly linked to disease development or understanding stem cell development for regenerative medicine.
After a very successful first period (4/04-9/08) the GRK 1048 is now in its second funding term by the German Research Foundation (DFG).

## Major Research Interests

The research program addresses questions in the field of Developmental Biology with a special emphasis of organogenesis and provides collaborations that offer Ph.D. students a broad interdisciplinary training basis. It is focused 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. 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 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 germ cell development. Experiments are done in four model organisms (mouse, frog, zebrafish and medaka) 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. The research training group is part of the “Graduate School of Life Science (GSLS)”. Structures of supervision such that each student has a Thesis Advisory Committee that mentors her/him during the entire training period his have been established. On an annual basis the project of each student is evaluated and restructured as necessary to guarantee a successful completion. The qualification program of GRK 1048 offers PhD students a broad interdisciplinary training in up to date methods and concepts of modern biomedical research with a thematic focus on developmental biology, cell differentiation and organogenesis. In order to optimally prepare the students for a career in research, the qualification programs combine seminars, lectures and retreats with workshops, soft skills and practical training modules. 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 career.


*Fig. 1: Double staining of spermatocytes from wildtype and lamin C2 deficient (ΔC2) mice for the synaptonemal complex (SC). The axial element protein SYCP3 is stained in green and the lateral element protein SYCP1 in red. Spermatocytes from ΔC2 mice have univalent sex chromosomes and show unpaired axes (arrowheads).*

# 5.3.3 International Research Training Group 1141, Signal Transduction: Where Cancer and Infection Converge

CONTACT DETAILS


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**(Speaker Würzburg)**

**Professor Dr. rer. nat. Thomas Rudel**
**(Speaker)**

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## General Information

The German-French DFG research training group GCWN (GK 1141) is a collaboration between the universities of Würzburg and Nice. The funding agency is the German Research Foundation (DFG) and the program runs from February 2005 until July 2010. Currently about a dozen PhD participate in the education program of this graduate college. Nine students have already acquired their PhD in the GK 1141.

In Würzburg the GK1141 was affiliated to the class of „Infection and Immunity“ of the Graduate School of Life Sciences (GSLS) in 2006. The GK 1141 receives additional funding by the German-French College (http://www.dfh-ufa.org), which is used for exchange programs and student education. This education is performed with a focus on interdisciplinarity, teaching a broad practical and theoretical knowledge in a number of scientific areas.

## Major Research Interests

One of the major similarities between the pathogenesis of some infectious pathogens and cell transformation leading to cancer are pathological alterations in cellular signalling processes. In this teaching program emphasis is placed on the similarities between infection and cancer. Three major research areas are covered:

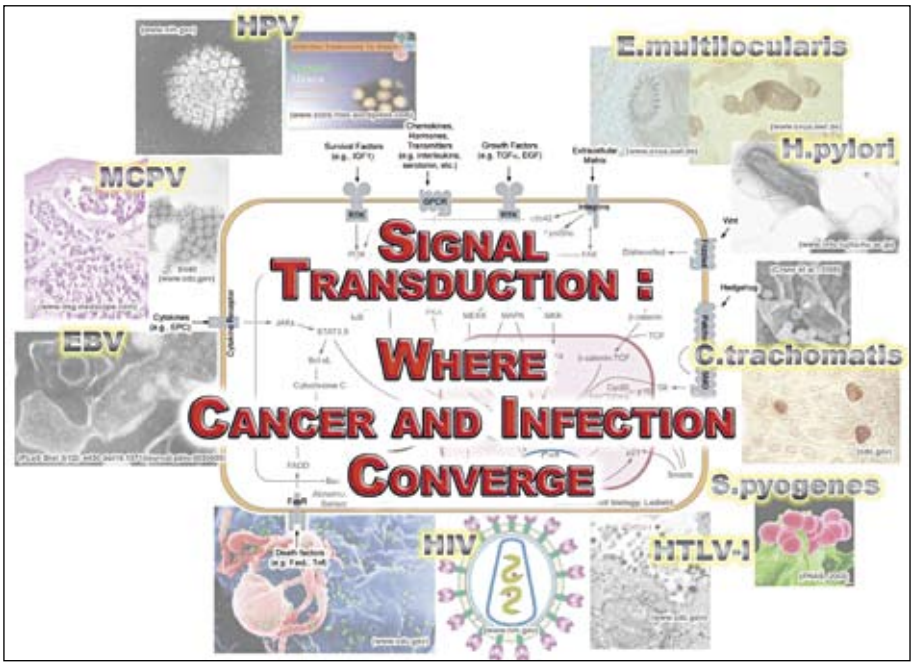
1) Regulation of the MAP-Kinase-Pathway under physiologic conditions and in disease
2) Manipulation of cellular signalling during the infection by pathogens
3) Utilization of bacteria as trojan horses for therapeutic manipulation of the cellular signalling cascades or direct triggering of anti-tumor responses

This research training group connects scientists from different scientific areas such as immunology, microbiology and cancer research. The overall aim of this group is the generation of synergies between these scientists for establishment of novel therapeutic approaches against infections and cancer.

## Teaching

The student training encompasses project specific and general aspects. During weekly seminars the members of the GK 1141 have to teach each other on current scientific ‚hot topics‘, current publications, textbook chapters or overviews and insights of general scientific interest. During these seminars the student members in addition invite and host external speakers. During a retreat once a year distinct topics are highlighted and examined in detail. Furthermore courses dealing with complex lab methods or science theory are conducted. Due to the affiliation with the GSLS the members of the GK1141 may participate in the courses and seminars offered by the International Graduate School Würzburg.

The student members are supervised during their thesis by an individual committee. This committee consists of scientists from the Universities of Würzburg and Nice. At least once a year all committee members meet with the student to discuss the status quo and the future focus of the thesis.



# 5.3.4 Research Training Group 1156, From Synaptic Plasticity to Behavioural Modulation in Genetic Model Organisms

CONTACT DETAILS

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## General Information

The Research training Group 1156 was set up in 2005 as a joint 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 are offered an interdisciplinary training programme aimed to study the genetic and cellular basis of synaptic plasticity using a methodologically broad approach. The research training group provides funding for 12 students from the Faculties of Biology and Medicine at the University of Würzburg. An integral part of the training 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 students of this International Research Training Group are also members of the class "Neuroscience" of the International Graduate School at the University of Würzburg.

## Major Research Interests

The major scientific research topic of the GK 1156 is the relation between brain and behaviour. 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", 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 co-

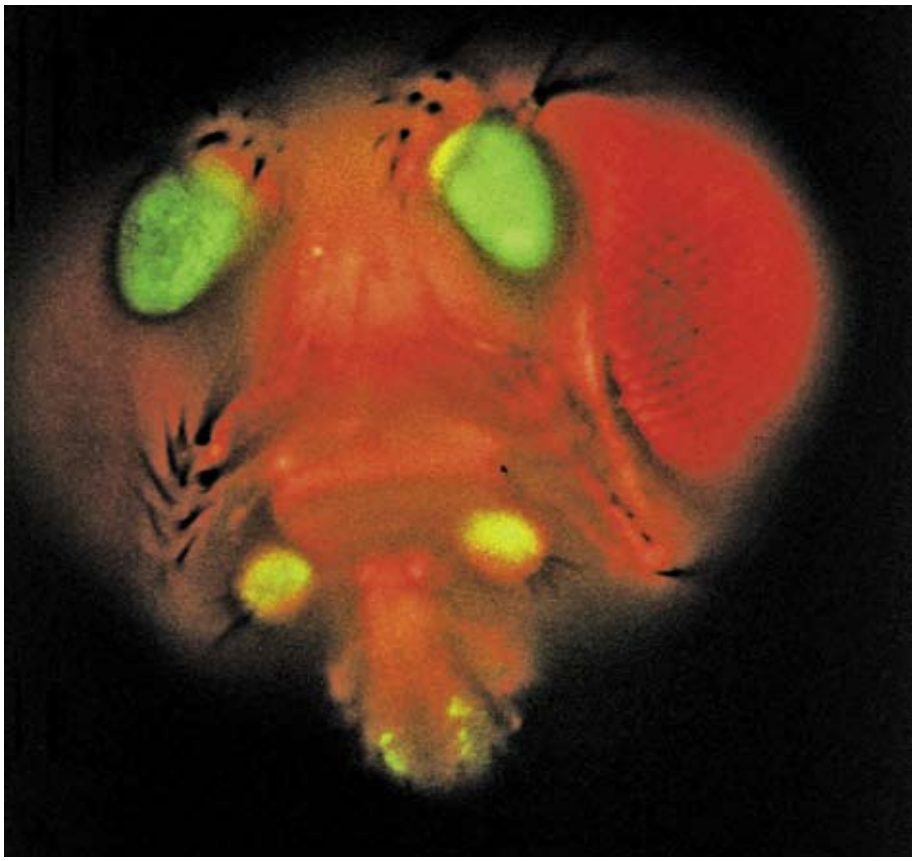

*Fig. 1: Brain of an adult fly (red; in green the mushroom bodies, the associative center for odour learning).*

operations 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 Imaging, 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.

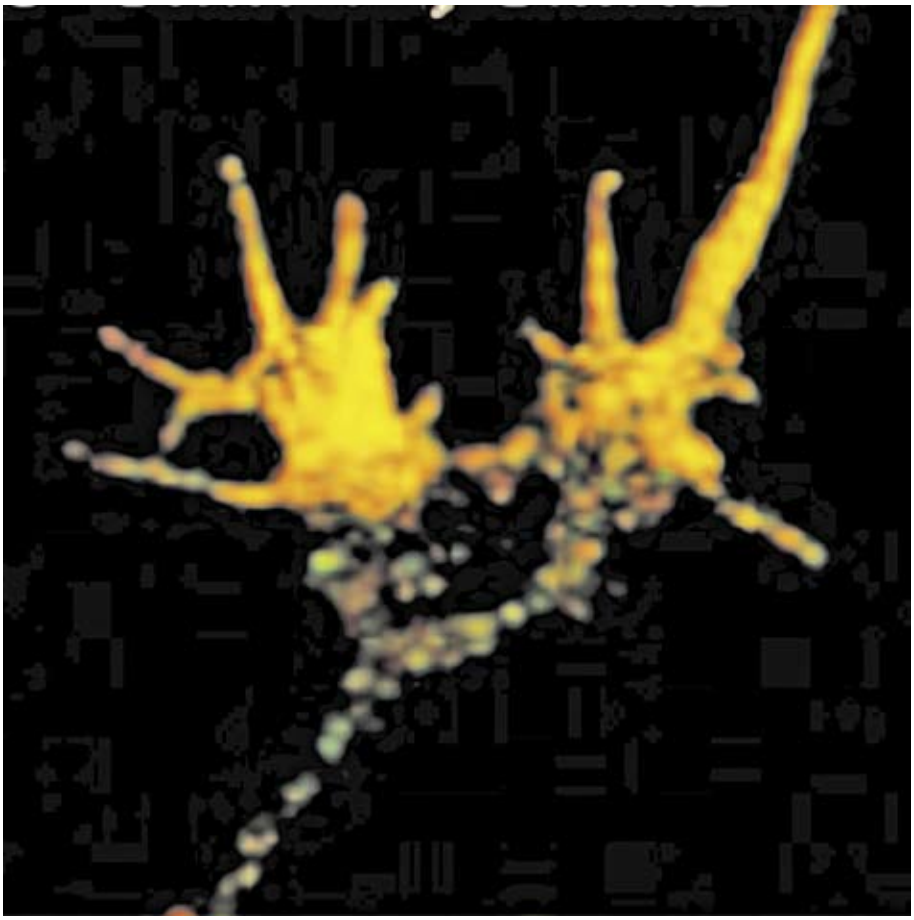

*Fig. 2: Presynaptic clustering of N-type Ca-channels in growth cones of isolated mouse motoneurons. Motoneurons form clusters of Ca-channels (green) with other components of the active zone (piccolo, stained in red), this process is disturbed in motor neuron diseases such as spinal muscular atrophy.*

# 5.3.5 Research Training Group 1253, Emotions

CONTACT DETAILS


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**Professor Dr. med. Klaus-Peter Lesch (Vice-Speaker)**
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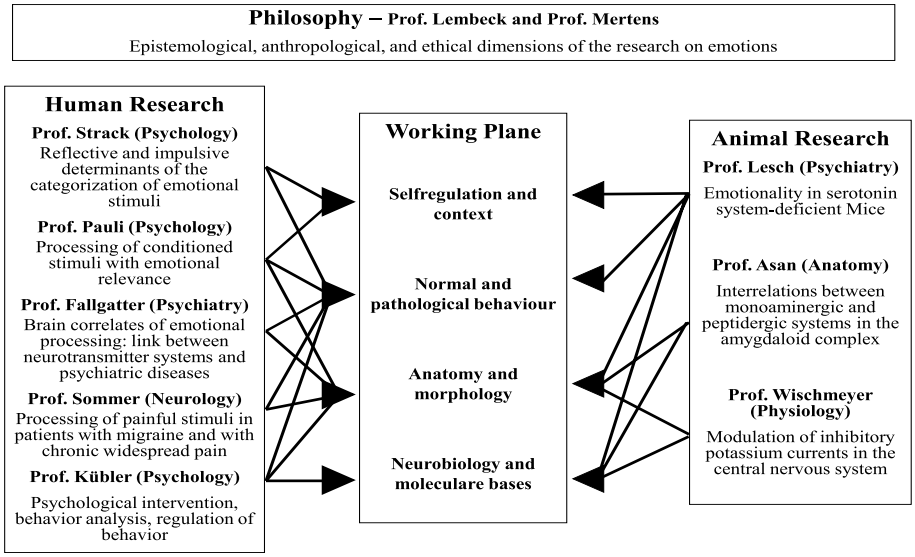


*Fig. 1: Principal Investigators and structure of the RTG.*

## 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.

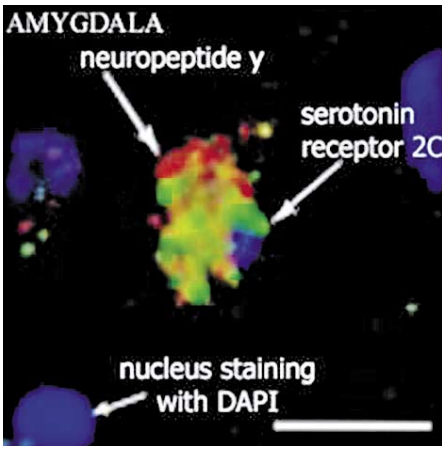


*Fig. 2: Lateral Amygdala (LA). Double Fluorescence in situ hybridization in the lateral nucleus of the rat amygdala. Red: neuropeptide y mRNA; green: serotonin receptor 2C mRNA; yellow: colocalization; blue: nuclear staining with DAPI; magnification: 20x; scale bar: 20µm.*

## 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 (Fig. 1). 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.

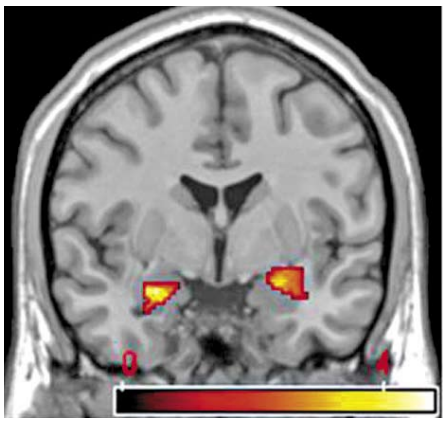


*Fig. 3: Sagittal view of a human brain. Red-yellow shadings indicate activation in the amygdala due to the view of a threatening stimulus.*

## Teaching

Internet: http://www.gk-emotions.uni-wuerzburg.de/teaching/
The weekly Jour Fixe (Journal Club) provides the possibility to discuss both new results and the research project of the PhD students. International guest speakers are invited for seminars, lectures and the two meetings, i.e. the spring and the summer schools outside Würzburg. The PhD students take part in lab rotation as well as attend soft skills courses, provided free by the RTG and the GSLS. The students can participate on external events any time. Every year the work of the PhD students is evaluated by their three principal investigators, who work in interdisciplinary institutions.

# 5.3.6 International Research Training Group 1522, HIV/AIDS and Associated Infectious Diseases in Southern Africa

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## General information

The principal aims of the International Research Training Group 1522 are to translate clinical into basic research on infectious diseases (ID) in South Africa (SA), to acquaint German PhD and medical students with conditions of transmissible diseases that are currently only very rarely seen in Germany (GE), and to broaden the fields of basic research currently undertaken at Würzburg (WÜ) University by adding a new quality into the spectrum of infectious agents/infectious diseases under study on an international level. The background of this proposal is the understanding that whilst Africa has the highest burden of ID of all continents, SA as the most developed country on the continent has excellent research facilities and an infrastructure that enables the research of this programme to be conducted at the same level with German institutions. Taking advantage of the excellent research conditions at the participating facilities in Cape Town (CT) and the experience and broadness of ID research at WÜ University, a programme is conducted that (a) allows the analysis of clinical samples with methods currently not available in SA, (b) complements ongoing research activities in WÜ by adding novel scientific aspects, (c) fosters basic research in SA in fields which are of utmost importance and in which expert teams are not currently present in the Western Cape region, and (d) guides young scientists through an organised postgraduate student education and exchange programme into basic research and into the medically important clinical conditions of ID in SA. In particular, the student exchange programme is central to this proposal. The research topics are divided into three main areas: In the focus of area I are clinical and basic research on HIV/AIDS and on general mechanisms of virus-induced immunosuppression. AIDS-associated opportunistic infections will be investigated in area II, while area III covers questions on the immunology of ID. There are numerous interconnections within one and between different areas, which foster inter-project scientific exchange between the groups involved. On the SA side the corresponding speaker is Prof. Dr. Wolfgang Preiser (Virology) at the University of Stellenbosch.

## Research topics:

**Area I:**
Project 1: The impact of therapeutic drug monitoring on antiretroviral therapy
Scientist: Prof. Dr. Hartwig Klinker
Project 2: Study of drug-resistant HIV
Scientist: Dr. Jochen Bodem
Project 3: Molecular Epidemiology of HIV
Scientist: Prof. Dr. Axel Rethwilm
Project 4: Influence of different HIV subtypes on HIV dementia
Scientists: Prof. Dr. Eleni Koutsilieri and PD Dr. Carsten Scheller
Project 5: Targets, mechanisms and consequences of regulated T cell pre-mRNA splicing and their relevance as genetic markers of virally induced or general T cell suppression.
Scientist: Prof. Dr. Sibylle Schneider-Schaulies

**Area II:**
Project 6: Epidemiology, diagnosis, and molecular mechanisms of multidrug resistance in Candida albicans and its impact on host-fungus interactions
Scientist: Prof. Dr. Joachim Morschhäuser
Project 7: Characterization of the influence of excretory/secretory products from Echinococcus multilocularis larvae on dendritic cell maturation and the interaction of Echinococcus E/S products with TLR and CTL surface receptors
Scientist: Prof. Dr. Klaus Brehm
Project 8: Staphylococcus aureus population structure and host cell interaction in chronic infections
Scientist: Prof. Dr. Dr. Bhanu Sinha
Project 9: Generation and characterization of candidates for malaria/HIV combination therapy
Scientist: Dr. Gabriele Pradel

**Area III:**
Project 10: Characterization of the role of C-type lectins in dendritic cell interactions with Leishmania parasites
Scientist: Prof. Dr. Heidrun Moll
Project 11: Protective and productive inflammatory responses induced by microbial products studied at the level of dendritic cells
Scientist: Prof. Dr. Manfred Lutz
Project 12: The role of CD28 mediated costimulation in the control of secondary immune responses to infectious agents
Scientist: Prof. Dr. Thomas Hünig (WÜ)

# 5.4 Research Units
# 5.4.1 Clinical Research Unit 103, „Osteogenic Stem Cell Differentiation and Therapy of Bone Loss“ and Orthopedic Center for Musculoskeletal Research

CONTACT DETAILS


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## General Information

The Clinical Research Unit 103 „Osteogenic stem cell differentiation and therapy of bone loss“ (KFG103) was funded by the German Research Society from 2001 to 2009 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. During the two funding periods the KFO103 was the core institution to establish the Orthopedic Center for Musculoskeletal Research. The Center consists of 4 sections developed from the 4 in-house KFO103 projects, which are lead by independent scientists. These are dealing with stem cell biology, molecular orthopedics and cell biology, tissue engineering, regenerative medicine and gene therapy. The state of Bavaria, represented by the district of Unterfranken, generously provides the infrastructure and overhead costs for this Center. The facility is run in a 600 sq. m. environment at two different locations with working and laboratory space equipped for S1, S2 and radioactivity working procedures. The Medical faculty decided to promote research on Musculoskeletal Diseases and Trauma as an emerging field at the Research Campus Wuerzburg, in order to establish a new Research Focus for Wuerzburg University. The Musculoskeletal Center Würzburg MCW, founded in 2007, combines all clinics and institutes dealing with Musculoskeletal Diseases and Trauma in research and patient care. The core institutions of the MCW are the chairs for Orthopedic Surgery, Trauma Surgery, Orofacial Surgery, Regenerative Medicine and Material Sciences in Medicine.

## Major Research Interests

The Orthopedic Center for Musculoskeletal Research (KFG103) is an interactive platform, which combines basic science with translational research and clinical implementation of innovative therapeutic strategies. Major Research interests are the biology and differentiation pathways of mesenchymal stem cells and their offspring. We focus on morphogenesis and cellular ageing to meet the needs of translation of e.g. guided differentiation induction and quality control in regenerative therapeutic strategies. The signaling pathways for FGFs, vitamin D, the wnt/frz pathway of differentiation, TGF receptors and their ligands like GDFs and BMPs and also the matricellular signaling molecules of the CCN family of proteins are important topics. We characterize subpopulations of mesenchymal stem cells using genome wide array analyses to enhance our knowledge about the basics of regenerative strategies and to translate this knowledge into standard operating procedures and quality control in cell based therapies. Scientists are involved in research networks funded by the DFG (FOR793 Osteoporotic Fracture Healing), the BMBF (Networks Osteopath and Preeclampsia), the Ministry of Economics (EXIST Phase I), the Bavarian Research Foundation (Network on cell based therapies in the elderly FORZEBRA) and the European Union (Networks ADIPOA and VASCUBONE on cell based strategies in bone and cartilage regeneration), and also the local IZKF of the Medical Faculty.

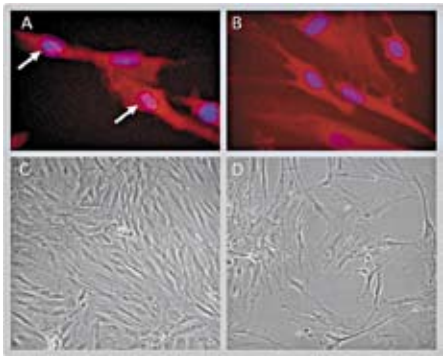


*Fig. 1: Mesenchymal stem cells in culture. Fluorescence staining of nuclear Oct4 expression (A = specific antibody, B = second antibody control) (B. Klotz). Morphology of young versus presenescent mesenchymal stem cells (C and D) (P. Benisch, R. Ebert).*

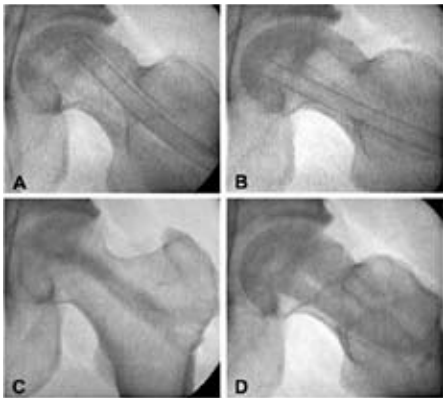


*Fig. 3: Application of mesenchymal stem cells for treatment of femoral head necrosis. A mixture of cells and scaffold material is transferred to the necrotic site of the femoral head via two bore holes using a special plastic funnel (A and B). The peripheral part of the bore holes is sealed with bone substitute material (C and D) (U. Nöth).*

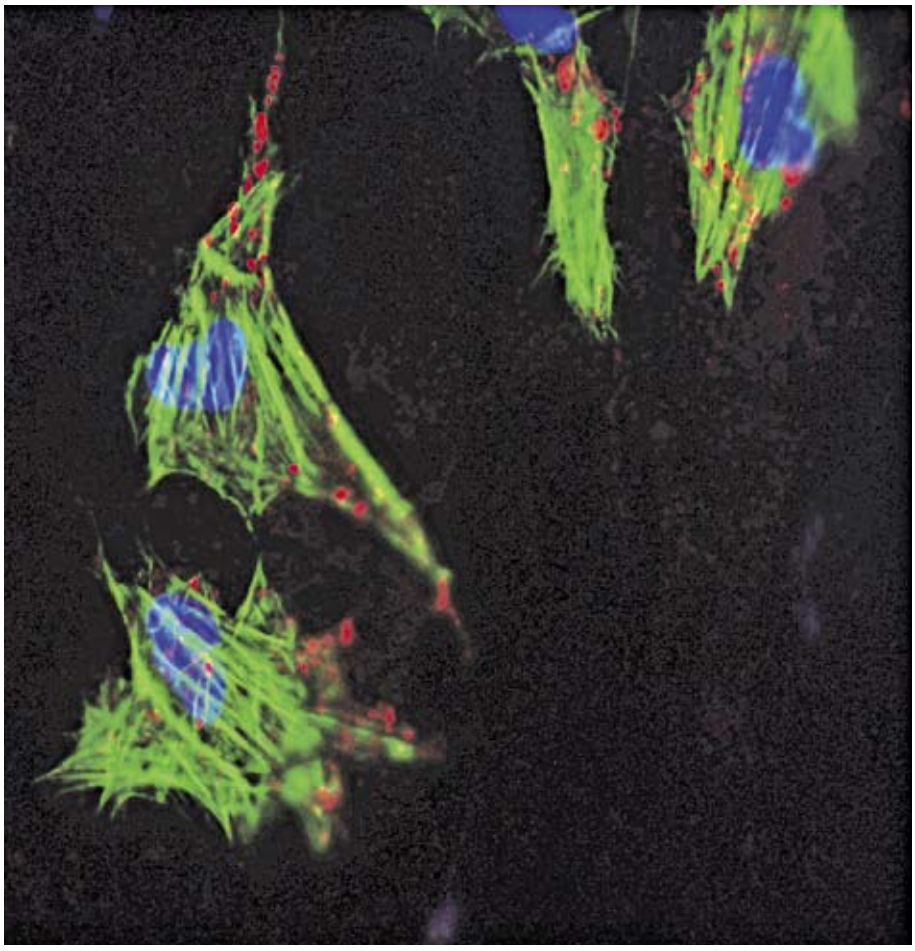

*Fig. 2: Immunofluorescence staining of the cytoskeleton and nuclei of mesenchymal stem cells grown on a collagen type II nanofiber scaffold 24 h after seeding (green = actin, red = tubulin, blue = nuclei) (R. Hallinger, L. Rackwitz).*

**Key Issues in Research**

- Biology of Mesenchymal Stem Cells, Signaling pathways for FGFs, TGFβ/BMP, vitamin D, cellular ageing, fracture healing after trauma and in osteoporosis (F. Jakob, R. Ebert, B Mentrup, P. Benisch, B. Klotz, N. Raijmaakers, S. Müller-Deubert, L. Seefried)
- Mechanobiology and Biomechanics (F. Jakob, L. Seefried, M. Hoberg, R. Ebert, S. Müller-Deubert, A. Steinert)
- Molecular Orthopedics and Cell Biology, Matricellular Proteins of the CCN family in Morphogenesis and Tissue Engineering (N. Schütze, T. Schilling, K. Schlegelmilch, R. Laug, A. Noll, S. Hilpert)
- Regenerative Medicine/Tissue Engineering/Translational Cell Therapy (U. Nöth, L. Rackwitz, R. Hallinger, M. Haddad-Weber, M. Hoberg, M. Rudert)
- Gene Therapy in Musculoskeletal Research and Therapy (A. Steinert, M. Kunz, P. Prager, N. Armbruster, C. Weber)
- Osteology Outpatient Clinic with a focus on osteoporosis and rare bone diseases (F. Jakob, L. Seefried, K. Osterhage, G. Baron)
- Rickets, Special Project on Calcium Deficiency Rickets in Nigeria (F. Jakob, P. Raab, R. Ebert, J. Eulert, C. Kitz (Childrens Hospital), B. Sponholz (Geographic Department)
- Genetics and Molecular Biology of Hypophosphatasia (F. Jakob, C. Beck (Childrens Hospital), B. Mentrup, C. Marschall)
- Molecular Mechanisms of metastatic Bone Disease (F. Jakob, R. Ebert, N. Schütze)

## 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
- TecFun, Technology of Material Sciences

## SELECTED PUBLICATIONS


*Reichert JC, Heymer A, Berner A, Eulert J, Nöth U. Fabrication of polycaprolactone collagen hydrogel constructs seeded with mesenchymal stem cells for bone regeneration. Biomed Mater. 2009 16;4:65001.*

*Ebert R, Zeck S, Krug R, Meissner-Weigl J, Schneider D, Seefried L, Eulert J, Jakob F. Pulse treatment with zoledronic acid causes sustained commitment of bone marrow derived mesenchymal stem cells for osteogenic differentiation. Bone. 2009 May;44(5):858-64.*

*Goebel S, Lienau J, Rammoser U, Seefried L, Wintgens KF, Seufert J, Duda G, Jakob F, Ebert R (2009) FGF23 is a putative marker for bone healing and regeneration. J Orthop Res. 2009 Sep;27(9):1141-6.*

*Steinert AF, Palmer GD, Pilapil C, Nöth U, Evans CH, Ghivizzani SC. Enhanced in vitro chondrogenesis of primary mesenchymal stem cells by combined gene transfer. Tissue Eng Part A. 2009 May;15(5):1127-39.*

*Kunzmann S, Seher A, Kramer BW, Schenk R, Schütze N, Jakob F, Sebald W, Speer CP. Connective tissue growth factor (CTGF) does not affect TGF- 1 induced Smad3 phosphorylation and T lymphocytes proliferation inhibition. Int Arch Allergy Imm 2008; 147(2):152-160.*

# 5.4.2 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 anti-cancer 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 placentation 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.

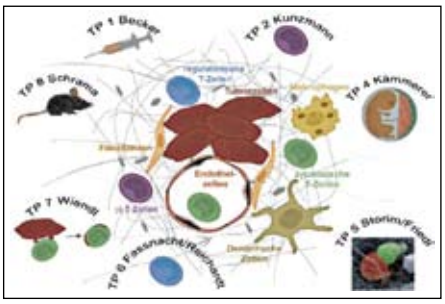


*Fig. 1: Cellular components of the tumor stroma and analysis of different aspects in the KFO124 subprojects.*

### SP Becker

In this project stroma-associated antigens are preclinically and clinically evaluated for anti cancer therapy by eliciting a vaccination induced immune response attacking the tumor stroma and thereby inhibiting tumor progression. In this regard, we not only have identified immunogenic peptides of tumor-stroma-associated antigens survivin, CD105 and S100A4, but also performed the first clinical tests with these peptides.

### SP Fassnacht/Reichardt

This project investigates the interaction of glucocorticoids and the immune system in patients with adrenocortical carcinoma. The group cares for a large number of these patients. Of particular interest is the tumor-induced immune suppression in glucocorticoid-secreting tumours. In addition, the effects of exogenous glucocorticoids on regulatory T cells will be analysed.

### SP Friedl

Immunological control of progressive tumors activation and expansion of tumor specific cytotoxic T lymphocytes (CTL) followed by an efficient effector phase in the tumor microenvironment. We established a real-time 3D matrix-based model of CTL function that allows the observation of active migration, interaction, dissociation and serial killing of CTL with target cells over up

to 24 hours. Using this model, we presently address whether factors present in the tumor microenvironment interfere or enhance of anti-tumor CTL response and serial killing. Ongoing experiments aim at imaging serial killing in vivo using orthotopic melanoma lesions in syngenic mice using adoptively transferred CTL. These studies will help to understand local and cellular determinants of effective, or defective, CTL function in cancer disease.

**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.

**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 immunemodulation in the milieu of the tumor.

**SP Schrama**

The project addresses the role of the nature of the antigen on the development of immune responses. Currently, the impact of natural regulatory T cells on different antigen specific immune responses is investigated. The specific immune responses are directed against antigens which are expressed a) ubiquitary b) localized, or 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


*Friedl P, Weigelin B: Interstitial leucocyte migration and immune function. Nat.Immunol.2008, Sept 9: 960-969.*

*Hofmeister-Müller V, Vetter-Kauczok CS, Ullrich R, Meder K, Lukanidin E, Bröcker EB, Straten P, Andersen MH, Schrama D, Becker JC. Immunogenicity of HLA-A1 restricted peptides derived from S100A4 (metastasin 1) in melanoma patients. Cancer Immunol Immunother. 2009;58:1265-1273.*

*Rieger L, Segerer S, Bernar T, Kapp M, Majic M, Morr AK, Dietl J, Kämmerer U. Specific subsets of immune cells in human decidua differ between normal pregnancy and preeclampsia--a prospective observational study. Reprod Biol Endocrinol. 2009 23:132.*

*Waschbisch A.,,Meuth SG,Herrmann AM, Wrobel B, Schwab N, Lochmüller H, Wiendl H. Intercellular exchanges of membrane fragments (trogocytosis) between human muscle cells: a potential mechanism fort he modulation of muscular immune responses. J Neuroimmunol 2009, 209: 131-138.*

*Weismann D, Briese J, Niemann J, Grüneberger M, Adam P, Hahner S, Johanssen S, Liu W, Ezzat S, Saeger W, Bamberger AM, Fassnacht M, Schulte HM, Asa SL, Allolio B, Bamberger CM. Osteopontin stimulates invasion of NCI-h295 cells but is not associated with survival in adrenocortical carcinoma. J Pathol. 2009;218:232-40.*

# 5.4.3 Clinical Research Unit 125, Attention-Deficit/Hyperactivity Disorder - Translational Research Focus on Molecular Pathogenesis and Treatment Across the Life Cycle


CONTACT DETAILS

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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.

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: 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 (Jacob et al. 2007). 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 environmen-

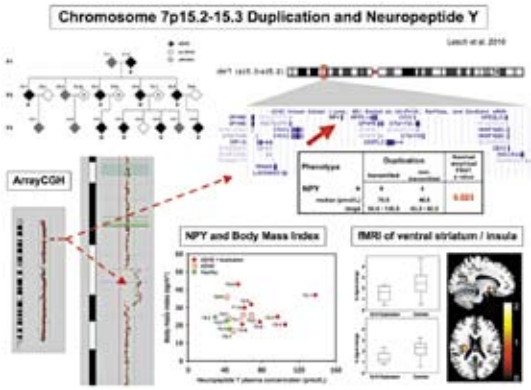


*Fig. 1: Chromosome 7p15.2-15.3 duplication and neuropeptide Y. Segregation of the chromosome 7p15.2-15.3 duplication (D) in a multigenerational family with ADHD is depicted. Affected members are symbolized by solid black symbols when the duplication is present, and by solid grey when absent; unaffected members are identified by open symbols. Moreover, the correlation between neuropeptide Y (NPY) plasma concentrations and body mass index (BMI) in 7p15.2-15.3 duplication carriers with ADHD, non-carriers with ADHD, and healthy family members is plotted. F numbers allow allocation to the pedigree. Finally, neural activation in the ventral striatum during the anticipation of large rewards (upper panel) and in the posterior insula during the anticipation of large losses (lower panel) for 7p15.2-15.3 duplication carriers with ADHD (n = 4) and healthy controls (n = 21) is shown (Lesch et al. 2010).*

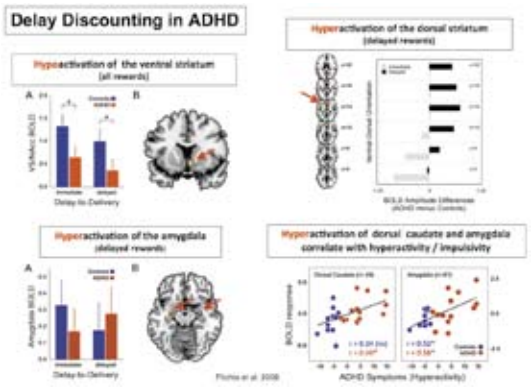


*Fig. 2: Delay discounting in ADHD. Dysfunctional reward processing, accompanied by a limited ability to tolerate reward delays, is a prominent feature in ADHD. Using fMRI, brain activation in adult patients with ADHD and healthy controls was examined during a series of choices between two monetary reward options that varied by delay to delivery. Compared with healthy controls, hyporesponsiveness of the ventro-striatal system was demonstrated in patients with ADHD and was evident for both immediate and delayed rewards. In contrast, delayed rewards evoked hyperactivation in dorsal caudate nucleus and amygdala of ADHD patients. In both structures, neural activity toward delayed rewards was significantly correlated with self-rated ADHD symptom severity. The findings support the concept of a diminished neural processing of rewards in ADHD and are in accordance with predictions of the delay aversion hypothesis (Plichta et al. 2009).*

tal 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 are being performed on extended multigenerational families with high density of ADHD and a sample of affected sib pairs. In addition, identification of SNP variants and copy number variation (CNVs) in genome-wide association (GWA) studies will provide a basis for subsequent studies on genetically modified mouse models of ADHD (Fig. 1) (Lesch et al. 2008, 2010). 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) (Fig. 2) (Plichta et al. 2009, Conzelmann et al. 2009). 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, SFB TRR 58 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 a central goal of the KFO 125. Complex approaches to neurobiological questions and the joint use of techniques and methods derived from genetics, cell biology, and imaging are the hallmarks of Molecular Psychiatry, thus being interdisciplinary by definition.

## SELECTED PUBLICATIONS

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# 5.4.4 Clinical Research Unit 216: Characterization of the Oncogenic Signaling-Network in Multiple Myeloma: Development of Targeted Therapies


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## General Information

The Clinical Research Unit 216 is funded by the Deutsche Forschungsgemeinschaft (DFG) and the Medical Faculty since 2009. The leading institution is the Department of Internal Medicine II. The speaker of the CRU is Prof. Hermann Einsele, the scientific head is Prof. Ralf Bargou. The CRU 216 focuses on key aspects of the molecular pathogenesis of multiple myeloma an uncurable cancer of the hematopoietic system. The ultimate goal of this research work is to identify target structures for the development of novel molecular therapies. The CRU 216 is closely linked to the Early Clinical Trial Unit of the Comprehensive Cancer Center Mainfranken which will facilitate rapid translation of knowledge in basic research into clinical trials. Within the framework of this Clinical Research group 20 scientists from 6 different institutes of Wuerzburg University cooperate in 6 subprojects and 3 core facilities (z projects). This includes the Department for Internal Medicine II, the Institute for Pathology, the Department for Biochemistry II, the Department for Immunology, the Institute for Pharmacy, and the Institute for Organic Chemistry. There is also a close cooperation with physicians and scientists from the Department of Internal Medicine II at Ulm University. Another important aim of the CRU is to implement novel structures for clinical research and to strengthen translational research in hematology and oncology at Wuerzburg University.

## Major Research Interests

The underlying hypothesis for the Clinical Research Unit is the assumption that in multiple myeloma the malignant phenotype results from deregulation not of a single but of a number of signaling pathways, and that these collectively constitute an *oncogenic signalling network*. Consequently, we assume that differences in this network may permit functional definition of novel subgroups of this disease.

It is therefore the aim of this Clinical Research Unit to attempt an extensive functional characterization of the *oncogenic signalling network* to permit the development of novel and effective therapeutic options. This aim will be pursued via two complementing methodical approaches: (1) a combination of functional, molecular and genetic *ex vivo* characterizations of primary myeloma cells, and (2) the development of different genetic mouse models to study and to verify the oncogenic pathways in primary human myeloma samples in vivo. These animal models will eventually serve in preclinical studies of novel therapeutic approaches.

Our previous work has led to the identification of a number of signaling systems that are activated in myeloma cells, such as Ras-, NF-kB-, and stress-response-pathways (e.g. the heat shock protein pathway). Our aim is to appraise the functional importance of these pathways in myeloma as accurately as possible and to analyze if and to what extent they co-operate with each other. In a complementary approach we plan to screen for still unknown signalling pathways by using shRNA-based screening techniques. Finally, we will try to identify the genetic lesions that might lead to the activation of these pathways. To this end we will apply novel genetic technologies such as for example high-throughput sequencing. The results should help to obtain a better understanding of the functional and molecular heterogeneity of this disease. They should also promote identification of novel therapeutically relevant targets and implementation of novel treatment approaches that may be designed to specifically target suitable myeloma subgroups.

**Subproject Chatterjee/Bargou**

Aim of this project is the analysis of Raf-dependent pathways and the interaction of these pathway with the oncogenic signaling network in myeloma cells. This work will clarify whether Raf-dependent signaling pathways might constitute relevant therapeutic targets.

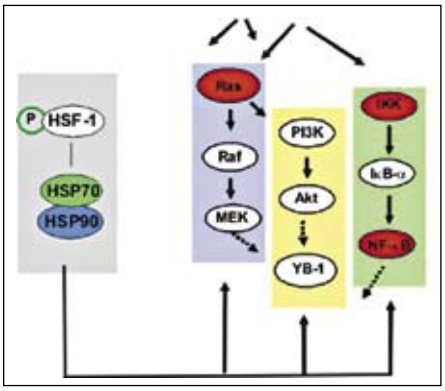


*Fig. 1: Pathways of the Oncogenic Signaling Network identified in multiple myeloma*

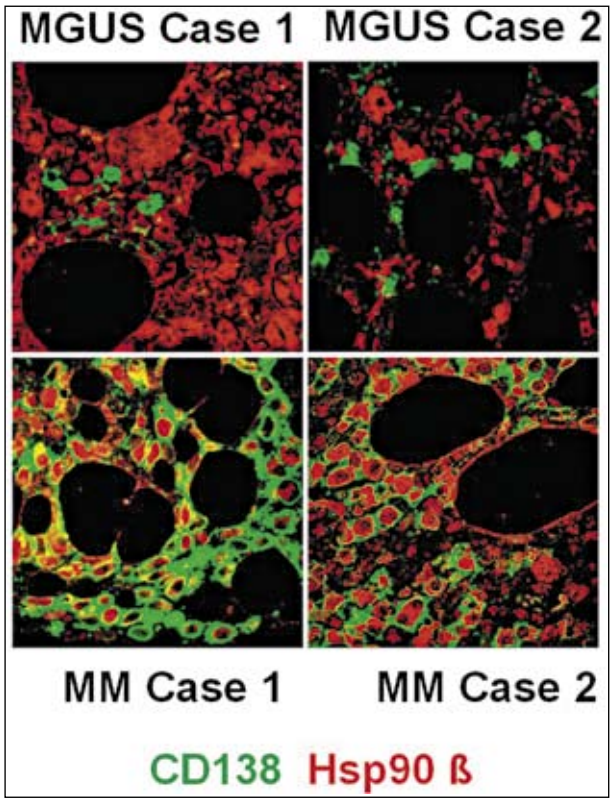


*Fig. 2: Immunohistochemical analysis of HSP90ß Expression in primary Myeloma cells compared to benign MGUS plasma cells (bone marrow biopsies).*

**Subproject Berberich/Hünig**

CD28 is an important co-stimulatory protein that plays a key key role in T cell activation. Expression of CD28 is also found in myeloma cells and is associated with diseae progression and poor prognosis. Aim of this project is to analyze the role role of CD28-dependent signaling in myeloma in vitro as well as in transgenic mouse models.

**Subproject Bommert/Beilhack/Bargou**

In vitro experiments indicate that the cold shock domain protein YB-1 plays a key role in the development of resistance to apoptosis and chemotherapy. Aim of this project is to analyze the role of YB-1 within the oncogenic signaling network *in vivo* in various transgenic mouse models.

**Subproject Topp/Einsele**

The proposed study will focus on the identification of common signaling pathways shared by primary MM cells and activated alloreactive T cells for the dual therapy of graft-versus-host disease (GvHD) and multiple myeloma. Targeted therapy of shared signaling pathway of multiple myeloma and T cells may therefore have the potential to eradicate minimal residual disease after allogeneic stem cell transplantation and to control GvHD.

**Subproject Holzgrabe/ Sotriffer/Bringmann**

Previous work of this project has demonstrated that the heat-shock-protein patheay is frequently activated in myeloma cells and critically contributes to the maintenance of the oncogenic signaling network. Aim of this project is therefore to develop novel pharmacological inhibitors of the heat-shock-protein pathway. This project focuses on HSP90, HSP70, and the transcription factor HSF-1 (heat-shock-stimulating-factor-1).

**Subproject Stühmer/Wajant/Siegmund**

There is increasing evidence that the NF-kB system is a central regulator of the oncogenic signaling network in multiple myeloma that integrates the signals of various other pathways. Aim of this project is therefore to analyze the interaction of NF-kB with other signaling pathways.

**Z Project Haralambieva/Einsele**

This core facility is responsible for isolation, processing and organization of the analysis of primary tumor samples which are obtained through diagnostic bone marrow trepanations. Another duty of this core facility is the analysis of signaling pathways in situ in primary tumor samples by immunohistochemistry.

**Z Project Langer/Döhner**

This z project performs a comprehensive genetic analysis of primary myeloma samples by FISH analysis and SNP Chip Arrays.

**Z Project Eilers/Rosenwald**

Aim of this z project ist the development and implementation of novel genetic and functional screening technologies for the identification of novel oncogenic pathways. This includes shRNA-based sreening approaches as well as high-through-put sequencing technologies.

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# 5.5 Research Alliances
# 5.5.1 Rehabilitation Research Network of Bavaria

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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 (BMBF) and the Germany Statutory Pension Insurance. The main reasons for its establishment were the increasing medical and economical importance of chronic disorders and the consequent need for a more scientific orientation in medical rehabilitation. The RFB's main tasks are to provide well-coordinated and high-quality research, to contribute to the efficient transfer of research results into practice, and to improve the regional research infrastructure on a long-term basis. The premises for these tasks have been funded through the Foundation Professorship for Rehabilitation Sciences at the University of Würzburg's Section of Rehabilitation Sciences and through the Network of Rehabilitation Research of Bavaria (NRFB), which comprises rehabilitation researchers, clinics and agencies.

## Main Research Interests

The main theme of the RFB is "Patients in Rehabilitation: Disease-specific and General Approaches to Motivation, Coping, Intervention and Evaluation". During two separate stages of funding through the BMBF and the Germany Statutory Pension Insurance, a total of 25 projects were established (22 research projects and 3 cross-sectional projects). The research coordination, including the research methods consultation, was carried out by the Section of Rehabilitation Sciences at the Institute of Psychotherapy and Medical Psychology at the University of Würzburg.

Examples of research projects conducted at the Institute or in its cooperation: sensitivity to change of generic health-related quality of life questionnaires; validation of the German version of the Short Musculoskeletal Function Assessment Questionnaire (SMFA) used to measure the functional state of orthopedic patients; evaluation of a generic health promotion program for medical rehabilitation; meta-analytical analyses of predictors for success of patient education programs based on pooled data; sociomedical assessments as part of the admissions process for rehabilitation.

### Implementation Phase

In order to effectively employ the knowledge gained through rehabilitation research in practice, several transfer projects were established. The goals of the ongoing project "Center of Patient Education" are the optimization of patient education and the dissemination of research results within rehabilitation practice (see Fig. 1). Descriptive and evaluative criteria for patient education were designed and consented, the conduction of patient education was measured on a national level, and the findings were systematically analyzed and made available in an online database. Criteria for quality management and qualification of educational staff were also developed.

The second implementation focus was on occupational orientation within medical rehabilitation. A generic screening instrument was developed to identify professional problem areas and to ascertain the need for occupational rehabilitation services. A second project in this area focused on surveying and analyzing occupational interventions in rehabilitation clinics and providing appropriate constituents for rehabilitative interventions. A current follow-up project at the Section of Rehabilitation Sciences concentrates on the dissemination of professionally oriented measures in medical rehabilitation into practice.

### Funding Program on Chronic Disorders and Patient Orientation

The Section of Rehabilitation Sciences is currently conducting five scientific projects in cooperation with rehabilitation clinics as part of a health services research program on patient orientation (funded by BMBF, Pension Insurance, Health Insurance). The topics of these projects include an evaluation of innovative concepts for the follow-up care of adipose patients (telephone-based follow-up) and chronic pain patients (live online follow-up) as well as the development and evaluation of an integrated patient education concept for chronic back pain patients (in cooperation with the University of Erlangen-Nürnberg). Further topics involve shared decision-making as a part of medical rehabilitation and the validation of a generic assessment instrument for measuring the proximal effects of patient education onself-management and empowerment (Health Education Impact Questionnaire, heiQ) (in cooperation with the medical school of Hannover and the Deakin University, Melbourne, Australia).

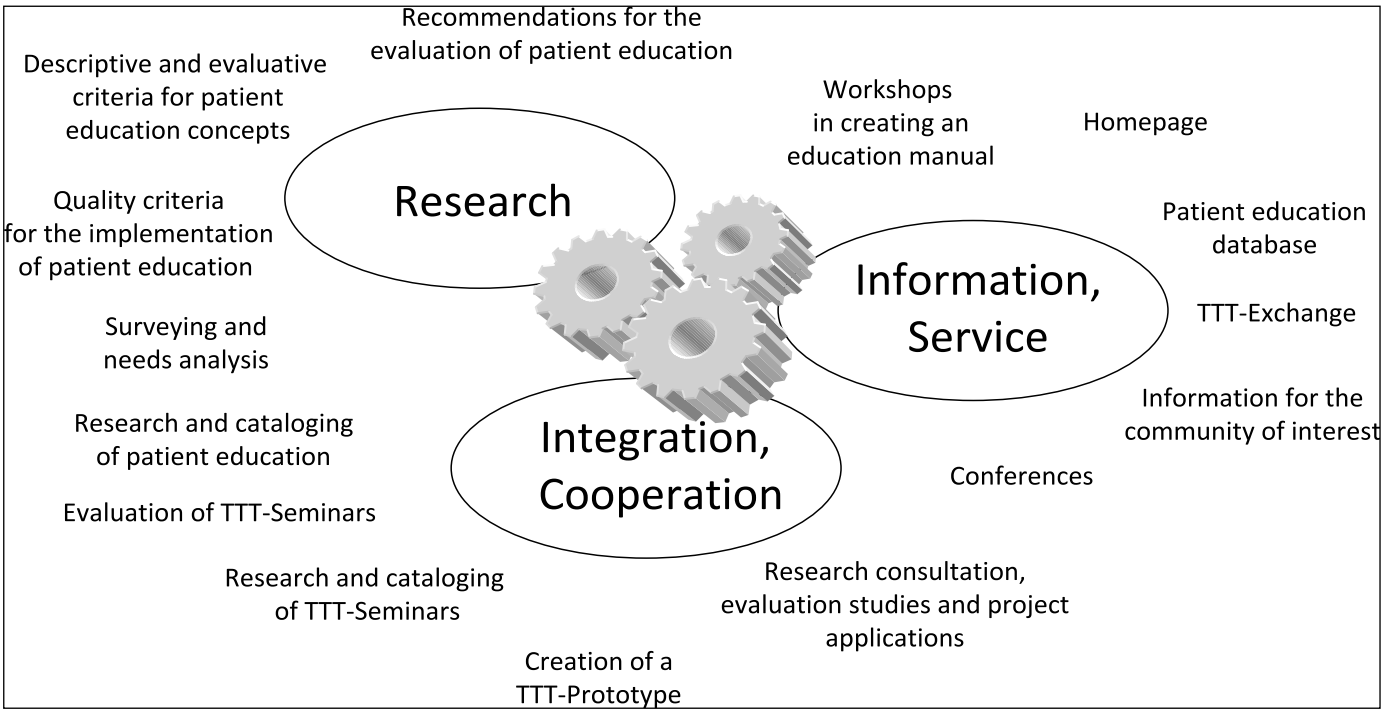


*Fig. 1: Goals and responsibilities of the Center of Patient Education*

**Networking**

One of the objectives of application-oriented rehabilitation research is the establishment of a network consisting of various stakeholders in research and practice. The Section of Rehabilitation Sciences' Center of Patient Education functions as the cross-regional intersection of this network. On a regional level, the close cooperation between the Section of Rehabilitation Sciences and the Network of Rehabilitation Research of Bavaria (NRFB) allows for the development of various research projects as well as an interdisciplinary communication and collaboration (e.g. the joined conference "Patient Orientation in Rehabilitation" held in 2008 in Würzburg to commemorate 10 years of joined rehabilitation research in Bavaria since the foundation of the RFB). Currently, a new initiative, "Bavaria's Rehabilitation-Practice researches", has been implemented in cooperation of the NRFB and the Section of Rehabilitation Sciences at the University of Würzburg. The new initiative will involve the development of practice-oriented research projects that will be supported until sponsorship. A corporate model project for an enhanced rehabilitation process based on the collaboration of business, rehabilitation clinics and rehabilitation agencies was also supported and evaluated by the Section of Rehabilitation Sciences.

## Education

The Section of Rehabilitation Sciences at the Institute of Psychotherapy and Medical Psychology is responsible for the organization of lectures in the interdisciplinary area 12, "Rehabilitation, Physical Medicine, Naturopathy", and offers an optional seminar in rehabilitation sciences. In addition, it contributes to the interdisciplinary areas 3, "Health Economy, Health Care System, Public Health", and 10, "Prevention, Health Promotion".

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# 5.5.2 BMBF-Competence Network: Genome Research on Pathogenic Bacteria - 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 socio-economic 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 Ro-_ bert-Koch Institute and the Research Center Borstel are members of the network.

## Major Research Interests

According to the wide spectrum of infectious diseases investigated in the network the research groups collaborate in four clusters.

Cluster 1 is coordinated by Prof. Dr. Dr. h.c. mult. J. Hacker (until 2008 head of the Institute for Molecular 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.

SELECTED PUBLICATIONS

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*Schoen C, Tettelin H, Parkhill J, Frosch M. 2009 Genome flexibility in Neisseria meningitidis. Vaccine 27: B103-111.*

# 5.5.3 Network of Excellence EuroPathoGenomics


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## 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. For instance, the comparative analysis of the genome content of uropathogenic *E. coli* (UPEC) isolates from symptomatic, asymptomatic as well as chronic cases of urinary tract infection (UTI) strains was accomplished. It was demonstrated that asymptomatic bacteriuria *E. coli* isolated are frequently characterized by genome loss, i.e. the inability to express several genes due to the acquisition of point mutations, genomic rearrangements and deletions. Furthermore, genomes of re-isolates from deliberate colonization of human patients with an asymptomatic-bacteriuria (ABU) isolate have been sequenced and compared to that of the parent strain. Genomic alterations could be described in the re-isolates that mirror bacterial adaptation in response to bladder colonization. Thus, under certain circumstances uropathogenic *E. coli* may evolve into harmless commensal-like variants. ABU strains acquire multiple genomic alterations upon *in vivo* colonization of the human urinary bladder.

**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 com-

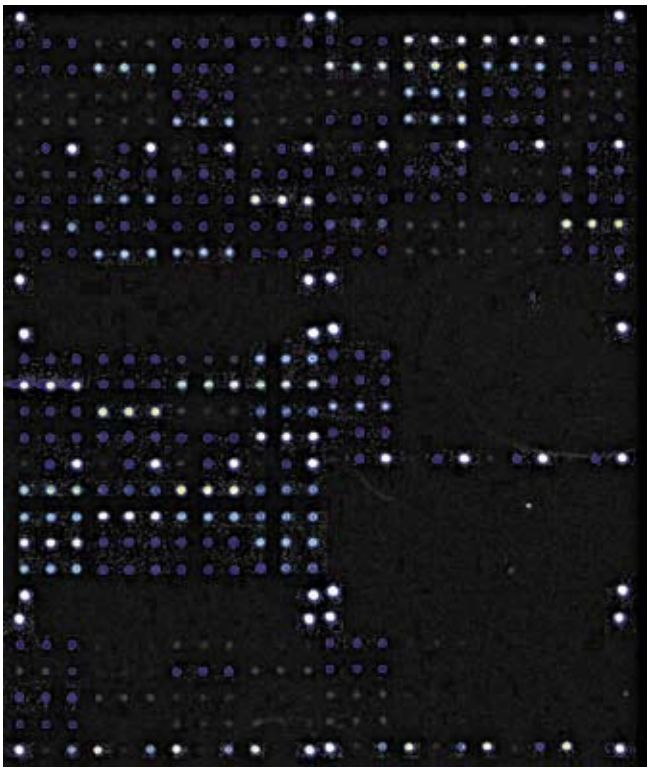

*Fig. 1: Genotyping DNA chip for the simultaneous assessment of antibiotic resistance and pathogenicity potential of extraintestinal pathogenic Escherichia coli (false colour fluorescence image). Source: T. Barl and T.T. Bachmann.*

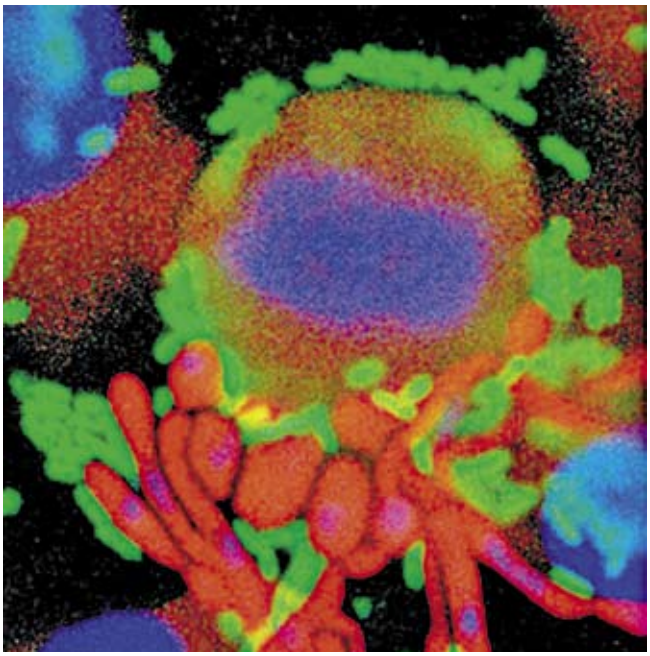

*Fig. 2: FISH (fluorescence in situ hybridization) detection of human epithelial bladder cells (T24), Citrobacter freundii and Candida albicans. Source: H. Merkert.*

parative 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 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*). It could be shown that biofilm-forming *Pseudomas aeruginosa* bacteria undergo lipopolysaccharide (LPS) structural modifications inducing enhanced inflammatory cytokine response in human monocytes.

**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 global assessment of host cell functions involved in the intracellular survival and replication of *Chlamydia trachomatis* using RNA interference in human cells has been performed. This analysis resulted in the identification of 59 host cell genes influencing *C. trachomatis* infection and infectivity.

## 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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# 5.5.4 Research program of the BMBF: Effects and Mechanisms of Psychotherapy in the Treatment of Attention Deficit-Hyperactivity-Disorder (ADHD) in Children and Adults

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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 comparing the outcome of psychotherapy, psychopharmacological treatment (methylphenidate) and the 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 (such as striatal morphology and 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 13 study centres: recruiting and manualized therapy are provided by clinics for adult psychiatry and psychotherapy (APP) and clinics for child and adolescent psychiatry and psychotherapy (CAPP) in Wuerzburg (APP, CAPP), in Freiburg (APP, CAPP), Mannheim central institute (APP, CAPP), Homburg (forensic psychiatry, CAPP), Berlin (APP, CAPP), Essen (APP), Mainz (APP) and Rostock (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 Wuerzburg (EPP). Data management, statistical analysis and monitoring will be provided by the Centre for Clinical Trials and LabConsult 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, founded by the German Research Association, DFG) in Wuerzburg and international cooperation.

## Major Research Interests

Main issue of the child psychiatric study groups (principal investigator: A. Warnke, CAPP Wuerzburg) is the project **"Does the treatment of maternal ADHD enhance the effectiveness of parent management training for children's ADHD?"**. 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. 144 mother-child-pairs will be randomized. Other research questions refer to the generalization, stability and prognosis of treatment outcome.

The project **"Evaluation of the efficacy and effectiveness of a structured disorder specific psychotherapy in ADHD in adults"** (principal investigator: 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: L. Tebarzt van Elst, APP Freiburg) is designed to investigate morphological and functional biological brain markers of treatment response using MR spectroscopy.

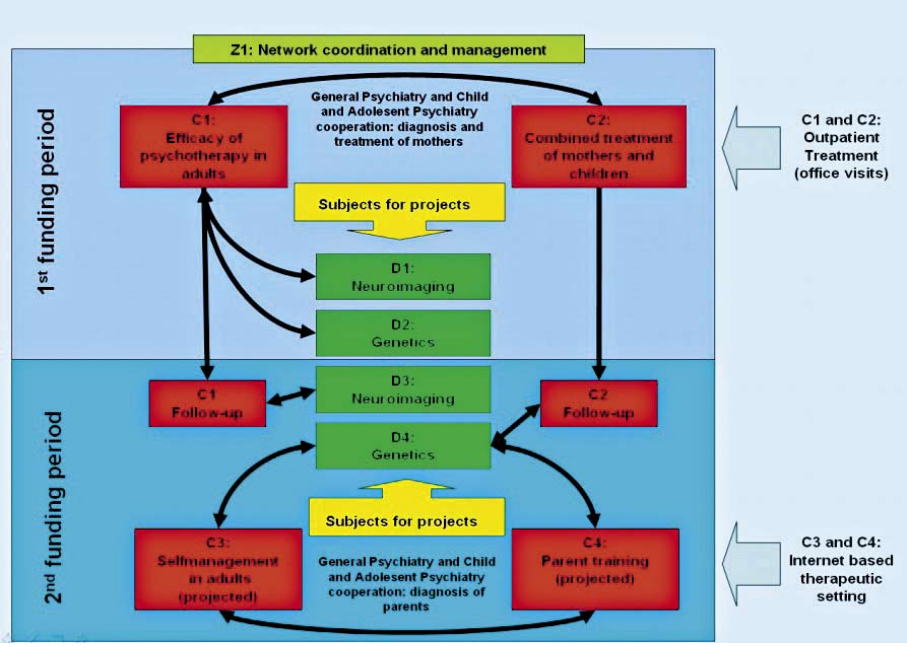


*Fig. 1: Network structure.*

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: K.-P. Lesch, APP Wuerzburg). Main study questions refer to the prognosis of treatment outcome and to associations between morphological or neurochemical abnormalities and specific genetic variants. Genotyping and statistical analysis will be performed in national (Institute of Human Genetics, Wuerzburg; Institute of Medical Biometry and Epidemiology, University of Marburg) and international (amongst others the National Human Genome Research Institute, NIH, Bethesda) cooperation.

During the second funding period of the network follow-up investigations and a health economic evaluation will be conducted in the clinical trials and the analyses of the projects on neuroimaging and genetics will be extended.

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*Konrad K, Dempfle A, Friedel S, Heiser P, Holtkamp K, Walitza S, Sauer S, Warnke A, Remschmidt H, Gilsbach S, Schäfer H, Hinney A, Hebebrand J, Herpertz-Dahlmann B. (2010). Familiality and molecular genetics of attention networks in ADHD. Am J Med Genet B Neuropsychiatr Genet, 5, 148-158.*

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*Philipsen A, van Elst LT, Lesch KP, Jans T, Warnke A (2009). Effects and mechanisms of psychotherapy in the treatment of attention deficit hyperactivity disorder (ADHD) in children and adults. Psychother Psychosom Med Psychol, 59,132-140.*

*Perlov E, Philipsen A, Matthies S, Drieling T, Maier S, Bubl E, Hesslinger B, Buechert M, Henning J, Ebert D, Tebartz Van Elst L (2009). Spectroscopic findings in attention-deficit/hyperactivity disorder: review and meta-analysis. World J Biol Psychiatr 10, 355-365.*

# 5.5.5 Bavarian Immunotherapy Network (BayImmuNet): Generation of Clinical Grade Antigen-Specific T-cells with an Early Effector Phenotype for Adoptive T-cell Immunotherapy

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## General Information and Research Interests

Immunotherapy using antigen-specific T-cells holds great promise as an additional strategy to complement standard cancer therapy. Among the patient groups in greatest need for novel treatment strategies are patients with glioblastoma, one of the most malignant form of brain tumors occurring in children and adults. Preclinical data suggest that immunotherapy for this patient-group may be beneficial. However, one major challenge arises from the low precursor frequency of such antigen-specific T-cells within the T-cell repertoire. We have developed a protocol, which allows the rapid expansion of antigen-specific T-cells to significant numbers. This protocol is suitable for different tumor-associated antigens with a lower precursor T-cell frequency. In this project, we want to establish the clinical usability of such short term expanded T-cells with an early effector memory phenotype, by translating our preclinical findings into an up-scaled protocol that allows the expansion of antigen-specific T-cells to clinically relevant numbers while being in adherence with the current regulations for the production of cellular products within the European Union (AMG). This will be the basis for first clinical studies using adoptive transfer of antigen-specific T-cells to treat patients suffering from glioblastoma.

SELECTED PUBLICATIONS


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*Wölfl M, Rutebemberwa A, Mosbruger T, Mao Q, Li H, Netski D, Ray SC, Pardoll D, Sidney J, Sette A, Allen T, Kuntzen T, Kavanagh DG, Kuball J, Greenberg PD, Cox AL. Hepatitis C virus Immune escape via Exploitation of a Hole in the T cell Repertoire. Journal of Immunology, 2008, Nov 1; 181(9): 6435-46*

*Wölfl M, Kuball J, Ho WY, Nguyen HN, Manley T, Bleakley M, Greenberg PD. Activation-induced expression of CD137 permits detection, isolation and expansion of the full repertoire of CD8+ T-cells responding to antigen without requiring knowledge of epitope-specificities, Blood, 2007 Jul 1;110(1):201-10.*

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# 5.5.6 German Research Foundation: SPP 1356, Pluripotency and Cellular Reprogramming

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## General Information

Research on cellular pluripotency is one of the most challenging and promising research fields in biomedicine. The potential to reprogram cells into any type of adult stem cell for the purpose of cell replacement therapy holds tremendous therapeutic implications. Cell reprogramming may circumvent current ethical considerations surrounding the derivation of new human embryonic stem cells for research and clinical applications. The molecular pathways controlling pluripotency and cellular reprogramming are now only beginning to be understood. A thorough understanding of regulatory pathways on the molecular level in pluripotent cells is essential for the development of effective and rational approaches to induce pluripotential reprogramming and direct pluripotent cells into specific differentiation pathways.
The priority program SPP 1356 focuses on two key areas crucial for the understanding of pluripotency and reprogramming:

a.) The identification and characterization of genetic and epigenetic networks that control pluripotency, i.e. the molecular basis for pluripotency;
b.) The mechanisms governing the reinstatement of pluripotency in a differentiated cell.

## Major Research Interests

Therefore the work schedule of the interdisciplinary program group includes: (1) the identification of novel as well as unsuspected genes and factors regulating pluripotency; (2) the determination of molecular interconnections between the genetic and epigenetic pathways regulating pluripotency; (3) the determination of the association between global and local chromatin nuclear structure and the regulation of pluripotency and (4) the identification of practical and effective strategies to induce and regulate pluripotency by nuclear reprogramming, cell fusion, and extrinsic factors.

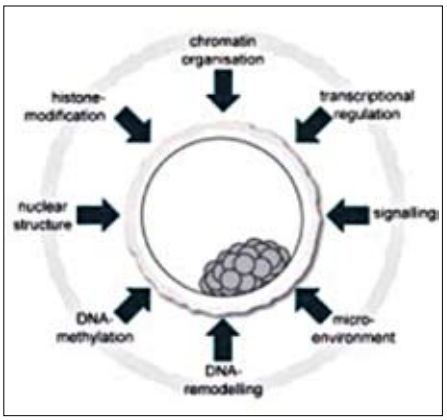


*Fig. 1: Features that influence pluripotency and reprogramming. Depicted is a murine preimplantation blastocyst -the origin of pluripotent cells- and features that influence pluripotency and reprogramming.*

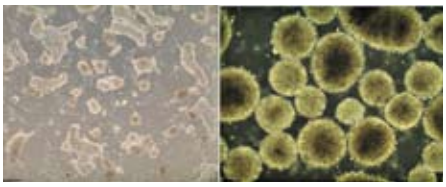

*Fig. 2: Pluripotent ES cells*

**Work package 1:**

Genetic and epigenetic networks that control pluripotent cells
- Genetic and epigenetic signatures of pluripotent cells
- Identification and functional testing of pluripotency factors
- Chromatin remodeling and nuclear structure

**Work package 2:**

Induction of pluripotency by nuclear reprogramming
- Analysis of natural reprogramming mechanisms
- Somatic reprogramming induced by SCNT, cell fusion and nuclear extrinsic factors
- Mathematical modeling of pluripotency

The SPP 1356 comprises 24 German research groups that are specialists in the molecular analysis of pluripotency, chromatin and cellular reprogramming.

Priority programmes represent topic-oriented funding programmes of the DFG. They provide the opportunity for interdisciplinary networking and nationwide coordination of research projects in fields of current research interest. Priority Programmes are established for a period of up to six years.

# 5.5.7 BMBF Project, SARA: Systems Biology of PGI2 and ADP P2Y12 Receptor Signaling

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Timmer J., Freiburg Center for Data Analysis and Modeling, Freiburg
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Blankenberg S., Center for cardiovascular prevention, Mainz
Schinzel R., vasopharm GmbH, Wuerzburg

## General Information

The SARA project consortium is supported by the research initiative „Medical Systems Biology - MedSys“ in the framework of the BMBF program „Biotechnology”.

Blood platelets play a key role in the regulation of hemostasis and in the genesis of thrombotic events. Platelets can attach almost instantly to injured vessel wall, subendothelial matrix or other, activated platelets and contribute considerably in development and progression of cardiovascular diseases. As a result of their central role, in physiological as well as pathological respect, platelets are tightly regulated by numerous factors acting either stimulatory or inhibitory and, occasionally, in both ways. Most of these factors bind to specific receptors thus governing distinct intracellular pathways . A strictly regulated equilibrium of activatory and inhibitory signals is apparently essential for the physiological function of platelets and vessel wall. Two endogenous factors, namely adenosine-diphosphate (ADP) and prostacyclin (PGI2), which play a particular role in physiology and pathophysiology by maintaining the equilibrium of platelet activation and inhibition are in the focus of this project. Though ADP is regarded a rather weak platelet agonist in recent years it became evident that a complete platelet aggregation is only possibly by activation of ADP stimulated pathways The sole inhibition of one of the three ADP receptors known for platelets is sufficient to prevent thrombus formation. PGI2 is clearly the most relevant and efficacious inhibitor of platelet aggregation. The short lived prostaglandin is formed by the endothelium lining the vessel wall and acts directly on the platelets passing by. As a matter of fact it turned out that PGI2 and ADP are indeed direct opponents in the physiological regulation of platelet function.

The SARA research consortium aims at a description of ADP and PGI2 evoked signaling pathways by applying molecular bio-

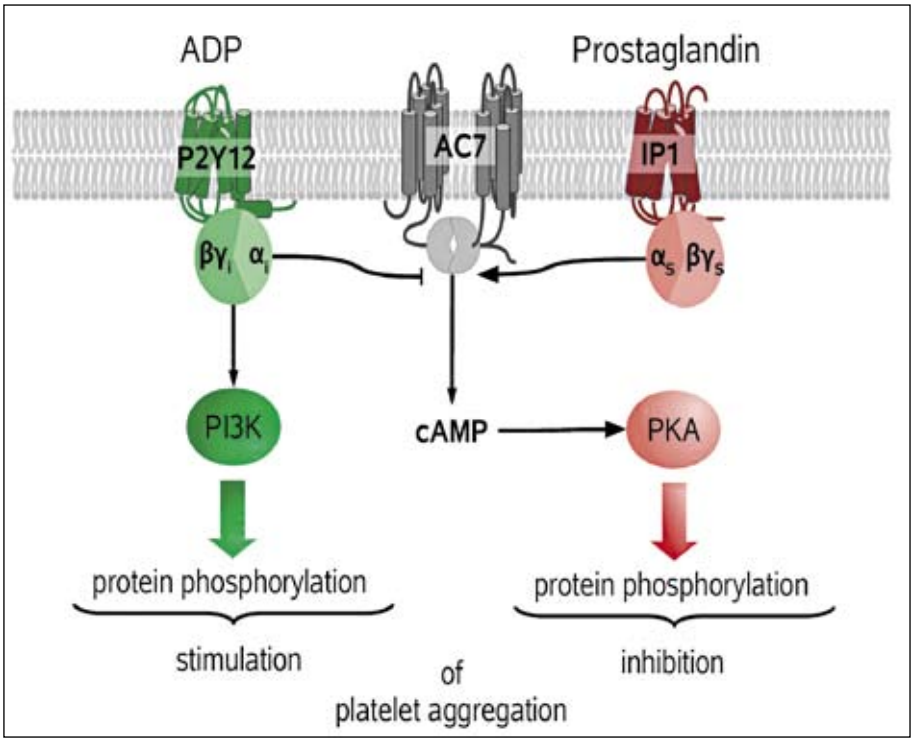


*Fig. 1: Interaction of ADP and PGI2 signal transduction pathways.*

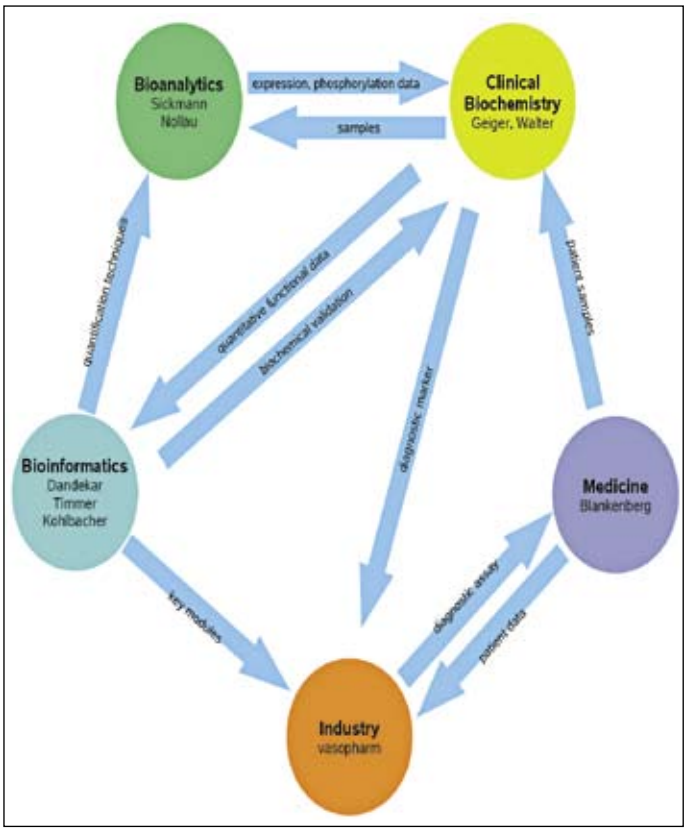


*Fig. 2: Structure of the research consortium*

logical, biomedical, biochemical and bioinformatical methods with respect to quantity and time course. In an iterative strategy protein phosphorylation, formation of messenger molecules as well as cellular responses such as secretion or aggregation after stimulation of ADP and/or PGI2 induced pathways are investigated. Protein phosphorylation is determined by innovative techniques allowing for identification of phosphorylation sites – by means of SH2-profiling – and an absolute quantification of phosphorylation by quantitative phosphoproteomics. The findings are integrated in a bioinformatical model of the signaling cascades which will be further refined by additional more specific analysis. Markers for platelet activation and inhibiiton identified coherently will then be verified in a large group of volunteers. Eventually a meaningfiukl model of platelet function regulation will be developed which will improve our understanding of the genesis and development of atherothrombotic diseases. In addition it is expected that the project will provide novel approaches for diagnosis and therapy of atherothrombosis.

The SARA consortium includes eight subprojects:
Albert Sickmann - Quantitative Phosphoproteomics, ISAS, Dortmund
Ulrich Walter / Jörg Geiger - Functional analysis of platelets, , Würzburg
Thomas Dandekar - Computational interactomics and kinomics, Bioinformatics, Würzburg
Peter Nollau - SH2 domain profiling, Universitätsklinikum Eppendorf, Hamburg
Jens Timmer - Modeling of signaling pathways, Freiburg
Oliver Kohlbacher - Computational proteomics, Tübingen
Stefan Blankenberg – PREVENT-it (Gutenberg heart study), Universitätsklinikum Mainz
Reinhard Schinzel – industry partner, vasopharm GmbH, Würzburg

**Project C: Functional analysis of platelets**

This project aims at a comprehensive definition and description of the role of P2Y12 ADP receptor and prostaglandin receptor mediated pathways in platelets.
All biochemical experiments required for the further analysis by other partners in this consortium are designed, carried out and analyzed in this project. As soon as available, the bioinformatical models generated by the collaboration partners will be validated biochemically. In close collaboration with both vasopharm and Roche Diagnostics, established and novel phosphoprotein markers will be verified and developed as diagnostic parameters for monitoring of human platelet function and inhibition in health and disease. Also, the data obtained will be used to characterize the quantitative biochemical effects of novel platelet ADP receptor inhibitors developed by other industry partners. Finally, the data obtained will be extended to the analysis of platelets from selected patients of a large prospective clinical study which monitors the development of coronary artery disease and their underlying risk factors.

The project is composed of 5 phases:
- Definition: defining the experimental setting, methods, conditions
- Characterization: characterize pathways and pathway components
- Identification: identify regulatory components
- Quantification: quantify cellular responses, role of regulatory components
- Prediction: testing predictions from bioinformatical models

SELECTED PUBLICATIONS

*Lewandrowski U, Wortelkamp S, Lohrig K, Zahedi RP, Wolters DA, Walter U, Sickmann A. Platelet membrane proteomics: a novel repository for functional research. Blood. 2009;114(1): e10-9.*

*Zahedi RP, Lewandrowski U, Wiesner J, Wortelkamp S, Moebius J, Schütz C, Walter U, Gambaryan S, Sickmann A. Phosphoproteome of Resting Human Platelets. J Proteome Res. 2008 7(2):526-34.*

*Begonja AJ, Geiger J, Rukoyatkina N, Rauchfuss S, Gambaryan S, Walter U. Thrombin stimulation of p38 MAP kinase in human platelets is mediated by ADP and thromboxane A2 and inhibited by cGMP/cGMP-dependent protein kinase. Blood. 2007;109(2): 616-8.*

# 5.5.8 BMBF Joint Project, CB-HERMES: Expansion of Cord Blood Stem Cells

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## General Information

Lifelong blood production depends on haematopoietic stem cells (HSCs) and their ability to self-renew and to differentiate. Cord blood (CB) banking is continually increasing due to the superior properties of CB compared to adult HSC. However our inability to expand HSCs renders insufficient stem cell numbers, a major constraint in many settings of CB-HSC transplantation. Despite optimization of isolation and processing techniques this restricts CB-HSC transplantation mainly to paediatric patients. New methods that generate sufficient numbers of HSCs from limited input cells are needed to make CB-HSCs available to adult patients and amenable to advanced cell and gene therapy approaches in regenerative medicine. Therefore, the aim of this consortium is to open CB-HSCs to new therapeutic applications by developing controlled strategies for expansion and transplantation. Specifically we plan to apply novel growth factor cocktails, nanostructured 3D surfaces, modifications of inhibitory pathways and epigenotype and specific stroma environments in order to expand and regulate HSCs *ex vivo*. The first clinical application of novel strategies developed by us is in the context of allogeneic CB-HSCs transplantation for elderly patients suffering from haematopoietic disorders.

Overall goal: to broaden the therapeutic application of CB-HSCs by developing robust means that allow significant HSC expansion and better engraftment.

## Major Research Interests

Specific aims: 1) to develop rational and robust means of *ex vivo* CB-HSC expansion: by novel growth factor cocktails, nano-structured 3D surfaces, modification of inhibitory pathways, induced epigenetic modifications and by specific stroma environments; 2) development of clinically applicable standard operating procedures for CB-HSC expansion using $CD34^+$ cells isolated from umbilical cord blood; 3) eludicate molecular pathways and intercellular networks operating in HSC ex vivo expansion cultures; 4) exploring genetic, epigenetic and functional integrity of expanded cells *in vivo*.

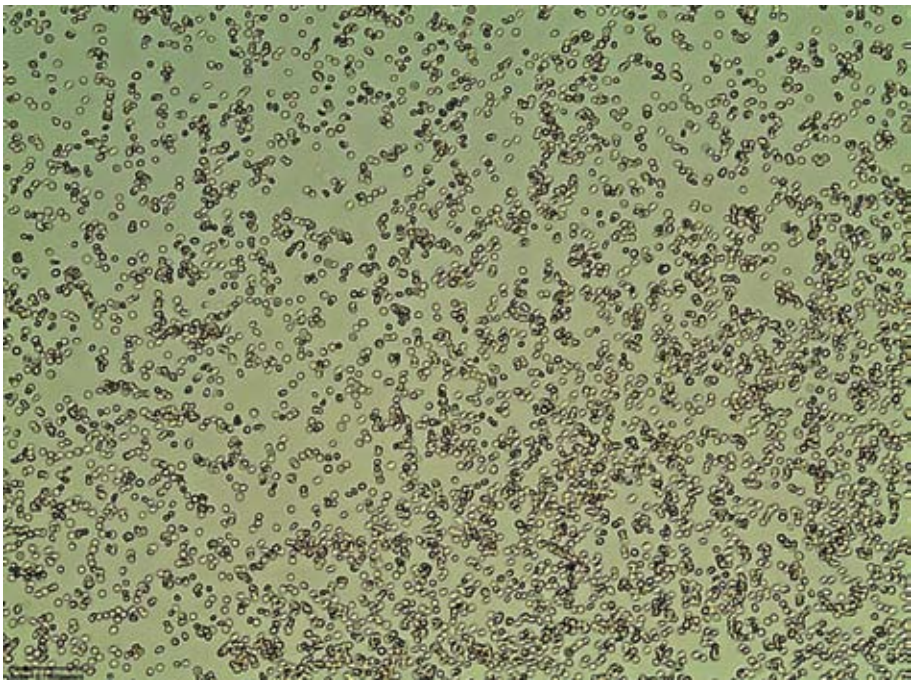

*Fig.1: Shown are human cord blood cells.*

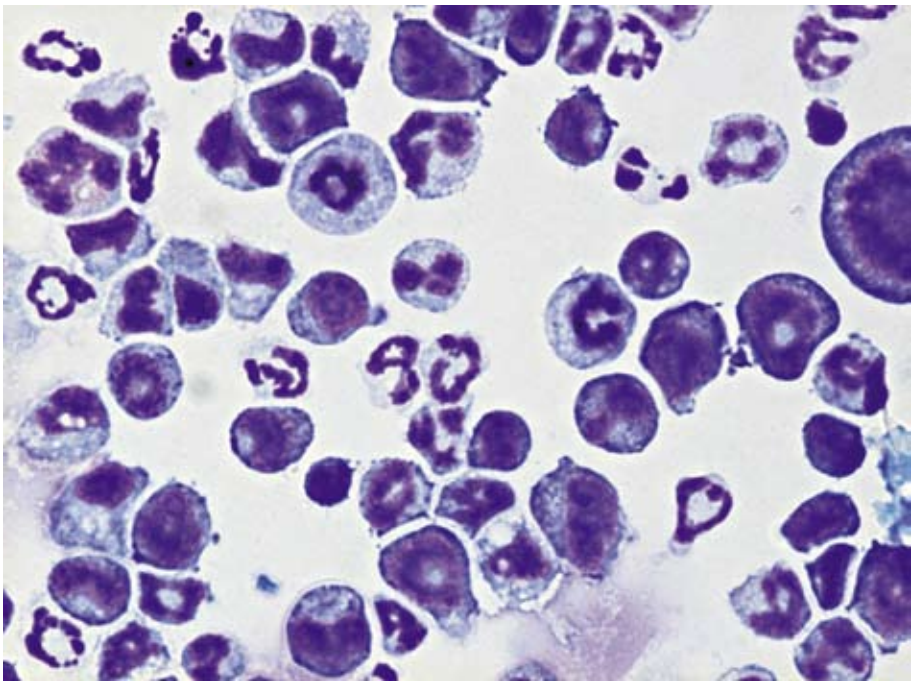

*Fig. 2: HoxB4-expanded bone marrow cells.*

| No. | Head of the project | Institution | Titel of the subproject |
|---|---|---|---|
| 1 | Dr. Bernd Schiedlmeier,<br>Prof. Dr. Christopher Baum | Hannover Medical School<br>Dept. Experimental Hematology | Pathway discovery and protocol development |
| 2 | Dr. Sabine Neuß-Stein,<br>Dr. Thomas Hieronymus,<br>Prof. Dr. Martin Zenke | RWTH Aachen University<br>Institute of Pathology<br><br>Helmholtz Institute for Biomedical Engineering | Biomaterial scaffolds for CB-HSC expansion |
| 3 | Prof. Dr. Albrecht Müller | University Würzburg<br>Institute of Medical Radiation and Cell Research | Epigenetic characterisation of CB-HSCs |
| 4 | Prof. Dr. Wolfgang Wagner | RWTH Aachen University<br>Helmholtz Institute for Biomedical Engineering | Expansion of CB-HSCs with human MSCs |
| 5 | Prof. Dr. Arnold Ganser,<br>Prof. Dr. Eva Mischak-Weissinger | Hannover Medical School<br>Dept. Hematology, Hemostasis, Oncology and Stem Cell Transplantation | Clinical Appli-cation of CB-HSCs |

# 5.6 MD/PhD-Program

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## 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 are registered MDs. Goal of the program is to earn the PhD degree according to the rules of the the International Graduate School of Life Sciences 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. Successful graduates of the curriculum “Experimental Medicine” may enter the MD/PhD program without passing the practical course phase.

The MD/PhD program started in summer 1997 and is funded and organized by the Interdisciplinary Center for Clinical Research Würzburg (IZKF). Until now, approx. 40 students were enrolled. Of these, more than 20 have already received their PhD, 6 obtained a medical specialization (“Facharztanerkennung”), 3 are in the USA as Postdocs, 5 obtained their “Habilitation” and 1 received a call for professorship. Although not very large, the MD/PhD-program of the Medical Faculty can be regarded to be a great success.

# 5.7 University of Würzburg Graduate Schools – 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 were therefore combined to found the Section Biomedicine in the International Graduate School (IGS) 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" (GSLS). The last years, and in particular 2006, have seen major steps towards this goal. The GSLS was successful in the "Excellence Initiative of the Federal and State Governments" and obtained funds to support fellowships and other activities within the GSLS. Separate graduate schools – The Graduate School of the Humanities (GSH) and the Graduate School of Science and Technology (GSST) have been founded as well.

### Foundation of the International Graduate School (2003-2005)

Discussions within 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 entire university, with separate sections ("Klassen") to cover the specific scientific and training needs and cultures of the diverse disciplines.

### Section Biomedicine

As a first step, a Section of Biomedicine was initiated 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
- Two DFG-funded graduate programs (GRK1048 "Molecular Basis of Organ Development in Vertebrates" and the IEC of SFB-TR 17 "Ras-Dependent Cancer"))

These programs came together to identify and develop common structures and curricula, to share activities and to set common standards (see box) for the graduate students. In 2006, the first graduate students received their PhD from this common program.

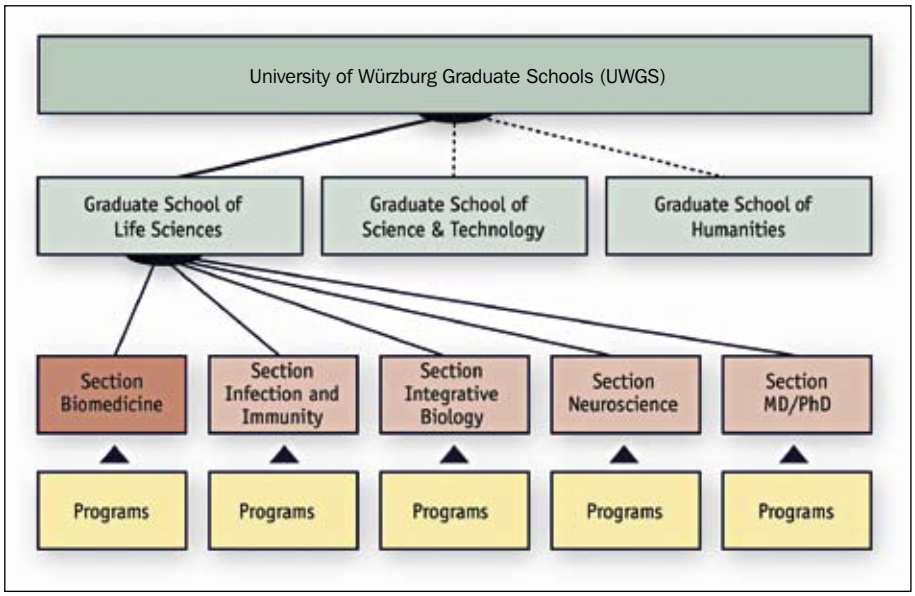


*Fig. 1: Structure of the University of Würzburg Graduate School.*

**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 IGS 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 and was renamed as University of Würzburg Graduate Schools (UWGS). 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). Each of these schools independently handles their specific affairs.

The holding, the UWGS, 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 UWGS and all the individual Graduate schools was passed by the Senate in August 2007, regulating issues of membership and operating procedures. The UWGS 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.

**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. The plans that were set forth in the successful application within the Excellence Initiative have been put into practice.

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. The school is currently divided into five separate Sections. In addition to the Section "Biomedicine" and the MD/PhD program, the Sections "Infection and Immunity", "Neuroscience" and "Integrative Biology" were established. 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 fourth round of international recruitment is currently underway. To date more than 1000 standardized written applications have been evaluated in a newly developed process in the recruitment rounds, and interviews with more than 200 candidates were performed by the admission board in Würzburg, by means of video conferencing and abroad. Nineteen of the 34 fellows are from 10 different countries, underscoring the international character of the GSLS.

Up to now, the number of formal members of the GSLS rose to 180 principal investigators from all participating faculties. In 2009 the number of doctoral students enrolled in the doctoral study program "Life Sciences" rose to more than 230. Recently the video "The Secrets of Life" has been published by the DFG video portal as part of the Excellence Initiative that describes the GSLS program in detail (http://www.excellence-initiative.com/wuerzburg-life-sciences).

*Key elements of training in the Graduate Schools*

- The traditional single advisor ("Doktorvater") is replaced by a committee with three principal investigators (PIs).
- 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, to exchange ideas and obtain 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, Research Training Groups, Clinical Research Units

**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

Transregio-Collaborative Research Center 52, Transcriptional Programming of Individual T-Cell Subsets

Transregio-Collaborative Research Center 58, Fear, Anxiety, Anxiety Disorders

**Research Training Groups:**

Research Training Group 520, Immunomodulation

Research Training Group 1048, Molecular Basis of Organ Development in Vertebrates

Research Training Group 1141, Signal Transduction: Where Cancer and Infection Converge

Research Training Group 1156, From Synaptic Plasticity to Behavioural Modulation in Genetic Model Organisms

Research Training Group 1253, Emotions

Research Training Group 1522, HIV/AIDS and Associated Infectious Diseases in Southern Africa

**Clinical Research Units:**

Clinical Research Unit 103, Osteogenic Stem Cell Differentiation and Therapy of Bone Loss

Clinical Research Unit 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

Clinical Research Unit 216, Characterization of the Oncogenic Signaling-Network in Multiple Myeloma: Development of Targeted Therapies

## 2. Honorary doctorates awarded by the medical faculty

1948 Dr. Albert Knoll
Ludwigshafen
1952 Prof. Dr. Georg Hohmann
München
1956 Dr. G. Wahl
Würzburg
1961 Prof. Dr. Ernst Freudenberger
Basel, Schweiz
1982 Dr. Johannes von Elmenau
München
1982 Prof. Dr. Wilhelm Feldberg
London, England
1991 Prof. Dr. Arno G. Motulsky
Seattle, USA
1995 Prof. Dr. Peter Vogt
La Jolla, USA
1995 Prof. Alan E.H. Emery
Budleigh Salterton, England
1997 Prof. Dr. Hans Thoenen
München
2000 Prof. Dr. Hermann Bujard
Heidelberg
2001 Prof. Dr. Hermann Wagner
München
2005 Prof. Dr. Volkmar Braun
Tübingen
2007 Prof. Dr. G. Fritz Melchers
Basel/Berlin
2008 Prof. Dr. Harald zur Hausen*
Heidelberg

(*Nobel laureate)

## 3. Rinecker- medals awarded by the medical faculty

1890 Prof. Dr. Robert Koch*
Berlin
1891 Prof. Dr. Camillo Golgi*
Pavia, Italien
1994 Prof. Dr. Emil von Behring*
Marburg
1897 Prof. Dr. Johannes von Kries
Freiburg i. B.
1900 Prof. Dr. Karl Schleich
Charlottenburg
1903 Dr. Ernst Overton
Würzburg
1909 Prof. Dr. Clemens von Pirquet
Breslau
1912 Geheimrat Dr. Max Rubner
Berlin
1917 Prof. Dr. Heinrich Albers-Schönberg
Hamburg
1922 Prof. Dr. Franz Hofmeister
Würzburg
1929 Prof. Dr. Ludolf von Krehl
Heidelberg
1936 Prof. Dr. Adolf Butenandt*
Danzig
1943 Prof. Dr. Bernhard Bavink
Bielefeld
1950 Prof. Dr. Georg Sticker
Zell a. Main
1956 Prof. Dr. Erich Grafe
Garmisch-Partenkirchen
1965 Prof. Dr. Hans Rietschel
Würzburg
1973 Prof. Dr. Dr. Viktor Emil Freiherr v. Gebsattel
Würzburg/Bamberg
1977 Prof. Dr. Georges Schaltenbrand
Würzburg
1982 Prof. Dr. Loris Premuda
Padua, Italien
1986 Prof. Dr. Shaul G. Massry
Los Angeles, USA
1993 Prof. Dr. Miklos Palkovits
Budapest, Ungarn
1995 Prof. Dr. Ernst J.M. Helmreich
Würzburg
2009 Prof. Dr. Volker ter Meulen
Würzburg

(*Nobel laureates)

## 4. Carl Caspar von Siebold-medals awarded by the medical faculty

2009 Prof. Dr. Walter Eykmann
Würzburg
2009 Manfred Ach
Margetshöchheim

## 5. Virchow-Lectures

1997 Prof. Dr. Melitta Schachner
Hamburg
1997 Prof. Dr. Donald Metcalf
Melbourne, Australien
1997 Prof. Dr. Carlo Croce
Philadelphia, USA
1997 Prof. Dr. Ralph Steinmann
New York, USA
1998 Prof. Dr. Salvador Moncada
London, England
1998 Prof. Dr. Max Perutz*
Maryland, USA
1999 Prof. Dr. Heiner Westphal
Cambridge, USA
2000 Prof. Dr. Harald zur Hausen
Heidelberg
2000 Prof. Dr. Rudolf Jänisch
Cambridge, USA
2001 Prof. Dr. Manfred Eigen*
Göttingen
2002 Prof. Dr. Axel Ullrich
Martinsried
2002 Prof. Dr. Alfred Wittinghofer
Dortmund
2002 Prof. Dr. Dieter Gallwitz
Göttingen
2003 Prof. Dr. Peter Gruss
München
2004 Prof. Dr. Kai Simons
Dresden
2004 Prof. Dr. Peter Walter
San Francisco, USA
2005 Prof. Dr. Hartmut Michel*
Frankfurt
2005 Prof. Dr. Svante Pääbo
Leipzig
2006 Prof. Dr. Günter Blobel*
New York, USA
2007 Prof. Dr. Oliver Smithies*
Chapel Hill, USA
2007 Prof. Dr. Klaus Rajewsky
Boston, USA
2008 Prof. Dr. Hans C. Clevers
Utrecht, Niederlande

(*Nobel laureates)

## 6. of the Albert Koelliker-Award for excellent teaching

| Semester | Winners |
|---|---|
| Autumn 2003 | Doctors of the Department for Anaesthesiology 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, Head of the Medical Policlinic |
| Autumn 2004 | Professor Dr. D. Patzelt, Head of the Institute of Forensic Medicine |
| Spring 2005 | Professor Dr. A. Warnke, Head of the Department for Child and Adolescent Psychiatry |
| Autumn 2005 | University lecturers of the Institute for Anatomy and cell Biology: Prof. Dr. D. Drenckhahn, Prof. Dr. E. Asan, Prof. Dr. P. Kugler, Dr. J. Waschke |
| Spring 2006 | Professor Dr. M. Gekle, Physiological Institute |
| Autumn 2006 | Professor Dr. M. Frosch, Head of the Institute for Hygiene and Microbiology |
| Spring 2007 | Professor Dr. M. Böck, Head of the Institute for Clinical 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 |
| Spring 2008 | Professor Dr. H. Hebestreit, Department of Pediatrics |
| Autumn 2008 | University Lecturers for General Medicine: Dr. M. Ertel, Dr. P. Rost und Dr. W. Heppner representative for more than fifty contracted physician‘s offices |
| Spring 2009 | Professor Dr. H. Klinker, Department of Internal Medicine II<br>Professor Dr. A. Renk, Department of Prosthodontics |
| Autumn 2009 | Professor Dr. C.-T. Germer, Head of the Department of General, Visceral, Vascular and Pediatric Surgery |

## 7. Habilitations

### 2008

**Clinical**

| | |
|---|---|
| Dr. med. Christoph Kleinschnitz | Neurology |
| Dr. med. Heinz-Theo Pelzer | Internal Medicine |
| Dr. med. Andreas Schäfer | Internal Medicine |
| Dr. med. Ralf Melcher | Internal Medicine |
| Ph.D. Edna Grünblatt | Clinical Neurochemistry |
| Dr. med. Jörn Maroske | Surgery |
| Dr. med. Martin Lauer | Psychiatry and Psychotherapy |
| Dr. med. Jan Kuhlencordt | Internal Medicine |
| Dr. med. Klaus Steger | Surgery |
| Dr. med. Peter Dahlem | Pediatrics |
| Dr. med. Gernot Stuhler | Internal Medicine |

**Preclinical**

| | |
|---|---|
| Dr. med. Ralf Kurzai | Medical Microbiology |
| Dr. rer. nat. Fred Lühder | Immunbiology |
| Dr. rer, nat. Angela Mally | Toxikology and Pharmacology |
| Dr. rer. nat. Frank Döring | Physiology |
| Dr. rer. nat. Christopher Volk | Anatomy and Cell Biology |
| Dr. med. Thomas Kerkau | Immunology |
| Dr. rer. nat. Thomas Müller | Physiological Chemistry |

### 2009

**Clinical**

| | |
|---|---|
| Dr. rer. nat. Siebke Stieler-Melfsen | Clinical Child- and Adolescent Psychology |
| Dr. med. Claudia Kauczok | Dermatology and Venerology |
| Dr. rer. nat. Jörg Wischhusen | Tumorimmunology |
| Dr. med. J örg Engel | Obstetrics and Gynecology |
| Dr. med. Christian Jacob | Psychiatry and Psychotherapy |
| Dr. med. Andreas Reif | Psychiatry and Psychotherapy |
| Dr. med. Giles Vince | Neurosurgery |
| Dr. med. Carsten Wessig | Neurology |
| Dr. med. Günther Schlunck | Ophthalmology |
| Dr. med. Ralf Muellenbach | Anaesthesiology |
| Dr. med. Thomas Wurmb | Anaesthesiology |
| Dr. med. Frank Schuster | Anaesthesiology |
| Dr. med. Dr. rer. nat. Antje Kroner-Milsch | Experimental Neurology |
| Dr. med. Ralph Kickuth | Radiology |
| Dr. med. Christoph Schimmer | Cardiovascular Surgery |
| Dr. med. Markus Lange | Anaesthesiology |
| Dr. med. Stephan Mielke | Internal Medicine |
| Dr. med. Dr. med. dent. Urs Müller-Richter | Dental-, Oral- and Maxillofacial Medicine, especially Oral and Maxillofacial Surgery |
| Dr. med. Thomas Thum | Internal Medicine |
| Dr. med. Robert Mlynski | Otorhinolaryngology |

**Preclinical**

| | |
|---|---|
| Dr. med. Tiemo Katzenberger | Pathology and Pathological Anatomy |
| Dr. med. Olaf Rolf | Orthopaedics |
| Dr. med. Alexandra Schubert-Unkmeir | Medical Microbiology |
| Dr. rer. nat. Heike Claus | Medical Microbiology |

## 8. Statistics

**Registration numbers**

| Year | human medicine / thereof female | dentistry / thereof female | biomedicinr Bc. / thereof female | biomedicine ma. / thereof female |
|---|---|---|---|---|
| WS 2007/08 | 154 / 83 | 60 / 40 | 34 / 27 | 12 / 6 |
| SS 2008 | 153 / 72 | 59 / 39 | - | - |
| WS 2008/09 | 149 / 86 | 58 / 36 | 31 / 23 | 15 / 14 |
| SS 2009 | 149 / 77 | 60 / 30 | - | - |
| WS 2009/10 | 151 / 92 | 62 / 40. | 31 / 25 | 7 / 7 |

**Graduations (Abschlüsse)**

| Year | human medicine / thereof female | dentistry / thereof female | biomedicine Bc. / thereof female | biomedicine Ma. / thereof female |
|---|---|---|---|---|
| Autumn 2007 | 96 / 64 | 40 / n. s. | 21 / 12 | 14 / 11 |
| Spring 2008 | 118 / 72 | 42 / n. s. | - | 6 / 3 |
| Autumn 2008 | 116 / 65 | 64 / n. s. | 22 / 17 | 15 / 11 |
| Spring 2009 | 150 / 99 | 30 / n. s. | - | 3 / 1 |
| Autumn 2009 | 123 / 73 | 61 / n. s. | 13 / 13 | 9 / 4 |

**Doctorates** (without doctorates in natural sciences)

| Year | preclinical | clinical | total |
|---|---|---|---|
| 2008 | 39 | 172 | 211 |
| 2009 | 47 | 178 | 225 |

**Habilitations**

| Year | preclinical | clinical | total |
|---|---|---|---|
| 2008 | 7 | 11 | 18 |
| 2009 | 4 | 20 | 24 |

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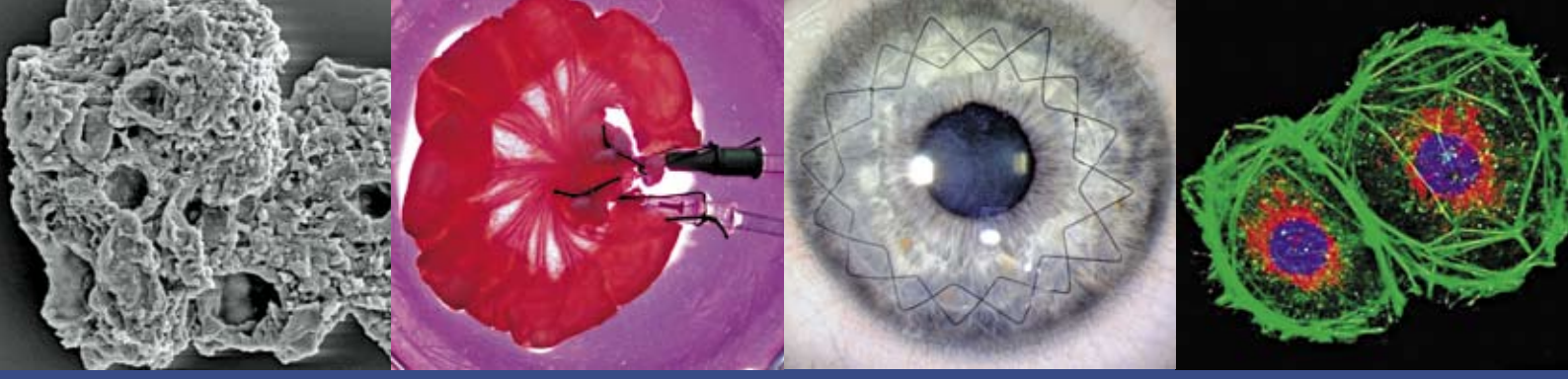

University of Würzburg

Universitätsklinikum Würzburg

# Medical Faculty

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