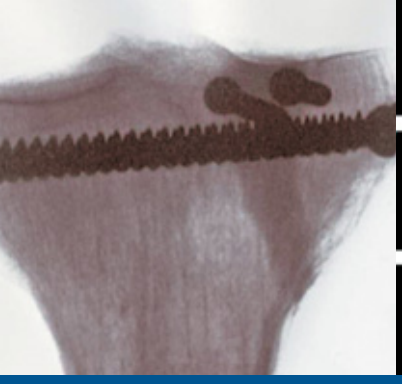
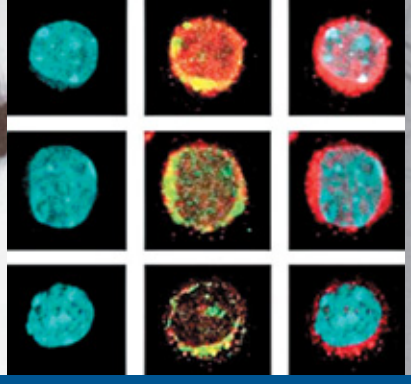
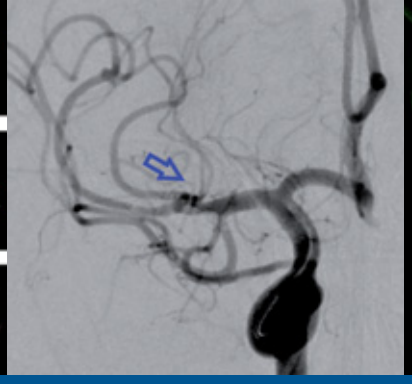
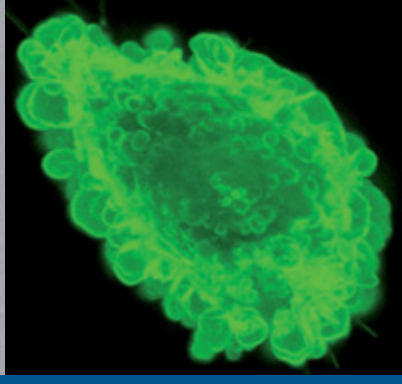
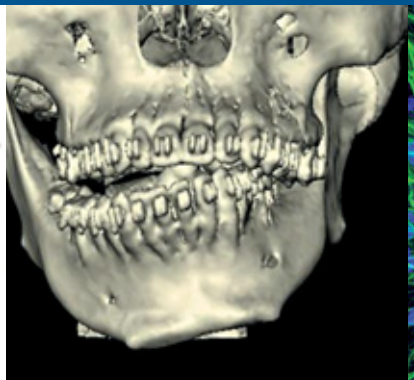
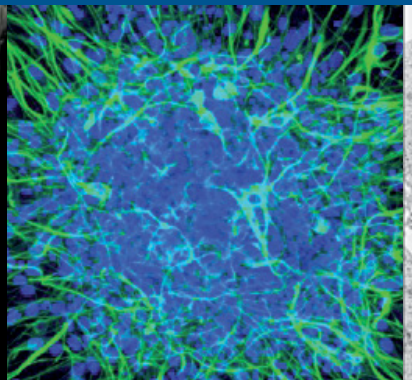
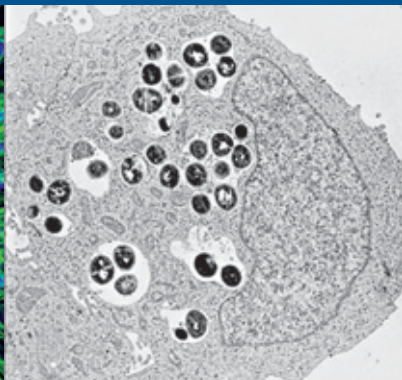





University of Würzburg
Medical Faculty

Research Report 2012

University of Würzburg
Medical Faculty

Research Report 2012

Content

1 General Part
1.1 Preface

It is a pleasure for me to show the Faculty of Medicine's development in the past years since 2010/2011 in the present research report and to present the scientific and clinical focus in each of the faculty's departments in depth. It is also of importance to me due to the generation change, which has taken place at our faculty during the past two years and which has generated new accents and made possible a sharpening of the research profile and a strengthening of the clinical care. In this context, I should like to draw your special attention to the next pages, in which our new professors present their departments: Prof. Dr. M. Bohnert and the Institute of Forensic Medicine, Prof. Dr. A. Buck and the Department of Nuclear Medicine, Prof. Dr. S. Ergün and the Institute of Anatomy and Cell Biology, Prof. Dr. M. Goebeler and the Department of Dermatology, Venerology and Allergology, Prof. Dr. J. Groll and the Department of Functional Materials in Medicine and Dentistry, Prof. Dr. P. Heuschmann and the newly created Institute of Clinical Epidemiology and Biometry, Prof. Dr. M. Romanos and the Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Prof. Dr. J. Volkmann and the Department of Neurology.

A special structural impact has been generated by the creation of the new research chairs: the Department of Psychiatry, Psychosomatics and Psychotherapy with chair holder Prof. Dr. H.-P. Lesch, and the Department of Internal Medicine II with chair holder Prof. Dr. R. Bargou. The appointment of Prof. Dr. Bargou has been bound up with his taking position of the directorship for the **Comprehensive Cancer Center Mainfranken**, which has been assessed by the German Cancer Aid in 2011 and which is now receiving a significant financial support as oncologic leading-edge cluster by the German Cancer Aid. By installing this department and joining the whole competence in the oncologic research and patient care, the Faculty of Medicine aims at transferring the successful creation of interdisciplinary centers in theoretical medicine, which has been successful years ago with the foundation of the Biocenter and the Center for Infection Research, onto clinical research and, by bundling basic research, translational and clinical research, at strengthening and expanding the Faculty's scientific and clinical profile in cooperation with the University Clinic. This is also the background concept for the creation of the **German Center for Heart Failure** in 2011, going back on the funding of the German Ministry of Education and Research [BMBF] in the context of Integrated Research Centers, uniting scientists of different clinical disciplines with scientists of basic research. Both interdisciplinary centres are gaining increasing importance for the clinical research by the **Institute for Clinical Epidemiology and Biometry**, which the Faculty of Medicine has recently founded and which is headed by Prof. Dr. P. Heuschmann. The work of all the scientists involved at the centers will enormously profit from the BMBF initiative for the establishment of biobanks. Würzburg has been successful in the competition process and is now receiving 5 million Euro for the implementation of the **Interdisciplinary Biomaterial Bank and Data Base (IBDW)**, which is being co-ordinated by Prof. Dr. R. Jahns.

The review on development and events in the past years cannot go without emphasizing the efforts towards the improvement of the medical doctoral thesis. The Faculty of Medicine is fully committed to graduation of young doctors and the award of the title Dr. med. The public discussion and the graduation experience, scientific misconduct of doctoral candidates and supervisors as well as our own experience have led us to introducing changes into the graduation regulation, which also have recently been recommended by the German Science Council, and which guarantee high quality standards and avoid scientific misconduct in the graduation process. In this connection, the **Graduate School of Life Sciences (GSLS)** is being attributed special importance. Medical graduation is being executed under the high quality standards of the Graduate School. In order to give the respective support, the Faculty of Medicine has introduced a scholarship programme for medical graduates.

The exposed positive development is the result of the huge efforts of our scientists. It has also been enabled thanks to the financial support of private and public investors as well as foremost by the critical look and constructive recommendations from reviewers and members of the scientific advisors of our centres. I would like to take this opportunity in order to thank them all for their contribution and their continuous support with all my heart in the name of our faculty.

Würzburg, February 2012
Prof. Dr. Matthias Frosch
Dean

Honours awarded by the Medical Faculty

Fig. 1: Awarding of the honorary doctorate to Prof. Dr. Ernst-Theodor Rietschel during the graduation ceremony on May, 21, 2010 in the Neubaukirche through the Dean Prof. Dr. M. Frosch (left) and the Vice-president of the University of Würzburg, Prof. Dr. M. Lohse (middle). From 1980 to 2005 Prof. E.-Th. Rietschel was full professor for immunochemistry and biochemical microbiology at the University of Lübeck and in parallel director at the Borstel Research Center – Leibniz-Center for Medicine and Biological Sciences. From 2005 to 2010 he was president of the Leibniz Society and from 2007 to 2008 also scientific director of the medical faculties at the universities of Lübeck and Kiel. The Medical Faculty honoured his outstanding scientific achievements in the context of the elucidation of the structure and function of the bacterial surface molecule lipopolysaccharide. Beginning in the 1970 he published more than 200 scientific papers in this research area. With Prof. E.-Th. Rietschel the Medical Faculty not only honoured an internationally regarded scientist, but also appreciated his several years' engagement as speaker of the Scientific Advisory Board of the Center for Infectious Diseases as well as his long-lasting connections to the Medical Faculty of the University of Würzburg in general.

Fig. 2: Awarding of the honorary doctorate to Prof. Dr. Ernst-Ludwig Winnacker during the graduation ceremony on May, 25, 2011 in the Neubaukirche through the Dean Prof. Dr. M. Frosch (left) and the Vice-president of the University of Würzburg, Prof. Dr. M. Lohse (right). Since 1977 Prof. E.-L. Winnacker is professor for biochemistry at the Ludwig Maximilians University in Munic, where he co-founded in 1984 the Gene Center which he headed until 1998. From 1998 to 2006 he was president of the Deutsche Forschungsgemeinschaft. From 2007 to 2010 he was also Secretary General (SG) of the European Research Council and since July 2009 he is Secretary General of the International Human Frontier Science Program. The Medical Faculty honoured his scientific contributions in the field of nucleic acid replication and his commitment in several national and international scientific organisations. With Prof. E.-L. Winnacker the Medical Faculty not only honoured an internationally regarded scientist and an outstanding science policy maker, but also appreciated his close connections to the Medical Faculty of the University of Würzburg.

Fig. 3: The Siebold-Medal honours people, who rendered outstanding services to the Medical Faculty and the University Hospital. On November, 18, 2011 Mrs Renate Schülke-Schmitt was honoured by the Dean Prof. Dr. M. Frosch (right) and the Managing Medical Director Prof. C. Reiners (left) with the Siebold-Medal. Mrs R. Schülke-Schmitt, who over 20 years played a significant role in shaping the University Hospital as a Member of the Board of Directors and as Administrative Director, was awarded with the Siebold-Medal on the occasion of her official retirement farewell ceremony.

1.2 Medical Education

The Faculty of Medicine's principal aim is to train the students by offering an excellent education, an extensive training of practical skills and a qualified scientific education.

In order to reach these aims, the medical courses as well as the practical year are continuously being evaluated each semester. The Faculty of Medicine's Albert-Köllicker-Teaching-Price, endowed with 10,000 Euro, is awarded twice a year to teachers for their outstanding performance. The award ceremony is integrated in the academic graduation celebrations at the University's Neubaukirche.

In the **agreement on targets** with the Bavarian State Ministry, the Faculty of Medicine has committed itself to temporarily increase the number of students in the discipline of human medicine by annually 30 students over a period of six semesters, starting in the winter semester 2011/2012. By the temporary increase of freshmen supplementary study places shall be created for the dual Abitur cohorts. In addition, ten supplementary students a year will be accepted in the first clinical semester for a period of four years starting with the winter semester 2011/2012. The financial means, which are being put at the Faculty's disposal in the framework of the agreement on targets, are being used for teacher positions as well as for equipment for the preclinical semesters. In the clinical section, the financial means are used for extension of bedside teaching capacities as well as for equipment of training rooms.

With the start of the winter semester 2012/2013 the University of Würzburg will include the test for medical students as selection criterion for the university selection process.

The University of Würzburg has increased the number of **Academic Teaching Hospitals** from 5 to 7: In the second semester of 2010, an agreement has been signed with the Caritas-Hospital Bad Mergentheim. At the beginning of 2011, a respective contract has been concluded with the Rothenburg ob der Tauber Clinic.

The **training hospital** where students can train their practical skills, not only has become a student magnet; it also has become indispensable for our future doctor's practical training. The constant expansion of **e-learning** programs contributes to the improved student training as well. In addition, students are offered a comprehensive **mentoring** program granting them good support during their studies. The continuous widening of international partnership allows the students a better **mobility** and the gaining of new experiences. Students of other countries or continents are enriching the studies on site. The budget gained by the **medical tuition fees** substantially contributes to finance the mentioned services for the students.

Training hospital

The team of Würzburg's training hospital has organized the annual **"Skills Lab – Symposium"** in its new facilities on the 8th and 9th of April 2011. With this event, the first construction phase has been concluded in the former rooms of the Nuclear Medicine Department. More than 150 participants from Germany and abroad have used the opportunity to attend an interesting and successful event which took place in the impressive new **training hospital**.

For the first time, the course 'practical clinical examination methods III (PKU)' has taken place as mandatory course in the 10th semester. In addition the offer for optional courses is continuously being expanded. Also new courses for students of the preclinical section as well as for dental students have been implemented.

E-learning

The Faculty of Medicine's e-learning offering is in a constant development process. On the one hand, e-learning better supports students in their learning habits. On the other hand, it supports the faculty to face the temporary capacity increase.

The electronic compilation and evaluation of exams is further developed and implemented by the e-learning program. The results and analyses of this program have been published in the following papers:

1. Hörnlein A, Mandel A, Ifland M, Lüneberg E, Deckert J, Puppe F: Akzeptanz medizinischer Trainingsfälle als Ergänzung zu Vorlesungen; GMS Z Med Ausbild. 2011;28 (3)
2. Mandel A, Hörnlein A. Ifland M, Lüneberg E, Deckert J, Puppe F: Aufwandanalyse für computergestützte Multiple-Choice Papierklausuren, GMS Z Med Ausbild. 2011;28(4).

The faculty has been successful in the fund acquisition for responding to challenges:

a) The Bavarian State Ministry for Science, Research and Culture has extended the support for the competence centre 'medical education in Bavaria' by three further years.
b) The interdisciplinary e-learning project, which is being financed by tuition fees, has also been further extended.
c) Many individual projects of the Faculty of Medicine are being financed by the Virtual University of Bavaria (vhb).

Mentoring

DAAD funding has been acquired for the mentoring project 'Support for international students - MENTORING INTERNATIONAL' which is replacing the previous funding by the medical tuition fees.

MENTORING international is a programme aiming at an improved personal and study focussed integration of international students and an intensified exchange between students. The idea is that students are learning from students: New students from foreign countries are paired with mentor students with whom they regularly meet; experienced tutors organize and lead disciplinary tutorials; joint events contribute to intensify the networking process (excursions with medical relation, information rounds with themes of general interest for medical students). The activity coordination by the project leaders and the collaboration with further coordinating university partners constitute the prerequisite for a further continuous qualitative development.

The mentoring programs 'Mentoring studmed' (career orientation and support for female medical students) as well as the program 'Förderung studmed" (study and career planning) are being financed by funds of the European Social Fund and by tuition fees respectively.

BMBF has allocated funds to the Faculty of Medicine for a half position and a quarter position, which the University implements for the improvement of the student education. The additional human resources allow a further expansion of the mentoring programs, especially for freshmen and preclinical students, as well as expansion of the evaluation program.

International Affairs

The number of ERASMUS partnerships has been increased to 35 partnerships with European universities.
In December 2012, the Universities of Nagasaki and Würzburg as well as their respective faculties of medicine have prolonged

their bilateral cooperation agreements. The partnership between the Universities of Nagasaki and Würzburg dates back about 20 years. An essential partnership component is the exchange of students. The student exchange is being financed (with a short interruption) by the German Academic Exchange Service (DAAD) since 1997. 32 German as well as many Japanese students have participated in the exchange program. The students generally stay at the institutes and clinics of the partner institutions for six to eight weeks. Thanks to the meanwhile impressive number of exchange students and scientists the culture exchange and the relationship between the partners participating at this program have become very intensive. Students having participated at the exchange program, or who are about to leave for their exchange period, are looking after the incoming students in Japan respectively Germany. An increasing network has thus been created. Close and vivid contacts as well as even permanent friendships have originated from the bilateral partnership.

Tuition fees are implemented for financing the following measures:

- E-learning/blended learning offering
- The project 'efficient exam preparation'
- International program
- Teaching coordinators in the clinical disciplines
- Equipment of the training hospital (phantoms for teaching purposes, simulators, medical models, etc.)
- Standardized patients project
- Equipment of facilities for skill training (technical devices, microscopes, etc.)
- Student tutors
- Scripts
- Exam preparation
- Teaching of didactic skills for lecturers

Biomedicine/Biochemistry

The Faculty of Medicine and the Faculty of Biology are offering the joint Biomedicine programme in which students are being educated at the interface between the classical natural sciences and clinical research. Ten years after its introduction, the B.Sc. curriculum has been reformed according to the Bologna process requirements and the M.Sc. program has been extended from originally 3 to 4 semesters. The core curriculum consist of a research-oriented training with intensive laboratory courses in small groups and an early immersion in current research topics. Additional internships in individual work groups guarantee an efficient and productive thesis project that concludes with the respective final Bachelor or Master thesis, which is written in English. In addition to scientific training, students can also gain further qualifications, ranging from regulatory and organisational expertise or lecture and presentation training to scientific ethics and technical English.

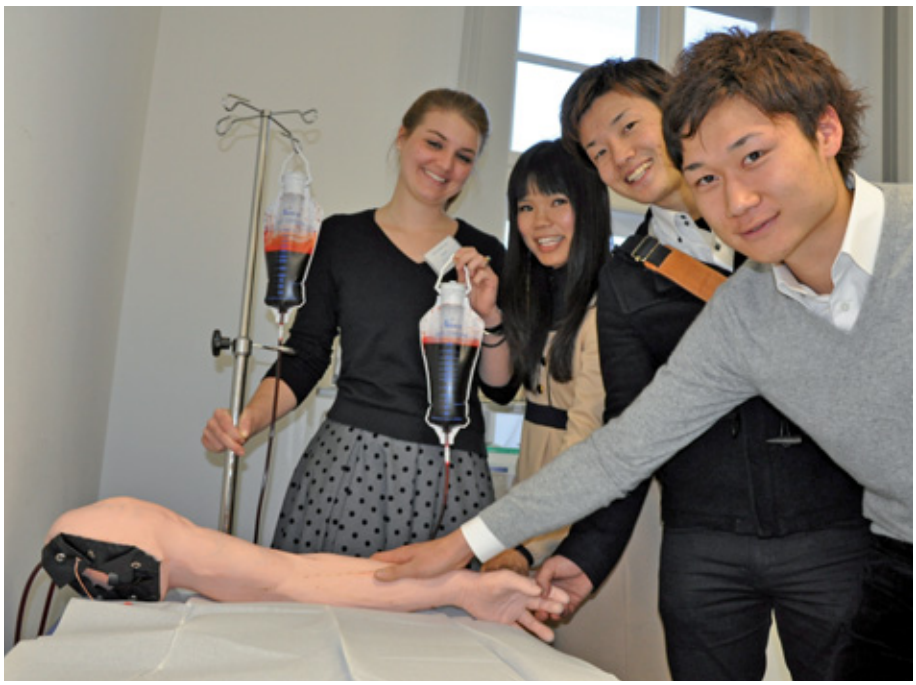


Fig. 1: The Japanese exchange students Shota Akenaga, Masayuki Fukomoto und Akari Sasamura (from right to left) are trained in blood withdrawal by tutor Annabelle Lumpp (left) in the training hospital in Würzburg.

While the Bachelor curriculum is densely structured, students are rather free to set their own priorities in the Master programme after finisching the first semester with a mandatory practical course in model organisms with accompanying lectures. A special feature of the Biomedicine programme is the high share of stays abroad. The majority of the students use this opportunity to widen their scientific and personal horizon.

The interest in the Bachelor programme continues to be impressive with sometimes more than 1,000 applications for 24 study places. 350 students have been enrolled in the B.Sc. programme and further 118 in the M.Sc. so far; the share of female students is extremely high with 83 % and 72 %, respectively. Most of the graduates so far have opted for a further scientific qualification, about 40 % of them in Würzburg, while the remaining graduates chose other institutions in German or abroad.

Since the beginning of the study year 2009/2010, the Faculty of Medicine and the Faculty of Chemistry and Pharmacy are jointly offering the additional Biochemistry B.Sc. programme. The demand for these 30study places is also very high. Here, the focus is not such much on a clinic-related research but rather on a reinforced molecular orientation. A consecutive M.Sc. study course will be implemented with the start of the winter semester 2012/2013.

With the Biomedicine and Biochemistry curricula, the faculty ensures that highly qualified up-and-coming basic scientists are well trained for medically relevant research. This complements the programmes of Experimental Medicine and the MD/Ph.D programmes that are intended for medical students to broaden their scientific basis.

Dental medicine

At present, 630 dental students are enrolled at the University of Würzburg, 320 of them in the preclinical, the remaining 310 in the clinical part of their education. The clinical curriculum is organized according to the currently valid Medical Licensure Act for dentistry students; all required practical and theoretical courses are offered. The dental clinic is located in the recently built dental clinic building in the centre of Würzburg. 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 that 28,000 out-patients and more than 1,350 in-patients have been treated in 2011. All the departments are equipped according to the newest technical standard. 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 education are now offered. With the new Medical Licensure Act for dentistry students the teaching concept will pass through further modifications.

In the winter semester 2010/11 a newly equipped phantom hall has been put into operation for the student training in dental preservation, a further phantom hall for the surgical training. The equipment of the surgical phantom hall has been made possible by tuition fee support.

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. The high financial burden, which dental students have to bear today, is thus reduced.

In the winter 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 had been announced for a long time, is about to be issued and is expected to require a significant effort for restructuring the studies of dental medicine.

Prof. Dr. J. Deckert,
Dean of Student Affairs Medicine
Prof. Dr. M. Gessler,
Dean of Student Affairs Biomedicine
Prof. Dr. A. Kübler,
Dean of Student Affairs Dental Medicine

1.3 Students' Representatives

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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, 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 of the Northern Italian universities, where they were commonly allowed to accompany the professors on their 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 Faculty 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 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 had 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 immat-

riculated 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 patients without families 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 Julius-Spital 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 Heyde, 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. The Anatomical Institute obtained numerous corpses of people who had been executed for political reasons as well as, through Heyde, about 80 corpses of men and women who by all appearances had been murdered – possibly in the gas chambers – with carbon monoxide. 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. 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 five MD-students. One Post-Doc and seven PhD-students funded by the Collaborative Research Centre (SFB 487 projects A4 and C1), an individual grant of the Deutsche Forschungsgemeinschaft (DFG KO872/5-1) and two grants of the interdisciplinary clinical center of Würzburg (IZKF grants E141 and N113) 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 polyspecific transporters for organic cations and organic anions. The transporters bind their respective substrate at the extracellular side of the plasma membrane and undergo structural changes during which the substrate is first occluded and then released at the intracellular side. Using site directed mutagenesis the research group identified seven amino acids in the organic

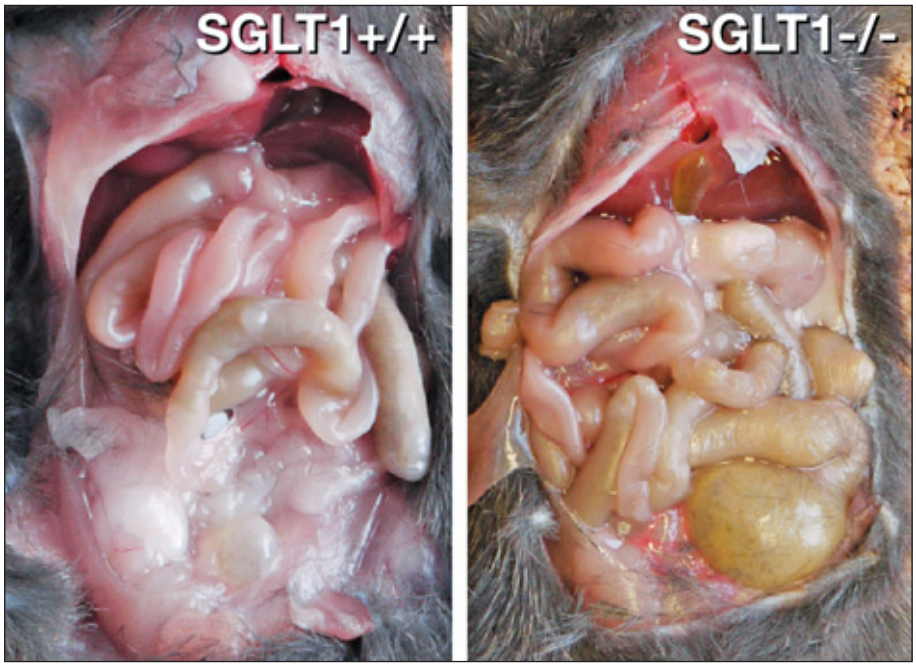

Fig. 1: Appearance of the intestine of mice in which SGLT1 is inactivated when they were fed with standard diet. Wildtype (SGLT1+/+) and SGLT1 -/- mice were kept for two months on a glucose-galactose free diet and then fed for two days with a glucose containing standard diet. Missing D-glucose and D-galactose absorption in the SGLT1-/- leads to an increased bacterial growth resulting in the generation of gas.

cation transporter OCT1 that are critical for binding of different substrates and inhibitors and/or are essential for translocation. During transport five of these amino acids become accessible from the extracellular and intracellular side of the plasma membrane. Computer modeling of the OCT1 tertiary structure in analogy to the elucidated structure of a bacterial transporter (lactose permease) allowed a structure-related interpretation of the data. Using fluorescent labeling of single amino acids of OCT1 motion of the 3rd, 8th and 11th transmembrane domain during binding and/or transport of organic cations could be demonstrated. Members of the SLC22-family were expressed in a cell free expression system. Furthermore, active transporters were purified and reconstituted 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.

Functions and regulations of the sodium D-glucose cotransporters SGLT1 and SGLT2

To elucidate functions and regulations of the Na^+-D-glucose cotransporters SGLT1 (gene SLC5A1) and SGLT2 (gene SLC5A2) mice were generated together with other scientific groups in which the SLC5A1 gene or the SLC5A2 gene was inactivated. With mice it was possible to determine the functions of SGLT1 in small intestine and kidney and the function of SGLT2 in kidney. Mice lacking functional SGLT1 developed a glucose-galactose malabsorption syndrome and died after weaning when they received a glucose containing standard diet. However, they survived and developed well when they were fed with a diet that did not contain D-glucose and D-galactose. A couple of years ago the intracellular regulator protein RS1 which is encoded by the intronless gene RSC1A1 was cloned in the group of H. Koepsell. RS1 is localized at the trans-golgi network, where it inhibits the budding of SGLT1-containing vesicles. During mitosis or in less differentiated cells, RS1 is localized in the nucleus, where it inhibits SGLT1-transcription. In mice with a RS1 (RSC1A1 gene) knock out, absorption of D-glucose in the small intestine was increased. A domain in RS1 was identified which is responsible for the post-transcriptional inhibition of SGLT1. Peptides derived from this domain mediate a posttranscriptional inhibition of SGLT1 expression at nanomolar intracellular concentrations. Several patents have been submitted trying to protect the use of these peptides for the treatment of obesity and diabetes.

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

Gorboulev V, Schürmann A, Vallon V, Kipp H, Jaschke A, Klessen D, Friedrich A, Scherneck S, Rieg T, Cunard R, Veyhl-Wichmann M, Srinivasan A, Balen D, Breljak D, Rexhepaj R, Parker HE, Gribble FM, Reimann F, Lang F, Wiese S, Sabolic I, Sendtner M, Koepsell H. (2012) Na(+)-D-glucose cotransporter SGLT1 is pivotal for intestinal glucose absorption and glucose-dependent incretin secretion. Diabetes 61:187-96.

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Ciarimboli G, Deuster D, Knief A, Sperling M, Holtkamp M, Edemir B, Pavenstädt H, Lanvers-Kaminsky C, am Zehnhoff-Dinnesen A, Schinkel AH, Koepsell H, Jürgens H, Schlatter E (2010) Organic cation transporter 2 mediates cisplatin-induced oto- and nephrotoxicity and is a target for protective interventions. Am. J. Pathol. 176:1169-80.

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

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Mission and Structure

In the past, research in the Department II of the Institute was focused on two main areas of interest. The former 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).

The future research in Department II of the Institute of Anatomy and Cell Biology (Head: Prof. Dr. S. Ergün) will focus in the field of new formation of blood vessels by angiogenesis and postnatal vasculogenesis as well as in the field of stem cell and tissue regeneration. 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. New microscopic facilities including live cell imaging, morphometric and cell motion studies, and automated analyses of cell migration and proliferation are established.

Main research focus

Angiogenesis, vasculogenesis, stem cells and tissue regeneration
(S. Ergün, R. Benndorf, D. Kremer, V. Ninichuck, J. Allmanritter)

Molecular and cellular processes of activation of pre-existing mature vascular endothelial cells as well as the role of vascular progenitor and stem cells in new formation of blood vessels in the frame of cardiovascular diseases, tissue regeneration, and tumor vascularization will be analyzed. In the field of progenitor and stem cells we will focus at the role of adult stem and progenitor cells residing in the vascular wall, in particular in the vascular adventitia. These cells have been shown to form and stabilize new vessels. We will study whether and how far these cells are involved in the neovascularization during diseases and processes mentioned above. In this context, we also want to analyze the contribution of these vessel wall-resident stem and progenitor cells to stabilization and maturation of new vessels, a process of clinical relevance. Recent analyses show that the vessel wall-resident stem and progenitor cells have the potential to differentiate into organ-specific cells or into inflammatory cells like macrophages. Thus, we also want to study, which non-vascular cells can be generated from the vessel wall-resident stem and progenitor cells. For these studies we want to use iPS technology for reprogramming and/or transdifferentiation of cells. Furthermore, we will study the impact of the cell adhesion molecule CEACAM1 in the regulation of endothelial barrier. In previous studies, we could show that CEACAM1 in endothelial cells acts proangiogenic and is essentially involved in the early morphogenesis of blood vessels. Using mouse models with CEACAM1-Knock-out, we want to analyze the role of this molecule in atherosclerosis and also in tumor vascularization and metastasis. Finally, we will study the role of isoprostanes in the angiogenesis and postnatal vasculogenesis in in vitro as well as in vivo models.

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

The endothelium lines the inner surface of the vascular wall. We investigate how inflammatory mediators induce the formation

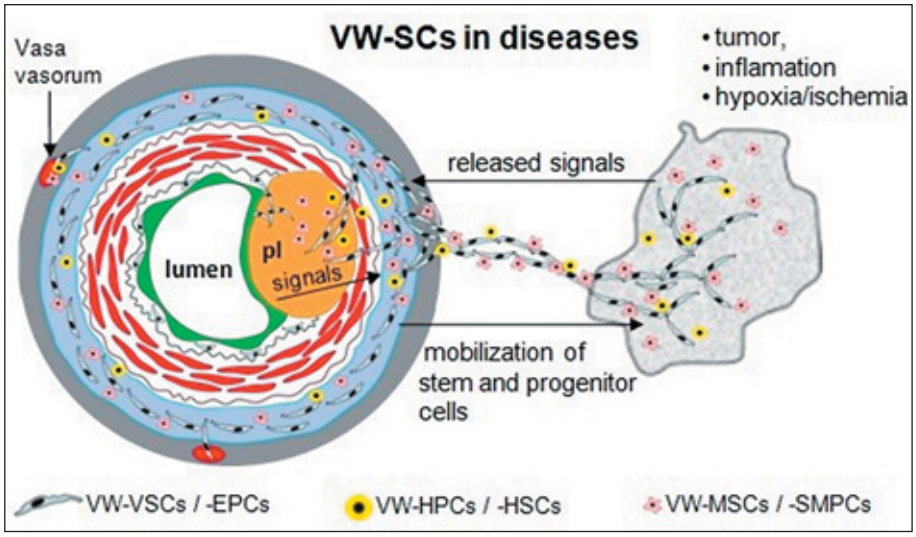

Fig. 1: Clinical impact of VW-SCs. As shown in this figure, VW-SCs can be mobilized in both directions: (i) toward the outside of the vessel wall, for example, by signals released from tumor cells, inflammatory processes, and tissue ischemia, and (ii) toward the vessel lumen, for example, hypoxia of the vessel wall, endothelial injury, and atherosclerotic plaque development (pl). In these processes, VWSCs may contribute to new vessel formation and also to accumulation of inflammatory cells. Finally, VW-SCs hypothetically can be mobilized from their niche into the vasa vasorum and thus may contribute to the pool of circulating stem and progenitor cells. (Ergün S, Tilki D, Klein D. Antioxid Redox Signal. 15;15(4):981-5 2011)

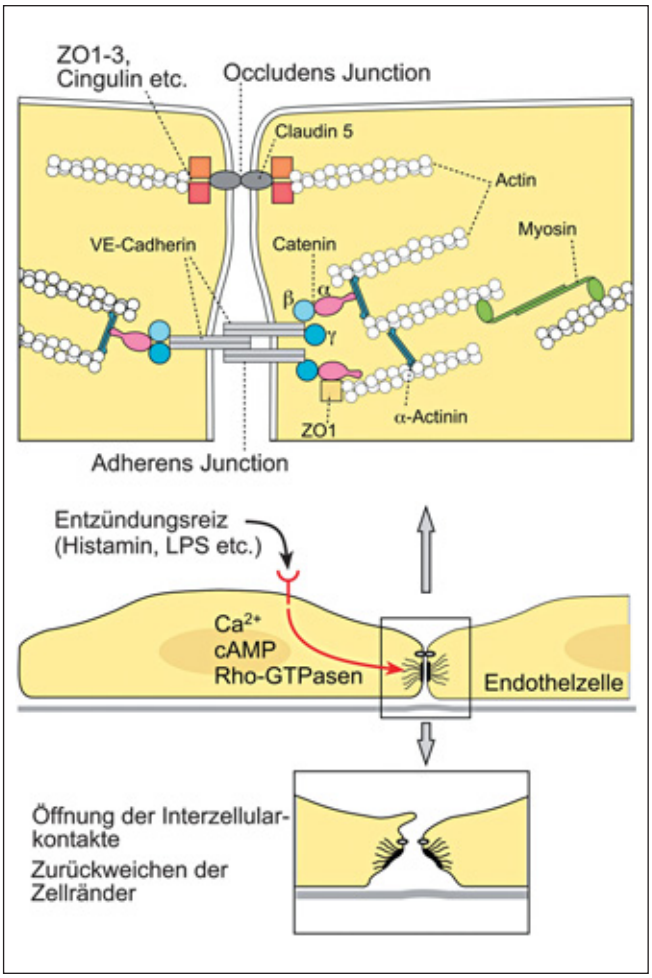

Fig. 2: Cytoskeleton and adhesion molecules (cadherins) control the barrier between blood and tissue (endothelial layer). How inflammatory stimuli modify the barrier is one aspect investigated by the group.

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 and developed peptides stabilizing the endothelial barrier.

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

The life-threatening blistering skin disease pemphigus is primarily caused by antibodies against cell adhesion molecules (desmocadherins). We investigate whether these autoantibodies directly interfere with binding of these adhesion molecules (AFM- and laser tweezer studies) or whether cell signalling pathways are responsible for skin blistering. We developed peptides that protect autoantibody-induced desmosomal dissociation.

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 pathophysi-ological aspects (i.e. laminopathies)

Glutamate transporters in the brain
(P. Kugler)

Glutamate is used as an excitatory neurotransmitter by numerous neuronal systems in the brain. Synaptically released glutamate has to be eliminated rapidly from the extracellular space via glu-tamate 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 networks and investigate which factors could be responsible for normal function and pathologic changes.

Light and electron microscopical morphology 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 developing, establishing and applying novel techniques and carrying out such investigations, we support studies in numerous clinical and basic science projects dedicated to elucidate molecular mechanisms of nervous system disorders.

Teaching

Courses in microscopic and macroscopic anatomy, neuroanatomy and cell biology are held for medical, biomedical and dentistry students (a total of 420 students per year). The department hosts a yearly meeting of the Anatomical Society (last week of September).

SELECTED PUBLICATIONS

Graziani A, Poteser M, Heupel WM, Schleifer H, Krenn M, Drenckhahn D, Romanin C, Baumgartner W, Groschner K. (2010) Cell-cell contact formation governs Ca2+-signaling by TRPC4 in the vascular endothelium: evidence for a regulatory TRPC4-beta-catenin interaction. J. Biol. Chem. 285:4213-4223.

Spindler V, Vielmuth F, Schmidt E, Rubenstein DS, Waschke J. (2010) Protective endogenous cyclic adenosine 5'-monophosphate signaling triggered by pemphigus autoantibodies. J. Immunol. 185:6831-6838.

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2.3 Institute of Physiology, Chair of Vegetative Physiology

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Professor Dr. rer. nat. Kai Schuh
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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-B for CNP and 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 and CHCF in Würzburg.

Cardiovascular functions and cellular signaling pathways of the cardiac hormones ANP and BNP
(M. Kuhn, K. Völker, B. Gaßner, H. Oberwinkler, M. Klaiber, W. Chen, F. Werner, T. Premsler, A. Spitzl, H. Nakagawa and Coworkers)

The cardiac hormones atrial (ANP) and B-type natriuretic peptides (BNP) are critically involved in the regulation of arterial blood pressure and intravascular volume. To dissect their cell-specific effects, we generated different mouse models with conditional deletion of their shared guanylyl cyclase-A (GC-A) receptor or putative downstream messengers. Our observations showed that concerted renal diuretic and endothelial permeability actions of endocrine ANP maintain intravascular volume homeostasis. BNP instead is more involved in the paracrine modulation of growth and viability of different cardiovascular cell types. Hence, BNP inhibits pathological cardiomyocyte growth and fibroblast proliferation, thereby moderating cardiac remodelling. Intriguingly, BNP exerts the opposite actions on endothelial cells, stimulating their proliferation and migration. In particular, BNP, produced by activated satellite cells within ischemic skeletal muscle or by cardiomyocytes in response to pressure load, regulates the regeneration of neighboring endothelia. Notably, all these pleiotropic actions of ANP and BNP are mediated by the same cGMP-producing GC-A receptor (Fig. 1).

In general, cGMP regulates the activity of different "third" intracellular messengers: cAMP-modulating phosphodiesterases and protein kinases. To study the cardiac role of cGMP-activated protein kinase I (cGKI), we generated transgenic mice with conditional, cardiomyocyte-specific ablation. Our comparative studies in GC-A- and cGKI-deficient mice and myocytes showed that NPs, via GC-A/cGMP/cGKI signaling, stimulate the phosphorylation of the regulator of G-protein (RGS) 2 (Fig. 2). Ultimately this pathway inhibits myocyte Ca^{2+}- and growth-stimulating effects of hormones activating Gq-coupled receptors, such as Angiotensin II (Klaiber et al., 2010). In addition, these studies revealed that cardiomyocytes express a second cGMP-synthesizing guanylyl cyclase, GC-B, a receptor for C-type natriuretic peptide (CNP). Notably, although both receptors, GC-A and GC-B, signal via cGMP and cGKI, their activation exerts distinct cellular effects. The CNP/GC-B/cGMP/cGKI signaling pathway enhances phospholamban phosphorylation and thereby intracellular Ca^{2+}- transients and contractility of myocytes (Frantz et al., 2011). Together, these observations indicate that two membrane-bound GC receptors mediate compartimentalized increases of cGMP and cGKI activity in myocytes, ultimately eliciting distinct, even opposite cellular responses.

In patients with hypertensive cardiac hypertrophy, ANP and BNP levels are markedly increased and GC-A/cGMP responses to NPs

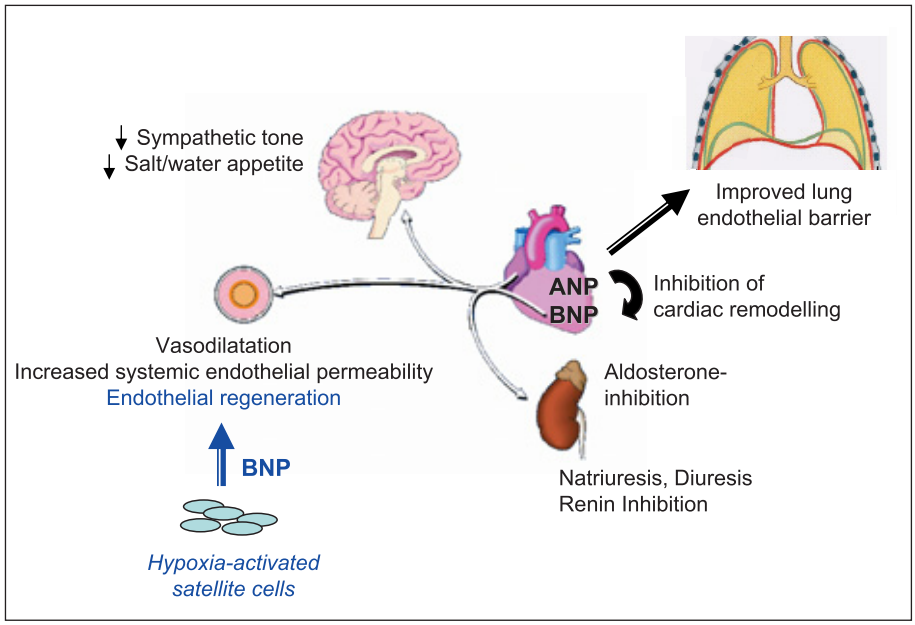

Fig: 1: Pleiotropic effects of natriuretic peptides.

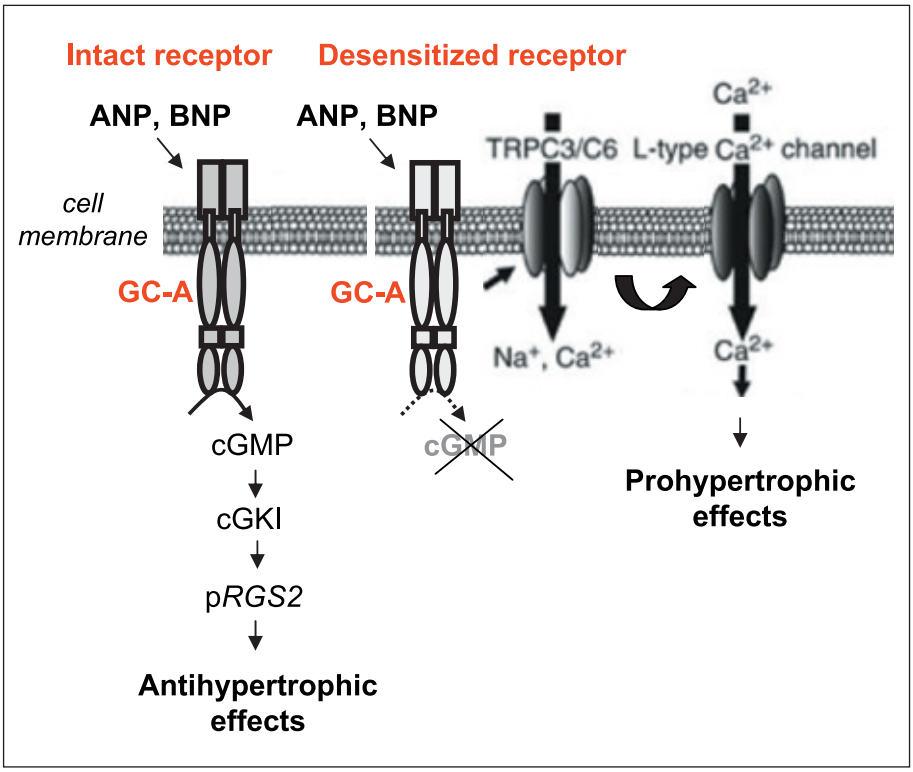

Fig: 2: Cyclic GMP-dependent and independent signaling of the GC-A receptor in cardiac myocytes.

are blunted due to receptor desensitization/dephosphorylation. Our studies showed that, in this situation, ANP binding to GC-A stimulates a unique cGMP-independent signaling pathway in cardiac myocytes, resulting in pathologically elevated intracellular Ca^{2+}-levels. This pathway involves the activation of Ca^{2+} permeable transient receptor potential canonical 3/6 (TRPC3/C6) cation channels by GC-A, which forms a stable complex with TRPC3/C6 channels. The resulting cation influx activates voltage-dependent L-type Ca^{2+} channels and ultimately increases myocyte Ca^{2+}i levels (Fig. 2). In sum, our observations reveal a dual role of the NP/GC-A–signaling pathway in the regulation of cardiac myocyte Ca^{2+}i homeostasis. Under physiological conditions, activation of a cGMP-dependent pathway moderates the Ca^{2+}i-enhancing action of hypertrophic factors such as angiotensin II. By contrast, a cGMP-independent pathway predominates under pathophysiological conditions when GC-A is desensitized by high ANP levels (Fig. 2). The concomitant rise in $[Ca^{2+}]$i might increase the propensity to cardiac hypertrophy and arrhythmias.

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

(A. Friebe, D. Groneberg, R. Jäger, M. Kümmel, N. Bettaga, B. Lies)

NO-sensitive guanylyl cyclase (NO-GC) has a key function in the NO/cGMP cascade by catalyzing the synthesis of the intracellular signaling molecule cGMP. As the most important receptor for the signaling molecule nitric oxide (NO) NO-GC is involved in many physiological regulatory processes. We have generated transgenic mice with global deletion of NO-GC. These mice show increased blood pressure, gastrointestinal dysmotility, early postnatal lethality and shortened bleeding time. The identities of the individual cell types and tissues responsible for the respective phenotypes are not yet clear. To characterize the role of NO-GC in gastrointestinal motility, we generated mouse KO lines in which NO-GC is specifically ablated in smooth muscle cells or interstitial cells of Cajal or both. Our observations in these mice showed that both smooth muscle cells and interstitial cells of Cajal mediate gastrointestinal nitrergic relaxation (Groneberg et al., 2011).

Physiological functions of SPRED

(K. Schuh, M. Ullrich, 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 (Ullrich et al., 2011).

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 (3rd - 4th term).

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Klaiber M, Kruse M, Völker K, Schröter J, Feil R, Freichel M, Gerling A, Feil S, Dietrich A, Londoño JE, Baba HA, Abramowitz J, Birnbaumer L, Penninger JM, Pongs O, Kuhn M. (2010) Novel insights into the mechanisms mediating the local antihypertrophic effects of cardiac atrial natriuretic peptide: role of cGMP-dependent protein kinase and RGS2. Basic Res Cardiol. 105:583-95.

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2.4 Institute of Physiology, Chair of Neurophysiology

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Mission and Structure

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

Major Research Interests

Neuronal expression of clostridial toxins
(K. Neuser, M. Heckmann)

SNARE proteins are key-molecules of the synaptic machinery and cleaved by clostridial tetanus- and botulinum-toxins. We use *Drosophila melanogaster* and a binary expression system to control presynaptic expression of these neurotoxins. Submaximal expression alters the kinetics of release and provides insight into the mode of action of the toxins and the function of SNARE proteins in transmitter release.

Nanoscopy of endplate active zones
(M. Pauli, M. Heckmann)

Presynaptic active zones are too small to be resolved by conventional light microscopy. In electron micrographs active zones of neuromuscular endplates appear as ordered structures. We study this preparation using super-resolution dSTORM light microscopy together with the Sauer laboratory (Department of Biotechnology and Biophysics) with the aim to identify the molecular components of this ordered structure.

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 fruit fly 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.

Regulation of cellular excitability by potassium background currents
(E. Wischmeyer, 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. As some members of the K_{2P} channel family (TREK, TRESK) are prominently expressed in neurons of the nociceptive system they most probably play an important role in pain reception. Therefore, we address the question whether excitable processes of nociception and inhibitory effects of K_{2P} channels are regulated by identical signaling cascades.

Antidepressive drugs are able to downregulate the activity of K_{2P} channels (TASK, TREK). These properties may explain the beneficial antidepressive effects in brain as well as unwanted arrhythmias in heart. The importance of K_{2P} channels for heart ac-

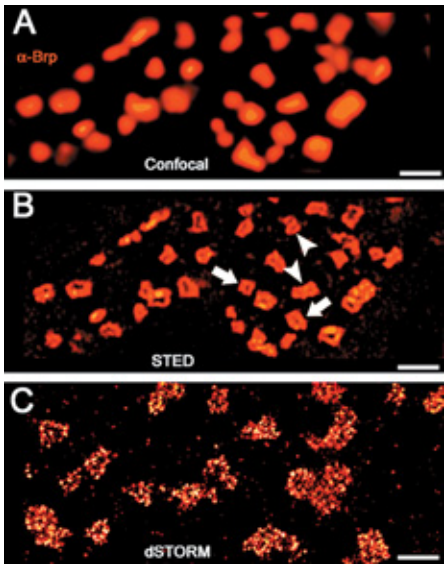

Fig.1: Molecular Structure of Active Zones. Investigations by the Kittel Emmy-Noether group in collaboration with the Sauer laboratory (Department of Biotechnology and Biophysics) concerning the spatial distribution of the Bruchpilot (Brp) protein in active zones. Application of „Super-Resolution" light-microscopy (STED and dSTORM) permits the identification of ultrastructural details concealed in conventional confocal imaging. A and B from Kittel et al., 2006. Scale bar: 1 µm (A, B), 500 nm (C).

tion and cardiac side effects of antidepressants are currently investigated in knockout mouse models.

Changes in serotonin metabolism substantially interfere with emotional states such as mood and anxiety. Neuronal potassium channels are controlled by the activation of different serotonin receptors and thus are molecular targets for changes in emotions. We investigate the contribution of K^+ channels to the regulation of emotional behavior especially anxiety disorders and depression.

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 (Ca^{2+}) 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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2.5 Biocenter Würzburg, Chair of Physiological Chemistry

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Mission and Structure

In accordance with the research perspectives at the Biocenter, the research interests at the department extend from functional molecular biology to questions concerning the development of organisms and their 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 reflected in the fact that scientists of the department are developmental biologists, molecular biologists, biochemists and biomedical researchers 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 tumor development and tumor 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 us to a better understanding of the intracellular processes, which are responsible for the transformation of normal, healthy pigment cells to highly malignant tumor cells. Through proteome and microarray analyses, as well as transcriptome seq analyses, novel melanoma molecules were identified. The usefulness of these as tumor 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 represent a benign, precancerous state of the malignant melanoma.
The intracellular signaling network is critically involved in neoplastic phenotype development of tumor cells. The changes that occur on this level during tumor formation, from the first transformed cell to the final malignant stage, are therefore the key for a better understanding of cancerous diseases. Consequently, components of the signaling network are intensively scrutinized for their usage as diagnostic markers and therapeutic targets.
In the Xiphophorus and medaka melanoma model systems the primary signal transduction events induced by the receptor tyrosine kinase Xmrk became recently reasonably well understood on the molecular level. Importantly, similar events occur during the generation of human melanoma. Examples are the activation of the MAP kinase pathway by BRAF V600E and NRAS Q61K, or the activation of the PI3 kinase pathway by NRAS Q61K or PTEN deletion. The “division of labor“ between the MAP kinase and the PI3 kinase pathways in human melanoma is one subject of our studies. Recent results point to an important cross-talk, which mediates sensitivity or resistance to chemotherapeutic drugs.
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

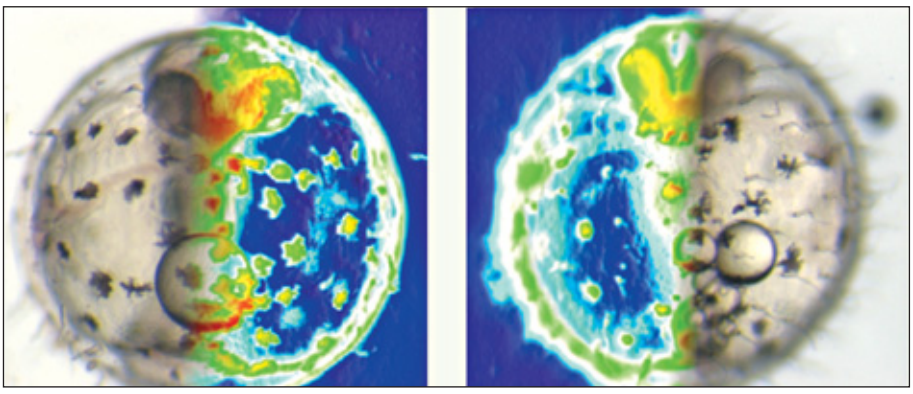

Fig. 1: Medakafish embryos, partially depicted in false color, from the analysis of a new melanoma overexpressed pigment cell gene.

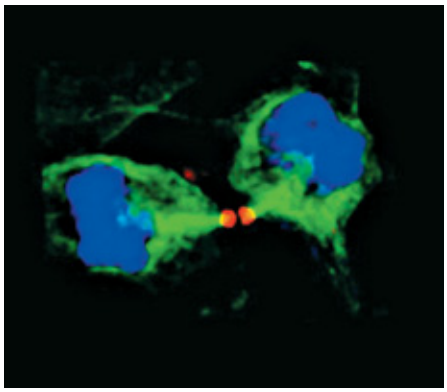

Fig. 2: Fig 2. Localization of the DREAM-target gene GAS2L3 to the midbody during cytokinesis. Red: GAS2L3, blue: DNA, green: tubulin.

for melanoma in general. Applying high-throughput methods to our in-vivo and in-vitro systems revealed a large number of genes and proteins that are regulated in response to Xmrk activation. 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, which can generate high amounts of reactive oxygen species. We have shown that high levels of reactive oxygen species lead to extensive DNA damage and to 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 offers the possibility of genetic manipulation by transgenesis, 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. We have found already several mutants that enhance or ameliorate the malignant process. Those were identified by their phenotypic effects. The corresponding genes will be isolated after outcrossing, fine mapping onto the genome and molecular cloning from an existing arrayed BAC library and then functionally characterized.

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. The composition of the complex is dynamic and in quiescent cells it associates with p130 and E2F4 and contributes to the repression of E2F-regulated genes. In late S phase, the interaction of DREAM with p130/E2F4 is lost and DREAM now binds to the B-MYB transcription factor. Genome wide expression studies have shown that DREAM-B-MYB is required for activation of a cluster of genes required for entry into mitosis, spindle assembly and cytokinesis. Inactivation of the LIN9 subunit of DREAM in the mouse results in early embryonic lethality at the peri-implantation stage. DREAM subunits have also been implicated in tumorigenesis. We are currently investigating the possibility that DREAM promotes tumorigenesis by interfering with the mitotic spindle checkpoint and by increasing genomic instability. We are also interested in the function of novel target genes of DREAM that play important roles in cytokinesis and genome stability.

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2.6 Biocenter Würzburg, Chair of Molecular Biology and Biochemistry

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Mission and Structure

The department of Physiological Chemistry II (PCII) is part of the „Biozentrum“ founded in 1990, in which 10 institutions from the faculties of Biology, Chemistry and Medicine co-operate in teaching and research. PCII teaches biochemistry for preclinical students in Medicine and Dentistry and for the Bachelor students of Biomedical sciences. Six research groups work at PCII, two of which are headed by junior investigators (Dr. Nikita Popov and Dr. Daniel Murphy). The major research aim of PCII is to understand the function of the Myc family of nuclear oncoproteins, which contribute to the majority of all human cancers. A second research aim is to use mouse models and functional genomic tools to identify novel strategies for the therapy of human cancers.

Major Research Interests

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

The MYC family of proto-oncogenes participates in the genesis of the majority of all human tumors. The three genes of this family encode nuclear proteins that are central regulators of cell growth and cell proliferation. They exert 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. The aim of our research is 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. In 2011, Armin Strauss started a new clinically oriented junior group (in co-operation with the Department of Surgery).

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

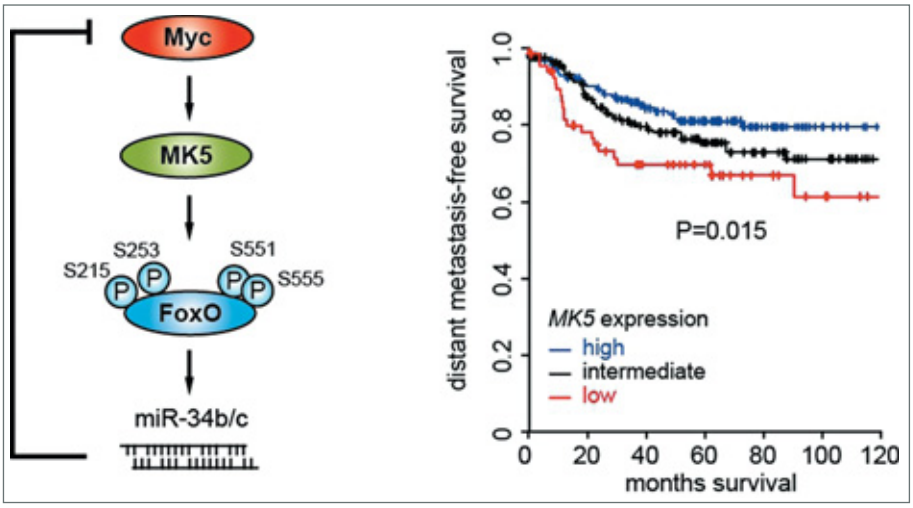

Fig. 1: A negative feedback loop controls expression of Myc in epithelial cells. The left graph shows that Myc induces expression of a kinase, MK5, which in turns phosphorylates members of the FoxO family of proteins that restrict Myc expression. The panel on the right shows that expression of Mk5 is silenced during progression of colon carcinomas and that loss of Mk5 correlates with an increased risk of distant metastases. The data are taken from Kress et al. (2011).

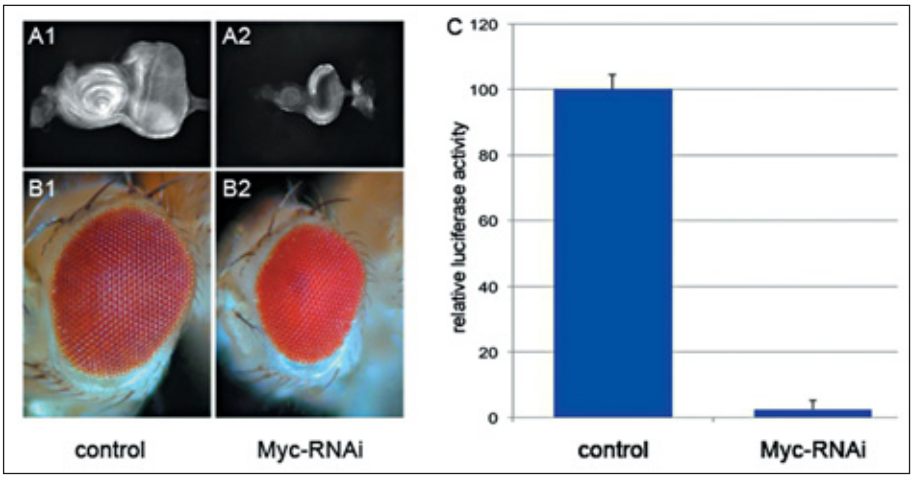

Fig. 2: Systemic growth effects exerted by Drosophila Myc. The knock-down of Myc exclusively in the larval fat body (corresponding to the vertebrate liver) reduces the growth rate of eye imaginal discs (panel A2) and results in adult flies with smaller eyes (B2). Panel C shows the result of an enzymatic assay we have developed that allows the rapid detection of such growth defects in total lysates of single larvae and can be used for a systematic genetic screen.

- 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

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 BMPs/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 students of Medicine and Dentistry per year. We also teach Biochemistry to the 24 annual students of Biomedicine (B.Sc./M.Sc.).

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2.7 Biocenter Würzburg, Chair of Developmental Biochemistry

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Mission and Structure

The scientific interests within the Chair of Developmental Biochemistry range from elucidation of the molecular control of development and differentiation processes to the uncovering of disease mechanisms that are brought about by deregulation of these pathways. The current focus is on the development of the cardiovascular system and the kidneys as well as on childhood kidney cancers, i.e. nephroblastomas (Wilms tumor). These projects are funded by the DFG, 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 our 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 build the cardiac septum and valves. This could be demonstrated through *in vitro* and *in vivo* analysis of cardiac precursors from knockout mouse embryos. Combinatorial gene deletions revealed 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 based on ChIPseq analyses. For this we employ various cell types including embryonic stem cells, which can be differentiated *in vitro* into cardiomyocytes or endothelial cells. In this way global as well as cell-type specific regulatory mechanisms of Hey proteins can be elucidated.
Hey genes are also important for embryonal angiogenetic remodeling and for arterialization of blood vessels. A lack of Hey1 and Hey2 results in a lethal angiogenesis defect. Both genes block expression of the venous regulator Coup-TFII (NR2F2) in the context of the hypoxia response. 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. While Hey2 functions in the inner ear appear to be independent of Notch signaling, the latter is essential in macrophages. Furthermore, Hey1 and HeyL are involved in bone homeostasis. This underscores that Hey genes can be activated by different stimuli in a variety of cell types and they likely regulate a multitude of physiological functions, as has been expected from their complex expression patterns in numerous organs.

Nephroblastomas / Wilms tumors

Wilms tumors are early childhood kidney cancers that originate from a failure of embryonic 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 1000

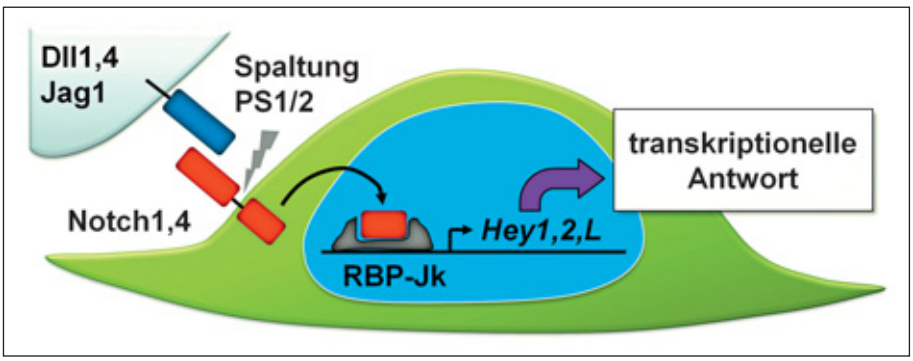

Fig. 1: The Delta/Notch signaling pathway activates transcription of Hey genes that in turn act as transcriptional repressors of target loci.

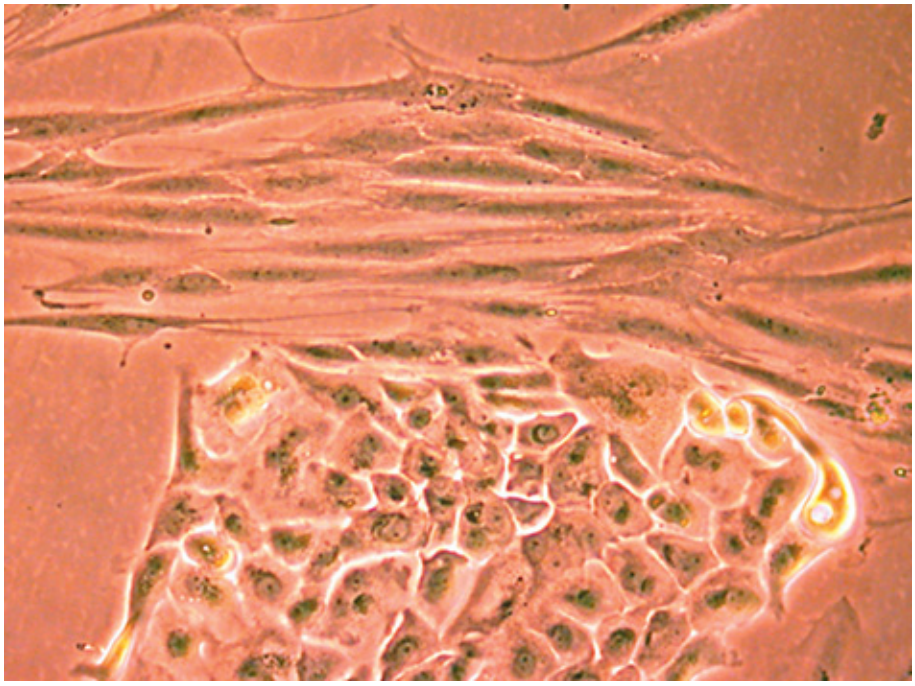

Fig. 2: Wilms tumors are often comprised of different cell types and these can initially be seen in cell culture as well.

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 biomarkers and target structures for improved diagnosis and treatment.

All attempts to analyse the biology of Wilms tumors through *in vitro* experimentation have been hampered by the lack of suitable cell culture systems. We have now established and characterized a series of primary cultures that can be used for functional studies. These cultures recapitulate critical features of these tumors, namely the stromal and epithelial components. We have not yet been able to establish conditions for the grow of the blastemal compartment. Several primary cultures could be immortalized through telomerase expression, yielding permanent stable lines. This now opens up the possibility to perform functional studies *in vitro* on standardized cells that are amenable to genetic manipulation and still represent typical Wilms tumors.

Our microarray analyses revealed that tumors which poorly respond to chemotherapy treatment are characterized by a decreased activity of the retinoic acid signaling pathway. Thus, activation of this pathway might in turn be beneficial for patients. This could be substantiated in experiments with primary tumor cell cultures. First therapeutic trials of individual cases have already been initiated based on these results. Using our series of additional primary and immortalized cultures we could show that retinoic acid derivatives slow down the growth of tumor cells and induce their differentiation. We observed differences in the effects of individual retinoids that may become relevant for future therapeutic application.

The large number of samples available from our tumor bank greatly facilitated the identification of a new gene locus that is affected in clear cell sarcoma, another pediatric kidney tumor. Furthermore, a tumor-specific antibody signature could be established from sera of Wilms tumor patients in a collaboration with the Institute for Human Genetics of Saarland University (Homburg). Such biomarkers are of special importance in the case of Wilms tumors to enable non-invasive early diagnostics and monitoring, since these tumors are generally treated by upfront chemotherapy without confirmatory tissue biopsy.

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, students of Biomedicine (B.Sc./M.Sc.) are taught in Biochemistry, Molecular Biology and Developmental Biology. For Biology and Biochemistry students advanced modules with a focus on Biochemistry, Developmental Biology and Tumor Biology are offered. 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).

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2.8 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 Bayerischen Akademie der Wissenschaften, a work group for the study of early modern physicians' correspondences has been 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 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. 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. After positive evaluation in the fall of 2011, the project has been accorded a first extension for another five years, as of January 2012.

Out-Patient Medical Care 1500-1850
(M. Stolberg, K. Nolte, S. Schlegelmilch, S. Neuner, 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. More recently, these projects have been complemented by research on the history of medical practice and medical note-taking in the 16th-century and on the role of medicine in the emergence of early modern empiricism and the scientific revolution of the 17th century.

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

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 originally 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. Work in this area is expected to reach its conclusion soon with the publication of a book on the cultural histo-

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

ry of the medical and nursing care of moribund patients in the 19th century.

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

The long pre-history of modern palliative medicine is virtually unknown. In this DFG-funded project we have pursued 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. The project, which has resulted in a number of papers, dissertations and a book on the history of palliative medicine from 1500 until today, was concluded in 2010.

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, online-courses in medical terminology have been developed which are open to all Bavarian students of medicine and dental medicine via the "Virtuelle Hochschule Bayern". 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 members support teaching activities at the Historical Faculty in Würzburg.

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2.9 Institute of Clinical Epidemiology and Biometry (ICE-B)

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Mission statement

The Institute of Clinical Epidemiology and Biometry at the University of Würzburg (ICE-B, Chair: Univ.-Prof. Dr. P. U. Heuschmann) was newly founded in October 2011. The Institute represents the disciplines of clinical epidemiology and biometry in research and training at the medical school of the University of Würzburg. The ICE-B primarily addresses research questions related to patients care. The research focus of the institute includes studies on: causes of diseases and respective risk factors; therapy and prevention; prognosis and outcome; diagnosis and screening; as well as adequacy and quality of medical care for diseases and syndromes. These clinically relevant patient-oriented research questions will be addressed by quantitative epidemiological methods.
The study portfolio of the institute comprises innovative interdisciplinary research projects in the field of clinical epidemiology and biometry. These projects are implemented in close cooperation with departments as well as research infrastructures of the University Hospital and the University of Würzburg, e.g. the Comprehensive Heart Failure Center or the Center for Clinical Studies. The research projects will be developed at the interface between clinical medicine and epidemiology using up-to-date epidemiological and biometrical methodology.

Research focus

The ICE-B is conducting independent research projects. The research objectives of the institute are structured into three main research areas: clinical research; prognostic studies; and health services research.

Clinical research

Main focus of this research area is to develop new methods for designing and analyzing various types of clinical studies. This area also includes the support of ongoing clinical studies within the University Hospital and the University of Würzburg. In addition, a close interaction with the Center for Clinical Studies of the University Hospital Würzburg is planned. For the scientific lead of this research area a W2 professorship is currently being appointed.

Prognostic studies

The research area prognostic studies aims to establish, maintain, and analyze cohorts of patients at increased risk for or with the diagnosis of a respective disease condition. These studies include for example: to investigate natural history, causes, and patterns of disease occurrence; to develop new models for predicting prognosis and outcome at various stages of the disease continuum; to determine strategies for preventing disease or complication occurrence; to develop interventions for improving mortality and morbidity in specific diseases.
One main research focus in this area is raising the research profile of disease specific registers as well as of routine data for determining the natural course of a disease as well as for identifying high risk patients in clinical care settings. For example, data from regional registers for quality assurance in acute stroke care collaborating within the German Stroke Register Study Group (ADSR, see figure 1) are used for prognostic research purposes, such as: identifying individual and structural factors influencing early outcome of diseases; prioritizing potential target conditions in routine care; and designing future intervention studies to improve morbidity and mortality.

Health services research

The theme health services research primarily addresses research questions related to adequacy and quality of medical care. These studies comprise the development of methods to monitor quality of routine medical care in different health care settings as well as of measures to improve

Fig. 1: Participants of the German Stroke Registers Study Group (as at 31.12.2010).

delivery of health care in the general population.
The focus of this area is to improve the translation of results from clinical studies into clinical care of the general population (phase II translation research). As an example, the collaborative project „The European Implementation Score (EIS) Collaboration“ shall be mentioned, which is funded within the framework 7 of the European Union and is coordinated by King's College London. Aim of this project is the development of a methodology to assess the degree of implementation of research evidence into clinical practice. Based on examples from clinical care of patients with stroke or established coronary heart disease, factors will be identified that predict a successful implementation of research evidence into clinical practice. For this purpose, data from national or regional stroke audits from 7 European countries will be analyzed by ICE-B researchers.
Furthermore, the EUROASPIRE (European survey of cardiovascular disease prevention and diabetes) study will start in 2012 as collaborative project between the ICE-B, the Comprehensive Heart Failure Center Würzburg (Prof. Dr. S. Störk) and a number of additional departments of the medical faculty. This multicenter European cross sectional survey will assess the quality of secondary prevention as well as the management of lifestyle factors, vascular risk factors and drug prevention in daily clinical practice in patients with established coronary heart disease. This study is coordinated by the European Society of Cardiology and the European Association of Cardiovascular Prevention and Rehabilitation.

Methodological research platform

The ICE-B will also be established as a comprehensive methodological platform for the medical faculty of the University of Würzburg for addressing patient-oriented research questions. Integrating epidemiological and biometrical expertise early in the process of developing and running a study considerably improves the quality of the research project as well as the likelihood of its success. The institute provides all methodological tools for developing, running and analyzing various types of patient-oriented research projects. Advanced tools for data management will be employed, such as the digital reading of questionnaires, which are established at the ICE-B.
A strong focus of the institute also covers methodological research for developing and applying new methods in the field of clinical epidemiology and biometry that will be used in collaborative research projects. These methods include for example: novel approaches in intervention studies (e.g. cluster trials, multistage interventions); new methods to control confounding in observational studies (e.g. propensity score analysis, multilevel analysis); potential utilization of routine datasets (e.g. needs assessment, outcomes evaluation in pragmatic trials); raising the research profile of disease specific registers (e.g. linkage for endpoint evaluation in cohort studies, determining external validity); medical decision analyses (e.g. economic modeling approaches, decision tree analyses); and developing new ways of implementing research findings in clinical care (e.g. telemedicine, inter-sectoral benchmarking).

Teaching

Another emphasis of the institute is to improve education and training of young scientists and physicians in epidemiology and biometry. For this purpose, teaching activities will be implemented early in the curriculum of medical students. Starting in summer 2012, the ICE-B will provide newly structured lectures and seminars in epidemiology and biometry for medical students. The training activities will focus on interactive elements and practical exercises, such as small group courses, to demonstrate the relevance of epidemiology in daily clinical practice.
Furthermore, advanced education activities in the area of clinical research, clinical epidemiology and health services research will be established in Würzburg to qualify young scientists to conduct independent patient-oriented research projects. For this purpose, the ICE-B will contribute in collaboration with a number of established research facilities in Würzburg (e.g. the Comprehensive Heart Failure Center) to various training and education activities in the area of clinical research currently being established. These activities comprise for example the establishment of a new section Clinical Sciences within the „Graduate School of Life Sciences (GSLS)“, the planned establishment of a program „Clinical Research“ and a Master course „Clinical Sciences and Epidemiology“ for medical students, and the support of a curriculum „Clinical Research“ for residents and fellows.

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2.9.1 Division of Medical Psychology, Medical Sociology, and Rehabilitation Research

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Mission and Structure

The focus areas of the Division of Medical Psychology, Medical Sociology, and Rehabilitation Research include research, education, and patient care. The research topics comprise psychosocial factors of somatic diseases and processes involved in disease coping and rehabilitation. The division also offers a variety of medical education courses, including "Medical Psychology and Sociology" in the pre-clinical study section and "Psychotherapy and Psychosomatic Medicine" as well as "Rehabilitation" in the clinical section. In the area of patient care, a psychotherapeutic out-patient division and consultation-liaison services for the University Hospital are provided.

Currently, 4.5 researchers are financed through the division's budget and another 18 through third-party payers. Several close clinical and research co-operations exist with the University Hospital. The division is a member of the Comprehensive Heart Failure Center and of the Comprehensive Cancer Center, with Prof. Faller serving as head of the Psychooncological Service.

Major Research Interests

Psychocardiology
(H. Faller)

Our research, which is performed in cooperation with the Department of Internal Medicine I (Prof. Angermann, Prof. Störk, Prof. Ertl), examines which factors put patients with chronic heart failure at risk for depression and whether depression itself is a risk factor for heightened mortality (Fig. 1). Moreover, an intervention for optimizing disease management programs that includes telephone-based patient education has been evaluated in regards to mortality, morbidity, re-hospitalization, and quality of life (INH Study). In another study, the efficacy of pharmacotherapy for depression is being examined in reference to mortality of chronic heart failure (MOOD-HF Study).

Psychooncology
(H. Faller)

The prevalence of psychological distress and psychological disorders among cancer patients, as well as the need for psychosocial support among these patients, are being determined in a multi-center study. For the development of the S3-Guidelines Psychooncology, a systematic review and meta-analysis regarding the effectiveness of psychooncological interventions was performed. A further research focus is on the impact of response shift on the assessment of quality of life.

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

Innovative educational concepts designed to improve patient-centeredness through the employment of new didactic methods have been developed and evaluated for various chronic conditions, including chronic low back pain, coronary artery disease, chronic heart failure, breast cancer and inflammatory bowel diseases. These concepts implement specific strategies to increase the sustainability of education effects and to transfer newly learned skills into common everyday situations. Examples of these concepts include behavioral planning

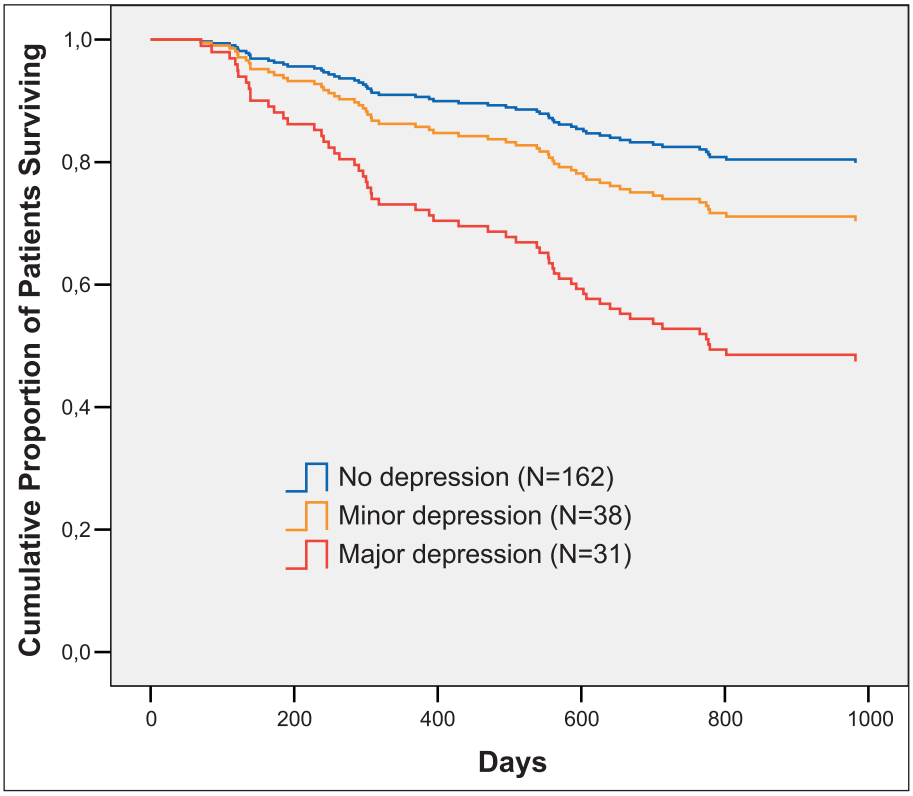

Fig. 1: Depression and survival rate of patients with chronic heart failure.

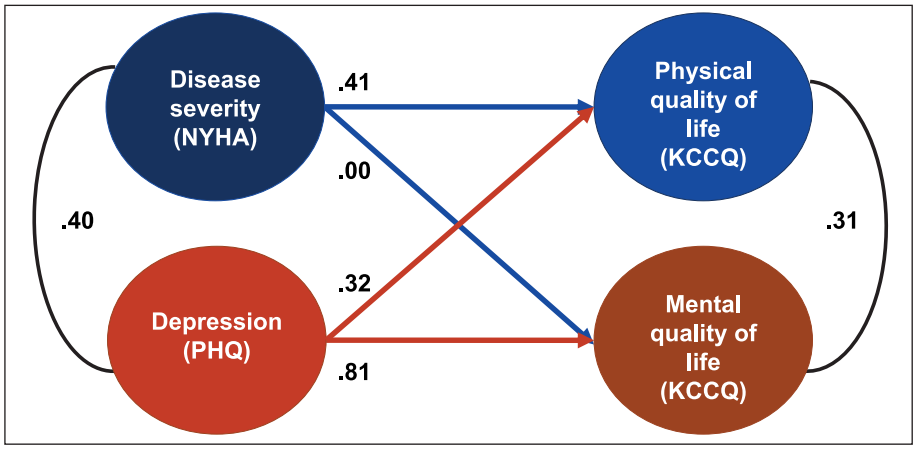

Fig. 2: Impact of disease severity and depression on patients' quality of life in chronic heart failure.

and after-care using modern media. Moreover, a survey covering the present state of educational programs offered for medical rehabilitation patients in Germany was performed and our online patient education database extended. In another project, the effectiveness of methods used to disseminate innovative educational programs into routine health care is being examined.

Patient-reported Outcomes
(H. Faller, M. Schuler)

A further research focus is on the development and psychometric evaluation of self-assessment instruments for health-related quality of life and other patient-reported outcomes. 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) has been translated, adapted and psychometrically evaluated in collaboration with the Medical University of Hannover. This is the first instrument to allow for a generic assessment of self-management skills used as proximal outcomes of patient education programs.

Occupational Rehabilitation
(S. Neuderth, H. Vogel)

To increase the chances of medical rehabilitation patients 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, to disseminate benchmark models into routine care, to foster shared decision making regarding treatment selection, and to evaluate medical-occupational rehabilitation.

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 division is responsible for the field of medical rehabilitation for children and youth. In addition, various projects address the quality management of social medicine assessments as performed by the German Statutory Pension Insurance.

Emotions and Eating
(M. Macht)

The consumption of food as a means of stress reduction, termed emotional eating, poses a considerable health risk. To explore the association of emotions and eating in everyday life, the experience-sampling method using personal digital assistants was employed. In an evaluation study, the effectiveness of a group intervention aimed at improving emotion regulation and reducing emotional eating is being examined.

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 "Research Methods and Evaluation (Evidence-Based Medicine)" is also offered. Moreover, the division coordinates the Lecture "Rehabilitation", offers the Seminar "Rehabilitation Research", and co-teaches the integrated lecture and integrated practical courses "Psychiatry, Psychosomatics, and Psychotherapy". The integration of simulation patients into various parts of the medical curriculum is coordinated, and both teaching and coaching to improve efficient learning and to prevent test anxiety are offered.

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2.10 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 80.000 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 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, 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 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.

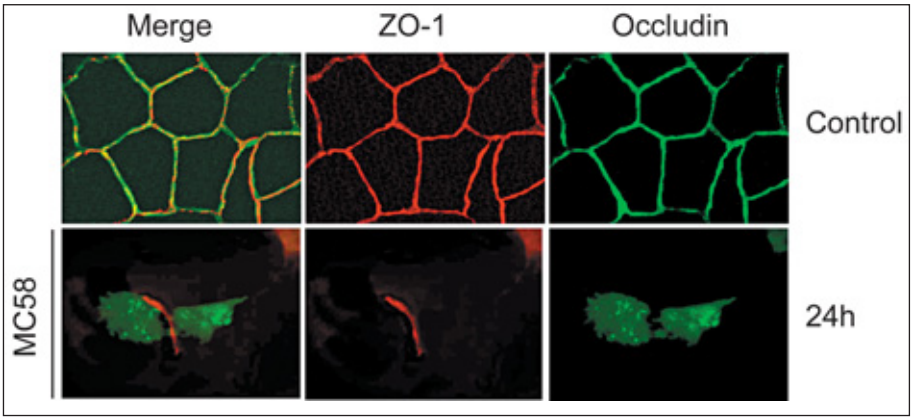

Fig. 1: Effect of N. meningitidis on the tight junction proteins occludin and ZO-1 (Schubert-Unkmeir, A. et al., 2011. PLoS Pathog. 6:e1000874). Human brain microvascular endothelial cells were infected with N. meningitidis strain MC58 and cells were immunostained for occludin and ZO-1. Cells infected with N. meningitidis strain MC58 showed dissociation of occludin (green fluorescence) from the cell membrane and a diffuse localization in the cytoplasm at 24 h p.i.

Population biology and pathogenesis of meningococcal disease
(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 interaction of meningococci with neutrophils and the serum complement system.

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

Neisseria meningitidis usually lives as a commensal bacterium in the upper airways exclusively of humans but occasionally can also cause life threatening diseases. Due to the lack of a suitable animal model the genetic basis of meningococcal virulence is only poorly understood so far. Consequently, the evolutionary and functional genomics of meningococci constitutes another main research focus of the institute. In particular, by comparing the genomes and transcriptomes of invasive and carriage isolates we experimentally investigate the genetic basis and the mechanisms of meningococcal pathogenicity as well as their evolution in *ex vivo* infection models.

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, induction of host cell death, cytoskeletal rearrangement upon invection, 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.

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 hormonal host-parasite cross communication via evolutionarily conserved signalling systems occurs during alveolar echinococcosis and that totipotent somatic stem cells play a central role in host-induced parasite development. Current analyses concentrate on the integration of host-controlled parasite signalling systems into stem cell signalling and differentiation as well as on excretory/secretory products of parasite larvae as immunomodulators that ensure long-term persistence of Echinococcus in the host. In genome-, transcriptome, and proteome-based approaches, parasite specific factors that could act 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.

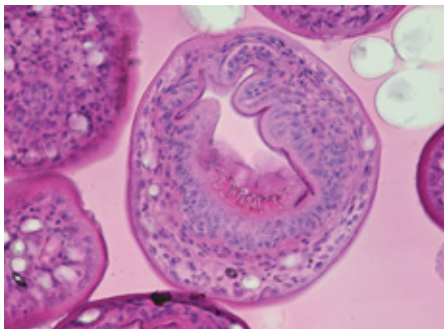

Fig. 2: Protoscolex larval stage of Echinococcus multilocularis in invaginated form.

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2.11 Institute of Virology and Immunobiology, Chair of Virology

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Mission and Structure

Research within the Chair of Virology is focussed on the analysis of the regulation of viral replication and gene expression, complex investigations of the pathogenesis of viruses, research into the sensitivity to antivirals and the development of viral vectors towards gene therapy. The Chair of Virology is also responsible for the provision of virus diagnostics to the University Hospital. We host approx. 65 scientists and work in close cooperation with the Chair of Immunology at our Institute as well as the Centre for Infectious Diseases, a number of Basic Research Programmes (SFBs), Graduate Schools and the Interdisciplinary Centre for Clinical Research. 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 continously high rates of measles associated morbidity and mortality. Most likely, the viruses 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 which acts as to enhance uptake. Though MV induces phenotypic DC maturation, these do not acquire allostimulatory activity. This is reflected at a cellular level by their inability to promote formation of stable conjugates with T cells scanning their surface in search of their cognate presented antigen. Evidently, the viral glycoprotein complex expressed on infected DCs mainly accounts for the relay of inhibitory rather than activatory signals to T cells by interaction with as yet unknown surface receptors. Signaling via the latter essentially targets the activity of the phosphatidyl-inositol-3/Akt kinase which regulates processes crucial for cell cycle entry, also including reorganisation of the actin cytoskeleton and associated receptor and signaling complexes. MV interference with actin dynamics relies on its ability to promote breakdown of membrane sphingomyelin and thereby formation of ceramide platforms in the outer membrane layer thereby causing morphological and functional T cell paralysis..

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

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

The group of Prof. Dr. Jürgen Schneider-Schaulies investigates mechanisms of virus spread, but also 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 transient immunosuppression and may persist in the central nervous system. Here it causes the non-curable disease subacute sclerosing panencephalitis (SSPE). Infected lymphocytes adhere strongly to endothelial cells and can infect them via close contact. This could mediate the infection of the central nervous system (CNS). As a potentially therapeutically usable antiviral approach the aplicabilty of short interfering RNA (siRNA) against measles was investigated. An effective inhibition of virus replication was achieved with siRNAs directed against transcripts of the components of the viral replicative complex. Interestingly, siRNA against the matrix protein-mRNA stimulated the replication complex. Using antiviral shRNA expressed from retroviral vectors it was possible to cure persistently infected neuronal cell. Antibodies against the cellular tetraspanin CD9 inhibit the virus-induced cell fusion by canine distemper virus, a close relative of measles virus. It was found that this antiviral activity is based on a relocation of membrane proteins and the induction of microvilli at cell contact areas. Similar test systems to identify inhibitors of virus uptake and spread are being developed for Nipah- and Denguevirus. Inhibitors of the Denguevirus entry were synthesized and tested successfully, and a promising lead compound for further optimization is now available.

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

Most retroviruses express all their genes form a single primary transcript. In order to allow expression of more than one gene from this RNA, differential splicing is extensively used. Cellular quality control mechanisms retain and degrade unspliced or partially spliced RNAs in the nucleus. Two pathways have been described how retroviruses circumvent this nuclear export inhibition. One involves a constitutive transport element in the viral RNA that interacts with the cellular mRNA transporter-protein TAP to facilitate nuclear export. The other pathway relies on the recognition of a viral RNA element by a virus-encoded protein, which interacts with the karyopherin CRM1. FVs do not encode an export-mediating protein. We could show that FVs use a so far undescribed pathway to export their mRNAs, in which the cellular proteins ANP32A/B and HuR contribute essentially. Another recently identified mechanism that discriminates FVs from all the other retroviruses (orthoretriruses) concerns the way how the viral protease is activated. Here the recognition of particular RNA motifs appears to play an essential role.

Development of Foamy Virus Vectors and Gene Therapy of M. Fabry
(T. Wiktorowicz, C. Scheller, A. Rethwilm)

The benign character of natural foamy virus infections and a variety of other favourable features has led to the development of foamy virus vectors for somatic gene therapy. Such vectors for efficient transduction of mesenchymal and haematopoietic stem cells are under development and are being applied in various animal models.
M. Fabry is a X-chromosomally-coupled inborn error of metabolism with low or no activity of the enzyme alpha-galactosidase resulting in deposits of globotriaosylceramide in various organs (heart, kidney, etc.). By autologous transplantation of gene corrected HSCs this shall be reversed.

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 as well as in SIV-infected rhesus macaques. 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 re search 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.

Characterization of resistance-associated mutations and possible transmission therapy-naïve people
(J. Bodem, C. Scheller, B. Weissbrich, A. Rethwilm)

The nucleotide and the corresponding amino acids sequences of the HIV PR and RT domains allow the estimation of the degree of resistance towards antiviral drugs. Viruses with certain resistance profiles may be introduced into the therapy-naïve population. Antiviral drugs are not only widely used in HIV therapy but also in the therapy of other chronic viral infections, such as HBV and HCV. This project focuses on the identification of resistance-associated mutations and the elucidation of the resistance mechanism.

Development of new screening platforms to identify antiviral compounds
(B. Nowotny, 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 by the 26S proteasome via the ubiquitin pathway and to the loss of antiviral activity. We engineered a double transgenic cell line constitutively expressing an EYFP-hA3G fusion as well as Tet-Off controlable Vif protein as a stable and convenient cellular testing platform for a high throughput screening of potential antiviral compound libraries.

Clinical Virology
(B. Weißbrich, J. Schubert)

30-35 thousand clinical samples are processed each year. Furthermore, a variety of clinical virological questions are being addressed. In cooperation with the children's hospital of the university clinic, recently discovered respiratory viruses are being studied. To this end, molecular and serological diagnostic methods have been developed for the human bocavirus and the polyomaviruses WU and KI in order to address the epidemiology and clinical relevance of these "new" viruses. Other areas of interest are the molecular epidemiology of HBV, which is studied in cooperation with the division of infectious diseases at the medical university clinic, and the epidemiology of hantavirus infections in Lower Franconia.

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

We are enforcing the collaborations with African countries to characterize African HIV isolates and to improve anti-retroviral therapy. We are in particular interested to determine the resistance profile of African HIVs. In this respect the recently installed DFG-funded International Research Training Group (IRTG 1522) with Cape Town, South Africa represents a landmark, because it is the first of its kind with the whole African continent. Furthermore, scientific co-operations with Asia/India were initiated.

Teaching

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

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2.12 Institute of Virology and Immunobiology, Chair of Immunology

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

The research focus of 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 so called non-conventional T 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-in-man 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.

Activation and evolution of 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“ which are produced by host cells with metabolic aberrations (e.g. tumor cells) and many pathogens. We investigate how to use these cells for tumor therapy and the phylogeny of their special mode of antigen recognition.

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)

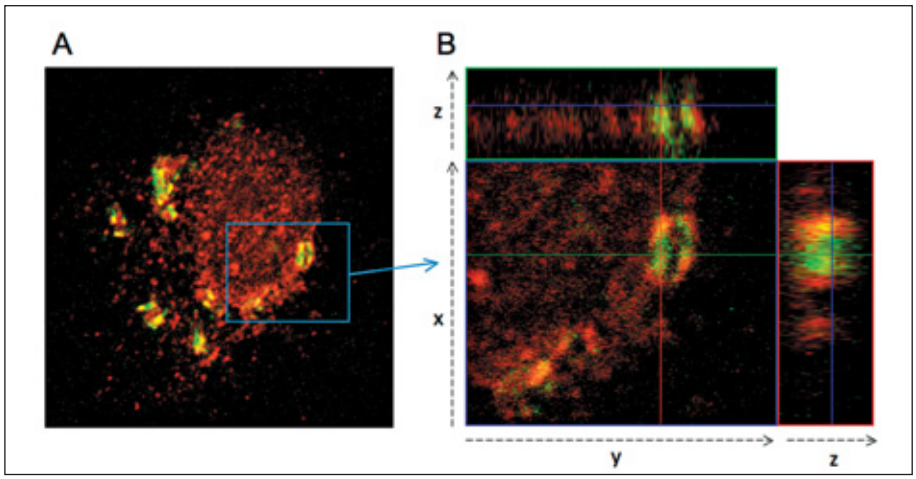

Fig. 1: Phagocytosis of mycobacteria by myeloide suppressor cells (MDSC) in caveosomes. Heat-inactivated mycobakteria (BCG) were coincubatet with MDSC at 37°C, centrifuged onto a slide and then stained for mycobactierial antigens (PPD in green) or caveolin-1 (red). The analysis of the immunefluorescence via confocal microskopy shows the overlay (yellow) of BCG in caveoli-1+ compartments (A). Displays of the threedimensional sight angles illustrate the result (B). (Fotos Dr. E. Ribechini and M. Münstermann).

Our latest investigations with myeloid-derived suppressor cells (MDSC) in the murine system show that myeloid progenitor cells 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
(T. Kerkau, N. Beyersdorf)

The team is working on the significance and therapeutic manipulation of regulatory T cells in the context of pathological immune reactions. 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

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2.13 Institute for Molecular Infection Biology

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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 part of the "Research Center for Infectious Diseases" (ZINF). 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 which are considered nationwide as an excellent and successful funding instrument for young scientists in the field of infection biology. 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 research 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 (functional genome analysis) and proteomic (protein expression analysis) approaches as well as high-throughput sequencing of RNA 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 and long noncoding RNAs which are induced in the host in response to a bacterial infection. Key technology for this type of research is the high-throughput sequencing (deep sequencing) of RNA which is used both for the detection of novel RNA molecules and the investigation of protein/RNA interactions.

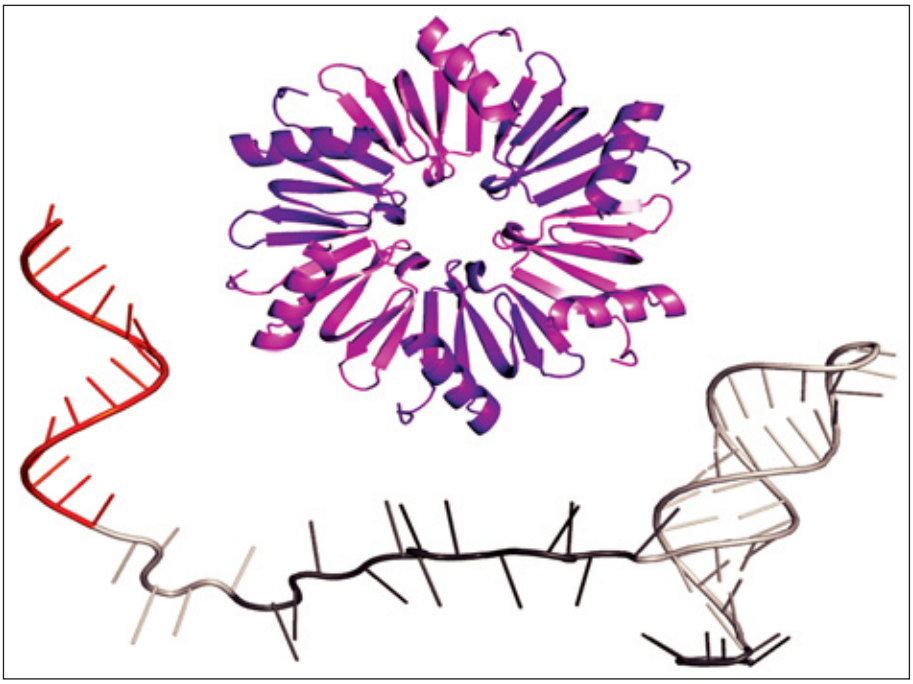

Fig. 1: Structure of the Hfq protein (top) which acts as a chaperone for many sRNAs such as RybB (bottom).

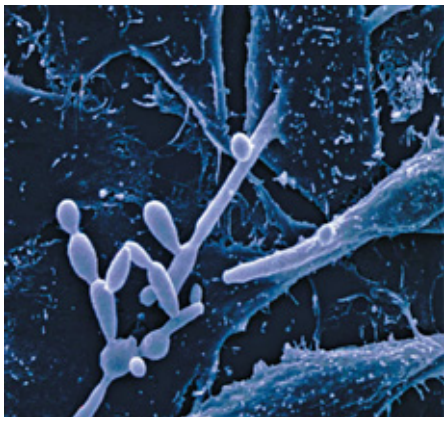

Fig. 2: Scanning electron micrograph of Candida albicans hyphae and pseudohyphae penetrating human endothelial cells.

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.

Molecular biology of biofilm formation in commensal and pathogenic E. coli
(A. Böhm)

Chronic colonization of medical implants and epithelia by bacterial biofilms represents a major problem in treating infectious diseases. Employing the model organism E. coli, the team uses a combination of molecular, genetic and systems biology approaches along with modern imaging techniques to study mechanisms of bacterial biofilm formation in molecular detail.

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.

Molecular biology of coagulase-negative Staphylococci (CoNS)
(W. Ziebuhr)

CoNS are notorious nosocomial pathogens which mainly affect immunocompromised patients carrying indwelling medical implants. In our laboratory we have a strong interest in teaming basic research with public health aiming at an in-depth understanding of CoNS infections and laying the basis for future innovative prevention and treatment strategies. Main research interests are factors and processes which contribute to the establishment of these bacteria as pathogens in the hospital environment.

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.

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2.14 Institute of Pharmacology and Toxicology, Chair of Toxicology

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Mission and Structure

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

The workforce of the department of Toxicology comprises between 50 and 60 members. Five research groups are led by the University Professor Dr. Helga Stopper, the Associate Professors Dr. Erwin Eder and Dr. Wolfgang Dekant, and the Research Associates PD Dr. Angela Mally and PD Dr. Nicole Schupp. Five 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.

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.

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

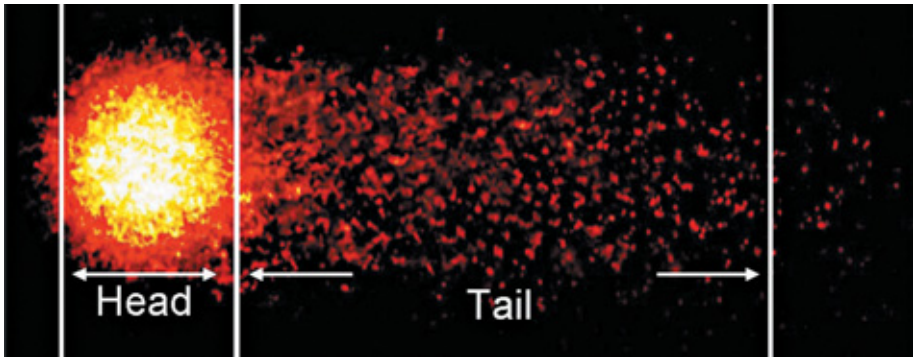

Fig. 1: "The Comet Assay": DNA fragments induced by a genotoxic agent migrate in an electric field out of the cell nucleus (Head) into a Tail.

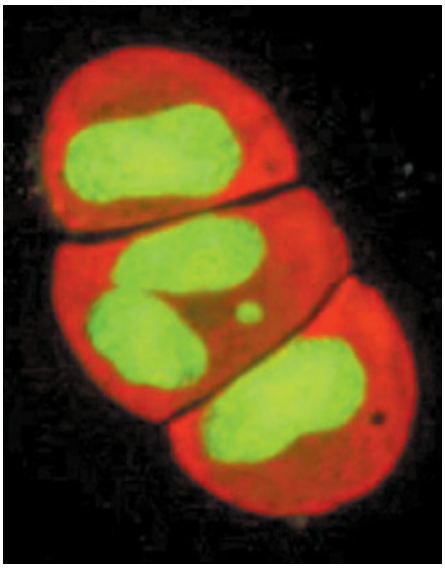

Fig. 2: "The Micronucleus Test": Chromosome damage is indicated by the presence of a DNA-containing fragment in the cytoplasm of the bi-nucleated cell in the middle of the three cells.

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 (angiotensin II, aldosterone) 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.

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2.15 Institute of Pharmacology and Toxicology, Chair of Pharmacology

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Mission and Structure

The Institute of Pharmacology and Toxicology comprises the Chairs of Pharmacology and of Toxicology. The institute is also home to several research groups of the Rudolf Virchow Center that was founded in 2001 and that is chaired by Prof. Lohse.
The chair employs ca. 75 staff members (about half of them grant-funded). All research groups focus on the molecular mechanisms of cellular communication, their role in physiological function and their potential to serve as targets for therapeutic drugs. In addition to standard biochemical and molecular biology equipment, the chair has a SPF unit for the generation of transgenic mouse models as well as equipment for rapid microscopic imaging, for confocal, 2-photon and TIRF microscopy, for electrophysiology and for cardiovascular phenotyping of transgenic mouse models.
The chair also provides a drug information service for the university hospital and medical faculty as well as outside physicians and pharmacists. The Ethics Committee of the medical faculty is also based at the institute.

Major Research Interests

A major research focus of the Chair of Pharmacology is on G-protein-coupled receptors. They transmit the effects of hormones and neurotransmitters, but also of therapeutic drugs such as opiates, beta blockers against high blood pressure and anti-allergic antihistamines. These receptors are investigated with a large array of methods to answer questions ranging from the structure of receptors and ligands to transgenic disease models and studies on patient samples. Another major research effort focuses on the mechanisms of cellular movement and its control by intracellular signaling processes. A third focus is on heart failure and the development of new therapeutic strategies. Our research is funded by grants from the DFG, the Rudolf Virchow Center/DFG Research Center for Experimental Biomedicine, the SFB487 and 688, the European Research Council, the BMBF (Federal Ministry of Education and Research), the Bavarian Research Foundation, the Fondation Leducq and others.

Mechanisms und Function of G-Protein-coupled Receptors

(M. Lohse, C. Hoffmann, D. Calebiro, V.O. Nikolaev)

Communication between cells occurs through 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 to explore general mechanisms and functional principles. Over the last few years, we have developed a variety of techniques to visualize receptor activation, inactivation and the resulting signals by means of new sensors and fluorescence microscopy methods. This allows us to directly observe receptors and signaling mechanisms „at work“, and to analyze the speed and localization of signals in isolated cells and *in vivo*.

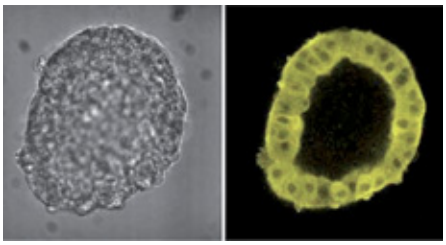

Fig. 1: Investigations of thyroid follicles with sensors for the intracellular messenger cAMP have demonstrated that only a stimulation of receptors inside the cell triggers hormone secretion (left: bright field image, transmitted light – right: confocal fluorescence image).

Phosphatases and Cellular Motility

(A. Gohla; also Rudolf Virchow Center)

The cytoskeleton regulates cell adhesion and motility. It is a new target for the development of drugs against cancer and cardiovascular diseases. We have discovered a new class of human phosphatases that play a major role in regulating the dynamics of the cytoskeleton. Using primarily biochemical and cell biological methods, we work on characterizing the interaction partners and substrates of these phosphatases. Furthermore, we are interested in signaling cascades that regulate phosphatase activ-

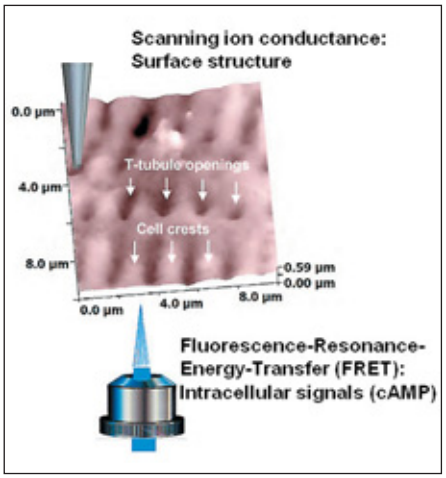

Fig. 2: Combining state-of-the-art microscopic technologies to study cardiac muscle cells. Scanning ion conductance microscopy scans the surface of cells; fluorescence resonance energy transfer (FRET) detects signals within the cells.

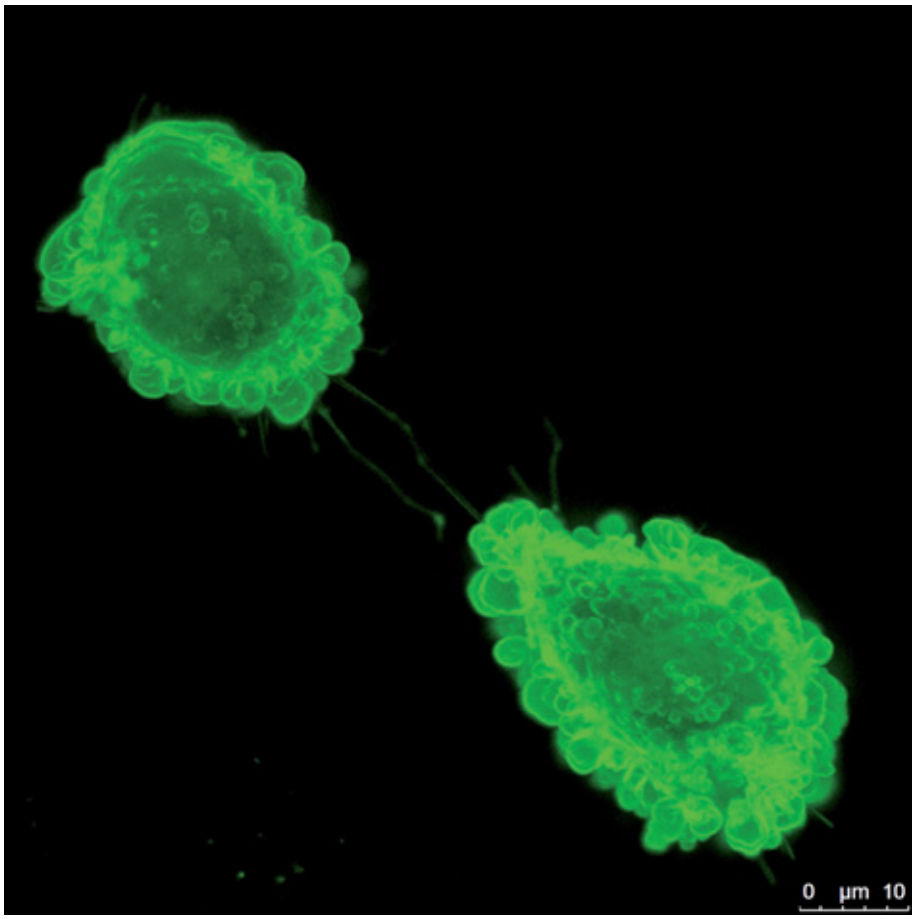

Fig. 3: Signal transduction in cells via novel phosphatases. Confocal microscopy allows us to study how cells with sensors for a lipid messenger process growth signals in real time.

ity through extracellular signals, and we also investigate the function of the enzymes in gene-deficient disease models.

The Effects of Bacterial Toxins
(A. Illiev, Emmy-Noether group; also Rudolf Virchow Center)

Some bacterial toxins such as pneumolysin are able to induce the formation of pores in the membrane of other cells resulting in cell lysis or apoptosis. But also in concentrations lower than those needed for pore formation, they cause cell damage as, for example, in meningitis. The effects of bacterial toxins can be transmitted via the cytoskeleton. We investigate mechanisms of their toxicity and explore therapeutic strategies.

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
(K. Lorenz, J. Schmitt)

Chronic heart failure is one of the main health problems of old age. Based on patient samples and transgenic mouse models, we search for genes and mechanisms that contribute to heart failure and dilatation. A number of biochemical mechanisms that play an important role in heart failure have been identified over the last few years. We are currently exploring whether they provide a target for the development of new therapies.

Receptor-Antibodies 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 β_1-adrenergic receptors in about a third of patients with chronic heart failure. These auto-antibodies reduce the chance of survival of these patients by 50%. We have generated a corresponding animal model by immunizing rats with receptor epitopes. Several BMBF-funded projects focus on therapeutic strategies based on cyclic peptides. In this context, Corimmun GmbH, a biotech company, was founded.

Teaching

The institute is responsible for teaching pharmacology and toxicology to students of medicine, dentistry, pharmacy, 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 MSc curriculum in Experimental Medicine. We also offer the full curriculum for medical doctors specializing in pharmacology.

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2. 16 Institute of Forensic Medicine

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Mission and structure

The Institute of Legal Medicine of the University of Würzburg provides services in legal medicine on behalf of courts of justice, public prosecutors and police departments for the region of Lower Franconia (as well as adjacent regions in Upper Franconia and Baden-Württemberg). Key respon-sibilities are investigation of deaths, examination of surviving victims of violence, forensic trace analysis, paternity testing, forensic-toxicological analyses to determine the cause of death and clar-ification of road traffic offences.

After Prof. Meißner left in April 2010, the Institute went through a year of change. Effective 1 Nov 2010, Prof. Bohnert (University of Freiburg) was appointed Acting Board Director. In May 2011, Prof. Bohnert accepted the offer for the chair in forensic and social medicine.

Apart from the Board Director, the academic staff of the University of Würzburg Institute of Legal Medicine consisted of 1 consultant (Oberarzt), 2 senior house officers (Assistenzärzte), 1 biologist and 1 toxicologist in 2011. A second biologist joined the institute in June. 8 of the 17 employees of the institute are paid from the institute's own resources. The other posts are financed on the basis of the Institute's tasks in research and teaching.

Major Research Interests

Legal medicine is defined as a medical specialty applying medical and scientific knowledge and techniques to the administration of justice. It is a strongly application-oriented and interdisciplinary subject with research activities geared to the requirements of the police and the judiciary. As in any other practical medical field, the daily activities and tasks determine the scientific issues to be ad-dressed. Scientific forensic research areas are studies on the assessment of findings, the evalua-tion of evidence, the reconstruction of events and the development of valid assessment criteria. Therefore, our subject plays a special role among the other medical fields, because its scientific focus can neither be defined as basic research nor is it primarily oriented to patient care. It is much more concerned with the individual case than other subjects.

When Prof. Bohnert changed to Würzburg, he took a research project on the post-mortem optical behaviour of the skin financed by the German Research Council with him. In collaboration with the Freiburg Materials Research Centre, this project uses reflectance spectrometry to systematically record the post-mortem decomposition processes of the skin (putrefaction and autolysis) and eval-uates the changes. Before, a mathematical skin model had already been developed, by means of which the scattering and absorption of light in relation to the scattering structures (cell nuclei, mito-chondria, collagen fibres) and the absorbers (haemoglobin, melanin, bilirubin) can be calculated. This skin model is to be improved by the systematic investigations. At the same time, a method to narrow down the time of death is being developed, which should be applicable also to the later stages of the post-mortem interval.

Together with the Department of Neuropathology (Dr. Monoranu) and the Department and Poli-clinic of Psychiatry, Psychosomatics and Psychotherapy (Prof. Heinsen) a project is continued which was started under Prof. Meißner. As nowadays Alzheimer's disease can usually be diag-nosed only in a very late stage, better diagnostic tools would be helpful. In the Policlinic of Psychia-try, Psychosomatics and Psychotherapy, the method of vagus nerve evoked potentials has been developed and validated for early diagnosis of Alzheimer's disease. Based on these clinical data, the project will examine the brainstem of Alzheimer's patients for the presence of morphological and biomolecular changes associated with oxidative stress. If it could be demonstrated that oxida-tive stress causes cell-specific deletions of the mitochondrial DNA and changes in gene expression patterns in these focal areas, this could lead to innovative diagnostic and therapeutic strategies.

Teaching

Forensic science is taught to students of medicine in a main lecture, practicals and seminars. The main lecture covers the fields of thanatology, various forms of violence, forensic and biomolecular subjects, forensic toxicology as well as issues of ethics and medical law. In small work groups, students gain practical experience in post-mortem examinations under medical supervision. An increase of the amount of practice-ori-

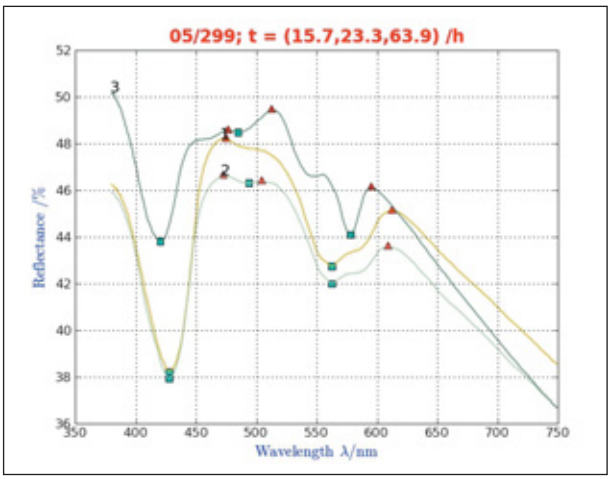

Fig. 1: Spectral reflectance curves of corpse skin in the post-mortem interval.

ented teaching in small groups seems desirable. An aspect regarded as especially important in teaching is to provide students with practical knowledge useful for their later work as general practitioners. In particular, many examples and comprehensive vis-ual material from the field of clinical forensic medicine are presented to illustrate domestic violence and differentiation between self-inflicted injuries and homicidal assaults.

In a well-attended lecture, legal medicine is also offered to students of law, and junior lawyers (be-tween the first and second state examination) are instructed on the effect of alcohol and drugs in road traffic with a scientifically monitored drinking test.

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2.17 Institute of Pathology

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Edgar Serfling
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Mission and Structure

The Institute of Pathology is an academic center with more than 100 employees including 20 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, high-resolution genomics and novel sequencing approaches are used to decipher molecular alterations in lymphoid neoplasms. In 2010 and 2011, novel biologically and clinically relevant lymphoma subgroups could be described, e.g. a subgroup of follicular lymphomas lacking the characteristic BCL2 translocation. The group plays a major role in several national and international research networks, such as in the International Cancer Genome Consortium (ICGC), the Leukemia and Lymphoma Molecular Profiling Project (National Cancer Institute, USA), as well as in the German Network Project 'Molecular Mechanisms in Malignant Lymphomas' and the local Clinical Research Unit 'Signalling in Multiple Myeloma'.

Prof. 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.

Transcriptional Control in T-Lymphocytes
(E. Serfling)

The head of Department of Molecular Pathology, Prof. Dr. E. Serfling, is speaker of the new SFB/Transregio (Collaborative Research Center) Würzburg/Mainz/Berlin, TRR52, of the German Research Association (DFG) which started its work in July 2008 with the topic 'Transcriptional programming of individual T-cell populations'. The research of Molecular Pathology is focused on the role of NFAT (nuclear factor of activated T-cell) transcription factors in both lymphocyte function and lymphocyte proliferation and apoptosis. Main topics are the creation of mouse lines for the conditional inactivation of the murine *Nfatc1* gene, and the transcriptional inactivation (and repression) of the *murine Nfatc1* gene. Current studies deal with the role of the "immunemodulatory" activity of NFATc1/A in controlling immune responses and the generation of lymphomas.

(F. Berberich-Siebelt)

Within the field of molecular and cellular immunology the major research is focused on $CD4^+$ T helper cells. Emphasis is placed on signal transduction, expression pattern and activity of individual isoforms of the transcription factors NFATc1, Foxp3 und C/EBPβ. Detailed molecular research is performed to reveal the influence of modifications, especially sumoylation, and interactions with further transcription-(co-)factors on the activity of these transcription factors, whereas their impact on physiology is addressed with the help of in vivo mouse – including diverse disease – models. The individual projects have been and are supported as follows: "Functional consequences of NFATc1 sumoylation on lymphocyte activation, differentiation and tolerance" (DFG/SPP1365); "Repression of Gene Expression in T lymphocytes mediated by multi-protein complexes of chosen transcription factors" (DFG/TRR 52); 'Diverse functions of the different NFAT transcription factors in animal models of multiple sclerosis and ischemic stroke' (IZKF).

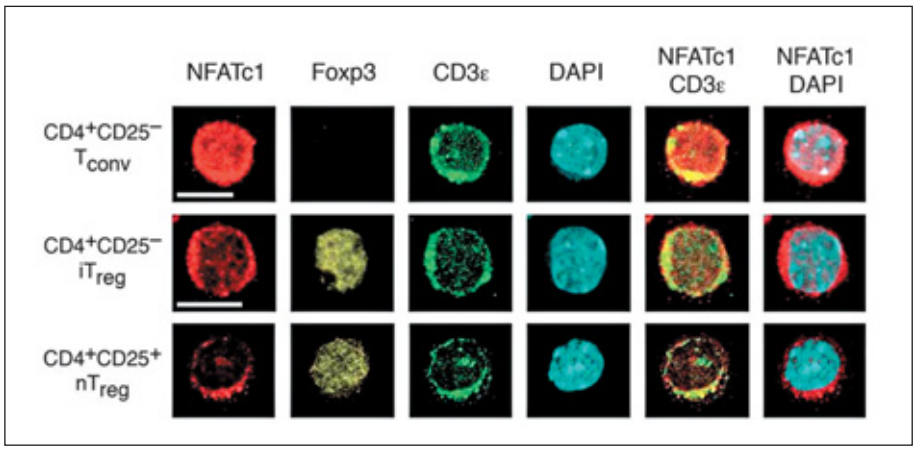

Fig. 1: Reduced nuclear translocation of NFAT transcription factors following T-cell receptor stimulation in regulatory T-cells. Significantly reduced NFATc1 nuclear staining (red), evident in induced (iTreg) and natural (nTreg) Foxp3+ regulatory T-cells, in contrast to conventional T-lymphocytes (Tconv).

Human Immunity to Cancer
(S. Brändlein)

The experimental work of this research group is focused on human innate immunity to cancer in which antibodies play an important role. Antibodies play a crucial role in immune surveillance. To elucidate their role in detection and elimination of malignant cells the group analysed a huge panel of antibodies. All tumour specific antibodies are part of the natural immunity and predominantly of IgM isotype. The antibodies are coded by distinct germ line genes, their targets being post-transcriptionally modified carbohydrate epitopes on tumour cell surface receptors. These tumor-specific modified epitopes could be found on proteins such as CD55, CFR-1, GRP78 and TAF15. All tested antibodies are able to attack malignant cells in vitro and in vivo by inducing different cytotoxic mechanisms. In collaboration with an Australian company, some of the identified antibodies are developed into clinical products. Currently, one antibody is part of a clinical study on melanoma patients, other clinical studies are in the planning phase. The ongoing scientific work is concentrated on the characterization of the antibody epitopes and the antibody-induced cytotoxicity.

Neurooncology and neurodegeneration
(W. Roggendorf, C. Monoranu)

The research in the Department of Neuropathology is currently focused on neurodegenerative diseases. A new project with duration of 3 years funded by the IZKF Würzburg has started in July 2010. The project is entitled: "Deletions of mitochondrial DNA (mtDNA) and gene expression in neurons, astrocytes and microglia in hippocampus and vagus nuclei of aged people and patients with Alzheimer's Disease" and will evaluate the damage of mtDNA and the gene expression profiles in different cell types in different regions (hippocampus, cerebellum, brainstem) of human postmortem brain from controls and patients with Alzheimer disease (AD). The aim of the study is to investigate (1) which changes in mitochondrial function and gene expression profiles are representative of the pathomechanism of AD and (2) to define specific early changes in brainstem nuclei of vagus/trigeminus which could lead to innovative diagnostic methods at early stage and the development of new therapeutic approaches in AD.
In the neurooncological field we started several cooperations with the Clinic for Neurosurgery and the Pediatric Clinic in Würzburg as well as with the DKFZ Heidelberg to study gliomas in adults and pediatric medulloblastomas.

Teaching

The Institute of Pathology is responsible for teaching pathology as part of the medical curriculum of the Wuerzburg Medical School. Specifically, 4 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.

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2.18 Institute for Medical Radiation and Cell Research (MSZ)

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Mission and Structure

The chair is provisionally headed by Prof. Dr. Müller and comprises a total of 22 people. The Institute houses two groups which are working on different aspects of regenerative cell biology. Prof. Müllers group (residing in the ZEMM, building E7, since 2010) is analyzing gene expression programs in mammalian embryonic and adult stem cells with a special emphasis on chromatin regulation. Prof. Raabes group (residing in building E4) 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.

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. Recently we also started to focus on induced pluripotent stem cells (iPS), which are generated by artificial reprogramming of somatic cells. Of central importance to our studies is the question of how global chromatin states guide stem cell behavior. 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. Indeed, more than two-third of human disease-associated genes are conserved in Drosophila. Thus studies in model organisms can contribute to a better understanding of the molecular mechanism underlying human diseases of the central nervous system. We are investigating a number of mutations, which cause an altered proliferation pattern of neural progenitor cells leading to hypo- or hypertrophy of the adult nervous system. Our current research focuses on the control of cell growth as a critical parameter to maintain the proliferation potential of progenitor cells throughout development. We have identified a novel protein which localizes in the nucleolus and might be involved in translational control. We also uncovered the transcriptional and post-translational regulation of this protein. A further main focus of our research are proteins constituting the family of p21-activated kinases (PAKs), which participate in the regulation of the cytoskeleton, cell division and apoptosis. In the context of development of the nervous system, PAK proteins are involved in proliferation of neural progenitor cells, axonal guidance and synaptic plasticity. We were able to uncover isoform specific but also redundant function of the three Drosophila PAK proteins during eye and brain development. The availability of single and combined knock-outs in combination with advanced genetic tools not only allows to perform a comprehensive phenotypic analysis but also a comparative transcriptome and proteome analysis in order to better understand the integration of PAK proteins in cellular processes. In collaboration with clinical research groups we are further analysing the function of the kinase RSK in synaptic plasticity. Mutations of the human RSK homologue are associated with mental retardation.

Teaching

The teaching activities correlate with the research interests of the two MSZ groups. Primarily, practical courses are offered for medical, biomedical and biological students. Our main emphasis lies on teaching principles of cell biology. Practical courses on cell biology and on model organisms introduce students of biomedicine to modern techniques in cell biology, biochemistry and mic-

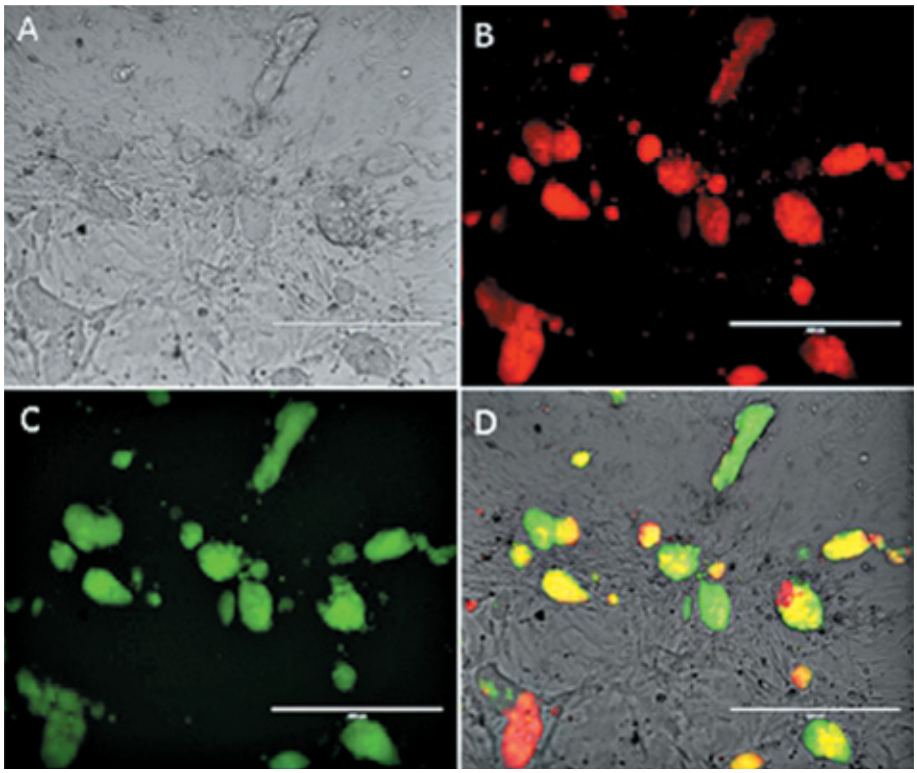

Fig.1: iPS cells derived from reprogrammed murine somatic cells (OG2 MEFs). OG2 MEFs were transfected with vectors coding for reprogramming factors. A: Light microscopic image of iPS colonies. B: Transfected cells (red). C: Green fluorescence indicates Oct4 expression and the pluripotent state of the reprogrammed cells. D: Overlay of A, B, and C. Scale bar = 100µm.

roscopy. Biologists have the opportunity to gather insight in specific questions of molecular biology in a laboratory course. The institute also offers a lecture on stem cell biology in clinics and research to students of medicine and biomedicine. Further the MSZ takes part in various practical courses and lectures of the medical and biological faculty.

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2.19 Institute of Human Genetics

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Mission and Structure

Human Genetics is an important area of biomedicine with increasing impact on the practice of medicine. Human Genetics investigates evolution, structure, function, inheritance and disorders of the human genome. Results of these studies are applied to genetic diagnosis, genetic counseling and patient care. The Institute is represented by different, both basic science and clinically oriented groups. It provides genetic services for patients and teaches 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 (Figure 1). 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. Aberrant programming of the fetal metabolism in utero (i.e. by maternal malnutrition or overnutrition) increases the risk for many complex diseases later in life. 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. Müller-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. While the role of vitamin K in coagulation may be a recent evolutionary specialization, the primary function of VKOR appears to be part of an ancestral antioxidant scavenger system against reactive oxygen species. 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 five novel of these FA genes *(FANCI, FANCJ, FANCN , FANCO and FANCP)*. As a partner and interactor of one of the high-penetrance breast and ovarian cancer genes, BRCA2, biallelic mutations in FANCN/PALB2 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. An association with the latter malignancies is also observed for monoallelic FANCJ und FANCO mutations. 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 mem-

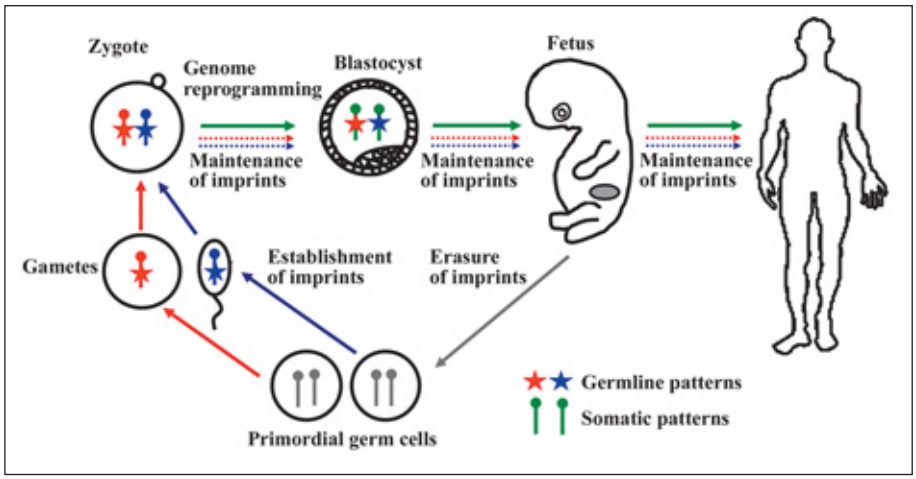

Fig. 1: Epigenetic reprogramming cycle. In the fetal germline all DNA methylation patterns are erased (gray line) and then paternal (blue) and maternal (red) methylation imprints are established during gametogenesis. The two germline genomes that are combined at fertilization undergo parent-specific genome reprogramming in the early embryo, during which most germline patterns are erased again and somatic patterns (green) are established. Only imprinted genes maintain their germline patterns during development of the new organism.

bers of the genomic maintenance gene networks, elucidating their function, and studying their phenotypic effects. This is achieved by functional and molecular studies.

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, Würzburg) and S. Blair Hedges (Department of Biology, Pennsylvania State University, USA) the group uses a large variety of vertebrate species, including amphibians, reptiles, fish, birds and mammals to improve our understanding of chromosomal and genomic evolution. A recently published monograph on *"The Chromosomes of Terraranan frogs - Insight into Vertebrate Cytogenetics"* represents the most comprehensive, original and comparative cytogenetic study of vertebrates. A further monograph on *"Origin, Structure and Pathology of Human Ring Chromosomes"* is currently under progress. 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.

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2.19.1 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.5.5.3). 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.
Better incidence data of Limb-girdle mus-

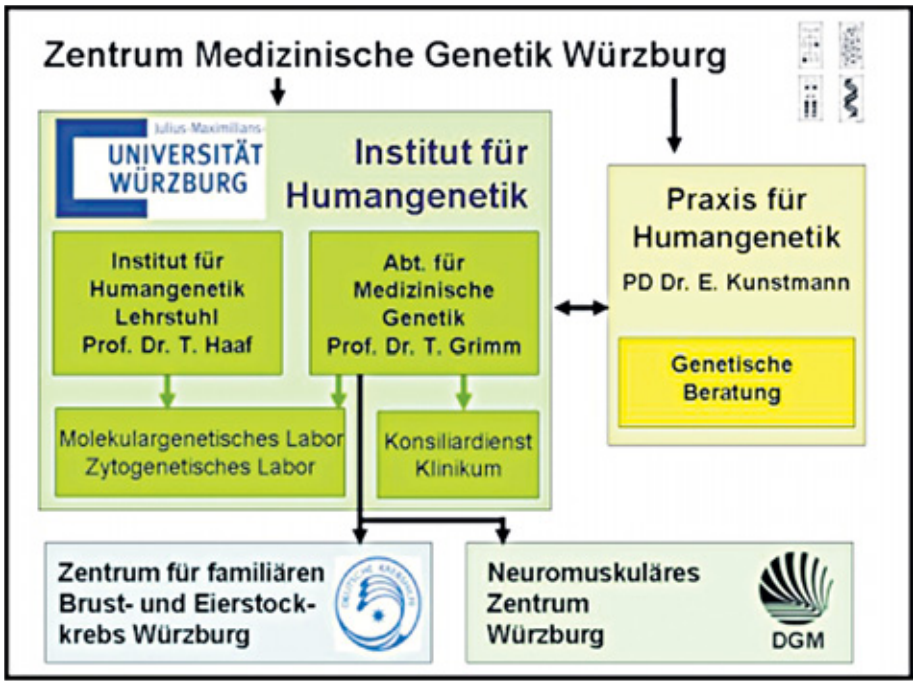

Fig. 1: Organisational structure of the Würzburg Center of Medical Genetics.

cular dystrophies in Germany were estimated.

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.

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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, 2 independent Chairs as well as 5 autonomous divisions in 2010. Furthermore there are 7 affiliated Training Colleges of Health Care, which together offer more than 500 apprenticeship training positions.

The University Hospital employs a total of 4.416 full-time employees, among them 768 physicians, 1.251 (male) nurses, 424 (male) nurses in OR and anesthesia as well as 1.075 medical-technical employees.

Interdisciplinary – and partially outreach collaboration is the focus of 24 **Clinical Centers:** Comprehensive Cancer Center (Interdisciplinary Centers for Breast-, Colorectal- and Skin Cancer, Interdisciplinary Center for Palliative Medicine and Center for Stem Cell Therapy and Transplantation), German Comprehensive Heart Failure Center Würzburg, Heart Center Würzburg, Regional Heart Attack Network Mainfranken, Center for Early Diagnosis/Socio-paediatric Center, Musculo-Scelettal Center Würzburg, Center for Rheumatism, Trauma Center, Interdisciplinary Thorax Center Mainfranken, Center for Kidney Transplant, Interdisciplinary Bank of Biomaterials and Data Würzburg (IBDW), Comprehensive Hearing Center, Center for Neuromuscular Disorders, Level I Perinatal Center, Center for Neurovascular Disorders, Center for Cleft, Lip, Jaw and Palate, Center for Craniofacial Diseases Würzburg, Center for Adiposity, Fabry Center for Interdisciplinary Therapy and The Center for Interdisciplinary Clinical Research (IZKF) build the bridge between clinical theoretical research and clinical research.

According to the official plan 2010, the University Hospital provides 1,433 hospital beds; the utilization rate of the 1.399 beds having been set up was 79,18% with an average resting time of 7,7 days. In the year 2010, 52.147 patients received inpatient treatment and a total amount of 399.046 care days were performed; additionally a total of 200.500 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.

In the year 2010 a continuing formation of Centers was the main focus at the University Hospital of Würzburg. A solid financial support for the recently founded German Comprehensive Heart Failure Center Würzburg (DZHI) by the Federal Ministry of Education and Research thus played a decisive part. According to the sponsor's intention the different clinical facilities closely work together under its roof with institutions for patients' and basic research. As an interim solution a separate building for this interdisciplinary Center for research and treatment was put into operation in 2010.
A further success in this year was the certification of the Comprehensive Cancer Center Mainfranken by the Deutsche Krebshilfe (German Cancer Aid). With its financial support an improved care for the regional cancer patients and for the cancer research of the University Hospital as well as of the Medical Faculty was possible.
A third hallmark for the University Hospital was the raise of financial support for the newly established
Interdisciplinary Bank of Biomaterials and Data Würzburg (IBDW). This setting up considerably contributes to a focussed research at the University Hospital of Würzburg.

The urgently needed redevelopment of the "Kopfklinik" (Departments of Neurology, Neurosurgery, Neuroradiology, Ophthalmology, Ear-, Nose- and Throat-Surgery and Radiation Oncology) was also advanced with commitment in the year 2010. The new building in 2 or 3 stages of construction was well prepared within numerous discussions between the interdisciplinary facilities.

With the present best possible infrastructure of the modern Health Care Center ZOM/ZIM (Centers of Operative and Internal Medicine) as well as the current and planned building projects for improving the building stock, the University Hospital will be well prepared to fulfill the future challenges of a changing healthcare market and will still be able to ensure patients' care as well as research and teaching of highest quality.

Professor Dr. med. Chr. Reiners
Managing Medical Director

Fig. 1: Interim building of the German Comprehensive Heart Failure Center Würzburg (DZHI).

3.2 Department of Anaesthesia and Critical Care

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Mission and Structure

The Department of Anaesthesiology annually performs anaesthesia for approximately 29.000 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. Doctors of the department staff the Intensiv-Transport-Wagen (ITW) and the Verlegungseinsatzfahrzeug (VEF) for the inter-hospital transfer of intensive care patients. 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

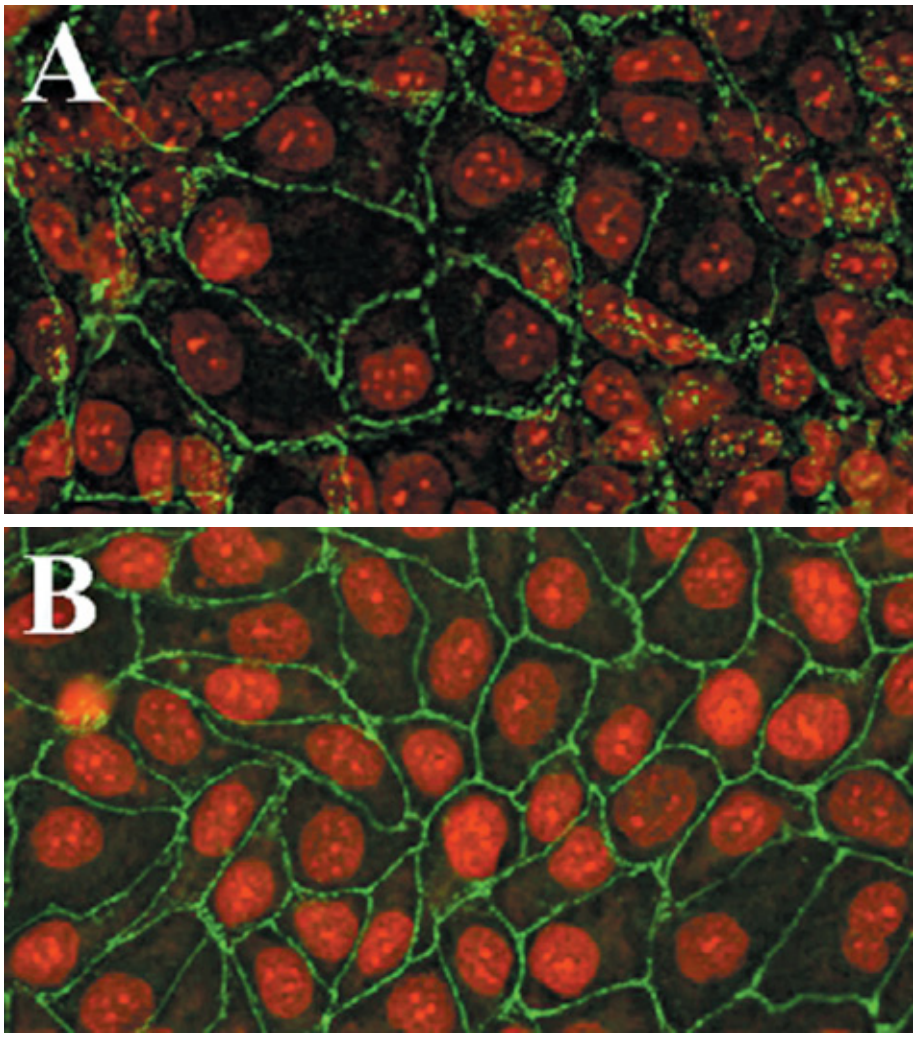

Fig. 1: Cell-cell contacts (tight junctions) of vascular brain endothelial cells with (A) and without growth factors of astrocytes (B). Cell-cell contacts are stained green, whereas the cell nucleus appears red.

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.

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 postconditioning 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.

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.

Trauma emergency room management
(T. Wurmb)

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

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3.3 Department of 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 these surgical fields. The department has 132 beds, including intermediate and intensive care units. Six thousand surgical procedures are performed every year. The department provides special consultation hours for patients in the following fields:

- adiposity
- endocrine diseases
- vascular surgery
- pediatric surgery
- coloproctology
- liver, gallbladder, pancreas and transplantation
- gastric, intestine and oesophagus diseases
- peritoneal carcinomatosis, (HIPEC)
- tumours

Surgery I is an intrinsic part, and the main treatment partner, of the Comprehensive Cancer Center Mainfranken, an advanced oncological center supported by the German Cancer Aid (Deutsche Krebshilfe).

The certified Pancreas Center provides hepatobiliary surgery and pancreas surgery for treating complex liver, bile duct and pancreas diseases. Liver transplants are standard therapy for liver failure and liver tumours in the Transplantation Center, Surgery I.

The Department of General, Visceral, Vascular and Pediatric Surgery was certified as a reference center for endocrinology and a competence center for obesity by the German Society for General and Visceral Surgery (Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie) for its surgical expertise in the treatment of endocrine and metabolic disorders.

The complex field of coloproctology is another major focus of therapy. In the certified Center for Intestinal Medicine, patients with colorectal carcinomas are treated with innovative concepts and surgical expertise to restore or retain continence.

The pediatric unit provides top treatment for the full range of pediatric surgery. This includes the surgical care of premature births, treatment of birth defects, basic pediatric urology, and pediatric traumatology. The children's surgical ward provides child-friendly pre- and postoperative care.

In the vascular surgery unit abdominal aortic aneurysms are treated with aorta-iliac bifurcation prostheses. Aorta and iliac vascular diseases are combated with endovascular surgical techniques. Our surgeons are well experienced in femur crural artery bypass surgery and carotid artery surgery. Since last year, a new hybrid operating room combines classic surgery and vascular diagnostic imaging for high quality treatment.

Major Research Interests

Research on infection, inflammation, metabolic disease, oncology, tissue engineering, and transplantation immunology takes place in modern research laboratories. Researchers network within the university and hospital, as well as with many national and international groups. Projects are also integrated in university research centres, such as the Interdisciplinary Centre for Clinical Research (IZKF). Successful third party funding (DFG, BMBF), patents, prizes, awards, and scholarships are additional project achievements. Further information is available on our website (http://www.zom-wuerzburg.de/).

Clinical Studies
(U. Dietz, M. Gasser, Th. Meyer/S. Grasshoff-Derr, J. Pelz, A. Thalheimer, A.M. Waaga-Gasser)

Currently, different studies are being conducted on oncology, pediatric surgery (compression therapy for burns and scalds, anorectal malformations), and laparoscopic care of incisional hernias. Prof. Dr. F. Puppe, Artificial Intelligence, and Prof. Dr. P. Heuschmann, Institute for Clinical Epidemiology and Biometry, are working together with the European Hernia Association (Europäische Hernien Gesellschaft) in setting up an internet-based Ventral and Incisional Hernia Register. Prof. Dr. A.M. Waaga-Gasser is presently working on a study on the downregulation of inflammation parameters in chronic pain patients.

Infection / Inflammation
(U. Lorenz, N. Schlegel, A.M. Waaga-Gasser)

Hospital infections with staphylococcus aureus are a major problem. A new therapeutic option with tailor-made antibodies is being investigated in a BMBF supported project. Further areas of investigation include pathogenesis, immune responses, and new therapy approaches for analyzing the resistance of surgical prosthesis material to infection. The project "Pathophysiology of the intestinal barrier in the case of acute inflammation", funded by the IZKF and the DFG, examines the intercellular signalling pathway following the breakdown of the intestinal barrier and aims to develop new pharmacological approaches to stabilize the intestinal barrier.

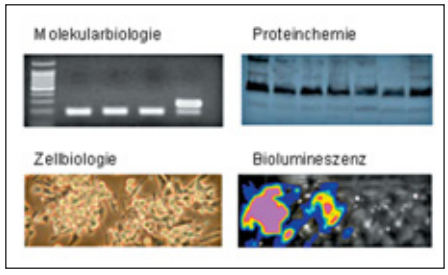

Fig.1: Many different in vitro and in vivo tests are part of a modern repertoire of analyses.

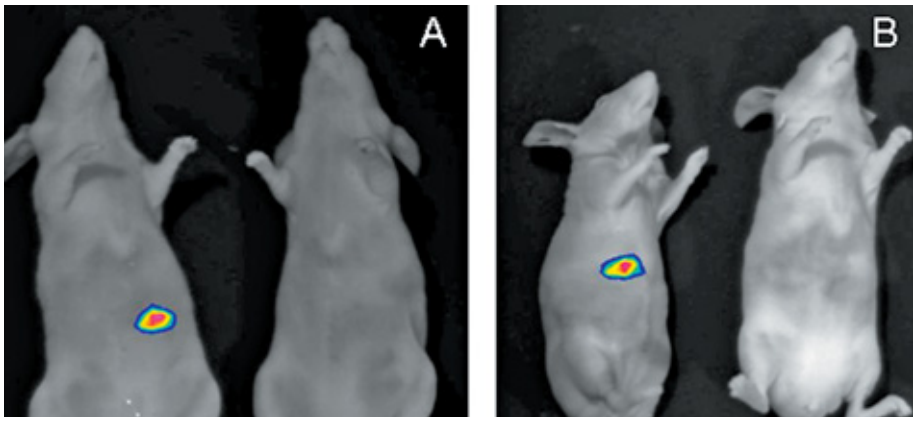

Fig. 2: Minimally invasive evidence of human tumours in bowel (A) and liver (B) in xenograft models using bioluminescence imaging.

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

The oncogenesis of tumours in the gastrointestinal tract is currently under investigation. New therapy concepts for cancer of the colon, colorectal liver metastases, and peritoneal carcinosis are being investigated; funded, among others, by the DFG and IZKF. One partner in this field is Prof. Dr. H. Stopper, 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. Another main point of interest, in cooperation with Prof. Dr. M. Eilers, Physiological Chemistry II, is analyzing therapy-relevant intercellular signalling pathways. Surgery I is a member of the Faculty of Medicine's National Biomaterial Bank and Database (funded by the BMBF). Patient tissue and fluid samples are collected and catalogued for investigating diseases and their causes.

Metabolic Disorders
(C. Jurowich)

Complex metabolic changes due to type 2 diabetes mellitus cause adiposity. In contrast to conservative treatments of morbid adiposity, different methods of bariatric surgery lead to a marked improvement and sometimes total recovery from type 2 diabetes. We are presently investigating these puzzling molecular mechanisms in cooperation with Prof. Dr. H. Koepsell, Anatomy and Cell Biology I, University of Würzburg, and Prof. C.W. le Roux, Department of Investigative Medicine, Hammersmith Hospital, Imperial College London, UK.

Tissue Engineering
(U. Dietz, Th. Meyer)

Biocompatible materials are being tested to determine their suitability for treating large congenital defects of the abdominal wall. One research project in the field of surgical wounds looks at controlling fibroblast migration in the areas surrounding synthetic nets. This research is being conducted in cooperation with Prof. Dr. H. Walles, Tissue Engineering and Regenerative Medicine, and Prof. Dr. J. Groll, Department of Functional Materials in Medicine and Dentistry, both University of Würzburg.

Transplantation-Immunology
(M. Gasser, I. Klein, C. Otto, U. Steger, A.M. Waaga-Gasser)

Regulatory immune cells play a very important role in transplantation medicine because of their involvement in the development of graft-specific tolerance. They prevent the patient's immune cells from destroying the essential but foreign organ or graft. Inhibiting immune responses are often found in the liver. We have several established animal models for in vivo testing. Another project, in cooperation with Prof. Dr. E. Serfling and Dr. al Avots, Institute of Pathology, involves finding new targets for inhibiting graft rejection with fewer side effects.

Teaching

The advanced education programme covers all aspects of modern surgery in lectures and seminars. Bedside teaching has been optimized to ensure high quality hands-on training. Surgery I plays an active role in student training, both in the teaching hospital and the SkillsLab in the Interdisciplinary Training and Simulation Centre (INTUS). Students can improve their operating skills on training simulators under realistic conditions. Another highlight is eLearning. The website www.elearning-chirurgie.de provides information on important topics of general and visceral surgery, as well as graphics, illustrations, and videos.

Training courses in coloproctology, thyroid and microsurgery, as well as laparoscopic operating procedures are offered on a regular basis. Surgery I provides authorized further education in surgical intensive care, general, visceral, vascular and pediatric surgery, and proctology.

SELECTED PUBLICATIONS

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Chua TC, Morris DL, Saxena A, Esquivel J, Liauw W, Doerfer J, Germer CT, Kerscher AG, Pelz JO. (2011) Influence of modern systemic therapies as adjunct to cytoreduction and perioperative intraperitoneal chemotherapy for patients with colorectal peritoneal carcinomatosis: a multicenter study. Ann Surg Oncol 18:1560-1567.

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3.4 Department of Trauma, Hand, Plastic and Reconstructive Surgery

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Mission and Structure

In the Department of Trauma, Hand, Plastic and Reconstructive Surgery, 22 medical doctors are employed. For the treatment of patients, 52 beds are available on our wards. Additional beds are available in the Intensive Care Unit and the Intermediate Care Unit.
Within the ZOM, there is a close collaboration between the Department of General Surgery, the Department of Anaesthesiology, and the Institute of Radiology with regard to the interdisciplinary treatment of patients. Polytraumatized patients are first examined in the modern shock room with spiral CT. Other functional facilities are also of the highest standard, including the certified central sterilization unit, the operating theatres, the intensive care units, and the physiotherapy facilities. Furthermore, angiography, CT and MRI are available.
The different focuses of the Department of Trauma, Hand, Plastic and Reconstructive Surgery are represented in different consultation hours. With our department being the transregional trauma centre, last year a trauma network was certified, which comprises 16 hospitals within the region.

Major Research Interests

The current **clinical studies** include prospective-randomized as well as retrospective studies. Major areas are spine traumatology and complex injuries of the knee joint, the cubital joint, the foot and the hand.
A BMBF-funded project investigates the effects of adipose-derived stem cells on fracture healing. In a clinical study, BMP-2-functionalized collagen carriers combined with adipose-derived stem cells are planned to be employed in the therapy of bone defects and pseudarthrosis.
The **experimental research** was dictinctly intensified over the last two years.

Bone Fracture Healing and Muscle Regeneration
(R. Meffert, S. Frey)

In an IZKF-funded project the influence of $VEGF_{165}$ on muscle and bone regeneration after musculoskeletal trauma is studied in an animal model. Promising results were achieved and, thus, additionally CYR61, another proangiogenic factor, is included in the study (cooperation with Prof. N. Schütze, Department of Orthopaedics). Furthermore, the effects of CYR61 on growth and differentiation of skeletal muscle cells are investigated in a newly established culture model. Human muscle cells of traumatized patients are included in the investigation.

Fracture Models for Stability Improvement through the Use of Locking Plates and Osteosynthesis Material
(R. Meffert, S. Doht)

Different fracture models were established for biomechanical studies of locking plates and bone substitutes. The primary goal is to improve the stability through the use of new implants and materials. The fracture models currently cover the areas of hand, ankle joint, and tibial plateau. In a current project, for example, a locking plate is developed which is mainly used for the treatment of osteoporotic ankle fractures and which has recently been made commercially available. In a further project, the effects of bone substitute, screws, and their combination on the stability of tibial plateau fractures are investigated (Fig. 1).

Tissue Engineering of Adipose Tissue
(T. Blunk, P. Bauer-Kreisel)

Tissue engineering of adipose tissue represents a new major research area. The primary goal is the development of adipose tissue constructs for reconstructive and plastic surgery. A main focus is the development of vascularization strategies for adipose tissue constructs (Fig. 2), which is investigated within a research consortium funded by the Bavarian Research Foundation (Speaker: T. Blunk). In a further project, cell-based implants are developed for the reconstruction of the subcutaneous fat layer to be used in defect coverage. Moreover, 3D adipose tissue models for basic research were estab-

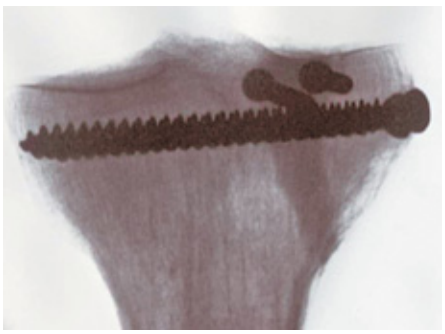

Fig. 1: Combination of osteosynthesis material and screws in the jail technique for stabilization of tibial plateau fractures.

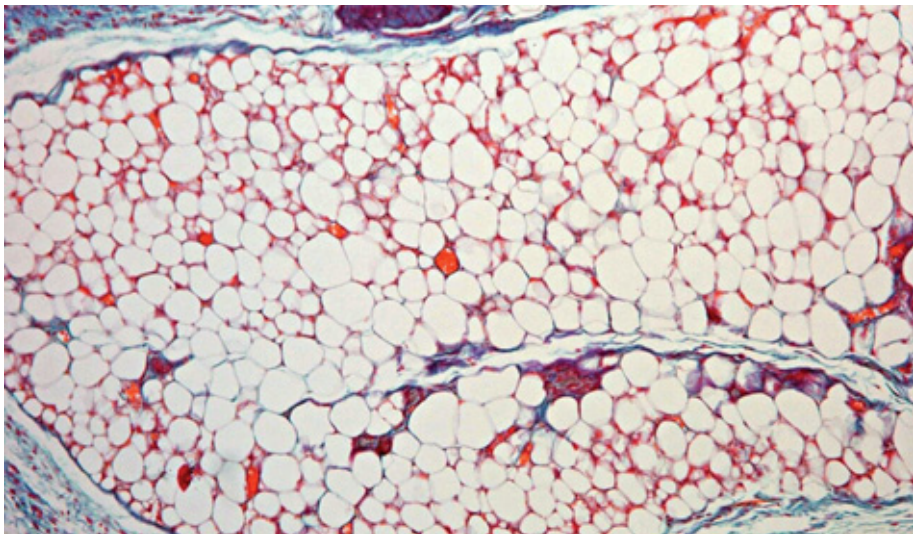

Fig. 2: Vascularized adipose tissue construct generated in a fiber scaffold after 3 months in a nude mouse model.

lished, in which, for example, the crosstalk of different cell types (e.g., stem cells and endothelial cells) and the role of the extracellular matrix in adipogenesis can be investigated.

Cartilage Regeneration
(T. Blunk)

Another new focus is the tissue engineering of cartilage. The chondrogenic differentiation potential of mesenchymal stem cells isolated from bone marrow and adipose tissue is investigated. Specifically, the effects of various growth factors on the differentiation of the two cell types are compared. In two new IZKF-funded projects the effects of biomimetic materials are investigated. In cooperation with Prof. J. Groll, Department of Functional Materials in Medicine, and PD A. Steinert, Department of Orthopaedics, new peptide-modified hydrogels for cartilage regeneration are evaluated. In cooperation with Prof. L. Meinel, Department of Pharmaceutical Technology, osteochondral constructs based on cell carriers made from silk fibroin are developed.

Investigation of Biocompatibility
(P. Zeplin)

In a further IZKF-funded project, the biocompatibility of coated alloplastic materials for plastic and reconstructive surgery is studied (cooperation with H. Walles, Department of Tissue Engineering and Regenerative Medicine, and Prof. T. Scheibel, Department of Biomaterials, University of Bayreuth). In a rat model, it is investigated if the biocompatibility of silicon implants can be improved by coating with spider silk.

Teaching

Teaching is divided into education of students as well as into education of our doctors on daily rounds and discussions and in specific seminars. Since last year the number of the weekly main lectures for students was doubled. At the end of the term, there are review courses in which the students are given the possibility to repeat the content of the semester with the help of patient-related cases.
Within the department, there are two grand rounds daily in which indications are discussed. For students, we offer a large variety of hospitations. Besides the local students, we continuously have foreign students visiting. The extensive curriculum offered to 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 organize an interdisciplinary polytrauma conference which is well accepted. At each conference, a specific topic is featured and therapy principles and reommendations are presented. Furthermore, the participants can present their own subject-related cases to be discussed. In order to improve practical examination techniques, a new course for the examination of the joints and the spine was recently introduced in the Skills Lab.

SELECTED PUBLICATIONS

Ochman S, Frey S, Raschke MJ, Deventer JN, Meffert RH. (2011) Local application of VEGF compensates callus deficiency after acute soft tissue trauma--results using a limb-shortening distraction procedure in rabbit tibia. J Orthop Res. 29:1093-8.

Zahn RK, Frey S, Jakubietz RG, Jakubietz MG, Doht S, Schneider P, Waschke J, Meffert RH. (2012) A contoured locking plate for distal fibular fractures in osteoporotic bone: A biomechanical cadaver study. Injury. 43:718-25.

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Bauer-Kreisel P, Goepferich A, Blunk T. (2010) Cell-delivery therapeutics for adipose tissue regeneration. Adv Drug Deliv Rev. 62:798-813.

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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

Clinical activities

The Institute of Transfusion Medicine and Haemotherapy supplies the university hospital of Wuerzburg with all required blood products, e.g. red cell concentrates, platelet concentrates and fresh frozen plasma. Additionally, it is competent for the production of autologous and allogenic stem cell concentrates for adult patients of the hospital. Beside 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”
- Practical training “Transfusion medicine and immunohaematology”
- Practical training “Blood group serology”

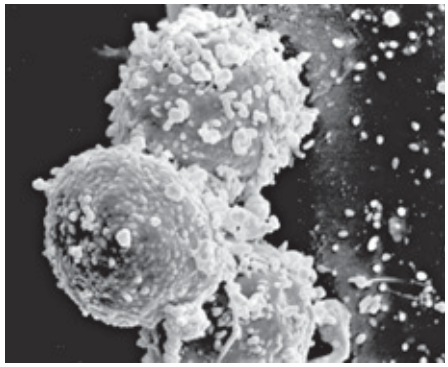

Fig. 1: Leucocyte depletion of red cells.

3.6 Department of Thoracic and Cardiovascular Surgery

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Mission and Structure

The department of Thoracic and Cardiovascular Surgery is a 54-bed department with 3 operating theaters and its own 12 bed intensive care/intermediate care unit. At present 22 physicians are employed.
Approximately 2000 procedures are performed annually covering the entire field of adult heart and thoracic surgery. 1050 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, reconstructive valve surgery including DAVID-, YACOUB-procedures. In 2009 a transapical/transfermoral minimally-invasive aortic valve replacement program was launched. This is a joint project with the Department of Cardiology. In selected patients we also offer the ROSS procedure.

Approx. 550 thoracic cases are performed per year. Main areas of interest are 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. We regularly perform extended thoracic procedures like tracheal resections utilizing the heart-lung-machine.
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

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.

Mitral valve reconstruction

All patients with a SJM rigid saddle ring are followed in order to define the quality and durability of the reconstructive procedure with this new type of ring.

Heart / lung transplantation

The working group led by Dr Sommer and Prof. Sinha (Institute of Microbiology) has successfully established a rat model for the induction of pulmonary ischemia-reperfusion-injury (IR). Susceptability to infection of pulmonary alveolar macrophages (AM) and function of pulmonary mitochondria during IR are determined. Since 2010 the group is supported by internal funding from the interdisciplinary center for clinical research (IZKF Würzburg, grant a-132).
The resistance of isolated AMs against bacterial toxins can be determined by a number of established cell culture tests. With this method, the relationship between IR and pulmonary infetions by nosocomial bacteria can be examined.

Several papers have been published by this group in 2010 and 2011 focussing on Glycine- and Glutathione-dependent modulation of IR-mediated mitochondrial dysfunction. At present the main focus of interest is on IR-induced mitochondrial dysfunction and oxidative stress. The application of antioxidants preserves mitochondrial function and maintains cellular thiol levels.
In 2011 a Langendorff working heart model was established in the same lab. In this setting the influence of phophsodiesterase-inhibitors on myocardial function is tested.
Another cooperation between Dr. Stefanie Sommer and Prof. Dr. Otto from the division of experimental tumorimmunology (ETI) assesses mitochondrial function of isolated tumor cells and the dependency of different tumors from glykolysis and oxidative phosphorylation.

Prevention and therapy of deep sternal wound infections (DSWI)

At present we are conducting a double-blind, two-center randomized study with 3 arms. In Kiel and in würzburg patients are randomized to an antibiotics-releasing felt (Gentacoll®), application of Integuseal® preoperatively or no intervention at all in order to assess the best preventive strategy in order to avoid mediastinal infetions. These studies are beased on previously published results from a randomized study which showed a beneficial effect of an antibiotics-releasing felt (Gentacoll®). We launched the working group “wound management” of the German society of Thoracic and Cardiovascular Surgery (DGTHG) and initiated a nationwide registry for DSWI plus a preventive program for avoidance of DSWI and hope to deduct scientific guidelines for the prevention and therapy of DSWI (Dr. Schimmer)

Thoracic surgery

On January 1st, 2012 Prof. T. Walles took over the newly created W2-position as

chairman of the division of thoracic surgery. His research interest is the application of tissue engineering techniques for tracheal replacement.

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.

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.

SELECTED PUBLICATIONS

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Schimmer C, Gorski A, Özkur M, Sommer SP, Hamouda K, Hain J, Aleksic I, Leyh RG. (2011) Policies of withholding and withdrawal of life-sustaining treatment in critically ill patients on cardiac intensive care units in Germany: a national survey. Interact Cardiovasc Thorac Surg 13: EPub ahead of print.

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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 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 2.000 conventional open, laparoscopic and endoscopic 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, a Da Vinci surgical roboter and several ultrasound units with colour-coded duplex sonography and transrectal probes.

The surgical spectrum encompasses the entire speciality of urology 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, robotic; 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 Cancer 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)

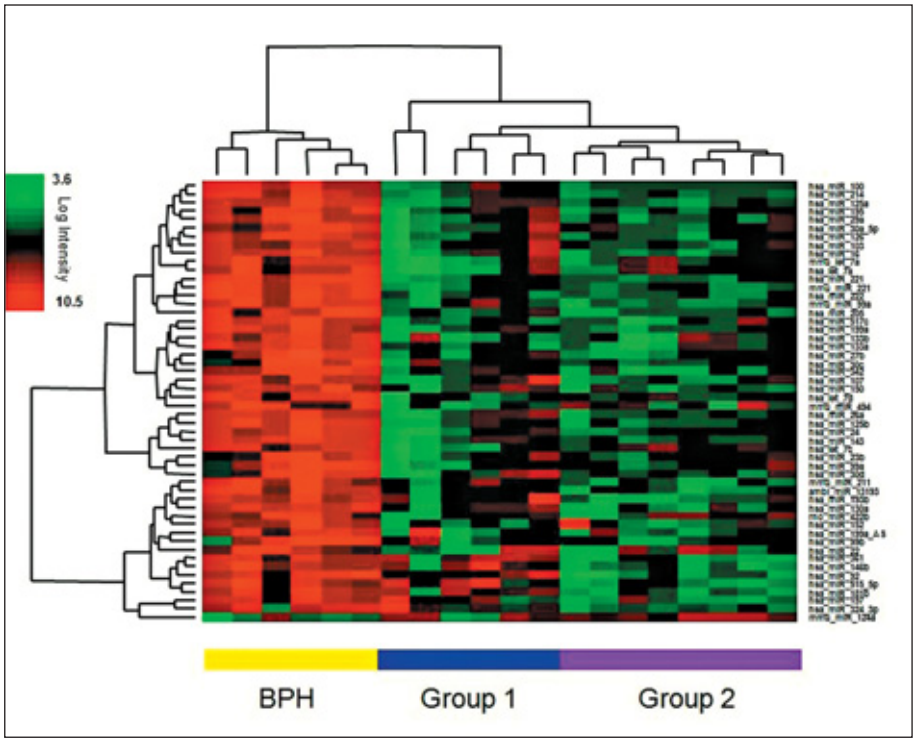

Fig. 1: MiRNA expression signature of Prostate cancer.

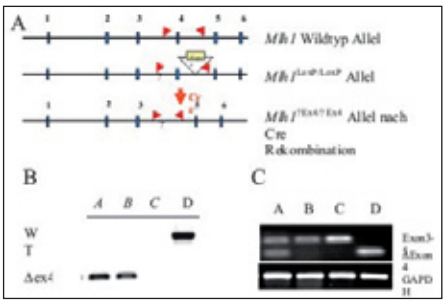

Fig. 2: Generation of a transgenic mouse model to inactivate mismatch repair activity in the prostate using the Cre-loxP system.

The aim of our studies is the analysis of 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 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 which 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.

Identification of tumorsuppressor- 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. Hospitation in the operating theatre and outpatient clinic is possible throughout the entire academic year.

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3.8 Department of Orthopedics

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Mission and Structure

The Orthopedic Clinic 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 Orthopedics and the Outpatient department for Orthopedics of the University, as well as the Orthopedic Center for Musculoskeletal Research. The Chairman of the Department, one full Professor of Osteology, 6 Associated Professors and 20 Residents are taking care of the patients and teaching. The hospital has 130 beds and in 5 operating theatres more than 4.100 surgical procedures are performed each year. The University Outpatient department 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 orthopedic patients are

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

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

The Orthopedic 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 scientific center supports the representation of the chair in the field of Orthopedic Surgery concerning research and teaching. The Head of the scientific center, Prof. Dr. Franz Jakob, is also the chairman 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 Orthopedic 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 (DFG Research Units FOR 793 and 1586, several single projects), the German Ministry of Research BMBF (BMBF-Consortium Osteopath, BMBF-Consortium Preeclampsia), the Ministry of Economy, the European Union (EU-Consortia ADIPOA and VASCUBONE), the Interdisciplinary Center for Clinical Research 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 and a Research Consortium on Sarcopenia and Osteoporosis – Consequences of impaired Regeneration in the Elderly FORMOsA), as well as several industrial cooperations. The number of positions funded is 28 (as of January 2012).

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, C. Hofmann (guest scientist Pediatric Hospital)
- Tumor Orthopedics and bone metastases (DFG FOR 1586)(M. Rudert, F. Jakob, N. Schütze, M. Lüdemann, J. Dotterweich)
- Molecular Orthopedics and Cell Biology (N. Schütze, T. Schilling, Simone Hil-

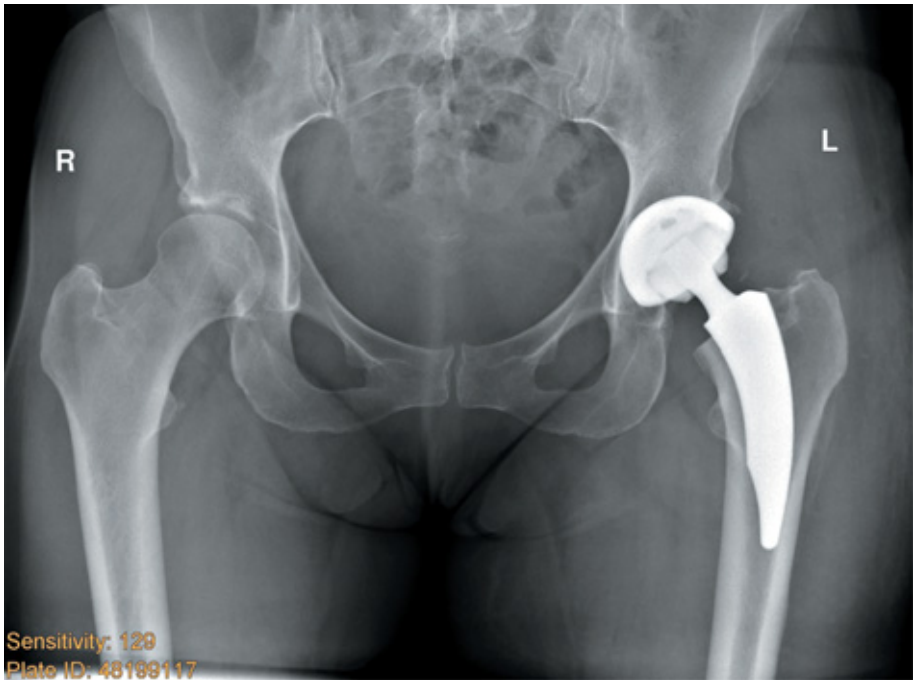

Fig. 1: Nanos Short Stem-Prosthesis (Fa. Smith and Nephew) for bone saving joint replacement at the proximal femur.

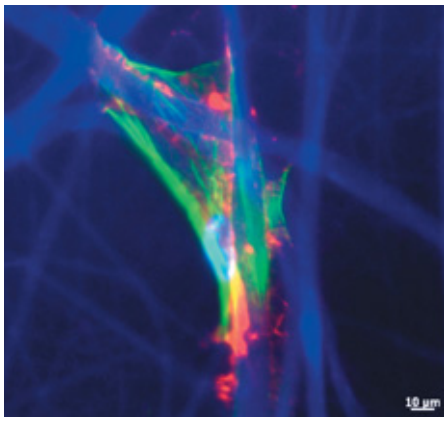

Fig. 2: Fluorescence staining of a mesenchymal stem cell homing on electrospun collagen type I nanofibers (green = actin filaments, red = vinculin/focal adhesion complexes, blue = nucleus).

pert, A. Noll, K. Schlegelmilch, R. Laug, S. Hondke, M. Simann, B. Hafen, S. LeBlanc)
- Tissue Engineering, Regenerative Medicine, Translation in Cell Therapy (U. Nöth, L. Rackwitz, R. Hallinger, A. Steinert, M. Rudert)
- Gene Therapy and Regenerative Medicine in Musculoskeletal Diseases (A. Steinert, P. Prager, N. Armbruster, C. Weber, F. Gilbert)
- Biomechanics and Mechanobiology (F. Jakob, L. Seefried, S. Müller-Deubert, A. Steinert, M. Hoberg, R. Ebert)
- Fracture Healing in Trauma and Osteoporosis (DFG FOR 793)
- Tumor Surgery and Modern Brachytherapy (M. Rudert, B. Holzapfel)
- 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, U. Nöth)
- Autologous Chondrocyte Transplantation (U. Nöth, L. Rackwitz, A. Steinert, 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, B. Baumann, M. Rudert)
- Special Orthopaedic Pediatric Surgery, Spine and Foot Surgery (P. Raab)
- Clinical Studies on Osteoporosis (F. Jakob, L. Seefried, G. Baron, K. Blume, S. Bau)
- Pain Research in Orthopedics (S. Goebel)

Teaching

- Courses in clinical examination techniques for operative and conservative orthopedics
- Lectures in Orthopedic basics (also accompanying the practical course)
- Practical Courses 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
- Courses in arthroscopic techniques at the knee and shoulder joint using simulator technology
- Molecular Aspects of Bone Diseases – Genes and Cell Biology
- Molecular Methods for osteology in basic science
- Integrated Seminar on Blood and Bone
- TecFun Technology of Functional Materials

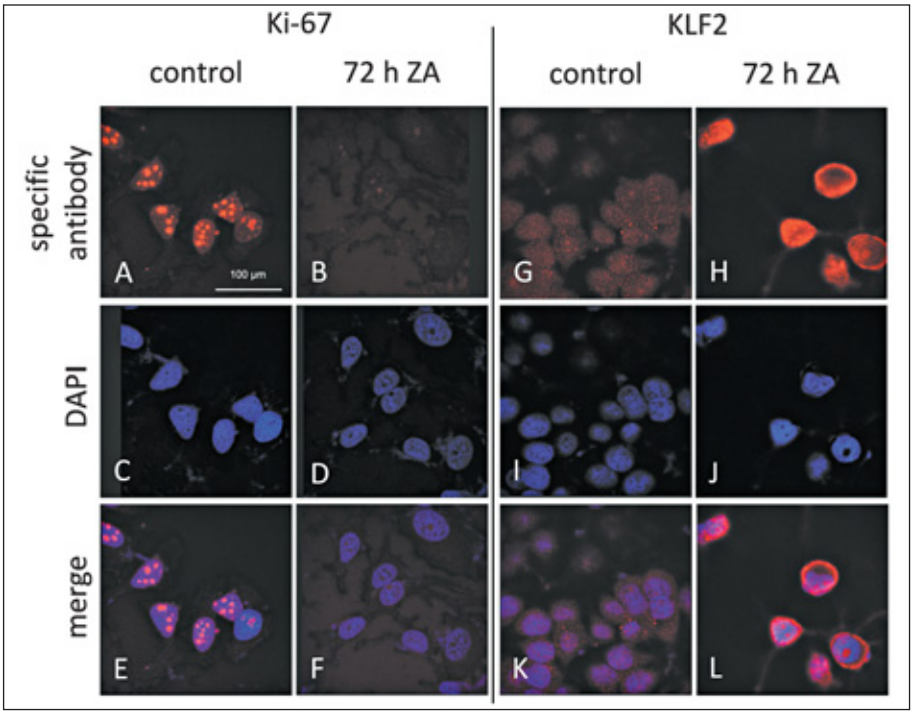

Fig. 3: Induction of putative tumor suppressors (krueppel like factor 2 as an example) and suppression of Ki-67 proliferation associated antigen in MCF-7 breast cancer cells following in vitro treatment with the bisphosphonate zoledronic acid.

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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, 32 doctors, 102 nurses, 15,5 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, 1,600 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

Research Project „Tumour progression and immune escape"
(J. Wischhusen, S. Häusler, A. Chandran, M. Junker, A. Seida, V. Bruttel, I. Montalbàn del Barrio, K. Becker, I. Vögele, F. Grän, B. Fischer, E. Horn)

The research group investigates interactions between tumor cells and the immune system during different phases of tumor development (see Figure 1).

Particular emphasis is placed on

- immunological properties of tumor-initiating cells.
  During early stages of tumor or metastasis formation (Dietl & Wischhusen, Nature Rev. Cancer 2011), the tumor microenvironment has not yet been established. Thus, genetically altered cells are fully exposed to the immune system and its extrinsic tumor-suppressor functions. Accordingly, low immunogenicity could be a prerequisite for the survival of tumor-initiating cells ("cancer stem cells"). In this context we have found that

a) tumor-initiating cells are selectively spared from cytotoxic effects of HER2-specific tumor immune therapy (Reim et al., Cancer Res. 2009),
b) tumor cells can escape from immune-mediated killing by de-differentiation into CSC.

- immune escape in advanced tumors, mediated by soluble factors from the microenvironment which

a) suppress effector functions of the innate and adaptive immune system and
b) preserve (or even induce) stem cell-like properties of tumor-initiating cells.
  Certain members of the TGF-β family (Roth et al., Clin Cancer Res. 2010) or the cytokine MIF (Krockenberger et al., J Immunol 2008) apparently combine both these effects and might therefore be good and druggable therapeutic targets. Pharmacological intervention also appears possible in order to prevent the degradation of immune-stimulatory ATP (that is released from dying cells) to immunosuppressive adenosine (Häusler et al., J Immunol Meth 2010, Cancer Immunol Immunther 2011).

- diagnostic potential of tumor-induced miRNA alterations in lymphocytes.
  Using peripheral blood from afflicted patients, we could already show that ovarian cancer induces disease-specific miRNA profiles in immune cells (Häusler et al., Br J Cancer 2010). These miRNA patterns most likely reflect tumor-host interactions which may occur long before a cancer is actually detected. As 14 different conditions were shown to be associated with distinct disease-specific patterns (Keller,… Wischhusen, Häusler, Dietl,…, Nature Meth 2011), we want to develop our original proof-of-principle study into a diagnostic test for the early detection of ovarian cancer.

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

Haemochorial placentation in humans still represents a 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 MIC-1 in human pregnancy decidua
(S. Segerer, U. Kämmerer, J. Dietl)

To date, the mechanisms which lead to the induction of tolerance against the semiallogenic fetus are not entirely resolved. However, several studies propose that a distinct composition of cytokines is essential for the establishment and maintenance of successful pregnancy. Macrophage inhibitory cytokine-1 (MIC-1), also named growth differentiation factor 15 (GDF15), is a member of the transforming growth factor-β (TGF-β) superfamily and is known to be expressed at high levels in human placenta. Women who subsequently miscarried or who had already miscarried exhibited significantly lower MIC-1 serum levels. As comparably low serum levels could even be detected three weeks before diagnosis of pregnancy failure, MIC-1 is thought to have a predictive role for pregnancy outcome.
So far, little is known about the decidual cell subsets producing MIC-1 and the effect of this cytokine on dendritic cells (DC), which are known to play a distinct role in the development of pro-fetal tolerance in pregnancy. We therefore investigate the impact and function of MIC-1 on DC (funded IZKF-projet Z3/5 to S. Segerer).

LASP-1 expression and function in trophoblast cells and dendritic cells
(S. Segerer, U. Kämmerer, E. Butt, J. Dietl)

The LIM and SH3 Protein 1 (LASP-1) has recently been reported to play a pivotal role in the actin cytoskeleton organization of metastatic breast cancer cells. Thereby, studies revealed that an overexpression of LASP-1 correlated with an increased rate of breast cancer metastasis. In contrast, silencing of LASP-1 resulted in a reduction of the migration and proliferation of breast cancer cells. During early pregnancy, a controlled invasion of trophoblast cells and immune cells

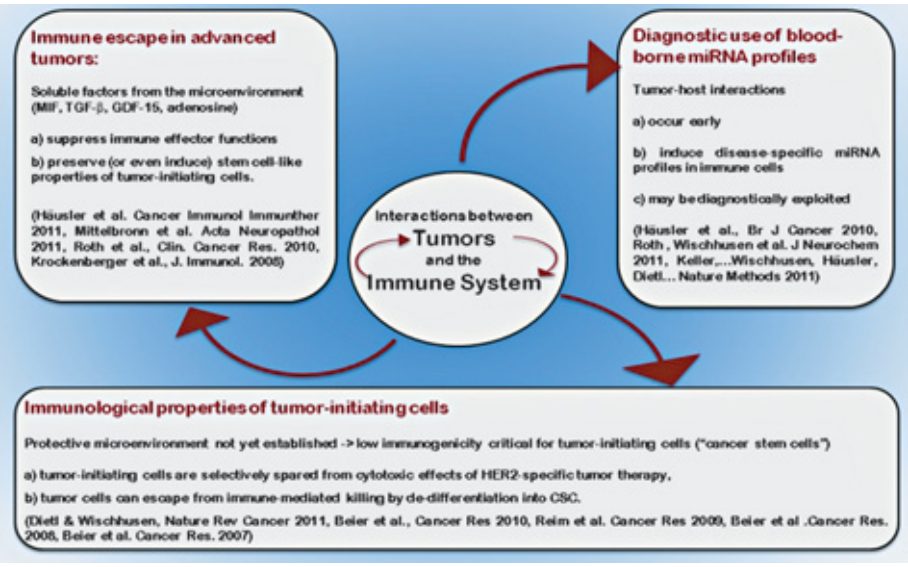

Fig. 1: Interactions between tumor cells and the immune system during different phases of tumor development.

into the decidualized endometrium is observed. So far, it is not known whether LASP-1 could play a role in this delicate migration processes at the fetomaternal interface. To this purpose, we investigate the expression of LASP in trophoblast cells and chorioncarcinoma cells as well as in maturing DC.

Studies on function and prognostic value of LASP in the dissemination of breast and ovarian cancer
(A. 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).

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.

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3.10 Department of Pediatrics

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Mission and Structure

The Children's Hospital of the University of Würzburg (staff: 64 MD's, 163 nurses, 45 technicians / administrative staff) comprises 115 beds including a pediatric-neonatal intensive care unit and a neonatal intensive care unit in the perinatal centre (obstetrics and gynecology). The Children's Hospital is divided into the following functional sections: neonatology, pediatric intensive care, oncology / hematology / stem cell therapy, cardiology, pulmonology / cystic fibrosis / sports medicine, gastroenterology, nephrology, endocrinology, diabetes, neuropediatrics / social pediatrics, immunology / infectiology, rheumatology, and others. Every year approximately 6500 patient in the inpatient and 15000 patients in the outpatient setting are being treated. There are many close collaborations to the other institutions of the university hospital.

Major Research Interests

Neonatology:
Characterization of airway remodeling in acute and chronic lung disease of premature infants and newborns

Very premature infants are at increased risk for acute and chronic morbidity. Likewise mortality is increased. New data indicate that a pulmonary or systemic inflammation may already start prior to birth and is perpetuated during the intensive care after birth. Among other projects, studies are conducted to analyze the influence of prenatal inflammation on the development of regulatory T-lymphocytes in the fetal thymus as well as the pathomechanisms leading to an inflammatory or pro-fibrotic reaction in the lungs. Other studies focus on the molecular events leading to airway remodeling in bronchopulmonary dysplasia (BPD). Specifically we are interested in the regulation and association of TGFß and connective tissue growth factor in BPD.

Pediatric Oncology, Hematology and Stem cell transplantation:
Cellular immunity and immunmodulation in patients with malignant diseases

The immune system is capable to destroy residual tumor cells after chemotherapy or stem cell transplantation. We analyzed the T-cell function in patients with leukemia or brain tumors and were able to correlate the findings with disease outcome. For the first time, we were able to show an association of a favorable cytokine profile with disease outcome in medulloblastoma patients. Furthermore preclinical concepts are being developed to reduce the difficult phase of aplasia after allogeneic bone marrow transplantation.
Moreover requirements for efficient T-cell priming is analyzed in a robust, antigen-specific in vitro model and the influence of immune response modifiers is studied.
We strive to develop new immunotherapies for patients with malignant diseases (dendritic cell vaccination, antigen-specific T-cells, Fig.1), and – in collaboration with the Comprehensive Cancer Center Mainfranken – aim to implement these techniques in clinical studies.

Pediatric Infectiology
Epidemiology and prevention of pediatric infectious diseases

In several studies, the effects of vaccination programs on the epidemiology of infectious diseases and their acceptance are evaluated in children and adolescents. Regional surveillance programs have been established in close cooperation with pediatricians in private practices and pediatric hospitals (e.g. "Bavarian Varicella Project" (BaVariPro)). Other studies in close collaboration with the institutes of virology in Jena and Würzburg, as well as with national reference centers (Aachen, Würzburg) aim to identify and type certain pathogens to identify changes (e.g. pneumococcal serotype replacement) under vaccination pressure.

Osteology:
Hypophosphatasia – pathophysiology and new treatment options

Hypophosphatasia is a rare disease of the bone characterized by reduced phosphata-

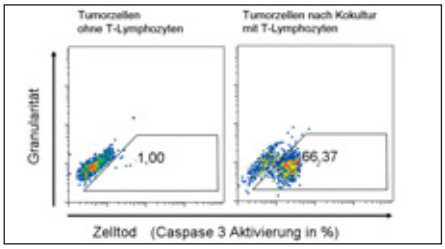

Fig. 1: Melan-A-specific T-cells induce apoptosis in tumor cells. Caspase-3 activation in tumor cells after T-cell contact (4h) is beeing displayed (400 000 T-lymphocytes for 20 000 tumor cells). Such clear activation of caspase 3 is a clear sign for the induction of apoptotic cell death in the tumor cells.

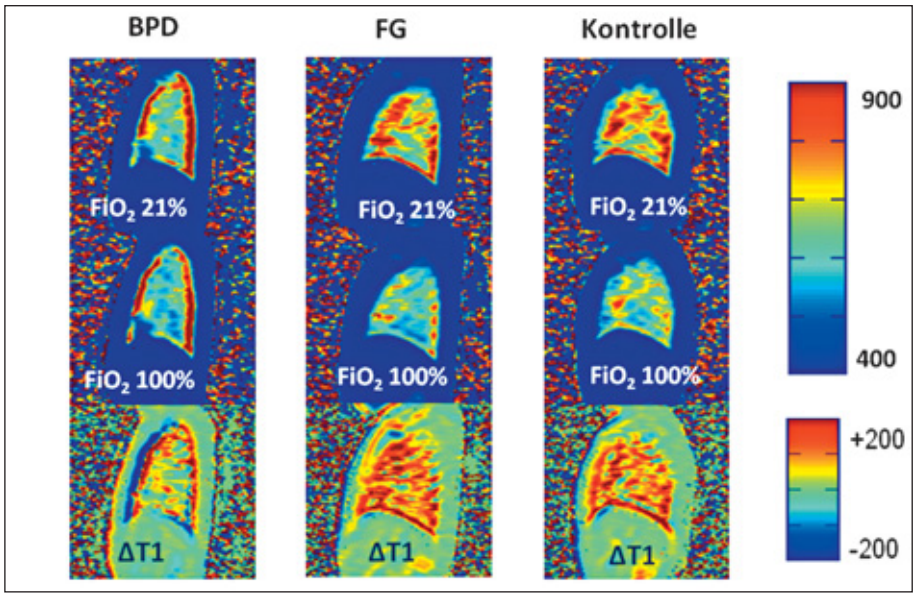

Fig. 2: Colour-coded images of pulmonary T1-relaxation times (MRI, 0.2 Tesla) from 3 children at school age, a former preterm neonate with bronchopulmonary dysplasia (BPD), a former preterm neonate without BPD (FG), and a healthy child born at term (Kontrolle). Upper panel: Values obtained when breathing room air. Middle panels: Values with pure oxygen. Lower panel: Differences in the T1-relaxation times (ΔT1) are lower in the child with former BPD than in the other children indicating impaired regional pulmonary function. (Images provided by Prof. Dr. M. Beer).

se. Bone mineralisation, renal function and possibly CNS function are impaired. Our interdisciplinary team (Children's Hospital/Orthopedic Center for musculoskeletal Research) provides patient care for the largest patient cohort throughout Europe.
Research projects range from pathophysiology to preclinical treatment approaches (gene transfer). An international phase II study for enzyme replacement was initiated in 2011.

Pediatric rheumatology:
Pathogenesis of rheumatoid and chronic-inflammatory diseases

Altered T-cell homeostasis is characteristic for autoimmune diseases. We evaluate changes in T-cell subsets, specifically pro-inflammatory Th17 T-cells and regulatory T-cells in these patients. Moreover the influence of latent infections with herpes viruses, such as the cytomegalovirus, on T-cell homeostasis and effector effector functions is analyzed.
We also cooperate with the Center for musculosceletal research to study the interaction between mesenchymal stem cells and T-cells in patients with rheumatoid arthritis.

Pediatric pulmonology, cystic fibrosis and sports medicine:
Exercise and physical training in healthy children and in children with chronic pulmonary diseases

Several studies evaluate the pathophysiology of the reduced exercise capacity in patients with cystic fibrosis or former BPD. In close collaboration with the Department of Pediatric Radiology (Prof. Dr. M. Beer), we could describe the turnover of energy-rich phosphates in skeletal muscle during exercise as well as the pulmonary ventilation and perfusion using MRI techniques (Fig. 2). Another project focused on the exercise-induced release of mesenchymal stem cells possibly involved in pulmonary repair mechanism.
A study sponsored by the BMBF evaluated the preventive effects of a physical activity program in a Kindergarten setting. The program proofed to be feasible and effective, and is now being implemented nationwide in collaboration with the Barmer GEK. With another partner, the Deutsche Lehrerbildungsinstitut Alexander von Humbold, the program will also be established in Chile. Other studies analyze the influence of special outdoor equipment ("Aktivschiff") in two preschools on activity behavior and motor skills of preschool kids.

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 haematolog and oncology, neuropediatrics, and 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 annually for more than 3000 outpatients. Since 2003 the division of endocrinology has become the international reference centre for the adrenal carcinoma; recently more than 130 patients with this very rare disease per year get advice and treatment in Würzburg. The endocrinologists coordinate the section Endocrine Tumors of the Comprehensive Cancer Center in Mainfranken. 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 six outpatient clinics including the (1) low clearance clinic with special focus on late stage diabetic nephropathy, (2) vasculitis clinic, (3) polycystic kidney disease clinic, (4) STOP IgA nephropathy (5) FAZIT, the Fabry center for interdisciplinary treatment (a national reference center) and the (6) transplant clinic for post kidney transplantation care. More than 60 transplants per year (including living donors) could be realized.
The Division of Pneumology cares for inpatients with bronchial carcinoma, pulmonary hypertension, severe pneumonia, severe COPD or interstitial lunge disease with more than 4.000 outpatient contacts. Special areas of interest include interstitial lung disease, sarcoidosis, severe asthma, pulmonary hypertension and alpha-1-antitrypsin-deficiency. The department of Pneumology is integral part of the interdisciplinary *Thorax-Centre Mainfranken* and of the Comprehensive Cancer Centre Mainfranken (CCC Mainfranken).
The Division of Cardiology performed more than 3300 invasive procedures per year 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 corporation with the Department of Cardiac Surgery more than 100 minimally invasive stent-based implantation of aortic valves were performed. More than 300 high frequency- or cryo-ablations are performed per year. In cooperation with the Department of Cardiac Surgery more than 100 cardiac pace maker systems and 100 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-cardiologic, arrhythmias, ICD and pacemaker. A cardiac transplantation program has been started; 2011 7 heart transplantations have been performed. The Department of Internal Medicine 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). Since 2003, M. Fassnacht and B. Allolio run the German Adrenocortical Carcinoma Registry that is now transferred to a European registry. The first randomized trial in adrenocortical carcinoma (FIRM-ACT) is internationally coordinated in Würzburg and has recruited more than 300 patients with advanced disease. Currently this largest trial in this rare disease is being analysed. Since 2011 another investigator-initiated phase III trial on the adjuvant treatment of adrenocortical carcinoma is (with support from the European Union) under way. Furthermore, the endocrine research group evaluates new therapeutic targets in an experimental and clinical setting. M.Fassnacht is head of the Adrenocortical Carcinoma Working Group of the European Network for the Study of Adrenal Tumors (ENSAT).
A second focus, initiated by B. Allolio and S. Hahner jointly with the Department of Nuclear Medicine, aims at developing and implementing new radioactive tracers for adrenal imaging and evaluation treatment opportunities in adrenocortical carcinoma. This research is supported by both the Sander-Stiftung (foundation) and the IZKF (Interdisciplinary Center for Clinical Research).

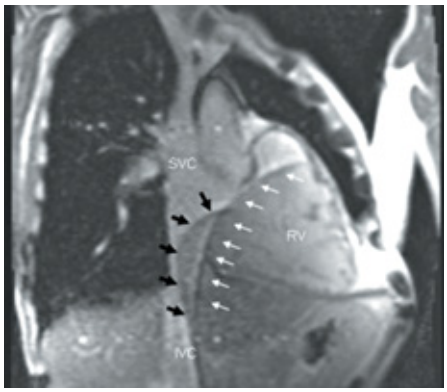

Fig. 1: Magnetic resonance-guided placement of catheters and electrophysiology (EP) mapping (right ventricular long-axis view). Two EP catheters were positioned via the inferior vena cava (IVC). The catheter for ablation (black arrows) is located at the tricuspid annulus (between RA and RV). The second catheter is placed in the right ventricular outflow tract (white arrows) for backup stimulation. SVC = superior vena cava.

Several international patents are submitted.
Moreover, several "investigator-initiated" studies on hyponatremia, acromegaly, and adrenal insufficiency are currently carried out. As part of an initiative for a German Conn Registry, patients with primary aldosteronism are prospectively evaluated to assess long-term outcome. Together with the Department of Nuclear Medicine, the endocrine unit participate on several phase II and III trials in thyroid cancer. 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.
B. Allolio is representative for endocrinology in the DFG Fachkolleg.

Cardiology/Angiology
(Coordination: G. Ertl, S. Frantz)

Cardiovascular research is performed in several research consortia. 2010 the Comprehensive Heart Failure Center (CHFC) was founded. It is an integrated research and treatment centre (IFB) "Prevention of heart failure and its complications" funded by the ministry of research and education with a special focus on translational and clinical research. The DIMI is also involved in the "Kompetenznetz Herzinsuffizienz" (speaker G. Ertl) and the collaborative research program SFB 688 (deputy speaker G. Ertl). G. Ertl is speaker for medicine in the DFG Fachkolleg Medicine and in the cardiovascular section of the DFG Fachkolleg Medicine. G. Ertl is also president of the German cardiac society.
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.

Basic science projects:
(W. Bauer, S. Frantz, R. Jahns, S. Maier, O. Ritter, H.-T. Pelzer)

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: ischemia perfusion injury, role of the immune system for remodeling, depression and heart failure (S. Frantz), role of receptor antibodies during development of heart failure (R. Jahns); role of calcineurin (O. Ritter); gender aspects, cardiac metabolism, pulmonary hypertension together with the division of pulmology (H. T. Pelzer).

Translational projects
(O. Ritter, 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.

Clinical projects (only investigator initiated studies)
(Coordination: C.E. Angermann, S. Störk)

Biomaterial bank (R. Jahns, S. Störk), 3D- and tissue doppler echocardiography, rare heart diseases (rare genetic 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. Etics 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; MRI for interventional electrophysiology. Würzburg (G. Ertl, C.E. Angermann, C. Wanner) is the German principal investigator of the REVEAL (Randomized Evaluation of the Effect of Anacetrapib through Lipid-modification) study recruiting internationally 30,000 patients.
Taking together the cardiovascular research in Würzburg is characterised by interdisciplinary basic science, translational and clinical

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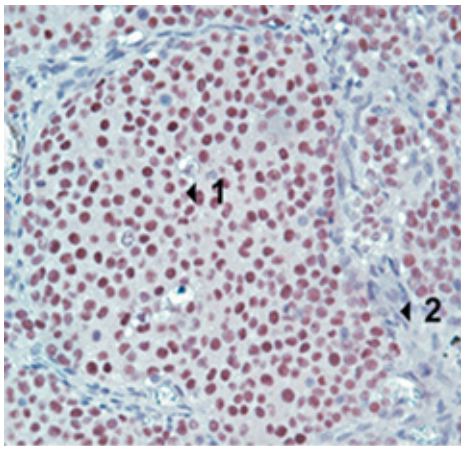
projects with the focus on heart failure and cell-cell-interactions.

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 – has given rise to results that produced 20 peer reviewed publications. Data sets of genetic results joined data bases of international consortia for meta-analyses. The results of the SHARP study (Study on Heart And Renal Protection) has been completed after 6 years of follow-up and published in The Lancet. Würzburg regional coordinating center has contributed with more than 900 patients to the German Chronic Kidney Disease (GCKD) cohort. Research questions about the progression of Fabry disease have emerged in more than 50 pubmed referenced publications so far. 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 completed by investigators of the academic hospital of Coburg and has offered co-chair function to Würzburg in the EPIC-CKD trial. Currently Nephrology is joining forces and bridging to the newly created Institute of Epidemiology and Biostatistics. 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
(M. Schmidt, H.-T. Pelzer)

Clinical research is directed towards novel regimes of radiochemotherapy of non-small-cell lung cancer and individualized, molecular targeted therapy of lung cancer. A second area of expertise and interest is on cardiopulmonary interactions in pulmonary hypertension.
The department participates in clinical phase III trials that are aimed to establish new treatment options for patients with severe pulmonary hypertension (IMPRES, CAESAR). Translational and experimental studies aimed to improve our understanding on the pathophysiology of pulmonary hypertension following pulmonary embolism (CTEPH) are conducted in cooperation with the department of physiology and supported by the Interdisciplinary Research Unit (IZKF) Würzburg (H.-T. Pelzer, K. Schuh). Further interest is on the recruitment and homing of blood fibrocytes to lung, and the role of fibroblasts and myofibroblasts in the exacerbation of idiopathic lung fibrosis.



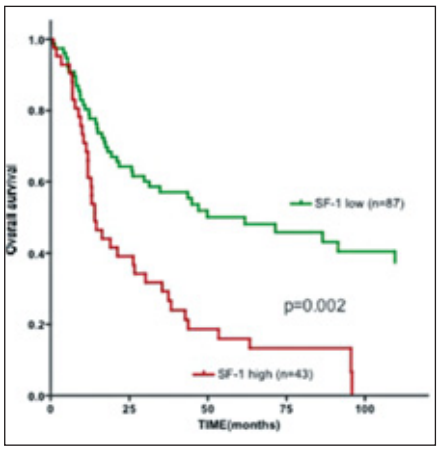


Fig. 2:Prognostic value of steroidgenic factor (SF)-1 in adrenal tumors. Left fig: Immunohistochemistry of adrenal carcinoma with (1) tumor cells and (2) negative stroma cell. Right fig: Kaplan-Meier survival depends on SF-1 expression in patients with adrenal carcinoma (modified after Sbiera et al., JCEM, 2010).

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
- Endocrine tumors: endocrinology, nuclear medicine, surgery, urology
- Interdisciplinary training and simulation center (INTUS): multiple hospitals and institutes

The Department of Medicine I together with the Institute of Experimental Biomedicine supervises the special research grant SFB 688 “Cardiovascular Cell-Cell-Interaction“ (see p. 164). In addition, clinicians and scientists of the department are active in the several research centers (e.g. cardiovascular centre, interdisciplinary centre for clinical research, Comprehensive Cancer Center Mainfranken, centre for infection research).
With the support of the ministry of research and education the integrated research and treatment centre (IFB) “Prevention of heart failure and its complications” or CHFC was established in 2010 in Würzburg. This center brings together several interdisciplinary research projects within the faculty of medicine and beyond, and plays 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 lec-

ture 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 12 Semester. With about 3,000 hours of teaching per semester, internal medicine is a major subject in the medical curriculum. Teaching of 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.

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3.12 Department of Internal Medicine II

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Mission and Structure

The Department of Internal Medicine II (DIM II) includes six divisions of internal medicine in research, teaching, and patient care: Gastroenterology, Hematology and Medical Oncology, Hepatology, Infectious Diseases, Psychosomatics and Rheumatology/Clinical Immunology. Excellent conditions for clinical research, teaching, and patient care were created by closest interdisciplinary contact that has emerged from the move of the Department of Internal Medicine II into the Centre of Internal Medicine (Zentrum Innere Medizin, ZIM) in 2009.

The Division of Gastroenterology (Prof. Dr. M. Scheurlen) is in charge of a specialized ward and the gastrointestinal outpatients clinic. More than 5000 endoscopic procedures are performed per year. The division of gastroenterology has a specific focus on chronic inflammatory bowel disorders and especially tumors of the gastrointestinal tract. Specific scientific programs address the diagnosis of hereditary neoplastic disorders of the gastrointestinal tract and the treatment of neuroendocrine tumors. Since many years these patients with new endocrine tumors are cared for in the PNETs center together with the colleagues from the department of visceral surgery. An additional scientific focus of the division of gastroenterology is the diagnosis and treatment of patients with stomach and pancreas carcinoma. Since 2007 a “Darmzentrum” is established together with the department of Surgery I and since 2011 additionally a modul pancreascarcinoma. In the beginning of 2012 the division of hepatology was specifically strengthened by the recruited team of Prof. Dr. A. Geier to further improve the patient care of patients with chronic liver disorders of all stages. An additional focus of the division of hepatology are metabolic liver disorders and malignant tumors of the liver including the diagnosis and treatment of hepatocellular carcinoma and cholangiocarcinoma. Together with the department of surgery I the liver transplantation program of the University Hospital Wuerzburg will be further developed in the newly established center of liver disease in Wuerzburg.

A completely new and state of the art stem cell transplantation unit (PD Dr. G. Stuhler) was established together with the department of pediatric hematology and oncology. The University Hospital Wuerzburg runs the second largest stem cell transplantation program in Germany with 280 stem cell transplantations per year. This highly innovative program of stem cell transplantation includes transplantation from haploidentical donors, cord blood transplantation and adoptive immunotherapy following stem cell transplantation to improve infection and tumor control post-transplant. In the division of hematology (Prof. Dr. R. Bargou) in special wards with hepafiltered rooms autologous stem cell transplantation and the treatment of patients with leukemia, lymphoma and myeloma are performed. The department of Internal Medicine II runs one of the largest study centers in Germany (one consultant, 4 clinician scientists, 34 study nurses and data managers). With an associated phase I unit (Early Clinical Trial Unit) in which clinical studies of phase I-III including trials with innovative antibodies are performed. Patients with multiple myeloma, lymphoma and acute leukemia from other European and Non-European countries are treated with innovative clinical trials in our department. The department of Internal Medicine II offers the largest treatment and research program for patients with multiple myeloma in Germany and in addition innovative clinical programs for patients with lymphomas and acute leukemia. More than 400 patients with multiple myeloma and more than 500 patients with lymphoma are treated in the division of hematology per year. Newly established is a specific lab for the diagnosis of non-malignant hematological disorders together with the department of pediatrics which is unique in Germany and offers specialized diagnostic procedures for patients with hemolytic anemias. In the division of Medical Oncology (Prof. Dr. V. Kunzmann) there is a special ward but also a large interdisciplinary oncological outpatient clinic in which more than 11.000 patients with all kinds of cancer are treated. In close collaboration with the Comprehensive Cancer Center Mainfranken the outpatient chemotherapy unit offers and performs chemotherapy for a broad spectrum of oncological disorders. A specific focus of the division of Medical Oncology in association with the divisions of gastroenterology and hepatology is the care of patients with gastrointestinal tumors esp. stomach and pancreas carcinoma, hepatocellular and cholangiocarcinoma, but also different subtypes of sarcoma. The division of Medical Oncology is heavily involved in the Brustzentrum, Darmzentrum, Pankreasmodul, the Center for Head and Neck Cancer, the skin tumor center and esp the oncological center of the University Hospital of Würzburg. In the division of psychosomatics Prof. Dr. H. Csef runs a specific outpatient clinic for oncological patients and for patients with psychosomatic disorders. In an outpatient department which is run in close collaboration with the department of psychi-

atry daycare of patients with psychosomatic disorders is offered. Research programs involve studies on psychosomatic disorders of the gastrointestinal tract. Specific Research activities are the care of patients undergoing stem cell transplantation.

In the division of clinical immunology of Prof. Dr. H.-P. Tony, patients with vasculitis and specific forms of rheumatoid arthritis, scleroderma and sjögren's syndrome are cared for. In the specific ward of the division of rheumatology and the rheumatological outpatient clinics more than 3.000 patients per year are cared for. Specific expertise of the division are the diagnosis and treatment of autoimmune disorders including novel therapeutic interventions in the frame of phase I-III studies, diagnostic and treatment of vasculitis and immunodeficiency disorders.

The research focus of the division of clinical immunology/rheumatology in basic but also translational research includes modulation of the B-cell-repertoire in autoimmune disorders. This research programs are funded by the Sander-Stiftung and the IZKF. Specific topics are the modulation of the memory B-cell-compartment and the depletion of B-cells following novel antibody constructs. Additional topics are immune reconstitution in patients with immunological disorders following more extensive forms of immune suppression, cardiovascular co-morbidity in patients with rheumatoid arthritis, the development of biomarkers for monitoring of treatment of autoimmune disorders and the pathological immunological regulation in lupus erythmatodes.
A division of infectiology (Prof. Dr. A. Ullmann, Prof. Dr. H. Klinker) was certified as one of the first centers in Germany by the Deutsche Gesellschaft für Infektiologie as a center of infectiology. The re-certification until 2016 could be obtained very recently. Patients with infectious disorders are cared for in the special ward for infectious disorders but also in a large outpatient clinic. More than 3.000 to 4.000 patients are treated there per year. The clinical focuses of the division are HIV-infections and chronic virus hepatitis, opportunistic infections in immunocompromised, esp hematological patients. The division of infectiology has a high reputation for the diagnosis and treatment of these infectious diseases. There are closed collaboration with the institutes for Microbiology and Virology/Immunobiology as well as with the Zentrum für Infektionsforschung of the University, a newly established center for liver diseases and the department of tropical medicine of the Missionsärztliche Klinik Würzburg. The Division of Infectiology is involved in a BMBF funded Kompetenznetz HIV/AIDS and hepatitis / Deutsche Leberstiftung. A new W2-Professorship for clinical infectiology with specific focus on mycology was established in 2011 (Prof. Dr. Andrew Ullmann).

Interdisciplinary projects, the speaker and the chair of the Clinical Research Unit 216 "Oncogenic Signalling in Multiple Myeloma" are members of the department of Internal Medicine II (H. Einsele, R. Bargou). Hermann Einsele is also the speaker of the EU-funded networks FP6 EU FP6 MANASP, EraNet PathoGenoMICs, AspBioMICS and a WP leader in the FP7 funded Nano II. The Department of Internal Medicine II is involved in projects of the Sonderforschungsbereich SFB TR 17. In addition, the department of internal medicine II was involved in the SFB 479 and the Clinical Research Unit KFO 124. H. Einsele is the co-speaker of the EU FP7 program OPTATIO addressing the interaction of microenvironment and multiple myeloma. In addition, PIs of the department of internal medicine II are active in different research centers: the stem cell transplantation center, the transplantation center, the oncological center and the comprehensive cancer center Mainfranken, the interdisciplinary center for clinical research, the center for infectious research. Since 2011 an additional chair was established in the department of internal medicine II (R. Bargou) to further strengthen translational and interdisciplinary research in oncology.

With the support of the IZKF and BMBF a tumor bank with focus on stomach cancer and colorectal carcinoma was established and in collaboration with the division of Medical Oncology treatment concepts in stomach cancer and pancreas carcinoma was developed. New innovative combinations of tyrosine kinase inhibitors and new cytotoxic agents in phase I-III studies are established. In addition a research group chaired by PD Dr. Melcher in collaboration with the institute of genetics offers a special outpatient clinic for diagnosis of hereditary tumor disorders of the gastrointestinal tract. In collaboration with the division of psychosomatics and infectiology cognitive and psychosomatic disorders in patients treated with interferon for hepatitis C are analyzed and genetic risk factors for this complication investigated. Additional research activities address the anti-micro-bioactivity of human colon epitheal cells. Research projects of the Center of hepatology (A. Geier, T. Kudlich, M. Rau), the division of hepatology addresses the pathophysiology of liver disorders and the improvement of therapeutic concepts. A specific focus are inflammatory and metabolic liver disorders and a translational research project in liver carcinoma. Additional projects address the role of multi-drug-resistance and the development of micro-RNAs in the pathophysiology of liver disease as potencial therapeutic strategies in a mouse model. Projects in the field of virushepatitis address genetic markers of the disease and response to the treatment. For patients with liver carcinoma combined treatment with RFA and Sorafinib are investigated. Funding is received from the Schweizer Nationalfond (SESNF), the Center for integrative human physiology (CIHP) of the University of Zürich, the European Association for the study of diabetes (EASD), and the Wilhelm Sander-Stiftung.

Research in Hematology/Oncology:

Research groups address the treatment of multiple myeloma in in vitro and in vivo models. In addition the treatment of other lymphoid malignancies is investigated.
Early clinical trials in the field of gastrointestinal tumors with their specific focus on stomach carcinoma, pancreas carcinoma and peritoneal carcinosis have been performed (V. Kunzmann). In the division of hematology/oncology more than 25 phase I/II studies and more thah 53 phase III studies are performed in the department of Internal Medicine II. H. Einsele is the speaker, R. Bargou the chair of the clini-

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Topp, MS, Kufer, P, Goekbuget, N, Goebeler, M, Klinger, M, Neumann, S, Horst, H-A, Raff, T, Viardot, A, Schmid, M, Stelljes, M, Schaich, M, Degenhard, E, Köhne-Volland, R, Brüggemann, M, Ottmann, O, Pfeifer, H, Burmeister, T, Nagorsen, D, Schmidt, M, Lutterbuese, R, Reinhardt, C, Baeuerle, PA, Kneba, M, Einsele, E, Riethmüller, G, Hoelzer, D, Zugmaier, G, and Bargou, RC. Targeted therapy with the T-cell engaging antibody blinatumomab of chemorefractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J. Clin. Oncol., 29(18):2493-8, 2011.

cal research group (CRU) 216 "Oncogeneic signaling in multiple myeloma". By newly defined oncogeneic signaling pathway, new therapeutic strategies for Multiple Myeloma are developed in close collaboration with research groups in the Department of Immunology, Pathology, Microbiology, Organic chemistry and Pharmacy. The CRU is further supported by clinical trial activities of the Deutsche Studiengruppe Multiples Myelom which is chaired by H. Einsele since 14 years. In addition a therapeutic treatment unit Multiple Myeloma is funded by the Carreras Foundation. Currently a large EU-sponsored consortium FP7 has been initiated in which novel animal models and biomarkers will be developed and evaluated in patients with multiple myeloma. Under the leadership of S. Knop several of phase I-III trials are performed for patients in multiple myeloma, esp looking at novel induction treatments, consolidation, maintenance therapy and allogeneic stem cell transplantation as well as novel antibody constructs. An additional immunotherapeutic program involving immune cells of the innate immunity (NK cells, γδ-T-cells) is chaired by Volker Kunzmann in collaboration with S. Gundermann and R. Seggewiss. Another important research focus of the Department of Internal Medicine II is the improvement of the results of the allogeneic stem cell transplantation. In current studies new technologies of haploidentical stem cell transplantation, cord blood transplantation, adoptive immunotherapy are evaluated in national and international studies chaired by Wuerzburg PIs (cord blood transplantation: G. Stuhler, haploidentical transplantation: S. Mielke, adoptive immunotherapy: U. Grigoleit, M. Kapp). These research programs are funded by the DFG, Carreras Foundation, BMBF and several national networks. The largest ever funded immunotherapy program of the EU (Allostem) was co-chaired by Wuerzburg PIs. In additional EU-projects MANASP, Nano II and OPTATIO Wuerzburg PIs are playing a leading role.
A third research focus is the development of immunotherapeutic strategies based on novel antibody constructs, esp. by functional and also natural (IgM-antibodies) are developed and evaluated by this group (G. Stuhler, M. Topp, R. Bargou, M. Wajant and L. Rasche). This constructs are currently evaluated in lymphoid malignancies but also solid tumors (breast cancer, colorectal carcinoma, pancreas carcinoma, prostate cancer and bronchial carcinoma). In addition, tri-functional antibodies with Ep-cam specifity are evaluated in solid tumors by V. Kunzmann.

Research programs of the division of infectiology:

New treatment strategies in HIV-infection are evaluated in early and phase III trials. Since several years the division of infectiology is a clinical study center in the international HIV-study network of the Institute of Health USA. Currently in a worldwide study with additional funding by the BMBF the optimal time point of the initiation of antiretroviral treatment is evaluated (H. Klinker, S.Wiebecke). In the DFG-funded international Graduate College (IRTG) 152-2: HIV –Aids/Aids and associated infectious diseases therapeutic drug monitoring for antiretroviral agents is performed by the division of infectiology in close association with the department of pharmacology. In the antiviral treatment strategies of chronic Hepatitis B and C the division of infectiology is one of the main recruiters in national and internation trials. Associated research programs address the pharmacokinetic of Ribavirin, drug monitoring of innovative antiviral agents and HCV/HIV-co-infection (BMBF and IZKF funded).
An additional research focus are infections in the immunocompromised patients. Main topics are antifungal therapy, antiviral and antifungal prophylaxis as well as therapeutic drug monitoring (W. Heinz). In BMBF, EU-programmes, Sander-Foundation funded research programs the group of PD Dr. Löffler develop new diagnostic strategies, risk stratification, biomarker determinations and new treatment developments for patients with invasive fungal infections. In addition the role of adoptive and innate immunity for the control of fungal infections are studied in the framework of BayImmuNet and of 2 EU-Networks (EU FP6 MANASP, EraNet PathoGenoMICs, AspBioMICS).

Zentrum für Innere Medizin (ZIM)

1. Center for Stem Cell Transplantation
1. Phase-I/II Unit (ECTU)
2. Department of Infectious Diseases (Center for Infectious Diseases DGI), comprising Infectious Disease-ward M43 and outpatients' department for infectious diseases
3. Department of Rheumatology / Clinical Immunology incl. ward M43 – Rheumatology, outpatient department for rheumatic diseases, musculoskeletal ultrasound.
4. Department of Gastroenterology including ward "Romberg" (M42), hepatological beds at M43 and the outpatients' department for gastroenterologic/hepatologic diseases Center for Endoscopy and Sonography
5. Laboratories for immunology and Infectiology/Therapeutic Drug Monitoring

Luitpoldkrankenhaus

6. Outpatients' department for the treatment of haematological and oncological diseases

Day Clinic for Psychosomatic Medicine (building C2)

The Department Internal Medicine II is divided into the following divisions:
Hematology (Prof. Dr. R. Bargou), Medical Oncology (Prof. Dr. V. Kunzmann)
Gastroenterology (Prof. Dr. M. Scheurlen)
Rheumatology / Clinial Immunology (Prof. Dr. H.-P. Tony)
Infectious Diseases (Prof. Dr. A. Ullmann, Prof. Dr. H. Klinker)
Section of Psychosomatics (Prof. Dr. H. Csef)

Teaching

The „Medizinische Klinik und Poliklinik II" offers numerous courses for medical students and for postgraduate professional education. Prof. Dr. H. Einsele is certified trainer for the whole field of Internal Medicine. In addition, authorized training and education is available for the following specialties (2 years each): PD Dr. F. Weissinger (Hematology/Oncology), Prof. Dr. M. Scheurlen (Gastroenterology), Prof. Dr. H.-P. Tony (Rheumatology) and Prof. Dr. H. Klinker (Infectious Diseases). The hospital organizes numerous advanced training courses and scientific meetings for both physicians and patients. Often, patient organizations are involved in planning and realization of the events.
A web-based teaching concept teaching concept is funded by the Virtuelle Hochschule Bayern (VHB). This joined project of the University Hospital Regensburg with 384 users and 14.810 included cases is extremely accepted.

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Muhammad, K.; Roll, P.; Seibold, T.; Kleinert, S.; Einsele, H.; Dorner, T.; Tony, H. P., Impact of IL-6 receptor inhibition on human memory B cells in vivo: impaired somatic hypermutation in preswitch memory B cells and modulation of mutational targeting in memory B cells. Ann Rheum Dis, 70, (8), 1507-10, 2011

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Zeuzem S, Buggisch P, Agarwal K, Marcellin P, Sereni D, Klinker H, Moreno C, Zarski JP, Horsmans Y, Mo H, Oldach D, McHutchison JG, Manns MP,Foster GR. The Protease Inhibitor GS-9256 and Polymerase Inhibitor Tegobuvir (GS-9190) Together and in Combination With Ribavirin or Peginterferon and Ribavirin in Genotype 1 Hepatitis C . Hepatology; doi: 10.1002/hep.24744 (Epub ahead of print), 2011

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3.12.1 Division of Molecular Internal Medicine

CONTACT DETAILS

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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 Interdisciplinary Centre for Clinical Research of the University of Würzburg

Major Research Interests

The research topic of the division is the tumor necrosis factor (TNF) ligand family and their receptors. Ligands and receptors of the TNF family are of pivotal importance in immunoregulation, but are also of relevance in development and the control of programmed cell death (apoptosis) in a variety of physiological and pathophysiological situations. The two major research foci of the division are, on the one hand, the development of therapeutic useful recombinant TNF ligand variants and anti-TNF receptor antibodies and, on the other hand, the investigation of clinically relevant aspects of TNF receptor signal transduction. These topics are addressed in three research groups.

Research Group: Therapeutic Fusion Proteins and Antibodies

Many ligands of the TNF family stimulate the immune system or trigger apoptosis. The potential therapeutic application of these properties, however, is limited due to the serious side effects that are usually associated with systemic activation of TNF receptors. The research group thus develops fusion proteins of TNF ligands that selectively activate their corresponding TNF receptor locally in the tumor areal. In one approach, the fact is exploited that a subset of TNF receptors (e.g. CD95) is naturally activated by membrane-bound ligands, but not by soluble receptor-binding variants derived from these molecules. However, if such inactive soluble TNF ligands are artificially immobilized on a surface they acquire the same TNF receptor-stimulating activities as their natural occurring membrane-bound counterparts. Now, the activating cell surface-immobilization can be reached by fusing the soluble TNF ligand genetically to a targeting domain (e.g. an antibody fragment) recognizing a cell surface-associated molecular structure (Fig. 1). Utilization of targeting domains that interact with tumor specific structures facilitates then the anticipated favorable local activation of TNF receptors without causing systemic side effects. Tumor-localized activation of TNF receptors is also aimed by development of TNF ligand prodrugs. In this approach, TNF ligands that already activate their receptors as soluble molecules are connected to an auto-inhibitory domain via a protease-sensitive linker. As the linker is designed in a way that allows cleavage by tumor-associat-

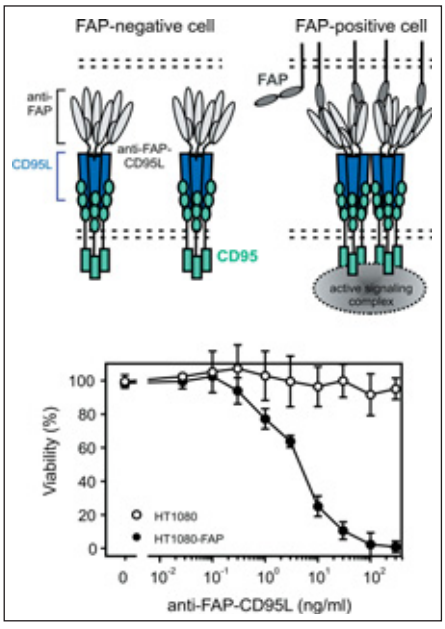

Fig. 1: A fusion protein (anti-FAP-CD95L) of soluble CD95L with an antibody domain specific for the tumor stroma marker FAP (fibroblast activation protein) interacts on FAP-negative tumor cells with CD95, but fails to trigger apoptotic signaling via this death receptor (open symbols). The same protein, however, efficiently stimulates CD95-mediated cell death upon binding to FAP on FAP-positive tumor cells (filled symbols).

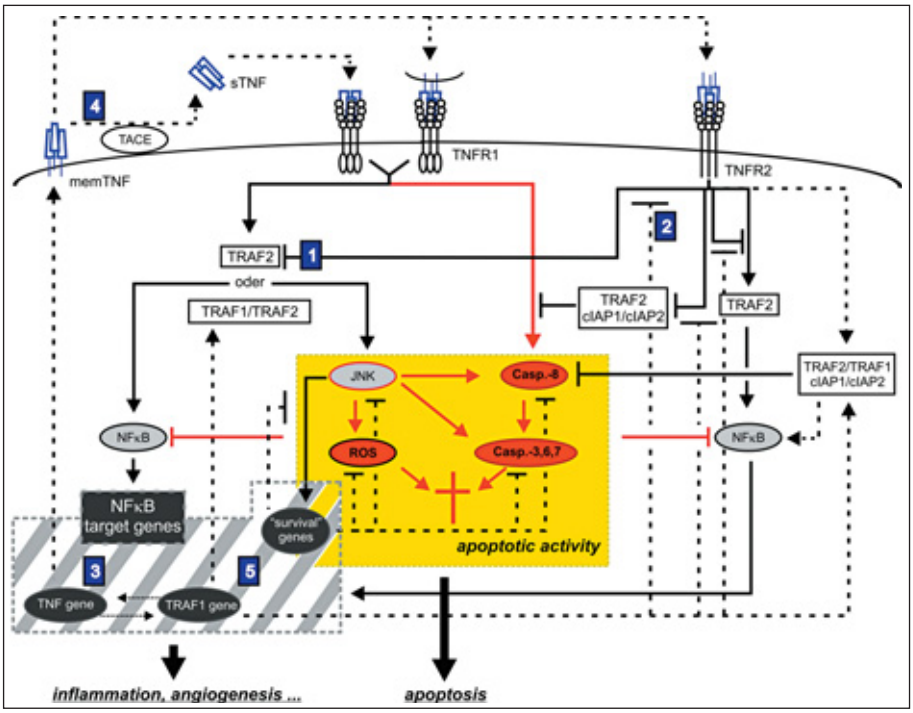

Fig. 2: TNFR1 and TNFR2 are functionally linked in a highly complex manner. Activation of TNFR2 by transmembrane TNF leads to degradation of the adapter protein TRAF2 (1). Because this protein is important for TNFR1-induced activation of the pro-inflammatory transcription factor NF-kappaB and recruitment of anti-apoptotic cIAP proteins into the TNFR1 signaling complex, cells are sensitized toward TNFR1-mediated cell death. Stimulation of TNFR1 by soluble TNF can induce NF-kappaB-dependent expression of endogenous TNF (3,4). In its membrane-bound form, it activates TNFR2 and sensitizes cells again for TNFR1-induced apoptosis, as described above. Another NF-kappaB target gene is TRAF1 (5). TRAF1 forms heteromeric complexes with TRAF2 and prevents its degradation by TNFR2 (2). TRAF1 antagonizes therefore TNFR2-mediated enhancement of TNFR1-induced apoptosis. Further, TRAF1 does also enhance TNFR2-induced non-apoptotic signal transduction, which contributes both to induction of TRAF1 and transmembrane TNF.

ed proteases, it is again possible to localize the TNF receptor-stimulating ligand activity to the tumor area.

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, where 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 TNF ligand family, occurs naturally in two forms, as a transmembrane protein and as soluble factor derived thereof by proteolytic processing. The two forms of TNF differ in their capacities to activate the two TNF receptors 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 are therefore dependent on TNF-receptor expression, cell type, extracellular conditions and, importantly, on the form of TNF that was used for receptor stimulation (Fig. 2). In this research group, the regulatory principles that cause the exceptional complexity of TNF signaling are investigated at the molecular level.

Teaching

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

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Rauert H, Wicovsky A, Müller N, Siegmund D, Spindler V, Waschke J, Kneitz C, Wajant H. (2010) Membrane tumor necrosis factor (TNF) induces p100 processing via TNF receptor-2 (TNFR2). J. Biol. Chem. 285:73947-404.

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

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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 a junior research groups), and the
b) Department of Clinical Biochemistry and Pathobiochemistry (Chair, Professorships 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 ambulant patients of the university medical center (ca. 4 million patient laboratory analyses/year). Affiliated with this division is an outpatient clinic specializing 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 system 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 until April 2011: Prof. Dr. med. U. Walter) which 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 measurement of ADP receptor (P2Y12) inhibition by antiplatelet drugs such as Clopidogrel and Prasugrel.

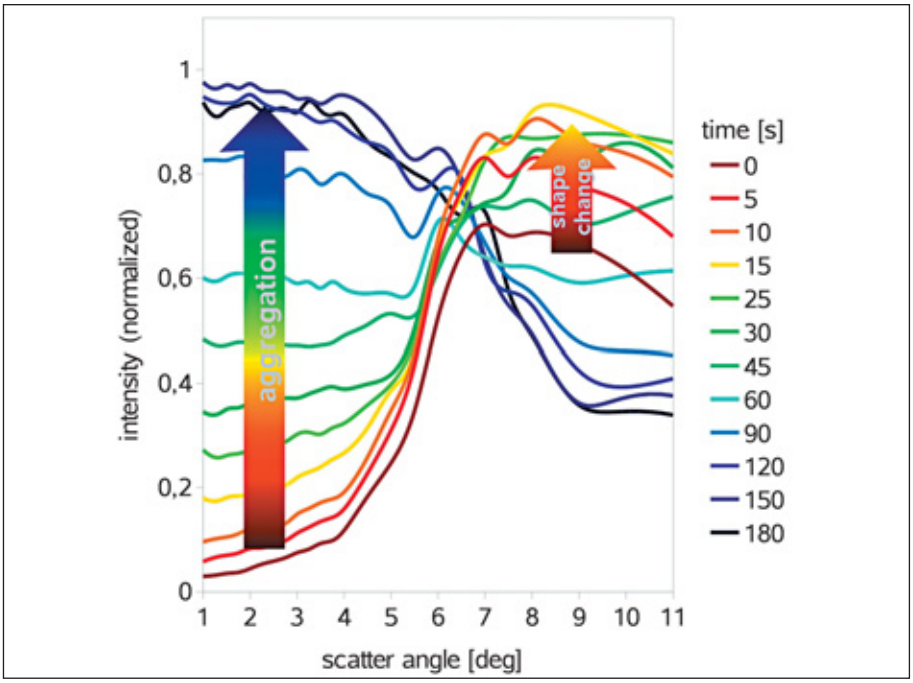

Fig. 1: Angle dependent light scatter intensity of an ADP-stimulated platelet probe measured with a newly developed laser method. Intensity increase at low angles corresponds to aggregate formation; at high angles to shape change. Late intensity decrease at large angles results from aggregate formation.

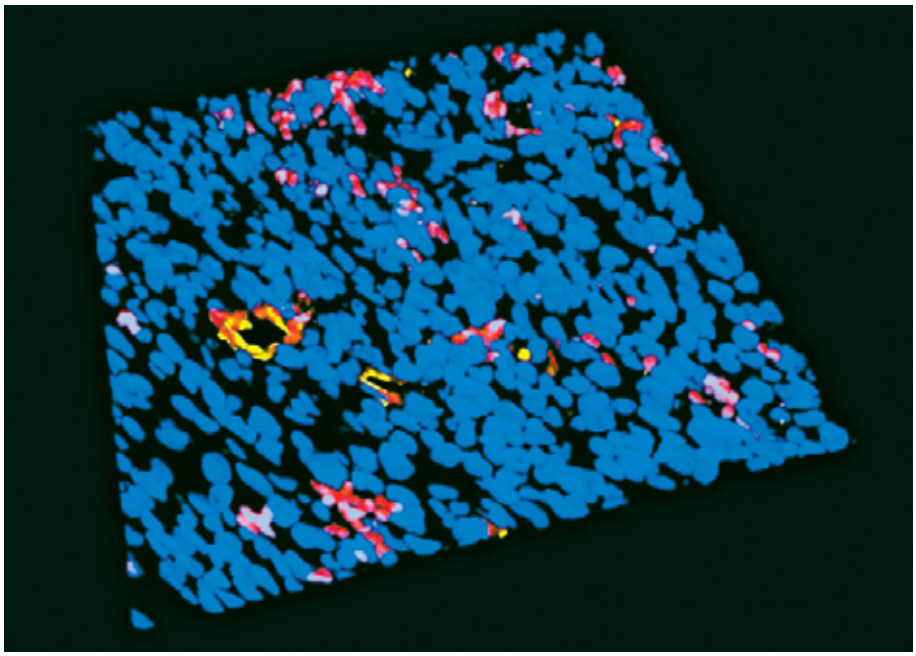

Fig. 2: Targeted delivery of a tumour vessel specific agent. The distribution of a vessel specific agent within the tumour is shown in yellow. Enrichment is observed in the blood vessels (red immuno staining), while the tumour cells themselves (blue counter stain) and blood cells (light blue) show only minor uptake.

The BMBF network project SARA (System biology of prostaglandin and ADP P2Y12 receptor signaling pathways) is funded until 2012 within the framework of the BMBF research initiative "System 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.

In January 2011, PD Dr. J. Schneider, who focussed on metabolic syndromes and vascular diseases, left the Institute after receiving professorship at the University of Luxembourg, Centre for Systems Biomedicine.

Clinical Molecular Biology Group
(M. Zimmer)

The group is interested in the genetics of cardiac diseases and cardiomyopathies. Currently, a new and further disease gene causing dilated cardiomyopathy is identified by positional cloning. Other research areas focus on laminopathies which result from haploinsufficiency of the lamin A/C gene, diagnostics for mutations of DCM genes, and high-throughput SNP-typing using MALDI-TOF/Sequenom technology.

Protein Biochemistry and LASP-1
(E. Butt, C. Reiss)

An additional group at the institute 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. A further topic is the role of LASP-1 in adhesion, aggregation and secretion of murine thrombocytes.
An additional research domain is the characterization of cyclic nucleotides and their effector proteins.

Angiogenesis and Tumour
(E. Henke)

In July 2010 Dr. Erik Henke joined the Institute coming from Memorial Sloan-Kettering Cancer Center in New York. As a Heisenberg Fellow he is establishing a research group focused on tumour angiogenesis and experimental therapeutics. The project centers on establishing methods for the targeted manipulation of vascularisation processes during tumour growth. This should result in improved drug delivery and subsequently in improved therapeutic efficacy.

Teaching

The institute provides medical school teaching in the areas of clinical biochemistry, pathobiochemistry, and laboratory medicine. It offers lectures, seminars and practical courses, as well as active participation in research projects 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 is also Medical Director of the Training School for Medical Technical Assistants (www.mta-schule.uni-wuerzburg.de).

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3.14 Department of Dermatology, Venereology and Allergology

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Professor Dr. med. Eva-Bettina Bröcker
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Professor Dr. med. Henning Hamm
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Mission and Structure

The Department of Dermatology, Venereology and Alllergology 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, dermatohistopathology and proctology. Since 2009 the department is certified according to DIN EN ISO 9001:2008, including all its laboratories. In 2010, a certified Skin Cancer Center was established, which is an integral part of the *Comprehensive Cancer Center Mainfranken*. Apart from the department head, up to 4 professors of dermatology and 1 associate professor have been working in research and education during the period under report. Ten attendings, 5 further specialists in dermatology and 17 residents are practising at the department. In research projects, 6 basic life scientists are employed on regular positions and third-party funds. The department comprises the following divisions:

- General outpatient clinic and consultations for specific skin diseases, outpatient clinic for private patients
- Wards for conservative dermatology and dermato-surgery
- Skin Cancer Center with ward for dermato-oncology
- day clinic
- Outpatient clinic for allergology
- Outpatient clinic for phototherapy
- Division of dermatohistopathology and autoimmune diagnostics
- Laboratory for dermatologic infectiology
- Research laboratories with focus on dermato-oncology and immunology

Focuses of Clinical Interest

- Dermatooncology (A. Gesierich; J. C. Becker until March 31, 2010; E.-B. Bröcker until September 30, 2011; S. Ugurel-Becker until September 30, 2010; A. Kerstan)
- Allergology (A. Trautmann, A. Kerstan, J. Stoevesandt)
- Autoimmune skin diseases (E.-B. Bröcker until September 30, 2011; M. Goebeler since October 1, 2011; S. Benoit; J. Stoevesandt)
- Hair diseases (H. Hamm, A. Kerstan), hyperhidrosis (H. Hamm)

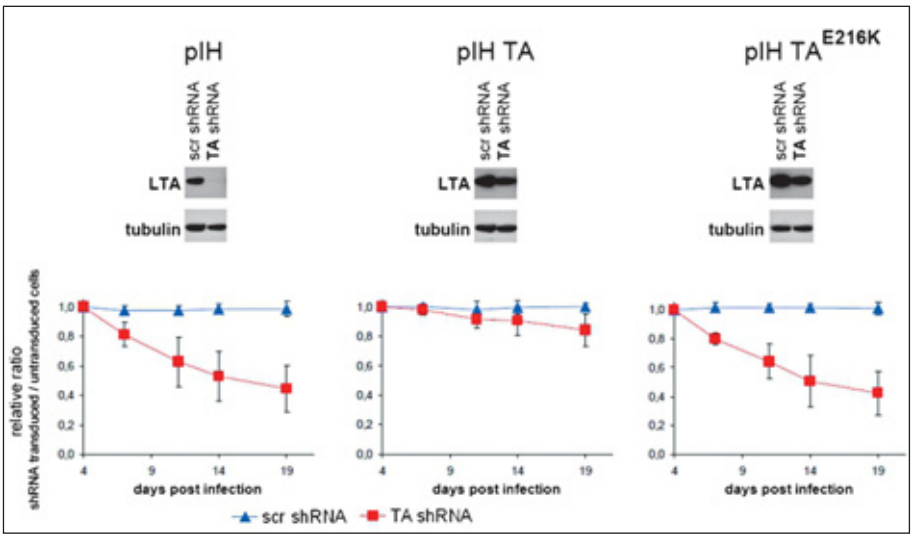

Fig. 1: Merkel cell carcinoma and Merkel cell polyoma virus T antigens. Merkel cell carcinoma cells strictly depend on expression of the Large T antigen (LTA) and interaction between LTA and the Retinoblastoma protein is essential for growth promotion by the viral LTA. Merkel cell carcinoma (MCC) is a rare but very aggressive skin cancer, which was found to frequently carry the DNA of a recently discovered virus termed Merkel cell polyoma virus (MCV). MCV codes for the so-called T antigens (TA). (pIH) T antigen knockdown by applying shRNA (TA shRNA), inhibits growth of MCV positive MCC cells, while a control shRNA (scr shRNA) does not affect proliferation. (pIH TA) Cells can be rescued by ectopic expression of a TA mRNA that was modified by silent mutations to be insensitive to the TA shRNA. (pIH TAE216K). However, there is no rescue after introducing a point mutation (pIH TAE216K) impairing binding of LTA to the cellular Retinoblastoma protein (RB). These results not only substantiate the role of the virus in the etiology of this deadly tumor entity but also identified these oncoproteins and especially the LTA/RB interaction as potential targets for future therapies.

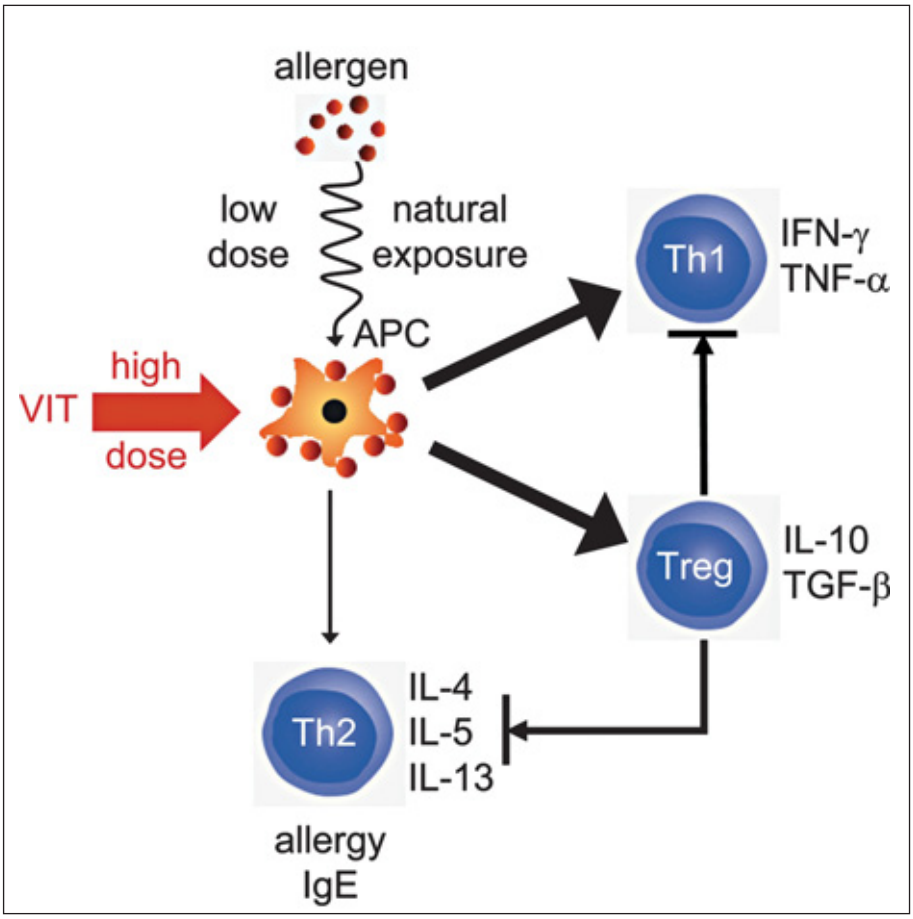

Fig. 2: Mechanistic insights into high-dose wasp venom immunotherapy (VIT). High-dose immunotherapy induces activation and increased lymph node homing of regulatory T cells (Treg). On the one hand activated Treg show an allergen-specific suppressive capacity promoting tolerance induction. On the other hand these Treg are able to efficiently control potentially harmful Th1 responses that strongly arise by high-dose antigen exposure in parallel. Therefore, Treg seem to balance between Th2 and Th1 responses rather than inducing a Th1 polarization.

- Dermatologic surgery (G. Weyandt; D. Presser since October 1, 2011; A. Gesierich)
- Phlebology and proctology (G. Weyandt Phlebology (D. Presser), Proctology (G. Weyandt)
- Paediatric dermatology (H. Hamm)
- Dermatologic infectiology (A. Kolb-Mäurer)
- Dermatohistopathology (E.-B. Bröcker, H. Kneitz, A. Kerstan)

Major Research Interests

Tumor biology and tumor immunology

One main field of research addresses several aspects of the biology of cutaneous tumors within the scope of the *Klinische Forschergruppe KFO 124* (funded by DFG until 2010) and various third-party funded projects.

Focuses during the period under report:

- signal transduction in Merkel cell carcinoma
- tumor senescence
- melanoma immunology
- melanoma genetics, chemoresistence and preclinical testing of innovative therapies
- molecular diagnostics of melanoma
- apoptotic signal pathways in epithelial cutaneous tumors
- cell migration and neoangiogenesis
- pathogenesis of primary B-cell lymphoma

Immunology and inflammation

- pathogenesis of allergic contact dermatitis
- interaction between T-lymphocytes and keratinocytes in dermatitis
- immunotherapy with wasp venom as model for therapeutic immune modulation in humans
- mechanisms of signal transduction in the context of innate immunity

Genodermatoses

Clinical and genetic characterization of genodermatoses in cooperation with the German Network for Ichthyoses and Related Cornification Disorders, the German Network Epidermolysis Bullosa and with national and international laboratories for research in molecular genetics

Teaching and further education

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

SELECTED PUBLICATIONS

Bergmann C, Wobser M, Morbach H, Falkenbach A, Wittenhagen D, Lassay L, Ott H, Zerres K, Girschick HJ, Hamm H (2011) Primary hypertrophic osteoarthropathy with digital clubbing and palmoplantar hyperhidrosis caused by HPGD loss-of-function mutations. Exp. Dermatol 20:531-533.

Houben R, Shuda M, Weinkam R, Schrama D, Feng H, Chang Y, Moore PS, Becker JC: Merkel cell polyomavirus-infected Merkel cell carcinoma cells require expression of viral T antigens. J Virol 84:7064-7072, 2010

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3.15 Institute of Radiology

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Mission and Structure

The Institute of Radiology is responsible for the entire modern radiological diagnostics at the University Hospital of Würzburg. Three professors, 13 senior staff radiologists, 20 residents and scientists as well as 53 technicians work together to ensure state-of-the-art diagnostics and interventional radiolgy. The Institute of Radiology includes a section of Neuroradiology and of Pediatric Radiology.
With 4 Spiral-CT scanners and 6 MRI systems, which are available for emergency patients 24 hours a day, more than 80.000 patients are examined each year. 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 assessment of breast lesions, using mammography, sonography and MR-mammography. In order to exclude or assess breast 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 surgery.
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 pediatric uroradiology, oncology, diagnostics of skeletal age and pediatric malformations.
In the section of Experimental Radiology new techniques of MR-spectroscopy and MR-imaging are developed, with a special focus on functional cardiovascular and thoracic examinations.
The Institute of Radiology offers a postgraduate training in Radiology including the subspecialties Pediatric Radiology and Neuroradiology.

Major Topics of Research

CT and Peritoneal Tumors
(W. Kenn, R. Kickuth, J. Pelz, C. Duhr)

The new therapeutic procedure of HIPEC has significantly improved the prognosis of metastatic peritoneal tumors. An important prerequisite is the precise location and assessment of extent of the tumor nodules inside the abdomen. For that aim the research group concentrates on the improvement of CT techniques and their clinical evaluation.

Würzburger Emergency Room Algorithm (sliding gantry MSCT)
(W. Kenn, P. Knödler, T. Wurmb, H. Jansen)

Since 2004 the sliding gantry MSCT technology has been established in the emergency room for an optimal supply for patients with a polytrauma. A new diagnostic algorithm integrates early multislice computed tomography as the primary diagnostic tool. The group is working on an extensive retrospective analysis of polytrauma data since 2004 to evaluate the influence of whole body MSCT on the outcome of patients with major trauma.

Assessment of Soft Tissue Damage after Minimal Invasive Hip Replacement
(W. Kenn, M. Luedemann, U. Nöth)

In recent years, minimal invasive hip replacement is increasingly being used. The post-operative soft tissue damage of these minimal invasive techniques is a matter of discussion. The group is working on a MRI based algorithm to measure the muscle damage after minimal invasive hip replacement assessing changes in muscle cross-sectional area and fatty infiltration of the muscles.

Basic Research and Clinical Investigation of Diffusion Weighted MR Imaging
(W. Machann, H. Neubauer, T. Pabst)

Diffusion weighted imaging (DWI) is a new aspect in the algorithm of diagnostic imaging. Basic research and clinical investigations concerning DWI is performed at a field strength of 1.5 T and 3.0 T in the areas of abdominal and head and neck imaging. Special topics are the evaluation of the clinical value of DWI for neoplasms of the oropharynx, the liver, the kidneys and the gastrointestinal tract (Fig. 1). Additional topics are the evaluation of DWI in Crohn´s disease and colorectal cancer.

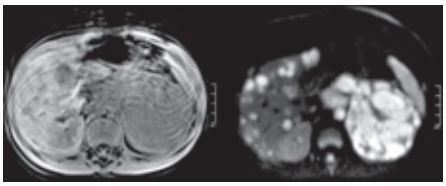

Fig. 1: Child with a nephroblastoma of the left kidney. Liver and lymph node metastases are present. The bad clinical condition of the child, limited compliance with breath-hold T1w imaging, causing severe motion artefacts (left image). Free-breathing diffusion-weighted MRI allows better delineation of the tumorous lesions (right image).

MRI of the Lung
(M. Beer, M. Beissert, A. Fischer, H. Köstler, T. Pabst, C. Ritter, D. Stäb, C. Wirth)

Improvements of morphologic characterization as well as implementation of new functional assessment methods are aims of several clinical investigations. 2D and 3D methods allow the detection of pulmonary perfusion with or -ideally- without contrast agents. Oxygen-enhanced functional lung imaging enables the assessment of pulmonary ventilation. Current clinical studies focus on patients with cystic fibrosis as well as previous preterm patients with chronic lung disease (BPD). Furthermore, optimized MRI protocols are developed for patients with chronic obstructive lung disease within a government-funded research project (BMBF program) in cooperation with the department of Experimental Physics 5 (Biophysics), University of Würzburg, Germany. Finally, diffusion-weighted sequences and late enhancement techniques are investigated for potential use for interstitial lung disease

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

The relationship between myocardial edema, perfusion deficit and tissue necrosis secondary to acute myocardial infarction is investigated within the framework of government-funded research projects (DFG/IFB/CHFC programs). One focus relies on imaging techniques for detection of myocardi-

al haemorrhage and of metabolic alterations. ^{1}H-MR-Spectroscopy (MRS)-protocols are implemented for detection of myocardial steatosis as a negative predictive factor. Imaging techniques that visualize endothelium-mediated vasoreactions are being investigated within further government-funded research projects (DFG programs). Finally, real-time imaging techniques of cardiac function are developed and evaluated in several studies to assess, whether they allow non-breathhold cardiac imaging (Fig. 2).

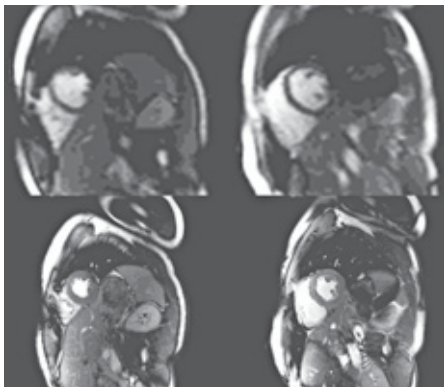

Fig. 2: Application of CAIPIRINHA to in vivo SSFP real-time (upper row) and segmented cine (lower row) imaging of the human heart. For both, reconstructed images of the two simultaneously excited slices are displayed.

Pediatric Radiology
(M. Beer, H. Neubauer, C. Wirth)

Multidisciplinary projects address the role of high-resolution whole-body MR-imaging techniques, including diffusion-weighted imaging, for the assessment of inflammatory and malignant diseases as well as for musculoskeletal disorders. Diagnostic aims are the early detection of pathological lesions and sensitive evaluation of therapeutic regimes without any radiation exposure. The relationship between pulmonary and musculoskeletal involvement is investigated by dynamic 31P-MR-Spectroscopy in children with cystic fibrosis using an in-house built MR-compatible ergometric device. Ultrasound-based elastography as a new functional diagnostic tool is evaluated in several clinical studies comprising children with lymph node enlargement, thyroid inflammation and hepatic steatosis/fibrosis/cirrhosis. The clinical impact of MR-urographic sequences (MRU) for determination of kidney function is investigated in cooperation with the Children's Hospital of Philadelphia. Conventional scintigraphy serves as the gold-standard in comparison to MRU data (Fig. 3).

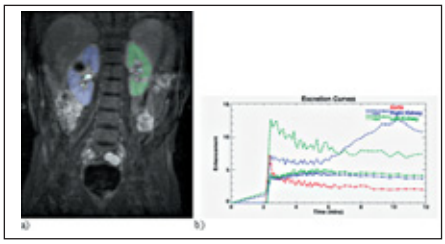

Fig. 3: Functional MR-urography: Segmentation of both kidneys and ureters (a) and calculated excretion curves (b) in a patient with compensated right-sided renal obstruction and a parenchymal cyst.

MR Mammography
(H. Köstler, Th. Pabst, 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-Mammography. The main focus lies on the development of high-resolution MR-techniques to detect smallest carcinomas/DCIS at the earliest possible stage without any radiation exposure. New acquisition strategies for magnetic resonance images like the diffusion weighted sequences and MR-Spectroscopy are developed and investigated systematically for their potential clinical use.

New Developments in MR-measurements
(M. Beer, H. Köstler, C. Ritter, M. Zeller)

In a DFG funded project the image quality of magnetic resonance images is improved by the new density weighted acquisition strategy. This technique is applied to MR real time imaging of the cardiac function and to MR-cholangiography.

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

Investigational key aspects in the interventional radiological field are the following:
Treatment of PAD with special focus on the therapy of bent artery segments (distal superficial femoral artery, popliteal artery segments P1 and P2). In this setting, a novel stent design is evaluated that is primarily used in bailout situations. Feasibility studies in patients with chronic critical limb ischemia have been completed. An evaluation of stent fractures after implantation in bent artery segments is planned. Participation in a multicenter trial, anticipated for 2012/2013, is scheduled.
Totally implantable, central venous port systems: technical success and rate of complications with a special focus on forearm systems. Clinical evaluation of novel systems (forearm- and pectoral port systems) specifically designed for high-pressure injections (e.g., CT/MRI). Quality-of-life evaluations in patients with port systems in daily care.

Ultrasound of the Kidneys and Adrenal Glands with Ultrasound Contrast Agents, Ultrasonography of Lymph Nodes
(D. Klein, F. Wolfschmidt, B. Petritsch)

Ultrasound examinations of the liver with ultrasound contrast agents are routinely performed. Studies in cooperation with the Department of Urology and Internal Medicine evaluate the contrast behavior in renal and adrenal tumors to improve a further differentiation of the entity / dignity. Another focus is the assessment of lymph nodes in patients with malignant melanoma. Whether a differentiation of metastases of melanomas is possible by the „stiffness" of the lesion (elastography) is investigated in clinical studies.

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

Gutberlet M, Roth A, Hahn D, Köstler H. (2011) Optimized Density-Weighted Imaging for Dynamic Contrast-Enhanced 3D-MR Mammography J. Magn. Reson. Imaging 33:328 – 339.

Beer M, Stamm H, Machann W, Weng A, Goltz JP, Breunig F, Weidemann F, Hahn D, Köstler H. (2010) Free breathing cardiac real-time cine MR without ECG triggering Int J Cardiol 145:380 – 382.

Machann W, Breunig F, Weidemann F, Sandstede J, Hahn D, Köstler H, Neubauer S, Wanner C, Beer M. (2011) Cardiac energy metabolism is disturbed in Fabry disease and improves with enzyme replacement therapy using recombinant human galactosidase A European Journal of heart failure 13:278 – 283.

Duhr CD, Kenn W, Kickuth R, Kerscher AG, Germer C-T, Hahn D, Pelz JOW. (2011) Optimizing of preoperative computed tomography for diagnosis in patients with peritoneal carcinomatosis. World Journal of Surgical Oncology 9:171.

Kerstan A, Albert C, Klein D, Bröcker EB, Trautmann A. (2011) Wasp venom immunotherapy induces activation and homing of CD4(+)CD25(+) forkhead box protein 3-positive regulatory T cells controlling T(H)1 responses. J Allergy Clin Immunol. 127:495-501.

3.15.1 Division of Neuroradiology

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Mission and Structure

The independent Department of Neuroradiology is integrated into the Head Clinic of the University Hospital Würzburg and was founded in 1977. All modern diagnostic exams and therapeutic interventions available in the field of neuroradiology are practiced at the technically highest standards. 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 and -nuclear support, one 1.5T MR scanner operated exclusively by the department and one 1.5T MR scanner operated in alternation with the Pediatric Radiology.
Staff: 3 senior physicians, 5.5 residents, 9.5 medical technicians, 2 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 our University Hospital.
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 Division of Pediatric Neurosurgery and 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 implants to limit the surgical risks and to increase the predictable benefits, respectively.

Major Research Interests

Neuroimaging
(B. Alkonyi, G. Homola, A. Schütz)

As part of the Comprehensive Heart Failure Centre (CHFC) Würzburg we focus on research and treatment of heart failure. Structural and functional consequences of chronic heart failure in the brain are investigated in animal models and long-term studies. The project area F2 is a joint venture with the neurology and cardiology. Research includes innovative imaging methods without applying contrast agents (ASL), as well as diffusion and perfusion protocols. Voxel-based statistics and volumetric analysis of individual brain regions are also performed. In cooperation with the MRB quantification of MR relaxation times for improved diagnosis of neurodegenerative disorders is being prepared.

Neurooncology
(M. Warmuth-Metz, C. Várallyay)

The department acts as the neuroradiological reference site to all German multicentric, 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 international 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.

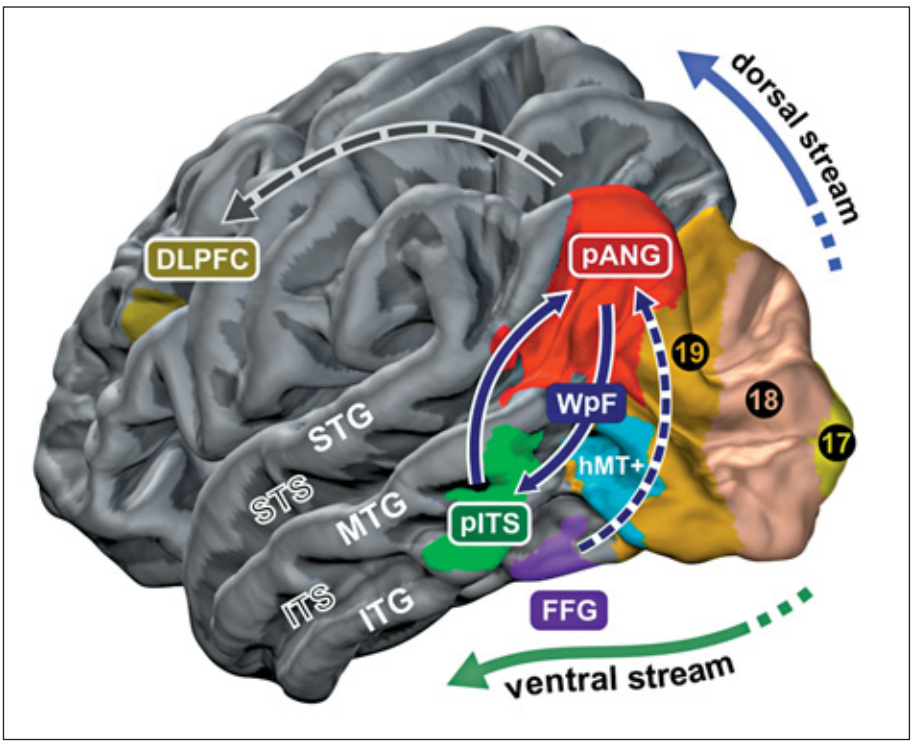

Fig. 1: 3D model illustrating the facial age processing network.

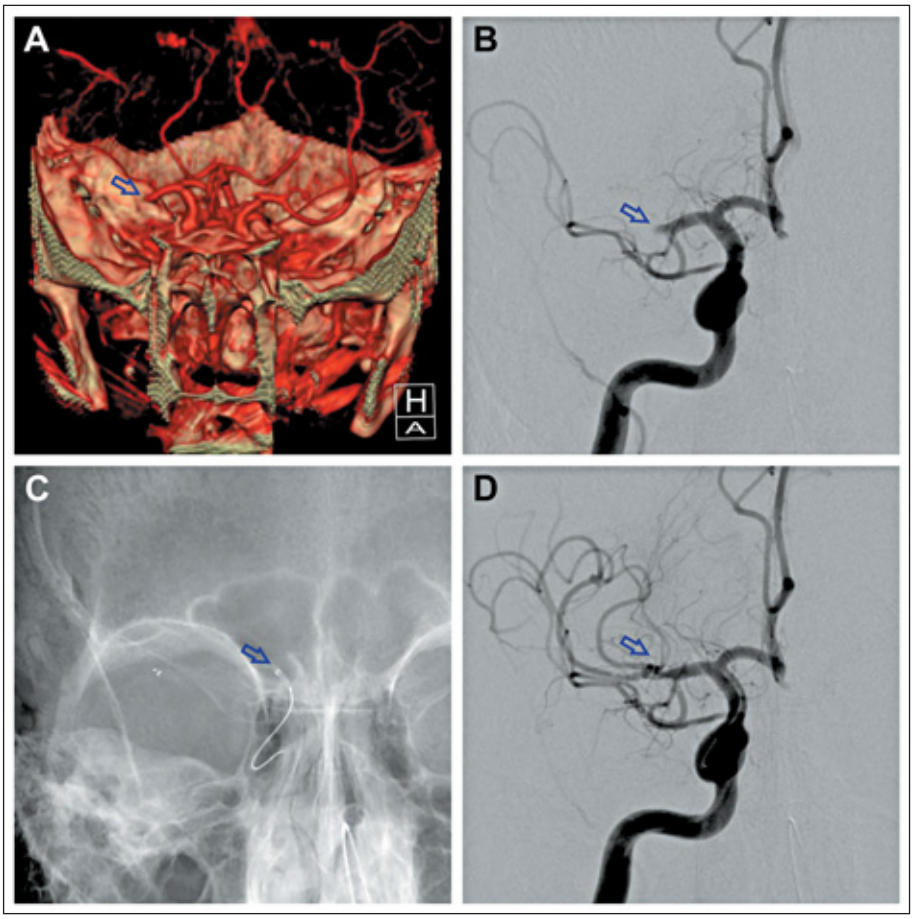

Fig. 2: Acute stroke. (A) Occlusion of the M1 segment of the middle cerebral artery in the 3D-CT-angiography, (B) in the DSA. (C, D) „Stentriever" in position to capture the thrombus. After thrombus extraction complete recanalization of the middle cerebral artery is enabled.

Pediatric Neuroradiology
(M. Warmuth-Metz)

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

MR Imaging of Neurovascular Diseases
(C. Várallyay)

Animal experiments and clinical studies on the detection of peripheral nerve injuries, strokes, inflammatory diseases of the CNS and denervated muscles.

Functional and Diffusion-MR-Imaging
(G. Homola)

In cooperation with the Depts. of Neurosurgery, ENT, Neurology and Psychiatry. as well as the Dept. of Neuroradiology of the University of Heidelberg. Exploration of the link between structure and function in the human brain on the basis of cognitive facial age processing by probabilistic tractography of diffusion data and by calculating spatial cross-correlations as well as creating minimum intersection maps between activation and connectivity patterns. Characterization and quantification of neuronal resting-state networks by fMRI. Examination of the effects of acute alcohol ingestions and dehydration 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 department participates in the university education of students by conducting lectures and courses within the radiological and neuroradiological teaching. The head of the department is authorized to full neuroradiological training (3 years).

SELECTED PUBLICATIONS

Weinstein JS, Varallyay CG, Dosa E, Gahramanov S, Hamilton B, Rooney WD, Muldoon LL, Neuwelt EA. (2010) Superparamagnetic iron oxide nanoparticles: diagnostic magnetic resonance imaging and potential therapeutic applications in neurooncology and central nervous system inflammatory pathologies, a review. J Cereb Blood Flow Metab. 30:15-35.

Schumacher M, Schmidt D, Jurklies B, Gall C, Wanke I, Schmoor C, Maier-Lenz H, Solymosi L, Brueckmann H, Neubauer AS, Wolf A, Feltgen N. (2010) EAGLE-Study Group. Central retinal artery occlusion: local intra-arterial fibrinolysis versus conservative treatment, a multicenter randomized trial.

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von Bueren AO, von Hoff K, Pietsch T, Gerber NU, Warmuth-Metz M, Deinlein F, Zwiener I, Faldum A, Fleischhack G, Benesch M, Krauss J, Kuehl J, Kortmann RD, Rutkowski S. (2011) Treatment of young children with localized medulloblastoma by chemotherapy alone: results of the prospective, multicenter trial HIT 2000 confirming the prognostic impact of histology. Neuro Oncol. 13:669-79.

Komakula S, Warmuth-Metz M, Hildenbrand P, Loevner L, Hewlett R, Salzman K, Couldwell W, Lin CT, Osborn A. (2011) Pineal parenchymal tumor of intermediate differentiation: imaging spectrum of an unusual tumor in 11 cases. Neuroradiology. 53:577-84.

Warmuth-Metz M, Blashofer S, von Bueren AO, von Hoff K, Bison B, Pohl F, Kortmann RD, Pietsch T, Rutkowski S. (2011) Recurrence in childhood medulloblastoma. J Neurooncol. 103:705-11.

3.16 Department of Nuclear Medicine

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Mission and Structure

The Department of Nuclear Medicine employs unsealed radioactive tracers for research purposes, education, diagnosis and therapy of a multitude of diseases. Using 1 state of the art PET/CT system, 1 PET, 3 gamma cameras, 1 SPECT/CT, 3 ultrasound devices, 2 bone densitometers and 1 whole body counter, more than 13,000 examinations are performed annually. In addition, more than 800 in-patients are treated with radioactive isotopes, mainly for thyroid disorders. Approximately 120 out-patients receive treatment for chronic inflammation of joints. The Division of Experimental Nuclear Medicine and Radiochemistry, headed by Prof. Dr. S. Samnick, operates a cyclotron to produce the PET-radioisotopes ^{18}F, ^{11}C, ^{15}O, ^{13}N and ^{124}I in a fully equipped GMP-certified radiochemical/radiopharmaceutical laboratory. The interdisciplinary PET/CT center (IPZ), the IZKF, IFB and SFBs, are networked for close cooperation in pre-clinical research. Full nuclear medicine specialist training is available.

Major Research Interests

Experimental Nuclear medicine - Radiochemistry/Radiopharmacy

Innovative radiopharmaceuticals for imaging and therapy are being developed and evaluated. Starting point is the selection of tracers and the organic synthesis of suitable radionuclide precursors for labelling of biomolecules. Such tracers are being investigated in-vitro (e.g. in human cell culture), ex-vivo using autoradiography, as well as in-vivo using animal models and preclinical imaging modalities (μ-PET and μ-SPECT) in the ZEMM. If usefulness is proven, they are candidates for clinical testing in cooperation with oncology, cardiology, neurology, psychiatry and others. GMP conformal production of ^{18}F-FDG, ^{18}F-FET, ^{11}C-Cholin, ^{18}F-FLT and ^{68}Ga-DOTATATE has been established at the IPZ. Other clinically relevant tracers are currently under evaluation. Projects within this scope received grants from DFG, IZKF, Deutsche Krebshilfe, BMBF and from coordinated research programs (SFB 688 and CHFC Würzburg). In cooperation with the Dept. of Endocrinology (Med. Klinik I), the SPECT tracer ^{123}I-Iodometomidate was evaluated. It shows a highly specific and prolonged adrenocortical uptake. Metabolically stable derivatives of iodometomidate were developed and filed for patent application including further PET tracers for the clinically challenging differential diagnosis of primary hyperaldosteronism.

Pre-clinical imaging/Cardiology

μ-PET and μ-SPECT are non-invasive imaging modalities which are employed in-vivo to evaluate new radiotracers developed by the radiochemistry working group. A special focus is cardiac imaging, which is chaired and enforced by Prof. Dr. T. Higuchi and the CHFC Würzburg. Numerous projects were initiated addressing cardiac innervation or apoptosis imaging. Investigations were continued including regulation of the cardiac metabolism in type 2 diabetes as well as studies of myocardial remodelling after infarction. The significance of transmembrane protease fibroblastic activation protein which is responsible for wound healing and fibrotic reaction after myocardial infarction was also assessed. In addition, small animal PET scans using stroke- and neurotrauma models were carried out. Animal models of solid cancers and lymphoma are also studied. In-vivo data are verified using autoradiography. In cooperation with cardiology, uptake of the radiotracers ^{18}F-FDG and ^{68}Ga-DOTATATE in large vessels was evaluated in a rodent model to study their suitability to non-invasively characterize inflammatory reactions.

Diagnosis and Therapy of Thyroid Disorders

Thyroid cancer is a major focus of clinical research, which is carried out in cooperation with the Comprehensive Cancer Center Mainfranken and an incidence registry. Long-term collaboration with partner institutions in Minsk and Nagasaki exists regarding improvement of diagnosis, therapy and follow-up after radiation induced thyroid cancer in children. The department participates in drug approval studies of new medications for the treatment of thyroid carcinoma. The Würzburg center for thyroid diseases (WSZ) was recently initiated by Prof. Buck and Prof. Schneider. The consortium supports visibility and interdisciplinary research, leading to an improved understanding of the disease, new therapeutic approaches, prevention and rehabilitation. Research activities will be extended to the use of PET isotopes for imaging and dosimetry of differentiated thyroid cancer, including production of the isotope ^{124}I. Using ^{124}I-PET/CT, it is expected to enhance the level of evidence for radioiodine remnant ablation in low risk patients with differentiated thyroid carcinoma in a randomised clinical trial.

Medical Physics/Radiation Safety

The main scientific research areas comprise radiation protection, internal dosimetry in nuclear medicine and the combination of biodo-

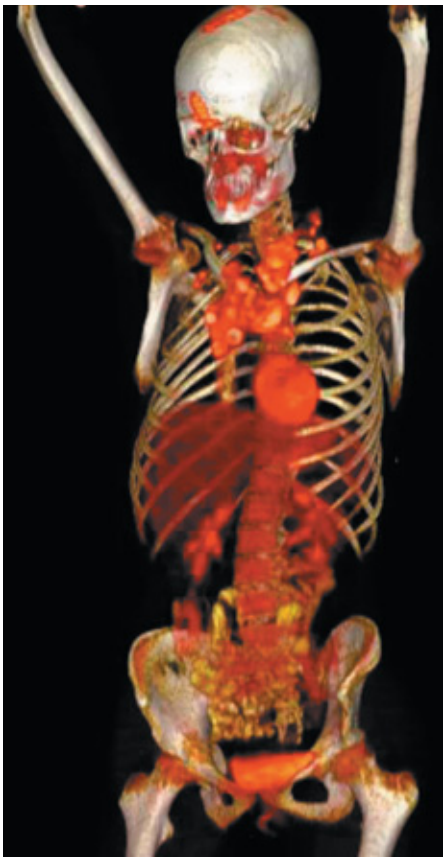

Fig. 1: Hybrid imaging modalities such as 18F-FDG-PET/CT allow the non-invasive visualization of tumors in the entire body. The figure shows a 3D view of a young female with Hodgkin`s disease and cervical / mediastinal lymphoma manifestations.

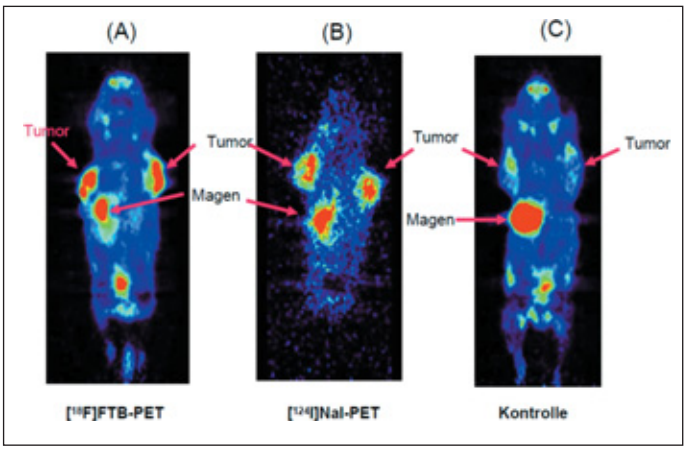

Fig. 2: µ-PET using 18F-fluortetrafluorborate (18F-FTB) as the tracer. Specific retention in hNIS expressing tumors transplanted in nude mice: (A)+(B) high specific uptake of 18F-FTB and 124I-NaI; (C) low uptake 18F-FTB in low hNIS expressing tumors (control).

simetric methods and physical dosimetry as well as improvement of dosimetric methods for radioiodine therapies of thyroid cancer and other experimental therapies. The following institutions participate in the EU funded 7th framework project "Dosimetry and Health Effects of Diagnostic Applications of Radiopharmaceuticals with particular emphasis on the use in children and adolescents" (www.peddose.net): BfS, University of Gent, INSERM and, as coordinator, the European Institute for Research and biomedical Imaging (EIBIR). It comprises data assessment for dose coefficients, and methods for dose reduction using analyses of hybrid imaging systems (i.e. 3D-PET, time-of-flight PET/CT and iterative reconstruction methods). Since June 2011, the BMBF funded research project NUKDOSE is carried out together with the University of Ulm and the BfS. In this project, solutions for methodological problems in patient-specific dosimetry in the context of targeted radiotherapy are being developed. The main focus is to identify the best suited isotopes for targeted radiotherapy such as 131I, 111In/90Y, and 177Lu. In cooperation with the Institute for Radiobiology of the Armed Forces, induction, persistence and disappearance of DNA-lesions will be investigated using gamma-H2AX-foci regarding scope and time of the radioiodine exposure.

Oncology

For clinical research, biomarkers of glucose utilization (^{18}F-FDG), lipid metabolism (^{11}C-choline) and protein biosynthesis / amino acid transport (^{18}F-FET, ^{11}C-MET) are available. For non-invasive diagnosis of neuroendocrine tumors, Ga-68-DOTATATE was established as surrogate marker of somatostatin receptor expression (SSTR). The spectrum of radiopharmaceuticals suitable for radionuclide based therapies was extended to innovative radiopeptides and radioimmunotherapies. SSTR-directed radionuclide therapies using ^{177}Lu-DOTATATE represents an effective treatment option for patients with neuroendocrine cancers and other neoplasias characterized by an overexpression of hormonal receptors. In patients with advanced stage adrenocortical carcinoma, a pilot trial was performed using ^{131}I-iodometomidate as therapeutic compound. Based on the high specificity of the tracer and rapid metabolization in-vivo, high doses of radioactivity up to 20 GBq ^{131}I-iodometomidate can be administered with high therapeutic effectiveness and only minor side effects.

Neurology/Psychiatry/Child- and Adolescent Psychiatry

In cooperation with the Dept. of Neurology, patients with Parkinson`s disease and atypical Parkinson's syndrome are investigated with dopamine transporter scintigraphy. Findings at functional imaging are compared to results of clinical-neurological investigations. In cooperation with the Dept. of Neurology of the Saarland University (Prof. Fassbender, PD Dr. Spiegel), a clinical study was initiated to quantify cerebral nicotinic and cholinergic function in patients with Parkinson's disease. The major aim of the study is to assess the contribution of the affection of the cholinergic system to the clinical phenotype. Automated parametric evaluations were introduced for the diagnosis of dementia.

Neuromuscular-Skeletal System

Peripheral quantitative computed tomography was successfully employed to assess biomechanics of the bone in an interdisciplinary cooperation with the Department of Surgery II and the Orthopaedic Center for Musculoskeletal Research, Experimental and Clinical Osteology.

WHO REMPAN-Center

The Collaborating Center for Radiation Emergency Medical Preparedness and Assistance (http://www.rempan.de) within the WHO REMPAN network was re-accredited in 2009 for another 4 years and continued the annual German wide survey of hospitals qualified in the management of nuclear accidents. The survey results of 2010 and 2011 documented in a database form the basis of a web-based allocation system for radiation accident patients to appropriate hospitals. Within the research project "education and advanced training of physicians in radiation accident management", a curriculum "prehospital radiation accident management" was developed, and tested and evaluated in 2 pilot courses.

Teaching

In addition to routine teaching, 14 complementary courses were offered to students as well as pilot courses „training in the management of radiation accidents". The 3rd International REMPAN seminar „radiation emergency medicine in research and practice" continued the seminar series in 2010 in cooperation with the WHO REMPAN center Moscow.

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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 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
(Head of workgroup: Prof. Dr. Otto Sauer)

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 and fast application methods like volumetric arc therapy (VMAT), - development of noncoplanar IMRT and VMAT-techniques, - 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 novel Hsp90 inhibitors as radiosensitizers
(Project supervisor – Priv.-Doz. Dr. Tcholpon Djuzenova)

Heat shock protein 90 (Hsp90) is a molecular chaperone that has been found overexpressed in many human cancers. Furthermore, it has been shown that in various tumor models Hsp90 contributes to malignant growth. Hsp90 plays a critical role in both the stabilization and regulation of a wide variety of proteins, including those related to radioresistance. Inhibition of Hsp90 may therefore provide a strategy for enhancing the radiosensitivity of tumor cells.
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 (IR) in human cells.
In order to enhance the cytotoxicity of radiation, two novel inhibitors of Hsp90, NVP-AUY922 and NVP-BEP800 (Novartis Pharma AG) were added to the four established cell lines originated from different tumor entities, including lung carcinoma A549, fibrosarcoma HT 1080, and two glioblastoma cell lines SNB19 and GaMG. Drug-treated and irradiated cells were then analyzed by cell and colony counts, cell cycle progression, expression of Hsp90, Hsp70, Akt, survivin, cleaved caspase 3, PARP, p53, as well as by the DNA damage analysis measured by histone H2AX and alkaline Comet assay. We found that NVP-AUY922 and NVP-BEP800 enhanced the radiotoxicity in all tested cell lines if cell and colony counts were used as the end-points. In all tested cell lines, the expression of histone H2AX, a marker of DNA double strand breaks, after combined drug-IR treatment was higher and its decay rate was slower than those after each single treatment modality. The

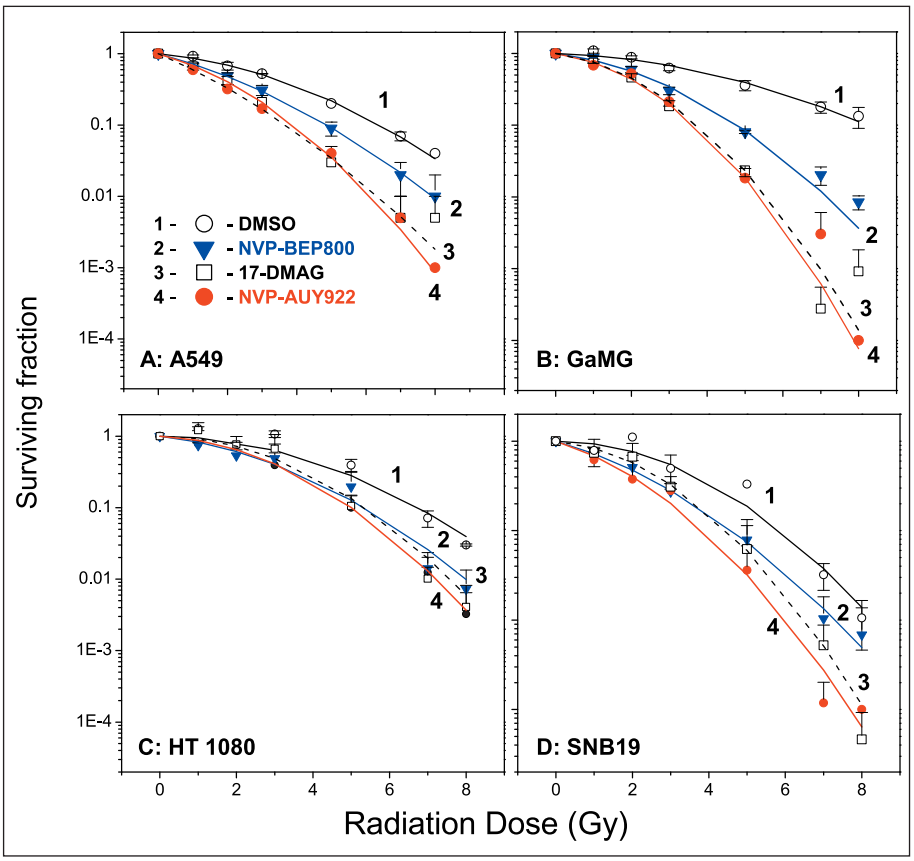

Fig. 1. Clonogenic abilities of tumor cell lines as functions of radiation dose and drug exposure. Control (DMSO treated, empty circles) and drug-treated (NVP-AUY922 – red circles; NVP-BEP800 – blue triangles; 17-DMAG – squares) cells were irradiated with single IR doses ranging between 1 and 8 Gy. After irradiation, cells were plated in complete growth medium and incubated under standard conditions. Two weeks later, colonies containing at least 50 cells were scored as survivors [Stingl et al., 2010].

levels of the anti-apoptotic proteins Raf-1 and to a lesser extent of Akt were reduced by the Hsp90 inhibitors in all tested cell lines. In addition, drug-IR treatment resulted in impaired cell cycle progression, as indicated by S-phase depletion and G2/M arrest (Stingl et al., 2010). In summary, the finding that both NVP-AUY922 and NVP-BEP800 strongly enhance the in vitro radiosensitivity of tumor cells may have important implications for the radiotherapy of tumor patients.

Clinical trials and quality assurance

The department is responsible for the conception and realisation of radiation therapy in national and international therapy studies for head and neck tumours and lung cancer.
Major contributions concern randomized studies for organ preservation in Larynx/ Hypo-pharynx Cancer (Delos 2) and in concurrent radio-chemotherapy in advanced lung cancer (GILT-CRT). The department is leading a study on dose escalation for spine metastases by means of high precision radiation delivery (Synergy Consortium). The department head is also heading the Ärztliche Stelle § 83 StrSCHV of the Bavarian State Medical Chamber and is member of the Radiation Protection Commission at the BMU.

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

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

Main Research Interests

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

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

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

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

Inner ear biology
(R. Mlynski, K. Rak, J. Völker in cooperation with the institute of neurobiology, M. Sendtner)

Effects of reversible and irreversible ototoxical substances on the active cochlear amplifier system to further investigate pathophysiological processes in inner ear diseases; in vitro and in vivo investigations of neurotophic 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 transduce to 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.

Stem cell research in ORL
(A. Radeloff, K. Rak, R. Mlynski)

Detection of adult stem cells in the inner ear and the auditory pathway. Animal experiments using stem cells in the damaged hearing system.

Pedaudiological tests and newborn hearing screening
(W. Shehata-Dieler, D. Ehrmann, R. Keim, in cooperation with K. Wermke)

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

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

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

Experimental audiology
(M. Cebulla, R. Keim, W. Harnisch)

Further development of diagnostic tools for objective frequency specific measurement

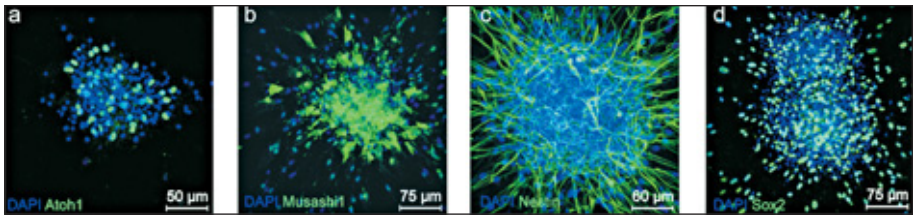

Fig. 1: Neuronal stem cells, dissected from the Nucleus cochlearis of 6 day old rats, show the formation of neurospheres after 4 week sin culture. The neurospheres are stained with neuro-specific stem cell markers. (K.Rak).

of the absolute threshold of hearing, standardisation of different methods of acoumetry, investigations in the fine structure of responses to click-stimuli in comparison to transit time corrected stimulation.

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

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

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

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

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

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

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

Establishment of stabile cartilaginous structures with different scaffold materials.

Functional electrostimulation of the larynx
(R. Hagen, W. Harnisch in cooperation with the university department of ORL Jena, Germany and Innsbruck, Austria)

Development of a laryngeal pacemaker for treatment of vocal cord paralysis.

Use of nanomaterials in tumor therapy
(S. Hackenberg, C. Ginzkey, A. Scherzed in cooperation with the institute for tissue engineering and regenerative medicine, H. Walles, institute for functional materials, J. Groll)

Constitution of an interdisciplinary research group for the use of nano-particles in tumor therapy.

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, Ecuador, Peru). Full-time hospitations for consultants.

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Rak K, Wasielewski NV, Radeloff A, Völker J, Scherzed A, Jablonka S, Hagen R, Mlynski R. (2011) Isolation and characterization of neural stem cells from the neonatal rat cochlear nucleus. Cell Tissue Res 343:499-508.

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3.19 Department of Ophthalmology

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Mission and Structure

A staff of 35 physicians and 81 nurses, technicians and scientists cares for approx. 20.000 outpatients and more than 5.000 inpatients annually. In 2010, more than 7.000 surgical procedures and about 1.700 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. Another main focus of the clinic is the department for strabismus and neuroophthalmology, where oculomotor disturbances, childhood eye diseases, and neuroophthalmological disorders are treated both conservatively and surgically. To supplement our services, a cornea bank meeting current and future regulatory requirements has recently been 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.

Major Research Interests

Clinical Research

Research activities focus on the fields of glaucoma, cornea, and retina. New strategies are developed to treat ocular surface disease, recent methods of cornea transplantation are studied, new surgical strategies to lower intraocular pressure (e. g., canaloplasty, see Fig. 2) are evaluated, 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 predisposition is studied for patients with glaucoma and macular degeneration. 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

Cell Biology

Cellular signal integration mechanisms are at the focus of the cell biology lab. Mounting evidence indicates an essential role of biomechanical cues in the regulation of cell differentiation and other cellular functions. Along these lines, the lab studies the influence of tissue elasticity on trabecular meshwork cells in a project funded by DFG. Another project funded by BMBF aims at the development of novel elastic cell culture substrata in a collaboration with Fraunhofer ISC, Würzburg and Mechatronic Research Unit, University of Applied Science Regensburg. It is our goal to gain further insight into glaucoma and scarring pathophysiology and to provide novel tools for regenerative medicine applications.

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.

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 (a) study retinal ganglion cell function, (b) characterize genetically encoded maculopathies, (c) to deter-

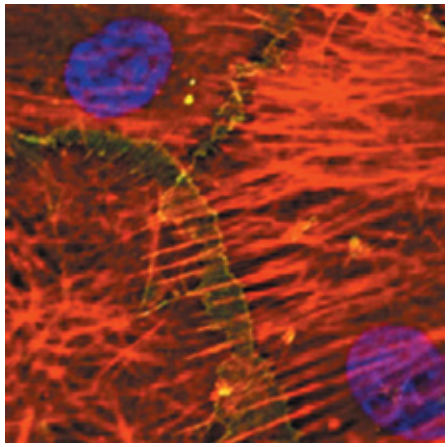

Fig. 1: N-cadherin based cell-cell adhesions (green) connect the actin cytoskeleton (red) of neighboring human trabecular meshwork cells in vitro.

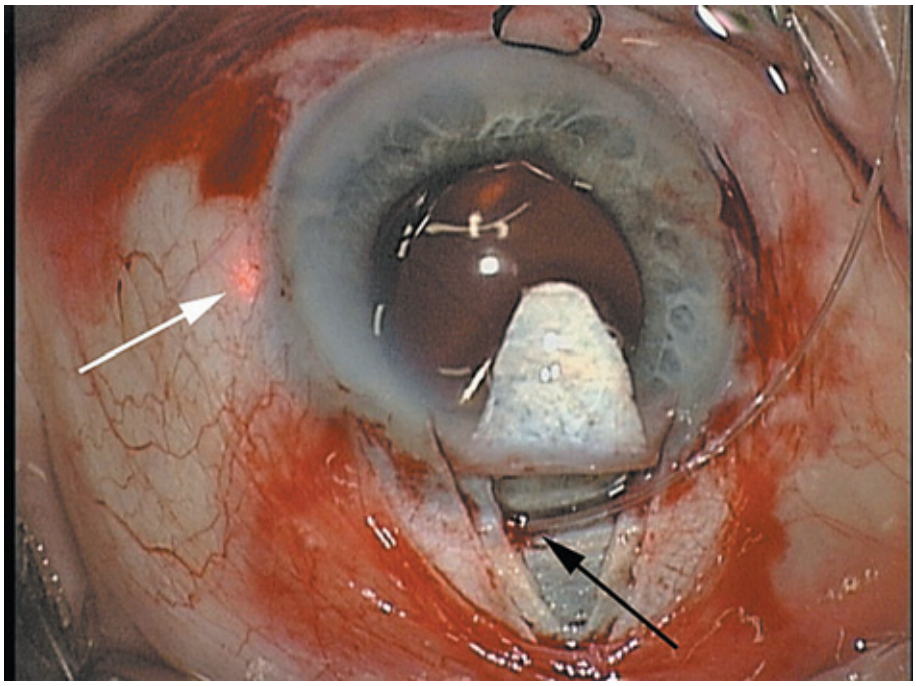

Fig. 2: Intraoperative constellation after opening of Schlemm's canal and after insertion of a micro-catheter (black arrow) into the canal during canaloplasty, a modern glaucoma surgery technique. Some laser light shines through the sclera (white arrow) and illuminates the head of the micro-catheter which allows a fine control of the surgical instrument.

mine retinocortical transmission speed, and (d) to allow an objective estimation of visual acuity with the visual evoked potential.

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.

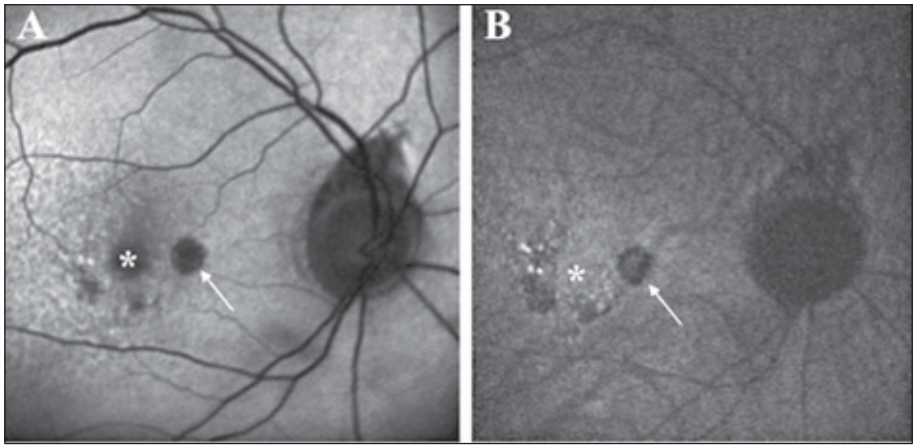

Fig. 3: Fundus autofluorescence after excitation by either blue light (A) or near infrared electromagnetic radiation (B) allows to easily and non-invasively illustrate even small areas of degenerated retinal pigment epithelial cells (arrows). This procedure is best suited for follow up examinations of patients with age related macular degeneration (AMD) oft he dry form and for the diagnosis of macular dystrophies. In this case of a 81 year old female patient with an early stage of a dry AMD, the macula is still preserved.

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3.20 Department of Neurosurgery

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Clinical Focus and Structure

The Department of Neurosurgery employs 29 medical doctors, 3 scientists, 96 nurses and 8 technicians. The clinical wards are comprised of a total of 70 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 5 operating theatres including one OR for outpatients and emergencies. Over the passed 2 years (2010-2011) 3,300 patients were treated surgically and 11,700 patients in the outpatient department. The out-patient clinic offers consultation for all neurosurgical diagnoses in specialized clinics such as brain tumours, degenerative spine and disc disease, pain syndromes, peripheral nerve lesions, pituitary tumours and dysfunction, neurovascular disease, skull base tumours (jointly with Department of ORL) 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 Paediatric 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 ORL 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

Neuro-oncology
(G. Vince, M. Löhr, C. Matthies)

The Deparment treats a large patient population with primary brain tumours. All treatment protocols have been certified by the Comprehensive Cancer Center Mainfranken. Tumour samples are obtained at surgery for primary cell cultures and are fzoen in liquid nitrogen. They form the basis for the research into specific molecular characteristics in the Tumour Biology Research Laboratory. Several experimental animal models, cell lines and functional assays have been established for investigation of tumour immunology, tumour cell invasion and cell cycle regulation. Tumour biology and mutation analysis in benign pathologies such as schwannomas and meningiomas, are investigated in national and international cooperations. Cell de-differentiation, adhesion molecules, tumour invasion, promotors of apoptosis are targets of investigation in benign tumour cell cultures are compared for different clinical courses despite identical histology. A basis for these laboratory investigations are large regular outpatient clinics for patients with skull base tumours, sporadic and genetically based vestibular schwannomas and meningiomas (neurofibromatosis types 1 and 2).

Functional Microsurgery & Neurostimulation
(C. Matthies)

Functional microsurgery refers to a microsurgical technique guided by information from continuous neurophysiological monitoring to treat 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 tumour 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 ORL. The current study shows – different to previous international reports – that also in patients with large tumours 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 and increasing rates of speech discrimination. This option applies for tumour patients

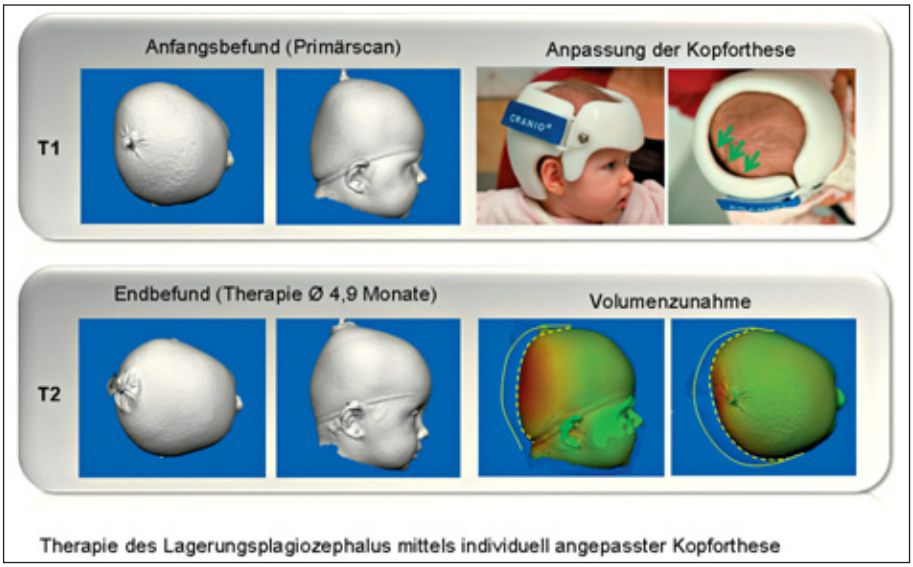

Fig. 1: Based on a radiation-free stereo-photo-grammetric method skull deformities are documented in a three-dimensional mode and treated by an individually calculated, produced and adapted skull orthesis.

as well as for others with post-infectious deafness or with inborn malformations.
In cooperation with the Departments of Neurology, Neuroradiology and Psychiatry patients with movement disorders (Parkinson's Disease, Tremor, Dystonia) are treated by high frequency stimulation therapy. Refined electrode placement is guaranteed by precise pre-operative imaging and target planning as well as intra-operative micro-recording and micro-stimulation tests in the thalamus, pallidum or subthalamic nucleus. Besides these established indications for deep brain stimulation, further patients are carefully selected, investigated and treated by stimulation in previous ischemic brain lesions and life threatening dystonic storms. A developing topic is the combination of neuroprotective and regenerative factors.

Neurovascular Disease
(J.-Y. Lee, E. Kunze, T. Westermaier)

In subarachnoid haemorrhage the cell-biological mechanisms of early brain injury and cerebral vasospasm are investigated with an aim towards developing new therapies and monitoring cerebral oxygenation and brain metabolism. Vascular dynamics are controlled by invasive monitoring, transcranial Doppler sonography and perfusion imaging during surgery and neurosurgical intensive care as well as in the experimental setting in animal models. These approaches are combined with electrophysiological techniques in order counteract cerebral vasospasm. 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 neuro-protection 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 patho-physiological cascades after traumatic brain injury.

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.

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3.21 Department of Neurology

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Mission and Structure

The in- and outpatient services of the Department of Neurology cover the entire spectrum of neurological disorders. In October 2010, Prof. Jens Volkmann succeeded Prof. K. Toyka as chairman of the department. The inpatient service has 86 beds including an 8 bed Stroke Unit and a 10 bed Neurological Intensive Care Unit serving over 4000 in-patients per year. The outpatient department provides for over 9000 out-patient visits per year and additionally runs an extensive in-house consulting service. In November 2011, an interdisciplinary neuro-geronto-psychiatric outpatient clinic ("day care clinic") was established together with the Department of Psychiatry which takes care of up to 18 mobile patients with neuropsychiatric disorders on a daytime basis. The neurological focus lies on the multi-disciplinary treatment of patients with advanced Parkinson´s disease. In December 2011, an emergency room for acute neurological and neurosurgical admissions was opened. The new W2-professorship for stroke medicine was filled with Priv. Doz. Dr. Kleinschnitz in November 2011.

The special expertise of the Neurological Department includes Parkinson´s disease and other movement disorders including treatment by deep brain stimulation, neuro-immunological diseases (multiple sclerosis, autoimmune neuromusclular disorders), degenerative neuromuscular disorders including an integrated nerve/muscle pathology service, cerebrovascular disorders, epilepsy, pain and neurointensive care. The Department has integrated a Division of Clinical Neurophysiology, a Clinical Research Group for Multiple Sclerosis and Neuroimmunology, a clinical laboratory for neurochemical and cerebrospinal fluid analysis, and specialized experimental laboratories including a Division for Developmental Neurobiology (led by Prof. R. Martini) allowing translational research from in vitro and in vivo disease models to the bedside. The Department has 36 full time academic members, 88 nursing staff members, 23 technicians and 10 staff members in in administration and special services. In addition 13 academic positions are supported by extramural grants. The Department contributes to the Sonderforschungsbereiche (Cooperative Project Center Grants) #581 and #688, the ERA-Net Neuron Consortium "DBSPhysiol", the Interdisciplinary Center for Clinical Research, and the Chronic Heart Failure Center Würzburg funded by the Federal Ministry of Education and Research (BMBF).

Major Research Interests

Parkinson´s Disease and Neurodegenerative Disorders
(J. Volkmann, F. Steigerwald, S. Klebe in cooperation with C. Matthies, Department of Neurosurgery)

Clinical studies to evaluate efficacy and safety of deep brain stimulation in movement disorders; imaging studies to define optimal target points for neurostimulation; intraoperative microelectrode recordings to disclose normal function and pathophysiology of basal ganglia; assessment of mechanisms underlying deep brain stimulation in animal models of movement disorders; biomarkers in Parkinson´s disease.

Multiple Sclerosis and Neuroimmunology (Clinical Research Group) including Neuroimaging and CSF-Laboratory
(G. Stoll, C. Kleinschnitz, M. Buttmann, A. Weishaupt)

Neuroimaging: Development and evaluation of new methods for in-vivo imaging of neuroinflammation by SPIO/USPIO-enhanced magnetic resonance imaging and $^{1}H/^{19}F$ MR-spectroscopy (cooperation with Prof. P. Jakob, Department of Physics V); pathogenesis of multiple sclerosis and polyneuritis (experimental autoimmune encephalomyelitis and neuritis; transgenic mouse models) focussing on the role of platelets and coagulation factors as mediators of inflammation; molecular mechanisms of disturbances of the blood brain barrier; molecular biomarkers in multiple sclerosis; international treatment trials.

Stroke
(C. Kleinschnitz, W. Müllges, G. Stoll)

Assessment of molecular mechanisms of thrombus formation in experimental cerebral ischemia and the contribution of innate immunity to stroke development ("thrombоinflammation"); development of novel anti-platelet strategies and anticoagulants not affecting hemostasis (cooperation Prof. B. Nieswandt; Rudolf Virchow Center); mechanisms and prevention of brain edema formation in stroke and traumatic brain injury (cooperation Prof. A.L. Sirén,

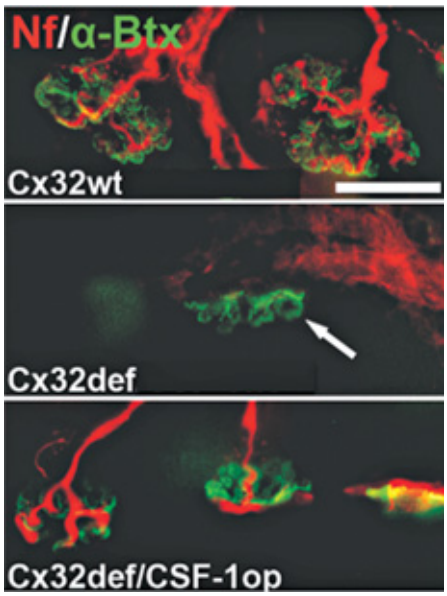

Fig. 1: Pathogenesis and therapy of peripheral nerve degeneration: neuromuscular endplates of a normal mouse (upper panel), a mouse with a hereditary neuropathy without (middle) and with "treatment" (lower panel). Postsynaptic acetylcholine receptors are marked in green, nerve fibres in red. Unexpectedly, mice lacking functional inflammatory cells (macrophages) are protected from genetically induced nerve degeneration (lower panel) (Source: Groh et al., Brain 2011).

Dep. Neurosurgery); functional and cellular stroke imaging using ultrahigh field MRI (cooperation Dep of Physics V); studies on cognitive decline and MRI abnormalities as a consequence of chronic heart failure as member of the Chronic Heart Failure Center, Würzburg); establishment of an interdisciplinary neurovascular board; international treatment trials.

Neuromorphology, Pain Research and Antibody-Associated Neurological Diseases
(C. Sommer, C. Geis, N. Üçeyler, K. Toyka)

Analysis of the 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; improvement of diagnostic procedures in polyneuropathies and small-fiber neuropathies; neuromorphological research on neuropathy pathophysiology; international pain and neuropathy treatment trials; pathophysiology of neurological complications in M. Fabry; pathophysiology of antibody-associated disorders of the CNS (stiff person syndrome, neuromyelitis optica).

Experimental Developmental Neurobiology
(R. Martini)

In the focus is the investigation of pathogenic mechanisms underlying genetically-mediated demyelination and neurodegenerative disorders in the central and 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 the immune system as "disease amplifier", and consequently, immunomodulation emerges as treatment strategy in the respective 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.

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

Neurophysiological examinations in patients with neuromuscular and CNS disorders (> 25,000 examinations per year); coordination of the Interdisciplinary Neuromuscular Center and participation in the Musculosceletal Center of the Würzburg University; development of neurophysiological parameters for the assessment of disease severity and progression in MS and ALS; molecular assessment of disease-modifiers in sporadic and familial ALS (in collaboration with Prof. Sendtner, Institute of Clinical Neurobiology); international treatment trials in ALS.

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.

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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 funded by the Deutsche Forschungsgemeinschaft ("clinical research group Neuroregeneration"). In 2000, it was established as an independent institute at the University Hospital and 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 and other neurodegenerative diseases at the Department of Neurology (Director Prof. J. Volkmann), in order to allow and ensure the transfer of scientific knowledge into clinical applications. Since 2010, the institute has moved to the building E4 (former MSZ), Versbacherstr. 5. Besides a transgenic mouse facility, laboratories for state-of-art confocal and 2-photon-microscopy and cell culture laboratories for primary motoneurons, stem cells and iPS cells are established.

Major Research Interests

Central research interests are studies on the mechanisms of neuronal cell death, the generation 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 contribute to 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. These projects are supported by iPS cell techniques from mouse and human fibroblasts.

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 correlate with reduced transport of the β-actin and other mRNAs 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 mimics the 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 special care centre for motoneuron diseases (Dept. of Neurology, Director Prof. J. Volkmann), 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-photon microscopy and life imaging, in order to study defects in structure and function in neurons from models of neurodegenerative diseases. In 2012, an independent research group (Prof. Carmen Villmann) was established. This group is interested in the structure-function relationship of Glycin- and Gaba-receptors, using a broad spectrum of techniques that ranges from patch-clamp analyses and characterization of the structure of these receptors to the characterization of mouse models in which specific mutations have been introduced into the genes for these membrane proteins.

Teaching

The Institute for Clinical Neurobiology is involved in the training of students in Neurolo-

Fig. 1: The building E4, Versbacherstr. 5, in which the Institute for Clinical Neurobiology is located.

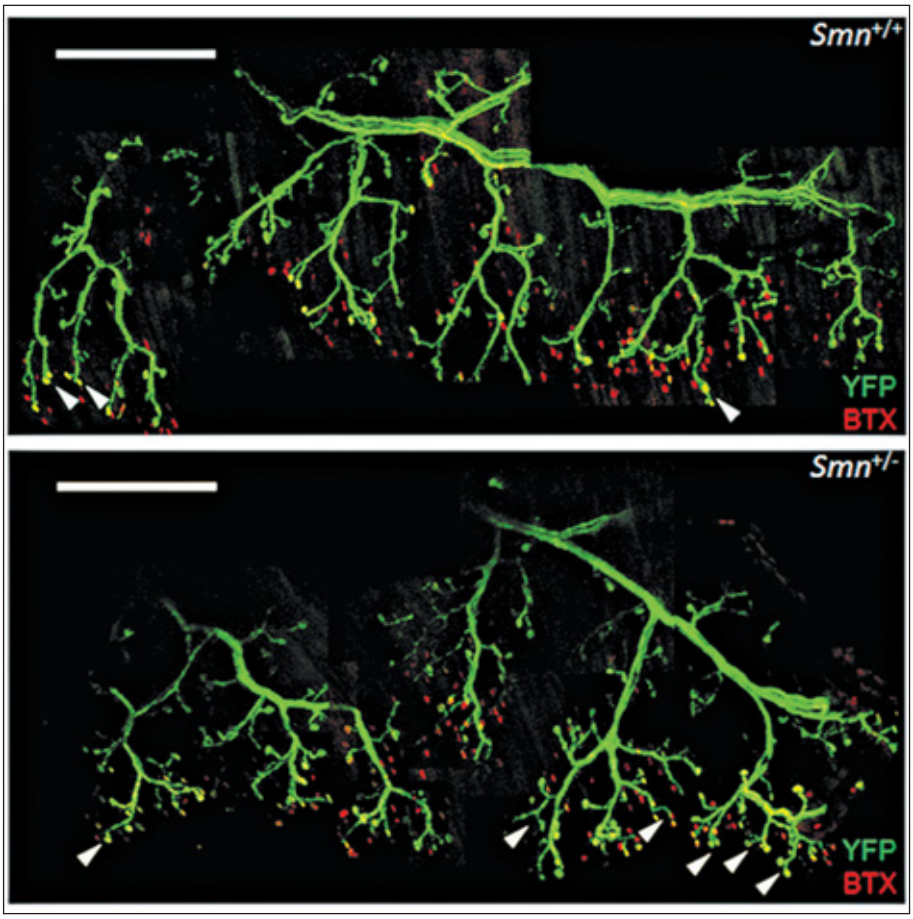

Fig. 2: Alterations in axonal branching in the gastrocnemicus muscle from a mouse model of spinal muscular atrophy (Smn+/-). The number of terminal sprouts is increased, a sign that compensatory mechanisms take place in the disease process.

gy 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 Würzburg. Further courses are offered for students of the course molecular medicine within the training program for MD students.

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

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Mission and Structure

The clinic of Psychiatry, Psychosomatics and Psychotherapy (PPP) at the UKWürzburg (UKW) offers 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 outpatient services as part of the outpatient unit as well as 51 day-care therapy slots for psychiatric, psychosomatic and neurogerotopsychiatric 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 division 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 and biologists and their internationality which is reflected not only by its cooperations, but also by its researchers who come from the Netherlands, Norway, Estonia Spain, Italy, Croatia, Bosnia, Brasil, Japan and China. Close ooperations at the level of the UKW exist in the context of the KFO 125, the SFB 581, the GK 1253, the GSLS, the IZKF and the CHFC, 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 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, 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, figure 1) 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, figure 2). This research structure has been considerably strengthened by the establishment of a Chair of Molecular Psychiatry.

For clinical studies according to GCP guidelines a specialized clinical studies group was established (J. Deckert, C. Jacob, T. Polak, S. Unterecker), which cooperates closely with the ZKS. Studies on suicide have resulted in defined proposals for suicide prevention (A. Schmidtke, B. Pfuhlmann). The signature of the department is the close interaction between translational research laboratories of the PPP, such as the laboratories on Psychobiology and Psychiatric Neurobiology (K.-P. Lesch, A. Reif), Morphological and Neurochemical Brain Research (H. Heinsen, P. Riederer, A.Schmitt) and Psychophysiology and Functional Imaging (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

Fig. 1: Near Infrared- Spectroscopy Labaratory (photo provided by MJ Herrmann).

Fig .2: Behavioural Unit at ZEEM (photo provided by K.P.Lesch).

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, epigenetics, 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, K.-P. Lesch, G. Stöber, B. Pfuhlmann, C. Jacob, A. Reif, T. Polak).
- Identification of morphological and neurochemical pathological processes in psychoses of the schizophrenia spectrum and neurodegenerative disorders (H. Heinsen, P. Riederer, E. Grünblatt).
- Identification of genetic factors in affective disorders, psychoses of the schizophrenia spectrum, anxiety disorders and ADHD (K.-P. Lesch, G. Stöber, J. Deckert, A. Reif).
- Imaging of emotional and cognitive processes in adults, adolescents and children (M.J. Herrmann, K.-P. Lesch, A. Reif, J. Deckert).
- Gene-environment-interactions, neuronal plasticity and adult neurogenesis in humans and in rodent models (K.-P. Lesch, J. Deckert, A. Reif, A. Schmitt).

Teaching

An integrated lecture and course on psychiatry and psychosomatics are organized and held by the PPP in cooperation with the KJPPP and other clinics and institutes. They are complemented by novel E-learning courses in the context of the VHB Bayern (M.Lauer). 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.

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3.24 Department for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy

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Structure and Functions

The Clinic for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy provides treatment for patients under the age of 18 affected by psychiatric and psychosomatic disorders. Facilities include two inpatient wards for children and adolescents, an outpatient clinic, an intensive care unit funded by the district of Unterfranken and a day care unit. A pavilion for parents has been financed by Verein Menschenskinder e.V. The Department is closely linkend to the Wichern-Schule Würzburg, a school for ill children.

Embedded in the clinical structures are the research projects: a clinical research group on ADHD supported by the German Research Foundation (DFG) and two national focus networks on ADHD and eating disorders, supported by the Federal Ministry of Education and Research (BMBF), a neurobiological laboratory and a clinical laboratory facilitating research on Therapeutic Drug Monitoring (TDM) within an international network of participating hospitals. For education and training a lecture hall shared with the Clinic for Psychiatry, Psychosomatics and Psychotherapy is used as well as rooms designed for meetings and workshops.

In March 2012 a specialized clinic for patients with multiple disabilities (*Klinik am Greinberg – Spezialklinik für Kinder- und Jugendpsychiatrie, Psychosomatik und Psychotherapie*, financed by district of Unterfranken) has been opened being the first specialized clinic for this group of patients in Bavaria.

Outpatient and day care clinic include staff and facilities for comprehensive co-therapies like occupational and physical therapy, kinesitherapy (therapy pool, gym, sports field, playground), music therapy and orthopedagogy (play therapy, animal-assisted therapy). The interdisciplinary team comprises 24 medical doctors, 8 psychologists, 4 psychologists in psychotherapeutical training, 5 medical-technical assistants, 13 nurses in outpatient units staff, 11 administrative members of staff and 72 nursing and educational staff. The clinic is operating at full capacity with a total of 59 in-patients and 14 children in the day care facility. Special emphasis is put on eating disorders, anxiety and affective disorders, obsessive-compulsive disorders, somatoform and conversion disorders, excretion disorders (enuresis, encopresis), psychotic, autistic and hyperkinetic disorders, specific developmental disorders of scholastic skills (dyslexia, dyscalculia) and psychological and behavioural disorders associated with organic diseases or mental retardation.

Research Focus

Anxiety disorders

(M. Gerlach, M. Romanos, E. Ziegler, A. Warnke, S. Stieler-Melfsen)

Affective disorders are highly prevalent in childhood and adolescence and have a high tendency to persist into adulthood, thus presenting a potential risk factor for the development of anxiety disorders in later life. The adaptation and standardization of a disorder specific self-rating instrument – the Social Phobia and Anxiety Disorder Inventory –, originally developed for English-speaking countries, into German language met demands for a comprehensive assessment of cognitive, somatic and behavioural aspects of social phobias in childhood and adolescence across different situations. Together with the phobia questionnaire for children and adolescents, this instrument will be used to globally assess a sample of elementary-school aged children in order to determine the prevalence of anxiety disorders in this age group. Furthermore, risk factors for the development of chronic anxiety disorders such as migration background will be accounted for with standardized questionnaires. These examinations will be performed in cooperation with the Clinic for Psychiatry, Psychosomatics and Psychotherapy and the Institute for Clinical Epidemiology at the University of Würzburg.

Attention-Deficit/Hyperactivity Disorder (ADHD)

(M. Gerlach, T. Jans, T. Renner, M. Romanos, R. Taurines, A. Warnke)

Longitudinal studies on ADHD pathogenesis and the role of endophenotypes as intermediate neurobiological correlates between genotypes and phenotypes and comorbid conditions in the course of the disorder employ methods ranging from formal and molecular genetics and analyses of gene expression over neuropsychological and neurophysiological measures and functional imaging to the development of animal models. Epidemiological studies in cooperation with the Institute and outpatient Clinic of Occupational and Social Medicine in Dresden and the Helmholtz Centre Munich are investigating interdisciplinary comorbidity patterns. These investigations are being performed in a methodologically cross-linked design and in close cooperation within the University of Würzburg including the Clinic for Psychiatry, Psychosomatics and Psychotherapy, the Clinic for Nuclear Medicine and the Department of Psychology I. Multi-centre clinical trials have been launched to critically examine the efficacy and safety of extended-release psychostimulants (methylphenidate and amphetamine salts) for treatment of ADHD in children and adolescents. Within the framework of the BMBF focus network ADHD, we evaluate the efficacy of parent training on ADHD in the offspring in contingent upon treatment of the also affected mother. The investigations are supported by the DFG (see KFO 125/1-2 ADHS), the BMBF and various pharmaceutical companies.

Biomarkers

(M. Gerlach, T. Renner, M. Romanos, R. Taurines)

A biological marker is defined as a characteristic that, after sufficient validation, can be used for the objective measurement of normal and pathological processes or pharmacological responsiveness to therapeutic interventions. By means of a variety of procedures on gene expression, protein expression or olfaction, a range of parameters is being evaluated with regard to their suitability as biomarkers. The overarching aim is a significant improvement in terms of the diagnostic process as well as the development of personalized therapies for psychiatric disorders like e.g. ADHD, autism spectrum disorders or schizophrenia. These investigations are facilitated in cooperation with the Clinic for Child and Adolescent Psychiatry, Psychosomatics and Psychothera-

py of the University of Frankfurt, the Clinic for Psychiatry, Psychosomatics and Psychotherapy of the University of Rostock and the Medical Proteome-Centre of the Ruhr-University Bochum.

Depression
(M. Gerlach, D. Störk)

Depressive disorders constitute a frequent and clinically relevant issue in childhood and adolescence.
While extensive research efforts have tested and confirmed a strong relationship between depression and increased cardiovascular risk in adults, this kind of data is still missing for children and adolescents. It is assumed that abnormal regulatory processes of the autonomic nervous system exert their negative influence on heart rate regulation particularly in stressful situations. We study heart rate variability and changes in the stress-axis through an activation of the sympathetic nervous system (rise in cortisol levels) in children suffering from depression compared to ADHD children and healthy controls. These investigations are carried out in cooperation with the Comprehensive Heart Failure Centre and the Institute for Clinical Epidemiology at the University of Würzburg.

Developmental Psychopharmacology
(K. Egberts, M. Gerlach, D. Hansen, R. Taurines)

As part of the International Multi-Centre Competence Network for standardized Therapeutic Drug Monitoring (TDM) in Child and Adolescent Psychiatry (www.tdm-kjp.de), the clinic is pursuing the aim of ensuring patient safety and establishing quality standards for pharmacotherapy. The principle of TDM is the incremental dosing of pharmaceuticals under close systematic monitoring of clinical efficacy and serum concentrations to explore the therapeutic range and prevent the use of suboptimal or potentially harmful dosages. Data is collected via a web-based patient registry. The project is supported by the BMBF and he BfArM.

Eating Disorders
(K. Egberts, B. Hoffmann, U. Zwanzger, A. Warnke)

In the recent years prevalence rates increased and a shift in the age-of-onset to a prepubescent age for anorexia nervosa is becoming more and more evident. A cooperative catamnestic study with the University Hospitals for Child and Adolescent Psychiatry of the Universities of Aachen and Berlin aims at potential phenotypes (including comorbidities), prognostically relevant factors and the course of childhood anorexia nervosa. In a multi-centre comparison of inpatient treatment versus treatment in a day care clinic we evaluate whether day care units offer an alternative therapeutic option with potentially better long-term sustainability of therapeutic outcomes. Additional analyses focus on biological and genetic parameters involved in the pathogenesis of anorexia nervosa and the course of the disorder. The collaboration comprises the University Hospitals for Child and Adolescent Psychiatry of the Universities of Aachen, Freiburg, Köln, Berlin and Würzburg as well as the clinic in Köln-Holweide and the day care clinic Düren.

Obsessive-Compulsive Disorders
(T. Renner, B. Martin)

Despite considerable research efforts, the pathophysiological mechanisms of obsessive-compulsive disorders remain largely unknown. Our clinic is part of a cooperation headed by Prof. Dr. Walitza (Centre for Child and Adolescent Psychiatry, University of Zurich), which comprises a selection of German university hospitals for child and adolescent psychiatry (Aachen, Essen, Freiburg, Köln) as well as the Department of Medical Biometry and Epidemiology in Marburg. In the framework of this cooperation, a large-scale family study on obsessive-compulsive disorders examines patients and their parents with standardized diagnostic methods. Furthermore, the project facilitates molecular genetic association studies which are performed in an international network, combining several samples on early-onset OCD worldwide. First results from these unique examinations point to changes in genes involved in serotonergic and dopaminergic neurotransmission. A cooperative genome-wide association study has been launched to uncover further relevant genetic variants. The investigations were supported by the DFG and the BMBF.

Teaching

The comprehensive interdisciplinary lecture on psychosomatics for medical students is a joint effort of the Clinic for Psychiatry, Psychosomatics and Psychotherapy, the Clinic for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, the Department of Neurology, the Department of Medical Psychology and additional medical clinics. Furthermore, the clinic provides academic trainings and examinations for bachelor and master studies and state exams in psychology and special needs education. In addition, courses covering topics from epilepsy over interdisciplinary methods to Ph.D. and general research seminars are held. This program is complemented by afternoon symposia dedicated to relevant themes in child and adolescent psychiatry and a "*Neurokolloquium*" in cooperation with the Departments of Neurology and Neurosurgery and the Clinic for Psychiatry, Psychosomatics and Psychotherapy. In recognition of the quality of these efforts, the clinic received a faculty award for exceptional teaching (*Lehrpreis der Fakultät*) in 2005. Finally, the Clinic for Child and Adolescent Psychiatry organizes scientific meetings (e.g. the "3rd International Congress on ADHD" in 2011 in Berlin with more than 2000 participants from 70 countries and a satellite meeting for patients and their families) and hosts periodic events like an annual "Doctor-Teacher-Conference" and the "Conference for Child and Adolescent Psychiatry and Youth Welfare Service".

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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 130), and is co-funded by the University Clinic Würzburg. 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 164 and SFB 487 page 155) at the University of Würzburg.

Major Research Interests

Our scientific 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 processes are studied *in vitro* and *in vivo*.

Inhibition of coagulation factor XII (FXII) as a novel antithrombotic therapy

Upon vascular injury the plasma coagulation system becomes activated and acts in concert with blood platelets to form a fibrin- and platelet-rich clot. Blood coagulation is a tightly regulated process of sequentially activated proteases which can be induced by the extrinsic or the intrinsic pathway. The factor XII (FXII)-induced intrinsic pathway, however, was long considered to be irrelevant for physiological clot formation based on the observation that FXII-deficient humans display no bleeding abnormality. In 2005 our studies with FXII-deficient mice changed this view and revealed that the FXII-induced pathway is essential for pathological thrombus formation and the pathogenesis of ischemic stroke but dispensable for hemostasis, which proposed FXII as a promising target for safe antithrombotic therapy. Based on these results CSL Behring (Marburg) developed the specific FXIIa inhibitor rHA-Infestin-4 (recombinant human albumin Infestin-4) which was then characterized and studied in thrombosis models in our laboratory. Intravenous injection of rHA-Infestin-4 in mice or rats resulted in completely abolished pathological thrombus formation, whereas it did not influence bleeding times. Additionally, rHA-Infestin-4 profoundly protects mice from ischemic stroke (Fig. 1). These results identify rHA-Infestin-4 as a promising agent to achieve powerful protection from ischemic cardio- and cerebrovascular events without affecting hemostasis and now serve as a basis for the clinical development of FXIIa inhibitors.

Mechanisms of Ca^{2+}-signaling

Changes in the intracellular Ca^{2+} concentration regulate fundamental processes in virtually all cell types. We have shown a central role of the Ca^{2+} sensor STIM1 and the *store-operated calcium* (SOC) channel Orai1 for platelet activation and subsequent thrombus formation. In further studies, we demonstrated an important function of STIM1 and the closely related STIM2 in T cell activation in experimental autoimmune inflammation of the central nervous system.

Cytoskeletal dynamics in platelet function and formation

Cytoskeletal rearrangements do 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

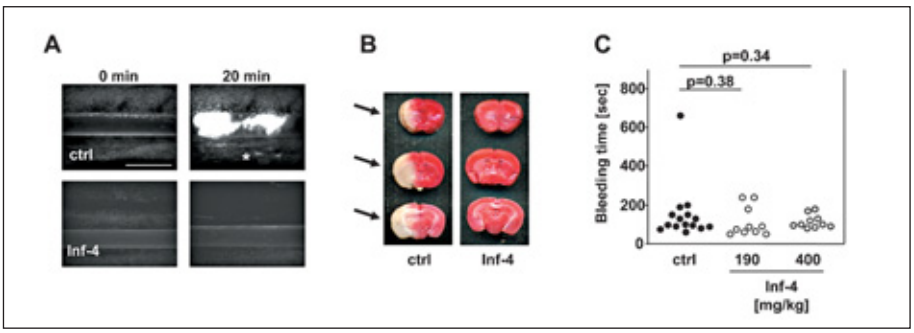

Fig. 1: (A) rHA-Infestin-4 completely blocks arterial thrombus formation in mice. Endothelial damage was induced by topical application of $FeCl_3$ on mesenteric arterioles and thrombus formation was monitored using intravital fluorescence microscopy. An asterisk indicates full vessel occlusion. Bar=50 µm. (B) rHA-Infestin-4-treated mice are profoundly protected from ischemic stroke. Representative coronal sections from control and rHA-Infestin-4-treated mice stained with TTC 24 h after transient middle cerebral artery occlusion. Arrows indicate infarct areas (white tissue). (C) Normal bleeding times in rHA-Infestin-4-treated mice in a tail bleeding model. Each symbol represents one individual. Ctrl=control; Inf-4=rHA-Infestin-4.

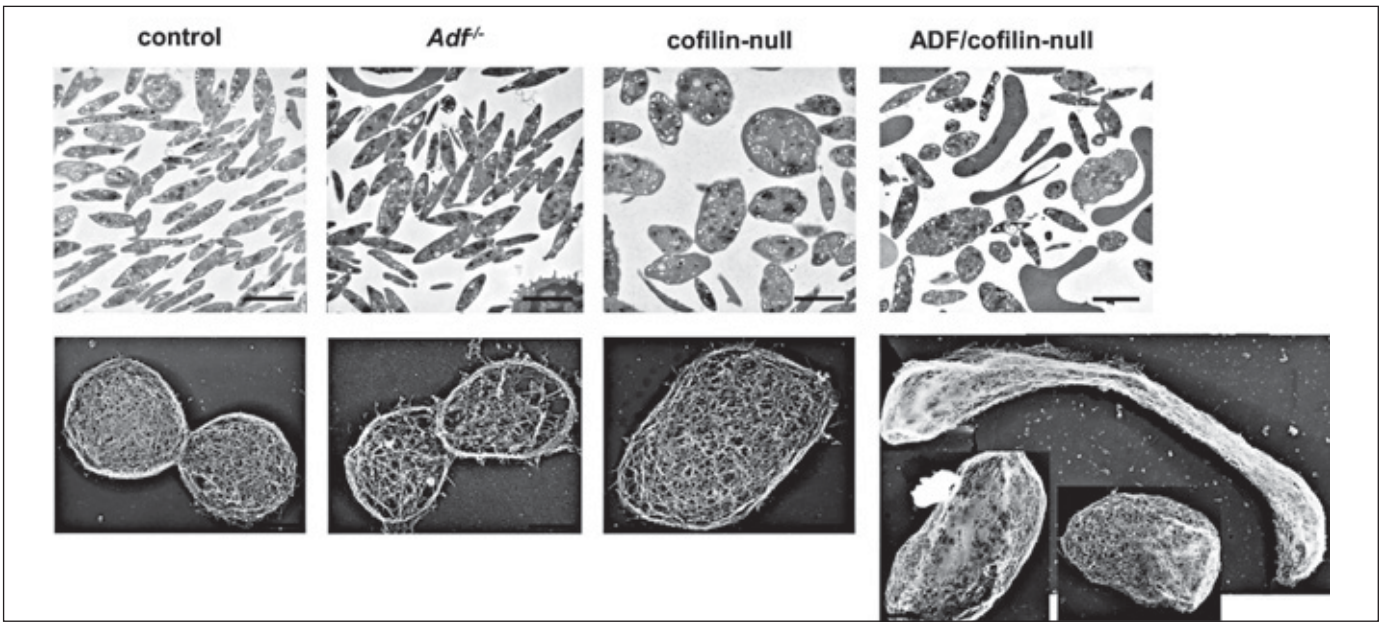

Fig. 2: Cofilin-deficient platelets are increased in size and ADF/cofilin-double deficient platelets display a marketly variability in size and morphology, and an abnormal platelet ultrastructure. Transmission electron microscopical analysis of resting platelets. Scale bar: 2 µm (upper panel). Visualization of the cytoskeleton of resting platelets on poly-L-lysine. Scale bar: 1 µm (lower panel). Note: ADF/cofilin-null platelets display even a proplatelet-like structure.

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. We could show that the actin regulating proteins n-cofilin and actin-depolymerizing factor (ADF) play central and partially overlapping roles for platelet formation from megakaryocytes. Unexpectedly, we found that cofilin is a critical regulator of platelet size, which could provide a possible explanation for idiopathic macrothrombocytopenias in humans.
We also analyzed the function of Rho-GTPases in platelet biogenesis and function. Unexpectedly, we found that a megakaryocyte-specific deficiency in Cdc42 results in a pronounced thrombocytopenia, but hyperreactivity of these cells which translates into a prothrombotic phenotype of the animals. Mice with a megakaryocyte-specific RhoA-deficiency also display reduced platelet counts but also defective activation of the cells, leading to protection of the animals in models of arterial thrombosis and ischemic stroke.

Regulation and function of the platelet collagen receptor GPVI

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 therapeutic strategies. We have shown previously that the activating collagen receptor GPVI can be depleted in circulating platelets in mice by injection of anti-GPVI antibodies (JAQ1) resulting in long-term antithrombotic protection but only moderately increased bleeding times. Similar mechanisms of GPVI downregulation were subsequently shown in human platelets. We have now analyzed the mechanisms underlying the targeted downregulation of GPVI *in vivo*. By the use of mice with single and double deficiencies we demonstrated central roles for the membrane-expressed metalloproteinases ADAM10 and ADAM17 (TACE) in this process. These findings may serve as a basis for the development of new antithrombotic therapies.

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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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 at the university clinic of Wuerzburg in 2009 and is headed by Prof. Heike Walles since August 2009.
Tissue engineering using body´s own cells allows the generation of transplants with a minimized immunological rejection potential which should grow with the patients body upon transplantation. In contrast to commercially available implants the tissue engineered transplants additionally are capable to enable and to support the body´s self-healing potential with the underlying biological mechanisms, features which are illustrated by the term "regenerative medicine". New substances have to be tested intensively concerning their quality, efficacy and harmlessness before they can be used as drug in medical treatment. For these testings animal experiments are still the golden standard due to the lack of comparable alternatives. However, based on species-specific differences animal experiments are not always reasonable.
The group of Prof. Walles has therefore focussed in the past years on the development of alternative human test systems (tissue models) reflecting important properties of the human body and allowing investigations according to the so-called ADMET-criteria (Absorption, Distribution, Metabolism, Excretion, Toxicity).
These test systems are based on human cells cultured *in vitro*. In order to guarantee their general functionality culture conditions have to be established resembling the natural microenvironment of this particular cell in the human body.
As a consequence the department focusses on the development of biomaterials, bioreactors, and co-cultivation of primary cells. By combining these technologies human tissue models in normal as well as in pathological situations can be designed in order to investigate the underlying molecular mechanisms causative for distinct diseases or infections. Based on the obtained results new regenerative therapies can be established.
In parallel to the department "Tissue Engineering and Regenerative Medicine" a Fraunhofer Project Group "Regenerative Technologies for Oncology" was established at the same location. Prof. Walles could show in initializing experiments, that a special scaffold (BioVaSc®) developed by her can be used for the generation of vascularized normal as well as tumorous tissue *in vitro* (Figure 1). The tumor models provide the methodical basis for numerous cooperations within the medical faculty and will be used for the development of new diagnostic methods as well as individual treatments in tumor therapy.

Major Research Interests

Bioreactor technology
(T. Schwarz, H. Walles)

In order to construct functional 3D tissue *in vitro* the microenvironment of the particular cells at their original sites in the human body has to be analysed and consequently simulated with in house developed computer-controlled culture vessels (bioreactors). In the last two years the complete bioreactor layout was also established in collaborating laboraties at the TU Berlin, the BoKu in Vienna and at the University of Bergen, Norway.

Vascularized human tissue- and disease models
(A. Appelt, G. Dandekar, M. Hadad-Weber, S. Nietzer, C. Moll, M. Schweinlin)

Based on the BioVaSc® technologie (see Figure 1A) intestine-, lung-, and neurofibrome tumor model (see Figure 1B) has been established and initial experiments focussing on the radiation resistance underlying mechanisms as well as the treatment with new antibody based therapeutics have been carried out. These experiments already showed, that certain methods like e.g. the immunhistochemical detection of EMT (Epidermal to Mesenchymal Transition) in the context of tumor invasion or the characterisation of the above mentioned models by their specific biological response to certain therapeutics could be validated.
In projects funded by the BMBF (PeTrA and LipoTrans) a human intestinal tissue model is used to develop nanomaterial based formulations for the transport of lipophilic substances.

Development of biomaterials
(J. Nickel, H. Kirch, C. Rückert, H. Walles)

In a IZKF-funded cooperation project with the accident surgery department surface- and material properties of carriers coated with recombinant spider silk have been analysed. Aim of these investigations is to examine if and how the biocompatibility of alloplasic materials like silicon based prosthesis, implants, and catheters being intended for a long retention period in the human body can be improved.
In a large scale EU project (VascuBone) coordinated by Frau Prof. Walles a bone tissue model will be developed in order to optimize the interactions of implant materials with human cells *in vitro*.
In another DFG funded program new optical technologies for the production of synthetically vascularized materials which can be used in tissue engineering will be developed in colaboration with the laser center Hannover, the University of Jena and the Fraunhofer ISC.

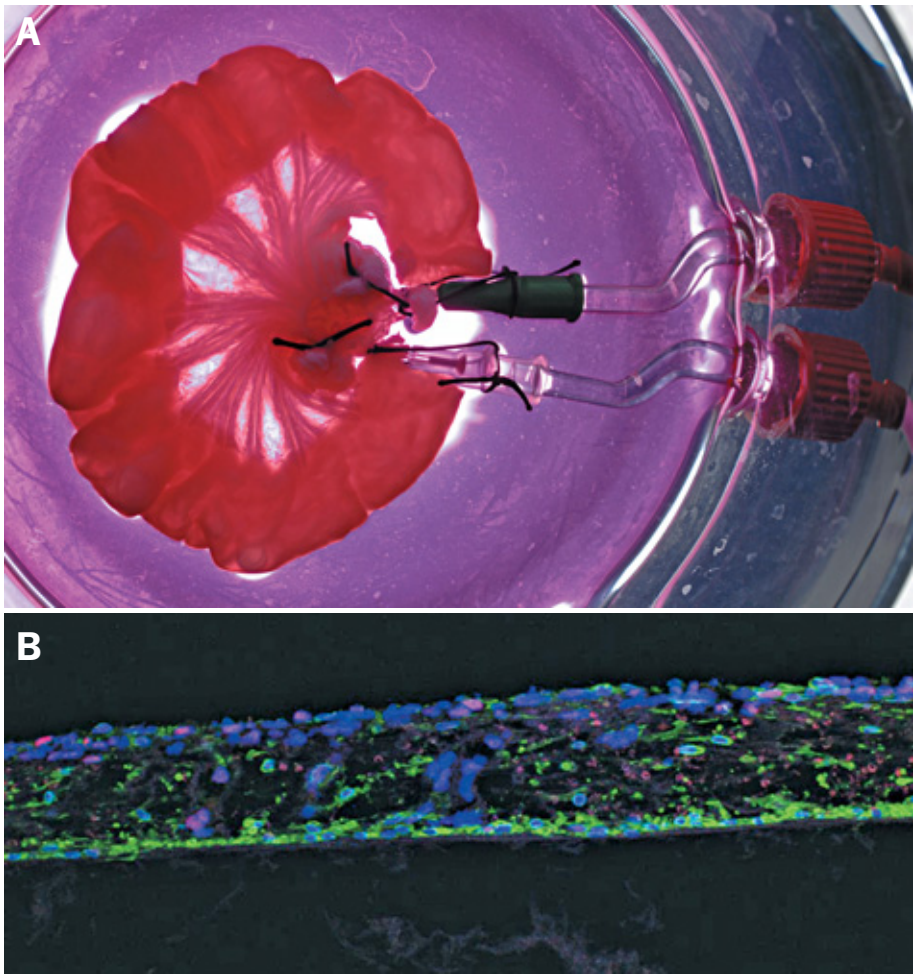

Fig. 1: (A) The biological vascularized scaffold (BioVaSc®) used as basis for the generation of autologuous transplants as well as human tissue and tumor models. (B) Immunhistological characterisation of a Biovasc® neurofibrome (NF-1) model (red: anti-p53, green: anti-CD44, blue: DAPI).

Transplantats
(H. Walles, S. Schürlein, J. Weyhmüller)

Ruptures of the meniscus in the avascular zone to not heal and have to be removed by surgery which is typically accompanied by the early onset of arthrosis. Up to date neither acellular implants nor vital constructs designed by tissue engineering resulted in a satisfactory repear or healing of these meniscal decfects which is mainly due to their minor integration potential. A clinical appliance therefore premisses the vascularisation of such constructs which might be essential for the healing process.
In colaboration with the orthopedic clinic in context of the „Orthopädisches Zentrums für Muskuloskelettale Forschung" (MCW) meniscal tissue with veritable neovasculaisation will be constructed by a multistage concept. This cooperation project is funded by the IZKF.
In another EU funded project (IDEA) vascularized tissue models are used to analyze the influence of cellular labelling techniques onto the function and homing of stem cells *in vitro*.
In context of a start-up project "G of the DZHI" different adult tissues have been analysed in light of their capabilities to generate functional cariomyocytes. After isolation, expansion and differentiation these cells can be used to generate 3D heart muscle tissue.

Fraunhofer Projektgruppe "Regenerative technologies for oncology"
(S. Kurdyn, M. Metzger, J. Nickel, H. Walles)

The experimental research and development focuses on the isolation and characterization of human (tumor-) stem cells isolated from intestine including the enteric nerve system. These cells will be used to construct complex human vascularized tumor tissues. In the project „Skinheal" the above mentioned established methods will be used to characterize a vascularized human skin melanoma model in light of metastatic processes.

Teaching

The degree program „Technologie der Funktionswerkstoffe" (TEC-FUN) is geared to engineering and covers all aspects for the construction of functionalized materials starting from the chemical synthesis of precursor molecules, the analysis of physicochemical characteristics up to their potential to be used in regenerative therapies. The program involves the faculties physics and astronomy, medicine (Prof. Dr. Walles, Prof. Dr. Jakob), the university of applied science Würzburg-Schweinfurt, the Fraunhofer Institute for Silicate research (ISC), the center for applied energy research and the süddeutsches Kunststoffzentrum.

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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 (Head: Professor Dr. Jürgen Groll) 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. Bernd Klaiber).

At this Hospital there are scarcely 660 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 222 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 2010 about 28200 persons got outpatient treatment and about 1500 were treated as in-patients.

Professor Dr. Bernd Klaiber
(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 caused 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. The treatment of newborns with a non synostotic plagiocephaly caused by unilateral positioning by a molding helmet therapy is conducted in close cooperation with the Department of Paediatric Neurosurgery and the Oral, Maxillary and Plastic Facial Surgery.

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.

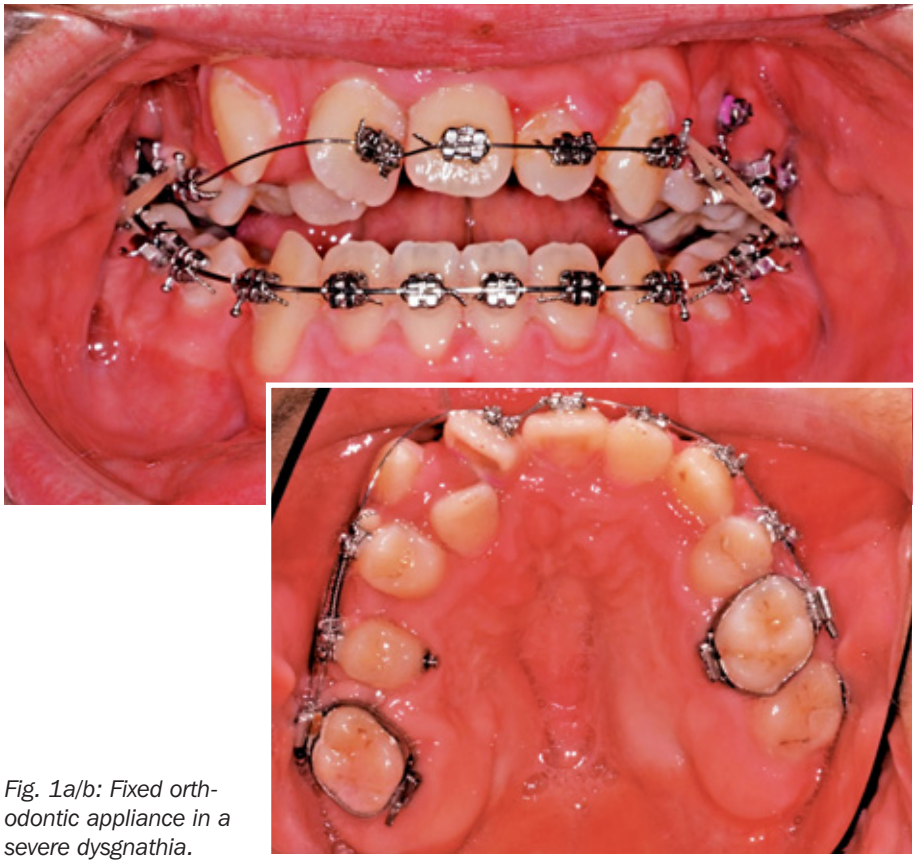

Fig. 1a/b: Fixed orthodontic appliance in a severe dysgnathia.

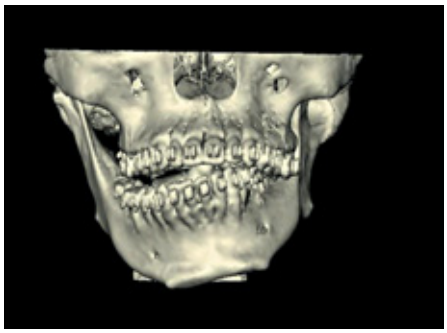

Fig. 2: 3D Reconstruction of a patient with hemifacial hypoplastic mandible (left) before a combined orthgnathic/ orthodontic therapy (fixed appliance in situ).

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 interdisciplinary project is supported by the research funding of the interdisciplinary center of clinical research. 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 and the morphometric analysis 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. This project was honored with the first prize of the German Society of Orthodontics (DGKFO) in 2011.

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 and hard 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 of Optics, Information and Photonics of Erlangen-Nuremberg University, three-dimensional soft tissue imaging was successfully integrated into orthodontic diagnostics and treatment (see 2008 Research Report).
In further research projects development the soft tissue analysis was expanded with a skeletal analysis of the hard tissue of the face and the nasopharyngeal space in 3D.

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. A part of these results were honored with the prize of the best publication in the „Journal of Orofacial Orthopedics" in 2011.

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. An application for research funding is submitted to the German Research Society (DFG).

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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4.3 Department for Functional Materials in Medicine and Dentistry

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Mission and structure

The Department for Functional Materials in Medicine and Dentistry is focused on materials development and positioned at the dental clinic. Mission of the department is the optimization and improvement of existing and especially the development of innovative biocompatible and biofunctional materials for applications in biomedical basic research and applications in humans. Accordingly, an interdisciplinary team of biologists, chemists, physicists and material scientists in cooperation with clinicians is engaged in realizing the mission statement "higher quality of life through innovative materials". Research activities are tailored for the special needs of the respective clinical challenge and divided into the 5 competence fields biointerface engineering, bioactive inorganic scaffolds, Nanobiotechnology, artificial extracellular matrix and (micro-) biological testing. These activities are financially supported by the Interdisciplinary Center for Clinical Research, the Deutsche Forschungsgemeinschaft (DFG), the Bundesministerium für Bildung und Forschung (BMBF) and the European Union (FP7).

Main Research Interests

Biointerface Engineering

The biocompatibility of a functional material arises from its surface and is determined by its composition, electrical and electronic properties, and its topography and biochemical activation. Current research deals with the modification of refractory-metal-based implant surfaces with low-crystalline calcium and magnesium phosphate coatings, which combine bactericidal and biocompatible properties and hence can lower the risk of post-surgical infection as well as support the osteointegration of the implant. Furthermore the department utilizes two methods of physical vapour deposition (arc-evaporation and magnetron sputtering) for the coating of metallic surfaces. As coating materials mainly refractory metals like titanium and tantalum as well as their oxides and nitrides come into operation. By combination of both PVD techniques, which is possible with the bigger one of the two available chambers (Figure 1), layer systems are being developed that can be provided with particular bioactive respectively anti-microbial properties by incorporation of suitable ion species.

Bioactive Inorganic Scaffolds

The development of inorganic scaffold materials for bone regeneration at FMZ is based on reactive calcium- and magnesium phosphates that set after addition of water under ambient conditions to form a stable implant without the need for sintering. These reactive cement powders are also used for rapid-prototyping by 3D printing techniques for the construction of individualized implants as well as bioactive and degradable scaffolds for tissue regeneration. The scaffolds are microporous which strongly enhances the bioactivity of the materials. The fabrication at room temperature additionally offers the possibility to modify the material with organic bioactives. Hence, recent developments concern the use of microporous CaP-scaffolds as bioactive drug carriers. Through the use of multicolour-printers, bioactive compounds can be added at desired locations in the 3D scaffolds for a spatial control of tissue response and drug release kinetics. It is possible to directly print antibiotics or growth factors into the structure such that a controlled release of pharmaceutical active doses is achieved in hard tissue applications without any systemic side effects. Besides protein based growth factors the ceramics are also modified with bioactive ions such as Sr^{2+} or Cu^{2+}. These offer the advantage of an ease of use and an unlimited availability.

Nanobiotechnology

Nanoparticles are big enough to take up and transport drugs but also small enough to be taken up by cells and to use active biological transport mechanisms. This opens a wide potential for targeted transport especially of sensitive drugs over barriers in the body to the area and tissue of interest.
Research at the Department focuses on nanoparticles for different purposes. Systematic studies regarding the influence of nanoparticle shape, size and surface chemistry on the interaction with cells are one area of interest. Recent results have demonstrated that rather simple changes in surface chemistry of nanoparticels can significantly affect the behaviour of human immune cells. This may be used to influence inflammation- and healing processes for example after implantation.
A special research focus are colloidal hydrogels, so called nanogels (Figure 2). Their high water content predetermines them for the transport of biological macromolecules. We use inverse emulsion techniques as well as cascade reactions of self-assembly and chemical cross-linking in homogenous phase for the preparation of nanogels. Oxi-

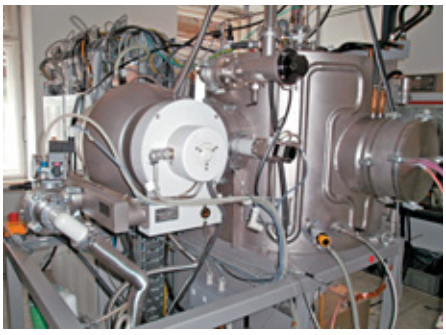

Fig. 1: PVD equipment for coating of implant surfaces

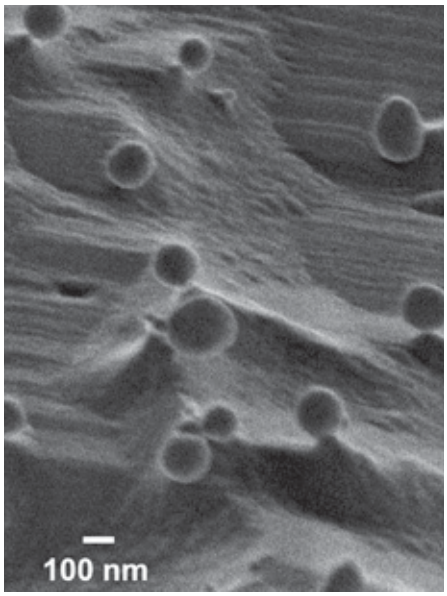

Fig. 2: Scanning electron micrograph of nanohydrogel particles

dative cross-linking of thiofunctional polymers for example yields nanogels that are stable in extracellular spaces in the body and in the blood, while the reductive cytosolic conditions after cellular uptake lead to rapid degradation of the particles and release of the payload. Application of these special nanoparticles for targeted drug delivery is at the moment one core activity.

Artificial Extracellular Matrix

In their natural environment, cells are surrounded by a matrix that enables their survival and determines their adhesion, growth, proliferation, migration, differentiation and function. Therefore, soluble factors that are reversible immobilized in the so called extracellular matrix (ECM) as well as specifically acting binding moieties are of utmost importance. Main components of the ECM are hydrogels and insoluble protein fibres that serve as mechanical scaffold for the cells. Another important structural element are basal membranes, ultrathin separation layers between tissues.
A core activity at FMZ is the preparation and evaluation of biodegradable materials and structures that mimic the ECM as closely as possible in its morphology, biochemical function and hierarchical composition. Modified biopolymers as well as biocompatible functional polymers are used as components for coatings, hydrogels and nanofibrous constructs to achieve this goal. For the generation of hierarchy, methods such as electrospinning and rapid-prototyping techniques are applied. In this field of activity, a novel and internationally unique method was developed for the preparation of fibrous scaffolds that morphologically and biochemically closely resemble the protein fibres of the ECM (Figure 3). Development of these fibres towards biomimetic *in vitro* cell cultures and clinical applications is at the moment an intensive research focus.

(Micro-)Biology

Focus of the biological laboratory is the interaction of cells with biomaterials and functional materials developed in the Department. For this purpose preferentially human cell types, primary cells as well as cell lines, and prokaryotic cells of different strains are used. Special matters of research are cell-substrate interactions depending on surface properties like biochemistry, structure and mechanics as well as tissue specific cell differentiation, co culture systems, and characterisation of cells in three dimensional matrices like gels and fibres.

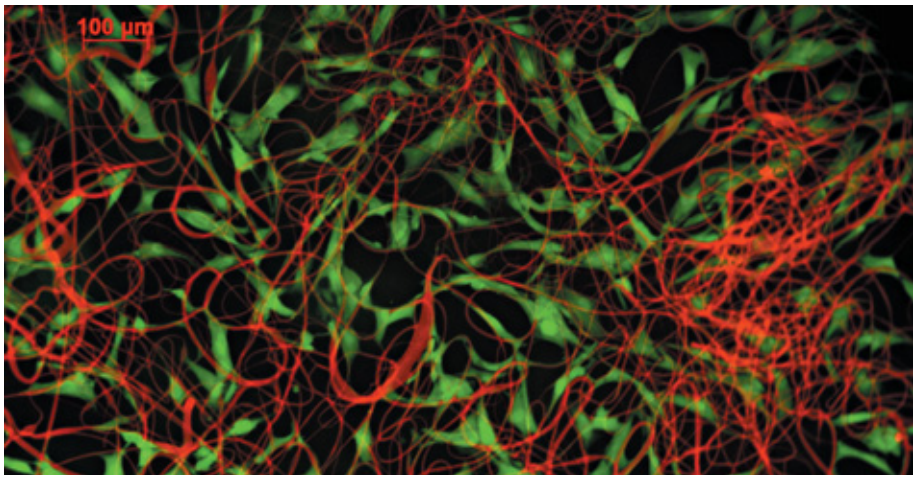

Fig. 3: Human dermal fibroblasts (green) on RGD cell adhesion peptide functionalised fibres (red) embedded in a three-dimensional hyaluronic acid based hydrogel matrix.

Furthermore an accredited and ZLG approved testing laboratory is associated to this competence field. Here cytocompatibility testing according to DIN EN ISO 10993-5 is performed for both home developed materials and materials by order of external customers.

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”. Special attention is laid on the transfacultative and interdisciplinary bachelor- and master programme “Technologie der Funktionswerkstoffe”.

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4.4 Department of Oral and Maxillofacial Surgery

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Mission and Structure

The clinic provides 40 permanent beds and covers the whole spectrum of oral and maxillofacial plastic surgery. Beside the in-patient care (about 1.400 patients each year), approximately 18.000 patients are treated in the outpatient clinic. Furthermore 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. The clinic is part of the *Comprehensive Cancer Center Mainfranken* and is certified as organ center for head and neck tumors as well. Furthermore the department belongs to the *Musculoskeletal Center Würzburg* and to the *Craniofacial Center Würzburg*.

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

Research team for tumor biology of oral squamous cell carcinoma
(U. Müller-Richter, S. Hartmann, R. Brands, C. Linz, U. Kriegebaum, 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. In particular the response to adjuvant tumor therapy like radiotherapy and chemotherapy are investigated. Furthermore distinct signal pathways (e.g. Sonic Hedgehog) are characterised to establish new concepts for personalised tumor therapy.

Clinical research team for differential diagnosis of oral mucosa lesions
(U. Müller-Richter, M. Freitag, A. Kübler)

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. Novel diagnostic tools like oral brush biopsy are included.

Clinical research team for bisphosphonate-associated necrosis of the jaw
(T. Bittner, U. Müller-Richter, A. Kübler)

In collaboration with the pathologic institute the histological characterisation of the affected bone as well as clinical prospective and retrospective studies concerning risk factors and concomitant diseases are conducted to isolate risk factors and provide prevention.

Research team for tissue regeneration of oral mucosa
(U. Müller-Richter, C. Linz, U. Kriegebaum, A. Kübler, K. Heffels, J. Groll (both Department of Functional Materials in Medicine and Dentistry))

The main focus is the evaluation of various dermal equivalents, i.e. biopolymer matrices with cultivated fibroblasts on their surface. The aim is the tissue engineering of oral mucosa. The comparison of typical cocultures (dermal equivalents plus keratinocytes) with dermal equivalents alone tends to reveal insights about dermal-epithelial interaction. A further topic is the investigation of the vascularisation capability using this model. The mechanical forces affecting a transplant in the oral cavity are emulated and analysed (mechanotransduction).

A further project is the development of a membrane for guided tissue and bone regeneration by means of electrospinning. Therefor a bipolar functionalised and bacterial-seal membrane is produced, which enables adhesion and growth of fibroblasts and keratinocytes on its topside and provides a continuous release of antibiotics at

the bottom. The degradable membrane has a life time of approximately 3 month.

Three dimensional stereophotogrammetric diagnosis and treatment evaluation of children with craniofacial anomalies
(H. Böhm, P. Meyer-Marcotty (Department of Orthodontics), T. Schweitzer (Department of Neurosurgery)

This clinical 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.

Research team for bone regeneration and bone substitution
(U. Klammert, U. Gbureck, E. Vorndran (both Department of Functional Materials in Medicine and Dentistry))

Novel bone replacement materials with calcium and magnesium phosphate chemistry which are fabricated by the rapid prototyping technique of 3D powder printing, are characterised concerning their physical, chemical and biological suitability. Implants are manufactured in a defect-specific design by means of a CAD/CAM processing chain. Furthermore the biological properties of the matrices are modified by addition of polymers for regulation of their degradation and by addition of bioactives (e.g. growth factors).

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.
Furthermore the clinic is involved in the advanced education for already approbated colleagues due to the organisation of certified meetings and courses, e.g. an annual international course on orthognathic surgery.

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4.5 Department of Prosthodontics

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Mission and Structure

The Department of Prosthodontics currently has 49 employees and 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 medical fields. The ambulatory care covers all fields with 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 about 12 years research has also focussed on the concept of “strategic” and angulated implants in conjunction with removable dentures. Furthermore, temporal and spacial measurements of tooth and implant mobility using a specialized CCD chip have been measured and analysed (Figure 1) (Project lead by Prof. Dr. Dipl.-Ing. E.-J. Richter).

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 2005 almost 250 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 indictations at improved useablilty and aesthetics, grace to new materials.

A workgroup in cooperation with other faculties (Department of Experimental Physics 5) is 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 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.

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.

Teaching

The premed curriculum comprises two classes (technical propaedeutics, 60 students and Phantom I, 60 students). The six week Phantom II course takes place annually during the summer off-term. 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 has been 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. 53 students are trained per class. The lecture on prosthodontics(Prof. Dr. Dipl.-Ing. E.-J. Richter) covers general fields of prosthetic dentistry, whereas the lecture on special prosthodontics aims at CMD and geriatric dentistry (Prof. Dr. T. Holste). Both lectures span two semesters.

On average, each student performs between two and three restorations which are subject to individual grades. In 2011 this equated to almost 600 prosthetic restorations which were made per class, as well

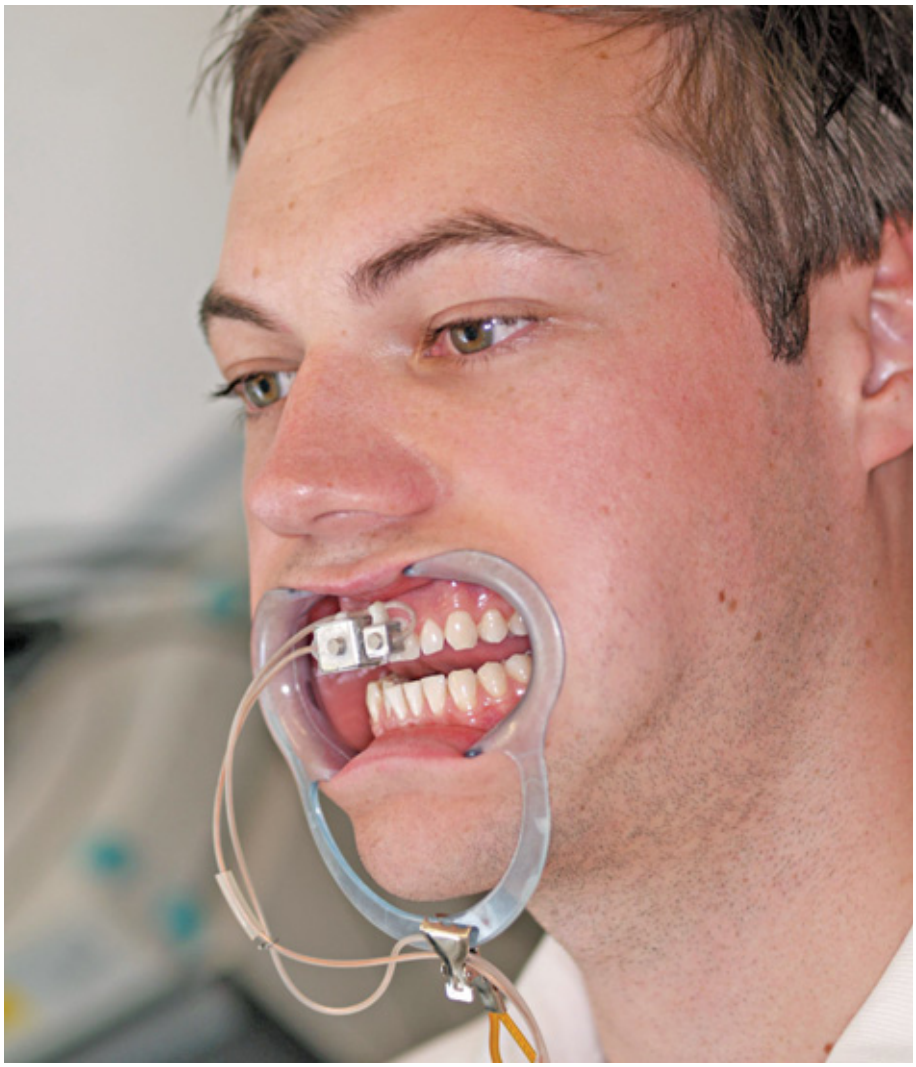

Fig. 1: Setup of emitter and CCD camera in situ for measurement of tooth or implant deviation during chewing force.

as about 400 during the ten-day final state examinations. In each course there are either one two written tests, summing up to roughly 300 corrections and gradings!
Eight movies, four clinical instructory scripts and two material science booklets have been made available to students, who also have download access to pdf files of lecture content.

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4.6 Department of Conservative Dentistry and Periodontology

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Mission and Structure

The Department of Operative Dentistry and Periodontology (16 dentists - 4 of them in the section of periodontology-, 12,5 dental assistants -2.5 of them in the section of periodontology-, 2 dental technicians) is endued with 10 dental chairs - 3 of them in the section of periodontology-, 2 working centres for the dental technicians and facilities for taking radiographs. For the practical part of the students´ education 24 dental chairs are available, 40 workings centres for laboratory dentistry as well as 55 working centres providing phantom-puppets.

The area of responsibility of the Department of Operative Dentistry and Periodontology contains prevention, diagnostics and therapy of diseases to enamel and dentine (caries, abrasion, erosion and trauma) as well as to the pulp (pulpitis, trauma) and to the periodontal ligament (periodontitis) and their sequelae. Each year approximately 4.000 patients are treated ambulatory. In co-operation with the Department of Paediatrics, the Department of Anaesthesiology and the Department for Oral and Maxillofacial Surgery patients can be treated in general anaesthesia.

In patient-care special emphasis is based on minimal-invasive preparation and its adequate supply with adhesive techniques: Due to the micro-mechanical anchorage of the restoring materials to the conditioned enamel and dentine, the preparation of macro-mechanical cavities - with further loss of healthy tooth-substance - can be set aside. Further emphasis is based on the Aesthetic Dentistry: adjustments of contour-, colour- and position-anomalies with non-invasive or minimal-invasive techniques are made possible through the use of adhesive materials and modern resin-based composites. In the majority of cases there is no more need to prepare the teeth for veneers or crowns. The conservation of healthy tooth substance and the renunciation of lab-made restorations are obvious advantages in respect of biologic and financial interests (Fig.1).

Major Research Interests

Research at the Department of Operative Dentistry and Periodontology is focused on the evaluation of restorative materials, appliances and devices required for conservative restorative therapy. In this context, the interactions between restorative materials and dental hard tissues and among different restorative materials are studied.

A universal testing machine allows the determination of mechanical properties (compressive strength, flexural strength, tensile

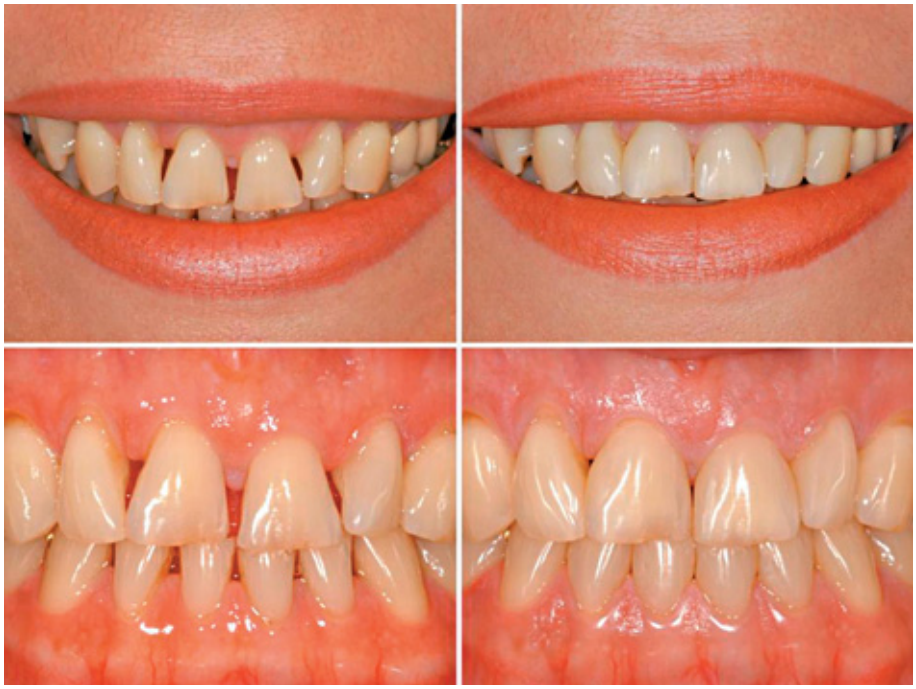

Fig.1: Estheticaly pleasing tooth corrections using noninvasive technique with composite materials.

bond strength, shear bond strength, extrusion shear bond strength). Deformation of teeth under load and during photo-activated polymerization of resin-based composite restorations can be studied using displacement transducers. Additional experimental setups allow the evaluation of the kinetics and the total amount of polymerization shrinkage of restorative resin-based composites, as well as the spectral irradiance of dental light curing units (Fig. 2).
The marginal seal of restorations is evaluated using dye penetration techniques and computer-based image analysis. The margin fidelity of restorations in vivo and in vitro is monitored morphologically by the replica technique and a scanning electron microscope, which is used together with other departments of the dental school.

An atomic force microscope is used in cooperation with the Department and Chair of Functional Materials in Medicine and Dentistry for studying the interface between dental hard tissues and restorative materials.

The purpose of the current clinical studies is to compare newly developed restorative materials and appliances with those considered to be the gold standard in the past. In some cases, undergraduate students can be involved in these studies. This lets them come to know the different tasks of a university hospital.

Currently, 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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4.6.1 Division of Periodontology

CONTACT DETAILS

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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 Deut-

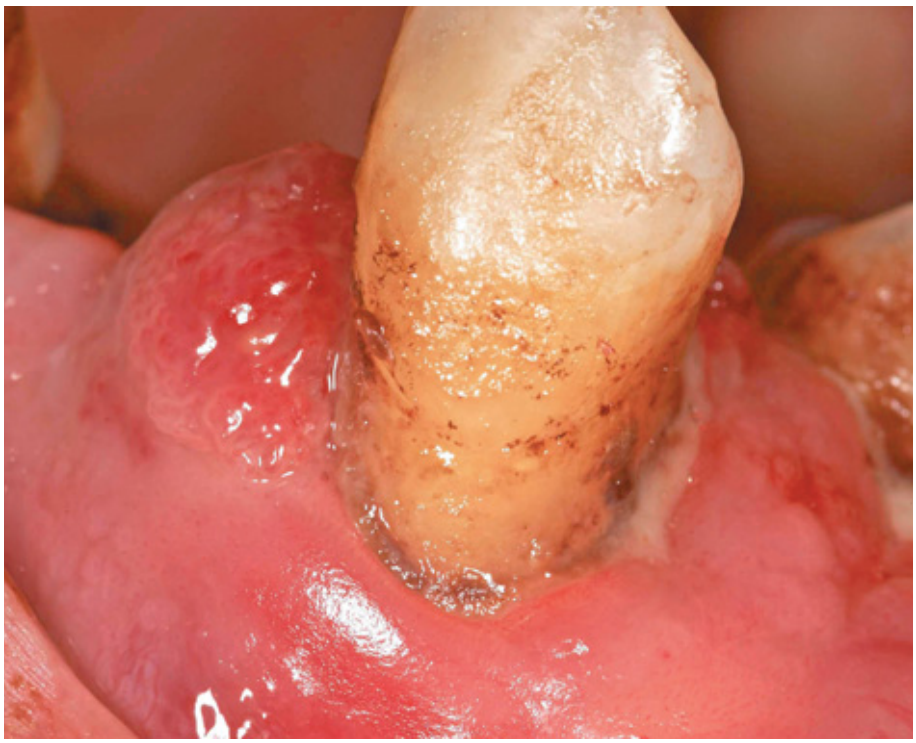

Fig. 1: Advanced chronic periodontitis in a patient suffering from angiomatosis Rendu-Osler.

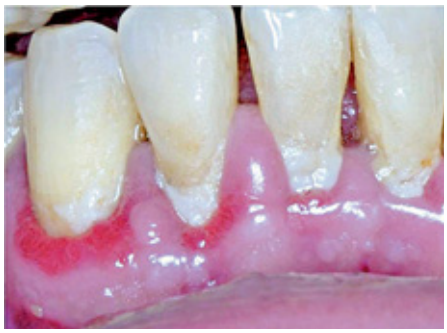

Fig. 2: Pronounced plaque-induced gingival inflammation in a patient with insufficently controlled diabetes type I.

sche Forschungsgemeinschaft (DFG) and is contributing more than 100 own study patients..

Periodontal diseases and cardiovascular health
(Y. Jockel, G. Ertl, C. Angermann, U. Schlagenhauf)

Recent investigations performed in collaboration with the Clinic for Internal Medicine I revealed, that patientes suffering from periodontal 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, K. Fischer, 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.

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5 Additional Scientific Units

In this chapter information on scientific institutions, cooperations and centers will be given which are initiated or partly organized by the Medical Faculty. The chapter comprises information on five Collaborative Research Centers (Sonderforschungsbereiche), four Transregios, two Clinicial Research Units, three Graduate Colleges, and other joint activities which are performed together with institutions of other faculties, especially of the Biological Faculty. Furthermore, four Research Centers, four Interdisciplinary Research Facilities, the Clinical Research an Training Centers and the International Graduate School are described.

5.1 Research Centers
5.1.1 Rudolf Virchow Center / DFG Research Center for Experimental Biomedicine

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Dr. Shashi Bhushan (since 2010)
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Professor Dr. Utz Fischer (since 2010)
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Professor Dr. Antje Gohla
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Professor Dr. Manfred Heckmann (until 2011)
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PD Dr. Heike Hermanns
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Dr. Asparouh Iliev
(Membrane/Cytoskeleton Interactions)
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Professor Dr. Caroline Kisker
(Structural Biology: DNA-Repair and Structure-Based Drug-Design)
Tel.: 0931/31-80381

Dr. Stephan Kissler
(Immune Tolerance)

Professor Dr. Bernhard Nieswandt
(Vascular Biology)
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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 m^2 of space with excellent facilities are now open for research, teaching and training, as well as events for the public.

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. 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 Rudolf Virchow Center also offers Senior Professorships to scientists who want to continue their research programs after their retirement to emeritus status; the research programs of these scientists are in the general field of the center, but they are largely funded by external grants. The Bio-Imaging Center comprises research groups funded by the State of Bavaria and the University of Würzburg as basic funding that analyse biological problems with optical methods. 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 Master's 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.

Fig. 1: Structure of the Rudolf Virchow Center.

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Dr. Ingrid Tessmer (since 2011)
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(Immunopathogenesis of Atherosclerosis)
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Finally, the "Public Science Center" offers several courses for pupils.

Major Research Interests

At the time of reporting fifteen research groups and projects within the RVZ Network are established at the Rudolf Virchow Center, including the Bio-Imaging 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.

Biophysics of Membrane Transport
(R. Benz)

Hydrophilic molecules and ions have a very low solubility in membranes because a considerable amount of energy is needed for their transfer from the aqueous phase into the low dielectric interior of biological and artificial membranes. Carriers and channels are needed for controlled transport of small hydrophilic solutes and proteins through membranes. We are interested in the biophysics of membrane transport. Of special interest in recent years was the interaction of cytolytic bacterial toxins with biological and artificial membranes, which form pores in the membranes followed by a collapse of membrane structure and the dissipation of membrane potential. Some bacterial protein toxins act as enzymes on intracellular targets of eukaryotic cells. These toxins have to be transported across membranes; otherwise the toxic activity cannot be developed inside the target cells. These transport processes were also studied in recent years for binary A-B types of toxins such as C2 and anthrax toxins.

Structural investigation of protein synthesis
(S. Bhushan)

Our group is interested in studying 3-dimensional structures of macro-molecular cellular machineries such as the Ribosome. Ribosomes are very important; first they make all the proteins required in a cell or organism. Secondly, they are also target for several antibiotics. Cryo-EM in combination with single particle reconstruction is our main method to study different functional states of the translating Ribosomes. Beside ribosomes, we are also very much interested in determining sub nanometer resolved structures of other macromolecular complexes such as the protein translocation machinery, DNA repair complex, etc.

RNA metabolism and neuronal diseases
(U. Fischer)

The generation and translation of eukaryotic mRNAs depends on the elaborate interplay of a large number of *trans*-acting factors. These factors are organized in functional units, which catalyze the steps in mRNA metabolism and coordinate their temporal progression. Our group studies the functional dynamics of key machineries acting on mRNA. These include the pre-mRNA processing spliceosome, as well as the ribosome. In addition, our group is interested in the question of how defects in mRNA metabolism can lead to human diseases.

Biology of Cytoskeleton
(A. Gohla)

Failure of cells to migrate or migration of 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.

Biophotonics
(K. Heinze)

In an interdisciplinary approach we combine high-resolution concepts of fluorescence microscopy with tricks from material sciences. Our approach involves designing and nanofabricating so-called metamaterials with negative refractive properties that can serve as modified microscope substrates for fast imaging of biological surfaces with superresolution. Suitable for live cell applications, this low-invasive approach offers a fascinating prospect of observing individual biomolecules in their native environment and understanding how they act in concert.

Brain and Behaviour
(M. Heisenberg)

We study the fly *Drosophila melanogaster* trying to understand how the brain organizes behaviour. No other organism offers similar tools to manipulate the brain in the living, behaving organism and to relate behaviour to its underlying substrate. We analyse operant behaviour and in particular operant learning, selective attention, and endogenously changing perceptual hypotheses. We pay special attention to initiating activity and the adaptive role of chance in the brain. The understanding of brain function at the behavioural level is still in its infancy.

Inflammatory Cytokine Signaling
(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 multimolecular complexes. This explains why many of the signaling cascades are common to a number of different cytokines, but disregards the question of signaling specificity. Using the family of interleukin-6-type cytokines as a model system the laboratory investigates this question.

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)

Maintenance of the genetic information is crucial for all living organisms. Thus different DNA repair mechanisms exist to protect our genome from endogenous and exogenous attacks. Defects in these repair mechanisms have serious consequences leading to a dramatically increased predisposition to cancer and accelerated ageing as well as many other diseases. 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 the pro- and eukaryotoc NER machinery to gain insight into the process of damage recognition/verification, incision and repair. A second focus is structure-based drug design against human pathogens to identify new therapeutics against infectious diseases.

Signalling Processes of Receptors
(M. Lohse)

Cyclic nucleotides – cyclic AMP (cAMP) and cyclic GMP (cGMP) – are among 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.

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.

Structural Biology: Protein Folding, Function and Degradation
(H. Schindelin)

The group focuses on protein folding in the endoplasmic reticulum (ER) and the degradation of mis-folded proteins via the ubiquitin-dependent protein degradation pathway. In a second topic the anchoring of of inhibitory neurotransmitter receptors and their transport is investigated. 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, for example, defects in the endoplasmic reticulum associated degradation (ERAD) pathway, lead to a variety of pathophysiological states, such as the neurodegenerative disorders Alzheimer's and Parkinson's.

Mass Spectrometric Analysis of Post-translational Modifications
(A. Schlosser)

The main focus of our research is the analysis of posttranslational modifications (PTMs) by mass spectrometry (MS). MS is a brilliant technique for analyzing protein modifications and many advances in this area have been made during the last years. However, the enormous potential of this technique for the analysis of PTMs is still far from being tapped. We develop new methods for the qualitative and quantitative analysis of protein modifications, such as phosphorylation, ubiquitination, deamidation, ADP-ribosylation, hydroxylation, methylation, acetylation, and others more.

Single molecule studies of DNA repair
(I. Tessmer)

We are using atomic force microscopy (AFM) in combination with other biophysical and biochemical techniques to study protein-DNA complexes involved in DNA repair. AFM enables us to directly visualize molecular assemblies at the level of the individual molecules. We are particularly interested in understanding the different DNA damage recognition strategies developed by the various DNA repair mechanisms as well their pathological disturbances.

Immunopathogenesis of Arteriosclerosis
(A. Zernecke)

Atherosclerosis is imminently becoming the leading cause of death worldwide. The exact functions of specific immune cells in controlling disease development, however, remain elusive to date. By targeting specific chemokines/cytokines as well as microRNAs the group addresses the role of different immune cell subpopulations in atherosclerosis. Understanding the complex equilibrium and interplay between immune-cells that contribute to the process of atherosclerosis will be important to identify new therapeutic approaches for treating this disease.

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R. Benz
Kronhardt A, Rolando M, Beitzinger C, Stefani C, Leuber M, Flatau G, Popoff MR, Benz R, Lemichez E. (2011) Cross-Reactivity of Anthrax and C2 Toxin: Protective Antigen Promotes the Uptake of Botulinum C2I Toxin into Human Endothelial Cells. PLoS One.6:e23133.

S. Bhushan
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U. Fischer
Dill H, Linder B, Fehr A, Fischer U. (2012) Intronic miR-26b controls neuronal differentiation by repressing its host transcript, ctdsp2. Genes Dev., 26:25-30.

A. Gohla
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K. Heinze
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Teaching

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5.1.2 Research Center for Infectious Diseases

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General tasks and organisation

The Research Center for Infectious Diseases (ZINF) at the University of Würzburg represents the first cross-faculty and interdisciplinary institution established in Germany that is exclusively dedicated to research in infectious diseases. This focus remains important since infectious diseases continue to be a major worldwide public health issue. ZINF was founded in 1993 by the Federal Ministry for Research and Technology and the State of Bavaria; it subsequently rapidly developed into a highly regarded and internationally visible scientific institution. The center includes eight chairs of the medical faculty and the university hospital as well as of the faculties of biology, chemistry and pharmacy. A core aspect of the programme is centred on four young investigator groups whose research focuses on emerging and important topics in microbiology and infectious disease. These Young Investigator groups are associated with and located together within the Institute for Molecular Infection Biology (IMIB). The structure of the centre facilitates cross-faculty communication, initiation of joint research activities and recruitment of extramural funding in addition to the joint organisation of international conferences and meetings. Numerous external advisory and evaluation boards have recognised the high scientific quality and significance of ZINF. Notably, the young investigator programme was identified as a showcase to successfully promote the research and careers of junior scientists throughout Germany. As a consequence, in 2009 the university administration and board decided to continue to fund and support ZINF on a permanent basis.

Research focus

Functional characterisation of small regulatory RNAs in Helicobacter pylori and Campylobacter jejuni
(Cynthia M. Sharma, since 2010)

Post-transcriptional regulation represents a central level of gene expression control for many physiological processes in the cell. Our overall goal is to establish *Helicobacter pylori*, the causative agent of gastric cancer, and *Campylobacter jejuni*, the most common cause of food-borne gastroenteritis, as new model organisms for riboregulation in pathogenic bacteria. Specifically, we focus on the identification of small regulatory RNAs and associated RNA-binding proteins as well as their functions and mechanisms in stress response and virulence of these Epsilonproteobacteria. Especially, we apply and develop deep sequencing-based approaches (RNA-seq) for transcriptome analyses and identification of novel RNAs in both host and pathogen.

Epigenetic gene regulation in Trypanosoma brucei
(Nicolai Siegel, since 2012)

Using the protazoan parasite *T. brucei,* the causative agent of African sleeping sickness, the group studies epigenetic mechanisms leading to the formation of transcription promoting and repressing chromatin

Fig. 1: The human-pathogenic mould Aspergillus fumigatus.

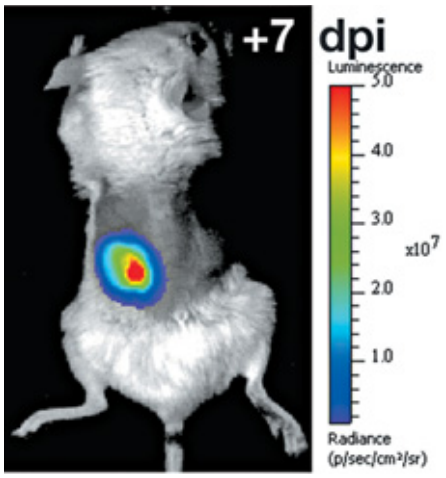

Fig. 2: Imaging of cutaneous aspergillosis in an animal model by bioluminescence.

structures. One key question is how changes in chromatin structure can help the parasite to evade the host immune response via antigenic variation. Central to this work is the use of deep sequencing technology to determine the genome-wide distribution of the various epigenetic factors.

Virulence determinants of the human pathogen Aspergillus fumigatus
(Sven Krappmann, since 2007)

Invasive fungal infections by the omnipresent mould *Aspergillus fumigatus* have gained increasing relevance as a life-threatening and hard to treat complication for immunosuppressed patients. Research in this Young Investigator Group covers various aspects of *A. fumigatus*, such as its metabolic versatility, its interaction with the host during hematogenous dissemination, or its restricted sexuality with the aim to elucidate virulence mechanisms of this opportunistic pathogen.

Bacterial cell differentiation
(Daniel Lopez, since 2010)

The laboratory is interested in elucidating the molecular mechanisms that lead microbial communities to form multicellular aggregates termed biofilms using the soil-dwelling bacterium *Bacillus subtilis* and the opportunistic pathogen *Staphylococcus aureus* as two gram-positive model organisms. We are particularly focused on the ability of microbial communities to differentiate into distinct subpopulation of cell types, which synchronize their roles within the community via secretion of extracellular signaling molecules. How these signals are sensed is of special interest to us. Specifically, we have identified that some receptor proteins are spatially organized into microdomains within bacterial membranes. The lipid composition of these microdomains differs to that of the surrounding membrane in an analagous manner to the lipid rafts found in eukaryotic cells.

Teaching

The young investigator groups participate in practical courses and lectures for undergraduate students of biology, medicine and biomedicine. The center regularly organises seminars, workshops and conferences covering current topics in medicine and microbiology. In addition, members of the center are involved in graduate students training.

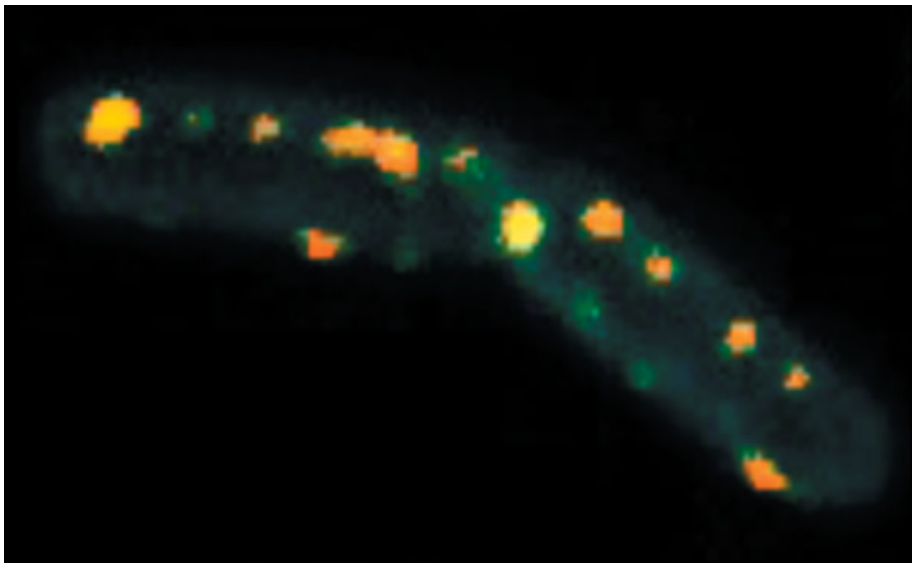

Fig. 3: Fluorescence micrograph of B. subtilis cells expressing the Yfp (yellow-fluorescent-protein)-labelled FloT protein. FloT is a protein that exclusively localizes in lipid rafts.

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5.1.3 Comprehensive Heart Failure Center (CHFC)

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Comprehensive Heart Failure Center

General Information

In November 2010, funding by the Federal Ministry of Education and Research in Germany has started for the Comprehensive Heart Failure Center (CHFC) at the University Hospital Würzburg, one of eight Integrated Centers for Research and Treatment. The CHFC aims to prevent heart failure and its complications.

Heart failure is a rapidly growing health care problem. The syndrome affects approximately one out of ten subjects above the age of 70 years, currently accounting for 2-3 millions patients in Germany. The prognosis is as severe as in many malignancies. Repeated hospitalizations are frequent and costly. Heart failure severely compromises physical performance, metabolism, endocrine and cognitive function, and quality of life. Various diseases may cause heart failure: hypertension, coronary artery disease, cardiomyopathies, valvular disease and others. Stroke, renal failure, anemia, cerebral dysfunction, depression and sudden cardiac death are frequent consequences. Hence, heart failure and its complications constitute an interdisciplinary multi-faceted problem mandating an interdisciplinary approach in research, teaching, and patient care.

The CHFC enhances and coordinates existing top-level basic, translational and clinical research activities in Würzburg. Theoretical institutes (e.g. Physics and Biophysics, Chemistry and Biochemistry, Biology, Pharmacology) cooperate with clinical departments (e.g. Cardiology, Cardiothoracic Surgery, Endocrinology, Nephrology, Psychiatry, Psychology, Neurology, Radiology, Epidemiology) to develop innovative concepts in diagnostics and clinical management as well as new therapeutic strategies, which intervene early in the healing and remodeling processes of the heart. In order to succeed in these ambitious endeavors, research at the CHFC is organized in eight Project Areas, which represent the most important structural subunits of the CHFC for interdisciplinary research and treatment. Six Core Facilities offer service functions for the research of CHFC members like laboratory analyses, genetic analyses, animal housing, tissue engineering, documentation of patient data and data mining.

The currently existing clinical study unit was transformed into the central clinical research facility of the CHFC, and will be complemen-

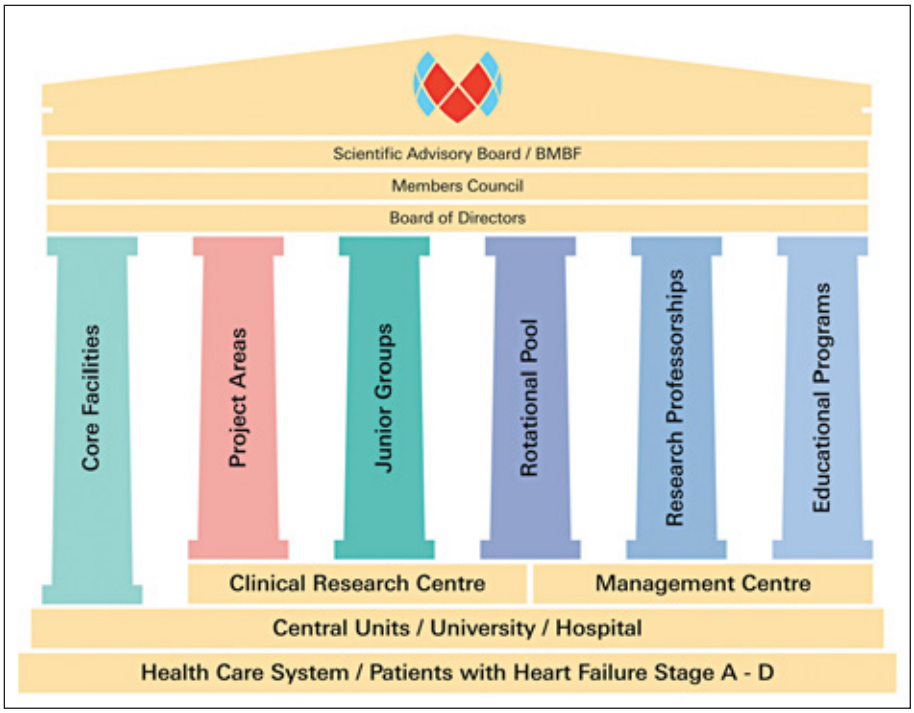

Fig. 1: Structure of the CHFC.

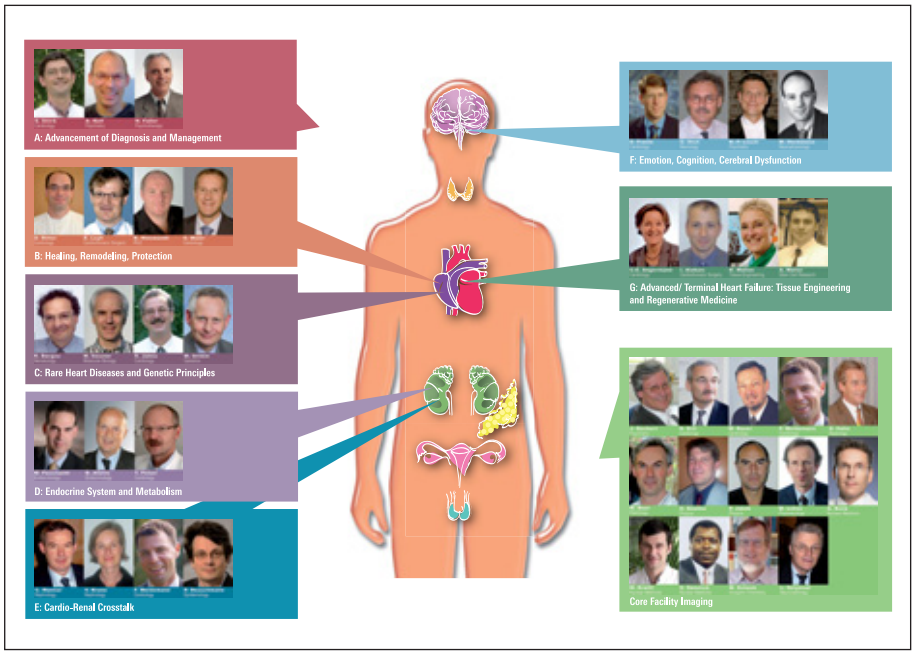

Fig. 2: Research at the CHFC is organized in eight Project Areas. They represent the most important structural subunits of the CHFC for the implementation, coordination, performance and advancement of interdisciplinary research and treatment.

ted by a Centre for Biometry, Study Coordination and Study Management (ZBSS). A Chair and Institute for Clinical Epidemiology and Biometry has been established at the Medical Faculty. Long-standing and very successful collaborations exist with the Collaborative Research Centers (SFBs), the Research Centre for Experimental Biomedicine of the DFG (Rudolf Virchow Centre), the Interdisciplinary Centre for Clinical Research (IZKF) of the BMBF, and the International Graduate School of Life Science (Excellence Initiative) as well as with the Coordination Centre for Clinical Trials, Leipzig (KKSL) , and the national Competence Network Heart Failure (CNHF).

The CHFC supports excellent researchers with ample opportunities to establish their independent scientific track, e.g. by supported research projects, protected research time while working in the hospital, junior research groups, and research professorships. A stepwise program for the training of young clinical researchers is currently being implemented in cooperation with the Graduate School for Life Sciences that will open a new section entitled "Clinical Sciences": the program features corollary studies in clinical research for medical students that may be extended into a masters degree shortly after finishing medical studies, a curriculum in clinical research for physicians, and a PhD track "Clinical science and epidemiology".

Major Research Interests

Research at the CHFC is organized in eight Project Areas. They represent the most important structural subunits of the CHFC for the implementation, coordination, performance and advancement of interdisciplinary research and treatment.

Project Area A: Advancement of Diagnosis and Management
(Coordinators: S. Störk, A. Reif, H. Faller)

Using large established and new cohorts Project Area A is investigating the individual and combined clinical utility of diagnostic and therapeutic options for heart failure. Project Area A aims to establish new diagnostic guidelines and complex multidisciplinary interventions for heart failure patients ("management"), which were successfully tested in real world settings. Project A1 characterizes the entire disease spectrum (stage A to D) in population-based longitudinal analyses. Biomaterials and standardized data sets are contributed by the prospect cohort study "Rheuma und Herz" (Associated Project A3), the "Handheld BNP Studie" (Associated Project A4) and the INH trial (Associated Project A5, completed). Additionally, an array of important basic and translational research projects focuses on mechanisms and consequences of cardiac hypertrophy (Project A2, Start-up Projects A6 and A7).

Project Area B: Healing, Remodeling, Protection
(Coordinators: O. Ritter, R. Leyh, B. Nieswandt, S. Maier)

Acute myocardial infarction is one of the most frequent causes for heart failure, often followed by chronic remodeling of heart tissue. Objectives of Project Area B are the identification of disease-specific mechanisms underlying those processes and identification of new therapeutic targets. The crucial role of clotting factor XIII for infarct healing will be investigated in clinical studies (Project B1). Project B2 investigates whether inhibition of the calcineurin /NFAT signaling pathway prevents cardial remodeling. The role of thrombocytes (Project B4), the effect of preoperative anti-oxidant rich diet (Associated Project B5), characterization of myocardial sodium channels in heart failure (Associated Project B6) and the impact of angiotensin receptor interacting protein ATIP1 (Start-up Project B8) are also key aspects of research in Project Area B.

Project Area C: Rare Heart Diseases and Genetic Principles
(Coordinators: R. Bargou, R. Jahns, M. Gessler, T. Grimm)

Project Area C addresses basic pathophysiological principles, clinical progression and new approaches for prevention and therapy of orphan cardiac diseases. Clinical studies focus on two important environmental factors: cardiotoxic cancer drugs (Project C2) and cardio-noxious antibodies (Associated Project C4). Start-up Project C5 recruits Myeloma-patients with primary cardiac amyloidosis for a diagnostic longitudinal analysis. Genetic factors for individual response to specific pharmacotherapeutics are investigated in Project C3.

Project Area D: Endocrine System and Metabolism
(Coordinators: M. Fassnacht, B. Allolio, H.-T. Pelzer)

For the first time clinical researches investigate the effect of a bariatic operation on cardial function and quality of life in an interdisciplinary randomized clinical trial (Project D1). Project Area D also focuses on influence of aldosterone and cortisol on development and progression of heart failure (Project D2) and effects of the different estrogen receptors in the vascular system (Associated Project D3). Start-up Project D4 designs a randomized clinical trial to

Fig. 3: The CHFC is housed in building A9 on campus of University Hospital of Würzburg.

investigate the impact of subclinical hyperthyreosis on heart function. Start-up Project D5 addresses the influence of PPARdelta, an common hormone receptor of myocard. Activated PPARdelta benefits glucose and fatty acids metabolism. The connection between hypotnatremia and advanced heart failure is subject of Start-up Project D6, which evaluates the potential of surrogates of electrolyte and water dysbalance as new prognostic markers.

Project Area E: Cardio-Renal Crosstalk
(Coordinators: C. Wanner, V. Krane, F. Weidemann, P. Heuschmann)

Pre-renal failure is a commonly observed complication of heart failure. Auto-antibodies that activate β1-adrenergic receptors may cause renal failure in heart failure patients (Project E1). Using an unique sample comprising 1,255 type 2 diabetic patients on hemodialysis from the Würzburg based 4D study, Project E2 evaluates biomarkers that are responsible for high cardiac mortality of these patients. In cooperation with the foundation "Stiftung Präventivmedizin des Kuratoriums für Heimdialyse und Nierentransplantation e.V." a shared platform for clinical research in Nephrology and Cardiology is established (Associated Project E3). Heart failure patients in Stage IV could benefit from peritoneal ultrafiltration. Start-up Project E4 investigates if this accessory therapy prevents rehospitalisation, restores cardiac and renal function and improves quality of life.

Project Area F: Emotion, Cognition, Cerebral Dysfunction
(Coordinators: S. Frantz, G.Stoll, K.-P. Lesch, M. Heckmann)

Interactions between heart failure and depression, cognitive and neurological dysfunction and changes in brain structure are subject of Project Area F. In a murine model, Project F1 studies whether heart failure leads to anxiety or depression-like behaviour, and if behavioural changes adversely affect left ventricular remodeling. To disclose the consequences of heart failure on structure and function of the brain, MRI techniques are used in Project F2 to analyze the thromboembolic as well as diffuse cerebral lesion development in relation to cognitive decline in patients with heart failure. In experimental studies in mice, the role of platelets and the coagulation system in the development of cerebral dysfunction in heart failure is investigated. Associated to Project Area F is the MOOD-HF trial assessing the effect of serotonin re-uptake inhibitors (SSRI) on mortality and hospitalisations in patients with heart failure and its sub-studies (GENE-MOOD and THROMBO-MOOD).

Project Area G: Advanced/ Terminal Heart Failure: Tissue Engineering and Regenerative Medicine
(Coordinators: C. Angermann, I. Aleksic, H. Walles, A. Müller)

Project Area G aims at a systematic prospective collection of data and biomaterials of patients with advanced or terminal heart failure (Full Project G1). The psychological effect of an internet-based platform for ICD-patients is investigated in Project G2. Sleep disordered breathing and heart failure is addressed by Associated Project G3. Common risk factors like obesity or arterial hypertension may lead in heart failure patients to a lower risk of mortality. Start-up Project G5 investigates the underlying mechanisms of this so called reverse epidemiology in cooperation with the national Competence Network Heart Failure and Projects A4 and A5 (Handheld-BNP and INH trial). Start-up Project G4 immunophenotypes and characterizes cardiospheres (CDC) derived from heart muscle tissue. Its potential for in-vi-

tro-testing of pharmaceuticals and as an autologous cell source is also addressed

Core Facility Imaging
(Coordinators: J. Deckert, G. Ertl, W. Bauer, F. Weidemann, D. Hahn, M. Beer, H. Köstler, P. Jakob, M. Lohse, A. Buck, M. Kreißl, S. Samnick, W. Schenk, L. Solymosi)

The Core Facility Imaging develops advanced morphologic, functional and metabolic imaging techniques to support the Project Areas. Further, researchers of the Core Facility investigate healing after cardiac infarction and cardiac energy metabolism with innovative approaches of imaging, implement strategies for quantitative cardiac perfusion measurement by magnetic resonance tomography (Associated Project CF 1.3), develop MRI contrast agents for molecular imaging (Start-up Project CF 1.4), and optimize free breathing cardiac MR imaging (Start-up Project CF1.5).

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5.1.4 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“. In 2011, the German Cancer Aid awarded the CCC Mainfranken the status “Onkologisches Spitzenzentrum”. As a multidisciplinary cancer therapy and cancer research center we 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.

The Trial Office and the Early Clinical Trial Unit provides the complete infrastructure for planning and conducting phase-I, II, and III studies in all departments of Wuerzburg University Hospital. This comprises study nurse support, documentation assistance, data management, quality management as well as training and education for physicians and study nurses. A particular strength of the CCC Mainfranken is the Early Clinical Trial Unit (ECTU, Phase-I Unit). The ECTU is a highly specialized and fully staffed interdis-

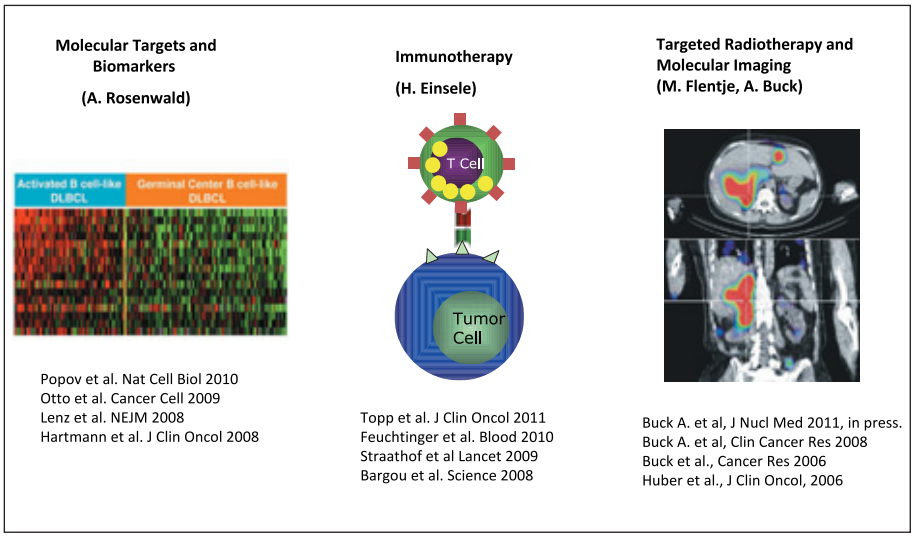

Fig. 1: Research programs of the CCCMF.

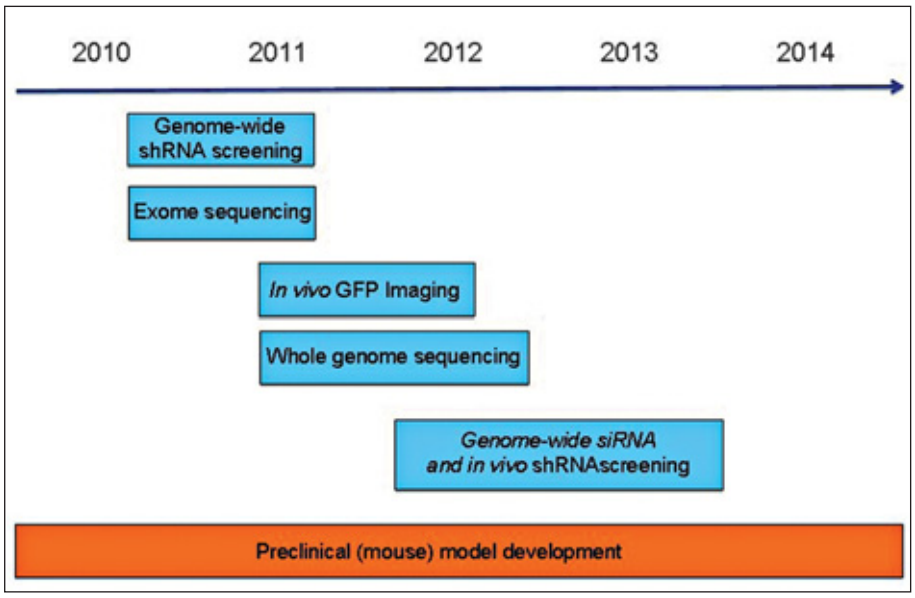

Fig. 2: CCCMF Core Units: Development 2010 to 2014.

ciplinary clinical unit focussing on the conduction of novel cancer therapies within the framework of phase-I, I/II and II clinical trials (early clinical development). Since its start in 2007 more than 24 phase-I and I/II trials have been initiated. Novel therapies tested in the ECTU include cellular and targeted therapies with novel antibodies, tyrosine kinase inhibitors heat shock protein inhibitors, HDAC inhibitors and other small molecules.

Major Research Interests and Research Infrastructure

The CCC aims to identify and validate novel molecular targets and novel therapeutic strategies for the treatment of cancer.
The Center has developed three main research programs aiming at the development of novel targeted and individualized therapies (Fig. 1). The first focuses on tumor cell signalling and target identification, the second on tumor immunology and immunotherapy, and the third on imaging and targeted radiotherapy. The three research programs are co-ordinated by members of the CCC Research Committee (Signaling: A. Rosenwald; Immunotherapy: H. Einsele; Radiotherapy: M. Flentje and A. Buck) together with the Deputy Director Research (M. Eilers) and the CCC Director (R. Bargou). In parallel the CCC Mainfranken offers a framework of interdisciplinary collaboration for scientists organized in the Research Committee. The research committee exerts major influence on the scientific strategy and profile of the CCC. It forms the platform for regular information about ongoing projects and progress and it explores opportunities for cooperation and joint grant applications. Membership demands regular funding, high standard publications and the proof of collaborative projects.
Research Core Facilities offer modern technologies to CCC members. The extension of existing and development of new platform technologies is planned for the next years (Fig. 2).

The clinical and basic research of departments embedded in the CCC Mainfranken is substantially funded through third-party grants. Collaborative funding by the German Research Foundation (DFG), the German Cancer Aid (DKH), the federal Ministry of Education and Science (BMBF), the European Union, the Bavarian State and the Interdisciplinary Center for Clinical Research (IZKF) as well as numerous individual projects form the basis and backbone of the three main research programs of the CCC Mainfranken.

Research Highlights in 2010 and 2011

Scientific milestones have been achieved in basic, translational and clinical cancer research throughout all three research programs of the CCC Mainfranken.

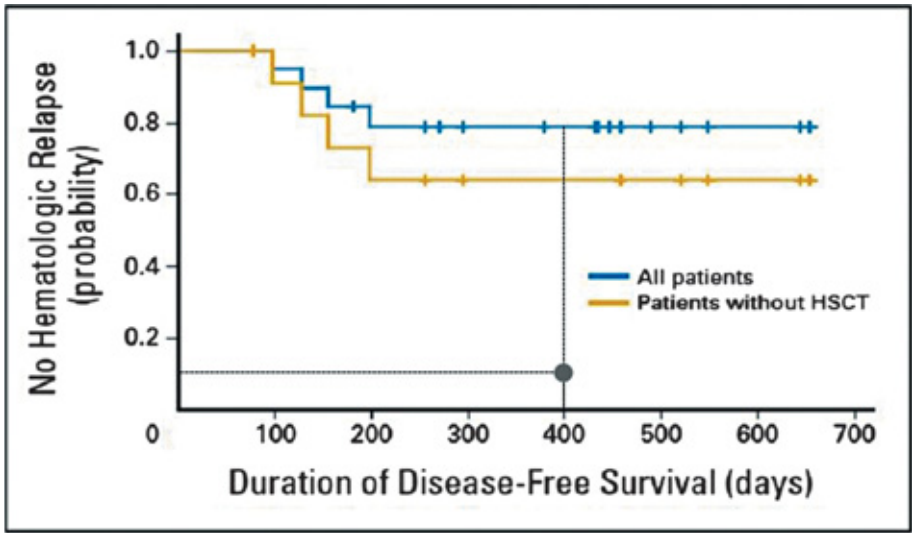

Fig. 3: Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. (Topp et al., J Clin Oncol, 2011).

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Common solid tumors:
A new mechanism of c-myc activation has been discovered as an important step in the molecular pathogenesis of colorectal cancer and in prostate cancer certain miRNAs were identified as biomarkers for high-risk patients. High precision radiotherapy achieved excellent local disease control in patients with stage I non-small cell lung cancer in an international multicenter study.

Hemato-Oncology and Pediatric Oncology:
In a phase II trial with a T cell engaging BiTE antibody high remission rates and long-term disease control was observed in patients with chemo-refractory acute lymphoblastic leukemia (Fig. 3). Novel target structures and molecular subgroups were identified in multiple myeloma and non-Hodgkin lymphoma and germline CBL mutations have been identified as genetic risk factor predisposing to juvenile myelomonocytic leukemia.

Orphan Diseases:
T antigens encoded by the polyoma virus were identified as potential targets for innovative therapeutic strategies for Merkel cell tumors and a new radio-conjugate was successfully tested for both imaging and therapy of patients with adreno-cortical cancer.

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5.2 Interdisciplinary Research Facilities
5.2.1 Interdisciplinary 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 strengthen clinical research based on interdisciplinary cooperations between clinical research groups and groups of biomedical sciences. The annual financial volume of direct funding was approx. 6 million Euro, the share of direct funding was approx. 4.9 million Euro.

To carry out its mission the IZKF uses three particular instruments:

- Support of cooperative research grants in the fields of immunology/infectiology, oncology, cardiac and vasular disorders imaging as well as neurosciences;
- Promotion of education and advancement of young researchers in medicine for all qualification phases;
- Improvement of scientific infrastructure by centrally funded core facilities and local research funding programmes.

The IZKF promotes research after an internal and external peer review. In this way, the IZKF guarantees quality-based differentiation in research funding of the Medical Faculty.
The statutory bodies at a glance:

- The General Assembly ("Zentrumskonferenz"),
- The Executive Board
- The External Scientific Advisory Board.

The IZKF Wuerzburg was founded in 1996 within the federal advancement programme "Health Research 2000" of the Federal Ministry of Education and Research as one of nine centers in Germany. Since 2004 it is entirely funded by the Free State of Bavaria. The statues which have been revised in 2010/2011 are documenting the progress of aims, duties, funding and decision-making structures of the center in the area of new structural and scientific challenges in the Faculty.

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 is the concept of combining the expertise of basic and clinical sciences to develop novel and effective diagnostics and therapeutic approaches. After up to 3 years of IZKF funding, the project's transfer into an external third-party funding is expected. All IZKF projects are selected on the basis of an internal and external review. In 2011 the Center changed the previous three-year review cycle to an annual review process in order to allow access to the IZKF under identical competitive conditions at shorter intervals. In 2012, 16 new projects are going to start their research.

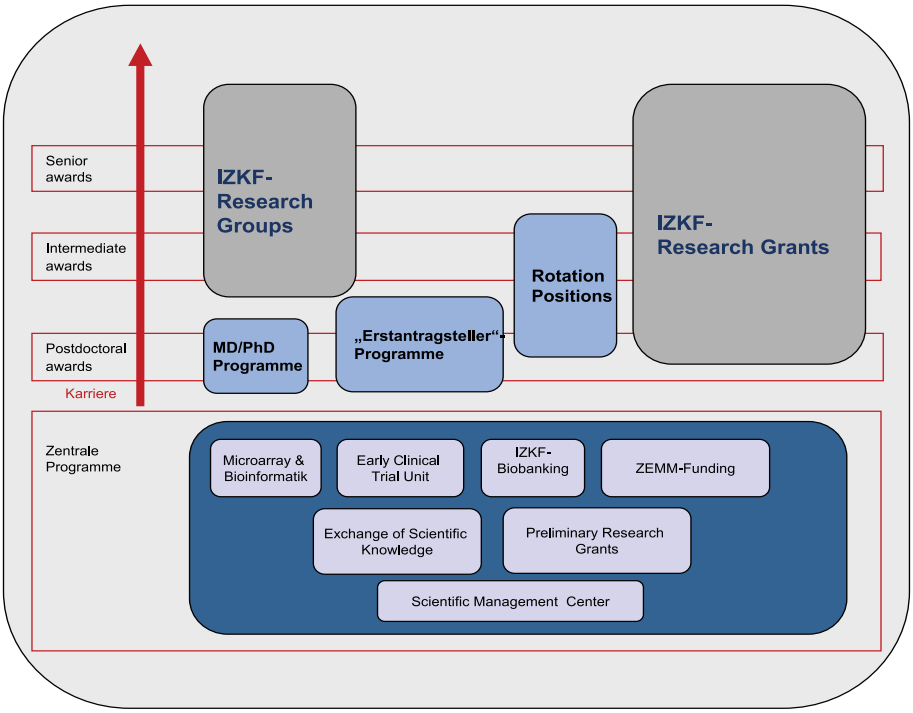

Fig.1: Chart IZKF Research funding 2011.

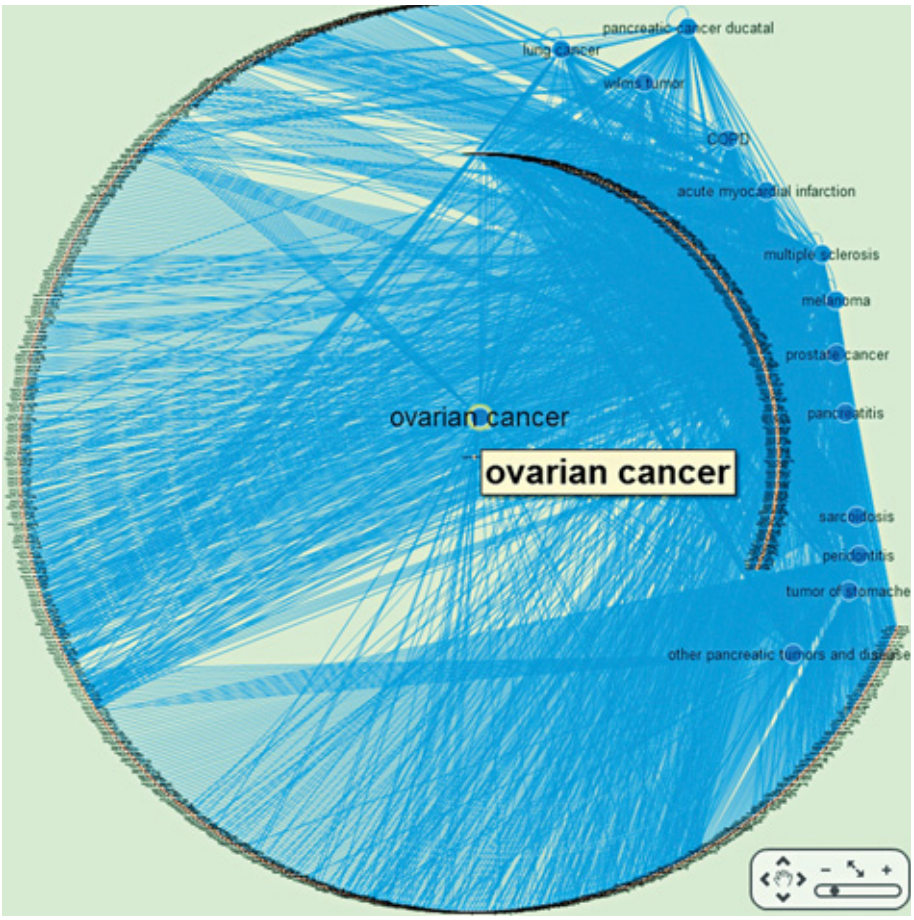

Fig. 2: Junior Research Group Wischhusen concerning publication Keller,… Wischhusen…et al 2011.

In 2011 the IZKF supported 36 research projects 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

For more information please visit: www.izkf-wuerzburg.de

Junior Career Programmes

To support young scientists in medicine is the second major commitment of the IZKF that involves a wide spectrum of sponsoring activities:

- The MD/PhD-Programme was jointly launched by the Medical Faculty and the Faculty of Biology in 1997 as the first German MD/PhD-Programme. Until 2010, 34 graduates participated in the programme. In 2012, the MD/PhD-Programme is going to be integrated completely into the Graduate School of Life Sciences of the University (GSLS). The plan is to continue the funding of the MD/PhD-Programme by a scholarship programme. The essential novelty of the funding is an option of an earlier return to the clinic by dint of a so-called "rotation position".
- The Erstantragsteller-Programm (The First Application) is awarded to young researchers of medicine who have finished their doctorate to carry out a clearly defined project. Supported by a mentor over a period of two years it will help these scientists to gain access to external research funding. During the first funding period 2008-2010, the programme supported seven junior researchers. One third of them was able to transfer their project idea into third party funding within the first year after the IZKF funding. A second season started in 2010 with eight female and male scientists.
- The Rotation Positions ("Rotationsstellen") ensure "protected" time for the research of young physician scientists by providing positions for physicians who cover for patient treatment and health care. Every year the IZKF provides five rotation positions. In 2010 and 2011, 10 physicians from eight clinics were supported.
- The Research Groups combine highly focused research funding with a career advancement in medicine. Altogether a funding of three groups is planned. It is planned to fund a total of three groups over a maximum period of five years. The aim of the Research Groups is a long-term- and sustainable strengthening of clinical research through scientific and structural impulses. An initial selection was made in a two-step procedure in 2011: At first, clinics did apply for the allocation of a Research Group by presenting a scientific and structural proposal. Within the scope of an internal selection and review process two proposals were chosen for an international advertisement of the group leader positions. After the selection of a group leader with an external review the following IZKF Research Groups will start their projects:
  1. „Common pathways of Cardiovascular and Neuropsychiatric Diseases", funded as common group of the IZKF and the CHFC, group leader: Dr. Leif Hommers
  2. „In vivo Imaging in preclinical modelst to develop, establish and va-

SELECTED PUBLICATIONS

See also: Annual IZKF Reports (available from IZKF-Office)

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lidate novel concepts in immune- and tumor therapies“, group leader: Dr. Andreas Beilhack.

The remaining third IZKF Research Group will be announced and selected in 2012.

Other activities

To improve the scientific infrastructure in clinical research the Center maintains the following four Core Facilities:

- The Microarray-Unit, which was established as a core facility in 2001, has expanded the spectrum of its service range as “IZKF-Service-Unit for Microarray applications and bioinformatics analyses from high throughput methods” in 2011.
- With the beginning of an IZKF funding in 2008 the Early Clinical Trial Unit could be established as a new highly specialised unit for experimental tumor therapy at the University of Würzburg. As an interdisciplinary platform the ECTU is used for treating tumour patients in phase I and IIa/b studies and it has strengthened the field of the translational medical research significantly.
- Since 2010, the IZKF supports the Infrastructure of the Center for Experimental Molecular Medicine, not least in order to gain access to all IZKF members.
- In 2011, the Center recommended the funding of the Biobank (Tissue) which is an integral part of the BMBF-funded „Interdisciplinary Bank of Biomaterial and Data Würzburg“. It is also linked to the CCC Mainfranken.

Finally, the center offers flexible funding moduls on-site in contrast to major external funding research organisations:

- Start-up financing for innovative research ideas
- Central budget for reimbursement of travel expenses
- Visiting researcher programme for external scientists
- Organization and funding of symposia, workshops and other meetings in order to encourage cooperations between scientists from internal and international universities.

Since 2010, the Center offers a consulting service for scientists, particulary young scientists and groups of scientists, who apply for an external research funding. In this connection the IZKF has also supported the CHFC, the Else-Kröner-Forschungskolleg for interdisciplinary translational immunology as well as the Interdisciplinary Bank of Biomaterials and Data Würzburg (IBDW) concerning the application and implementation phase as well as conceptual and operational project management.

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5.2.2 Interdisciplinary Bank of Biomaterials and Data Würzburg (IBDW)

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General Information

Research involving clinical information analysed in conjunction with human biological or genetic data will be essential to foster improvements in the detection, prevention, diagnosis, and treatment of multi-factorial diseases. Embedded in the Initiative of the Federal Ministry of Education and Research (BMBF) to build up centralized National Biomaterial Banks, the Interdisciplinary Bank of Biomaterials and Data Würzburg (IBDW) aims to systematically collect liquid (blood/DNA/urine) and solid biomaterials (BM) from patients and study participants of the Medical Campus Würzburg.

In the developmental concept of the IBDW priority has been set towards a concerted establishment and sharing of IBDW resources consisting of clinical data, human biological samples, and information derived from their analysis. The concept comprises a systematic, simultaneous and sequential collection of liquid and solid BM from patients and study participants of the University's Hospitals. Each collection will comply with the legal framework and ethical principles applicable, meeting highest quality standards according to the OECD recommendations (10/2009) and the OECD Guidelines for Biological Resource Centres. Collected biomaterials will be linked with the corresponding clinical data sets in accordance with current data protection and safety regulations as well as current ethical recommendations securing the donors' privacy.

Structure, aims, and major research interests of the IBDW

The cooperative IBDW is composed of a central database and two central bio-sample repositories (Fig. 1), one for liquid and the other for solid/tissue biomaterials, and a limited number of specialized decentralized biobanks, all adhering to IBDW standards. The Medical Faculty holds full responsibility for the IBDW governed by its own steering committee. Each central and decentralized collection of data and biomaterials will meet highest quality standards according to the current OECD recommendations.

Implementation of the IBDW concept will be achieved by a uniform IT structure across all departments and institutes of the Medical Research Campus correlating the individual bio-samples with their patient-specific, pseudonymized clinical data sets collected along the clinical patient management paths (Fig. 1). Information derived from the analysis of the patients' bio-samples will be accessible on request by a specified data and privacy protecting regulation involving the IBDW Executive Board for decisions, the IBDW Management Board for feasibility, and the IBDW Scientific Advisory Board for scientific merits.

Existing high quality BM collections within the University Hospital have been identified to be integrated into the IBDW. In addition, the IBDW will manage and operate human bio-samples as well as access to corresponding clinical and laboratory data provided by existing national and international pu-

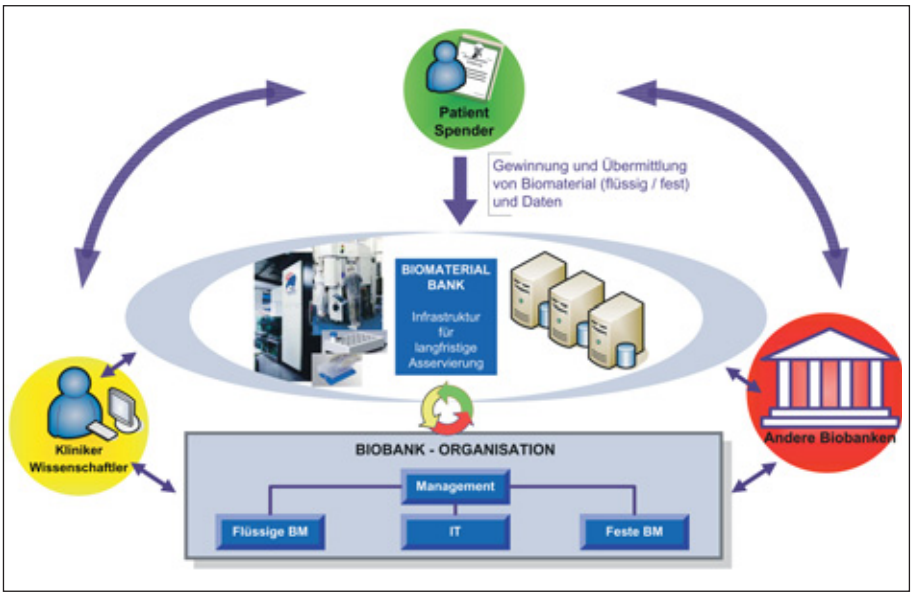

Fig. 1: Organizational structure of the IBDW.

Fig. 2: Construction of the IBDW cryostorage-building (A8).

blic funded basic and clinical research programs at the University and University Hospital of Würzburg that have been successfully executed in the past years: Interdisciplinary Center for Clinical Research (IZKF), Comprehensive Cancer Centre Mainfranken (CCCM), Comprehensive Heart Failure Centre (CHFC), Rudolf Virchow Centre (RVZ). These research activities represent an ideal basis for future national, European and global networking.

Main principles of the IBDW comprise:

- Concurrent liquid and solid sampling of human biomaterials using a consistent bio-sample labelling, registration, tracking, storage, and retrieval system enabling parallel analysis of matching blood and tissue samples along the course of the respective disease(s);
- Short term storage of bio-samples for 2-5 years (-80°C, immediate access, rapid sample read out, rapid sample compilation) (Fig.2);
- Long-term storage for more than 10 years (-140°C, gas phase liquid nitrogen) for pre-specified liquid BM (Fig.2);
- Implementation of a multi-level data storage and access concept ensuring consistency of data and bio-sample identity under consideration of current data and privacy protection regulations;
- Implementation of hierarchical pseudonymized clinical data sets (uniform data sets for annotation, basic, and disease-specific information);
- Participation in the National Registry of German Biobanks
- Project-based cooperation and networking on a national, European and global level.

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5.2.3 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 from 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 (DNA pronuclear microinjection, ES cell-based technology), embryo- and sperm cryopreservation and rederivation of mouse lines by embryo transfer for the entire network of biomedical research at the University of Würzburg.
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 for researchers. In addition, sperm freezing and in vitro fertilisation procedures have successfully been established.
To ensure the microbiological security of the SPF-area embryo transfers for the rederivation of mouse lines are performed under sterile conditions in laminar flow benches while preparation of embryos is performed within a separated laboratory.
In 2011 a total of 58 mouse lines could successfully be transferred into the SPF-area via rederivation and in vitro fertilisation. Breeding colonies under specific pathogen-free (SPF) conditions could be established and maintained from all these mouse lines.
The production of transgenic mice is performed in the Institute of Pharmacology and Toxicology. The ES cell-based technology for generating knock-in and knock-out mice (gene targeting) is currently being established at the Rudolf-Virchow-Center. A new state-of-the-art microinjection microscope will be used for conventional blastocyst injection and laser-assisted injection into 8-cell stage embryos.

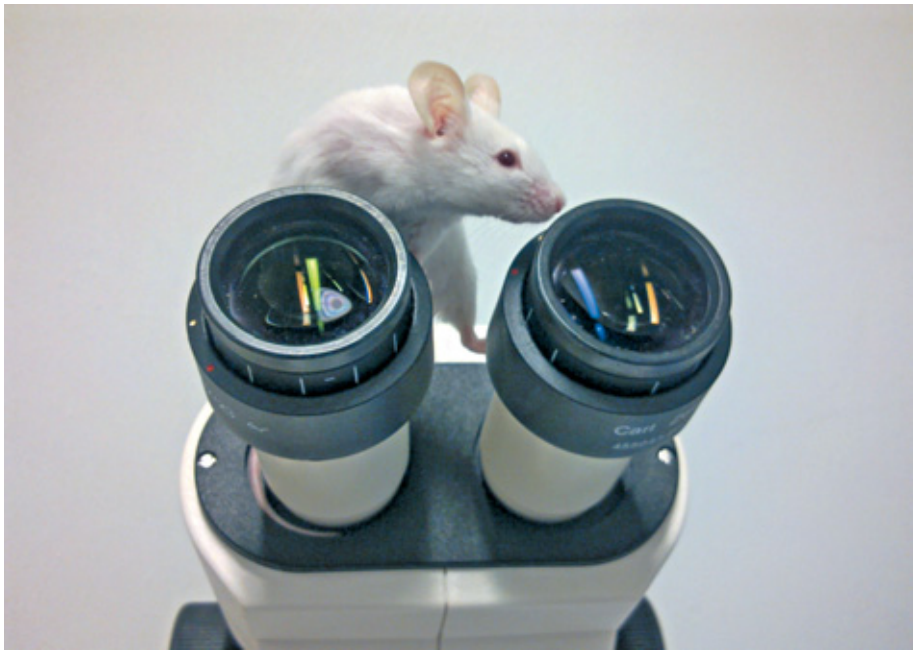

Fig. 1: Albino BL/6-mouse.

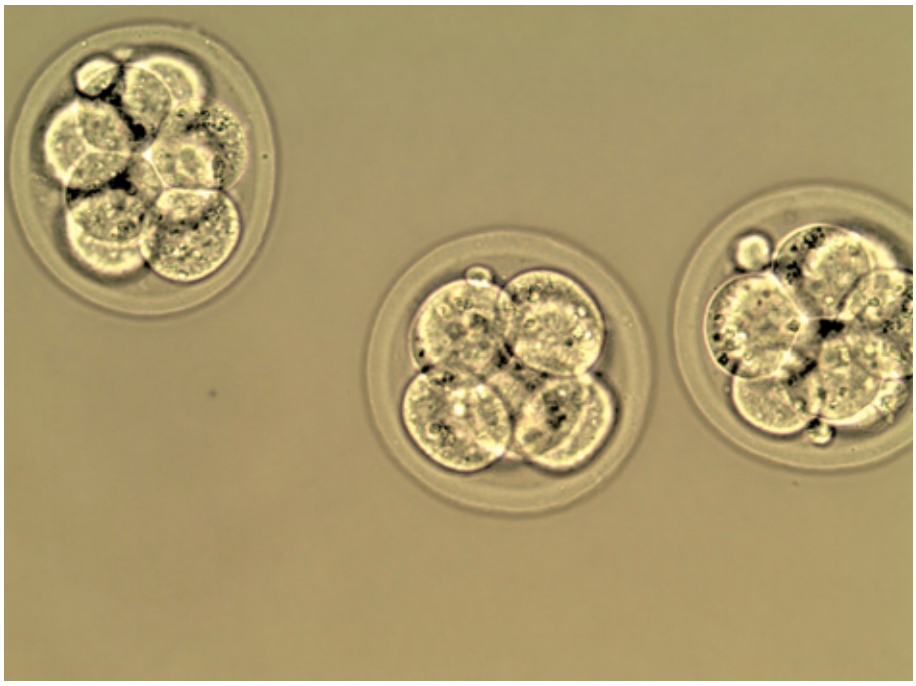

Fig. 2: 8-cell stage embryos used for rederivation.

5.2.4 Else-Kröner-Forschungskolleg Würzburg – Interdisciplinary Physician-Scientist Program in Translational Immunology

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General Information

The Else-Kröner-Forschungskolleg Würzburg for Interdisciplinary Translational Immunology is a multidisciplinary research and training program which aims at providing a structured, science-based training for physician-scientists oriented towards clinical immunology.

The application from Würzburg University Hospital under the leadership of Dr. Andreas Beilhack (Department of Medicine II) and PD Dr. Jörg Wischhusen (Department of Obstetrics and Gynaecology) together with other two applications from Bonn and Ulm University Hospital won the highly competitive nationwide selection process of the Else-Kröner-Fresenius-Stiftung and excelled over 55 other applicants. During the first three-year funding period the Else-Kröner-Forschungskolleg Würzburg will receive an amount of one million Euros.

The Else-Kröner-Forschungskolleg Würzburg has been designed to provide optimal support for the careers of young physicians at the interface between medical work and clinical and experimental research. Within the program framework eight selected fellows will receive an optimized training in medical skills in their respective speciality. Furthermore the Else-Kröner-Fellows participate in a special training program in research, including a 12 month research period, integration into clinical trials and a mentoring program.

The eight Else-Kröner-Fellows will be introduced to new methods of biomedical research within the eight participating departments and institutes and through this new curriculum will gain comprehensive insight into the immunobiological basics of medicine.

Malfunctions of the immune system have a profound impact on various diseases throughout many disciplines of medicine. An improved interconnection between basic immunological research and the translation of those results into clinical applications is imperative for innovative therapeutic approaches. Therefore, training of young physicians in the concepts of immunobiology should not be limited to the curriculum at medical school alone, but preferably should also play a major role during continuous clinical training.
The Else-Kröner-Forschungskolleg Würzburg recognises the demand of patient-oriented personalization of immunotherapeutic concepts. Tolerance mechanisms responsible for insufficient protection from cancer and infectious diseases and excessive immune responses in transplant rejection, autoimmune diseases and allergy are two sides of

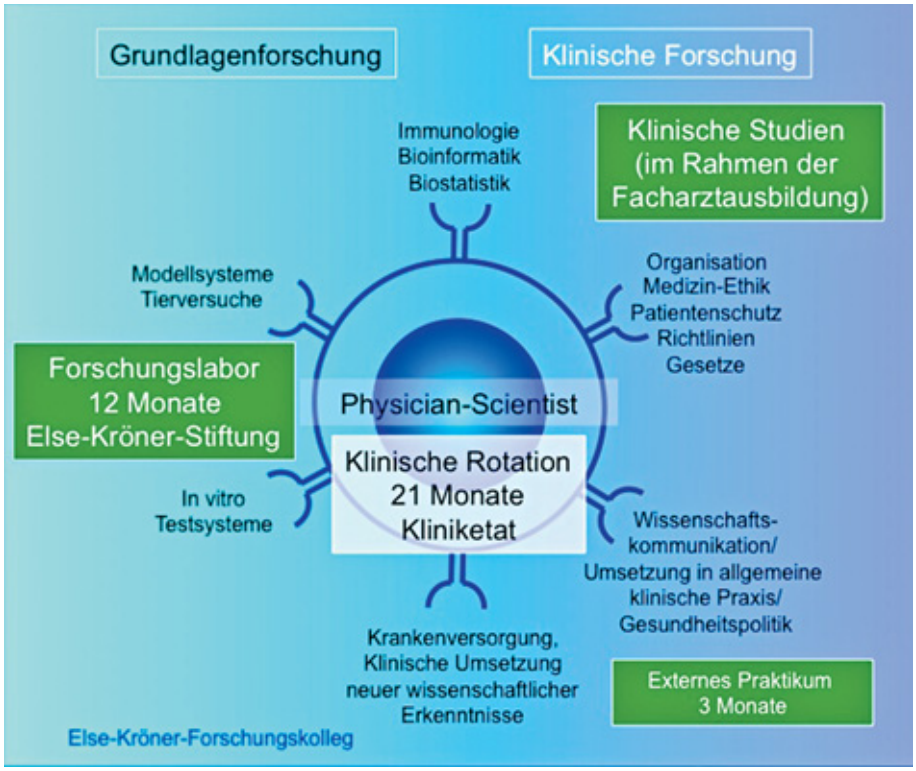

Fig. 1: The general training elements of the Else-Kröner-Forschungskolleg.

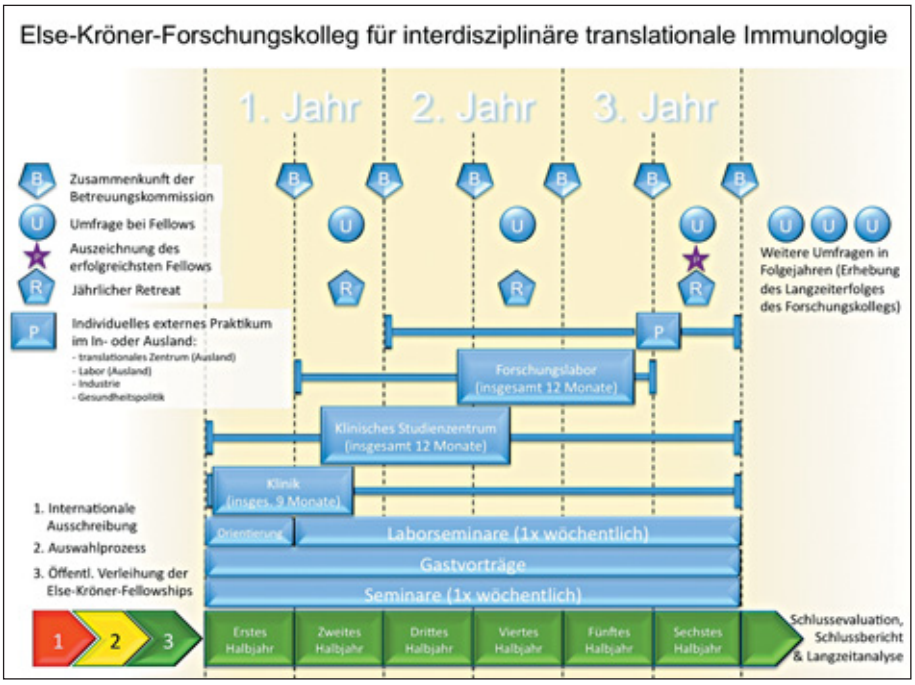

Fig. 2: The individualised educational structure of the Else-Kröner-Forschungskolleg.

the same coin. Consequently, all these topics will be included in the curriculum of the Else-Kröner-Forschungskolleg Würzburg. Ultimately, the Else-Kröner-fellows should gain knowledge of the broad impact of immune function on common diseases beyond conventional disciplinary borders.

The Else-Kröner-Forschungskolleg Würzburg is thus very well suited to support a long term interdisciplinary cooperation. This offers the unique chance of promotingtranslation of therapeutic approaches that have proven to be successful in some immune-related diseases towards new not yet exploredpathologies.

Patient-oriented immunological research

To guarantee an optimal interaction between experimental immunological and clinical research, eight different clinical departments and institutes at Würzburg University Hospital and Würzburg University joined to collaborate in the Else-Kröner-Forschungskolleg.

State-of-the-art individualised immunotherapy inevitably begins with the identification of target genes. These are analysed at the Institute of Pathology Würzburg, an internationally recognized centre for lymph node pathology with state-of-the-art sequencing technology (Leukemia and Lymphoma Molecular Profiling Project, International Cancer Genome Consortium).

Proteins, essential players in all key functions of the cell and therefore also in the development, diagnosis and treatment of various diseases, are characterized at the DFG Rudolf-Virchow-Centre with various methods including high resolution microscopy and x-ray analysis.

In cooperation with the Department of Medicine I it was demonstrated that autoantibodies against ß1/2-adrenerge receptors can play a major role in the pathogenesis of cardiac insufficiency. The clinical concepts emerging from this research will be further explored and developed at the new founded German Center for Heart Failure (DZHI) (which is connected to the Department of Medicine I).

The Department of Medicine II focuses particularly on innovative immunotherapies for hematological malignancies and has initiated the nationally unique Early Clinical Trial Unit. A center of stem cell transplantation has been built in close collaboration between the Department of Medicine I and the Würzburg University Children´s Hospital where new approaches of stem cell transplantation are evaluated. The recently established IZKF-research group “In vivo Imaging in preclinical models for immune and cancer therapies” is testing new immunological therapeutic concepts for leukaemia, solid tumours, infections and graft-versus-host disease after stem cell transplantation in preclinical models.

Adoptive immunotherapies may benefit from novel protocols for efficient generation of tumour-antigen-specific T-lymphocytes under GMP-conditions. Such a special protocol has been developed at the Würzburg University Children´s Hospital. Another focus of the Children´s Hospital is set on dendritic cell-based vaccination for the treatment of pediatric brain tumors.

Immune responses are investigated in close collaboration with the Institute of Virology and Immunobiology. Scientists in this institute test novel concepts to regulate immune responses via cell surface receptors. This approach includes research on the regulatory role of rare T-cell populations such as gamma-delta-T-cells and NK-T-cells.

The Department of Dermatology, Venerology and Allergy has investigated tumour microenvironments as modulator and target structure of anti-tumoral immune reactions. It has successfully carried out trials of peptide based vaccination against tumor-stroma-antigens. Additionally, with the appointment of Prof. Goebeler as the new department chair the field of Allergy research will be strengthened.

At the Department of Obstetrics and Gynaecology antibody-based therapies play a key role in the treatment of breast carcinoma. Scientifically the examination of tolerance mechanisms in tumors as well as at the feto-maternal interface forms the primary focus of interest. The junior research group “tumor progression and immune-escape” develops clinically relevant strategies for the immunotherapeutic “targeting” of tumour stem cells. Based on mRNA-profiles in the peripheral blood lymphocytes new diagnostic approaches have been developed.

Structured training for the physician-scientist

The actual participation of the selected fellows in the training program of the Else-Kröner-Forschungskolleg will last for 3 years. This time frame allows to personalize the program to suit the individual interests and talents of the participants. In that way a structured and goal-oriented training as a physician scientist will be adjusted to the individual career paths of the Else-Kröner-fellows. The Else-Kröner-Forschungskolleg embodies three major training components for the young researchers: The clinical training in the individual medical subspecialty, a basic training in biomedical research with an interdisciplinary focus on immunology as

well as a profound training in the translation of preclinical results into clinical trials. The mentoring program of the Else-Kröner-Forschungskolleg is supposed to support prospective physician-scientists in mastering the numerous challenges of the daily life in the clinics and in academia and help them to improve their individual career options. A first orientation semester with weekly meetings of the Else-Kröner-fellows with clinicians and researchers will facilitate the rapid acquisition of a program overview and also create personal contacts with experts in the various disciplines.

During the orientation semester, the Else-Kröner-fellows pass weekly lab rotations in three different research laboratories. This will enable them to make a well-founded decision about their personal research project and also help them to explore future possibilities for collaboration opportunities for their research project.

Together with their supervisors, each fellow will design his/her individual program that should offer him/her an optimized coordination for the 12-month research project consisting of clinical training, including a clinical trial. The supervisory commission, consisting of a scientist, a physician and a clinical director, will be well equipped to ensure that both clinical and scientific needs are considered. An external faculty mentor will provide personal guidance to each fellow's individual career development. This policy of external mentors should limit potential conflicts of interest between the faculty and the supervisors. Based on the desired career path and the project proposal the supervisory board of the Else-Kröner-Forschungskolleg will issue a recommendation for each fellow's individual program.

According to individual wishes the lab rotation or the work on a clinical trial can be divided into various time intervals that all together guarantee a time-span of 12 months of research time. Flexible and individually tailored rotation-schemes or so-called tandem programs have already proven to be successful at the Interdisciplinary Centre for Clinical Sciences (IZKF) Würzburg.

There is no strict time setting for the program to begin. This allows the fellows to start their rotation into a research lab according to their clinical training. The fact that the Else-Kröner- fellows can pick the lab of their choice ensures that the principal investigators of these laboratories will have to accommodate the particular needs of the fellows. During this protected laboratory research period, the fellows are freed from all clinical obligations.

During the three-year training program there will be weekly lectures and seminars to provide a deeper insight into a variety of relevant topics such as statistics, bioinformatics, methods, applied immunology, guidance in study design, biobanking, bioethics, to name a few. Additional training courses and qualification programs shall promote work-related social skills and successful coping strategies for challenges related to clinical and research work and optimal work-life balance.

As a perspective, successful Else-Kröner-fellows are expected to advance their research projects sufficiently to secure external research funding. The First-Application-Program of the IZKF Würzburg offers a good first funding opportunity. Furthermore the IZKF Scientific Management Center supports applicants in the process of grant writing for external funding organizations. This will ensure that the Else-Kröner-fellows will be capable in establishing their own independent research groups and become future leaders as physician-scientists.

5.3 Collaborative Research Centers
5.3.1 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. It was in its fourth period of funding and terminated in the December 2011. The SFB 487 consisted in the end of 17 research groups from the faculties of medicine and biology. The research was 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 was applied ranging from measurements on isolated proteins to investigations in living animals. Biochemical methods were 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 were analysed using methods of cell biology, biochemistry, and genetics. Finally the physiological function of membrane proteins was investigated in intact organs and living animals after knock out or over-expression of certain genes. Thus, the SFB 487 was a methodological platform that allows access to a variety of methods for the investigation of membrane proteins. The ultimate goal of all efforts was the identification of novel pharmaceutical targets in membrane proteins. This may lead to novel therapies of diseases caused by membrane protein malfunction or mal-regulation.

Major Research Interests

The common research topics of the SFB 487 were 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 were to determine structures of physiologically and biomedically relevant membrane proteins and to identify their functional epitopes. This includes binding sites for hormones, neurotransmitters, substrates and interacting proteins. The structural results were supplemented with functional investigations to understand the physiology role of individu-

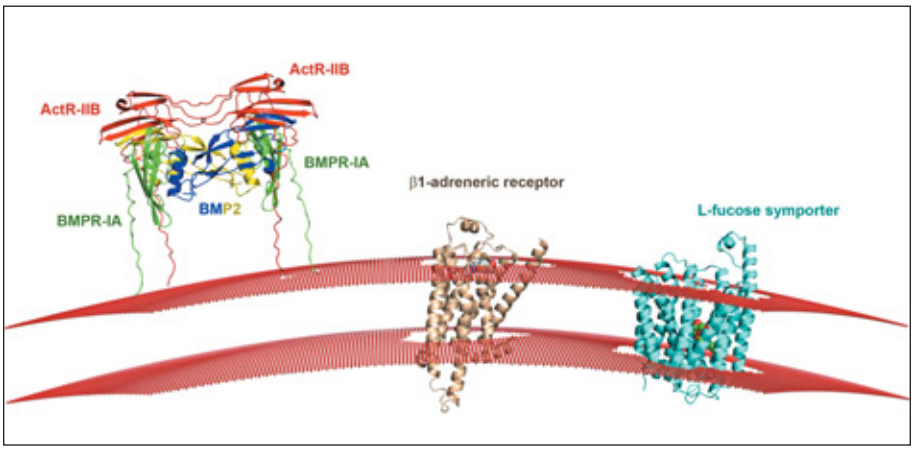

Fig. 1: Schematic representation of the three membrane protein classes investigated in the SFB 487. The complex of BMP-2 bound to a receptor complex formed by two receptor subtypes represents the class of receptors with a single transmembrane segment. The beta1-adrenergic receptor and the L-fucose symporter represent two classes of membrane proteins with several transmembrane segments.

al proteins. Functional data of membrane proteins in vivo were acquired from cultivated cells, intact organs or living animals. After the establishment of functional mechanisms of individual membrane proteins the acquired knowledge will be used for the development of novel therapeutic drugs.

Research area A: Proteins with several transmembrane domains

A1 Lohse/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

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 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 $Ca2^+$-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

Central administration

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:
July 23 – 24, 2010, Bad Brückenau

International Symposia:
"Molecular Pharmacology of Receptors, Channels and Transporters", July 28-30, 2011

SELECTED PUBLICATIONS

Patino E, Kotzsch A, Saremba S, Kraich M, Nickel J, Sebald W, Mueller TD. (2011) Structure analysis of the IL-5 ligand-receptor complex reveals a wrench-like architecture for IL-5R . Structure 19:1864-75.

Dadacz-Narloch B, Beyhl D, Larisch C, López-Sanjurjo EJ, Reski R, Kuchitsu K, Müller TD, Becker D, Schönknecht G, Hedrich R. (2011) A novel calcium binding site in the slow vacuolar cation channel TPC1 senses luminal calcium levels. Plant Cell 23:2696-707.

Klaiber M, Dankworth B, Kruse M, Hartmann M, Nikolaev VO, Yang R-B, Völker K, Gaßner B, Oberwinkler H, Feil R, Freichel M, Groschner K, Skryabin BV, Frantz S, Birnbaumer L, Pongs O, Kuhn M. (2011) A cardiac pathway of cyclic GMP-independent signalling of guanylyl cyclase A, the receptor for atrial natriuretic peptide, involves a GC-A – TRPC3/C6 – signalling complex. Proc Natl Acad Sci USA 108:18500-5.

Mukherjee J, Kretschmannova K, Gouzer G, Maric HM, Ramsden S, Tretter V, Harvey K, Davies PA, Triller A, Schindelin H, Moss SJ. (2011) The residence time of GABAARs at inhibitory synapses isdetermined by direct binding of the receptor α1 subunit to gephyrin. J. Neurosci 31:14677-14687.

Ehrenschwender M, Siegmund D, Wicovsky A, Kracht M, Dittrich-Breiholz O, Spindler V, Waschke J, Kalthoff H, Trauzold A, Wajant H. (2010) Mutant PIK3CA licenses TRAIL and CD95L to induce non-apoptotic caspase-8-mediated ROCK activation. Cell Death Differ 17:1435-1447.

5.3.2 Collaborative Research Center 567, Mechanisms of Interspecific Interactions of Organisms

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Professor Dr. rer. nat. Rainer Hedrich (Vice-Speaker)
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General Information

The Coordinated Research Center (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 Center 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.
Funding of the SFB 667 ended in December 2011.

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

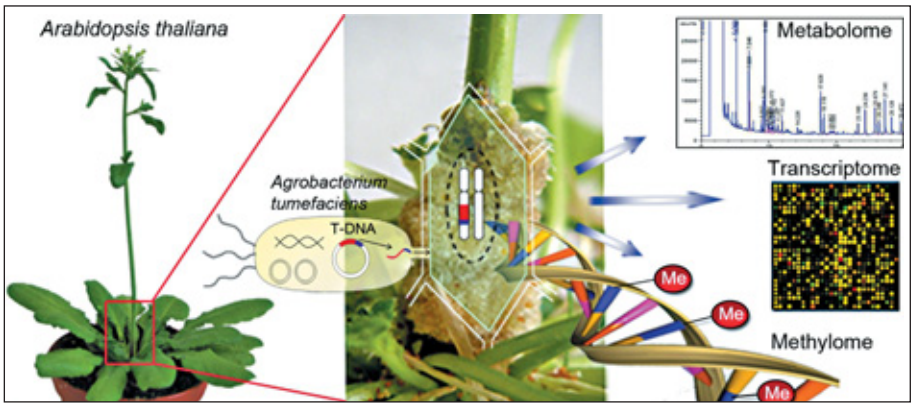

Fig. 1: Molecular Mechanisms controlling the interaction between Arabidopsis thaliana and Agrobacterium tumefaciens (TP B5).

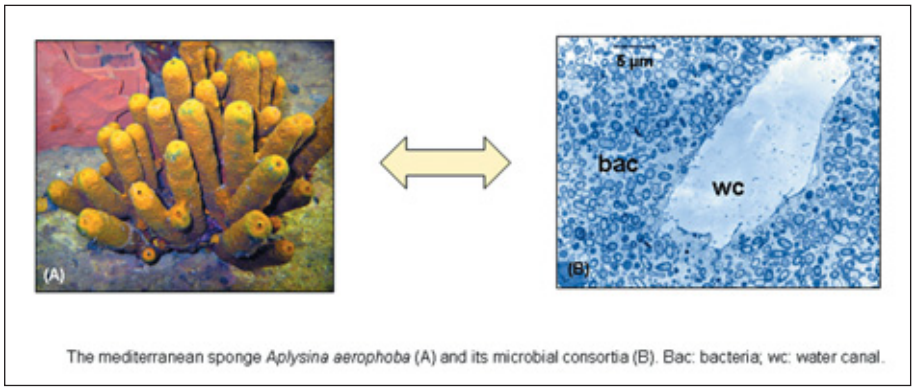

Fig. 2: Interactions between the marine sponge Aplysina aerophoba and its symbiotic microbial consortia (TP C3).

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”.

Symposia

The Coordinated Research Center organized two symposia: 22 to 24 February 2010 in Pommersfelden and 28 to 29 November 2011 in Veitshöchheim.

SELECTED PUBLICATIONS

Jeworutzki E, Roelfsema M, Anschuetz U, Krol E, Elzenga J, Felix G, Boller T, Hedrich R, Becker D. (2010) Early signaling through the Arabidopsis pattern recognition receptors FLS2 and EFR involves Ca2+-associated opening of plasma membrane anion channels. Plant Journal 62:367-378.

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Wippel K, Wittek A, Hedrich R, Sauer N. (2010) Inverse pH Regulation of Plant and Fungal Sucrose Transporters: A Mechanism to Regulate Competition for Sucrose at the Host/Pathogen Interface? Plos One 5:e12429.

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5.3.3 Collaborative Research Center 581, Molecular Models for Diseases of the Nervous system

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General Information

The "Collaborative Research Centre" SFB 581 „Molecular models of diseases of the nervous system" has been established in 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 corresponding 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 SFB connects 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

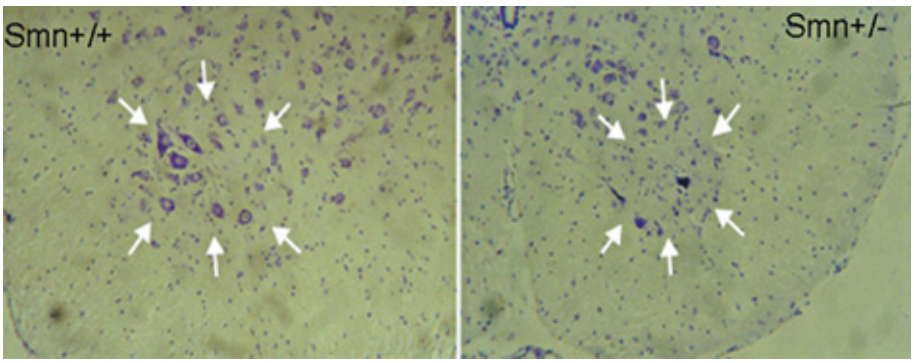


Fig. 1: Degeneration of spinal motoneurons in a mouse model for spinal muscular atrophy (Smn+/- right side). The area where motoneurons degenerate is labelled with white arrows.

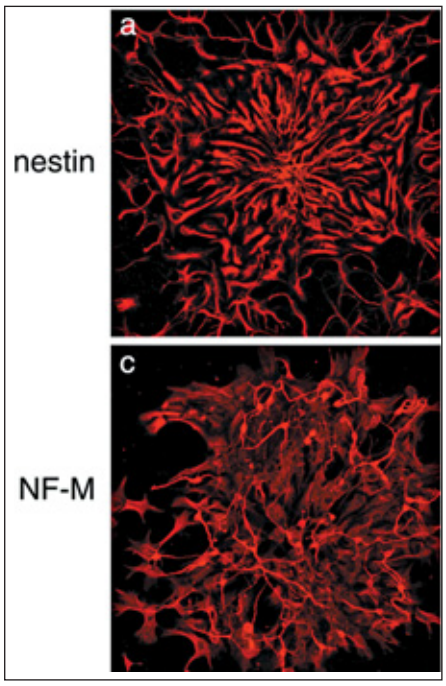


Fig. 2: Differentiation of neural stem cells in cell culture. Immature stem cells are labelled with an antibody against Nestin (panel a), 24 hrs after plating on Laminin, differentiated neurons that grow long neurites can be identified by labelling with antibodies against Neurofilament-N (lower panel).

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

A7 Toyka/Sommer (Neurologie): Immunpathogenese des Stiff-Person-Syndroms

A8 Wiendl (Neurologie, until 2010): 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, until 2010):* Pathophysiologische Relevanz von Zwei-Poren-Kalziumkanälen (K_2P) für Inflammation und Neurodegeneration in T-Zell-vermittelten Autoimmun-erkrankungen des zentralen Nervensystems

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

B28 *Förster (Genetik/Neurobiologie)): Störungen im Schlaf-Wachverhalten verursacht durch Transmissionsdefekte an dopaminergen und serotonergen Tripartite Synapsen am Modell Drosophila*

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

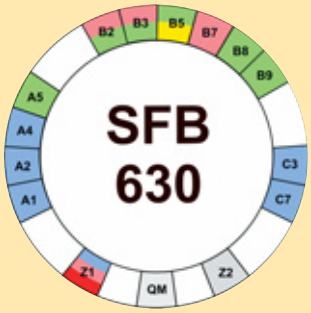
December 1st, 2009: International symposium "Latrophilin-2"

April 2012: International Meeting of the SFB 581

June 2012: NGF 2012 international conference

5.3.4 Collaborative Research Center 630, Recognition, Preparation and Functional Analysis of Agents against Infectious Diseases

CONTACT DETAILS



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General Information

The fight against infectious diseases is one of the biggest current and future challenges. For the 2.7 Billion people living on less than US$2 per day neglected tropical diseases are the most common cause for morbidity. These diseases are infections caused by viruses, bacteria and parasites. Additionally, in the industrialized countries a serious health problem arises due to the occurrence of resistancies against the common drugs. In the EU, 25 000 people per year die because of infections with multi-resistant bacteria. Eight years ago the SFB 630 initiative has accepted this challenge with the goal to contribute to the development of urgently needed novel anti-infective drugs. The highly interdisciplinary research of presently 13 groups of four different faculties and the medical mission institute accounts for the success of the network that was again positively reviewed by the DFG in 2011.

Three distinct project areas refer to the different aspects of agent-based anti-infective research. The topic of Area A is the preparation of novel agents and the characterization and optimization of their physico-chemical properties. The interactions of these compounds with biological molecules and cellular compartments of pathogens are examined in project Area B. Based on these results, theoretical calculations and modellings in Area C lead to a better understanding of the molecular mechanisms of the anti-infectives and allow their rapid optimization. The evaluation of the anti-infective potential of all compounds against a broad spectrum of clinically relevant bacteria, parasites and fungi is performed by the Central Laboratory under the regiment of a Quality Management (QM) system.

Major Research Interests

The research in the SFB focuses on the development of new drugs against infections caused by trypanosomes, leishmania, plasmodia, Staphylococci, especially MRSA, mycobacteria, *Candida*, *Neisseria,* and *Chlamydia*. The outstanding interdisciplinary teamwork of the research groups has formed networks connecting all parts of the SFB. One example is the search for protease inhibitors. Proteinases are major virulence factors in several pathogens and therefore they are attractive targets. We have identified novel inhibitors against fungal, trypanosomal, leishmanial, and plasmodial proteinases, which were further optimized after elucidating their modes of action in the parasites. Knowing the molecular interactions of enzyme and inhibitor in the protein structure, e.g. in the trypanosomal protease rhodesain, quantum mechanical calculations may model the inhibition process and permit valuable predictions for inhibitors with better selectivity.

In the focus of the development of antimycobacterial agents are enzymes of the fatty acid synthesis that are essential for the cell wall building. Elucidation of the three-dimensional structures led to the design and analysis of novel inhibitors. In addition, novel potential inhibitors were identified by virtual screening of pharmacological databases using the pharmacophore of known inhibitors.

Similar networks exist for all target-based projects which were extended this year by the variant surface glycoproteins of trypanosomes and bacterial adhesion and invasion as targets for anti-infective agents.

In addition to these target-based approaches, the best compound classes that were identified without knowing their targets are also further optimized. Not only synthetic and recombinatoric chemistry, but also plant extracts and sponge-associated actinomycetes are used as rich sources for novel agents. The derivatives of naphthylisoquinoline alkaloids and simplier versions thereof are examples of highly active and selective molecules against different parasites dependent on the individual structure of the compound. Some of them already convinced even in animal models curing a *Plasmodium* infection in mice. Excellent anti-trypanosomal activities are exhibited by novel fluoroquinolone amides. The understanding of their mode of action due to cell-biological, molecular-biological, spectroscopic, and bioinformatic analysis supports, also in this agent-based approach, the further optimization of their properties.

In the second funding period, comprehensive and successful structure-activity relationships were determined, which resulted in a pool of exceptionalyl active and remarkably selective compounds. In addition to basic research, another goal for the now started third funding period is therefore the further development of these hits into leads and drug candidates. Sound examinations of their pharmacokinetic properties, their efficiency in animal models, and the effective formulation will provide comprehensive information to convince putative investors like “Drugs for Neglected Diseases Iinitiative” (DNDi) or industrial dialogue partners to support preclinical and clinical studies.

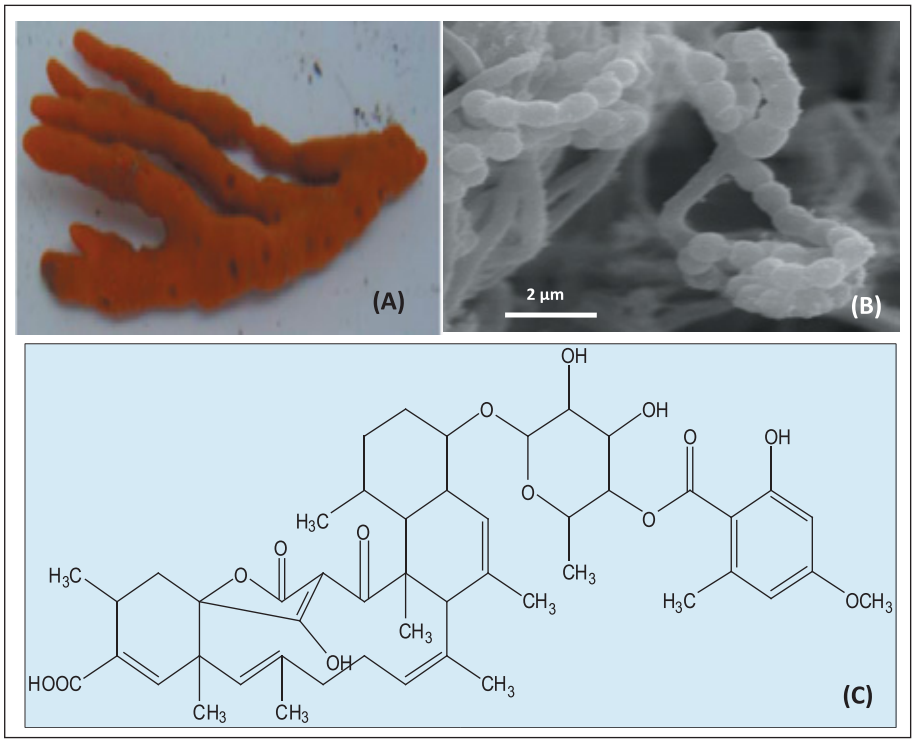

Fig. 1: The mediterranean sponge Axinella polyploides (A), source of the novel bacterial species, Streptomyces axinellae, (B) from which four new tetromycin derivatives with pronounced anti-trypanosomal and protease inhibitory activities were isolated (C). (Photography by S. Pimentel-Elardo, University of Würzburg, now at McMasters University, Canada).

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 of 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-Humeida (Julius-von-Sachs Institute for Biological Sciences)
Sponge-associated actinomycetes as sources for novel anti-infectives

Project Area B: Interaction with cellular and molecular systems

B2 J. Morschhäuser (Institute for Molecular Infection Biology)
Inhibition of virulence and resistance mechanisms of *Candida albicans*

B3 H. Moll / U. Schurigt (Institute for Molecular Infection Biology)
Mitochondria, endosomes and autophagolysosomes as targets of leishmanicidal agents

B5 K. Ohlsen / P. Jakob (Institute for Molecular Infection Biology / Institute for Physics)
Drug-induced gene expression in staphylococci and magnetic resonance-based imaging of infections

B7 C. Kisker (Rudolf-Virchow Center)
Structure-based drug design on essential enzymes from pathogens

B8 M. Engstler (Theodor-Boveri Institute for Biosciences)
VSG as an unexpected drug target for sleeping sickness

B9 T. Rudel / V. Kozjak-Pavlovic (Theodor-Boveri Institute for Biosciences)
Active agents against acute and disseminating *Neisseria* infections

Project Area C: Characterization of the molecular mechanism of anti-infectives and predictions for their accelerated optimization

C3 B. Engels (Institute for Physical and Theoretical Chemistry)
Theoretical studies to characterize inhibition mechanisms and ligand-target complexes

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)
L. Meinel (Institute for Pharmacy and Food Chemistry)
Laboratory for the central evaluation of potential anti-infective agents

Quality Management

QM H. Bruhn

SFB 630 Office
Z2 A. Dreher

Symposia since 2010

Joint PhD-student meetings of the SFB 630, SFB 544 and SFB 766
New Trends in Infectious Disease Research
22. – 24.11.2010

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Cecil A, Rikanovic C, Ohlsen K, Liang C, Bernhardt J, Oelschlaeger TA, Gulder T, Bringmann G, Holzgrabe U, Unger M, Dandekar T. (2011) Modeling antibiotic and cytotoxic effects of the dimeric isoquinoline IQ-143 on metabolism and its regulation in Staphylococcus aureus, Staphylococcus epidermidis and human cells, Genome Biology 12:R24.

Hirschbeck MW, Kuper J, Lu H, Liu N, Neckles C, Shah S, Wagner S, Sotriffer CA, Tonge PJ, Kisker C. (2012) Structure of the Yersinia pestis FabV Enoyl-ACP Reductase and Its Interaction with Two 2-Pyridone Inhibitors, Structure 20:89-100.

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Schurigt U, Schad C, Glowa C, Baum U, Thomale K, Schnitzer JK, Schultheis M, Schaschke N, Schirmeister T, Moll H. (2010) Aziridine-2,3-dicarboxylate-based cysteine cathepsin inhibitors induce cell death in Leishmania major associated with accumulation of debris in autophagy-related lysosome-like vacuoles. Antimicrobial Agents and Chemotherapy 54:5028-5041.

5.3.5 Collaborative Research Center 688, Mechanisms and Imaging of Cell-Cell Interactions in the Cardiovascular System

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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 innovative imaging techniques such as magnetic resonance (MR) imaging methods, positron-emission tomography (PET) and *in vivo* fluorescence microscopy 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), novel fluor-based MRT contrast agents and PET tracers 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 and immune defense, but also for vascular thrombosis and inflammation leading to organ dysfunction. During the last two years important new insights have been obtained:

By the generation and analysis of mice carrying a null-mutation in the gene encoding phospholipase D1 (PLD1) we could for the first time show a crucial role of this enzyme for intravascular thrombus formation. As a consequence, Pld1$^{-/-}$ mice were profoundly protected in a model of ischaemic stroke (Elvers et al., 2010). Furthermore, we have recently established the Platelet Web Knowledgebase as a web-based repository on all described human platelet proteins as well as their interactions, modifications and available knowledge on these from literature, software predictions or databases (Boyanova et al., 2011).
A further project assessed the interaction of T cells and components of the haemostatic system (e.g. platelets) in the pathogenesis of ischaemic brain infarction. Unexpectedly, we found that mice completely lacking T cells are profoundly protected from brain infarcts. Interestingly, this effect was not dependent on antigen-specific immunologic functions of the cells, but rather seems to be based on pathological interactions of T cells, platelets and endothelium in the ischaemic brain (Kleinschnitz et al., 2010).
The cardiac hormones ANP and BNP exert well characterized endocrine functions regulating arterial blood pressure and volume. Their cGMP-forming guanylyl cylclase receptor-A (GC-A-R) is densely expressed in microvascular endothelium. Studies in transgenic mice with a conditional, endothelial-restricted deletion of the GCA-R showed for the first time that NPs have an additional function modulating postischaemic angiogenesis. Accordingly, angiogenesis and tissue regeneration are markedly impaired in

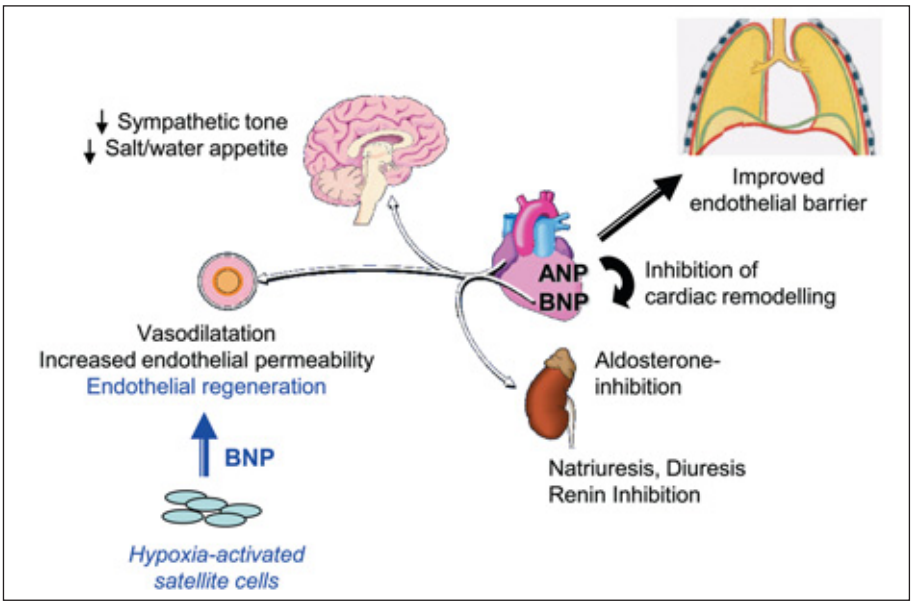

Fig. 1: Pleiotropic effects of natriuretic peptides.

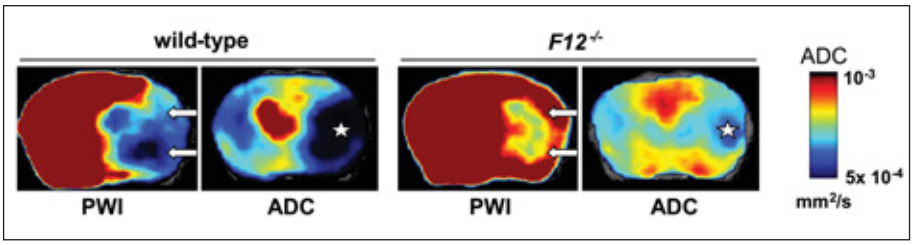

Fig. 2: 17.6 T ultra-high field MRI of cerebral infarcts in mice at 24 h after tMCAO. PWI: perfusion weighted imaging as measure for cerebral blood flow; ADC: apparent diffusion coefficient based on diffusion weighted imaging as a measure for tissue damage. Note that the perfusion deficit (PWI) in wild-type mice involves the whole MCA territory with ensuing complete infarctions (asterisk in ADC), while F12$^{-/-}$ mice show complete restoration of blood flow in the neocortex (PWI, arrows) and salvage of brain tissue with minimal infarction only, at the level of the basal ganglia (asterisk in ADC). For further details, see Pham et al. NeuroImage 49:2907-14, 2010.

endothelial GC-A-R deficient mice. Intriguingly, BNP produced by activated satellite cells within ischaemic skeletal muscle or by cardiomyocytes in response to pressure load, regulates the regeneration of neighbouring endothelia via GC-A-R. This paracrine communication might be critically involved in coordinating muscle regeneration/hypertrophy and angiogenesis (Kuhn, et al., 2009). Intriguingly, these cell growth-modulating actions of the NP/GC-A-R system seem to be mediated by a novel cGMP-independent signalling pathway. This pathway involves the activation of Ca^{2+}-permeable transient receptor potential canonical 3/6 (TRPC3/C6) cation channels by the GC-A-R, which forms a stable complex with TRPC3/C6 channels (Klaiber et al., 2011). In the heart, this "non-canonical" pathway predominates under pathophysiological conditions when the GC-A-R is desensitized by high local NP levels (Klaiber et al., 2011). The concomitant rise in $[Ca^{2+}]_i$ might increase the propensity to cardiac hypertrophy and arrhythmias.

Mitogen activated protein kinases such as ERK1/2 are not only involved in pathological growth responses of cardiac and vascular cells, but also trigger protective, anti-apoptotic cellular effects. Research in the SFB 688 demonstrated that autophosphorylation of ERK1/2 at one specific amino acid residue directs these different signalling functions. In transgenic mice inhibition of this site-specific ERK1/2 phosphorylation prevents pathological cardiac growth, without affecting apoptosis. Our current investigations suggest that this phosphorylation enhances nuclear translocation of ERK and ERK-dependent transcription of pro-hypertrophic genes. Hence, this regulatory mechanism of differential ERK activity provides an important therapeutical target to inhibit pathological cell growth in the cardiovascular system.

The heart is very sensitive to vascular dysfunction and cardiac ischemia is a major cause of heart failure. Therefore another important goal within the SFB 688 is the clarification of the mechanisms leading to ischaemic cardiomyopathy. We could show that ischaemia locally activates the complement cascade. Complement component 3 (C3a) – triggered accumulation of inflammatory cells contributes to cardiac dysfunction after myocardial infarction.

The long-term objective of these 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 and PET 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. Using perfusion and diffusion weighted ultra high field MR imaging we could show for the first time that the blockade of FXII or the platelet receptor GPIb indeed results in improved blood flow in the microcirculation after cerebral ischaemia (Pham et al., 2010). Measurements of the cardiovascular magnetic resonance transit time allowed *in vivo* assessment of pulse wave velocities in mice and could discriminate between normal and atherosclerotic vessel walls. By this novel MR technology it is possible to detect early stages of atherosclerosis in transgenic mice and to monitor treatment effects. Moreover, $^{1}H/^{19}F$ MR-spectroscopy was established within the SFB facilitating cellular imaging of macrophage responses in animal models of atherosclerosis and stroke with a higher specificity than iron-nanoparticle based cellular MRI.

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5.3.6 Transregio-Collaborative Research Center 17, Ras-Dependent Pathways in Human Cancer

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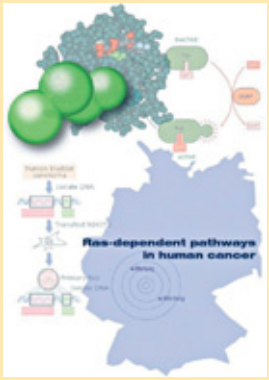

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Aufgaben und Struktur

Der Transregio 17 setzt sich aus Forschern der Universitäten Würzburg und Marburg zusammen und wird von Martin Eilers und Andreas Neubauer koordiniert. Der Transregio nahm im Jahr 2004 seine Arbeit auf und ist nach dem erfolgreichen Abschluss der Begutachtung im Februar 2008 in eine zweite Phase gegangen. Insgesamt arbeiten im Transregio ca. 20 Projektleiter und ihrer Arbeitsgruppen. Diese sind in drei Projektgruppen zusammengefasst, die sich auf die beiden beteiligten Universitäten aufteilen. In jedem Teilprojekt arbeiten auch Bachelor- und Masterstudenten und Doktoranden, wobei zwischen den verschiedenen Arbeitsgruppen und –gebieten ein intensiver Austausch und Zusammenarbeit stattfindet. Alle Doktoranden sind Mitglieder eines integrierten Graduiertenkollegs, welches von den Mitgliedern des Transregio organisiert und gestaltet wird. Ein besonderer Schwerpunkt des Transregio ist die Integration der klinischen und translationalen Forschung und die Etablierung von Schlüsseltechnologien durch zentrale Einrichtungen und einzelne Teilprojekte.

Forschungsschwerpunkte

Ziel des Transregio ist es ein besseres Verständnis zu erlangen wie zelluläre Schlüsseleigenschaften von Tumorzellen, wie z. B. deregulierte Proliferation, Apoptose, Therapieresistenz und Metastasierung, aus der Interaktion zwischen deregulierten Signalwegen und dem genetischen Status der Tumorzelle entstehen. Ein wesentliches Element der Entstehung aller humaner Tumoren ist die Störung von Signaltransduktionswegen. Entsprechend sind die Gene, die für die an diesen Übertragunsmechanismen beteiligten Proteine kodieren, sehr häufig bei der Krebsentstehung mutiert. Während die einzelnen Moleküle der Signaltransduktionswege, ihre biochemische Funktion und die Art ihrer Mutation in humanen Krebsformen immer besser verstanden werden, wissen wir noch wenig darüber wie eine deregulierte Signaltransduktion zu den zellulären und klinischen Phänomenen führt, die letztlich den Krankheitsverlauf im Patienten bestimmen. Dies trifft insbesondere auf den Ras Signalweg zu, der sich als Schlüssel-Signaltransduktionsweg herausgestellt hat, welche zur Bildung einer großen Vielfalt von humanen Tumoren beiträgt.

Eine bemerkenswerte Beobachtung, die vielen Ansätzen im Transregio zugrunde liegt, ist dass das Resultat eines deregulierten Signals über den Ras-Signalweg nicht stereotyp ist, sondern vom genetischen Status der Zelle bestimmt wird. Es bestehen offensichtlich Schutzmechanismen, die eine Tumorinduktion durch eine einzelne Mutation eines Proto-Onkogens wie Ras verhindern. Dies bezieht sich nicht nur auf zelluläre Phänotypen, sondern auch auf klinische Phä-

Abb. 1: Ankündigungen der zwei Konferenzen des Transregio in den Jahren 2010 und 2011.

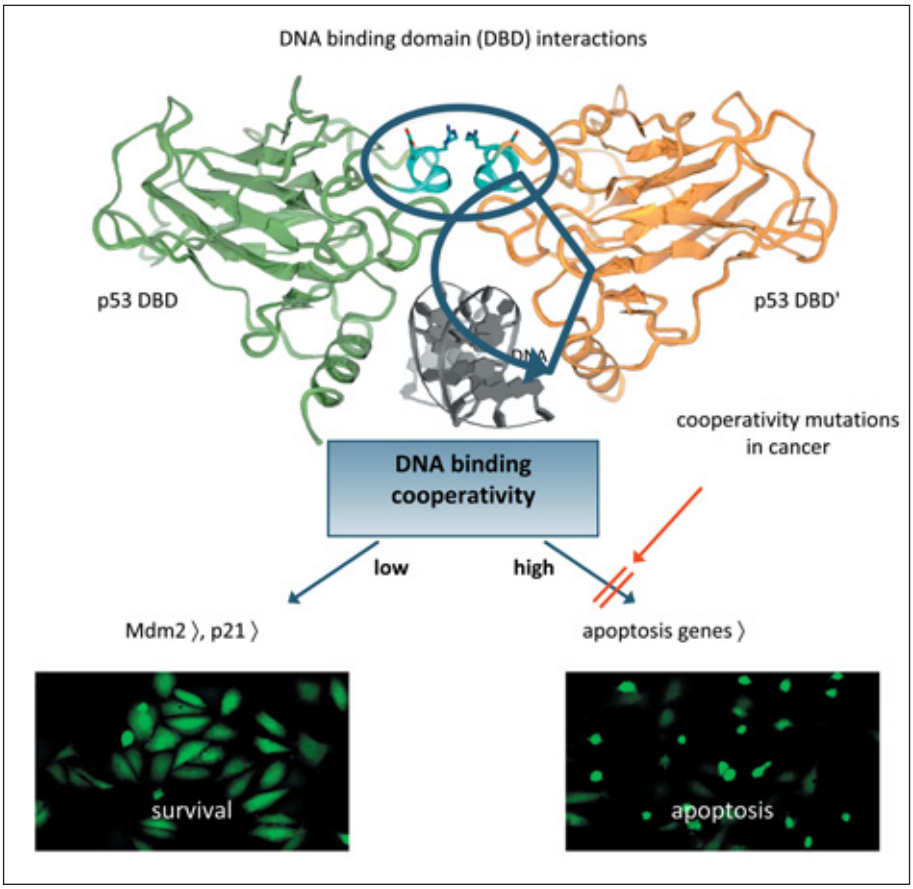

Abb. 2: Struktur des p53 Tumorsuppressorproteins. Die Figur zeigt, dass das p53-Protein Zellen je nach dem auf eine Zelle ausgeübten Stress entweder Gene, die zu Zellzyklusarrest und Überleben führen, aktiviert oder Gene, die zu Zelltod (Apoptose) führen. Forscher des Transregios haben zu dieser für die Tumorentstehung fundamentalen Entscheidung einen wichtigen Beitrag geliefert (Schlereth K, Beinoraviciute-Kellner R, Zeitlinger MK, Bretz AC, Sauer M, Charles JP, Vogiatzi F, Leich E, Samans B, Eilers M, Kisker C, Rosenwald A, Stiewe T (2010) DNA binding cooperativity of p53 modulates the decision between cell-cycle arrest and apoptosis. Mol Cell 38: 356-368).

nomene, wie Invasion, Metastasierung und die individuellen Reaktionen auf Therapien, die wir letztlich verstehen müssen.

Um diese Fragen zu beantworten konzentriert sich das Forschungsprogramm im Transregio auf die Aufklärung der Signaltransduktion über den Ras-Signalweg (Projektbereich A), die Analyse der zellulären Antworten auf den Ras-Signalweg und deren genetischer Kontrolle (Projektbereich B) und die Untersuchung der Ras-abhängigen Signalgebung in humanen Tumoren (Projektbereich C).

Die Mitglieder des Transregio stellen mehrere Schlüsseltechnologien zur Verfügung und arbeiten an der Entwicklung von Tiermodellen für die Untersuchung von Ras-abhängigen Signalwegen in menschlichen Tumoren, Erstellung von Genexpressionsprofilen, RNAi Screening mittels automatisierter Hoch-Durchsatz-Mikroskopie, gewebsbasierte Pathologie und massenspektrometrischer Proteinanalytik.

Von der medizinischen Fakultät der Universität Würzburg sind folgende Institutionen beteiligt: Physiologische Chemie I (Stefan Gaubatz, Svenja Meierjohann, Manfred Schartl), Physiologische Chemie II (Martin Eilers, Peter Gallant) und Medizinische Klinik und Poliklinik II (Ralf Bargou). Der Transregio 17 ist zugleich zentraler Bestandteil des Forschungsprogramms des Comprehensive Cancer Center Mainfranken.

Symposien des TR17

The Puzzling World of Cancer
Ort: Würzburg Residenz
Datum: 06.10.2010 - 08.10.2010
Organisatoren: Studenten des Graduiertenkollegs

Transregio Meeting: Cancer, Inflammation and Metabolism.
Ort: Rothenburg ob der Tauber
Datum: 10.04.2011 - 13.04.2011
Organisatoren: Martin Eilers und Andreas Neubauer

5.3.7 Transregio-Collaborative Research Center 34, Pathophysiology of Staphylococci in the Post-genomic Era

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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, Münster 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 four 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 is the focus of part B (3 projects). Project area C (7 projects) deals with the behaviour of the pathogen in the host and will provide new information on the host-pathogen interaction. Part Z (4 projects) offer state of the art technologies to all projects to discover and analyze *S. aureus* metabolism and pathogenicity.

Project leader Würzburg:

PD Dr. K. Ohlsen (A2, Z3)
Prof. Dr. T. Dandekar (A8, Z1)
PD Dr. W. Ziebuhr (B4)
Prof. Dr. J. Vogel (B4)
Prof. Dr. Dr. B. Sinha (C6, C11)
Prof. Dr. T. Rudel (C11)

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.

In the A8 project, functional genomics technologies are used to identify concentrations and complex formation of proteins involved in central carbon metabolism. Furthermore, systems biology approaches will be applied to construct models which will allow prediction of key complexes and their roles in adaptation scenarios that are also of importance in infection settings. A new and emerging field that is becoming the increasing focus in model bacteria such as *E. coli*

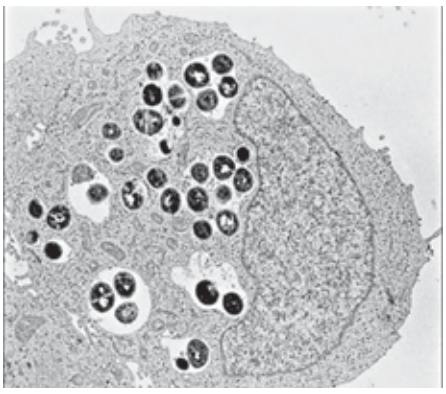

Fig. 1: Kidney epithelial cells after invasion of S. aureus.

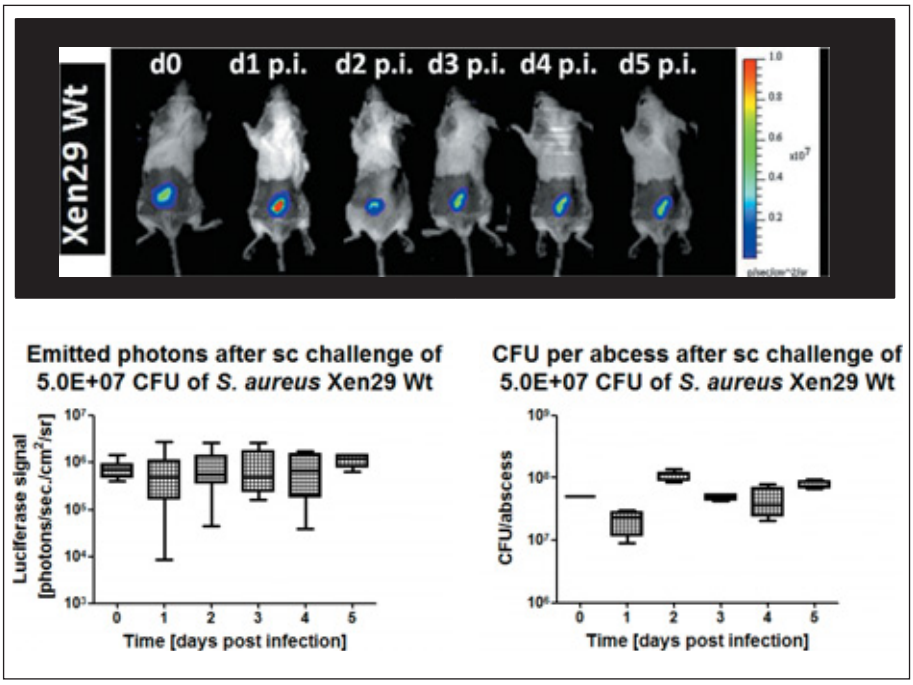

Fig. 2. Bioluminescent S. aureus strain Xen29 in an abscess infection model (top) and quantification of bioluminescent signals and determination of CFU (bottom center).

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 addition, a bioinformatic approach that aims at the prediction of additional small RNAs will be followed. Also, the search for novel sRNAs will be continued by applying state-of-the-art high-throughput sequencing to *Staphylococcus* strains and mutants currently under investigation within the collaborative research network. Subsequently, such new small regulatory RNAs can be analyzed for their role in cell physiology, stress adaptation, and virulence. The fate of the *S. aureus*–containing phagosomal compartment after invasion of host cells remains controversial. In project part C6 the fate of this compartment and virulence factors involved in phagosomal modulation/escape are characterized. Additionally, the fate of *S. aureus* residing in this compartment and its adaptive response to this environment is analyzed using a combination of functional genomics and cellular microbiology. The aim is to generate a first, integrated view of the intracellular behavior of *S. aureus (Fig. 1)*.
S. aureus isolates have been shown to exert a strong cytotoxic effect on host cells during infection. The aim of project C11 is the molecular definition of host cytotoxicity induced during *S. aureus* infection. The signaling pathways responsible for cytotoxic effects of different *S. aureus* strains will de delineated and the role of bacterial effectors involved in these pathways will be defined. In particular, the role and mechanism of mitochondrial association of alpha-toxin and PVL will be analyzed. Finally, the in vivo relevance of cell death signaling induced by *S. aureus* infection will be verified in animal models using the imaging platform of the SFB in project part Z3.

In project part Z1 a S. aureus database will be established processing large-scale datasets. This database will create new insights into physiology and pathophysiology of *S. aureus* by integration of metabolite data, enzyme data including kinetics, protein data including protein interactions, and offers analysis of genomes, regulatory motifs, gene expression and cellular networks in *S. aureus*.
The aim of the project Z3 is the implementation of *in vivo* imaging platform techniques (bioluminescence, fluorescence, MRI, and PET) to visualize the dynamics of *S. aureus* infections and corresponding morphological and physiological changes in host tissues (Fig. 2). High-resolution morphology and functional/physiological parameters will identify systemic or local response to infection in real-time images, building the basis for the development of novel strategies to prevent staphylococcal diseases. Overall, these data will provide an overview on the dynamics of bacterial spread in the host and its 3D distribution.

Symposia

International symposium “Pathophysiology of Staphylococci”, Greifswald, 1 - 3 June 2010

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5.3.8 Transregio-Collaborative Research Center 52, Transcriptional Programming of Individual T-Cell Subsets

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General Information

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:
Z1: Generation of Genetically Modified Mice
Z2: In vivo Imaging

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 the 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 Interest

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.
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 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-

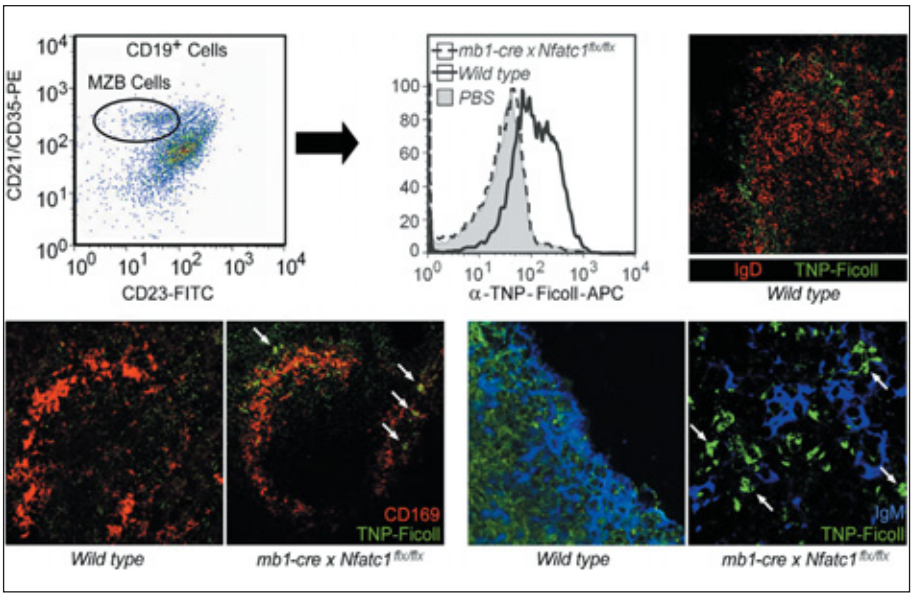

Fig. 1: Marginal zone B cells need the transcription factor NFATc1 for their function (from Bhattacharyya et al., J. Exp. Med. 208, 2011, 823-839). Marginal zone B (MZB) cells are a particular fraction of B cells which react rapidly upon antigens which are transported by the blood stream into the spleen. Above left, flow cytometry showing the population of MZB cells. When an antigen, such as TNF-Ficoll, is injected intravenously into mice, it is rapidly bound by the MZB cells from wild-type mice but not by NFATc1-deficient MZB cells (as shown in the mid of figure, above, by the full and dotted lines). The histochemical stainings of sections through a murine spleen show the binding of the antigen TNP-Ficoll to the MZB cells from wild type, but not to those from NFATc1-deficient mice (mb1-cre x Nfatc1$^{fx/fx}$ mice).

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.

In Würzburg, four projects are situated at the Institute of Pathology (TPA3, Berberich-Siebelt, Jonuleit and Sickmann; TPA8, Gattenlöhner and Schmitt; TPB2, Serfling and Avots; TPC5, Avots and Serfling), two projects at the Institute of Virology and Immunobiology (TPA5, Hünig; TPB7, Lutz) and one, the Central Project Z2 (Beilhack), at the Medical Clinic and Polyclinic II.

Symposia

Apart from the bi-annual retreats of the TR which were organized in each of the three TR cities, one highlight of scientific activities of the TR within the past two years was the International Workshop on "Transcriptional Programming in the Immune System". This workshop took place from 17th to 20th October 2010 at the Virchow Center in Würzburg and assembled more than 200 scientists. The workshop was introduced by Meinrad Busslinger`s (IMP, Vienna) Virchow Medal Lecture who spoke about `Lineage Commitment and Plasticity in the Hematopoietic System". In his lecture, Meinrad Busslinger presented his excellent experimental work on the fundamental role of transcription factors Pax5 for the lineage commitment of lymphoid progenitor cells to B lymphocytes which – due to the production and secretion of antibodies – represent key components of immune system. The 25 lectures of the workshop were devoted to themes on lymphocyte signalling, on the differentiation and function of T and B lymphocytes, including regulatory T cells, and, finally, on the transfer of research results to the development of causal therapies of autoimmune and further diseases of the human immune system. The presentations of a large number of renowned international guest speakers – such as by Oreste Acuto (Oxford, UK), Harald von Boehmer (Boston), Michael Neuberger (Cambridge, UK), William Paul (Bethesda), Klaus Rajewsky (Boston), Alexander Rudensky (New York) and Ranjan Sen (Baltimore) – contributed to the great success of the meeting.

SELECTED PUBLICATIONS OF MEMBERS OF THE TR52

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 IL2 repression by HDAC. J. Biol. Chem. 284:10935-10946.

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Römer PS, Berr S, Avota A, Na SY, Battaglia M, Ten Berge I, Einsele H, Hünig, T. (2011) Preculture of PBMCs at high cell density increases sensitivity of T-cell responses, revealing cytokine release by CD28 superagonist TGN1412. Blood 118:6772-6782.

5.3.9 Transregio-Collaborative Research Center 58, Fear, Anxiety, Anxiety Disorders

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Professor Dr. Hans-Christian Pape
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Professor Dr. Christian Büchel
(Speaker Hamburg)

Mission and Structure

The Transregio-SFB 58 was initiated in 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 GK1253 which was extended for a second period in 2011.
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 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 are validated in humans by innovative experimental approaches (*imaging genomics, pharmacogenomics)*. Genetic findings in humans are in turn 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 suf-

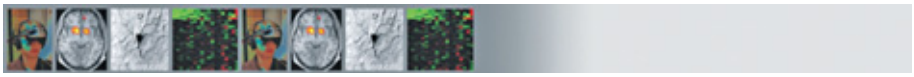

Fig. 1: Experimental approaches of the SFB TR 58 (http://sfbtrr58.uni-muenster.de/).

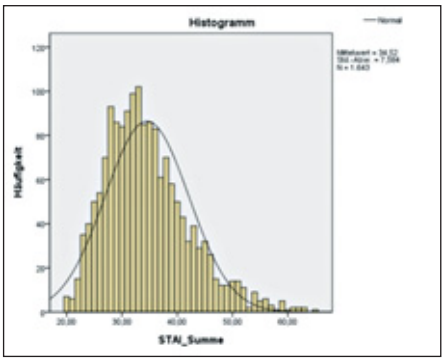

Fig. 2: Distrubution of an anxiety dimension in the central cohort of SFB TR 58 (courteously provided by C.Baumann).

fering from panic disorder in the third project (Fallgatter/Deckert, Ehlis/Herrmann). The role of genetic variants is again under investigation in all three projects.
A large (n=1643) cohort with ex ante phenotypically and genetically well defined control subjects (figure 2) for the studies of areas B and C was made available by the *central project 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.

A paradigmatic example for the interdisciplinary and synergistic research in the context of the SFB is the research on the novel Neuropeptide S and its receptor. Its role for fear and anxiety was studied in animal models, experimental human studies employing functional imaging techniques and in clinical human studies employing molecular genetic techniques. Results were published in 8 publications so far.

At the University of Würzburg, the following institutions currently are involved:
Medical Faculty, Department of Psychiatry, Psychosomatics and Psychotherapy (project leaders: J.Deckert, K.P.Lesch, M.J.Herrmann, A.Reif, A.Schmitt); Institute of Phyiology (associated member: E.Wischmeyer)
Faculty of Philosophy, Institute of Psychology I (project leaders: A.Mühlberger, P.Pauli).
A.Fallgatter and B.Gerber left for W3 chairs at Tübingen (Department of Psychiatry and Psychotherapy) and Leipzig (Institute of Biology, Genetics) respectively, but are still associated with the SFB.

Symposia
1st International Symposium on Fear, Anxiety, Anxiety Disorders; Münster, 10.-12.12.2009

2nd International Symposium on Fear, Anxiety, Anxiety Disorders; Würzburg, 15.-17.9.2011

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5.4 Clinical Research Units
5.4.1 Clinical Research Unit 125, Attention-Deficit/Hyperactivity Disorder – Translational Research Focus on Molecular Pathogenesis and Treatment across the Life Cycle

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General Information

The molecular pathogenesis of Attention-Deficit/Hyperactivity Disorder (ADHD) and the significance of its endophenotypes and comorbid disorders, such as substance abuse, affective disorders, and antisocial personality disorders, for the course of illness is both clinically and health politically a highly relevant but largely unsolved problem. The Clinical Research Program (KFO 125), as a joint facility of the Departments of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (KJPPP) and Psychiatry, Psychosomatics and Psychotherapy (PPP), deals with the interdependent relationships between the molecular and functional-structural mechanisms of the pathogenesis of ADHD and its significance for its long-term course using interdisciplinary and translational research strategies. The primary goals are based on the following concept: By joining preclinical and clinically oriented research groups, who work on ADHD-specific molecular mechanisms of neuronal cell activity 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.

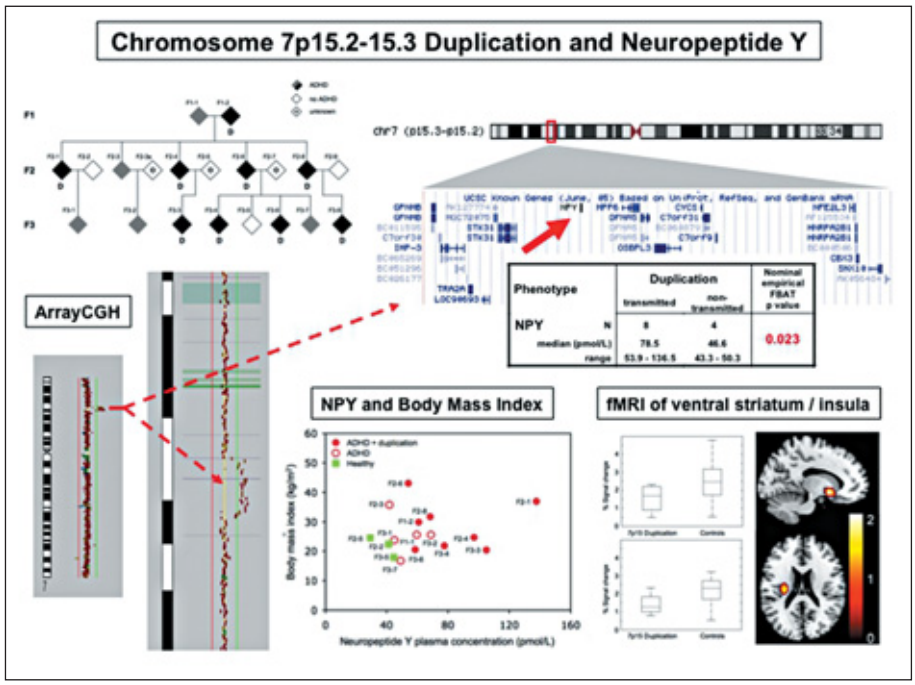

Fig. 1: Chromosome 7p15.2-15.3 duplication and neuropeptide Y. Segregation of the chromosome 7p15.2-15.3 duplication (D) in a multigenerational family with ADHD is depicted. Affected members are symbolized by solid black symbols when the duplication is present, and by solid grey when absent; unaffected 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. 2011).

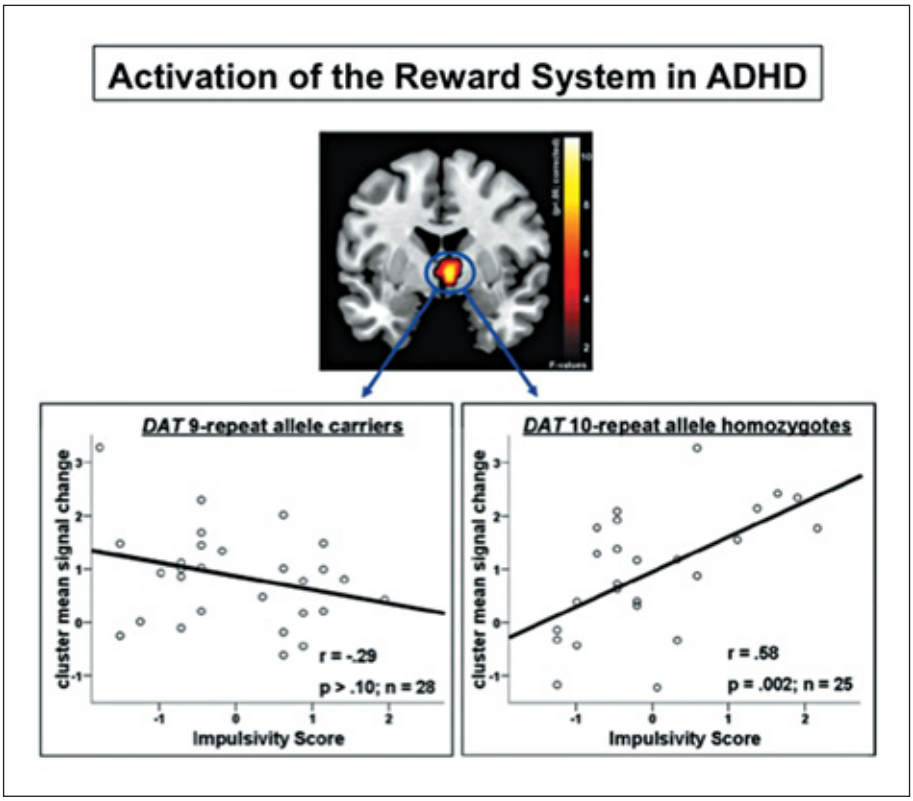

Fig. 2: Interaction of dopamine transporter gene (DAT) 3' VNTR polymorphisms and trait sensitivity to reward (SR) scores affecting reward-related activation of the ventral striatum (VS, P < 0.05, corrected; top panel). Scatter plots (bottom) display the association between z-standardized trait SR scores and ventral striatal activation (averaged over activation-clusters showing a significant interaction of the 3' VNTR and SR scores). The correlation between ventral striatal activation and SR scores is present only in the DAT 10-repeat allele homozygotes, while no such association is found in 9-repeat allele carriers (Hahn et al. 2011).

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. 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 characteristics including diagnostic evaluation of ADHD and co-morbid disorders across the life cycle as well as ascertainment of patients and their families for genetic study. In addition, these two subproject assess etiological heterogeneity, clinical symptoms of subtypes and outcome, as well as psychosocial impact of ADHD within the framework of a family-centered outpatient unit. In contrast to previous longitudinal studies, a multi-layer analysis facilitates a novel approach in follow-up research which is likely to provide a more profound understanding of the interaction between genetic disposition and environmental influences on the course of juvenile and adult ADHD. In synergy to SP 1 and 2 a BMBF-supported study entitled "Effects and Mechanisms of Psychotherapy in the Treatment of ADHD in Children and Adults – The First Randomized Multicentre Study" exclusively focuses on the treatment of ADHD across the life cycle.

Three subprojects (SP 3-5) represent an integrated approach toward elucidation of specific molecular genetic and neurobiological mechanisms of complex behavior related to ADHD. Genome-wide linkage scans 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 provide a basis for subsequent studies on genetically modified mouse and zebrafish models of ADHD (Fig. 1) (Lesch et al. 2011; Weber et al. 2011; Reif et al. 2011). 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) (Dresler et al. 2010; Hahn et al. 2011). 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, SFB TRR 58, GRK 1253, GSLS, IZKF, CHFC) as well as into a wide spectrum of national (e.g. BMBF Multicentre ADHD Treatment Study, Nationales Schwerpunktnetzwerk ADHS, MPI für Molekulare Genetik) and international collaborations (e.g. IMpACT, IMAGE2, NIMH, NHGRI, NIDA, NIAAA, Maastricht University, University of Tartu). 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.

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5.4.2 Clinical Research Unit 216, Characterization of the Oncogenic Signaling-Network in Multiple Myeloma: Development of Targeted Therapies

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Aims and structure

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. 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. Thus, the CRU is an important element of the Comprehensive Cancer Center Mainfranken, which is one out of eleven Cancer Centers of excellence in Germany funded since 2011 by the German Cancer Aid. The CRU 216 is closely linked to the Early Clinical Trial Unit (ECTU, Phase-I Unit) of the CCC Mainfranken, which facilitates rapid translation of knowledge in basic research into clinical trials.

Scientific Program

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 (Figure 1). 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.

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

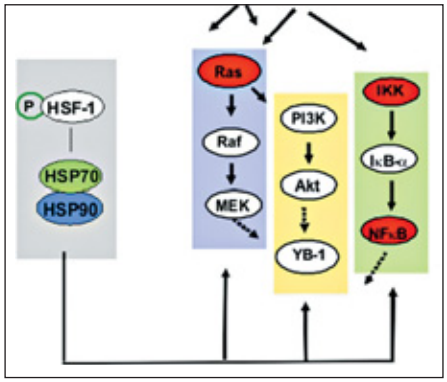

Fig. 1: Pathways of the Oncogenic Signaling Network identified in multiple myeloma

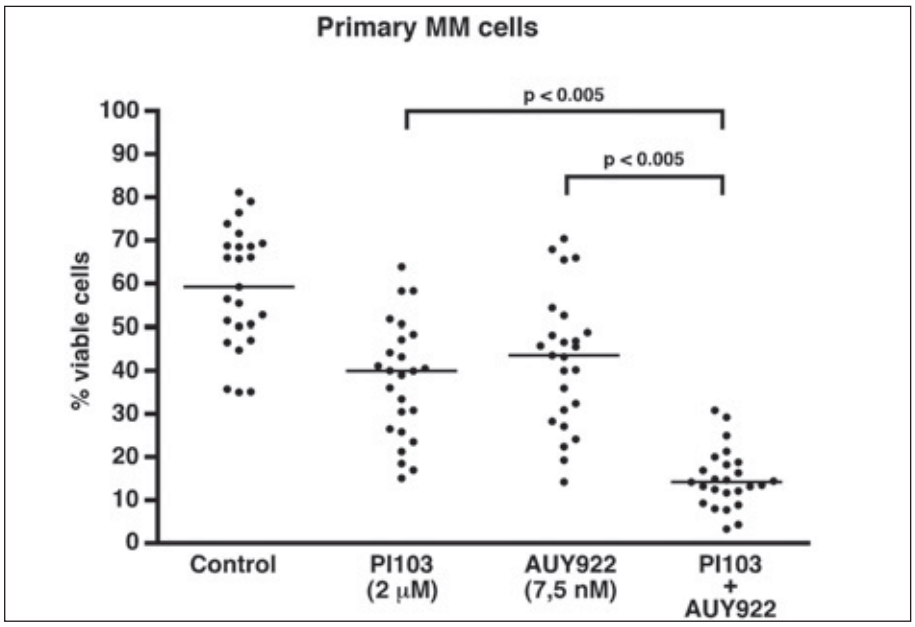

Fig. 2: Combined pharmacological blockade of HSP90 (AUY922) and PI3K (PI103) induces apoptosis of primary human MM cells (ex vivo cell culture system).

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 Rosenwald/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.

Research Milestones in 2010 and 2011

The role of the Ras/MAPK and the PI3k/Akt pathways for the malignant phenotype of multiple myeloma (MM) could be defined for the first time in various preclinical models. Thus, combined blockade of both pathways led to strong induction cell detah in a subgroup of MM patients. These findings form the foundation for the development of new targeted therapies.

Besides Ras-dependent pathways, we could describe fort the first time the role of certain stress response proteins as therapeutic targets in MM mouse models. This research led tot he initiation of a phase-I/II trial with a new HSP90 inihibitor in patients with relaosed multiple myeloma (*ClinicalTrials.gov NCT00708292*). Furthermore, a series of novel pharmacological inhibitors of the heats shock protein pathway have been developed and are currently being tested in preclinical models. Interestingly, we found that blockade oft the heat shock protein pathway strongly enhances the anti-tumor efffect of inhibitors of Ras-dependent signaling (Figure 2).

Another stress response protein, which critically contributes to the malignant phenotype, is the cold shock domain protein YB-1. We could show that YB-1 regulates the expression of the oncogene c-myc, which seems to be a key mechanism, how YB-1 mediates its oncogenic effect in MM cells.

Finally, we found that only parts oft he NF-kB network are important for the malignant phenotype of MM, whereas other parts are less relevant or have even tumor suppressive functions. This work will lead to a more precise description of novel therapeutic targets.

Important technological progress was made in the field of functional genetics. Whole exome sequencing analysis and functional shRNA screening technologies have been established. The implementation of these novel technologies will lead to the identification of novel therapeutic targets in MM.

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5.5 Clinical Research- and Treatment Centers
5.5.1 Comprehensive Hearing Center Würzburg

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Mission and Structure

The Comprehensive Hearing Center Wuerzburg (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).

Fig. 1: Structure of the CHC.

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
(S.Schraven, 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

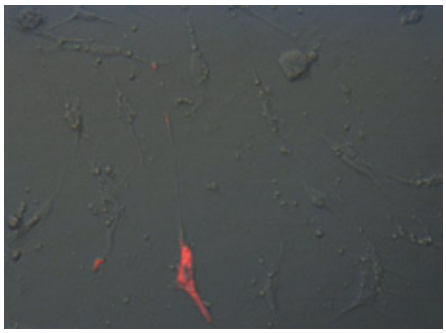
Fig. 2: Neuronal differentiation of adult stem cells for application in the inner ear (guinea pigs).

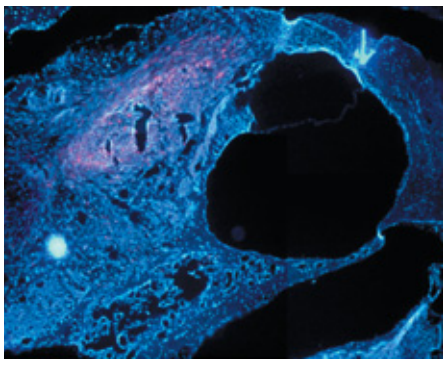
Fig. 3: Active migration of stained stem cells (pink) from basal cochlear turn (guinea pigs).

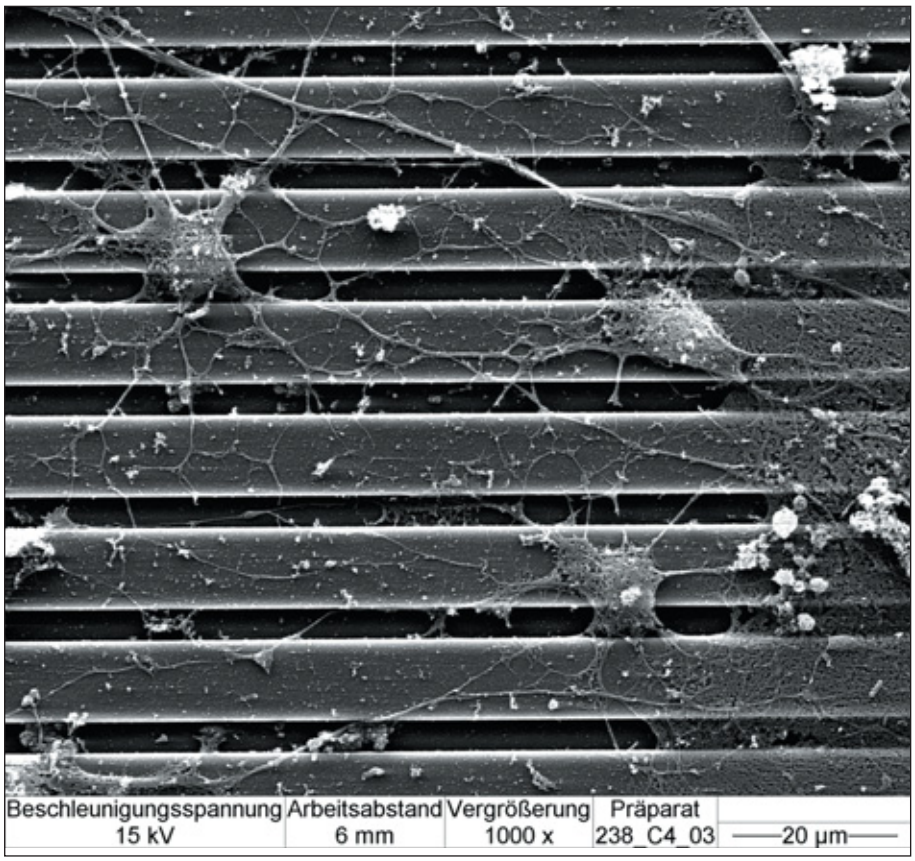

Fig. 4: Collateral sprouting of neuronal cells on semiconductor-material.

supported documentation. Intraoperative monitoring of transmission function in active middle ear prostheses.

Inner ear biology
(R. Mlynski, K.Rak, S.Frenz 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 transduce to 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-knockout 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, P.Schendzielorz)

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
(R.Mlynski, 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)

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, A.Wiegner 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.

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Vollmer M, Beitel RE. (2011) Behavioral training restores temporal processing in auditory cortex of long-deaf cats. J Neurophysiol 106:2423-243.5

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Rak K, Wasielewski NV, Radeloff A, Völkers J, Scherzed A, Jablonka S, Hagen R, Mlynski R. (2011) Isolation and characterization of neural stem cells from the neonatal rat cochlear nucleus. Cell Tissue Res 343:499-508.

Cebulla M, Elberling C. (2010) Auditory brain stem responses evoked by different chirps based on different delay models. J Am Acad Audiol 21:452-460.

5.5.2 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 substance related and non substance related addiction. Advancement of traineeship, teaching, qualification in addiction associated topics, inpatient and outpatient interventions and political decision guidance are additional topics. Due to the success of the first IZSW research workshop, repetition is planned annually.

Major Research Interests

Biopsychological mechanisms of nicotine craving
(P. Pauli, R. Mucha, M. Winkler, L. Wu, Department of Psychology)

Generally, smoking associated stimuli are considered to act as strong incentives in dependent smokers, thereby motivating excessive consumption. In two projects we use biopsychological methods (startle-Modulation, EMG, EDA, EEG, fMRI) to examine the motivational basis of addiction specific learning processes (FOR 605) and the capacity of smokers to self-regulate their emotions (GRK 1253/1). In particular, we are interested in the precise mechanisms underlying the reactivity of smoking cues and stimuli from the terminal stage of the smoking ritual. Furthermore, we examine the impact of different appraisal strategies on the neural processing of affective and smoking related stimuli.

ADHD as a risk factor for the development of addiction
(C. Jacob, K.P. Lesch Dept. of Psychiatry, Psychosomatics and Psychotherapy, Molecular Psychiatry)

Comorbid drug developments are often the result of a failed "self-treatment trial." On the other hand, the treatment of ADHD with stimulants is protective against substance use disorders. 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 or emotional lability are directly or indirectly related to morbidity.

Addiction and Mental Disorders
(J. Deckert, Dept. of Psychiatry, Psychosomatics and Psychotherapy)

The relevance of substance and non substance related addiction 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)

Parallels between substance dependence and excessive ('addictive') eating can be found in behaviour and cardiac-autonomic regulation. Further overlapping cognitive, behavioral, and physiological aspects are investigated.

We found deficits in reward learning from positive reinforcers in smokers and alcoholics. We are currently investigating whether such deficits can be shown in social drinkers, women with compensatory buying behaviour and women with aberrant eating behaviour.

Chromosomal effects of stimulants and stress in adult ADHD patients
(C. Jacob, S. Kittel-Schneider, S. Spiegel, T. Renner, A. Reif, H. Stopper)

The effect of the long-term administration of MPH on chromosomal integrity has not yet been investigated in adult ADHD patients. Besides various toxic environmental factors, aversive experienced stress is an essential risk factor for the development of physical illness and probably also chromosomal damage. One aim of the study is to investigate the long-term effects of MPH on the chromosomes. Contrary to prior studies, we hypothesize that the application of MPH reduces the psychological distress lo-

wering the number of micronuclei frequencies compared to untreated AADHD probands.

Teaching

The seminar "neurobiology of addiction"is an advanced training for young scientists and students of medicine, psychology and biology. The annual basic and advanced training workshop of addiction medicine is an additional teaching activity. Research projects are presented on the annual meetings of the ICAW.

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5.5.3 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 fifteen interdisciplinary centers for familial breast and ovarian cancer (Zentren für Familiären Brust- und Eierstockkrebs - Deutsche Krebshilfe). These centers 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 center is known as "*Interdisciplinary Center 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 principal BRCA and other susceptibility genes (BRCA1, BRCA2, RAD51C, p53, CHEK2 and PTEN). Optimal use of resources and assurance of high quality care has been achieved through close cooperation within the local center.

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 1100 of these families were followed in the Würzburg center. Mutations in either BRCA1 (139 families) or BRCA2 (70 families) 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 centers, a database was established at the University of Leipzig. Each center 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 p53, 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 possibility which needs to be explored is the interac-

tion 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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5.5.4 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 2011 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), 2 in the last 4 months. It is planned to further built up the liver program in 2012. To support the liver transplantation programme in Würzburg a W2-professur (Prof. Klein) was appointed at the Department of Surgery after recrual from one of the largest LTx programme in the US (USCL) and a W2-professur for hepatology appointed in the department of Internal Medicine II.

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.

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5.5.5 Center for Intestinal Medicine

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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 best therapy for each individual patient through interdisciplinary cooperation. Nutrition counselling, and psychological and social services provided by family physicians are also important aspects of therapy. Individual therapy concepts are developed in the weekly tumour board meetings. The exceptional structure of the Center for Intestinal Medicine, which includes all the main medical partners, optimizes planning for more quality of care.

Family physicians and other partners in the region perform the outpatient examinations wherever possible and, when necessary, refer patients to the Center for Intestinal Medicine. Here, they benefit from having all their therapies in one place. We provide several cancer therapies along with special services in cancer screening and rehabilitation. An effective pain therapy and counselling for colostomy patients 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 colon cancer patients.

Participating Clinics and Institutes:

- Clinic for General, Visceral, Vascular and Pediatric Surgery (Surgery I)
- Department of Radiation Oncology
- Institute of Radiology
- Department of Internal Medicine II (Hematology and Oncology)
- Institute of Pathology
- Institute of Psychotherapy and Medical Psychology

Appointments for screening and colon cancer treatment can be made through the central patient management unit (ZPM) in Surgery I, Tel. (0931) 201-39999.

5.5.6 Center of Rheumatic diseases

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General Information

The diagnosis and treatment of immune mediated diseases is one topic of the medical faculty of the university of Wuerzburg. The centre of Rheumatology founded in 2003 is an association of different institutes and clinical centres which attend to rheumatic diseases. In addition to members of the university also hospitals and physicians in private practice outside the university are integral parts. The aim of the centre of rheumatology 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 centre of Rheumatology is a member of the working group of centres of rheumatology within the German society of rheumatology.

Major Research Interests

The centre 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 centre organises interdisciplinary meetings and regular informal scientific workshops. At national level the centre of Rheumatology contributes regularly to the German epidemiological register for rheumatic diseases.

Teaching

The centre of Rheumatology 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.

5.5.7 Center for Stem Cell Therapy

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Activities

The stem cell therapy unit was established in 2005. In 2011, we offered an allogeneic graft to more than 100 adult and paediatric patients. To accomplish this ambitious 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 distinct 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“ is the precise analysis of the multifacetted interactions between human hematopoietic stem cells and Notch-ligand expressing stroma cells. Emphases of the investigations are the lymphoid differentiation pathways resulting from these interactions under various conditions.

Novel cellular therapies for malignant brain tumors

Under the umbrella of a EU-wide network, innovative cellular therapies for patients with malignant brain tumors are developed, validated and 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. Implementation of production procedures compatible with regulatory constraints in a GMP-facility represent a particular challenge of these concepts. Once established,

Fig.1: The building D30 hosts the Center for Stem Cell Therapy.

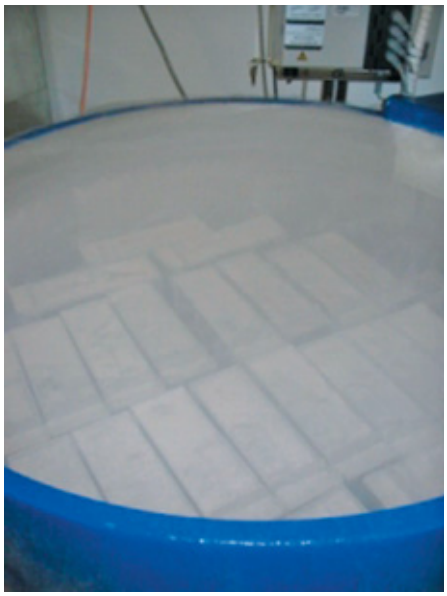

Fig. 2: The stem cells are stored in liquid nitrogen at minus 196 °C.

these clinical trials will underline the dedicated immunotherapeutic emphasis of our stem cell transplantation program.

Specific immunization of chronic CMV-infection

Vaccination with antigen-loaded dendritic cells (DC) leads to induction of specific immune responses by cytolytic T lymphocytes in vivo. Infections or reactivation of cytomegalovirus is a frequent and live threatening problem after allogeneic stem cell transplantation. Due to the delayed reconstitution of specific competence, the patient's immune systems in many cases fail to mount an efficient defence line against the virus. In a phase I/II study, we treat patients after allogeneic stem cell transplantation with vaccine, individually constructed from donor derived dendritic cells.

Adoptive transfer of antigen specific immune T lymphocytes by streptamer technology

Within a multi-centre phase I/II clinical study, we investigate toxicity and efficiency of an adoptive immune strategy using CMV specific T cells which were selected by streptamer technologies. Strepamer-technology allows quantitative isolation of T cells with desired specificities by reagents which are fully detachable from the isolated cell populations. This is important for immune functions because the selection agents might interfere with the antigen sensing machinery of the T lymphocytes thus potentially attenuating anti viral functions. Moreover, removable reagents fully comply with regulatory demands and safeguard the cellular product. We treat patients after allogeneic stem cell transplantation that do not clear CMV infection or reactivation.

Cord blood transplantation

Cord blood transplantation is an alternative option for patients who urgently need an allogeneic stem graft but lack a suitable donor. Well established in the paediatric setting, cord blood grafts are increasingly employed for adults. Central for 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 precisely investigate the haematological and immunological reconstitution of bone marrow function after cord blood transplantation. To this end and supported by the Deutsche Jose Carreras Leukaemia Foundation, we successfully established a clinical and scientific protocol within a multicenter, non-interventional phase I/II study.

Mismatched allogeneic stem cell transplantion – Depletion of alloreactive T cells

Haploidentical blood stem cell transplantation is facilitated by the removal of donor T cells from the stem cell allgraft and profound immunosuppression of the host to prevent primary rejection. As an unfortunate consequence T cell reconstitution is largely impaired leading to increased rates of infections and non-relapse mortality (NRM). Mielke and colleagues have established a method where host-reactive donor T cells are removed by ex vivo TH9402-based photodepletion allowing the add-back of allodepleted lymphocytes to overcome infectious complications after haploidentical blood stem cell transplantation from family donors. An international trial on both sides of the Atlantic has been launched where patients with no potential donor are offered mismatched transplants with add-back of allodepleted lymphocytes (Coordinating Investigator Europe: S. Mielke, Würzburg; Sponsor Kiadis Pharma, NL). This trial is accompanied by a translational research program.

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Wilhelm K, Ganesan J, Müller T, Dürr C, Grimm M, Beilhack A, Krempl CD, Sorichter S, Gerlach UV, Jüttner E, Zerweck A, Gärtner F, Pellegatti P, Di Virgilio F, Ferrari D, Kambham N, Fisch P, Finke J, Idzko M, Zeiser R. (2010) Graft-versus-host disease is enhanced by extracellular ATP activating P2X7R. Nat Med. 16(12):1434-8.

5.5.8 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 syndromes 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 Institute for Human Genetics. The treatment starts immediately after birth and continues to adulthood.
A special institution focusing on research of early vocal development in patients and healthy infants, the Center for Prespeech Development & Developmental Disorders (director: Prof. K. Wemke), comes under 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, F. Strnad, M. Staufer, 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 multicenter 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.
(J. Kochel, F. Strnad, M. Staufer, 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, D. Eiband in cooperation with the Department of Otorhinolaryngology, Plastic, Aesthetic and Reconstructive, Head and Neck Surgery, University of Wuerzburg and the Department of Special Education, Speech and Language Pathology, University of Wuerzburg, Germany.)

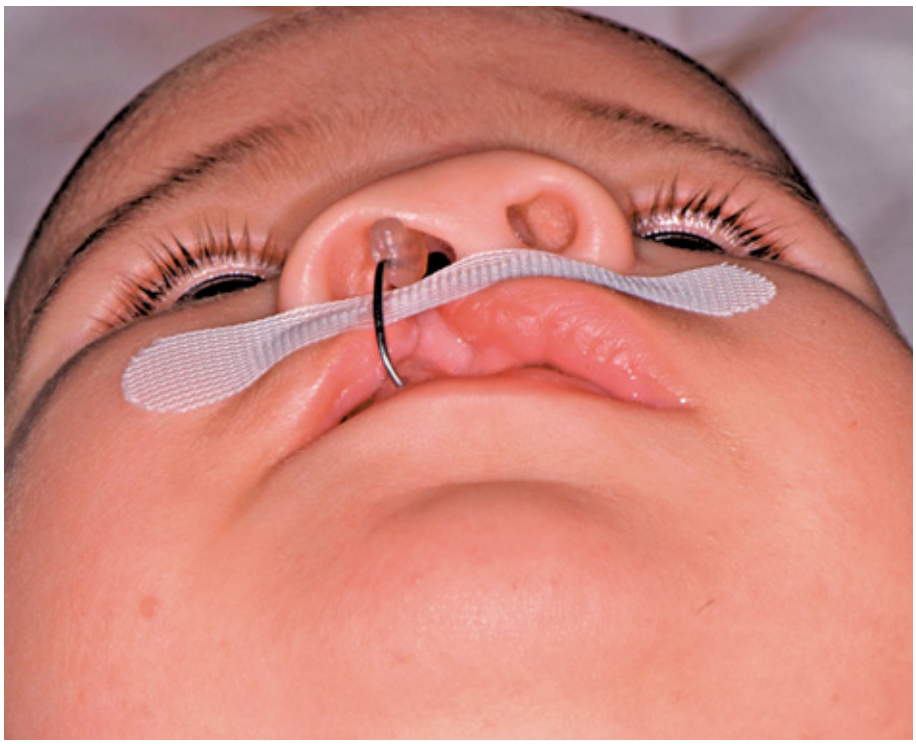

Fig. 1: Preoperative nasoalveolar molding with an orthopedic plate in a newborn with a cleft lip and palate.

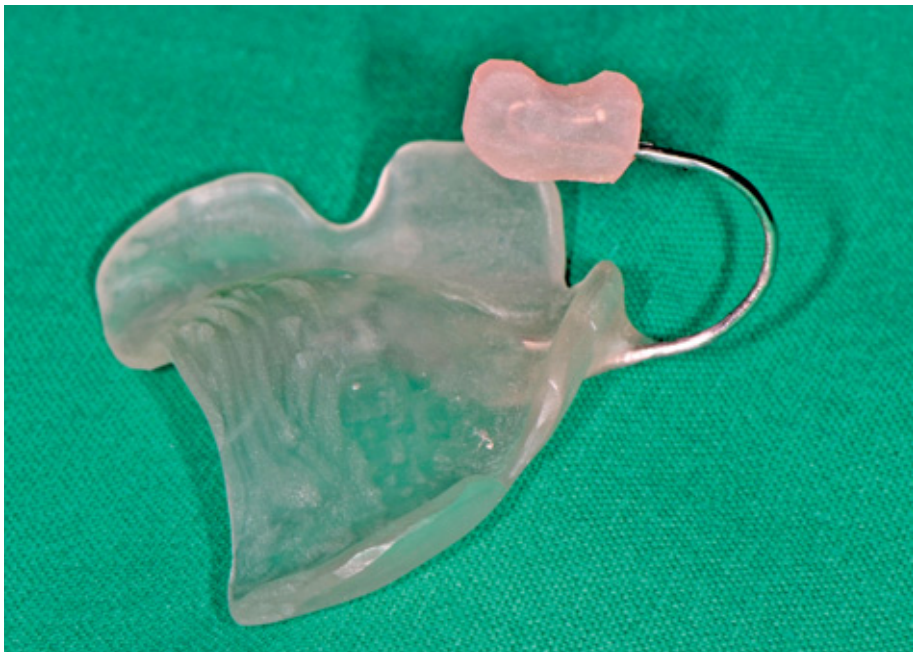

Fig. 2: Orthopedic appliance with a nasal stent.

It is well-known that prosodic features such as melody and rhythm are crucial for an infant acquiring language. In a recent study, we demonstrated a very early impact of the surrounding language on human infants' vocalization: Newborns were found to modify their cry melody in response to the surrounding language. In contrast to the old ''brainstem model'' of cry production, which suggests that no structures rostral to the midbrain are required for infant crying, our recent studies support the assumption of an involvement of cortical structures in infants' vocal production. For example, cry melody structure of 2-month-old infants with and without clefts was analyzed using adequate signal analysis techniques (Wermke et al. 2011). The main finding of this study is that infants with clefts differ in their cry melody development from typically developing infants at 2 months of life. Neither melody complexity and rhythmicity (as reflected by segmentation features), however, had differentiative power with respect
to the cleft type. The analysed acoustic properties (melody complexity, segmentation characteristics) proved valuable in helping to focus the search for currently unidentified neurological or genetic factors that are associated with clefting. Since 2010 these and further developmental risk-markers have been applied in a project that investigates vocal development of infants with plagiocephali (in a cooperation with the Craniofacial Center Wuerzburg - cfcw).

A New Model of Vocal Development: From Emotion to Notion—From Melody to Words

(K. Wermke, S. Pachtner, A. Prochnow, V. Voit in cooperation with W. Mende, Berlin-Brandenburg Academy of Humanities and Sciences, Berlin, Germany)

Our developmental model supports the hypothesis that for the production of cries, comfort sounds, speech-like babbling, and of first words, not only are the same "architectural principles" at work but that the prosodic constituents (melodic building blocks) for the later spoken language are also developed. Our longitudinal data across the first 10 – 12 months reveal a clear coherence and a strong developmental continuity from first crying via cooing and babbling toward speech and first language competence. The aptitude of newborns and young infants to produce increasingly complex melodies by combining basic melody types and rhythmical elements, while not yet possessing the skills of intentional articulation, might represent an "incidental feature of maturation that just happened to be co-opted in languages' race" (Deacon, 1998, p. 137) during the evolution of spoken language (Wermke & Mende, 2011). Our longitudinal studies have been providing new evidence for a coherent progression from emotion to notion, from melodies to words, a development that is recapitulated in each infant's acquisition of language. This new perspective and an improved model of vocal development allows a better understanding of normal versus pathologic development during the earliest stages of language-relevant development in infants with orofacial clefts.

Interdiciplinary consultation-hours cleft lip and palate:
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SELECTED PUBLICATIONS

Kochel J, Meyer-Marcotty P, Wirbelauer J, Böhm H, Kochel M, Thomas W, Bareis U, Hebestreit H, Speer C, Stellzig-Eisenhauer A. (2011) Treatment modalities of infants with upper airway obstruction-review of the literature and presentation of novel orthopedic appliances. Cleft Palate Craniofac J. 48:44-55.

Meyer-Marcotty P, Alpers GW, Gerdes AB, Stellzig-Eisenhauer A. (2010) Impact of facial asymmetry in visual perception: a 3-dimensional data analysis. Am J Orthod Dentofacial Orthop. 137:168.e1-8; discussion 168-9.

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5.5.9 Interdisciplinary Center for Palliative Medicine

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Tasks and Structure

The University Clinic has had a palliative ward with a consultation service since October 2009. The Interdisciplinary Center for Palliative Medicine is located in building D20 (formerly Heilmeyer ward) and has 10 beds in single rooms, overnight accommodation for relatives, a living room, a café for patients, a quiet room and a room for physiotherapy (cf. ill. 1 and 2). Patients of age with incurable underlying diseases and limited life expectancy, whose complex symptoms require inpatient treatment, are attended to on the palliative ward. The aim of treatment is to relieve symptoms and improve quality of life. By the end of 2011, a total of 651 patients had been attended to, 86% of these patients were tumor patients. 281 patients died on the palliative ward (43.1%) and 370 patents could be stabilized and discharged (66.9%). The Interdisciplinary Center for Palliative Medicine is linked to the Clinic for Radiotherapy. The multi-professional team consists of three physicians, 13 nurses, one social worker, one psychooncologist, two physiotherapists and two pastors. Art and music therapy are offered by a therapist who is employed on a freelance basis. Additional further training in palliative medicine is possible.

Research Focus

We focus on palliative radiotherapy and radiotherapy for alleviation of symptoms in palliative medicine. The multi-centric pattern-of-care study revealed that palliative radiotherapy significantly alleviates pain, dyspnea and neurological deficits. The patient's general condition also improved significantly (cf. ill. 2) 1
The "advance directives for radiotherapy patients" study was completed in 2010. A recent doctoral thesis looked at the development of a tool that could be used for geriatric risk assessment before starting oncotherapy. Based on the results of our multi-centric study on quality of life of patients who suffer from multiple brain metastases (Steinmann 2009), a prospective randomized study was started in December 2011 to examine the effects that palliative medical care has on radiotherapy patients with multiple brain metastases.
A study on nutrition has been under way on the palliative ward since August 2010 (cf. ill. 3: Pathway nutritional medicine). In November 2010, a study was started which is being conducted in the context of a dissertation and deals with the meaning of life and with the individual burden of palliative patients in inpatient care.

Training

The physicians, psychooncologist and pastors give different lectures and seminars on palliative medical contents of learning (history, theory and medical ethics; medical psychology and sociology; medicine of aging and interdisciplinary oncology). Since 2007, communication training with

Fig. 1: Palliative ward, impressions of the ward.

Fig. 2: Room for physiotherapy.

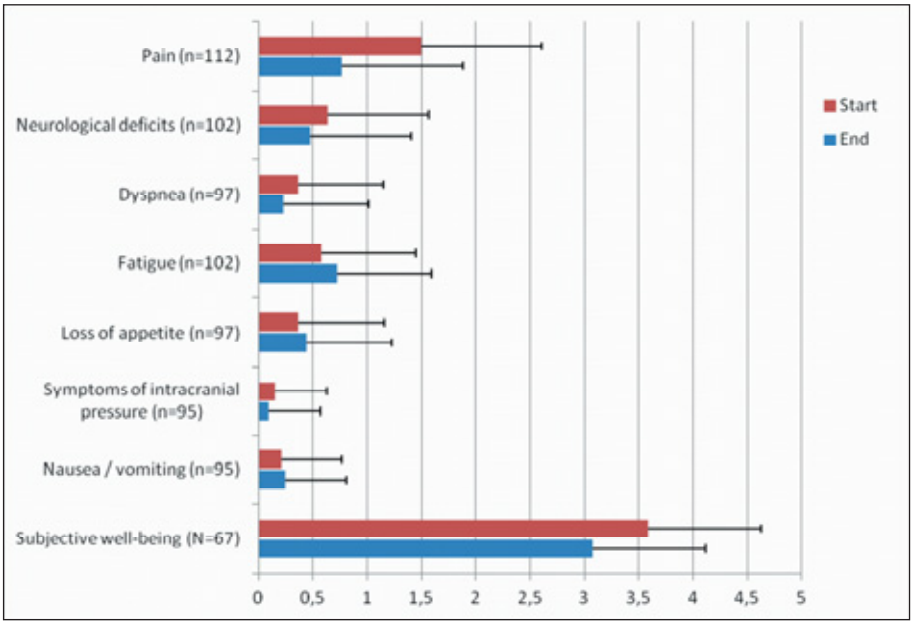

Fig. 3: Clinical symptoms at the beginning of and after radiotherapy, scale values between 0 (no symptoms) and 3 (severe symptoms) and between very high well-being (=0) and very low well-being (=3). Significant improvement in the course of symptoms with regard to pain, dyspnea, neurological deficits and well-being ($p<0.01$, mean value comparison, t-test for independent random samples). From: van Oorschot B, et al. 2011.

standardized patients (amateur actors) has been a compulsory seminar in the context of interdisciplinary oncology (7th semester). Dr. van Oorschot and Dr. Neuderth (medical psychology) were awarded the Albert-Kölliker Teaching Award of the Medical Faculty Würzburg in 2011, for setting up the training with standardized patients. The elective subject palliative medicine is offered in cooperation with lecturers of the palliative ward of the Juliusspital Foundation and the Missionsärztliche Clinic. The compulsory curriculum of palliative medicine is to be offered starting in the winter semester 2012 for students in the 9th semester. Moreover, lecturers of the Interdisciplinary Center for Palliative Medicine are involved in the further training of nurses, in seminars and lectures of the Palliative Academy of the Juliusspital Foundation and in other national further training opportunities. On the occasion of the visit by our Japanese partner university's delegation from Nagasaki, a first international symposium with the topic "psychosocial and spiritual issues in palliative care - a transcultural perspective" took place on 13 December 2011.

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5.5.10 Musculoskeletal Center Würzburg MCW

CONTACT DETAILS

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General Information

The Musculoskeletal Center Würzburg MCW is a consortium of 20 hospitals and departments to establish medical care and research in musculoskeletal diseases and trauma. Along with the increasing longevity in our aging societies musculoskeletal diseases and trauma are more and more relevant. At present the total expenditure for this field amounts to 16% of our health budget. Musculoskeletal diseases and trauma are the most common causes for inability to work, for early retirement and for dependence and institutionalisation of the elderly. Diseases of the musculoskeletal unit, e.g. bone, muscle and joint structures comprise the widespread diseases osteoporosis, osteoarthritis, rheumatoid arthritis and the ever expanding epidemic condition of sarcopenia. The core institutions for interdisciplinary clinical care are the Orthopedic Department, and the Orthopedic Hospital König-Ludwig-Haus, the Department of Trauma, Hand, Plastic and Reconstructive Surgery and the Clinic and Policlinic for Plastic Facial, Mouth and Maxillary Surgery, There is intensive problem-oriented interaction with many other clinical partners and institutes of our faculty. Interdisciplinary basic and translational research is run by the chair for Tissue Engineering end Regenerative Medicine together with Fraunhofer IGB, the Department for Functional Materials in Medicine and Dentistry, the chair for Technology of Material Synthesis and Fraunhofer ISC, the chair for Pharmaceutical Technology and Biopharmacy and by the research units of the core institutions. The consortium is embedded into local, national and international research networks, there is intense cooperation with the Faculties of Biology, Biophysics, the Institute for Bioinformatics as well as with the faculties of Theology and Law for ethical and legal issues. The core mission of the MCW is to promote the interdisciplinary trans-faculty basic research with a strong translational focus, high end interdisciplinary patient care and the training and continuous education in medicine and medical technologies at the university and beyond.

Major Research Interests

Major research interests are the principles of tissue regeneration in musculoskeletal diseases and trauma. We have established special competence for mesenchymal stem cell biology and aging and in the development of cell based therapeutic strategies, in Tissue Engineering and material development, in the development of pharmaceutical delivery devices and in the synthesis of new surfaces. Important fields of activity are regeneration of bone, cartilage, muscle, adipose tissue, tendons and ligaments, and the rapid translation of therapeutic strategies to treat injuries and degenerative diseases of the musculoskeletal system including face, mouth and maxillary problems. MCW scientists are involved in local, national and international research net-

Fig. 1: Clean Room Concept for cell based treatment strategies and tissue engineering.

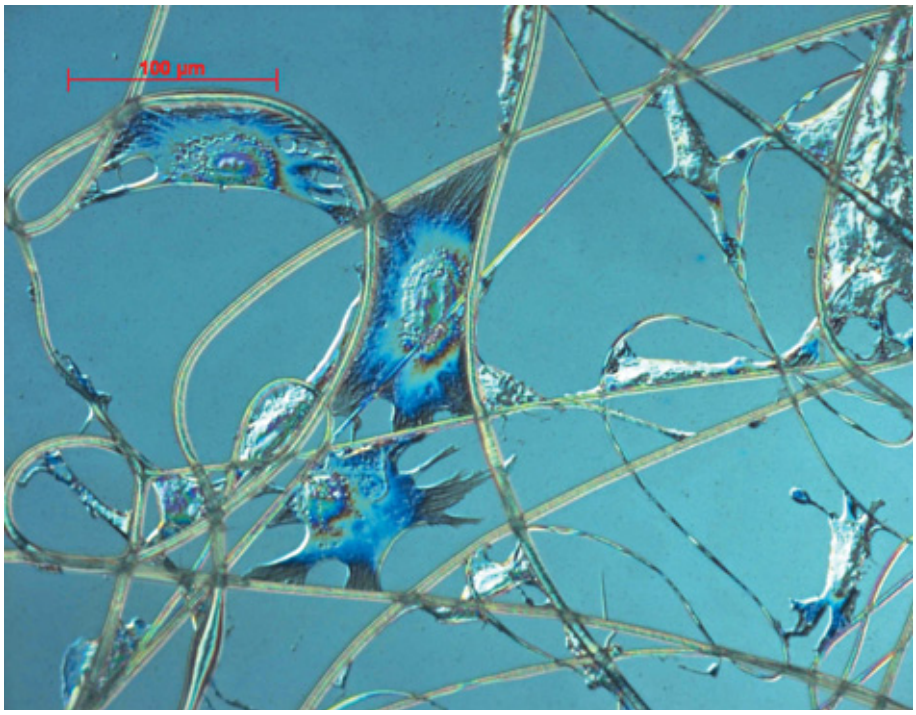

Fig. 2: Fibroblasts growing on electrospun and GRGDS-functionalized PLGA/sP(EO-stat-PO) fibres.

works, e.g. DFG-Research Units FOR 793 and 1586, SFB630, BMBF-Consortium Osteopath, BMBF-Consortium Preeclampsia, EU-Consortia ADIPOA and VASCUBONE.

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5.6 Research Training Groups
5.6.1 Research Training Group 1048, Molecular Basis of Organ Development in Vertebrates

CONTACT DETAILS

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Professor Dr. med. Manfred Gessler
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General Information

A profound knowledge of the regular development of organisms in a prerequisite to contribute to the elucidation of mechanisms that lead to pathological development and human disease it is mandatory to study normal development. Under the paradigm that normal and pathological development often use 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. The aim of the research training group GRK 1048 is to contribute to a better understanding of the molecular mechanisms as the basis for the establishment of a fully functional, healthy organism and to provide a structured PhD research and training environment in Developmental Biology.

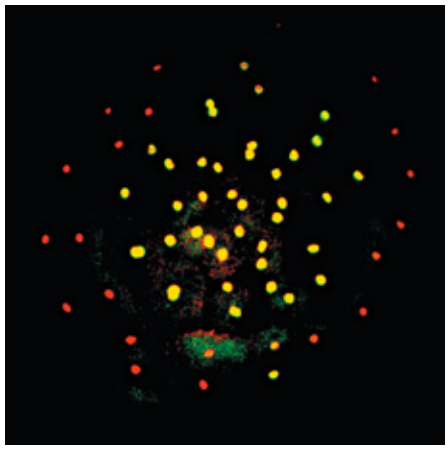

Fig. 1: Phosphorylated RNA-polymerase II in embryos from medaka (Oryzias Latipes) demonstrates transcriptional activity before genome activation at the midblastula transition (MBT). Shown is an embryo at the embryonic stage with 64 cells; nuclei are stained with Hoechst (red), nuclei that also show phosphorylation of RNA-Pol II appear yellow.

Major Research Interests

The research program addresses questions in the field of Developmental Biology with a special emphasis on organogenesis and provides interactions 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 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 positive 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 the 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 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 in biomedicine.

5.6.2 Research Training Group 1253, Emotions

CONTACT DETAILS

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Professor Dr. med. Klaus-Peter Lesch
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Tel.: 0931/201-77600

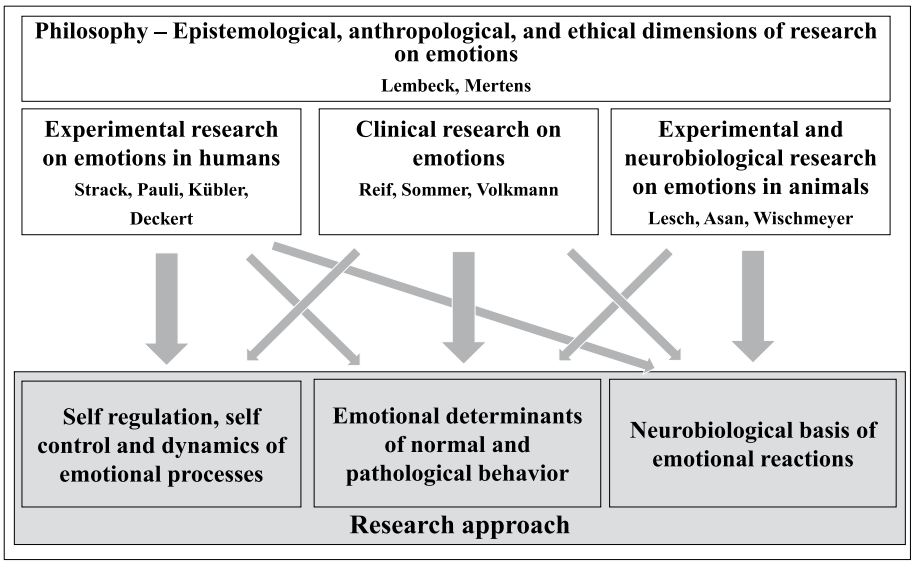

Fig. 1: Principal Investigators and structure of the RTG.

General Information

An intense and interdisciplinary supervision of the doctoral students is ensured by doctoral committees with three 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 with regularly success control 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. Graduation will be realized within the Graduate School of Life Sciences, which also allows a fast-track dissertation.

Major Research Interests

The present Research Training Group (RTG) aims at identifying important mediators and moderators influencing the processing of affective stimuli. The cooperation of renowned research groups from philosophy, psychology, psychiatry, neurology, anatomy, and physiology will allow the RTG's doctoral students to develop excellent and internationally visible interdisciplinary research projects within the Affective Sciences. Based on the realized interdisciplinary approach and the expertise of the RTG researchers the projects of the RTG will converge on three levels, each addressed by human, clinical and animal research: (1) self-regulation, self-control and dynamic of emotional processes, (2) emotional determinants of normal and pathological behavior, and (3) neurobiological basis of emotional reactions (especially serotonergic and dopaminergic systems). A special interest hereby is to identify interactions between these 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.

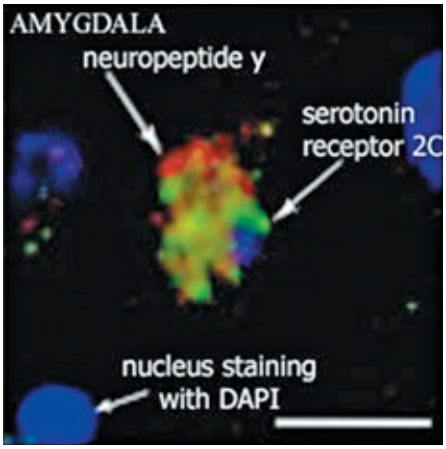

Fig. 2: Lateral Amygdala (LA). Double Fluorescence in situ hybridization in the lateral nucleus of the rat amygdala. Red: neuropeptide y mRNA; green: serotonin receptor 2C mRNA; yellow: colocalization; blue: nuclear staining with DAPI; magnification: 20x; scale bar: 20µm.

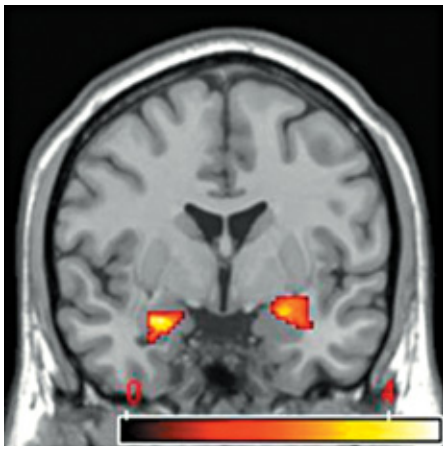

Fig. 3: Sagittal view of a human brain. Red-yellow shadings indicate activation in the amygdala due to the view of a threatening stimulus.

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.

5.6.3 International Research Training Group 1522, HIV/Aids and Associated Infectious Diseases in Southern Africa

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www.gk-1522.uni-wuerzburg.de

General

The International Research Training Group 1522 (IRTG1522) on „HIV/AIDS and associated Infectious Diseases in Southern Africa" between Universities in Würzburg and Cape Town is the only one between Germany and the whole of Africa. The higher aim is to intensify the scientific relations between Germany and South Africa. At Würzburg University 11 PhD student plus 2 MD student stipends financed be the DFG and complementary 12 PhD student stipends financed by the NRF at the Universities of Stellenbosch and Cape Town were created by the 2008/2009 founded IRTG. Thematically divided in three areas 12 research projects on infectious diseases are conducted. South Africa can supply patient samples that cannot be obtained in Germany and can be investigated by methods available in Würzburg but rarely applied in South Africa. The IRTG fully acknowledges that the Republic of South Africa as the most developed country of whole Africa has a infrastructure that allows biomedical research to be conducted on the same level with Germany so that enormous synergies are created. The main corner stone of this IRTG is a student exchange programme between the participating universities that permits students from Würzburg to spend some research time in Cape Town and *vice versa*. In early summer the IRTG is scheduled for evaluation of a second funding period.
Questions on clinical virology and basic questions on HIV and virus-induced immunosuppression are investigated in Area one. In area two some HIV-associated infectious agents are investigated. And in area three questions on the immunology of infectious agents are followed. Numerous connecting aspects bridge the research fields of different areas. The speaker on the South African side of this IRTG is Prof. Wolfgang Preiser
from t „Medical Virology„ of Stellenbosch University.

Research projects

Area I

Project 1: The impact of therapeutic drug monitoring on antiretroviral therapy
Supervisors: Prof. Dr. Hartwig Klinker and Prof. Dr. August Stich (Missio)
Project 2: Study of drug-resistant HIV
Supervisor: Dr. Jochen Bodem
Project 3: Molecular Epidemiology of HIV
Supervisor: Prof. Dr. Axel Rethwilm
Project 4: Influence of different HIV subtypes on HIV dementia
Supervisors: Prof. Dr. Eleni Koutsilieri und 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.
Supervisors: Prof. Dr. Sibylle Schneider-Schaulies und Dr. Susanne Kneitz

Area II

Project 6: Epidemiology, diagnosis, and molecular mechanisms of multidrug resistance in *Candida albicans* and its impact on host-fungus interactions
Supervisor: 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
Supervisor: Prof. Dr. Klaus Brehm
Project 8: *Staphylococcus aureus* population structure and host cell interaction in chronic infection
Supervisor: Prof. Dr. Dr. Bhanu Sinha
Projekt 9: Generation and characterization of candidates for malaria/HIV combination therapy
Supervisor: Dr. Gabriele Pradel

Area III

Project 10: Characterization of the role of C-type lectins in dendritic cell interactions with *Leishmania* parasites
Supervisor: Prof. Dr. Heidrun Moll
Project 11: Protective and productive inflammatory responses induced by microbial products studied at the level of dendritic cells
Supervisor: Prof. Dr. Manfred Lutz
Project 12: The role of CD28 mediated costimulation in the control of secondary immune responses to infectious agents
Supervisor: Prof. Dr. Thomas Hünig

SELECTED PUBLICATIONS

Kasang C, Kalluvya S, Majinge C, Stich A, Bodem J, Kongola G, Jacobs GB, Mllewa M, Mildner M, Hensel I, Horn A, Preiser W, van Zyl G, Klinker H, Koutsilieri E, Rethwilm A, Scheller C, Weissbrich B. (2011) The prevalence of drug resistant HIV in therapy-naive patients in Tanzania is significantly higher than estimated by WHO surveillance criteria. PLoS One 6:e23091.

Pretorius E, Klinker H, Rosenkranz B. (2011) The role of therapeutic drug monitoring in the management of patients with human immunodeficiency virus infection. Ther Drug Monit. 33:265-274.

Nowotny B, Schneider T, Pradel G, Schirmeister T, Rethwilm A, Kirschner M. (2010) Inducible APOBEC3G-Vif double stable cell line as a high-throughput screening platform to identify antiviral compounds. Antimicrob Agents Chemother. 54:78-87.

Aminake MN, Schoof S, Sologub L, Leubner M, Kirschner M, Arndt HD, Pradel G. (2011) Thiostrepton and derivatives exhibit antimalarial and gametocytocidal activity by dually targeting parasite proteasome and apicoplast. Antimicrob Agents Chemother. 55:1338-1348

Kleynhans L, Du Plessis N, Black GF, Loxton AG, Kidd M, van Helden PD, Walzl G, Ronacher K. (2011) Medroxyprgesterone acetate alters Mycobacterium bovis BCG-induced cytokine production in peripheral blood mononuclear cells of contraceptive users. PLoS One 6:e24639.

5.7 Research Alliances
5.7.1 BMBF Joint Project: Effects and Mechanisms of Psychotherapy in the Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in Children and Adults

CONTACT DETAILS

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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.

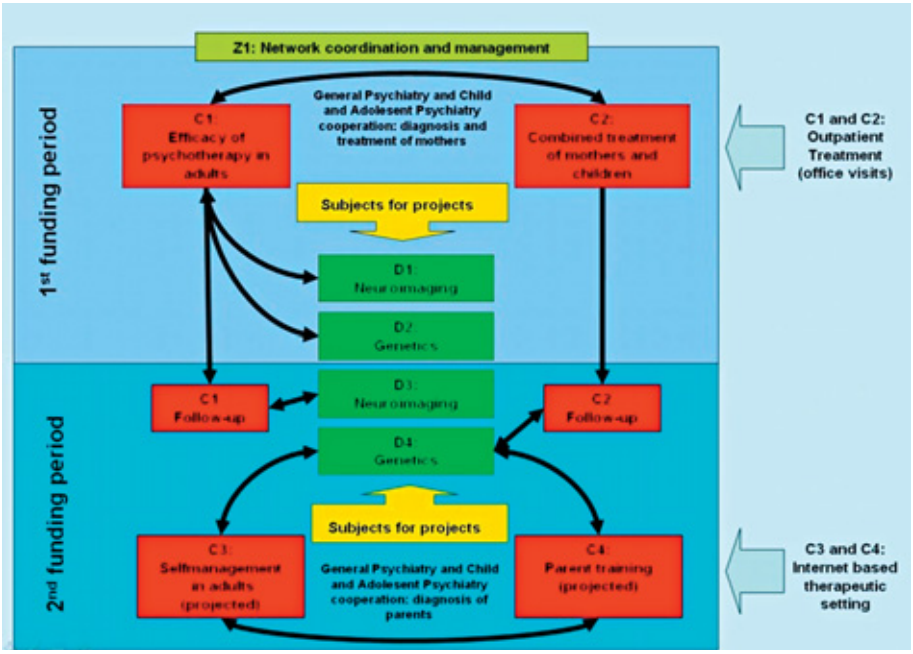

Fig. 1: Network structure.

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.

The two clinical trials were closed in 2011. Last follow-up investigations will be conducted in 2012. Results on clinical outcomes and associated neurobiological findings will successively be published as of 2012.

SELECTED PUBLICATIONS

Ahrendts J, Rüsch N, Glauche V, Wilke M, Philipsen A, Eickhoff E, Perlov E, Hennig J, Tebartz van Elst L: Abnormal Visual Cortex in Adults with ADHD (2010). A Structural MRI Study. World J Biol Psychiatry. 2010 Sep 29. [Epub ahead of print].

Philipsen A, Graf E, Tebartz van Elst L, Jans T, Warnke A, Hesslinger B, Lesch KP, Gerlach M, Matthies S, Colla M, Jacob C, Sobanski E, Alm B, Rösler M, Kis B, Huss M, Lieb K, Schlander M, Berger B. (2010). Evaluation of the Efficacy and Effectiveness of a Structured Disorder Tailored Psychotherapy in ADHD in Adults – Study Protocol of a Randomized Controlled Multicentre Trial. ADHD Attention Deficit and Hyperactivity Disorders, 2:203–212.

Lesch KP, Selch S, Renner TJ, Jacob C, Nguyen TT, Hahn T, Romanos M, Shoichet S, Dempfle A, Heine M, Boreatti-Hümmer A, Walitza S, Romanos J, Gross-Lesch S, Zerlaut H, Allolio B, Heinzel S, Fassnacht M, Fallgatter A, Wultsch T, Schäfer H, Warnke A, Reif A, Ropers HH, Ullmann R. (2010) Genome-wide copy number variation analysis in ADHD: association with neuropeptide Y gene dosage in an extended pedigree. Molecular Psychiatr, 16:491–503.

Christiansen H, Kis B, Hirsch O, Matthies S, Hebebrand J, Uekermann J, Abdel-Hamid M, Kraemer M, Wiltfang J, Graf E, Colla M, Sobanski E, Alm B, Rösler M, Jacob C, Jans T, Huss M, Schimmelmann BG, Philipsen A. (2011) German validation of the Conners Adult ADHD Rating Scales (CAARS) II: Reliability, validity, diagnostic sensitivity and specificity. European Psychiatry [Epub ahead of print].

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5.7.2 BMBF Joint Project, SARA: Systems Biology of PGI2 and ADP P2Y12 Receptor Signaling

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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

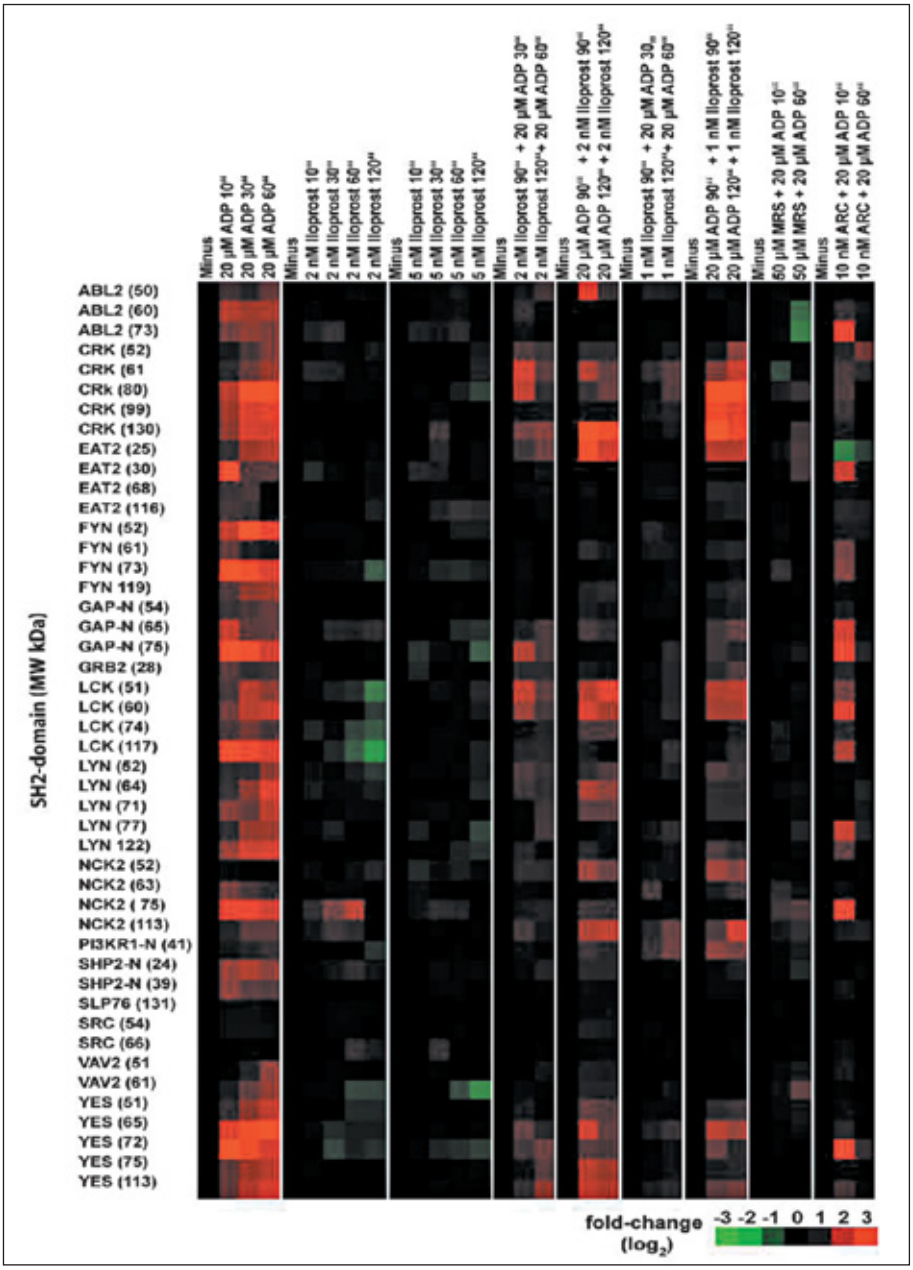

Fig. 1: Time course of protein tyrosine phosphorylation changes in stimulated human platelets visualized by SH2-profiling

Members

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Dandekar T., Institute of Bioinformatics, Wuerzburg
Nollau P., Department of Clinical Chemistry/ Central Laboratories, Hamburg
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Kohlbacher O., Center for Bioinformatics, Tuebingen
Blankenberg S., Center for cardiovascular prevention, Mainz
Schinzel R., vasopharm GmbH, Wuerzburg

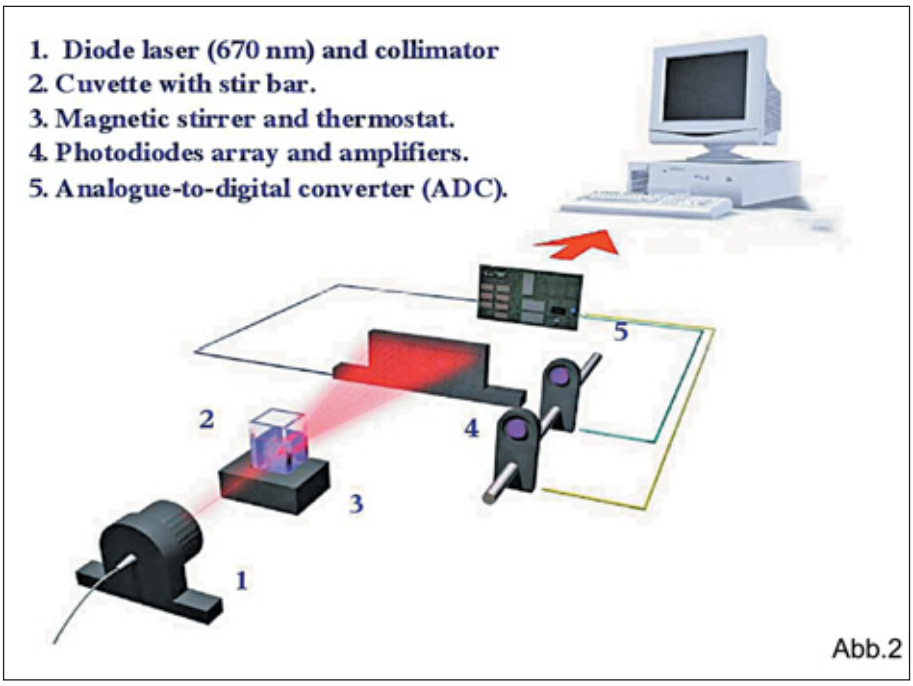

Fig. 2: LASCA (low angle light scatter analysis) setup.

weak platelet agonist in recent years it became evident that a complete platelet aggregation is only possibly by activation of ADP stimulated pathways. 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 biological, 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 inhibiton identified coherently will then be verified in a large group of volunteers. Eventually a meaningful 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.

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

Gambaryan S, Kobsar A, Rukoyatkina N, Herterich S, Geiger J, Smolenski A, Lohmann SM, Walter U. (2010) Thrombin and collagen induce a feedback inhibitory signaling pathway in platelets involving dissociation of the catalytic subunit of protein kinase A from an NFkappaB-IkappaB complex. J Biol Chem. 285:18352-63.

Geiger J, Brandmann T, Hubertus K, Tjahjadi B, Schinzel R, Walter U. (2010) A protein phosphorylation-based assay for screening and monitoring of drugs modulating cyclic nucleotide pathways. Anal Biochem. 407:261-9.

Mindukshev I, Gambaryan S, Kehrer L, Schuetz C, Kobsar A, Rukoyatkina N, Nikolaev VO, Krivchenko A, Watson SP, Walter U, Geiger J. (2012) Low angle light scattering analysis: a novel quantitative method for functional characterization of human and murine platelet receptors. Clin Chem Lab Med. 2012, [Epub ahead of print].

5.7.3 BMBF Joint Project: Medical Infection Genomics – Genome Research on Pathogenic Bacteria

CONTACT DETAILS

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General Information

The funding initiative "**Medizinische Infektionsgenomik**" (Medical Infection Genomics) is a research program financially supported by the Federal Ministry of Education and Research (BMBF). It consists of eleven research clusters focussed on the genome research on pathogenic microorganisms.

During the funding period from 2010 to 2013 the participating groups of the Medical Infectious Genomics network focus on human pathogenic bacteria that are of high socioeconomic relevance for the public health system in Germany due to their wide dissemination in, e. g., hospitals or that pose a particular threat for the public health system due to their high rate of antibiotic resistance or their high virulence potential.

The eleven research clusters aim at a comprehensive understanding of the infectious agents and their adaptation to the human host during the infectious process. By unravelling the complex interactions between the pathogen and the human host the ultimate goal of the funding initiative is to provide the basis for the further improvement of the prevention, diagnosis and therapy of infectious diseases.

The Medical Infection Genomics network is coordinated by Prof. Dr. Matthias Frosch, head of the Institute for Hygiene and Microbiology of the University of Würzburg. Besides scientists of the University of Würzburg further research groups from different German universities and non-university research institutions, hospitals and industry are members of the network.

Major Research Interests

Four research groups of the University of Würzburg are involved in the funding initiative:

The research cluster "Next generation transcriptomics for bacterial infections" is coordinated by Prof. Dr. Jörg Vogel (head of the Institute for Molecular Infection Biology) and aims to establish next-generation sequencing as a novel tool to study the gene expression profiles of the bacterial pathogen and the eukaryotic host in parallel over the course of infection.

Prof. Dr. Ulrich Vogel (Institute for Hygiene and Microbiology) is member of the research cluster "Proteomics of meningococci and pneumococci - from *in vitro* biofilms to *in vivo* infection" coordinated by Prof. Dr. Sven Hammerschmidt from the University of Greifswald. The aim of this project is to employ a time resolved protein profiling of meningococci and pneumococci to gain new information on the cellular physiology and virulence of these human pathogens.

PD Dr. Knut Ohlsen (Institute for Molecular Infection Biology) is part of the research cluster "Host-pathogen interactions: effects of secreted proteins of *Staphylococcus aureus* on cells and components of the immune system " coordinated by Dr. Susanne Engelmann from the University of Greifswald. The research groups want to gain new insights into immune evasion mechanisms of this important pathogen.

The research cluster "Pathogen-host interactomes and signalling complexes in bacterial infections" is coordinated by Prof. Dr. Thomas Rudel (head of the Department of Microbiology) and focuses on the investigation of the pathogen-host interactome of the etiological agents for a range of important human infections such as typhoid fever, tuberculosis, trachoma, Legionnaires disease, gastritis and peptic ulcer diseases.

5.7.4 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 derived HSC (CH-HSC) 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, nano-structured 3D surfaces, modifications of inhibitory pathways and epigenotype as well as 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 allogenetic 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 oper-

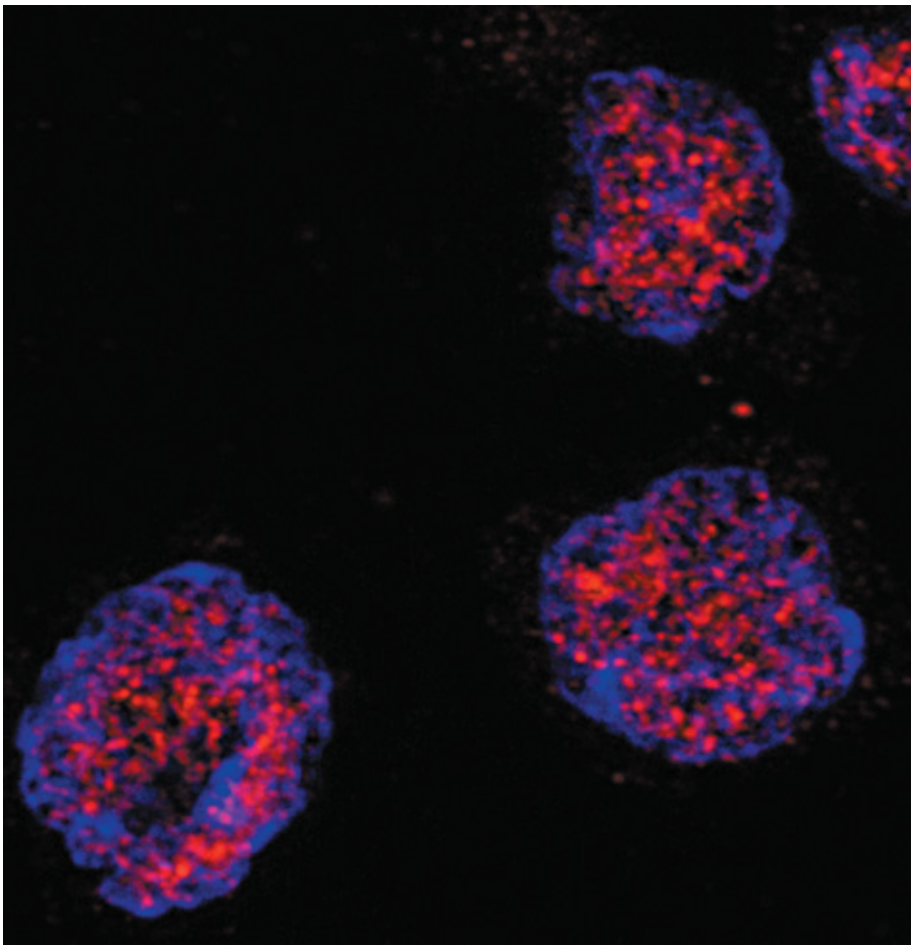

Fig. 1: Immunostaining of histon H3K4me³ in cord blood hematopoietic stem cells.

No.	Head of the project	Institution	Title of the subproject
1	Dr. Bernd Schiedlmeier, Prof. Dr. Christopher Baum	Hannover Medical School, Dept. Experimental Hematology Carl-Neuberg-Straße 1, 30625 Hannover Phone: +49 511 532 6067, Fax: +49 511 532 6068 Email: experimental.hematology@mh-hannover.de	Pathway discovery and protocol development
2	Dr. Sabine Neuß-Stein, Dr. Thomas Hieronymus, Prof. Dr. Martin Zenke	RWTH Aachen University, Institute of Pathology Pauwelsstraße 30, 52074 Aachen Phone: +49 241 8080622, Fax: +49 421 8082439 Email: sneuss-stein@ukaachen.de RWTH Aachen University, Helmholtz Institute for Biomedical Engineering – Cell Biology – Pauwelsstraße 30, 52074 Aachen Phone: +49 241 8085249 (T.H.) Phone: +49 241 8080760 (M.Z.) Fax: +49 241 8082008 Email: Thomas.hieronymus@ewth-aachen.de Email: martin.zenke@rwth-aachen.de	Biomaterial scaffolds for CB-HSC expansion
3	Prof. Dr. Albrecht Müller	University Würzburg Institute of Medical Radiation and Cell Research Zinklesweg 10, 97078 Würzburg Phone: +49 931 - 201 45848 (office) Phone: +49 931 - 201 45478 / 45146 (secr.) Fax: +49 931 - 201 45147 Email: albrecht.mueller@uni-wuerzburg.de	Epigenetic characterisation of CB-HSCs
4	Prof. Dr. Wolfgang Wagner	RWTH Aachen University Helmholtz Institute for Biomedical Engineering – Cell Biology – Pauwelsstraße 20, 52074 Aachen Phone: +49 241 80-88611, Fax: +49 241 80-3388611 Email: wwagner@ukaachen.de http: www.ukaachen.de/sites/lfg/stammzellbiologie	Expansion of CB-HSCs with human MSCs
5	Prof. Dr. Arnold Ganser, Prof. Dr. Eva Mischak-Weissinger	Hannover Medical School, Dept. Hematology, Hemostasis, Oncology and Stem Cell Transplantation KMT-Ambulant/ TPFZ OE 6863 Carl-Neuberg-Straße 1, 30625 Hannover Phone: +49-511/532-9518, Fax: +49-511/532-6843 Email: mischak-weissinger.eva@mh-hannover.de Email: Ganser.Arnold@mh-hannover.de	Clinical Application of CB-HSCs

ating in HSC *ex vivo* expansion cultures; 4) exploring genetic, epigenetic and functional integrity of expanded cells *in vivo*.

5.7.5 German Research Foundation: SPP 1356, Pluripotency and Cellular Reprogramming

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General Information

Understanding the molecular processes that generate and control the capacity of pluripotent cells to proliferate indefinitely in culture while maintaining the ability to differentiate into any of the cells of the body will allow us to harness their potential and develop rational strategies that control their differentiation. Numerous observations demonstrate that pluripotency and cellular reprogramming are both controlled by combined genetic and epigenetic programs. An understanding of these pathways is essential for the development of effective and rational approaches to induce pluripotential reprogramming and direct pluripotent cells into specific differentiation pathways. The SPP 1356 will focus on the multiple levels of control in pluripotency.

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.

The following questions should be at the core of the second funding period of the SPP 1356:

- Which molecular processes are crucial for the establishment and maintenance of natural pluripotency?
- What defines the exit from pluripotency?
- What crosstalk and interdependence exist between genotype and epigenotype?
- What determines the global and local chromatin organization in pluripotent cells?

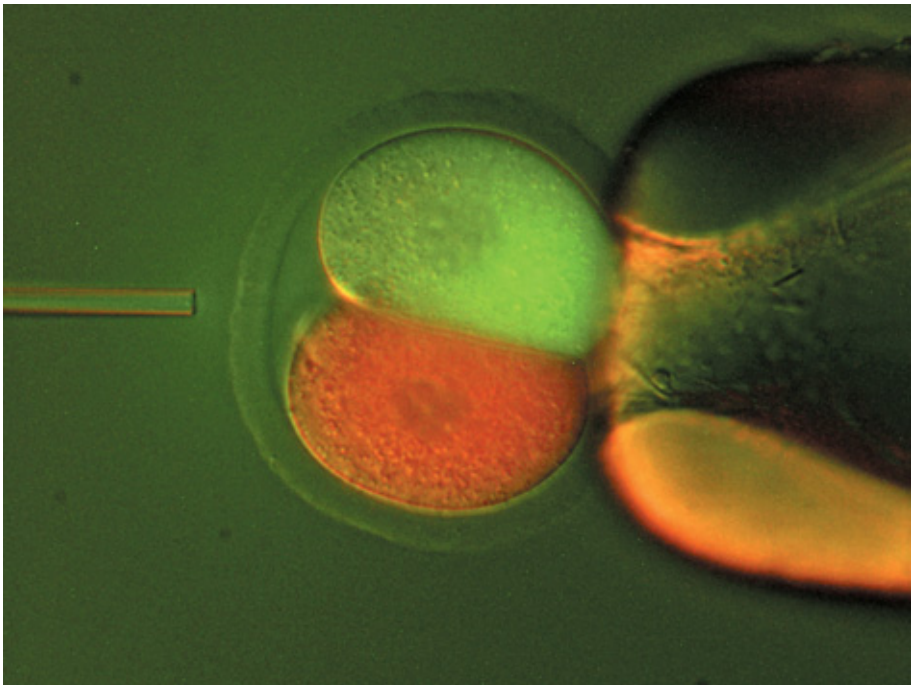

Fig. 1: 2-cell stage mouse embryo injected with mRNA and fluorescent tracer in both blastomeres (Oct4, red; eGFP, green). Picture: M. Bioani, MPI Münster.

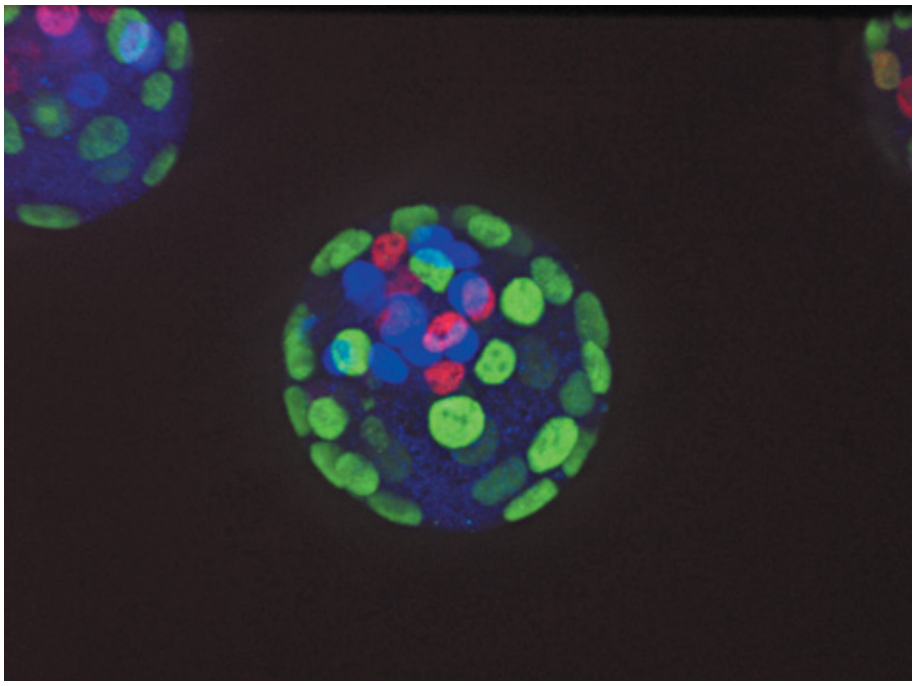

Fig. 2: Mouse blastocyst after confocal immunofluorescence (Cdx2, green; Nanog, blue; Sox17, red). Picture: M. Bioani, MPI Münster.

- What are the molecular and epigenetic mechanisms leading to induced pluripotency?
- What is the interrelation of regulatory processes that generate pluripotent cells in mammals versus non-mammals?

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 26 German-wide groups that are specialists in the molecular analysis of pluripotency, chromatin and cellular reprogramming.

In aggregate, the scientific focus of the SPP1356 is at the heart of international pluripotency research.

5.7.6 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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(Vice-Head)

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

Wölfl M, Merker K, Morbach H, Van Gool SW, Eyrich M, Greenberg PD, Schlegel PG. (2011) Primed tumor-reactive multifunctional CD62L+ human CD8+ T-cells for immunotherapy. Cancer Immunol Immunother. 60:173-86.

Pufnock JS, Cigal M, Rolczynski LS, Andersen-Nissen E, Wölfl M, McElrath MJ, Greenberg PD. (2011) Priming CD8+ T-cells with dendritic cells matured using TLR4 and TLR7/8 ligands together enhances generation of CD8+ T cells retaining CD28. Blood 117:6542-51.

Kuball J, Hauptrock B, Makina V, Antunes E, Voss RH, Wölfl M, Strong R, Theobald M, Greenberg PD. (2009) Increasing functional avidity of T-cell receptor (TCR)-redirected T-cells by removing defined N-glycosylation sites in the constant domain. Journal of Experimental Medicine 206:463-475.

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. (2008) Hepatitis C virus Immune escape via Exploitation of a Hole in the T cell Repertoire. Journal of Immunology 181:6435-46.

Wölfl M, Kuball J, Ho WY, Nguyen HN, Manley T, Bleakley M, Greenberg PD. (2007) 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 110:201-10.

5.8 University of Würzburg Graduate Schools – Graduate School of Life Sciences

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General Information

For many years the Faculties of Medicine and Biology have offered high-level structured graduate training. Several DFG-funded graduate programs (Graduiertenkollegs) provided early experience with structured graduate training at the University of Würzburg. A prime example of graduate training is also the MD/PhD program initiated by the Faculties of Biology and Medicine in 1996/7 as the first such program in Germany. Discussions within the entire university on modern forms of graduate training led to the foundation of the "International Graduate School" (IGS) by the University Senate in December 2003. This "International Graduate School" was initiated to cover the academic spectrum of the entire university, with separate graduate schools catering for the specific scientific and training needs and cultures of its diverse disciplines.

Section of Biomedicine

As a first step, the Section of Biomedicine was initiated in the IGS in 2003 by unifying several programs and their doctoral researchers:

- 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 (GK1048 "Molecular Basis of Organ Development in Vertebrates" and the IGC of SFB-TR 17 "Ras-Dependent Cancer")

These programs joined forces to identify and develop common structures and curricula, to organize joint activities and to set common standards (see box) for their doctoral researchers. In 2006, the first doctoral researchers received their PhD in this common program.

Several generations of basic and clinical scientists have successfully completed this program since 2006. The section Biomedicine has not only built up new structures and developed key training 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. In addition to the section Biomedicine and the MD/PhD program three further sections, i.e. Infection and Immunity, Neuroscience and Integrative Biology, were founded.

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 affected both its internal structure and its 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). Other graduate schools – The Graduate School of the Humanities (GSH), the Graduate School of Science and Technology (GSST) and the Graduate School of Law, Economics and Society (GSLES) have since been added to the UWGS.
These Graduate Schools cater for the needs of different broad fields of science, uniting research in the Life Sciences, the Humanities, the Natural and Social Sciences (see

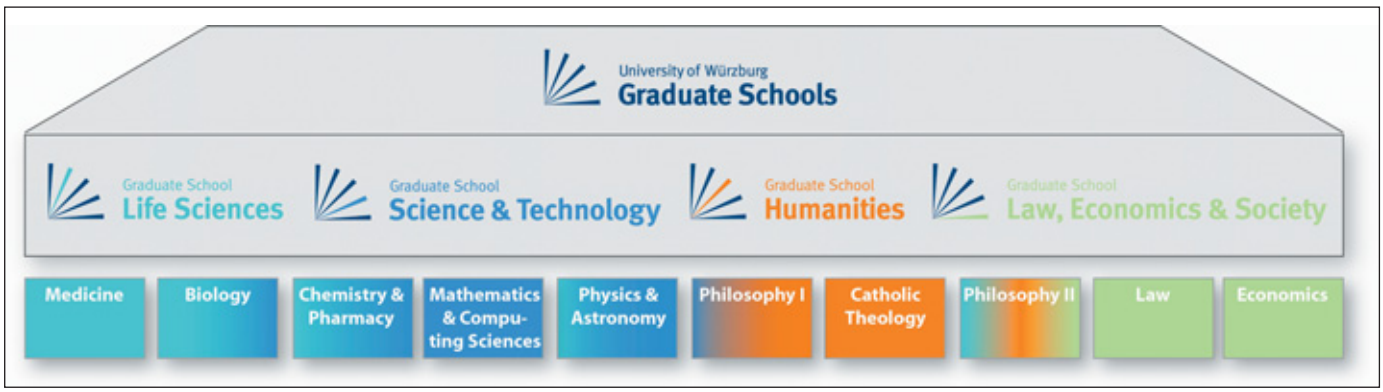

Fig. 1: Structure of the University of Würzburg Schools.

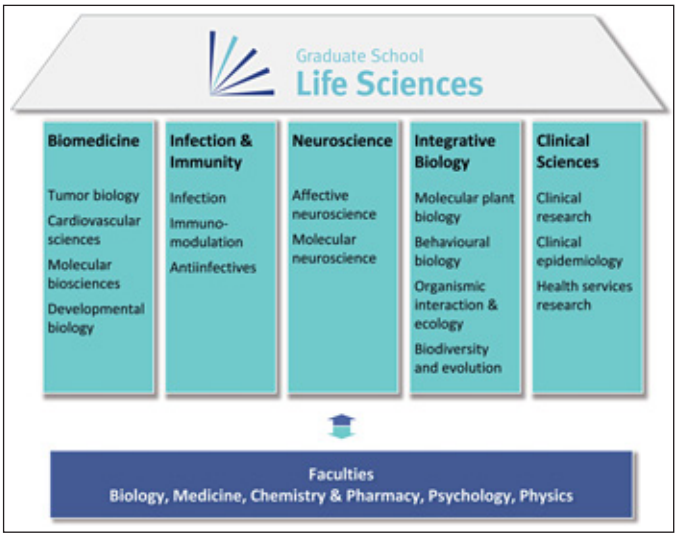

Fig. 2: Structure of the Graduate School of Life Sciences.

Fig. 1). Each school manages their day-to-day business independently.

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 the largest and most strongly integrated graduate school at the University of Würzburg. The plans were set forth in the successful application within the Excellence Initiative and have been put into practice.

The GSLS now houses doctoral researchers 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 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 sections "Biomedicine", "Infection and Immunity", "Neuroscience" and "Integrative Biology", the section "Clinical Sciences" was established. Doctoral researchers of the MD/PhD program were integrated into the respective sections according to their research interests. Each section usually comprises different programs of about 15 to 25 doctoral researchers. These programs are the scientific as well as social "home" of the doctoral researchers (see Fig. 2).

A special fellowship program of the GSLS is the core element of funding by the Excellence Initiative. The sixth round of international recruitment is currently underway. To date more than 1500 standardized written applications have been evaluated in the recruitment rounds so far, and interviews with more than 250 candidates have been performed by the admission board in Würzburg, by means of video conferencing and abroad. The fellows, currently 67, come from 19 different countries, underscoring the international character of the GSLS.

To date, the number of formal members of the GSLS has risen to more than 180 principal investigators from all participating faculties. In 2011 the number of doctoral researchers enrolled in the doctoral study program "Life Sciences" rose to more than 300. In August 2011, the GSLS submitted a renewal proposal in the framework of the 2nd phase of the Excellence Initiative. Besides establishing an international MSc program and a program for postdoctoral fellows to foster their early independence, the introduction of an excellence program for MD doctoral studies is envisaged.

Key elements of training in the Graduate Schools
- The traditional single supervisor ("Doktorvater") is replaced by a thesis committee of three principal investigators (PIs).
- A panel of training activities is offered, from which an individual program is tailored to each doctoral researcher.
- Doctoral researchers 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 doctoral researcher has an individual thesis committee, which meets with the doctoral researcher at regular intervals to monitor progress and adjust the research and training activities. Additionally, the doctoral researchers 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 4-6 hours per week (depending on the specific graduate school) and consist of 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 common Graduation Commission within the respective 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, Clinical Research Units, Research Training Groups

Collaborative Research Centers:

Collaborative Research Centre 487, Regulatory Membrane Proteins: From Molecular Recognition to Drug Targets

Collaborative Research Centre 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

Clinical Research Units:

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

Research Training Groups:

Research Training Group 1048, Molecular Basis of Organ Development in Vertebrates

Research Training Group 1253, Emotions

Research Training Group 1522, HIV/AIDS and Associated Infectious Diseases in Southern Africa

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
2010 Prof. Dr. Ernst-Theodor Rietschel
Borstel
2011 Prof. Dr. Ernst-Ludwig Winnacker
München

(*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
2011 Renate Schülke-Schmitt
Würzburg

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
2010 Prof. Dr. Meinrad Busslinger
Wien, Österreich
2011 Prof. Dr. Roger Tsien*
San Diego, USA

(*Nobel laureates)

6. Winners of the Albert Koelliker-Award for excellent teaching

Semester	Winners
Autumn 2003	Doctors of the Clinic and Policlinic 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, Director of the Medical Policlinic
Autumn 2004	Professor Dr. D. Patzelt, Head of the Institute of Forensic Medicine
Spring 2005	Professor Dr. A. Warnke, Director of the Clinic and Policlinic for Child and Adolescent Psychiatry
Autumn 2005	University lecturers of the Institute for Anatomy and cell Biology: Professor Dr. D. Drenckhahn, Professor Dr. E. Asan, Professor 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, Director 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 Professor Dr. A. Renk, Department of Prosthodontics
Autumn 2009	Professor Dr. C.-T. Germer, Director of the Department of General, Visceral, Vascular and Pediatric Surgery
Spring 2010	Professor Dr. med. Eva-Bettina Bröcker, Professor Dr. med. Henning Hamm, Professor Dr. med. Jürgen C. Becker, Professor Dr. med. Axel Trautmann, Department of Dermatology, Venereology and Allergology
Autumn 2010	Professor Dr. Roland Jahns, Department of Internal Medicine I
Spring 2011	Dr. Birgitt van Oorschot, Department of Radiation Oncology – Center for Palliative Medicine Dr. Silke Neuderth, Division of Medical Psychology, Medical Sociology, and Rehabilitation Research Professor Alexander Kübler, Director of the Department of Oral and Maxillofacial Surgery
Autumn 2011	Professor Dr. Rainer Meffert, Director of the Department of Trauma-, Hand-, Plastic and Reconstructive Surgery

7. Habilitations

2010

Clinical

Dr. med. Julian Widder	Internal Medicine
Dr. med. Marcel Romanos	Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy
Dr. med. Matthias Guckenberger	Radiation Oncology
Dr. med. dent. Philipp Meyer-Marcotty	Orthodontics
Dr. med. Melanie Schmdit	Obstetrics and Gynecology
Dr. med. Vera Krane	Internal Medicine
Dr. med. Stefan Knop	Internal Medicine
Dr. med. Jens-Albert Broscheit	Anaesthesiology
Dr. med. Andreas Thalheimer	Surgery
Dr. rer. nat. Klaus Bratengeier	Medical Physics
Dr. med. Georg Jochen Schneider	Clinical Biochemistry
Dr. med. Ruth Seggewiss	Internal Medicine
Dr. med. Nurcan Üceyler	Neurology
Dr. med. Frederik Verburg	Nuclear Medicine
Dr. med. Rainer Guthoff	Ophthalmology

Preclinical

Dr. med. Eva Geissinger	Pathology and Pathological Anatomy
Dr. med. Andre Steinert	Orthopaedics
Dr. phil. Karen Nolte	History, Theory and Ethics in Medicine
Dr. med. Dennis Tappe	Medical Microbiology
Dr. med. Hans-Ullrich Völker	Pathology and Pathological Anatomy

2011

Clinical

Dr. med. Stefanie Hahner	Internal Medicine
Dr. med. Andreas Radeloff	Otorhinolaryngology
Dr. med. Thomas Westermaier	Neurosurgery
Dr. med. Johannes Wirbelauer	Pediatrics
Dr. med. Martin Spahn	Urology
Dr. med. Detlev Krieter	Internal Medicine
Dr. med. Nicolas Schlegel	Experimental Surgery
Dr. med. dent. Stefan Fickl	Dentistry
Dr. med. Roland Houben	Tumor Biology
Dr. med. Udo Lorenz	Surgery
Dr. med. Matthias Wölfl	Pediatrics
Dr. med. Tobias Renner	Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy

Preclinical

Dr. med. Schmitt, Joachim Paul	Pharmacology and Toxikology
Dr. rer. nat.Schupp, Nicole	Toxikology and Pharmacology
Dr. rer. nat.Carsten Hoffmann	Pharmacology and Toxikology
Dr. med. Dr. rer. soc. MA phil. Stefan Brunnhuber	Medical Psychology, Psychotherapy and Medical Sociology
Dr. rer. nat. Dr. med. Christoph Schoen	Medical Microbiology
Dr. rer. nat. Svenja Meierjohann	Biochemistry and Molecular Biology

8. Statistics

Registration numbers

Year	human medicine / thereof female	dentistry / thereof female	biomedicine Bc. / thereof female	biomedicine Ma. / thereof female
WS 2009/10	151 / 92	61 / 39	31 / 25	07 / 07
SS 2010	149 / 77	60 / 41	0	0
WS 2010/11	155 / 85	53 / 36	30 / 22	17 / 12
SS 2011	149 / 91	57 / 33	0	0
WS 2011/12	167 / 108	61 / 38	30 / 27	13 / 11

Graduations (Abschlüsse)

Year	human medicine / thereof female	dentistry / thereof female	biomedicine Bc. / thereof female	biomedicine Ma. / thereof female
Autumn 2009	123 / 73	61 / 35	13 / 13	09 / 04
Spring 2010	127 / 71	31 / 19	01 / -	02 / 02
Autumn 2010	165 / 101	59 / 35	24 / 19	14 / 13
Spring 2011	121 / 71	53 / 30	0	01 / 01
Autumn 2011	116 / 67	44 / 24	23 / 15	06 / 06

Doctorates (without doctorates in natural sciences)

Year	preclinical	clinical	total
2010	59	182	241
2011	40	178	218

Habilitations

Year	preclinical	clinical	total
2010	5	15	20
2011	6	12	18

9. The Deans of the Medical Faculty since 1945

1945 to 1947	Prof. Dr. med. Dankwart ACKEMANN
1947 to 1948	Prof. Dr. med. Jürg ZUTT
1948 to 1949	Prof. Dr. med. Max MEYER
1949 to 1951	Prof. Dr. med. Curt SONNENSCHEIN
1951 to 1952	Prof. Dr. med. Werner WACHSMUTH
1952 to 1953	Prof. Dr. med. Hans SCHEUERMANN
1953 to 1954	Prof. Dr. med. Hermann WOLF
1954 to 1955	Prof. Dr. med. Dr. phil. Wilhelm NEUMANN
1955 to 1957	Prof. Dr. med. Heinrich SAAR
1957 to 1958	Prof. Dr. med. Georges SCHALTENBRAND
1958 to 1959	Prof. Dr. med. Kurt NEUBERT
1959 to 1960	Prof. Dr. med. Hans FRANKE
1960 to 1961	Prof. Dr. med. Erich BAUEREISEN
1961 to 1962	Prof. Dr. med. Ernst WOLLHEIM
1962 to 1963	Prof. Dr. med. Horst WULLSTEIN
1963 to 1964	Prof. Dr. med. Hans-Werner ALTMANN
1964 to 1965	Prof. Dr. med. Horst SCHWALM
1965 to 1966	Prof. Dr. med. dent. Rudolf NAUJOKS
1966 to 1967	Prof. Dr. med. Wolfgang SCHWERD
1967 to 1968	Prof. Dr. med. August RÜTT
1968 to 1969	Prof. Dr. med. Erich BAUEREISEN
1969 to 1970	Prof. Dr. med. Helmut RÖCKL
1970 to 1971	Prof. Dr. med. Theodor Heinrich SCHIEBLER
1971 to 1973	Prof. Dr. med. Karl Heinz WEIS
1973 to 1975	Prof. Dr. med. Johannes LANG
1975 to 1977	Prof. Dr. med. Erich BAUEREISEN
1977 to 1979	Prof. Dr. med. Otto SCHRAPPE
1979 to 1981	Prof. Dr. med. Karl-Heinrich WULF
1981 to 1983	Prof. Dr. med. Karl-August BUSHE
1983 to 1985	Prof. Dr. med. Volker ter MEULEN
1985 to 1987	Prof. Dr. med. Gerhardt NISSEN
1987 to 1989	Prof. Dr. med. Stefan SILBERNAGL
1989 to 1991	Prof. Dr. med. Kurt KOCHSIEK
1991 to 1994	Prof. Dr. med. Hans Konrad MÜLLER-HERMELINK
1994 to 1996	Prof. Dr. med. Klaus WILMS
1996 to 1998	Prof. Dr. med. Klaus TOYKA
1998 to 2002	Prof. Dr. med. Volker ter MEULEN
2002 to 2004	Prof. Dr. med. Stefan SILBERNAGL
2004 to 2006	Prof. Dr. med. Georg ERTL
since 2006	Prof. Dr. med. Matthias FROSCH

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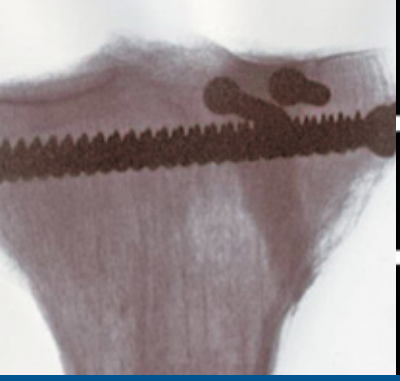
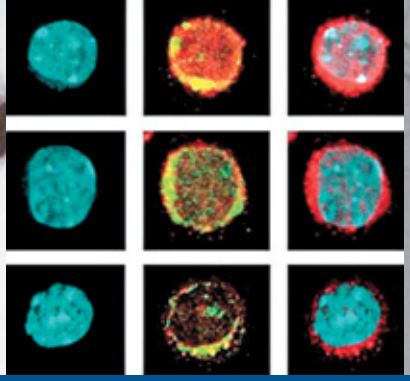
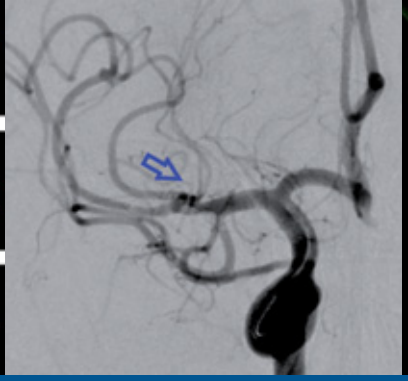
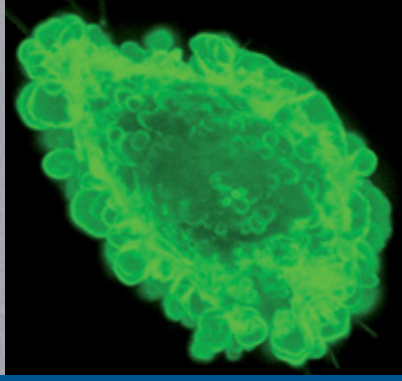

University of Würzburg

Uniklinikum Würzburg

Medical Faculty

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