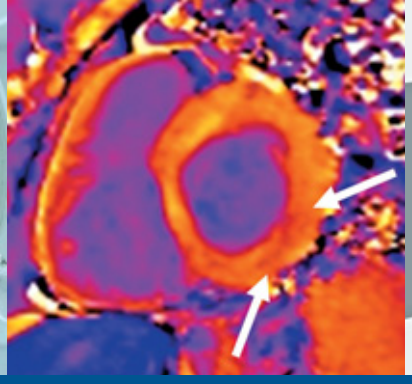
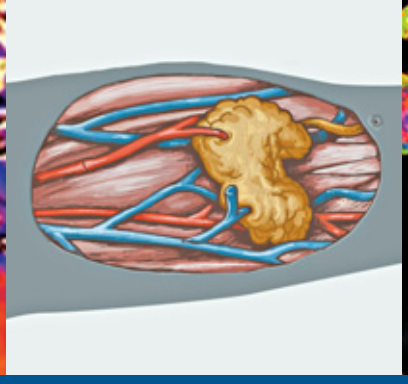
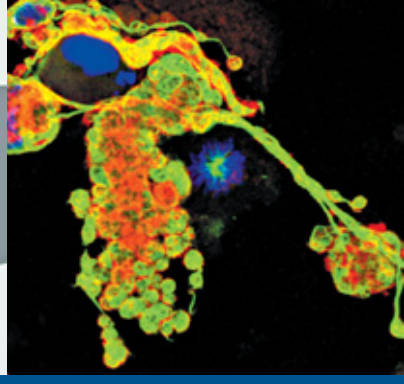
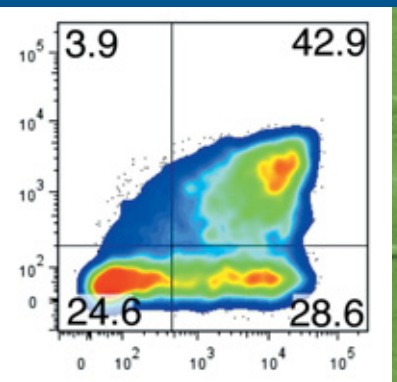
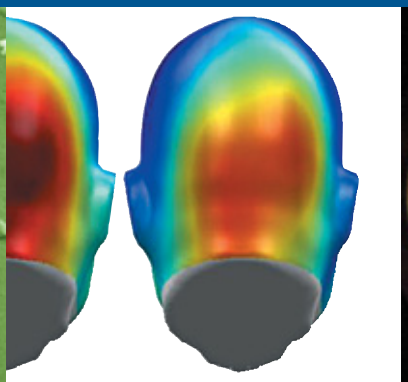





University of Würzburg
Medical Faculty

Research Report 2014




University of Würzburg
Medical Faculty

Research Report 2014

Content

1 General Part
1.1 Preface

Dear ladies and gentlemen,
Dear readers,

The present research report, which refers to the 2012 and 2013 periods, places emphasis on the progress made of the medical faculty of the University of Würzburg and the participating scientists. I would like to invite you to take the time to study this document.

The Julius Maximilians University of Würzburg belongs to a group of the strongest research universities in Germany. This position owes largely to the achievements in life sciences and medicine, which are outstanding on an international standard. The latest ranking by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) from 2012 placed the life sciences in Würzburg in second position (measured in funding per professorship), after Freiburg. Medicine is ranked at the excellent third place after Heidelberg and Hannover. Also, in other international rankings, medicine and life sciences are placed in leading positions. The Leiden ranking for 2013, which values the performance of universities after publication achievements, places medicine / biomedicine worldwide on rank 132, in Europe on rank 57 and in Germany on rank 6. The portion of publications which accounts for 10% of the most-cited publications per field formed part of this evaluation. We owe this success to the single achievements of many engaged and creative scientists, but also to structure-building measures which were created and further developed as interdisciplinary research centers since the 1990's. Thus, the prevailing part of the received research funds also flows to scientists of the research centers.

An important landmark in the development of the research centers was the consolidation of the funding of the Rudolf Virchow Center for Experimental Biomedicine in the Bavarian State budget in 2013. With the allocation of positions, both the university and the medical faculty have made substantial contributions to the permanent financing of the Rudolf Virchow Center – with the expectation that there important impulses may go out to the local scientific community and that third-party funded joint research projects will be initiated in the future. Indeed, the Collaborative Research Center 688, "Mechanisms and Imaging of Cell-Cell Interactions in the Cardiovascular System", to which numerous members of the Rudolf Virchow Center belong, was recommended for further funding. Together with the activities within the Comprehensive Heart Failure Center (Deutsches Zentrum für Herzinsuffizienz, DZHI), this collaborative research center is the crystallization point of cardiovascular research in Würzburg.

A new Transregio-Collaborative Research Center 124, "Pathogenic Fungi and their Human Host: Networks of Interaction" was initiated together with Jena. Together with two other collaborative research centers within infection research (Collaborative Research Center 630, "Recognition, Preparation and Functional Analysis of Agents against Infectious Diseases", Transregio-Collaborative Research Center 34, "Pathophysiology of Staphylococci in the Post-genomic Era"), is this newly established collaborative research center also an expression of the research strength of the scientists working in the Research Center for Infectious Diseases (Zentrum für Infektionsforschung, ZINF) as is the DFG-funded research group "Sphingolipid Dynamics in Infection Control" established in 2013. The scientists from the areas of oncology, neurosciences as well as regenerative medicine and biomaterial research were also very successful, and their activities are supported by numerous funding agencies and they have received many distinguished honors and awards.

Of outstanding importance for the scientific location of Würzburg is the decision of the Max Planck-Society and the Bavarian State Government to establish Max Planck-Research Groups for "Systems immunology" in Würzburg. On the 11th of June, 2013 the president of the Max Planck-Society, Prof. Dr. Peter Gruss, and the president of the University of Würzburg, Prof. Dr. Alfred Forchel, signed, in the presence of the Bavarian Minister for Science and Arts, Dr. Wolfgang Heubisch, a cooperation agreement. With this agreement, funding has been guaranteed for three research groups for at least five years. The thematic focus allows a large number of interactions with the research groups and the scientific main focuses of the faculty, which will stimulate, in the long term, biomedical research in Würzburg. Presently, the medical faculty pursues the appointment of the three professorships who will lead the Max Planck-Research Groups.

The former Science Minister Dr. Wolfgang Heubisch has played a decisive role in the establishment of the Max-Planck-research groups. I would like to take this opportunity to convey my sincere thanks to Dr. Wolfgang Heubisch for his constant support of our faculty during his term of office. Thanks also to all scientists of the medical faculty. Their collective effort and their creativity were the basis of the success in the last years. I enclose the public and private donors also in my acknowledgement, like the numerous reviewers and the members of the scientific advisory boards who took a critical look at our research projects. I would also like to thank everyone who have committed themselves to our faculty, to the basic conditions of the excellent research and teaching as well as to the support of the young scientific and medical generation.

Fig.1: Signing the cooperation agreement for the Max Planck-Research Group for "system immunology", in the presence of Science Minister Dr. Wolfgang Heubisch (middle), the president of the Max Planck-Society, Prof. Dr. Peter Gruss (left), and the president of the University of Würzburg, Prof. Dr. Alfred Forchel. (Photo: Peter Henza).

Würzburg, March 2014
Professor Dr. Matthias Frosch
Dean

Inauguration of the new building for the Interdisciplinary Bank of Biomaterials and Data Würzburg (ibdw) on June, 21, 2013

Group photo in front of the new building housing the Interdisciplinary Bank of Biomaterials and Data. From left: Director the Bank of Biomaterials and Data Professor Dr. R. Jahns, Mrs. A. Bauer-Chesauan (architect), Medical Director Professor Dr. C. Reiners, behind him Nursing Director G. Leimberger, Member of Parliament V. Halbleib, Member of Parliament O. Jörg, keynote speaker Professor Dr. E. Böttinger (New York), Administrative Director Mrs. A. Simon, Dean Professor Dr. M. Frosch, P. Mack (building authority Würzburg), Dr. H. Braun (Federal Ministry of Education and Research) and Member of Parliament P. Lehrieder.

Handing over of the keys for the Interdisciplinary Bank of Biomaterials and Data. From left to right: Medical Director Professor Dr. C. Reiners, Dean Professor Dr. M. Frosch and Director of the Bank of Biomaterials Professor Dr. R. Jahns.

Honours awarded by the Medical Faculty

*For his long standing achievements in the Medical Faculty of the University of Würzburg, the Rinecker-Medal in gold was awarded to Professor Dr. med. Dr. h.c.mult. Kurt Kochsieck (*1930, +2013) on May, 11, 2012 during the graduation ceremony of the faculty in the Neubaukirche. The medal and the certificate were handed over by the Dean Professor Dr. M. Frosch (left). In his laudation, Professor Dr. G. Ertl (right) appreciated, besides the scientific achievements of the internist and cardiologist, especially his contributions to the development of a scientific strategy of the Medical Faculty.*

The „Elterninitiative leukämie- und tumorkranker Kinder e.V“ was honored on November, 25, 2013 by the Medical Faculty and the University Hospital with the Siebold-Medal. The Siebold-Medal honors people and organizations, which rendered outstanding services to the Medical Faculty and the University Hospital. In occasion of the 30th anniversary of the „Elterninitiative“, the Medical Faculty and the University Hospital thanked the society for their protruding credits in the support of children with cancer as well as the support of cancer research. Expressing their appreciation the Medical Director Professor Dr. C. Reiners (left) and the Dean Professor Dr. M. Frosch (right) presented to the “Elterninitiative” the Carl Caspar von Siebold-Medal. The honored society was represented by the chair Jana Lorenz-Eck (2nd from left) and the founding chair Heidrun Grauer (2nd from right).

1.2 Medical Education

Professor Dr. med. Jürgen Deckert
Dean of Student Affairs Medicine

Professor Dr. med. Christoph-Thomas Germer
Dean of Student Affairs Medicine
(01. 01. 2014)

Professor Dr. med. Dr. med. dent.
Alexander Kübler
Dean of Student Affairs Dental Medicine

Professor Dr. med. Manfred Gessler
Dean of Student Affairs Biomedicine

Student numbers, Student evaluation, examinations

Due to a temporary student influx, each semester currently holds 155-160 students instead of 140-150. This feat can only be managed with the help and enormous effort of the university teaching staff. This commitment and dedication is validated when looking at the results of the bi-annual evaluations and examinations that are regularly completed by students. The class of autumn 2013, for example, impressively placed 4th place in the second medical state examination, which is taken nationally. Additionally, the Würzburg Medical Faculty can be pleased by their exceptional grades in the CHE University ranking, in the category of teaching.

Revision of Medical Licensure Act

Starting in July 2012 the Medical Licensure Act has undergone an amount of changes with far reaching consequences. These modifications especially concern the so-called practical year (PJ), the number of taken state exams and the clinical clerkships.

Students now have the possibility to absolve their practical year at other Universities or teaching hospitals without needing to enroll in these. This new mobility required several adjustments such as modifications to the 10th semester and a renewal of contracts with our own academic teaching clinics.

Furthermore, the revision of the Medical Licensure Act has given the specialty general medicine a boost, by making it a required field in which students must complete a clinical clerkship. Moreover, each university must now ensure enough placements for all students who wish to do their PJ in the area of general medicine. We accomplished this by extending our, for the 10th semester already existent, agreements with surrounding medical practices, to include PJ placements as well.

The education around the topic of doctor-patient relationships and interaction has also been expanded. This has been achieved by adding further pre-clinical and clinical courses to the medical curriculum, including classes with standardized patients and discussions with psychology students.

For the newly incorporated subjects palliative and pain medicine, new lectures have been designed and those for palliative medicine have already been instituted.

"PJ-license"

In the frame of the KTQ- certification of the university hospital a new "PJ-license" has been conceived as an add-on to the already regularly used PJ-log book. The idea of this "license" is to demonstrate which tasks are to be accomplished by students in their PJ and which are only to be completed by doctors. It follows the "street-light" model, in which the red light covers medical tasks that fall under the provision of doctors and should under no circumstance be completed by students. The green light describes the area of duties, which mostly can be performed by students autonomously, while the yellow light encompasses those activities, which are more clinic specific and may need physician supervision.

Teaching hospital

The course offerings in our teaching hospital constantly undergo improvement. The required course "practical clinical examination methods" for students in the 5th semester has been expanded to incorporate new modules, such as neurology. Furthermore, optional classes, including sewing and knotting techniques for the advanced or echocardiography, have been added to the new program. Intermittently more than 17 clinics and institutes make use of the teaching hospital's various offers. On top of this, a further expansion of required courses and classes with students of nursing is currently being developed.

Second place in the Goethe-Contest in Frankfurt

Five students who participated in the yearly Goethe-Contest in Frankfurt in 2013 placed an impressive second place. For 15 consecutive years, medical students throughout Germany and its neighboring countries compete against one another in an interuniversity contest. Over the course of two days and under constant time pressure the student teams compete in clinical and practical exercises.
Würzburg's team consisting of: Lisa Bergauer, Larissa Joyce Mayer, Mira Möll, Charlotte Morgner und Julia Taschik was coached by PD Dr. Stefan Knop of the Medical Clinic II, who took the role as the team's supervisor and consistently helped with the preparation and studying.

Internationalization

The number of Erasmus partner universities has increased to 35. Within this program frame, Würzburg's Medical Faculty receives 30 foreign students who enroll in classes at our University. In exchange we send 40 of our own students to do a semester abroad at one of our partner universities. Additionally, through the funding with DAAD sources, non-European partnerships with Mwanza/Tansania, Stellenbosch/South Africa, Nagasaki/Japan and Wuhan/China have also been initiated or prolonged. The DAAD and BMBF funding (KOMPASS) has also made the renewal and expansion of the mentoring program for foreign students possible. In order to help the newcomers, the Medical School of Würzburg University was the first Würzburger faculty to issue its website in English.

Competence center for medical education in Bavaria

The ministry of education and culture, science and art has granted the network for medical education in Bavaria a third time of funding for the years 2014 through 2016. With the help of these resources the Medical Faculty wants to particularly concentrate on enlarging its E-Learning-/ Blended Learning projects.

Chair for General Medicine

As a result of the expansion of the specialty general medicine and due to the amendments to the Medical Licensure Act in July 2012, the tasks concerning this specialty have become too comprehensive to be accomplished by only a subsidiary office of the School of Medicine. As a result we have now initiated the establishment of a chair for general medicine.

Chair for medical didactics

To support the professionalization of the School of Medicine and the education in both medicine and dentistry the initiation of establishing a chair for medical didactics has also been set in motion. The new chair holder will support the dean of student affairs in reforming and redesigning the curriculum plan for medical students, addressing the results of the latest evaluation and including all clinics and institutions. He/she will also help further the training of teachers and professors, as well as the research completed in the area of teaching in the Medical Faculty. By creating this new institution our Medical Faculty is sending a clear message of wanting to develop and foster the area of education and working on maintaining a top placement when it comes to teaching.

B.Sc/M.Sc. program in Biomedicine and Biochemistry

The Faculty of Medicine and the Faculty of Biology offer a joint program in Biomedicine where students are trained 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 its original 3 semesters to 4. The core curriculum consists 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 final Bachelor or Master thesis, which is, respectively, written in English. In addition to scientific training, students can also gain further qualifications, ranging from regulatory and organizational expertise or lecture and presentation training to scientific ethics and technical English.
While the Bachelor curriculum is densely structured, students are rather free to set their own priorities in the Master program after finishing the first semester with a mandatory practical course in model organisms with accompanying lectures. A special feature of the Biomedicine program is the high number of stays abroad. The majority of students use this opportunity to broaden their scientific and personal horizon.
The interest in the Bachelor program continues to be impressive with more than 1,000 applications for 24 placement spots. So far 384 students have been enrolled in the B.Sc. program and further 148 in the M.Sc. ; the share of female students is extremely high with 80 % and 76 %, respectively. Most of the graduates opt for further scientific qualification; about 40 % of the graduates continue to reside in Würzburg, while the remaining graduates choose other institutions in Germany or abroad.
Since 2009 the Faculty of Medicine and the Faculty of Chemistry and Pharmacy jointly offer the additional Biochemistry B.Sc. program. The demand for the current 60 study places is also very high. Here the focus is not positioned as much on a clinic-related research, but rather on a reinforced molecular orientation. A consecutive M.Sc. study course was implemented with the start of the winter semester 2012/2013 and it already proved to be under high demand.

Fig. 1: In the operating-theater of the teaching hospital, the students are instructed in the correct behavior in an operating-theater.

Concurrent programs for medical students

For medical students there is also the option of a concurrent program in Experimental Medicine, which offers additional training in molecular sciences with a clinical focus. Practical courses and internships provide first exposure to research projects. Various seminars help to promote the knowledge of diverse biomedical science topics, as well as the training of skills for scientific data presentations. The program can be expanded to include a thesis project and can then lead to a full M.Sc. degree.
A similar concept is being pursued with the concurrent study program in Clinical Research and Epidemiology, which offers advanced training in patient-oriented clinical research, including applied epidemiological and statistical methods. With these diverse training opportunities, the faculty ensures that highly qualified up-and-coming scientists are well trained for medically relevant research.

Dental medicine

Presently, 600 dental students are enrolled at the University of Würzburg, 300 of them in the preclinical and the remaining 300 in the clinical part of their education.
The clinical curriculum is organized according to the currently valid Medical Licensure Act for dentistry students and requires an extensive vocational education and training. The dental education program is mainly based on sciences and dental techniques and medicine. The clinical education program deals with diagnosis and therapy of dental and dentofacial anomalies and jaw diseases, restorative dentistry, oral and maxillofacial surgery, prosthetics, orthodontics, as well as periodontics. During their course of studies, students practice, develop and enhance their manual skills at simulation units with training dolls. Beginning with the 7th semester students start to treat patients.
Since 100 years the clinic is located in the center 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 than 28,000 outpatients, as well as upwards of 1,750 in-patients have been treated in 2012.

All the departments are equipped according to the newest technical standard. State-of-the-art equipment necessary for a modern dentist training is available. With the new Medical Licensure Act for dentistry students the teaching concept will pass through further modifications. In order to be prepared for future developments a newly equipped simulation unit hall was established in the winter semester 2010/2011 for student training in dental preservation. A further simulation unit hall for the surgical training was set up in 2011. The equipment of the surgical simulation unit hall was acquired with the help of tuition fees. In diverse departments interactive training concepts and problem-based learning integrated in the clinical education are now offered. Students have access to an extensive library with numerous computer workstations with Internet connection for their private studies. Since the winter semester 2013/14 the government grant allotted to the dental clinic is mainly used for the financing of tutors and a full-time teaching coordinator, as well as for the financing of 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 (ZÄPrO) for dentistry, which had been announced for a long time, is about to be issued and is expected to require significant effort for restructuring the studies of dental medicine.

1.3 Students' Representatives

CONTACT DETAILS

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www.fi-med.de

The student representative is a group of students who advocate voluntarily on the interests of the medical students. It is our objective to enhance the conditions for studying and teaching by our student engagement in cooperation with the academics at our faculty and to establish a convenient working atmosphere.

We mainly work on two major aspects: On the one hand we represent the medical students in various committees: in the faculty council, in the committee of study affairs, the student council and in the appointment board of the faculty. Since the tuition fees were disposed we have worked for a wise and efficient use of the money in the tuition fees replacement committee.

On the other hand we care for consultation and support of the students. This includes the organization of informative meetings, parties, cinema evenings and live assignments of the soccer European championships and Word Cup that gives the students the chance to socialize with each other and with students from other semesters in a more informal way.

At the beginning of the studies we welcome the beginners in the context of the first semester days. We give them the opportunity to get to know their new fellow students, the city of Würzburg and the university. At the beginning of the clinical part of the 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. We publish an information booklet which informs the students about the faculty, lectures, courses, examinations, books, events and further topics. All information can also be found on our homepage. During the lecture time our office serves as a contact point for all problems and questions students cope with. Furthermore we are up to e-mail and facebook. In addition we offer different study and informative material around the study of medicine and the course "Medical English". We plan a similar course in French for the next semester. The "Anamnesegruppe" which is supposed to help both medicine and psychology students to acquire better perception and communication skills represents cooperation with the psychological institute.

The Segmed, a nationwide association of medical students which offers favorable medical equipment (e.g. stethoscopes), as well as the bvmd, that among other things cares for international exchange programs for medical students, find a room in our premises for their consultation hours. Since last semester we have cooperated intensively with the student representatives of the dentistry faculty and are pleased about a productive collaboration.

The prevention project MSV ("Mit Sicherheit verliebt") which informs pupils about save dealing with sexuality and contraception and the teddy bear clinic that leads small children up to the situation at the physician´s and at the clinic to take their fear away enlarge the supply around the students´ engagement. Furthermore we work together with the working groups of emergency medicine, homoeopathy, TCM and EMSA and support social projects. To improve the assistance to our Erasmus students we want to induce a new program.

Our students´ council meeting takes place weekly. This serves the exchange of information and offers room for discussion about current requests and for planning new projects. Students and docents are very welcome to join us. Once in the semester we organize a student representative weekend to discuss special topics for which we do not have enough time in the regular meeting.

Among others results of our engagement are the working group teaching coordinators who represents a close cooperation with the teaching coordinators to initiate innovative teaching strategies and the PromoMed convention that shall help students to find a medical dissertation.

Within the next semesters we want to commit ourselves to the improvement in the teaching methods. The active use of the new equipped teaching clinic with library, practical examination courses, recreation, study and conference rooms and offer of optional courses by the students confirms the success of our work. We are looking forward to a furthermore 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 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 the physician-poet Johannes Posthius. Only with the second foundation of the University in 1582, however, formal academic medical teaching was put into place again. Again, medicine ranked among the University's three higher faculties from the start, though it took several years until the medical faculty truly came to life. In 1587, the faculty's statutes were approved. By 1593, finally, the professors had been appointed and began teaching. Würzburg had come to offer exceptionally good conditions for a sound medical education. Adriaan van Roomen, also known as Adrianus Romanus, had been appointed to the first and most prestigious professorship, the chair for medical theory. Within a couple of years, van Roomen, who was also a mathematician of international acclaim, succeeded in establishing a flourishing culture of medical dissertations and disputations and promoted a number of medical students to doctors. At the same time, conditions for clinical, practical training had markedly improved, thanks to the newly founded Julius-Spital. In contrast to many other contemporary hospitals which cared almost exclusively for the aged and invalid, the Julius-Spital was, from its very beginning, explicitly designated also as a hospital "in aegrorum curationem", i.e. for the medical treatment of the curable sick. With its many patients, the Julius-Spital thus offered a welcome opportunity to medical students to observe manifold diseases and to witness the effects of different curative approaches. Such bedside teaching was very popular among contemporary medical students and was a major reason, why a number of medical students crossed the Alps and frequented one the Northern Italian universities, where they were commonly allowed to accompany the professors on 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 the hospital care and medical instruction. Johann Barthel von Siebold who worked primarily as an anatomist and surgeon lectured on pathological anatomy for the first time. Adam Elias von Siebold continued his father's efforts to improve obstetrical training for medical students and midwives. In 1805, he opened the first obstetrical hospital in Würzburg in a building which 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 immatriculated in one year. Soon, growing disillu-

sionment 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. Based on his method Schönlein described various diseases for the first time and some like the Schoenlein-Henoch purpura (Vasculitis allergica) carry his name to this day. Nikolaus Anton Friedreich gave an account of facial nerve paralysis. Johann Georg Pickel and Johann Joseph von Scherer helped lay the groundwork for a modern science of pharmaceutics and medical chemistry respectively. Around the middle of the 19th century, Franz von Rinecker was the Faculty's dominant figure. He made important contributions to pediatrics, psychiatry and dermatology alike and thanks to his efforts Würzburg can boast one the first pediatric hospitals at any university in the world. Under Rinecker's leadership, Rudolf Virchow and Albert Kölliker were appointed professors, who helped turn anatomy and pathology into modern laboratory sciences and, in the case of Virchow's cellular pathology, provided contemporary medicine as a whole with a new theoretical basis. Outstanding contributions also came from researchers outside of the Medical Faculty, from the biologists Julius Sachs and Theodor Boveri, for example, and from the physicist Wilhelm Conrad Röntgen who discovered the x-rays.

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

The National Socialist period left deep marks on the Würzburg Medical Faculty. The Institut für Vererbungswissenschaft und Rasseforschung (Institute of Genetic Science and Racial Research) conducted large scale genetic surveys of the population in the area around Würzburg. Werner Heyse, who was appointed professor of psychiatry in Würzburg in 1939, played a leading role in the so-called „Aktion T4", the organized mass murder of 10.000s of psychiatric patients and handicapped men, women and children between 1939 und 1941. Based on the „Gesetz zur Verhütung erbkranken Nachwuchses" (1933) sterilizations and abortions were performed in the Maternity Hospital under Carl Gauß. 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 also plays a major role in the "Graduate School of Life Sciences". Würzburg 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" (large, often interdisciplinary research networks) 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).

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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

In 2013 new research groups were established at the Department of Anatomy and Cell Biology I. The neuroimmunological research group (Head: Prof. Dr. Stefanie Kürten) focuses on the B cell-dependent immunopathology of the human autoimmune disease multiple sclerosis (MS), the role of microglia cells in the disease as well as the development of neuroprotective therapeutic strategies. The focus of the research group tumor angiogenesis and drug delivery (Head: Dr. Erik Henke; Prof. Dr. Süleyman Ergün) is to examine the underlying mechanisms, identify targets and devise novel ways to improve drug delivery in and distribution within the tumor tissue. Central to our understanding of these pharmacological effects are the blood vessels that supply the tumor with oxygen and nutrients but also transport therapeutic agents into the tumor.
The research at the Department of Anatomy and Cell Biology I is carried out by 3 postdocs, 5 doctoral candidates and 2 technical assistants.

Focus of research

The B cell-dependent immunopathology of multiple sclerosis
(S. Kürten, N. Wagner)

Multiple sclerosis (MS) is thought to be a chronic autoimmune disease of the central nervous system (CNS). While its dependence on T cells is widely acknowledged, the contribution of B cells to the pathogenesis of MS is still questionable. Next to the production of autoantibodies and the presentation of antigens B cells could be involved in the disease through the formation of ectopic lymphoid structures in the CNS. The focus of our group is to study the mechanisms underlying B cell autoimmunity in MS. On the one hand, we have established a model of experimental autoimmune encephalomyelitis (EAE) that is based upon active immunization of mice with the myelin basic protein (MBP)-proteolipid (PLP) fusion protein MP4. One of the unique features of MP4-induced EAE compared to other commonly employed models is its dependence on B cells. Using this model, we are currently studying the role of the cell adhesion molecule CEACAM1 in the development of lymphoid organs in the CNS. On the other hand, following a translational approach our group is also devoted to developing strategies for monitoring the B cell dependence of MS in individual patients. For this purpose, we are detecting CNS antigen-specific B

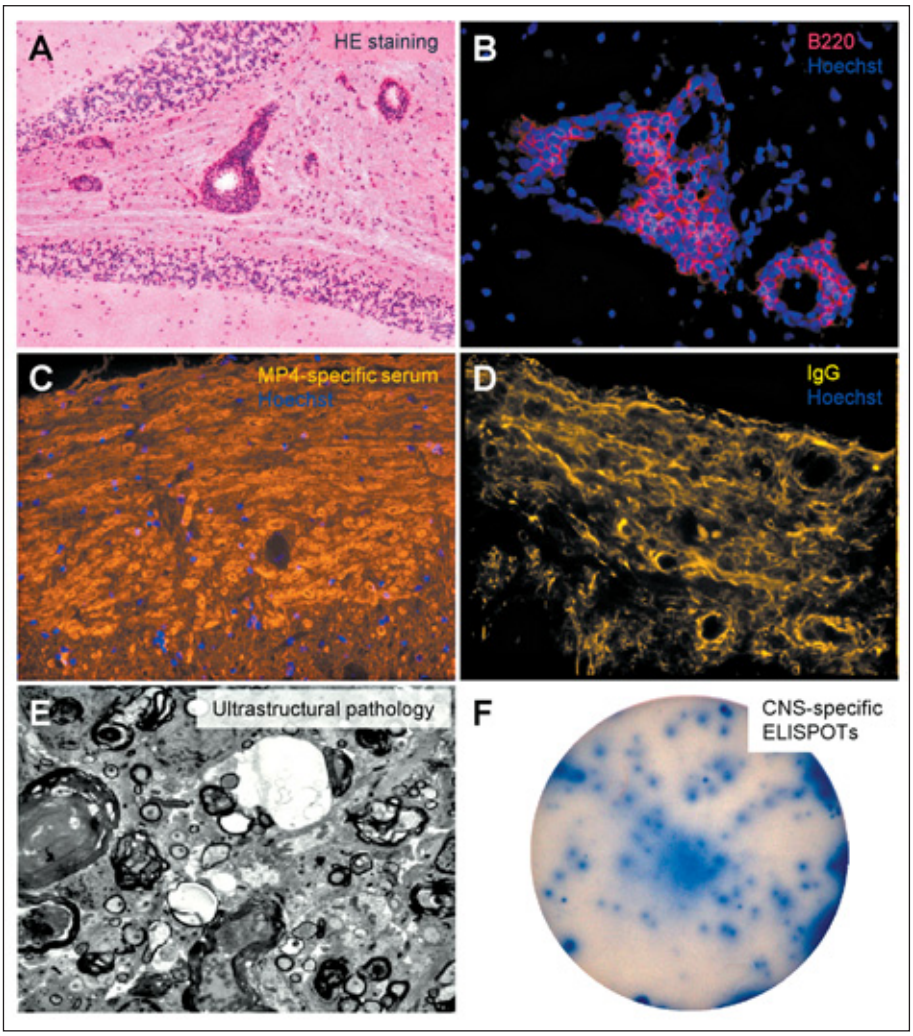
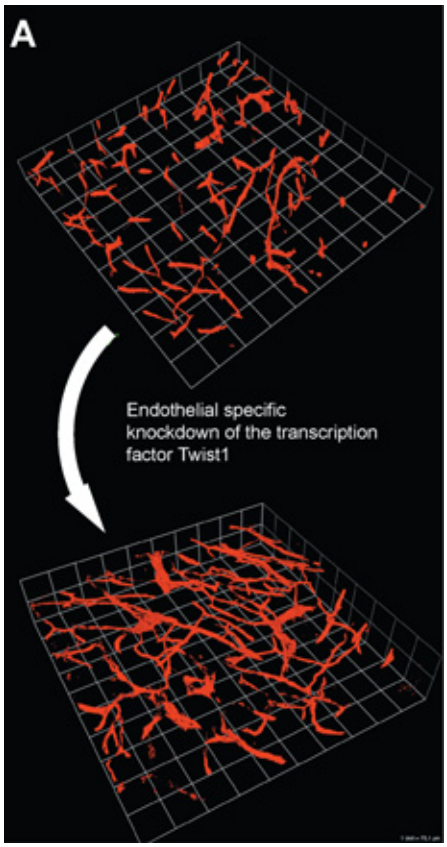


Fig. 1: The immunopathology of multiple sclerosis. (A) Immune cell infiltrates in the CNS. (B) Aggregation of B cells (B220+) in the CNS. (C, D) Deposition of myelin-reactive antibodies on spinal cord nerve fibers. (E) Demyelination and axonal damage in the spinal cord. (F) Production of CNS-specific antibodies in the blood of MS patients as detected in ELISPOT assays.



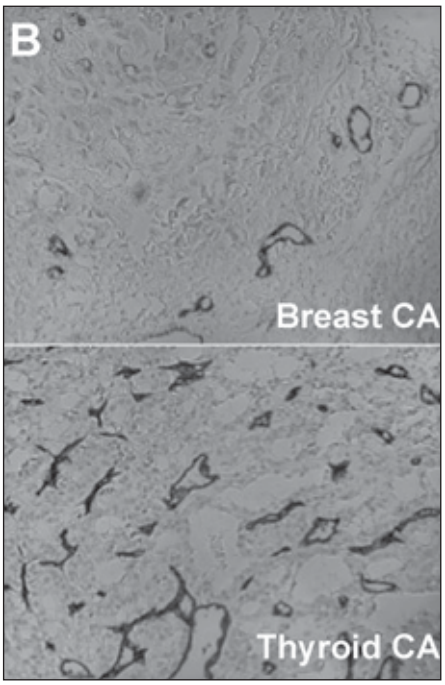


Fig. 2: A:Targeting transcription factors that are strongly expressed in tumor endothelial cells results in an improved vascularization. B: Density, shape and size of blood vessels differ significantly in different tumors. Immunohistological staining for CD31 for visualization of blood vessels in two different tumors.

cell responses in the blood of patients using the *enzyme-linked immunospot technique* (ELISPOT). It is our ultimate goal to develop novel therapeutic strategies for MS that target the B cell component of the disease.

Development of neuroprotective therapeutic strategies for the treatment of multiple sclerosis
(S. Kürten, N. Wager, V. Gorboulev)

Currently available treatment options for multiple sclerosis (MS) mainly target the inflammatory component of the disease. However, it is known that neurodegeneration occurs already early on in the disease and leads to the irreversible loss of axons. Studying an animal model for MS, our initial analyses have shown that treatment with the calcium channel antagonist nimodipine leads to a decrease in axonal damage and demyelination while supporting remyelination. This project aims to further study the mechanisms underlying the neuroprotective effects of nimodipine.

Development of microglia cells from the walls of CNS blood vessels
(S. Kürten, S. Ergün)

Next to the contribution of the adaptive immune system to the pathogenesis of multiple sclerosis (MS), a critical role for blood-derived macrophages and CNS-resident microglia cells is widely acknowledged. Macrophages and microglia occur in two subtypes. Whereas the subtype M1 asserts a pro-inflammatory role, an anti-inflammatory role is assigned to the subtype M2. Here, we would like to investigate whether microglia cells can develop from the walls of CNS blood vessels. Subsequently, we are going to study the role of these microglia cells in neuroinflammation. A local neogenesis of microglia cells in patients with MS would underline the need for treatment strategies that pass the blood-brain-barrier, are effective in the CNS itself and also target the innate immune system.

Re-engineering of the tumor vasculature for improved drug delivery
(E. Henke, S. Ergün)

The vasculature in tumors is characterized by an immature and defective vessel phenotype. This is at least partially caused by the constant overstimulation of the vasculature in the permanently remodeling tumor microenvironment. We successfully dampened these stimulatory pathways by targeting transcription factors in the blood vessels' endothelial cells. As a result the re-engineered vasculature was more mature and better organized, and was able to supply the tumors with increased levels of anti-tumor agents. In individual tumors the vessel phenotype can vary strongly, because different cellular pathways that are involved in generating the defective tumor vessel phenotype are variably activated. A large variety of regulating proteins have been identified as potential targets to improve vessel quality. To identify the most promising targets for changing the vessel structure, we established methods to assess the various defects in the tumor vessels and correlate them with expression profiles of key mediators in these pathways.

Teaching activity

Courses in microscopic and macroscopic anatomy, neuroanatomy and cell biology are held for medical, biomedical and dentistry students (a total of about 420 students a year).

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

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Mission and Structure

The research groups at the Department II of the Institute of Anatomy and Cell Biology are focusing on a) endothelial barrier in vascular inflammation and atherosclerosis, b) new vessel formation by angiogenesis and postnatal vasculogenesis in tumor growth and metastasis, c) stem cell biology including embryonic stem cells and adult vascular wall-resident stem cells, and d) structural basis of the complex central nervous functions. The cardiovascular group (Head: Prof. S. Ergün) investigates mechanisms of the endothelial barrier which are essential for vascular hemostasis. The damage of this barrier is one of the leading causes of vascular disease such as endothelial dysfunction, vascular inflammation and atherosclerosis. In particular the role of the cell adhesion molecule CEACAM1, the Isoprostanes and the CEACAM1-Isoprostane-interaction in vascular inflammation and atherosclerosis will be studied. The tumor angiogenesis group (Head: Prof. S. Ergün) studies the role of CEACAM1 in remodeling of tumor vasculature under therapy and its impact on tumor metastasis, in particular in prostate and urinary bladder cancer using experimental *in vivo* tumor models. In a further project we want to explore the contribution of local progenitor and stem cells to tumor vascularization, particularly those resident in the wall of pre-existing blood vessels. The stem cell and regenerative medicine group (Head: Prof. F. Edenhofer; Prof. S. Ergün) is working on experimental generation of neuronal stem cells (iNS cells) from adult fibroblasts and on endogenous mechanisms of cellular reprogramming of stem and progenitor cells from the adventitial "vasculogenic zone" of the adult blood vessels. The research of neuromorphology group (Head: Prof. E. Asan; Prof. P. Kugler) studies structural basis of complex functions in the nervous systems such as monoaminergic and peptidergic systems and their interactions on neuronal networks in the amygdala.
The research work at the Department II is carried out by 10 postdocs, 6 doctoral candidates and 5 technical assistants.

Focus of research

Endothelial Barrier, Vascular Inflammation and Atherosclerosis
(S. Ergün, N. Wagner, H. Bömmel, A. Hübner, J. Bauer)

Cardiovascular diseases are leading among the deadly ending disorders worldwide. The statement "one is as old as the own vessels" is still ongoing. The research of the cardiovascular group is aiming on exploration of mechanisms governing the endothelial barrier, formation of neointima and atherosclerosis and regeneration of blood vessels using *in vitro*-(endothelial migration, proliferation and tube formation assays), *ex vivo*-(arterial ring assays) and *in vivo* models (mouse models). In particular, the contribution of vessel wall-resident progenitor and stem cells to the formation of neointima and atherosclerosis, as well as the mechanistic role of CEACAM1 and CEACAM1-Isoprostan interaction in these processes and in the regulation of the endothelial barrier, will be studied *in vitro* and *in vivo* using mouse models as *Ceacam1-KO, Ceacam1 endothelial transgene* and thromboxane *receptor-KO.*

Tumorangiogenesis, Lymphangiogenesis and Tumor Metastasis
(S. Ergün, S. Hübner, J. Allmannritter, M. Veyhl-Wichmann, V. Pfeiffer)

Cancer is the second leading cause of death worldwide. Tumor growth and metastasis require new blood vessels. "Tumor

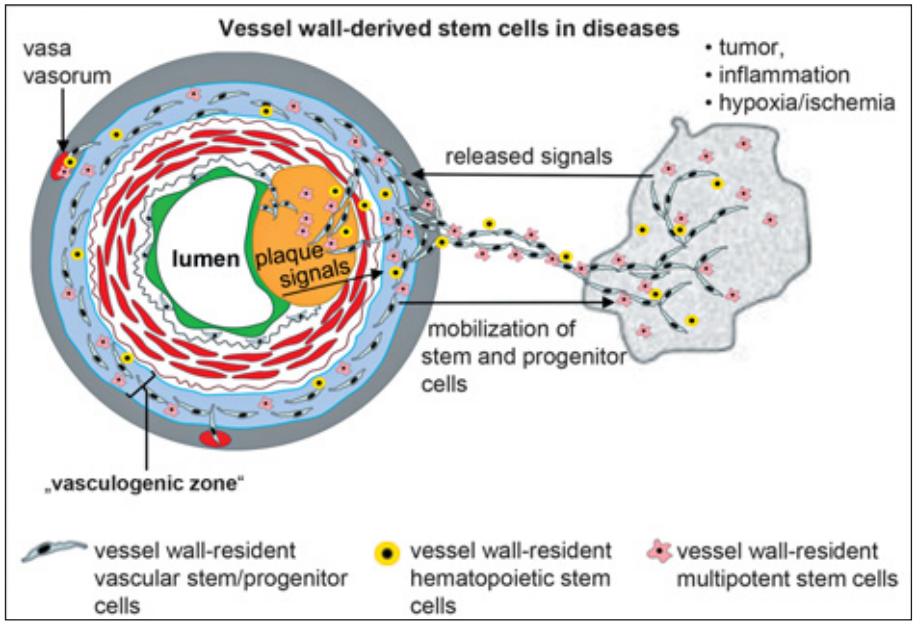

Fig. 1: Clinical impact of VW-SCs. As shown in this figure, VW-SCs can be mobilized in both directions: (i) toward the outside of the vessel wall, for example, by signals released from tumor cells, inflammatory processes, and tissue ischemia, and (ii) toward the vessel lumen, for example, hypoxia of 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.

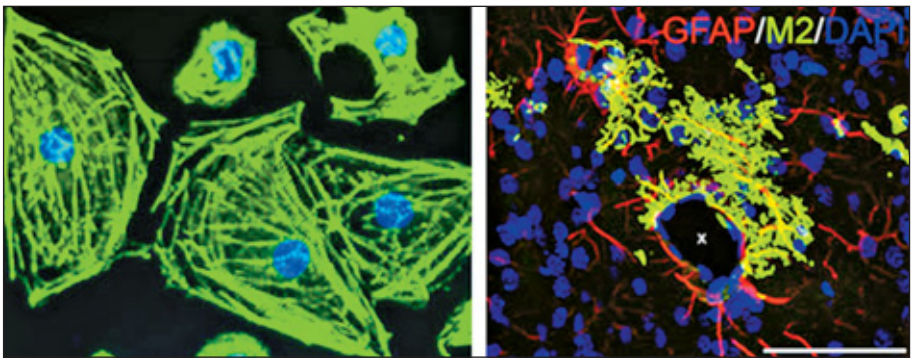

Fig. 2: Examples of re-programmed cells. Left figure panel: skin keratinocyte-derived cardiomyocytes (green: α-actinin; blue: nucleus). Right figure panel: induced neuronal stem cells (iNS cells) directly converted from mouse fibroblasts differentiate into astrocytes in an in vivo model.

dormancy", by cutting the tumor from the blood supply, e. g. via therapeutic inhibition of new vessel formation in tumors, is still one of the important aims of tumor research. Our group is working on molecular and cellular mechanisms of tumor vessel formation via angiogenesis and postnatal vasculogenesis using *in vitro-*, *ex vivo* und *in vivo* models. A particular focus of our research lies in understanding of the role of the cell adhesion molecule CEACAM1 in tumor new vessel formation. In a project granted by the DFG, we focus on the role of this molecule in lymphangiogenesis and lymphatic metastasis of prostate cancer. Furthermore, we are studying the mechanisms of vascular remodeling under anti-angiogenic therapy, e. g. the vascular stabilization, which apparently influences the efficacy of tumor therapy. In this context also the role of stem and progenitor cells resident in the adventitia of pre-existing blood vessels will be investigated.

Stem Cells and Regenerative Medicine
(F. Edenhofer, P. Wörsdörfer, V. Stoll, S. Ergün)

Recently developed methodologies of targeted cellular reprogramming enable thus far unattainable promising biomedical applications. Patient-derived reprogrammed cells, such as induced pluripotent (iPS) cells, represent an attractive platform for both, the modeling of diseases in the cell culture dish and the development of cell and tissue repair strategies. For the first time, our group was able to derive artificially induced neural stem (iNS) cells from mouse fibroblasts. iNS cells exhibit full self-renewal and are able to differentiate into the three main cell types of the central nervous system neurons, astrocytes and oligodendrocytes. Additionally, we showed that transplanted iNS cells yield in partial recovery in animal models for demyelinating diseases. In a second line of research we identified in the adventitia of human blood vessels a niche (which we termed vasculogenic zone) harboring stem and progenitor cells that are able to differentiate beyond the vascular lineage. Our research activities aim at the reprogramming and recruitment of endogenous stem cells, respectively, of the cardiovascular system for cell replacement therapy.

Neuromorphology
(E. Asan, P. Kugler)

Research of the neuromorphological groups is focused on analyses of the structural basis of complex functions in the nervous system. Investigations are, for instance, carried out on the influence of monoaminergic and peptidergic systems and of their interactions on neuronal networks in the amygdala, a brain area with key functions for emotional processes. Another central project is aimed at elucidating the subcellular localization and translocation of transport molecules for glutamate in glutamatergic neurons. Glutamate is the most important excitatory neurotransmitter and has to be eliminated after being released from the synapse by glutamate transporters to prevent neurotoxic effects. Further light- and electron microscopic studies are carried out in cooperation with clinical groups, for instance as contributions to investigations into alterations of specific neurons in genetic mouse models for disorders of the nervous system, into the exact morphology of specific projection systems in the basal ganglia, and into the cellular and subcellular localization of molecules involved in various signal transduction processes in the central and peripheral nervous system.

Proteins of the nucleus
(S. Hübner)
The nucleus of eukaryotic cells is of paramount importance. A plethora of nuclear proteins play an important role in the integrity of the nucleus. We investigate such proteins (e. g. Kanadaptin, Lamins) in the context of fundamental and pathophysiological processes (e. g. laminopathies).

Teaching activity

Courses in microscopic and macroscopic anatomy, neuroanatomy and cell biology are held for medical, biomedical and dentistry students (a total of about 420 students a year). The Department II organizes an annual workshop of the Anatomical Society every two years (next event in the last week of September 2015).

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2.3 Institute of Physiology, Chair of Vegetative Physiology

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Mission and Structure

The Institute of Physiology comprises Chairs for Vegetative Physiology and for Neurophysiology (Professor M. 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, Dr. Andreas Friebe and Dr. Kai Schuh.

Major Research Interest

We investigate the regulation and function of guanylyl cyclase (GC) receptors and of their second messenger cyclic GMP. Some of these receptors are transmembrane proteins, such as GC-A, the receptor for atrial (ANP) and B-type natriuretic peptides (BNP), and GC-B, receptor for C-type NP (CNP). In contrast, the GC receptor for nitric oxide is intracellular (NO-GC). To dissect the regulation, pleiotropic functions and disease relevant alterations of these hormones and of cGMP, we generate and characterize genetic mouse models with conditional, cell-specific deletion of these receptors or of regulatory proteins involved in their signal transduction. Other projects focus on the function of cytoskeleton-associated proteins containing EVH1 domains, such as SPRED (Sprouty-related protein with an EVH1 domain), MENA and VASP. Our research is supported by the DFG (SFB 688, etc.), the IZKF und the CHFC Würzburg. Our teaching duties are financed by the University of Würzburg.

Cardiovascular functions and cellular signaling pathways of ANP and BNP and role of CNP in long bone growth
(M. Kuhn, B. Gaßner, K. Völker, H. Oberwinkler, W. Chen, F. Werner, T. Premsler, S. Hupp, H. Nakagawa, M. Klaiber and coworkers)

All cardiovascular cell types express both particulate GC-receptors, GC-A and GC-B, although at very different densities. Cardiomyocytes mainly express GC-B, whereas endothelial cells have a much higher density of GC-A receptors. Hence, in myocytes ANP provokes only very small, local (submembrane) increases of cGMP, whereas CNP additionally increases cytosolic cGMP levels. The ANP/GC-A system activates cGMP-dependent protein kinase I (cGKI) to an inhibitory phosphorylation of TRPC3/C6 channels, thereby attenuating pathological calcium influx. Such auto/paracrine actions of the cardiac, hypotensive hormone ANP mediate local, antihypertrophic and antifibrotic effects which counteract pathological cardiac remodelling. CNP influences electromechanical coupling, for instance by stimulating cGKI-mediated phosphorylation of phospholamban and troponin I, ultimately enhancing inotropy and lusitropy. The role of these signaling pathways in cardiac homeostasis is emphasized by the phenotype of mice with cardiomyocyte-restricted inactivation of cGKI, which develop severe dilatative cardiomyopathy in response to enhanced cardiac afterload (Frantz et al., 2013).
Our research demonstrates interesting similarities of ANP signal transduction in cardiomyocytes and endothelial cells. Similarly to myocytes, in endothelial cells the ANP/GC-A/cGMP/cGKI pathway counterregulates the activation of TRPC3/C6 channels, for instance by mast cells or by their main inflammatory mediator histamine. Thereby ANP stabilizes the endothelial barrier and attenuates an acute inflammation. In contrast, the CNP/GC-B system apparently does not directly modulate endothelial permeability.
The peptide CNP received this name based on its sequence homology to ANP, but in fact CNP barely stimulates renal function. Instead, this hormone, which is made by chondrocytes and endothelia, critically stimulates long bone growth. In collaboration with Dutch colleagues we characterized an heterozygous activating mutation of the GC-B receptor in a patient with skeletal

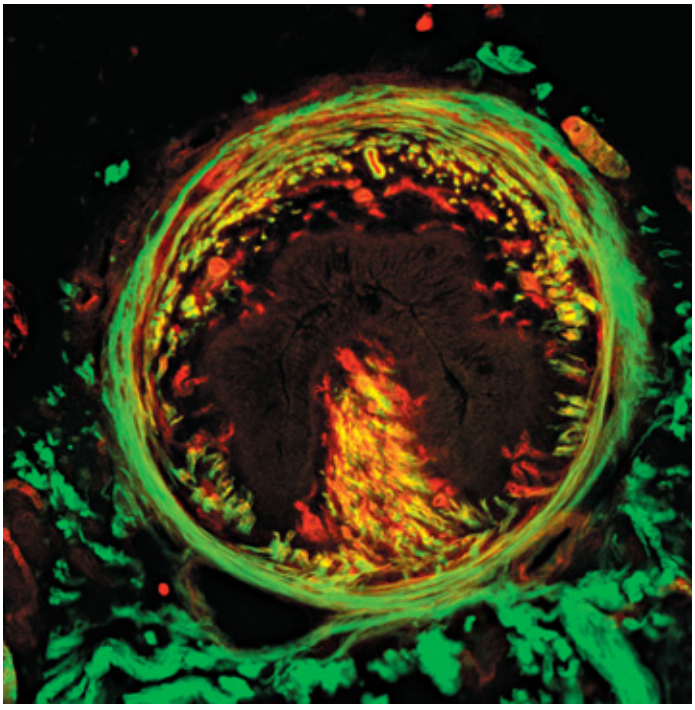

Fig. 1: Immunohistochemical localization of nitric oxide-sensitive guanylyl cyclase in internal urethral sphincter. It is a merge of an image stained red for nitric oxide-sensitive guanylyl cyclase and green for α-smooth muscle actin (Lies et al., J. Phys., 2013).

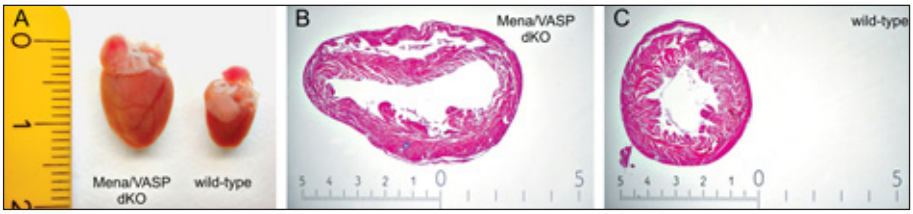

Fig. 2: Mena/VASP gene deficiency results in cardiac hypertrophy (A) and leads finally to a dilated cardiomyopathy with a severly reduced cardiac performance (B,C; Benz et al., 2013).

overgrowth. Interestingly, this specific point mutation (Arg->Cys) is located near to the ATP-binding pocket of the kinase homology domain (KHD) of GC-B; the guanylyl cyclase domain is unaltered (Hannema et al., 2013). Yet, the mutation greatly enhances the stimulatory effect of ATP on CNP-dependent synthesis of cGMP. The role of the KHD is uncertain. Our observations unravel a new potential molecular target for the treatment of achondroplasia Type Maroteaux. Most of these dwarf patients are homozygous for inactivating mutations in the genes encoding CNP or GC-B.
In summary, our research demonstrates that "natriuretic peptides" exert multiple important physiological extrarenal actions.

The significance of NO/cGMP signaling in the cardiovascular and gastrointestinal system
(A. Friebe, D. Groneberg, R. Jäger, B. Lies, N. Bettaga, S. Dünnes, L. Kehrer)

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 and lower urinary tract function, 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., 2013) and lower urinary tract relaxation (Fig. 1; Lies et al., 2013).

Physiological characterization of EVH1 domain-containing proteins
(K. Schuh, M. Ullrich, M. Abeßer, P. Benz and co-workers)

Gene trapping is an elegant tool to combine the ablation of a specific gene with parallel analyses of promoter activity of the trapped gene. We used this technique to characterize the relevance of various EVH1 domain-containing proteins *in vivo*. At present, we investigate the effects of SPRED and Mena/VASP-deficiency on the cardiovascular system. Of particular interest are the involved intracellular signalling pathways and the regulation of the cytoskeleton. We could show that Mena/VASP gene ablation leads to a disarrangement of the actin cytoskeleton in the heart with severe consequences for the electrical conduction and contractile performance, finally resulting in cardiac failure (Benz et al., 2013).

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). In winter 2013 Professor Andreas Friebe received the Albert Kölliker-award for his outstanding seminars and courses. These university fundings must be dedicated to improve teaching.

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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

Presynaptic proteins and spatial working memory in Drosophila melanogaster
(K. Neuser, M. Heckmann)

Intelligent behaviour is based on learning and usage of memorized contents. *Drosophila melanogaster* flies show intelligent behaviour as well. For example, they possess a spatial working memory. That is, they are able to store the position of visual objects and to use that memory content to show goal-directed movement even if the object has disappeared. This project aims to test whether the neuronal correlate of working memory can be linked to the molecular organisation of presynaptic proteins. Distinct sets of necessary neurons will be identified and the learning performance of transgenic fruit flies with altered compositions of presynaptic active zone proteins will be tested.

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 endplate active zones 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.

Molecular mechanisms of synaptic differentiation
(M. Paul, M. Heckmann)
Information processing in the nervous system is regulated by interaction of numerous proteins. Electrophysiological techniques as well as confocal and super-resolution microscopy are used to investigate the molecular mechanisms of functional and structural differentiation of active zones.

Adhesions-GPCRs – Signaling molecules with versatile physiological functions
(T. Langenhan)

Adhesion-GPCRs are evolutionarily highly conserved receptors that are present on cell surfaces of all major tissue types from earliest developmental stages onwards until adulthood. Several physiological functions of Adhesion-GPCRs have been determined including their contribution to tissue polarity, cell fate induction and the facilitation of specific cell-cell interactions. We are currently investigating the molecular properties of Adhesion-GPCRs using animal and cell culture models, which permit the large functional versatility of Adhesion-GPCRs. We are specifically interested in the processes involved in Adhesion-GPCRs signal perception and transduction.

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 action 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+ chan-

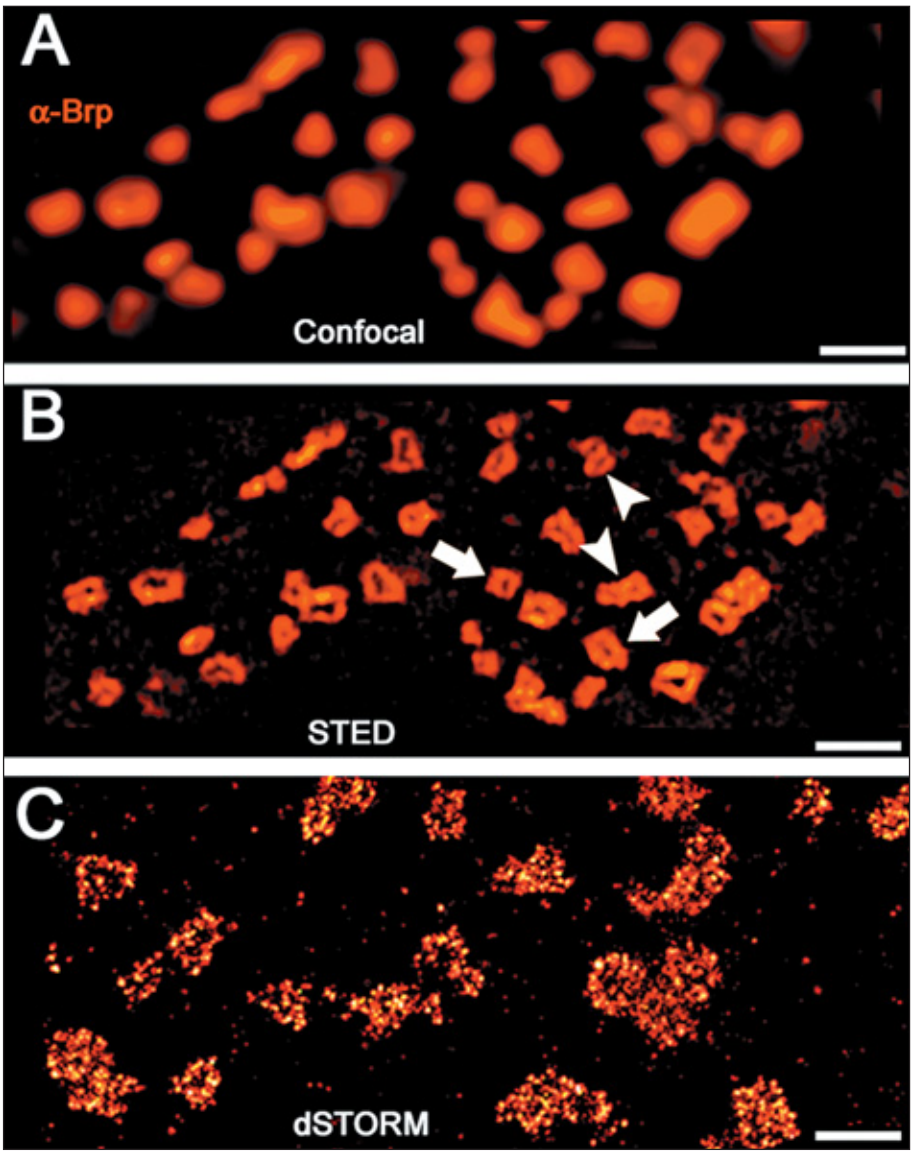

Fig. 1: Molecular structure of active zones. Investigations by the Kittel Emmy-Noether group in collaboration with the Sauer laboratory (Department of Biotechnology and Biophysics) concerning the spatial distribution of the Bruchpilot (Brp) protein in active zones. Application of „super-resolution" light-microscopy (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).

nels 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 necessary because they are well suited to analyse basic mechanisms of tumor development and tumor progression on the genetic and molecular level. Our group is mainly interested in the processes and mechanisms of melanoma development, which is studied in several elaborate model systems, including laboratory fish and mouse models, in vitro cell culture systems and patient material. One focus is traditionally the studies on the small aquarium model species, Xiphophorus and Medaka, which represent well established and useful melanoma models. During the last two years, we have performed DNA high throughput sequencing transcriptome analyses of different types of melanoma, induced by the oncogenic receptor tyrosine kinase Xmrk in both model systems. We found a high level of similarity in expression regulation of known and novel tumor related genes in fish melanoma and human melanoma. These are now further investigated for their functional relevance for melanoma development. Recently, we have also included the analysis of microRNA and other non-coding RNA classes because those molecules are expected to play a role in tumor development. However, their function for the oncogenic processes are so far not understood.
Fishes of the genus Xiphophorus are the oldest animal model for melanoma development. The system was first described in the twenties of the last century and the causative oncogene *xmrk* has been isolated more than twenty years ago. Many aspects of tumor development, however, are still not understood. Since 2013 we now have the full genome sequence of this animal model. This is a milestone for our research because the availability of the genome and other genomic resources is a rare condition for ans-

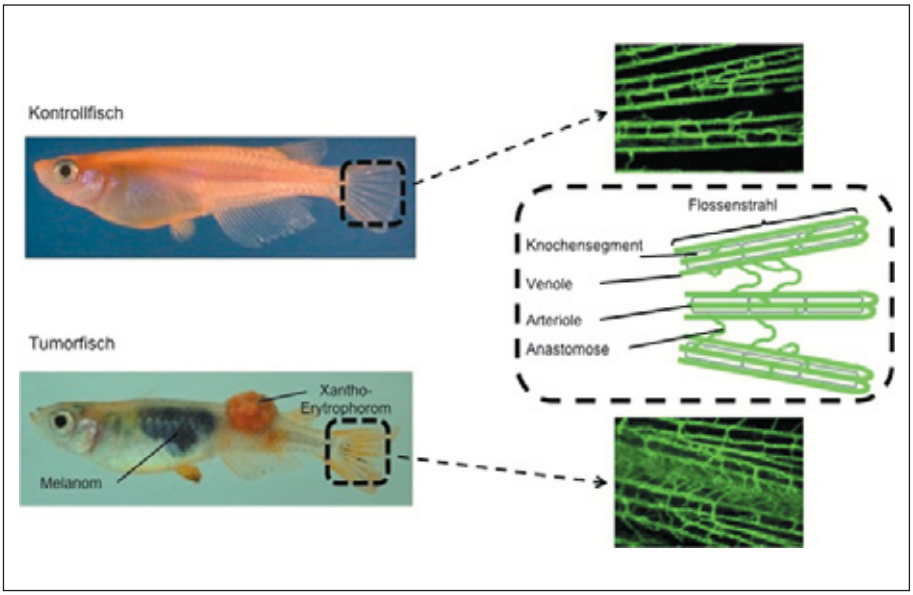

Fig. 1: Melanoma induced tumor angiogenesis in Medaka. The picture above shows a control fish, the picture below shows the tumor fish. Blood vessels express GFP and therefore glow green. (from: Schaafhausen et al., J Cell Sci 126:3862-3872, 2013).

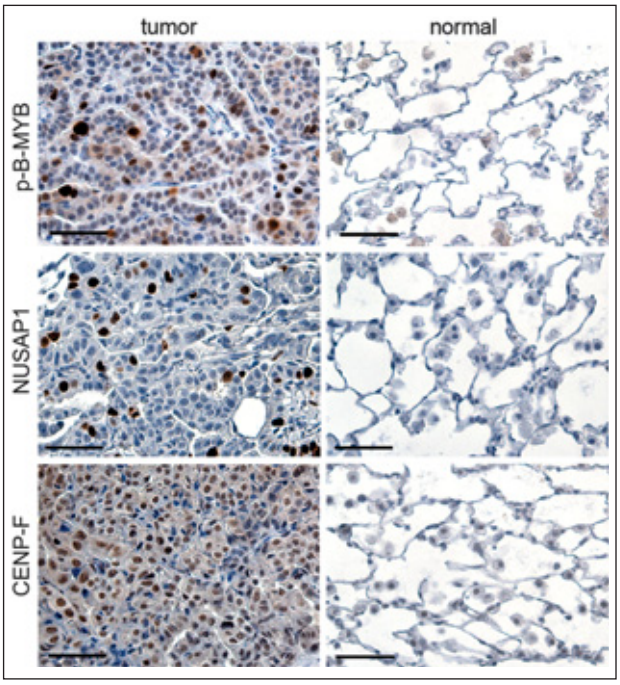

Fig. 2: Overexpression of the DREAM subunit B-MYB and DREAM target genes NUSAP1 and CENP-F in lung cancer. Immunohistochemistry staining of lung tumors and adjacent normal lung tissue from a mouse model of lung cancer 13 weeks after activation of oncogenic Ras and loss of p53. Bar: 50 µm.

wering many open questions of melanoma development in this animal system and provide unique resources for the future to study cancer from the evolutionary and comparative pathobiochemical point of view.

The analysis of the Xmrk mediated signal transduction is another focus of our research. We could show that Xmrk activates the transcription factor NF-kB through the production of reactive oxygen species (ROS). This leads to an extremely efficient and hypoxia-independent tumor angiogenesis, which can even be elicited from single *xmrk* expressing transformed pigment cells (Figure 1).

Similarly, human melanoma cells exhibit high intrinsic levels of NF-kB, which also display a strong angiogenic effect. However, if ROS levels are too high, this leads to senescence. We have found that the transsulfuration pathway, which is responsible for de novo synthesis of cysteine, can inhibit ROS mediated senescence. Melanoma cells show an enhanced ROS production. Consequently the inhibition of the transsulfuration pathway caused the induction of senescence and apoptosis. A possible therapeutic use of this observation is currently studied in mouse models for human melanoma. The ROS induced senescence of melanoma cells is just one example for therapy induced senescence. In collaboration with the dermatology clinic in Würzburg we have found that treatment of melanoma cells with the BRAFV600E inhibitor vemurafenib also leads to senescence, which is, however, ROS independent. We have indication that secreted factors from vemurafenib treated melanoma cells contribute to resistance and we are currently testing this hypothesis.

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 this DREAM 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 mediates the activation of a cluster of genes required for entry into mitosis, spindle assembly and cytokinesis. It has been proposed that overactivity of these mitotic proteins contributes to chromosomal instability and thus promotes tumorigenesis. We are currently investigating the role of DREAM in an *in vivo* mouse model of lung cancer driven by oncogenic Ras and mutant p53. These studies could lead to the development of new therapeutic approaches for lung cancer.

We are also interested in the function of novel target genes of DREAM such as GAS2L3, an actin and microtubule-interacting protein that plays important roles in cytokinesis and genome stability.

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2.6 Biocenter Würzburg, Chair of Biochemistry and Molecular Biology

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Mission and Structure

The department of Biochemistry and Molecular Biology 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. Biochemistry and Molecular Biology teaches biochemistry for preclinical students in Medicine and Dentistry and for the Bachelor students of Biomedical sciences. Five research groups work at BMB, two of which are headed by junior investigators (Dr. Nikita Popov and Dr. Armin Wiegering; Dr. Daniel Murphy, a third junior group leader was promoted to a faculty position at the Beatson Institute, Glasgow, in 2012). The major research aim of BMB 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 clinically oriented junior group of Armin Wiegering investigates c-Myc interacting proteins and activating pathways in colorectal cancer to define new therapeutic strategy (in co-operation with the Department of Surgery I); the group of Daniel Murphy (in Glasgow since 2012) develops novel mouse models to study the role of Myc in tumor progression.

Control of Cell Growth in Drosophila
(P. Gallant)

The fruit fly *Drosophila melanogaster* offers a unique model system that allows the genetic analysis of pathways controlling cellular growth, and of their effects on organismal growth and on cell proliferation. We use this system to investigate the evolutionarily conserved function of Myc in cellular growth. In addition, we characterize the systemic pathways that coordinate the rate of growth between different organs within the animal.

Metabolic Pathways in Peroxisomes: alpha-Methylacyl-CoA-Racemase
(E. Conzelmann)

- Elucidation of structure and mechanism of the enzyme

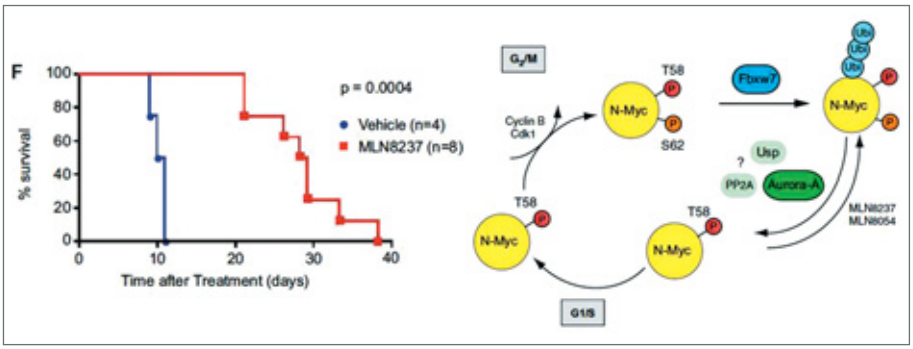

Fig. 1: Inhibition of Aurora-A leads to N-Myc degradation and subsequent regression of N-Myc overexpressing childhood neuroblastomas. The left panel shows the survival of mice with neuroblastoma induced by N-Myc overexpression, after control treatment (blue curve) and after treatment with an inhibitor of Aurora-A (red curve). The right panel explains the putative effect of Aurora-A on N-Myc stability. The data are taken from Brockmann et al. (2013).

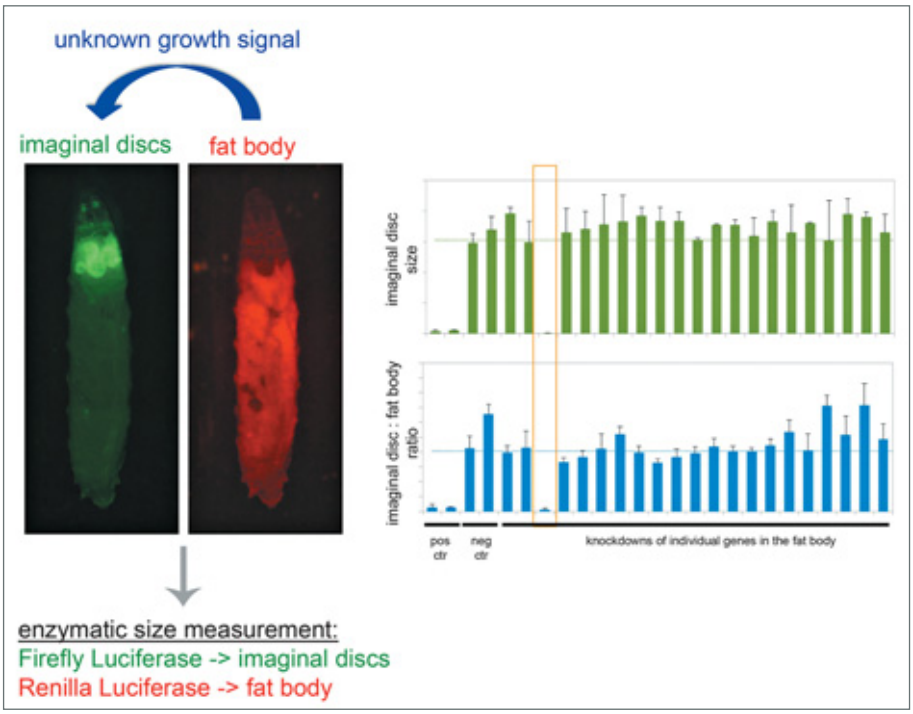

Fig. 2: Genetic screen for systemic growth signals in Drosophila. Upon systematic manipulation of individual genes in the fat body (red tissue in the left panel), the resulting effect on imaginal disc size (green tissue in the left panel) is measured enzymatically. The right panel shows an example of 20 tested genes that do not significantly affect the fat body derived systemic growth signal, and one that does (marked by a yellow box).

- 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

Teaching

The chair of Biochemistry and Molecular Biology 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 the 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) that are characterized by high throughput methods. 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, Biomedicine and 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. These could be utilized to gain novel insight into cardiac electric activity and conduction, where Hey2 seems to play an important and previously unrecognized role.
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. Furthermore, we could gain novel mechanistic insight into the parallel activation of the usually antagonistic factors Coup-TFII and Hey1/2 in the differentiation of lymphatic endothelial cells.
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 through a failure of

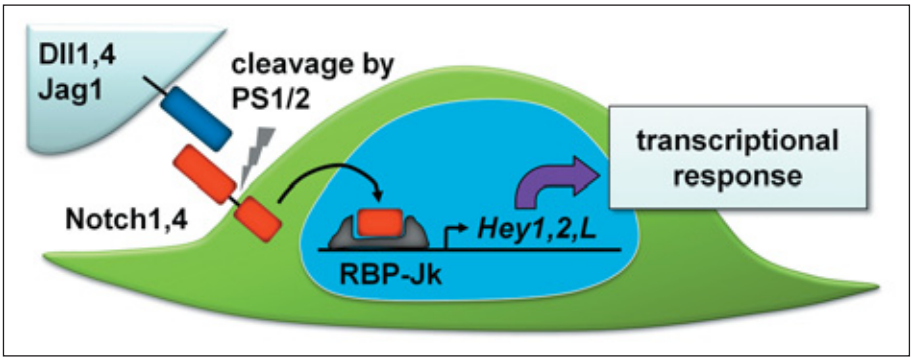

Fig. 1: The Delta/Notch signaling pathway activates transcription of Hey genes that in turn act as transcriptional repressors of target loci.

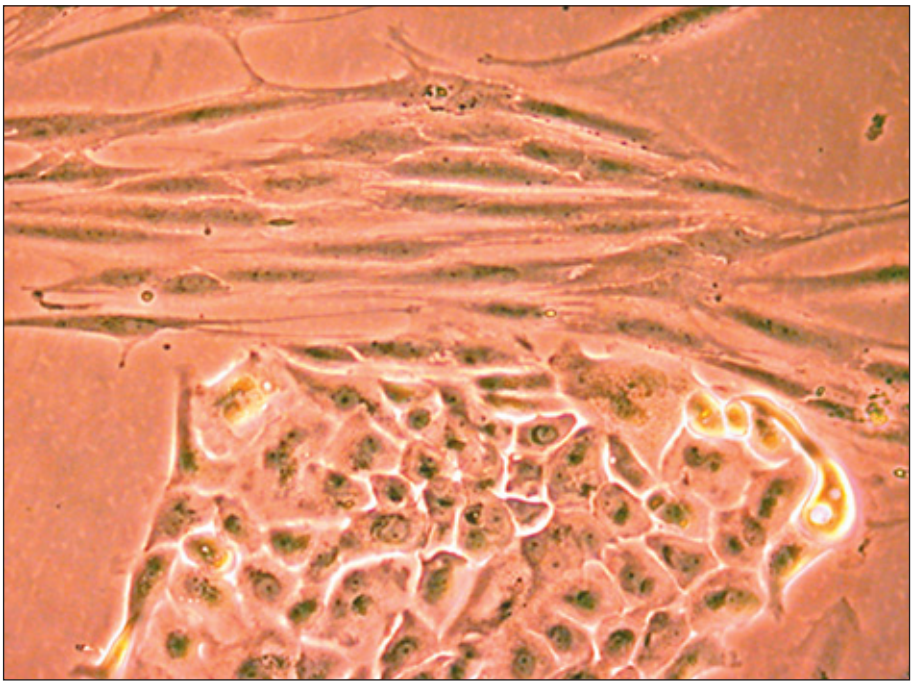

Fig. 2: Wilms tumors are often comprised of different cell types and these can initially be seen in cell culture as well.

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 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 analyze 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 growth 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.

In cooperation with hipo (Heidelberg Initiative for Personalized Oncology) we could employ high-throughput methods for mutation screening and expression analysis in the high-risk group of blastemal-type Wilms tumors. We were able to identify several novel candidate genes that currently undergo extensive validation. The pathways affected already now provide us with new and unexpected insights into the biology of these tumors and their genetic makeup.

Teaching

Together with the Chairs of Physiological Chemistry and Biochemistry and Molecular Biology we 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 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. Since the 1990s it has been housed in a former private ONT-clinic that was generously donated 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 the history of medicine from the late Middle Ages to the 19th century (ca. 1400-1850). More recently, the history of nursing, palliative care and medical ethics across the ages has emerged as a second area of special interest.

Early modern physicians' correspondence
(M. Stolberg, U. Schlegelmilch, T. Walter, A. Döll, S. Herde, A. Rappert-Sälzer)

Under the auspices of the Bayerische Akademie der Wissenschaften, a work group for the study of early modern physicians' correspondences has been established in early 2009. Funding has been approved for a period of 15 years, during which 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 a wide range of topics. They reflect professional networks and the dissemination of new medical findings and theories but they also offer 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 are made accessible to the international research community via OPAC. Selected collections and types of letters are analyzed in greater depth.

Out-Patient Medical Care 1500-1850
(M. Stolberg, K. Nolte, S. Schlegelmilch, S. Neuner, L. Al-Deri)

In two projects which are part of a German-Swiss-Austrian research network funded by the Deutsche Forschungsgemeinschaft (coordinator M. Stolberg, Würzburg, vice-coordinator M. Dinges, Stuttgart) 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 bedside. More recently, these projects have been complemented by research on the history of medical education and practice in the 16th-century as well as on and medical note-taking 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. In this project, which was originally funded by the Fritz Thyssen-Stiftung, we study the ways in which physicians and nursing staff dealt with moribund and dying patients and the ethical issues that arose in this context. Our work has challenged 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,

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

relatives, physicians, nurses and priests. A monograph with an overview on the history of terminal care has already been published. Our work in this field area is expected to reach its conclusion soon with the publication of a book which looks in depth at the cultural history of the medical and nursing care of moribund patients in the 19th century.

Monastic Medicine
(J. G. Mayer)

An 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, we have developed online-courses in medical terminology that are open to all Bavarian students of medicine and dentistry 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 are 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 and structure

The Institute of Clinical Epidemiology and Biometry at the University of Würzburg (ICE-B, Chair: Univ.-Prof. Dr. P. U. Heuschmann) was founded in October 2011. The Institute represents the disciplines epidemiology and biometry in research and teaching at the medical school of the University of Würzburg. The main research focus of the ICE-B is clinical epidemiology comprising research questions related to patients care including studies on: causes of diseases and respective risk factors; therapy and prevention; prognosis and outcome; diagnostis and screening as well as adequacy and quality of medical care for different diseases and syndromes. Hereby clinical relevant patient-oriented research questions will be answered applying appropriate study designs. One other main aim of the ICE-B is improving education and training activities of medical students, young scientists and physicians in the areas of epidemiology and biometry at the University of Würzburg.

Research focus

The ICE-B is conducting independent interdisciplinary research projects at the interface between clinical medicine and epidemiology in three main research areas: clinical research; prognostic studies and health services research. The research projects are conducted in close cooperation with various departments and institutes of the University Würzburg and the University Hospital as well as other research infrastructures, e.g. the Comprehensive Heart Failure Center (CHFC) of the University of Würzburg or the Clinical Trial Center of the University Hospital Würzburg (CTC).

Clinical research

Main focus of this research area is developing new methods for designing and analyzing various types of clinical studies. This area also includes the support of clinical studies of different phases being planned or conducted by institutions within the University Hospital and the University of Würzburg as well as with external partners. In addition, a close cooperation with the Clinical Trial Center of the University Hospital Würzburg is established, especially for biometrical aspects of clinical studies. For strengthening the thematic focus biometry, Prof. Dr. G. Gelbrich was appointed in July 2012 as W2 professorship in biometry at the ICE-B.

Prognostic studies

The research area prognostic studies aims to establish, perform and analyze cohort studies being conducted with high risk participants from the general population as well as patients with specific disease conditions.
One main research focus of the ICE-B is investigating the natural history of diseases and identifying high risk individuals for defined outcomes, such as complications, comorbidities or survival within routine clinical practice settings. For example, prognostic models were developed for identifying factors influencing long-term outcome as well as for predicting occurrence of relevant complications in stroke patients. Recently, the SICFAIL study was established as cooperative project between the ICE-B, the Department of Neurology (Prof. Dr. C. Kleinschnitz) and the Comprehensive Heart Failure Center (Prof. S. Frantz, Prof. S. Störk) for investigating the natural course of heart failure in ischemic stroke patients.
In 2013, the STAAB cohort study was initiated as joint project between the Comprehensive Heart Failure Center (Prof. S. Störk) and the ICE-B. Within the STAAB study, frequency of early stages of heart failure (stages A and B) and its determinants in the general population will be identified. For this purpose, a representative sample of initially 3000 men and women between 30 and 79 years of age from the study region of Würzburg will be investigated. Participants will be randomly selected from the local registration office and will be interviewed comprehensively regarding life style, health related factors and comorbidities. In addition, standardized vascular and heart diagnostic procedures (e.g. echocardiography, ECG) will be performed as well as anthropometric investigation (e.g. bioimpedance), neuropsychological and laboratory testing (including extensive biobanking). The baseline examination takes place in the joint epidemiological survey unit of the ICE-B and the CHFC (see figure 1). It is planned to invite all participants for a standardized personal follow up three years after the baseline examination.

Health services research

The theme health services research addresses research questions related to adequacy and quality of medical care. These stu-

Fig. 1: Assessment of carotid arteries within the STAAB study in the epidemiological survey unit.

dies comprise for example the development of methods to monitor the quality of routine medical care as well as the evaluation of measures to improve translation of research from clinical trials into clinical care of the population.

The EUROASPIRE IV (European survey of cardiovascular disease prevention and diabetes) study was successfully completed in 2013 as collaborative project between the ICE-B, the Comprehensive Heart Failure Center Würzburg (Prof. S. Störk), additional departments of the medical faculty (Prof. G. Ertl, Prof. R. Leyh) and the hospital Kitzinger Land (Dr. W. Karmann). Within this multicenter European cross sectional survey the quality of secondary prevention as well as the management of lifestyle factors, vascular risk factors and drug prevention in daily clinical practice was assessed in 550 patients with established coronary heart disease within the study region Würzburg and Kitzingen. This study was coordinated by the European Society of Cardiology and the European Association of Cardiovascular Prevention and Rehabilitation and was performed in 24 European countries.

Furthermore, within this research area the collaborative project „The European Implementation Score (EIS) Collaboration“, funded within Framework 7 of the European Union and coordinated by King's College London, was successfully finished. Aim of this project was developing 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, potential factors influencing successful implementation of research evidence into clinical practice were identified. For this purpose data from national or regional stroke audits from 7 European countries were combined and analyzed by ICE-B researchers.

Teaching and training

The ICE-B gives specific emphasis to improve education and training of medical students, young scientists and physicians in epidemiology and biometry at the University of Würzburg.

Teaching activities include for example establishing new structures for undergraduate training of medical students, including specific lectures and small group courses in epidemiology and biometry for medical students. Within these courses, practical clinical examples were addressed to demonstrate the relevance of epidemiology in daily clinical practice. In addition, extended modules for medical students on epidemiological and biometrical topics were implemented.

Furthermore, the ICE-B contributes actively in establishing advanced education activities in the area of clinical research, clinical epidemiology and health services research in Würzburg in close collaboration with a number of other research facilities (e.g. the Comprehensive Heart Failure Center). These activities include for example the establishment of a program "clinical research and epidemiology" for medical students since the winter term 2012/2013 in which participants will gain basic skills in clinical research as well as in theory and praxis of epidemiological and biometrical methods in clinical research.

For qualifying young scientists to conduct independent patient-oriented research projects, the ICE-B contributes to establishing a new section Clinical Sciences within the „Graduate School of Life Sciences (GSLS)“ together with various other institutions of the University and the University Hospital of Würzburg. Within this new section for example a curriculum „Clinical Research“ was established for qualifying residents and fellows. In addition, an annual "Winter School in Clinical Epidemiology" takes place since 2012 including practical exercises and theoretical lectures on recent patient-oriented research topics with participation of a national and international faculty of clinical epidemiologists.

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

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Mission and Structure

The focus areas of the Department of Medical Psychology, Psychotherapy, 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 department 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 department and consultation-liaison services for the University Hospital are provided. Several close research co-operations exist with the University Hospital. The department 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), explores the association of both quality of life and depression with somatic parameters among patients with chronic heart failure. Additional analyses aim at clarifying the mechanisms conveying the prognostic value of depressive symptoms for survival in heart failure. Moreover, an intervention for optimizing disease management 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, have been determined in a multi-center study including the centers Würzburg, Hamburg, Freiburg, Heidelberg, Leipzig. For the development of the S3-Guidelines Psychooncology, a systematic review and meta-analysis regarding the effectiveness of psychooncological interventions was performed. The impact of response shift, i.e. change of patients' internal judging standards, on the assessment of quality of life among prostate cancer patients is being examined in a project involving two university centers (Würzburg, Hamburg), which is performed in collaboration with the Departments of Radiotherapy (Prof. Flentje) and Urology (Prof. Riedmiller).

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

Innovative educational concepts 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 were designed to improve patient-centeredness through the employment of new didactic methods. They also implement specific strategies to increase the sustainability of education effects and to transfer newly learned skills into everyday life. In other projects, a generic self-management program, an educational intervention for smoking prevention for nurses, and different methods used to disseminate innovative educational programs into routine health care are being evaluated.

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

A 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 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 iden-

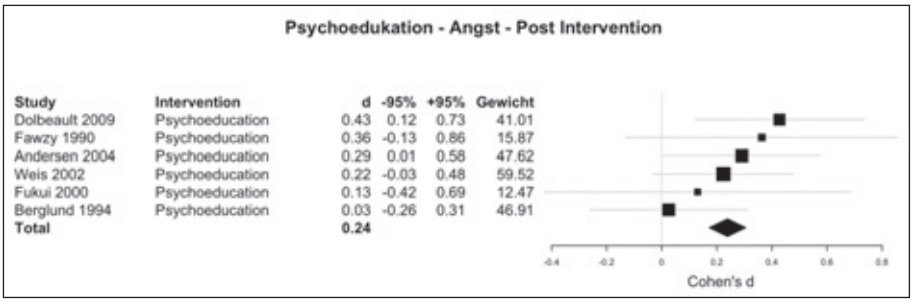

Fig. 1: Effects of psycho-educational interventions on anxiety in cancer patients.

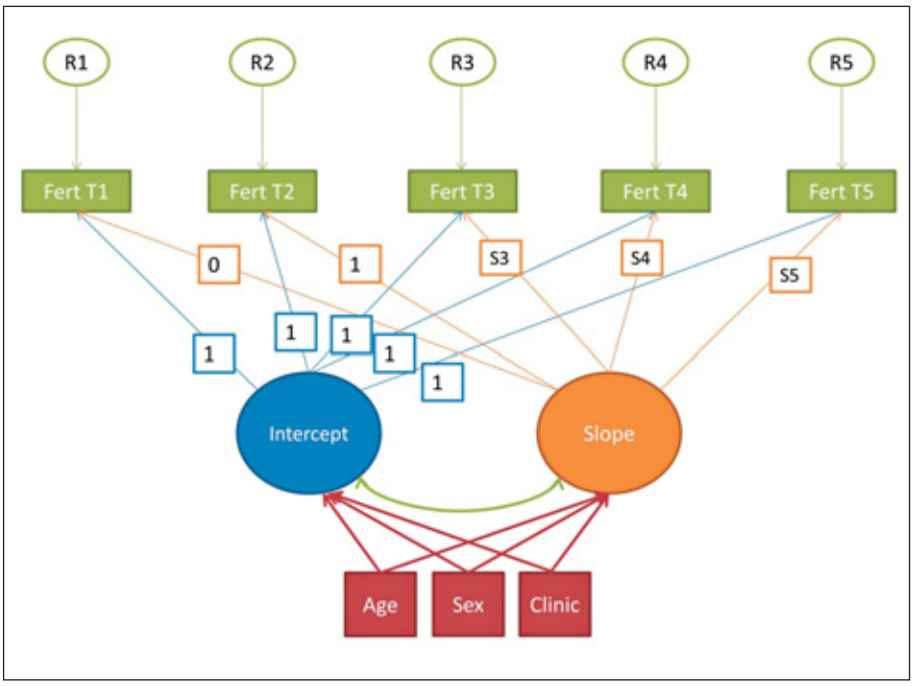

Fig. 2: Latent growth model for the heiQ scale Skill and Technique Acquisition (Fert) using five assessment time points and three predictor variables.

tification of patients with vocational impediments and provision of treatments addressing work (so-called work-related interventions) are necessary. Members of our team participated as experts in the development and revision of standards for medical work-related rehabilitation issued by the German Statutory Pension Insurance. Current projects deal with the formative evaluation of the implementation of these standards in rehabilitation clinics, the evaluation of specific work-related interventions for neurological disorders, the role of health literacy in the context of medical work-related rehabilitation, the classification of work-related educational programs and the dissemination of benchmark models into routine rehabilitation.

Quality Assurance and Quality Management
(H. Vogel, S. Neuderth)

Quality management programs have been developed for various clinical institutions. These include quality management concepts for medical rehabilitation carried out by the German Statutory Accident Insurance, the revision of the rehabilitation clinic auditing guidelines of the German Statutory Pension 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 department is responsible for the field of medical rehabilitation for children and youth. In addition, various projects address the quality assurance of social medicine assessments as performed by the German Statutory Pension Insurance.

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 Department 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.

In several research projects, innovative educational methods, such as the use of simulation patients in both medical education and psychotherapy training, are being evaluated.

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Meng K, Musekamp G, Seekatz B, Glatz J, Karger G, Kiwus U, Knoglinger E, Schubmann R, Westphal R, Faller H (2013) Evaluation of a self-management patient education program for patients with chronic heart failure undergoing inpatient cardiac rehabilitation: study protocol of a cluster randomized controlled trial. BMC Cardiovascular Disorders 13:60.

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 and infection control 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 Institute for Hygiene and Microbiology which focuses on the establishment of an European 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)

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 major signalling pathways resulting in cytoskeletal remodelling and bacterial engulfment.

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.

Fig. 1: Echinococcus multilocularis protoscolex stained with phalloidin (muscles) and acetylated tubulin (nerve cells, flame cells). From Koziol et al., Front. Zool. (2013) 10:24.

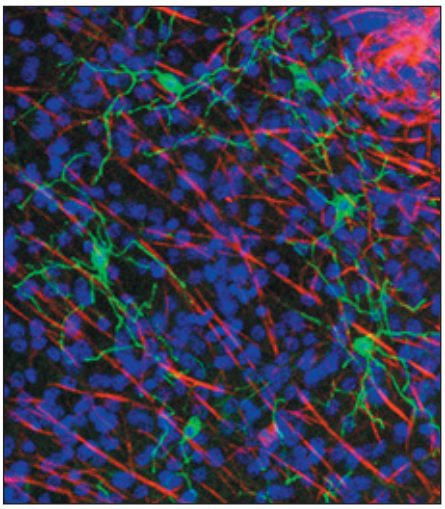

Fig. 2: Neuronal network of the E. multilocularis metacestode (stained with phalloidin (muscles), DAPI (nuclei), AcTub (nerve cells). Koziol et al., Front. Zool. (2013) 10:24.

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

Neisseria meningitidis is an important commensal, accidental pathogen and model organism with a small but hyperdynamic genome. Meningococcal fitness and genome evolution result from a fine-tuned balance between mechanisms for genome variability and maintenance where chromosomal alterations and polymorphisms provide the meningococcus with adaptability and ensure a lasting coexistence with their human host. The study of the genetic mechanisms shaping meningococcal genome diversity as well as causing differences in genome expression among different strains are thus another main research focus of the institute, ultimately aiming at a better understanding of the genetic factors that separate purely commensal from accidentally invasive strains.

Fox-tapeworm and alveolar echinococcosis
(K. Brehm)

Alveolar echinococcosis, caused by the cancer-like growth of the metacestode larva of the fox-tapeworm Echinococcus multilocularis, is a life-threatening human parasitosis that leads to liver tissue destruction and metastases formation in secondary organs. We have recently characterized the whole genome sequence of this parasite and thus gained valuable information on novel drug targets and molecules that govern host-parasite interaction. These studies are currently complemented by extensive transcriptomic and proteomic analyses on in vitro cultivation systems for parasite larvae and stem cells that we have developed. 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 immune-modulators that ensure long-term persistence of Echinococcus in the host.

Teaching

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

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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 mechanisms of measles virus induced immunosuppression
(S. Schneider-Schaulies)

A generalized immunosuppression associated with measles virus (MV) infections accounts for the majority of their morbidity toll. Central topics of the reaserch groups address 1) the interaction of MV with dendritic cells which are primary targets for infection and most likely mediate viral transport to lymphatic tissues and transmission to lymphocytes, and 2) the inhibition of T cell expansion upon exposure to MV which reflects a hallmark of MV induced immunosuppression in vivo. This inhibition is largely induced upon contact of the viral glycoprotein complex expressed on infected dendritic cells which thereby transmit inhibitory signals to T cells in a receptor dependent manner. These include activation of sphingomyelinases which catalyze ceramide release by breakdown of membrane sphingomyelin and thereby influence the dynamics and composition of membrane microdomains.

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. Thus, the research group combines model systems for RSV with the surrogate in vivo model of the RSV-mouse homolog, the pneumonia virus of mice (PVM), to investigate pathogenicity factors of virus and host with a focus on a virus-induced immunopathology. Methodologically this includes the use of reverse genetic systems for RSV and PVM that permit introduction of defined mutations into the virus genomes. Thus, these systems enable the targeted modulation of protein functions and the generation of reporter viruses permitting the spatio-temporal analysis of the of infection and immune response. The results of these studies will contribute to a better understanding of the mechanism of RSV-induced disease and, consequently, to the development of targeted therapy approaches.

Pathogenesis of measles and canine distemper virus infections
(J. Schneider-Schaulies)

Acute measles is accompanied by a transient immunosuppression, many complications, and the virus can persist in the central nervous system (CNS) causing years later the disease subacute sclerosing panencephalitis (SSPE). We established a model of a persistent viral CNS infection using immunologically normal (genetically unmodified) mice and recombinant measles virus (MV), in which the role of regulatory T cells (Tregs) as regulators of the immune response in the brain is being assessed. Canine distemper virus (CDV) is a Morbillivirus closely related to measles virus. When measles may be eradicated – which is an aim of the world health organization (WHO) declared for 2020 – and the vaccination against measles may be stopped, it is possible that related animal viruses such as CDV may mutate and infect the human host. Therefore, the group investigates the species barrier protecting humans from infections with animal Morbilliviruses.

Molecular Biology of Foamy Viruses
(A. Rethwilm)

Aside of the wellknown Orthoretroviruses (HIV, MLV etc.) the family of Retroviruses consist of another subfamily that is made up by the non-pathogenic and evolutionary extreme old Spumaretroviruses (Foamy Viruses). These viruses follow an unprecedented replipcation pathway. The work concentrates on the elucidation of this foamyvirus-specific pathway.

Pathogenesis of HIV-associated neurocognitive disorders (HAND)
(E. Koutsilieri, C. Scheller)

HIV infection causes neuropsychiatric complications manifesting in HIV-associated neurocognitive disorders (HAND). They occur in various forms in up to 60% of the HIV-infected population and affect medication adherence. We study the pathogenetic mechanisms involved in these disorders and especially the role of the regulation of the neurotransmitter dopamine on phenotype and progression of the disease. A focus of our work is specifically the influence of genetic polymorphisms which modulate dopaminergic neurotransmission on the prevalence of HIV immunodeficiency infection and progression of disease in cohorts of German and African HIV-infected drug-naïve and HAART-medicated people.

Studies on lithium carbonate as adjunctive treatment for HIV-associated neurocognitive disorders (HAND)
(E. Koutsilieri)

Sub-Saharan Africa is the area with the majority of HIV infections worldwide. Although antiretroviral therapy (ART) improves neuropsychiatric performance in a lot of patients with HAND, the prevalence of people with HAND increase. As the social and economic burden of HAND is great, there is an urgent need to identify effective adjunctive treatments for HAND. We conduct a randomized double blind placebo controlled trial to determine as primary endpoints the efficacy, safety and tolerability of lithium in patients with clade C-HIV with HAND stabilized on ART. Key interests are the influence of lithium on the dopaminergic neurotransmission and the factors which regulate the relase of dopamine as well as the pharmacogenetics of lithium.

Pathogenesis of HIV-AIDS
(C. Scheller)

HIV was being transmitted from SIV-infected monkeys to humans about 100 years ago. In contrast to humans, most of the natural hosts of SIV-infection do not develop AIDS despite high viral loads. Whereas the human immune system responds to HIV infection with a chronic hyperimmune activation, most natural hosts downregulate the initial immune activation shortly after primary infection to normal levels. Our team investigates whether the hyperimmune activation observed in human HIV infection is a causal factor in the development of AIDS.

Mechanisms of HIV-1 resistance and fitness compensation
(J. Bodem)

During the last few decades, the treatment of HIV-infected patients by highly active antiretroviral therapy has become standard, but was often hampered by the occurrence of drug resistance viruses. Resistance associated mutations were strongly correlated with losses in viral fitness. This assumption was contradicted by clinical data from patients having highly resistant viruses, which replicated at high viral loads. Furthermore, the genomes of resistance-associated viruses were found to be stable even in the absence of selective pressure. We have shown, that compensatory mutations, which even occur outside of the drug target regions, compensate losses in viral fitness. The mutations that accumulated in the vicinity of the processing sites spanning the p2/NC, NC/p1 and p6pol/PR proteins lead to much more efficient hydrolysis of corresponding peptides by patient-derived PR in comparison to the wild-type enzyme. We have reported a novel mechanism, which explains fitness compensation and HIV-1 resistance.

Mechanisms of cellular and retroviral polyadenylation
(E. Schrom, J. Bodem)

Most cellular mRNAs are polyadenylated. Retroviruses had to develop mechanisms to regulate polyadenylation, since retroviral genomes are flanked at the 5' and at the 3' end by identical regions, which both encode all signals required for polyadenylation. Active polyadenylation at the 5' end would result in non-coding RNAs. Thus, retroviruses need to suppress polyadenylation at the 5'end. In cooperation with colleagues from Bayreuth and Hannover, we were able to decipher the mechanisms used by foamy viruses to regulate polyadenylation. We have shown that the major splice acceptor is required for the suppression of polyadenylation at the 5' end. Furthermore, we could show that foamy viruses use at the 3' end a secondary structure to presumably block access of splice complexes and thereby activate polyadenylation at the end of the genome. Especially this novel mechanism might be helpful for the analysis of cellular polyadenylation.
In collaboration with others, we took part characterizing the molecular basis of an inherited immune deficiency syndrome, which reveals the importance of a correct polyadenylation signal. The disease is based on single nucleotide exchange in the 3' untranslated region of the *p14/robld3* gene, giving rise to a pseudo 5' splice site (ss). Binding of U1 snRNPs to the pseudo 5'ss leads to suppression of polyadenylation. The non-polyadenylated transcripts are subsequently degraded, which ultimately results in the inherited syndrome.

Foamy viral protease regulates the onset of reverse transcription
(R. Spannaus, J. Bodem)

Foamy viruses express a unique protease, which is unable to form active dimers. In collaboration with colleagues from Bayreuth, we were able to show that this protease is only active as a protease - reverse transcriptase fusions protein and requires viral RNA for dimerization. Thus, the foamy viral protease is the only RNA-dependent protease described so far. During reveres transcription the viral RNA will be transcribed into cDNA, which inactivates the protease. We have shown that the reverse transcription is dependent on Gag maturation and that a certain amount of Gag proteins has to be cleaved by the protease to allow reverse transcription to be completed. Thus, the foamy viral protease is the only retroviral protease, which controls the time-point of reverse transcription.

Clinical Virology
(B. Weißbrich, J. Schubert)

In the diagnostic unit of the institute approximately 40,000 samples are processed and evaluated every year; the University Hospital being the main consumer of our service. In addition, a variety of clinical-virological research questions are addressed on a collaborative basis. Among which the cooperation with clinical units in the Hospital of Child Medicine need to be mentioned first.

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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Mission and Structure

The research interests of the individual research groups focus on a broad spectrum of basic and applied immunological topics. These include the regulation of B cell maturation, 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 infections, allergies, autoimmune diseases, transplant rejection and graft-versus-host-disease. Our research is supported by local and international funding and by various cooperations within Germany and abroad. The institute also provides diagnostic services for autoantibodies for the University Clinic (head PD Dr. T. Kerkau).

Major Research Interests

Function of the costimulatory receptor CD28
(T. Hünig)

CD28 is the key costimulator of T-cell responses, i.e. in addition to antigen recognition, this receptor needs to be engaged for full T-cell activation. Using conditionally CD28 deleting mice and blocking as well as stimulating CD28-specific monoclonal antibodies, we study the contribution of this receptor to maintenance of immune homeostasis and the regulation of CD8 T-cell responses.

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 of 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 have clarified why rodent and tissue culture experiments did not predict this and have established new preclinical test systems.

CD8 T-cell-mediated autoimmunity in a 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 target these cells with “killer” CD8 T-cells. We have found that in the absence of an intracerbral infection, the killer cells are deleted whereas in its presence, they destroy the oligodendrocytes, causing MS-like lesions. We are currently investigating the molecular basis for this switch between autoimmunity and tolerance.

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. Additionally, “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). In humans so called Vγ9Vδ2 T cells are investigated, a cell population which has been found so far only in humans and higher primates. These cells recognize metabolites of isoprenoid synthesis, the “phosphoantigens“, which are produced by host cells with metabolic aberrations (e.g. tumor cells) and many pathogens. We investigate how these cells can be used in tumor therapy. Furthermore, we have initiated a search for genes controlling the presentation of phosphoantigens and the analysis of the phylogeny of this spe-

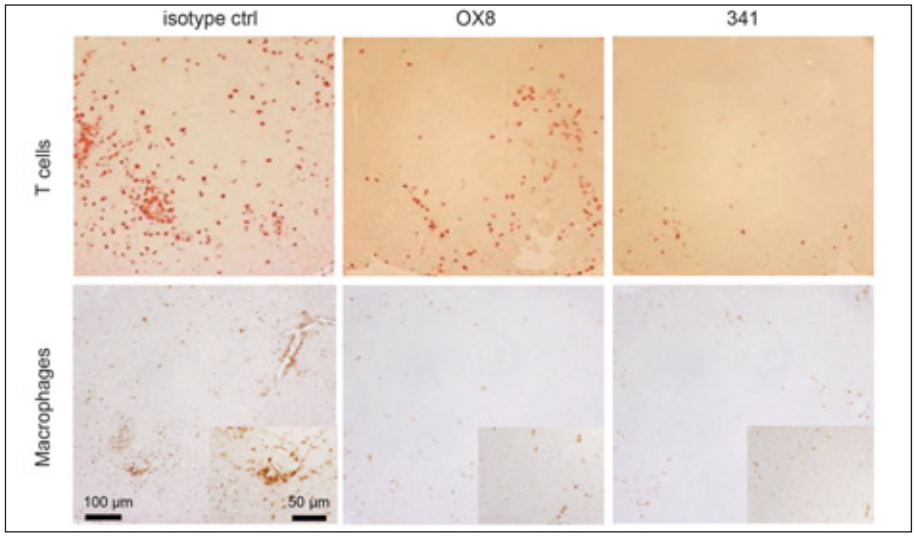

Fig. 1: The depletion of CD8+ T cells by monoclonal antibodies (OX8, 341) reduces disease symptoms of EAE in the Lewis rat, an animal model for human multiple sclerosis and in comparison to the control group is associated with reduced infiltration of immune cells /Tcells, macrophags)in the CNS of the animal. Thus, CD8+ T cells can contribute to the pathogenesis of this disease.

cial cell-type with the long term perspective to generate non-primate animal models for this unique type of T cells.

RelB expression in dendritic cells as a regulator of regulatory T cell frequencies
(M. Lutz)

Under steady state conditions dendritic cells (DC) transport self-antigens to the draining lymph nodes to induce T cell tolerance. These DC are characterized among other features by the expression of the transcription factor RelB of the NF-κB family. After genetic ablation of RelB in CD11c+ DC by using a Cre-lox system in mice an increased frequency of regulatory T cells (Treg) can be observed. They are induced by an augmented IL-2 productioin by autoreactive memory T cells which in turn are regulated by IL-7/IL-15 from lymph node stroma cells. The data show that DC do not only determine the self-antigen specificity for presentation to Treg but also control their frequency by indirect control of IL-2 production.

Immune deviation and -suppression by mycobacteria
(M. Lutz)

Myeloid-derived suppressor cells (MDSC) represent immunosuppressive populations of early myeloid cell differentiation stages. Our analyses *in vitro* and in mice have indicated that activation of MDSC by *Mycobacterium tuberculosis* (Mtb) leads to suppression of T cell immune responses. In humans infections with Mtb lead to strong immune responses but not to elimination of the microbes. In collaboration with a research group from South Africa we could show now the infection and accumulation of MDSC in the blood of tuberculosis patients. In another project in which the 30-kDa and 38-kDa Mtb antigens were tested on human dendritic cells (DC), we could show that besides the expected induction of IFN-γ+ Th1 cells also immune deviation towards IL-4+ Th2 takes place.

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 pathophysiology of and novel immunotherapeutic for pathological immune reactions. For this, we are focusing on animal models of multiple sclerosis (MS) and Graft-versus-host-disease (GvHD), a major complication after allogeneic bone marrow transplantation. In case of MS, we could recently identify an important role of CD8+ T cells in the induction of an MS-like disease in rats. For GvHD, we are currently studying novel protocols for its prevention without the need for regulatory T cells as these are very difficult to obtain for therapeutic purposes in humans. Apart from animal models, our group is collaborating with that of Prof. Dr. R. Jahns, Internal Medicine I, to analyse B and T cell responses in patients developing autoantibodies against the β1-adrenergic receptor of the heart to get a better understanding of the factors inducing this form of life-threatening autoimmunity in humans.

The role of CD4+ T cells in myocardial wound healing
(T. Kerkau, N. Beyersdorf)

While the role of innate immunity in wound healing after myocardial infarction (MI) is well established, little is known about the contribution of adaptive immunity, in particular CD4+ T cells, to this process. In collaboration with Prof. Dr. S. Frantz and PD Dr. U. Hofmann, Internal Medicine I, the group has already identified CD4+ regulatory T cells to crucially contribute to these processes. Future work aims at translating these findings into novel therapeutic approaches for improved wound healing in patients post MI.

Modulation of T cell responses against *Candida albicans*
(N. Beyersdorf, T. Hünig)

T cells crucially contribute to immunity against opportunistic pathogens like *Candida albicans*. It is, thus, the aim of a joint project of us and Prof. Dr. P. Zipfel, Jena, to better understand the host-Candida interaction focussing on the modulation of anti-*Candida* T cell responses by secreted fungal proteins.

Teaching

Various theoretical and practical courses are provided to students. These include basic immunology lectures for medial, biomedical, biochemistry 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) is an interdisciplinary institution within the Medical Faculty of the University of Würzburg and it is part of the Research Centre for Infectious Diseases (ZINF). It also accommodates the young investigator groups of the ZINF. The research at the institute aims to elucidate fundamental principles of infection processes. This is being achieved by studying the molecular aspects of infections caused by a variety of bacteria, parasites and fungi, to identify common strategies employed by the pathogens to interact with host cells and the immune system. While the majority of research at the institute focuses on basic research, several important clinically related projects are performed in collaboration with the University Clinics, ZINF and IZKF.

Main Research Interests

The main research interests at the institute are related to understanding the biology of the pathogens and their interaction with host cells and the immune response. This is primarily achieved by using molecular and cell biological methods and global high through-put approaches, such as genomics (functional genome analysis), proteomics (protein expression analysis) and bioinformatics as well as high-throughput sequencing of RNA with the aim of understanding the infection process from a new global viewpoint.

RNA biology of bacterial infections
(J. Vogel)

Next generation sequencing technologies have enabled approaches such as RNA-seq for the global identification of non-coding RNAs in prokaryotes and eukaryotes, revealing that these molecules are much more diverse than previously thought. The Vogel group are focusing on the identification and functional analysis of noncoding RNAs that play an important role in host-pathogen interactions and the immune response. This includes the characterisation of small regulatory RNAs in bacterial pathogens and long noncoding RNAs in eukaryotic host cells. In addition, they are using global approaches to study RNA binding proteins in bacteria and their role in virulence.

Immunological and cell biological studies of Leishmania pathogenicity
(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 yeast *Candida albicans* is a harmless commensal in the digestive tract of most healthy people, but it can also cause superficial infections of the mucosae as well as life-threatening systemic infections, especially in immunocompromised patients. The Morschhäuser group is investigating how *C. albicans* adapts to different host niches and changes in its environment. They are especially interested in the elucidation of signalling pathways that control morphological switches and virulence gene expression and of genetic alterations that are responsible for the evolution of variants with novel phenotypic traits.

Pathogenic enterobacteria and probiotic Escherichia coli
(T. Oelschlaeger)

An early and often essential step in the establishment of a bacterial infection is the adhesion to host cells. The Oelschlaeger group is focusing on identifying bacterial adhesins and their corresponding eukaryotic receptors. Additionally, substances including phytopharmaceuticals with unknown modes of action are being tested for their ability to inhibit bacterial adherence and invasion of host cells. The probiotic *E. coli* strain Nissle 1917 has been licensed as a drug and they have shown that it interferes with the adhesion and invasion of pathogenic bacteria. Another research focus is the elucidation of the causative molecular mode(s) of action of this probiotic *E. coli* strain.

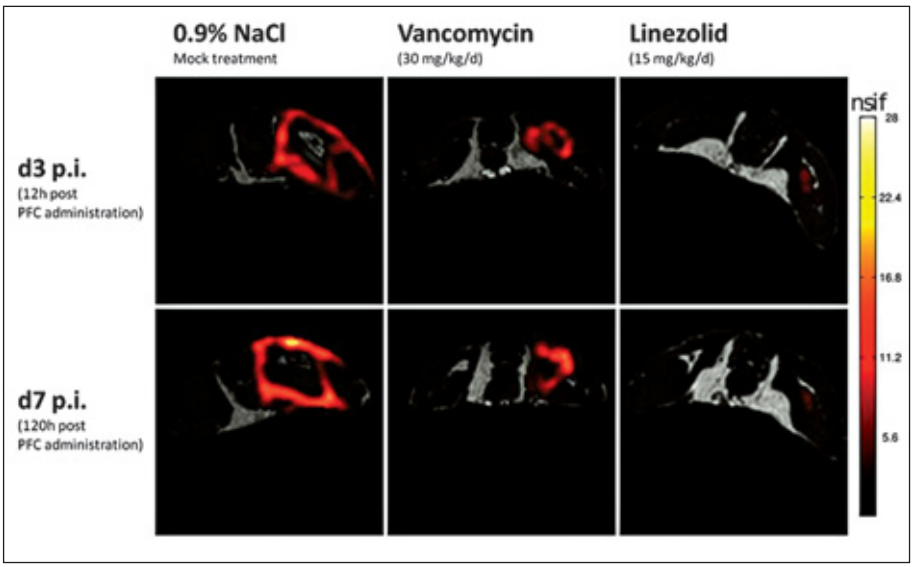

Fig. 1: Magnetic-Resonance-Image of a S. aureus infected mouse thigh treated with different antibiotics.

Virulence and resistance mechanisms of pathogenic staphylococci
(K. Ohlsen)

Staphylococcus aureus is currently one of the most important nosocomical pathogens. The Ohlsen group is interested in understanding the molecular mechanisms involved in its virulence and resistance to antibiotics. One focus is the elucidation of the function of protein kinases and corresponding phosphatases. In addition, they are developing *in vivo* imaging technologies to visualise the infection process and host defense mechanisms *in situ*. Furthermore, they are developing strategies to combat this pathogen including antibody-based therapy approaches and the search for new targets and drugs.

Molecular biology of pathogenic staphylococci
(W. Ziebuhr)

Staphylococcus aureus and *Staphylococcus epidermidis* are common causes of health care-associated (nosocomial) infections which often affect immunocompromised patients carrying medical devices. The Ziebuhr group works on factors and processes contributing to the establishment of staphylococci as pathogens in the hospital environment. Their main research interest is to team basic research with public health by covering epidemiology, genetics and the molecular biology of staphylococci.

RNA metabolism in host cells
(A. Eulalio)

A proper RNA metabolism is essential to a number of host cell functions and therefore it is not surprising that pathogens have evolved sophisticated mechanisms to subvert these pathways for their own benefit. The research within the Eulalio group focuses on determining the impact of bacterial infections on the RNA metabolism of the host cell, and the reciprocal effect of host RNA regulation on the life cycle of pathogenic bacteria. A major research focus has been on human and mouse microRNAs. To achieve this they are using automated microscopy coupled with high-throughput screening approaches of RNA libraries, as well as RNA-seq.

Teaching activity

The scientists at IMIB teach undergraduate and master students from medicine, biology and food chemistry, which include both lecture-based and practical courses. 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, pathogenicity and immunology, as well as seminars on current topics of Infection Biology, in addition to hosting internships. The institute also 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.

AUSGEWÄHLTE PUBLIKATIONEN

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2.14 Institute of Pharmacology and Toxicology, Chair of Toxicology

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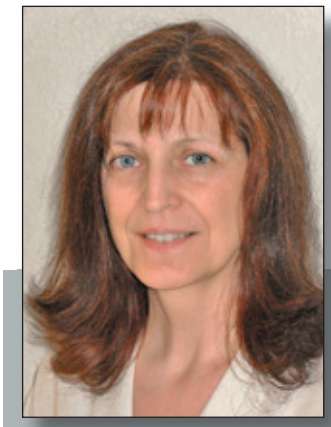

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Mission and Structure

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 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. Four research groups are led by the University Professor Dr. Helga Stopper, the Associate Professor Dr. Wolfgang Dekant, and the Research Associates PD Dr. Angela Mally and PD Dr. Nicole Schupp. Five postdocs and on average 15 Ph.D. students with degrees in chemistry, food chemistry, biology, pharmacy, and medicine accomplish the experimental work, supported by about an equal number of technicians.

Major Research Interests

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 elaborate statistical analysis as well as kinetic modeling.

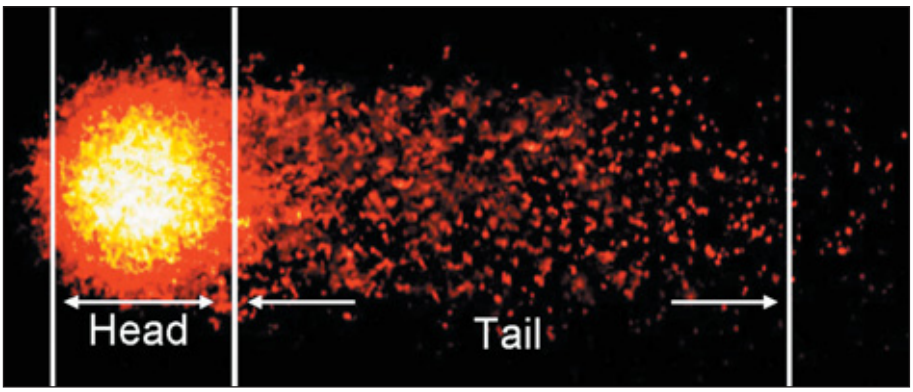

Fig. 1: "The Comet Assay": DNA fragments induced by a genotoxic agent migrate in an electric field out of the cell nucleus (Head) into a Tail.

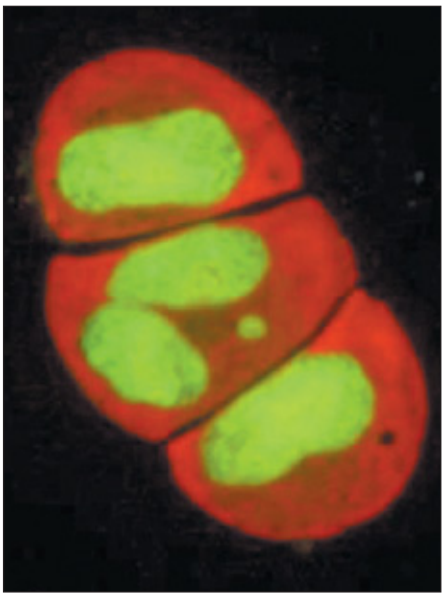

Fig. 2: "The Micronucleus Test": Chromosome damage is indicated by the presence of a DNA-containing fragment in the cytoplasm of the bi-nucleated cell in the middle of the three cells.

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 B_1), heat-derived products (acrylamide, furan), migrants from polymers and phytoestrogens. 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 appr. 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 for Experimental Biomedicine, the SFB688, 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, D. Calebiro, C. Hoffmann; also Bio-Imaging Center/ Rudolf Virchow Center)

Communication between cells occurs through signaling molecules like hormones or 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“. This approach enables us to analyze the speed and localization of signals and receptor even at the level of single molecules in isolated cells and *in vivo*. We have recently succeeded in precisely characterizing the dynamics and localization of prototypical G protein-coupled receptors on the cell surface at the single molecule level. Furthermore, we study the sustained signal transduction by G protein-coupled receptors at the endosomal compartment.

Phosphatases and Cellular Motility

(A. Gohla; also Rudolf Virchow Center)

We have discovered a new class of human phosphatases that play major roles in regulating cellular metabolism and the cytoskeleton. These enzymes may represent novel targets for the development of drugs against cancer and cardiovascular diseases. Using biochemical and cell biological methods, we study their regulation and substrates. We further investigate their (patho)physiological functions in gene-deficient mouse models.

The Effects of Bacterial Toxins

(A. Iliev, 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 G-protein-coupled receptors. In collaboration with chemists we develop selective ligands for

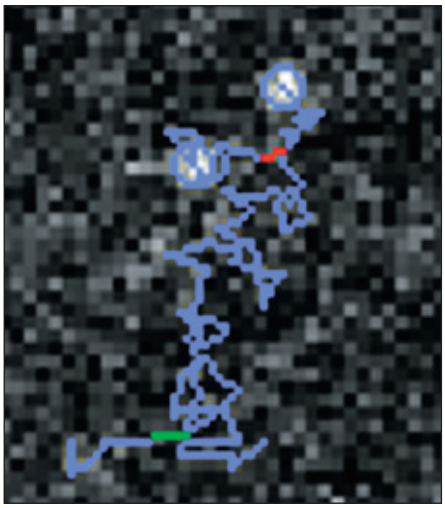

Fig. 1: State-of-the-art single molecule microscopy reveals transient interactions of two G protein-coupled receptors on the cell surface.

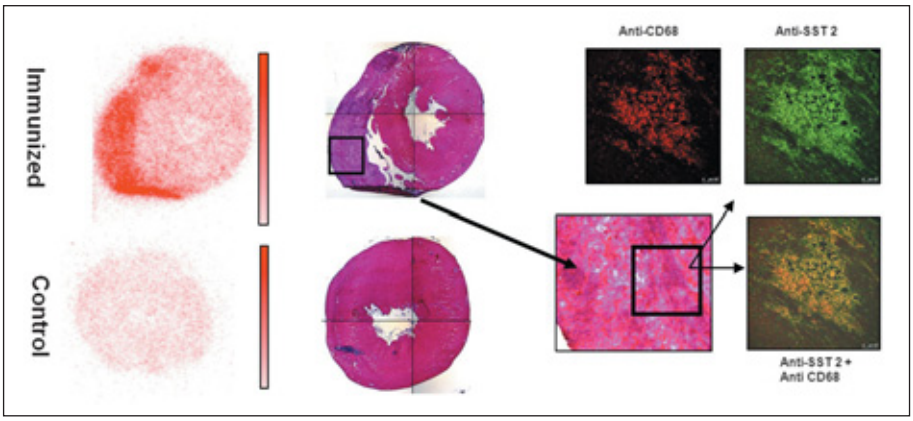

Fig. 2: Left and Middle: Autoradiograms and histological stains of inflamed rat hearts (upper panels) and of control animal hearts (lower panels). Right: Enlargements of the inflamed rightventricular myocardium show the colocalization of inflammatory cells and SST-2 receptors.

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. Based on patient samples, transgenic mouse models and freshly isolated primary cells, we investigate genes and mechanisms that contribute to heart failure and dilatation. A number of biochemical mechanisms that play an important role in heart failure, but also in vascular diseases such as atherosclerosis, have been identified over the last few years. Currently, we are exploring strategies to interfere with these signaling pathways in order to find new targets for heart failure therapy.

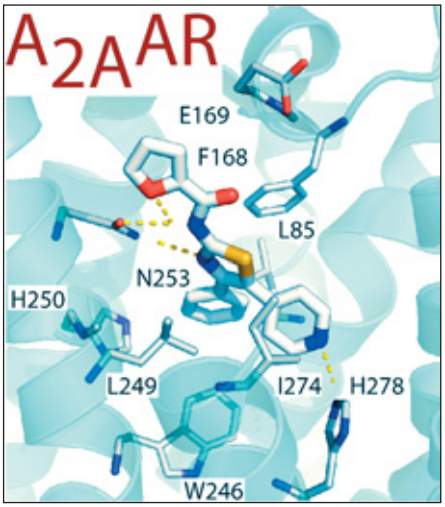

Fig. 3: A novel adenosine receptor antagonist docked into the ligand binding domain of the A2A adenosine receptor.

Receptor-Antibodies in Heart Failure/ Myocarditis
(R. Jahns, together with the Comprehensive Heart Failure Center and the Rudolf Virchow Center)

Stimulating auto-antibodies against the β1-adrenergic receptor can be detected in about a third of patients with dilated or inflammatory heart muscle damage; the cardiovascular mortality-risk of antibody-positive patients is increased about 3-fold. By immunization of rats we have generated corresponding animal models. In several BMBF-funded projects, we investigate whether formation of such antibodies in patients is triggered by ischemic (myocardial infarction) or inflammatory heart muscle injury (acute myocarditis), and how such stimulating antibodies can be therapeutically neutralized with cyclic peptides. For further development and clinical phase I and II studies we have founded the Biotech company Corimmun.

Role of microRNAs in Neuropsychiatric and Cardiovascular Diseases
(L. Hommers, also Department of Psychiatry and Interdisciplinary Center for Clinical Research)

Comorbidity of cardiovsacular and neuropsychiatric diseases results in a significant excess mortality. We aim to identify microRNAs regulating candidate genes of neuropsychiatric diseases, predominantly those in G-Protein coupled pathways, and investigate their mechanisms of action and test their relevance in on-going clinical studies of the Comprehensive Heart Failure Center.

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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Tasks 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 responsibilities are the investigation of deaths, post-mortems, clinical forensic medicine, assessing fitness to drive, forensic trace analysis, paternity testing and forensic-toxicological analysis of body fluids and pieces of evidence.

Apart from the Board Director, the academic staff of the University of Würzburg Institute of Legal Medicine consisted of 1 consultant (Oberarzt), 3 senior house officers (Assistenzärzte), 2 biologists and 1 toxicologist in 2011. 9 of the 19 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 practice-oriented medical field, the daily activities and tasks determine the scientific issues to be addressed. Scientific forensic research concentrates on the assessment of findings, the evaluation of evidence, the reconstruction of events and the development of valid assessment criteria. Thus, 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.

Current key research areas are the post-mortem optical behaviour of the skin, the expression of glucose transporters in craniocerebral trauma, the determination of the post-mortem interval by means of bones as well as the detection and documentation of blood traces using infrared optical imaging techniques.

Optical behaviour of the skin
(M. Bohnert, V. Sterzik)

To analyse the optical behaviour of the skin after death, the post-mortem decomposition processes (putrefaction and autolysis) are systematically recorded by serial measurements of spectral reflectance and evaluated in collaboration with the Institute of Mathematics of the University of Würzburg (Prof. Dr. Borzi). Before, a mathematical skin model has already been developed, by means of which the scattering and absorption of light in relation to the scattering structures (cell nuclei, mitochondria, collagen fibres) and the absorbers (haemoglobin, melanins, bilirubin) can be calculated. This skin model is to be improved by these 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.

Expression of glucose transporters in the brain in the presence of craniocerebral trauma
(M. Bohnert)

In a collaboration project between the Hospital and Polyclinic for Anaesthesiology (Prof. Förster) and the Institute of Legal Medicine the issue is investigated whether it is possible to demonstrate the sodium-dependent glucose transporters SGLT1, SGLT2 as well as the uniporters GLUT1 and GLUT3 in human brain tissue of decedents undergoing forensic autopsy because of craniocerebral trauma or asphyxiation. Further issues to be investigated are the chronological course of the expression of the various forms of sodium-dependent glucose transporters after traumatisation and whether the volume and distribution of SGLT1, SGLT2, GLUT1 and GLUT3 as well as their relationship to each other provides information as to the vital or post-mortem origin of a trauma and its survival time. The results obtained from the human brain specimens are compared with the results from an in vitro trauma model with endothelial cells of human brain. The objective is to generate an expression pattern for glucose transporters depending on the time and cause of death.

Determination of the post-mortem interval of bones
(K. Jellinghaus, M. Bohnert)

The forensic and anthropological assessment of bone finds is not only concerned

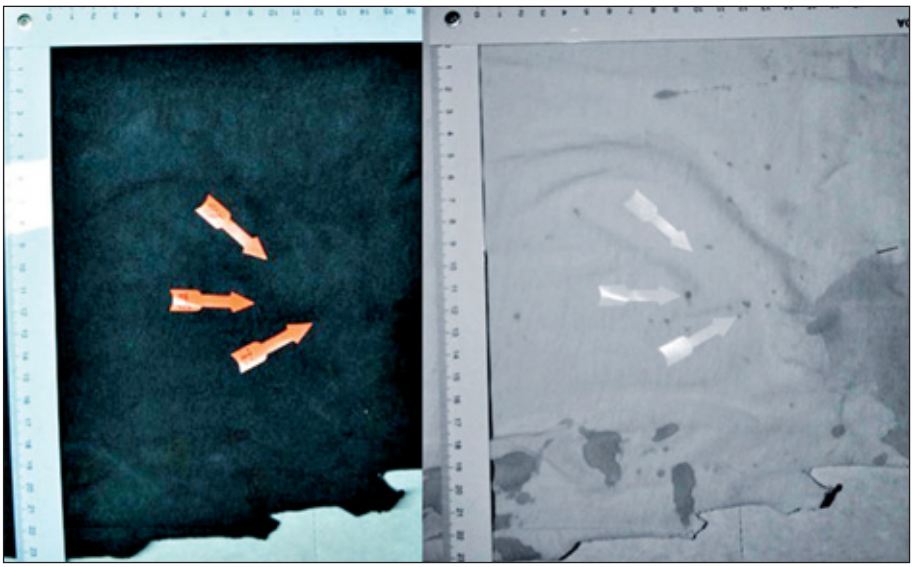

Fig. 1: Blood spatter stain on dark clothing under daylight (left) and infrared light (right).

with questions such as sex, age, presence of trauma and individual features but also the time since death. This is of significant importance under legal aspects, as apart from genocide and murder a crime becomes barred by the statute of limitation and can no longer be prosecuted after 3, 5, 10, 20 or 30 years depending on the punishment provided for in the law (Section 78 Criminal Code). Usually the Criminal Investigation Department investigates bones up to a post-mortem interval of 30 years or less. However, due to the different preservation state of bones or bone parts it is often difficult to make a precise statement with regard to the post-mortem interval. A bone's state of preservation is essentially influenced by the ambient conditions, which are ultimately more important for the condition of a bone than the time since death itself. Due to these diagnostic uncertainties the age of bone finds is often over- or underestimated. This in turn has consequences for the investigations. The aim of the present study is to extend and improve the methodological spectrum to estimate the post-mortem interval of human bones. For this purpose, the conventional methods to estimate the post-mortem interval are checked by means of bones with an exactly known post-mortem interval and used together with new techniques (fluorescence, histology, molecular degradation, densitometry) to develop low-cost routine parameters for the medico-legal routine which can be used for unknown bone finds. Collaboration partners are the Institute for Diagnostic and Interventional Radiology (Prof. Dr. Bley) of the Würzburg University Medical Centre and the Institute of Anthropology of Freiburg University (Prof. Dr. Wittwer-Backofen).

Infrared optical imaging of latent blood traces

(V. Sterzik, M. Bohnert)

In collaboration with the Institute of Legal Medicine of the University of Munich techniques for optical visualization and documentation of latent and small to very small blood traces on a dark background have been developed. Especially the small blood traces forming during dynamic courses of events are highly important for the reconstruction of a crime, especially if they can be demonstrated on the clothing of the persons involved in the event. By using lamps emitting light in the near infrared region in combination with filters it is possible to make such traces visible without destroying them, so that they are available for molecular biological analysis. With a modified single-lens reflex camera these traces can also be documented photographically (Fig. 1).

Teaching

Forensic science is taught to students of medicine in a main lecture held over 2 semesters, a laboratory course and a compulsory optional subject. In the 6th semester, fundamentals are taught, in the 7th semester special topics are addressed and students do a course on post-mortems. Fundamentals include the fields of thanatology, forensic traumatology, medical law, forensic alcohology, forensic genetics and forensic toxicology. In the 7th semester, the post-mortem examination, traffic medicine, clinical forensic medicine and forensic case work are covered. In the laboratory course, students learn how to perform a post-mortem examination. An aspect regarded as especially important in teaching is to make students aware of forensic aspects in their clinical work. Those particularly interested in the field can attend the compulsory optional subject "Medical Criminalistics".

In a well-attended lecture, legal medicine is also presented to students of law and biomedicine. Junior lawyers (between the first and second state examination) are regularly instructed on the effect of alcohol and drugs in road traffic with a scientifically monitored drinking test. Regular training courses are also held for the police and the German Armed Forces.

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2.17 Institute of Pathology

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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 haematological malignancies. The diagnostic expertise in this field and the scientific achievements are internationally visible.

Major Research Interests

Research in Hematopathology and Consultation Center for Hematological Malignancies
(A. Rosenwald)

The Reference Center for haematological malignancies 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)'. Prof. Rosenwald's group has a major research focus on the molecular pathogenesis of malignant B- and T-cell lymphomas as well as of multiple myeloma. Genetic and novel sequencing approaches are used to decipher molecular alterations in lymphoid neoplasms. In 2012 and 2013, novel biologically and clinically relevant molecular alterations could be described (e.g. in diffuse large B-cell lymphomas and Burkitt lymphomas). 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) and the local Clinical Research Unit 216 'Signalling in Multiple Myeloma'.
Prof. Geissinger's group is interested in the molecular and immunophenotypic characterization of T-cell lymphomas and cutaneous lymphomas.

Transcriptional Control in T-Lymphocytes
(E. Serfling)

Prof. Serfling was the speaker of the SFB/Transregio (Collaborative Research Center) Würzburg/Mainz/Berlin, TRR52, of the German Research Association (DFG) with the topic 'Transcriptional programming of individual T-cell populations'. The research work of his group which was also supported by the Wilhelm-Sander Foundation and the German Cancer Foundation dealt with the role of the inducible transcription factor NFATc1 in lymphocyte differentiation and function. Using several mouse models it was shown that NFATc1 - the most prominent NFAT factor in activated peripheral lymphocytes - is critically involved in the generation of autoimmune diseases and the rejection of transplanted organs (e.g. hearts). Current studies shall elucidate the target genes of NFATc1/αA, the strongly inducible NFATc1 isoform, and of further NFAT factors. These studies shall identify the gene network(s) controlled by NFATc1 and, in addition, the nuclear multi-protein complexes in which NFATc1 is organized. One final goal of these studies is the selective inhibition of NFATc1/αA induction in (pathogenic) lymphocytes.

Molecular and Cellular Immunology
(F. Berberich-Siebelt)

Within the field of 'Molecular and Cellular Immunology' the major research is focused on $CD4^+$ T cells. Momentarily, emphasis is especially placed on the central role of the family of NFAT transcription factors for activation and function of T helper and regulatory T cells. It became evident that the level and ratio of expression of the individual NFAT members and their isoforms as well as their posttranslational modifications (among them the sumoylation of NFATc1/C) are decisive for the direction of differentiation. A vision - due to the partly divergent functions - is to target them individually during therapy; this could lead to immunomodulation instead of general immunosuppression. Therefore, the impact of NFAT in general, but also of the individual members/isoforms is analysed for different disease models. This is mostly performed in animal models making use of our various NFAT-deficient mice, but always also in cooperation with the Reference Center for haematological malignancies and funded by the DFG, IZKF, Wilhelm-Sander- and Thyssenstiftung.

Human Immunity to Cancer
(S. Brändlein)

The experimental work of this research group is focused on human innate immunity to cancer in which natural antibodies play an important role. Their targets are 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 eliminate malignant cells *in vitro* and *in vivo* by inducing different

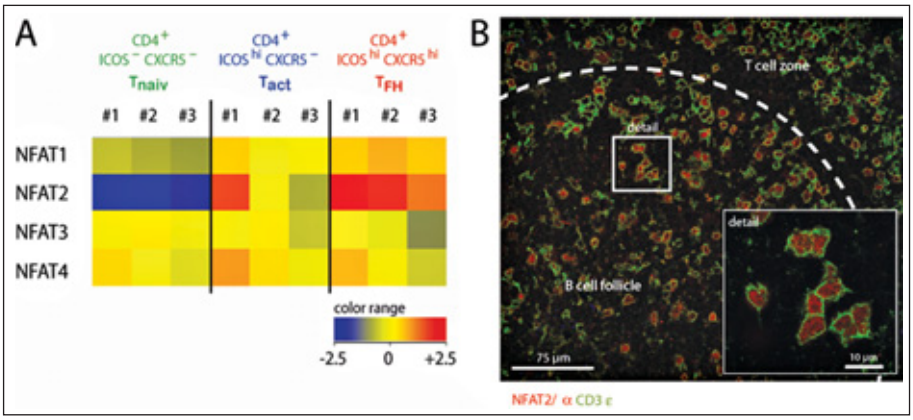

Fig. 1: NFAT2 (NFATc1) is especially well detectable in follicular T cells. (A) Microarray-analysis of FACS-sorted naïve, activated, and follicular T cells of KLH-immunized mice. (B) Histological analysis of a chronically inflamed human tonsil.

cytotoxic mechanisms. The combination of effectiveness/potency, safety, and new mechanisms for killing cancer provides a very promising profile for the therapeutic use of natural human antibodies for cancer.
In collaboration with an Australian company, some of the identified antibodies are developed into clinical products. The natural human IgM antibody PAT-SM6 targeting GRP78 has been shown to have potent anti-cancer properties in a large number of laboratory and animal studies. Currently, PAT-SM6 shows potential therapeutic benefit in the ongoing Phase I/IIa clinical trial in patients with relapsed and refractory multiple myeloma. Another Phase I clinical trial to evaluate PAT-SM6 as a therapy for melanoma was also successfully completed. The ongoing scientific work is concentrated on the antibody-induced cytotoxicity mechanisms and the preclinical development of additional tumor specific IgM antibodies.

Neurooncology and Neurodegeneration
(C. Monoranu)

The research in the Department of Neuropathology is currently focused on neurodegenerative diseases. Within the project "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" funded by the IZKF, 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 was evaluated. Early affected regions such as the hippocampus showed differences in gene expression compared to more resistant regions such as the cerebellum. Candidate genes responsible for the development of neurofibrillary changes were identified. The gene expression analysis will be continued and complemented by epigenetic studies and proteomics with the aim to provide insight into specific molecular events underlying the pathogenesis of Alzheimer disease.
In the neurooncological field we focused on the identification of prognostic markers for ependymomas, molecular features of glioblastomas and the role of the T-cell mediated immunity on the clinical outcome of medulloblastoma patients.

Teaching

The institute of pathology is responsible for teaching pathology as part of the medical curriculum of the Würzburg Medical School. Specifically, 3 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. Raabe´s 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)*.

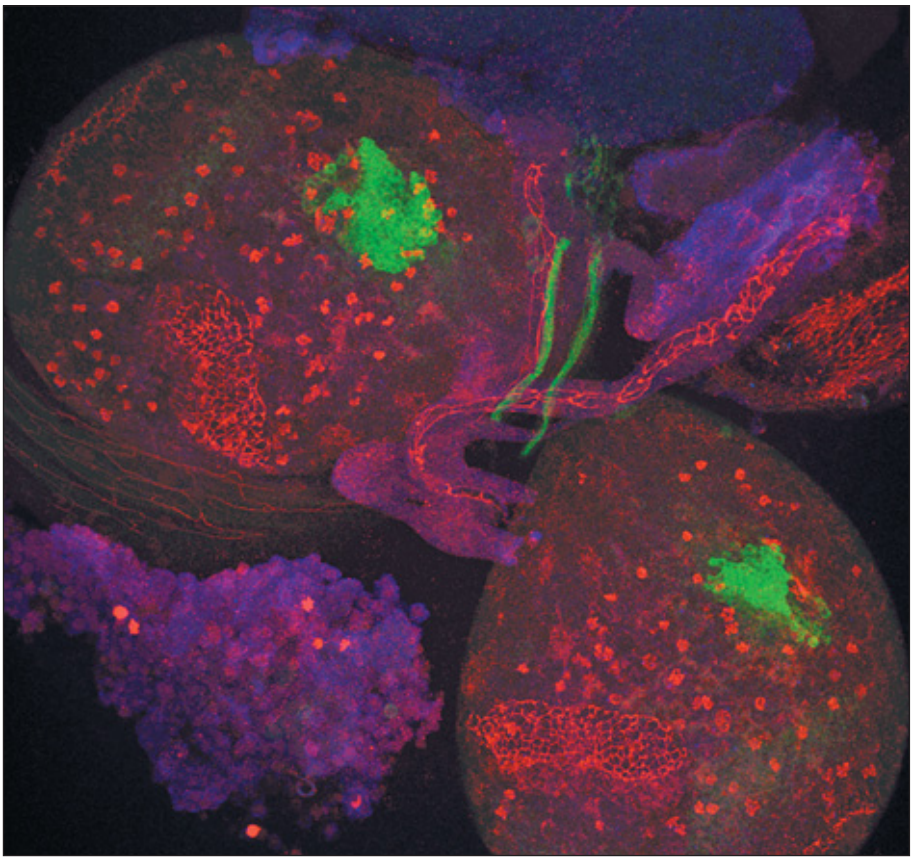

Fig. 1: Larval brain of Drosophila: Neural progenitor cells in both brain hemispheres are marked in red. Neurons of the mushroom bodies, which are involved in learning and memory, are labelled in green (Figure: Juliane Melzer).

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. On one hand, 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. In collaboration with Prof. Gallant (Biochemistry & Molecular Biology) we have characterized a new nucleolar protein, which is transcriptionally controlled by Myc, and is required for ribosome biogenesis and cell growth selectively in neural progenitor cells. In cooperation with external partners, a novel function of one member of the p21-activated kinases (PAKs) in neural progenitor cells was described. A further focus of our research lies at the neurophysiological level. In collaboration with clinical groups (Dr. Fischer, Psychiatry; Dr. Kittel, Physiology II) we are analysing the function of the kinase RSK in synaptic plasticity. Mutations of the human RSK homologue are associated with mental retardation but the underlying molecular mechanisms are poorly described so far. The function of RSK and protein kinase CK2 in the molecular circadian oscillator are investigated in a project within the newly established Collaborative Research Center SFB1047 ("Insect timing"). 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.

Teaching

The teaching activities relate to the research activities of the MSZ groups. 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 microscopy. 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, biochemistry and biology. Located in the Würzburg Biocenter, the Institute belongs to the University of Würzburg School of Medicine.

Major Research Interests

Medical genetics

As an application of human genetics, medical genetics translates scientific insights from basic human genetic research into the clinics. Preventive and predictive medicine are an important focus. Medical genetics deals with a large spectrum of inherited disorders and familial predispositions. Interactions with patients and their families are established during genetic counselling sessions. 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. The Center for Muscular Disorders of the German Society of Muscular Diseases (together with the Department of Neurology) provides diagnostic, counselling and social services for patients and families affected by muscle disease. The Center for Familial Breast and Ovarian Cancer (together with the Department of Gynecology) takes care of patients and families affected by or at risk of familial breast and ovarian cancer. Services include genetic counselling and testing as well as provision of medical and preventive care. In addition to neuromuscular, neurodegenerative and familial cancer diseases, the medical genetics group studies the molecular pathology of craniosynostoses and developmental disorders.

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.

Molecular genomics

(E. Klopocki)

The research focus is on pathogenesis of congenital malformations. In recent years genomic copy number variations (CNVs) were shown to be responsible for phenotypic variability and furthermore to be causal for congenital malformations. Clinically relevant CNVs affect coding regions (genes) as well as non-coding sequences with regulatory function. In addition to congenital limb malformations the group investigates craniofacial malformations within the framework of the BMBF-funded consortium FACE (Forschungsverbund ausgewählter craniofacialer Entwicklungsstörungen). A broad range of methods is applied, including microarray-based comparative genomic hybridization (array CGH) and next generation sequencing to detect CNVs, point mutations and small insertion/deletions, respectively. For further functional characterization of candidate genes and the phenotypic consequences of CNVs zebrafish (*Danio rerio*) was established as model organism (Fig. 1).

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, the Fanconi anemia (FA) family of genes. Recently, the group participated in the identification and characterization of six novel of these FA genes (*FANCI, FANCJ, FANCN, FANCO, FANCP and FANCQ*). As a partner of one of the high-pe-

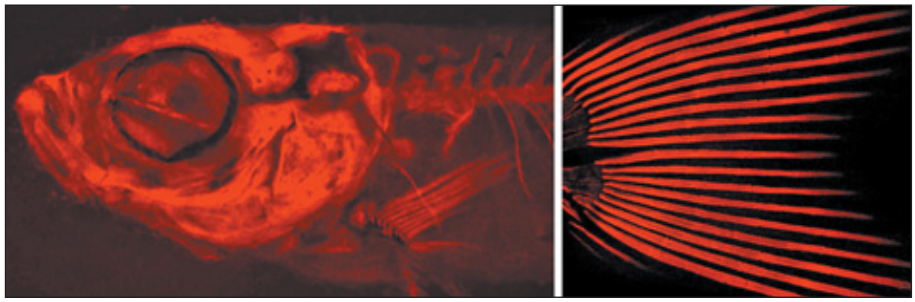

Fig. 1: Bone staining of skull and tail fin in zebrafish.

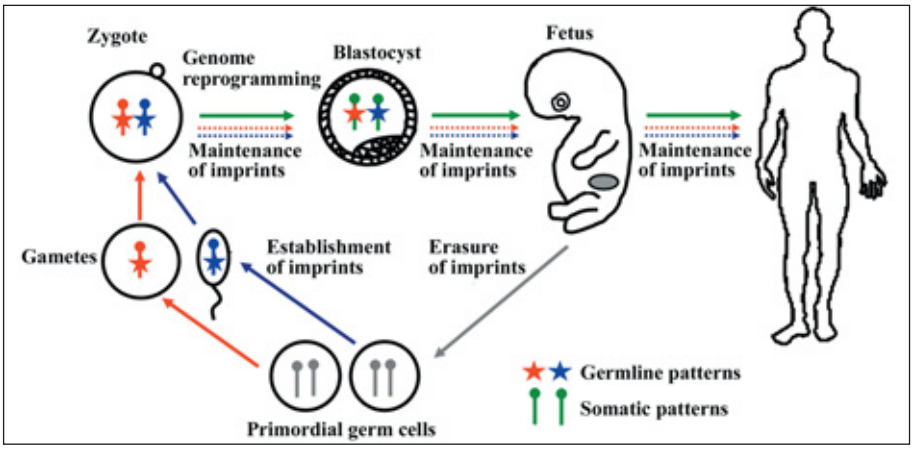

Fig. 2: Epigenetic reprogramming cycle. In the fetal germline all DNA methylation patterns are erased (gray line) and then paternal (blue) and maternal (red) methylation imprints are established during gametogenesis. The two germline genomes that are combined at fertilization undergo parent-specific 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.

netrance breast and ovarian cancer genes, *BRCA2*, *FANCN/PALB2* plays, in case of biallelic mutations, a significant role in the emergence of embryonic tumors. Monoallelic mutations of *FANCN*, but also of *FANCJ* or *FANCO* predispose for breast and ovarian cancer. Collaborating with groups from Germany and abroad, the Schindler laboratory has made major contributions to cell genetic and cellular aspects of FA and other caretaker gene syndromes. 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 roles. Current efforts are directed at identifying new members of the genomic maintenance gene networks, elucidating their function, and studying their phenotypic effects.

Cytogenetics
(M. Schmid)

Using classical and molecular cytogenetic methods, this group studies the structure, evolution and pathology of chromosomes. Comparative cytogenetic analyses of fish, amphibians, reptiles, birds and mammals (including the human species) disclose the understanding of the chromosomal mechanisms of vertebrate evolution. Prof. Schmid serves as Editor of the journals *Cytogenetic and Genome Research, Sexual Development* and *Molecular Syndromology*, and the book series *Genome Dynamics* and *Monographs in Human Genetics)*.

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 (Fig. 2). Stochastic and/or environmentally induced errors (epimutations) in this highly coordinated process may contribute to human disease. The group 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. Another project searches 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.

Teaching

The medical school curriculum includes a lecture course entitled “Clinical Human Genetics” which is taught in the 6th semester, together with an interdisciplinary course on “Disease prevention”. Medical students can choose human genetics as an elective during their rotating internships, with emphasis on genetic diagnosis, dysmorphology and genetic counselling. In addition to teaching medical students, the Institute also offers courses to students of biomedicine, biochemistry 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.Sc. or Ph.D. degrees within one of the research groups of the Department.

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3 University Hospital
3.1 Introduction

In 2012 the members of the Executive Committee at the University Hospital of Würzburg changed: the CEO Renate Schülke-Schmitt retired after more than two decades of significant contribution to the interests of the University Hospital and the Medical Faculty. For her merits she was honored with the Carl-Caspar-Siebold Medal of the University Hospital of Würzburg; from the University of Würzburg she received the Bene-Merenti Medal in Gold. Further honors at state and federal level followed. Regrettably she died on November 30, 2012, at the age of 64 years. Renate Schülke-Schmitt left her successor Anja Simon who took over in August 2012 a well-ordered house.

Certifications – Quality Management

In the reporting period 2012/2013 various certifications were in the focus of the activities of the University Hospital: based on legal requirements the University Hospital aimed at a certification to the KTQ procedures ("cooperation for transparency and quality in health care").

The KTQ certification was next requirement for further financial support of the Comprehensive Cancer Center Mainfranken (CCC) by the Deutsche Krebshilfe (German Cancer Aid). The audit was successfully completed end of 2013 and thus marks an essential prerequisite for the upcoming 2014 recertification of the Cancer Center.
It was also in 2013 that the re-certification of the Oncology Center of the University Hospital took place; situated under the umbrella of the CCC the Oncology Center comprises the Breast-, Skin-, Head and Neck Cancer Center as well as the Interdisciplinary Center for Colorectal Cancer and Pancreatic Cancer and the Center for Neuroendocrine Cancer. In 2013 also the Center for Neuro-Oncology received a DKG certification and became a member of the Oncology Center. Further certifications in 2012/2013 followed: the accreditation of the Histological Laboratory of the Department of Dermatology, the accreditation of the Stemm Cell Therapy, the certificate "Excellent for Children" of Pediatric Surgery and the accreditation as a National Schock Trauma Center. Successful certifications and surveillance audits in accordance with DIN ISO 9001 have taken place in the Stroke Unit, in the Division of Neuroradiology, in the Interdisciplinary Center for Colorectal Cancer and Pancreatic Cancer as well as in the Department of Dermatology in 2008.

The implementation and further development of a quality and clinical risk management are part of a consequent corporate strategy based on patients' contentedness and safety. In all bed leading clinics of the University Hospital risk audits were held in 2012. The auditors identified and assessed interviews, conversations and observations of the strengths and potential risks involved in the patient-related processes. They hereby focused on the aspects of patient care and education, organization and documentation. Additionally a software-based reporting system for near-fault CIRS was rolled out within the University Hospital as a continuous risk management tool in 2013.

Cooperations

The rapidly changing environment in healthcare requires close cooperation with other healthcare providers. Thus the basis for networking has to be created to ensure modern, patient-oriented, close to home and intersectoral care. The University Hospital maintains several cooperations in various fields, i.e. with teaching hospitals or in the context of other networkers and interdisciplinary centers.

In 2013 the recently founded Interdisciplinary Bank of Biomaterials and Data Würzburg (ibdw) was put into operation. As one of five national sites Würzburg received funding in the millions from the Federal Ministry of Research and Development. The Bank of Biomaterials helps to improve the detection and treatment of diseases in the sense of "personalized medicine".

Further cooperations exist in the field of professional training on-the-job for medical and nursing staff, medical care, apprenticeship and education as well as industrial cooperations.

During the reporting period a new agreement was concluded with the Hospital Main-Spessart for close cooperation within the regional Heart Attack Network Mainfranken, the Cardiac Catheter Laboratory, Neurology and the improvement of Vascular Surgical Care in the district of Main-Spessart. The Director of the Department of General, Visceral, Vascular and Pediatric Surgery at the University Hospital was put in charge of the medical management in surgery in Marktheidenfeld and Lohr. In Karlstadt a new section for Hand and Plastic Surgery was established under the management of the Director of the Department of Trauma, Hand, Plastic and Reconstructive Surgery at the University Hospital.

An Interdisciplinary Neurogerontopsychiatric Day Care Unit was put into operation in 2011 focusing on the treatment of mental diseases with neuro-degenerative background. This unit is operated by the Departments of Neurology and Psychiatry at the University Hospital and the Geriatric Rehabilitation Unit of Bürgerspital.

Due to a lack of comprehensive expert care in stroke units, the Trans-Regional Network for Stroke Intervention with Telemedicine (TRANSIT-Stroke) was founded in 2013. It aims to sufficiently cover the medical supply in stroke-units. Stroke-Patients in rural areas of Upper and Lower Franconia should be best possibly cared for. Twelve regional hospitals therefore closely cooperate by using high tech equipment. The new network is coordinated by the Department of Neurology of the University Hospital.

Reorganizations

The University Hospital of Würzburg is faced with a challenging situation: on one hand it has to permanently generate growth in research, medical care and external funding, on the other hand it is very limited in its bed capacity. Thus goal in the new complexes of ZOM and ZIM was to create central patient management units for an optimized planning and organization of the patients' entire stays. This model allows more flexibility and efficiency in bed usage as well as a regular assignment of beds according to the likely requirement of each individual department.

In this context the structural modification of the intermediate-care area at the Department of Thoracic and Cardiovascular Surgery was put forward: a steady increase in

Clinics with Policlinics	19
Autonomous Policlinics	3
Clinical Institutes	4
Affiliated Vocational Schools	7
Employees	5.721
among: Medical Service	821
Nursing Service	1.265
Medical Technical Service	1.202
Arranged Beds	1.430
Average length of stay (care days)	6,5 days
Inpatients	55.257
Outpatients	209.508
Provided care days	409.968
Income in Mio. Euro	482
Catchment Area: Bavaria	82 %
Catchment Area: Baden-Württemberg	11 %
Catchment Area: Rest Domestic and Foreign	7 %

Facts & Figures - University Hospital Würzburg in 2012

performance demanded further bed capacity which could not be covered elsewhere in the portfolio. Construction and completion are planned for 2015.

Construction activities

During the reporting period the planning of a separate research building for the German Comprehensive Heart Failure Center Würzburg (DZHI), an interdisciplinary center for research and medical care, was advanced. Construction should be completed by the end of 2016. The first delve of the spade took place in January 2014. Under the umbrella of the DZHI a variety of clinical disciplines work closely together with facilities for patients' and basic research.

The urgently needed new building of the "Kopfklinik" (Departments of Neurology, Neurosurgery, Neuroradiology, Ophthalmology, Ear-, Nose- and Throat-Surgery and Radiation Oncology) was taken forward with great commitment in the years 2012-2013. The Ministry of Science issued the contract for the first construction phase in 2013. Completion of construction work is planned for 2020.

The Dental University Hospital of Würzburg celebrated its 100th anniversary in 2012. At the beginning of the 20th century a new building for dentistry was necessary to face the rising number of students in dentistry. The Dental Hospital was completed in 1912 and inaugurated by the former Bavarian King Ludwig 3rd. It has been situated in the heart of Würzburg and used for student education, research and patient care for around 50 years in almost unchanged form. Some expansions took place in the 1960s. In July 2012 the ultra-modern and high tech complex with building costs of 75 million euro was completed after 14 years of profound spatial transformations. Nowadays the Dental University Hospital of Würzburg is on a top level concerning therapy and medical technology. With the recently established Head and Neck Tumor Center as part of the Comprehensive Cancer Center Mainfranken (CCC) the catchment area of patients extends far beyond the boundaries of Würzburg.

The revision of the 2004 developed mission statement of University Hospital and Medical Faculty was one of several projects in terms of corporate culture and strategy in 2012/2013. A team of different occupational and hierarchical groups has updated its guidelines. Numerous actions and events were offered along the theses with focus on patients in 2012 and on employees in 2013.

Prof. Dr. Chr. Reiners
Medical Director of the University Hospital of Würzburg

3.2 Department of Anaesthesia and Critical Care

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Mission and Structure

The Department of Anaesthesiology annually performs anaesthesia for approximately 31.000 surgical patients. The outpatient and daycare pain center of the department of Anaesthesiology have each 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 those being treated in our Level I trauma center. Each intensive care bed is fully equipped with state-of-the-art bedside monitoring and data management systems as well as for various organ failures. Patients with severe lung injury in the south of Germany can be locally equipped with artificial lung support (ECMO) and transferred to our ICU for further treatment. Over 35 patients are treated annually.
The department further consists of a section for trauma and emergency medicine which is responsible for clinical education as well as research. Doctors of the department staff the Intensiv-Transport-Wagen (ITW) and the Verlegungseinsatzfahrzeug (VEF) for the interhospital transfer of intensive care patients.
The department further provides a modern simulation centre for anaesthesia and emergency cases. An artificial patient equipped with computer technology provides the resource for a realistic training of routine anaesthetic procedures as well as the management of rare emergency events.
The section "Experimental Anesthesiology" (chair: Prof. Dr. rer. nat. C. Förster) forms the foundation of a collaborative basic science research of clinicians and scientists using state of the art molecular research techniques.
In addition to patient care and education of students and residents the department runs a laboratory for the diagnosis of malignant hyperthermia. Malignant hyperthermia is a rare hereditary disorder which might occur quickly and be life-threatening during anaesthesia. The outpatient clinic takes care of about 1500 patients from middle and southern Germany. Individual counseling is offered for susceptible patients as well as for attending physicians.

Major Research Interests

Drug delivery
(N. Roewer, J. Broscheit)

Drug delivery can be optimized by nanocarriers. Nanocarrier-based delivery systems (i) enhance drug delivery to the site of action, (ii) to prevent degradation during transport through the body, and (iii) to improve solubility (e.g. in blood) in order to achieve therapeutic drug plasma levels. Such carrier systems were designed for biogenic, especially plant derived drugs that could not be used for therapeutic purposes due to their chemical properties. The devolopment of drug delivery systems aims to ensure drug release in defined regions of the body at specified time points.

Pain research
(H. Rittner, A. Brack)

The major aim of the research is the improvement of care for patients with acute and chronic pain. One approach aims to enhance drug transport across the perineural barrier of peripheral nerves. This involves the elucidation of the molecular mechanisms regulating the permeability of the barrier. Novel therapeutic strategies for the selective and temporary opening of the barrier are being developed (e.g. molecules interfering with barrier forming tight junction molecules and agonsists for regulatory receptors [LRP-1]). In a further approach novel pronociceptive mediators (e.g. oxydized phospholipids) are being characterized. Innovative strategies aim to selectively target these mediators and thereby decrease pain at the site of inflammation. As part of a research grant of the European Union individual risk factors (e.g. miRNAs) for the development of neuropathic pain syndromes are being evaluated in clinical and animal studies.

Clinical Trials & Evidence Based Medicine
(P. Kranke)

Evidence Based Medicine aims to provide current best evidence based on the results of clinical trials and systematic reviews for clinical decision-making. The facilitation of an evidence based thinking and behaviour in the perioperative medicine is the aim of this group. For this purpose the clinical trial unit, apart from conducting clinical trials in perioperative medicine (Phase II-IV, including registration trials), performs systematic reviews in the field of anaesthesia, pain therapy, palliative medicine, intensive care medicine and affiliated disciplines.

Organ protection
(T. M. Smul, J. Stumpner)

Ischemia-reperfusion injury occurs in multiple patients and scenarios. Clinicians face this issue during emergencies like cardiac arrest and surgical procedures. Perioperative protective strategies, e.g. ischemic and anesthetic-induced pre- and postconditioning are powerful strategies and of enormous interest to facilitate best medical care for our patients. Eliciting the underlying mechanisms of protection and its interaction of concomitant diseases and medical therapy are the focus of our research.

Acute respiratory distress syndrome
(R. Muellenbach)

The acute respiratory distress syndrome (ARDS) is still associated with a mortality rate of 40-60%. Beside the specific therapy of the underlying disease mechanical ventilation is crucial to ensure oxygenation and decarboxylation. However, mechanical

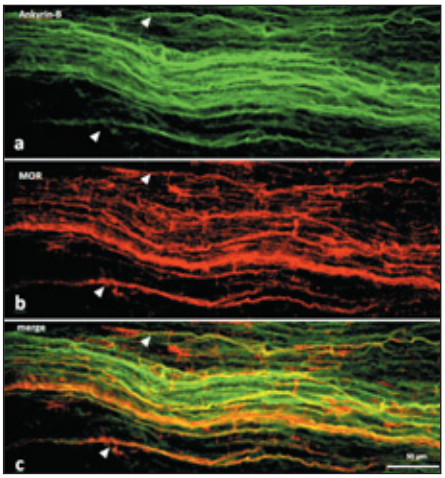

Abb. 1: Opioid receptors in peripheral nerves (longitudinal section): (A) ankyrin B (green): a marker for sensory nerves (B) μ-opioid receptors (MOR, red) as a target for pain therapy in regional anesthesia (C) Arrow: MOR-expressing nociceptive fibers (cooperation with the Institute of Anatomy).

ventilation induces further damage of the lungs. Therefore, lung protective ventilation strategies are used allowing lung healing and recovery. Using experimentally induced ARDS the influence of different ventilation modes and profiles on lung function and inflammation are investigated. In addition, clinical studies evaluating ultraprotective ventilation in ARDS-patients are performed. A special focus of our research is the use of extracorporeal membrane oxygenation (ECMO) in severe ARDS failing conventional ventilation.

Blood-Brain-Barrier
(C. Förster)

The blood-brain barrier (BBB) is formed by the endothelial cells of brain capillaries. These cells interact with other cellular components of the central nervous system (CNS) maintaining a tight barrier with specialized transport systems. Disorders of the CNS, e.g. multiple sclerosis, stroke and dementia are associated with disturbances of the BBB. Our research focuses on the regulatory mechanisms of the BBB and the development of therapeutic strategies. In our projects the role of steroid hormones and their signaling pathways in the BBB are being investigated. Furthermore, injuries of the CNS such as traumatic brain injury or brain tumors lead to the formation of cerebral edema. Here, glucose transporters at the BBB seem to be involved and their role is being elucidated. A further focus aims to enhance drug delivery across the BBB and to selectively enhance drug concentrations at the site of action.

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 and the underlying changes in the vascular endothelial cells 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, in-vitro cell culture experiments and clinical studies, the underlying mechanisms of microcirculatory failure in the liver and intestine and the potential therapeutic interference are investigated.

Trauma management
(T. Wurmb)

The initial diagnostic and therapeutic treatment of patients with multiple trauma is performed by a multidisciplinary team in our level I trauma center. The development of algorithms and operating procedures to provide optimal support for these patients at high risk are performed in clinical studies.

Malignant hyperthermia
(F. Schuster)

The diagnosis of malignant hyperthermia is based on the diagnostic criteria of the European MH Group. It involves an in vitro contracture test, histological examinations and genetic analysis. The research focuses on the development of a minimal-invasive test to the diagnosis of malignant hyperthermia susceptibility and on interactions of clinically applied drugs on skeletal muscle metabolism.

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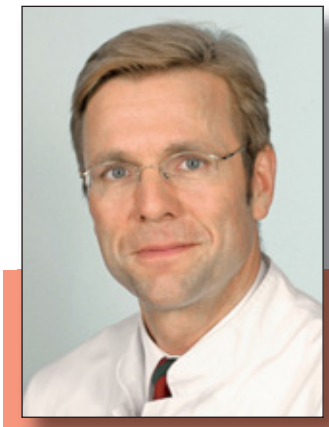
3.3 Department of General, Visceral, Vascular and Pediatric Surgery (Surgery I)

CONTACT DETAILS



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Mission and Structure

The Department of General, Visceral, Vascular and Pediatric Surgery offers excellent services for the whole spectrum of general and visceral surgery. In addition, we have two special units for vascular and pediatric surgery and a unit for transplantation and hepatobiliary surgery. 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, a leading oncological center supported by German Cancer Aid (Deutsche Krebshilfe) and certified by the German Cancer Society (Deutsche Krebsgesellschaft; DKG). The DKG also certified the Center for Intestinal Medicine and the Pancreas Center.

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. In addition, the department is a member of the integrative Liver Center that provides up-to-date interdisciplinary treatment of acute and chronic liver diseases.

The Department of General, Visceral, Vascular and Pediatric Surgery is especially skilled in the surgical treatment of endocrine and metabolic disorders. It was certified by the German Society for General and Visceral Surgery (Deutschen Gesellschaft für Allgemein- und Viszeralchirurgie; DGAV) as a reference center for endocrinology and is a founding member of the Thyroid Center Wuerzburg. The DGAV also certified the Center for Obesity Medicine and the Competence Center for Peritoneal Carcinosis.

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

The pediatric unit provides top surgical treatment for a wide range of diseases and conditions. 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. Endovascular surgery is available for aorta and iliac vascular diseases. Our surgeons are well experienced in femur crural artery bypass surgery and carotid artery surgery. Since last year, a hybrid operating room provides high quality interventional care.

Major Research Interests

Research on infection, inflammation, metabolic disease, oncology, tissue engineering, and transplantation immunology takes place in modern research laboratories. Research projects are networked throughout 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 complement the project achievements. Further information is available on our website (http://www.zom-wuerzburg.de/).

Clinical Studies
(U. Dietz, M. Gasser, T. Meyer, S. Grasshoff-Derr, J. Pelz, 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-Gas-

ser 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 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.

Oncology
(M. Gasser, M. Lazariotou, C. Otto, J. Pelz, A. Wiegering, 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) where patient tissue and fluid samples are collected and catalogued for investigating diseases and their causes.

Metabolic Disorders
(C. Jurowich, C. Otto, S. Seyfried)

Type 2 diabetes mellitus and complex metabolic changes lead to 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 with the support of the IZKF and DFG, among others. Our cooperation partners are Prof. Dr. H. Koepsell, Institute of Pharmacology, University of Würzburg, and Prof. C.W. le Roux, Department of Investigative Medicine, Hammersmith Hospital, Imperial College London, UK.

Tissue Engineering
(U. Dietz, T. 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, J. Baur, 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. A. Avots, Institute of Pathology, involves finding new targets for inhibiting graft rejection with fewer side effects.

Teaching

Our advanced education programme offers lectures and seminars covering all aspects of modern surgery. This commitment and the quality of our teaching have been honoured by the Bavarian State Ministry for Education, Science and the Arts with a prize for outstanding education. Bedside teaching has been optimized to ensure high quality hands-on training. The department 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, including graphics, illustrations, and videos.

Training courses in coloproctology, thyroid and microsurgery, as well as laparoscopic operating procedures are offered on a regular basis. The department has the authorization to provide advanced training and education in surgical intensive care, general, visceral, vascular and pediatric surgery, and proctology.

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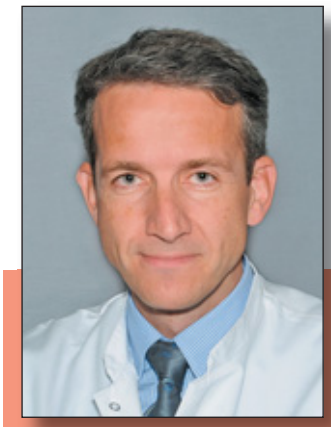
3.4 Department of Trauma, Hand, Plastic and Reconstructive Surgery

CONTACT DETAILS



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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, 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 further intensified over the last two years.

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

In a unique rabbit model, the influence of proangiogenic factors on muscle and bone regeneration after musculoskeletal trauma is studied. Promising results were achieved with well-established factors, such as $VEGF_{165}$. Furthermore, in collaboration with N. Schütze, Orthopedics, applying CYR61 also resulted in distinct improvement of bone regeneration. Currently, the set-up of the rabbit model for investigating the restoration of muscle force is transferred to a mouse model.

Biomechanics in Traumatology
(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 an IZKF-funded project (S. Doht), 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 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 within the consortium FORMOsA (Bavarian Research Foundation, Speaker: F. Jakob), a 3D adipose tissue construct made from genetically modified stem cells will be developed that serves as a biodelivery device (collaboration with F. Jakob, Orthopedics, and H. Walles, Tissue Engineering). Moreover, 3D adipose tissue models for basic research were established in which the crosstalk of different cell types (e.g., stem cells and endothelial cells) and the role of

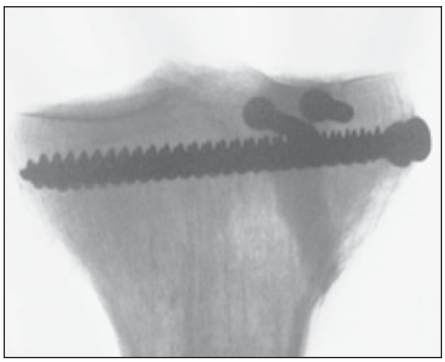

Fig. 1: Combination of osteosynthesis material and screws in the jail technique for stabilization of tibial plateau fractures.

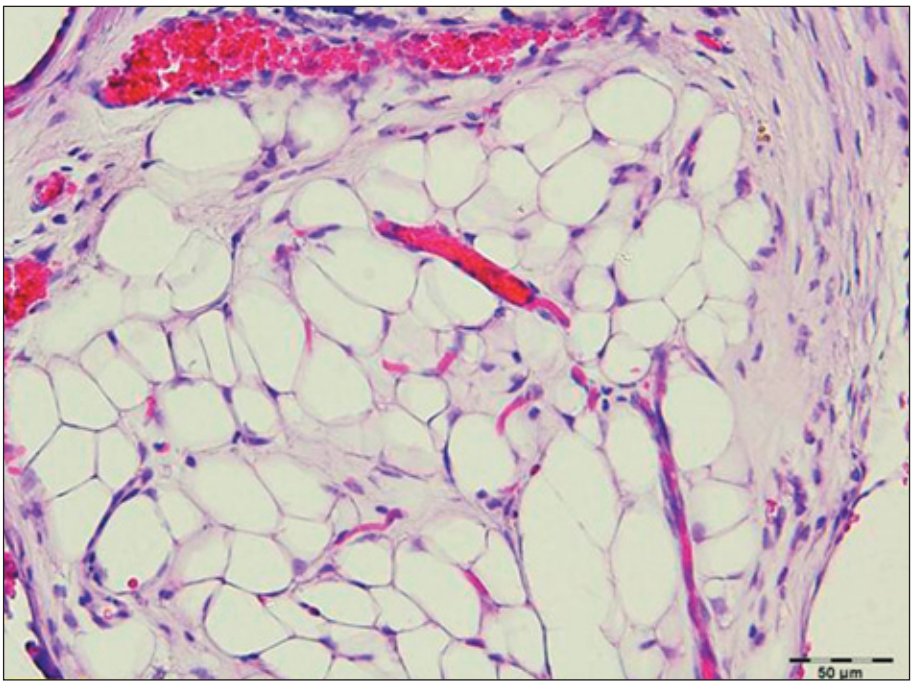

Fig. 2: Vascularized adipose tissue construct generated in a composite scaffold made from polyurethane foam and fibrin hydrogel after 4 weeks in a nude mouse model.

the extracellular matrix in adipogenesis are investigated.

Cartilage Regeneration
(T. Blunk)

Another focus is the tissue engineering of cartilage. Mainly, bone marrow-derived stem cells are employed. In two IZKF-funded projects, the effects of biomimetic materials are investigated. In collaboration with J. Groll, Functional Materials in Medicine, and A. Steinert, Orthopedics, new peptide-modified hydrogels for cartilage regeneration are evaluated. In collaboration with L. Meinel, Pharmaceutical Technology, osteochondral constructs based on cell carriers made from silk fibroin are developed. Within the EU-funded consortium HydroZONES (Speaker: J. Groll), integration of cartilage is investigated biomechanically and in cell culture. Besides fundamental studies, innovative materials (collaboration with J. Groll) to improve cartilage integration are investigated.

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. For students, there are two main lectures per week. 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. In order to improve practical examination techniques, specific courses, e.g., for the examination of the joints and the spine, are offered in the Skills Lab.
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.

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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 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

Storage of of platetel concentrates: biochemical and functional changes

Platelet concentrates are stored for up to four days. One of the research activities of the Institute of Transfusion Medicine and Haemotherapy is the characterization of biochemical and functional changes during this storage period.

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”

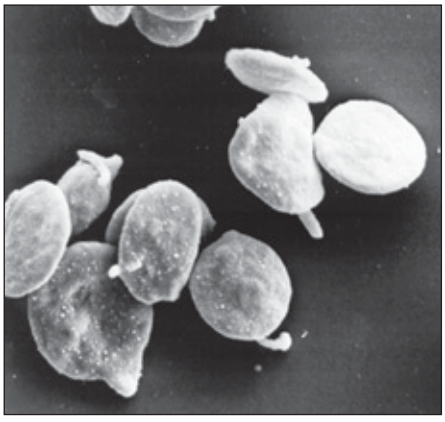

Fig. 1: Platelets in a stored platelet concentrate.

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3.6 Department of Thoracic and Cardiovascular Surgery

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Mission and Structure

The department of Thoracic and Cardiovascular Surgery is a 54-bed department with 3 operating theaters and its own 12 bed intensive care/intermediate care unit. At present 23 physicians are employed.
Approximately 2100 procedures are performed annually covering the entire field of adult heart and thoracic surgery. 1130 procedures are open heart surgeries with extracorporeal circulation.
In 2008 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 like video-assisted lobectomies and new techniques for the treatment of sternal deformities like pectus excatavum. 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

Cardiac surgery:

Ross operation:

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

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.
Tricuspid valve reconstruction: Follow-up study of all patients after trucpid valve reconstruction with a ring (CE MC3 ring) or a band (SJM tailor band)

Heart / lung transplantation:

The working group led by Dres Stefanie and Sebastian Sommer has examined the impact of positively inotropic substances on the myocardial ischemia/reperfusion damage (IR) in a rat heart Langendorff model.
Targeted perfusion and interruption of perfusion allow for controlled induction of IR. Vital mitochondria are isolated from rat hearts and their function regarding Calcium metabolism, electron transport chain and membrane integrity is studied. For the last two years much research has been dedicated to the effects of enoximone on IR.
The underlying mechanism for the beneficial effects of enoximone on IR is a modulation of mitochondrial Calcium uptake and Ca^{2+}-modulated Ca^{2+} release. Presumably, enoximone stabilizes the mitochondrial membran potential. e Resistenz gegenüber Ca^{2+}-Provokation.

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. Currently, 350 patients are included in this registry. An S3 guideline for the prevention and therapy of DSWI has been published (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 and the establishment of VATS-lobectomy. The division is the leading investigational site for the WOPP-study regarding the best management of pneumothorax.

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.
Students and residents are offered regular wet lab training in the department's own wet lab, where all surgical technqiues relevant for cardiothoracic surgery can be practiced in pig hearts and aortas.
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

Schimmer C, Hamouda K, Özkur M, Sommer SP, Hain J, Aleksic I, Leyh R. (2013) Influence of storage time and amount of red blood cell transfusion on postoperative renal function: an observational cohort study. HSR Proceedings in Intensive Care and Cardiovascular Anesthesia 5:148-157.

Sommer SP, Wagner C, Sommer S, Krannich JH, Aleksic I, Schuster C, Leyh RG. (2012) Cardiac Surgery in Presence of Myeloproliferative Neoplasms: An Independent Risk Factor for Stroke. Asian Cardiovasc Thor Ann 20:398-403.

Schreiber JU, Lance MD, de Korte M, Artmann T, Aleksic I, Kranke P. (2012) The effect of different lung protective strategies in patients during cardiopulmonary bypass. A meta-analysis and semi-quantitative review of randomized trials. J Cardiothorac Vasc Anesth 26:448-454.

Schimmer C, Gorski A, Özkur M, Sommer SP, Hamouda K, Hain J, Aleksic I, Leyh RG. (2012) 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 14:294-299.

Sommer SP, Sommer S, Sinha B, Walter D, Aleksic I, Gohrbrandt B, Otto C, Leyh RG. (2012) Glutathione preconditioning ameliorates mitochondria dysfunction during warm pulmonary ischemia–reperfusion injury. Eur J Cardiothorac Surg 41:140-148.

3.7 Department of Urology and Paediatric Urology

CONTACT DETAILS

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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 open, laparoscopic and endoscopic procedures and more than 1.800 endourologic interventions per year. The equipment comprises besides an own, independent x-ray department a multifunction unit for extracorporal shockwave lithotripsy, a computer-assisted (video-) urodynamic set-up, lasers of the latest generation, a Da Vinci surgical robot and an ultrasound facility including colour-coded duplex sonography and transrectal probes of the latest generation.

The surgical spectrum encompasses the entire speciality of urology with special expertise in urooncology (cystoprostatectomy/ anterior exenteration (nerve sparing techniques) and orthotopic bladder substitution and continent cutaneous urinary diversion; radical perineal, retropubic and robot-assisted prostatectomy (nerve-sparing techniques); nephron-sparing surgery of renal cell cancer; surgical and medical treatment of testicular 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, urethral reconstruction, complex fistula repair) including implantation of artificial urinary sphincters and penile prosthesis, urogynaecology and renal transplantations (cadaver and living related transplantation).

Major Research Interests

Translational Prostate Cancer Research

Treatment of patients with high risk prostate cancer

(B. Kneitz, C. Kalogirou, M. Krebs)

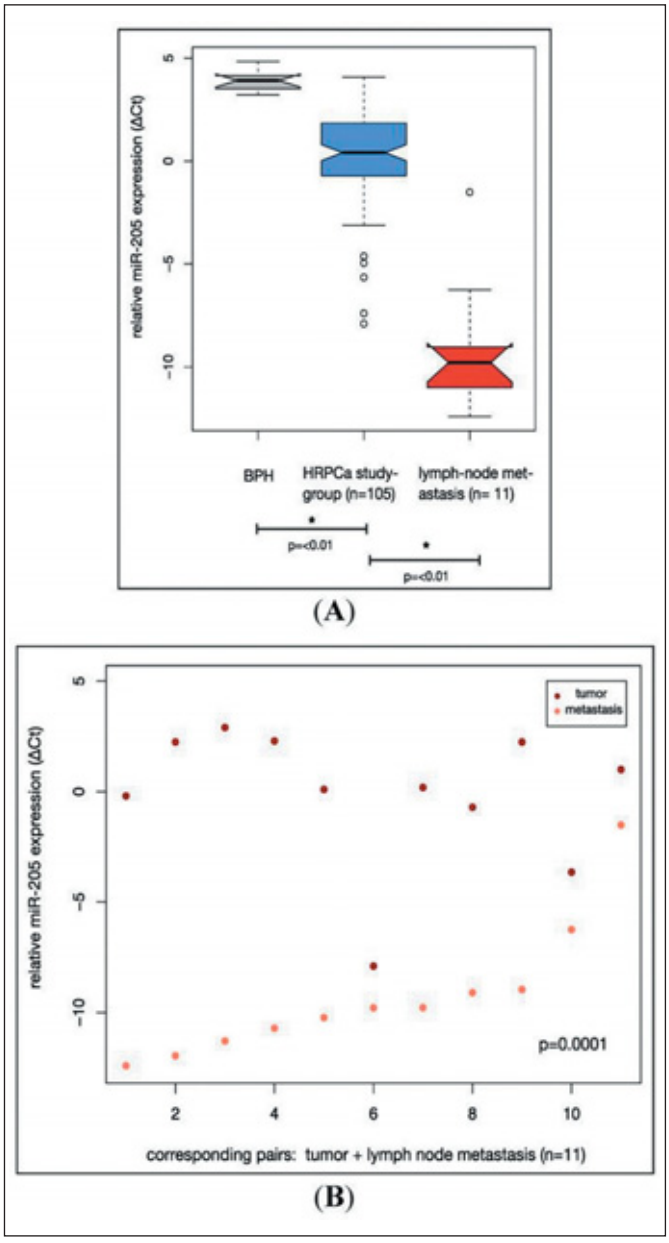

Fig. 1: Progressive down-regulation of miR-205 in high-risk-PCa-lymph node metastasis.

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 after radical prostatectomy within a 5-year period is approximately 40%.
Prostate cancer represents a heterogeneous malignant entity according to the risk of progression. Referring to this our study group evaluates biomarkers which aim to improve continuative diagnostic approaches and trading forecasts of high risk prostate cancer in the future.

Molecular mechanisms of onco- microRNAs in high risk prostate cancer
(B. Kneitz, C. Kalogirou, M. Krebs)

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 1). 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 analysing the function of specific miRNAs *in vitro and in vivo*.

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

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 and description of tumor-suppressor- und onco- microRNAs in renal cell carcinoma.
(B. Kneitz, D. Vergho)

The aim of our studies is to analyse the role of miRNAs for the development and progression of 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.

T-cell mediated therapy in invasive bladder cancer
(M. Wölfl, A. Kocot, C. Kalogirou)

Cancer/testis (CT) antigens, which are expressed in various cancer cells but not in normal cells except germline cells of the testis, have been used as targets for cancer therapy. The aim of our study is to identify and characterize specific CT antigens on invasive urothelial cancer cells. Specific T-cells against these epitopes are isolated from peripheral blood cells of healthy donors and mixed with urothelial (tumor-) stem cells ("killing-assay"). A further aim is a targeted and individualized tumor therapy.

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 tumour 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.

SELECTED PUBLICATIONS

Schubert M, Spahn M, Kneitz S, Scholz CJ, Joniau S, Stroebel P, Riedmiller H, Kneitz B. (2013) Distinct microRNA expression profile in prostate cancer patients with early clinical failure and the impact of let-7 as prognostic marker in high-risk prostate cancer. PLoS One. 8:e65064.

Kalogirou C, Spahn M, Krebs M, Joniau S, Lerut E, Burger M, Scholz C, Kneitz S, Riedmiller H, Kneitz B. (2013) MiR-205 Is Progressively Down-Regulated in Lymph Node Metastasis but Fails as a Prognostic Biomarker in High-Risk Prostate Cancer. International journal of molecular sciences 14: 21414-21434.

Vergho DC, Loeser A, Kocot A, Spahn M, Riedmiller H. (2012) Tumor thrombus of inferior vena cava in patients with renal cell carcinoma - clinical and oncological outcome of 50 patients after surgery. BMC Res Notes 5:5.

Kocot A, Vergho DC, Riedmiller H. (2012) Use of bowel segments for ureter reconstruction. Urologe A. 51:928-36.

Loeser A, Katzenberger T, Vergho DC, Kocot A, Burger M, Riedmiller H. (2014) Frozen Section Analysis of Ureteral Margins in Patients Undergoing Radical Cystectomy for Bladder Cancer: Differential Impact of Carcinoma in situ in the Bladder on Reliability and Impact on Tumour Recurrence in the Upper Urinary Tract. Urol Int. 92:50-54.

3.8 Department of Orthopedics

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Mission and Structure

The Orthopedic Department König-Ludwig-Haus is a top level hospital for the treatment of musculoskeletal diseases and injuries. The hospital is operated by the district of Unterfranken. Integrated are the Chair of Orthopedics and the Outpatient Department for Orthopedics of the University Hospital, as well as the Orthopedic Center for Musculoskeletal Research. The Chairman of the Department, Prof. Dr. Maximilian Rudert, 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.

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 Center supports the representation of the chair in the field of Orthopedic Surgery concerning research and teaching. The Head of the 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.

Specialities in the treatment of orthopedic patients are

- Arthroplasty of the Hip, Knee, Shoulder, Elbow and Tumor Prostheses
- Shoulder and Elbow Surgery
- Sports Medicine
- Arthroscopy of the Knee, Shoulder, Elbow and Ankle
- Ankle and Foot Surgery
- Pediatric Orthopedic Surgery
- Spine Surgery
- Tumor Surgery
- Orthopedic Rheumatology
- Osteology (metabolic and degenerative diseases with a special focus in osteoporosis and malignant bone disease)
- Rare dieseases with a special expertise for hypophosphatasia, phosphate wasting syndromes in oncogenic osteomalacia and paget´s Disease

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

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 and DIMEOs, the German / French Consortium OBELICS), the Ministry of Economy, the European Union (EU-Consortia ADIPOA, VASCUBONE and HydroZONES), 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 on Sarcopenia and Osteoporosis – Consequences of impaired Regeneration in the Elderly FORMOsA), as well as several industrial cooperations. The number of positions funded is 25 (as of December 2013). The clinic provides a clinical study Unit (Head L. Seefried) which runs Phase II-IV clinical studies and is operated in close connection with the scientific projects.

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, Sanderstiftung Treatment Unit Multiple Myeloma)(M. Rudert, F. Jakob, N. Schütze, R. Ebert, M. Lüdemann, J. Dotterweich)
- Molecular Orthopedics and Cell Biology (N. Schütze, T. Schilling, K. Schlegelmilch, R. Laug, S. Hondke, M. Simann, B. Hafen, S. LeBlanc)

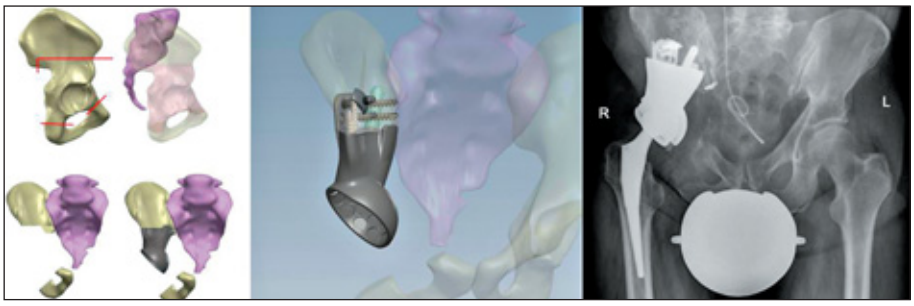

Fig. 1: Partial reconstruction of the pelvis after resection of a chondrosarcoma. Preoperative 3D design and clinical results one year after resection.

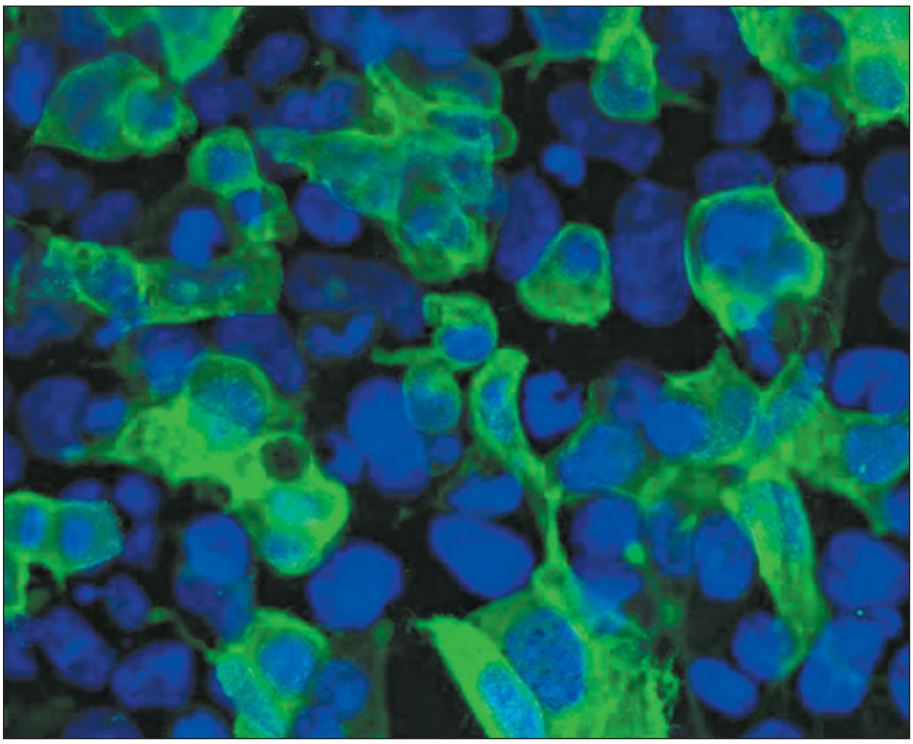

Fig. 2: Subcellular localization of alkaline phosphatase after transfection of guest cells (HEK397). The procedure is part of molecular diagnosis and characterization of mutations in hypophosphatasia.

- Tissue Engineering, Regenerative Medicine, Translation in Cell Therapy (U. Nöth, L. Rackwitz, 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 3D Surgical Reconstruction (M. Rudert, B. Holzapfel)
- Special Techniques in Shoulder Joint Reconstruction (P. Plumhoff, L. Seefried)
- 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, L. Seefried)
- Endoprosthesis of Hip and Knee (U. Nöth, M. Rudert, A. Steinert)
- Special Orthopaedic Pediatric Surgery, Spine and Foot Surgery (P. Raab, M. Walcher)
- Clinical Studies on Osteoporosis and Metbolic Bone Diseases (F. Jakob, L. Seefried, G. Baron, M. Lüdemann, S. Bau)
- Rickets in Nigeria (P. Raab, R. Ebert, F. Jakob)

Teaching

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

SELECTED PUBLICATIONS

Holzapfel BM, Chhaya MP, Melchels FP, Holzapfel NP, Prodinger PM, von Eisenhart-Rothe R, van Griensven M, Schantz JT, Rudert M, Hutmacher DW. (2013) Can bone tissue engineering contribute to therapy concepts after resection of musculoskeletal sarcoma? Sarcoma 153640.

Weber C, Armbruster N, Scheller C, Kreppel F, Kochanek S, Rethwilm A, Steinert AF. (2013) Foamy virus-adenovirus hybrid vectors for gene therapy of the arthritides. J Gene Med. 15:155-67..

Hofmann C, Liese J, Schwarz T, Kunzmann S, Wirbelauer J, Nowak J, Hamann J, Girschick H, Graser S, Dietz K, Zeck S, Jakob F, Mentrup B. (2013) Compound heterozygosity of two functional null mutations in the ALPL gene associated with deleterious neurological outcome in an infant with hypophosphatasia. Bone 55:150-7.

Benisch P, Schilling T, Klein-Hitpass L, Frey SP, Seefried L, Raaijmakers N, Krug M, Regensburger M, Zeck S, Schinke T, Amling M, Ebert R, Jakob F. (2012) The transcriptional profile of mesenchymal stem cell populations in primary osteoporosis is distinct and shows overexpression of osteogenic inhibitors. PLoS One 7:e45142.

3.9 Department of Obstetrics and Gynaecology

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Mission and Structure

The Woman's Hospital (bed capacity of 78, 31 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 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 2,500 operations, 1,800 deliveries, 5,900 DRG cases, 25,000 outpatient therapies (of which 1,800 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

Section for Experimental Tumor Immunology
(J. Wischhusen, S. Häusler, J. Diessner, R.G. Stein, M. Junker, D. Pühringer, T. Schäfer, A. Chandran, V. Bruttel, I. Montalbàn del Barrio, L. Gerloff, A. Schmidt, B. Fischer, E. Horn)

The research group investigates interactions between tumor cells and the immune system during different phases of tumor development.

Particular emphasis is placed on
- immunological properties of tumor-initiating cells.
During early stages of tumor or metastasis formation, 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,
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 or the cytokine MIF 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.

- 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 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, we want to develop our original *proof-of-principle* study into a diagnostic test for the early detection of ovarian cancer.

The group is funded (sponsored) by the BMBF (GO-Bio program), the DFG (via the Graduate School of Life Sciences), the Else-Kröner-Fresenius-Stiftung and others.

GnRH antagonists in the treatment of gynaecological malignancies and triple negative breast cancer
(A. Hönig, J. Engel, in cooperation with the University of Regensburg)

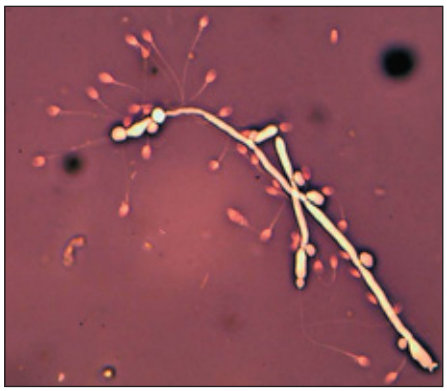

Fig. 1: Light microscopic picture shows a strong adhesion of human spermatozoa (red) to Candida albicans hyphae.

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 triple 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
(A. Hönig)

The AKT-pathway is overactivated in various tumors 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 cancers 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-and PI3K inhibitors display substantial anti-tumor activity in models of human ovarian and endometrial cancers and show beneficial immunemodulatory effects.

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

Microbial contaminations of the female urogenital tract often cause infections and may even be associated with infertility. The mucosal surfaces of the lower part of the female reproductive tract are highly populated by a complex microbial flora, and in addition, microbes can also be transmitted by the male ejaculate. Yet, little is known of the complex mechanisms of interaction between host, pathogens and gametes in this special niche. In the present work, selected factors of the extracellular matrix (ECM) were tested for their potential impact on spermatozoa and *Candida albicans*. By means of fluorescence microscopy, flow cytometry, western blot analysis and co-incubation experiments the interaction of *C. albicans* with human spermatozoa and the ECM-protein thrombospondin-1 (TSP1) was characterized. Further experiments have addressed the question whether TSP1 may influence sperm chemotaxis and calcium influx, both factors important for fertilization.

Reproductive immunology
(U. Kämmerer, S. Segerer, C. Bartmann, M. Kapp)

Within the reproductive immunology field of our research we actually focus on two major subjects:
a) The role of Thrombopoietin (TPO) for early human pregnancy. Analyzing the impact and function for TPO in human early pregnancy decidua, we intend to expand our knowledge on the regulation of a healthy human pregnancy. Further, the experimental ratification of a putative immunomodulatory effect of TPO should add further insight into the question, how a tolerogenic milieu is established which allows the immunologic acceptance of the semiallogeneic fetus and protects pregnancy from abortions.
b) A detailed quantitative analysis of the diverse immune cell populations found within the human decidua of healthy as well defected pregnancies. Aim of this research area is the apportion of the role of specific immune cell types in relation to putative complications of pregnancy. Hereby, we focus on antigen presenting cell types, especially dendritic cells (DC) and myeloid derived suppressor cells (MDSC) and their role for the induction of the local tolerogenic milieu within the human uterus.

Teaching

The curricular teaching in Obstetrics and Gynaecology consist of a main lecture (8th semester), seminars, clinical visits (9th semester) and a practical training (10th semester). Additionally, a „Skills Laboratory" focuses on practical aspects of the subject. With gynaecological models and case studies, students learn to deal with clinical situations and to handle diagnostic equipment. The training is complemented by a number of interdisciplinary subjects like ethics, preventive medicine, emergency medicine, infectious diseases, tumour biology and oncology. For doctors in private practice, we organize regular interdisciplinary conferences as part of the perinatal centre.

SELECTED PUBLICATIONS

Häusler S, Montalban del Barrio I, Diessner J, Stein RG, Strohschein J, Hönig A, Dietl J, Wischhusen J. (2013) Anti-CD39 and anti-CD73 antibodies A1 and 7G2 improve targeted therapy in ovarian cancer by blocking adenosine –dependent immune evasion. Am J Transl. Res 6:129-39.

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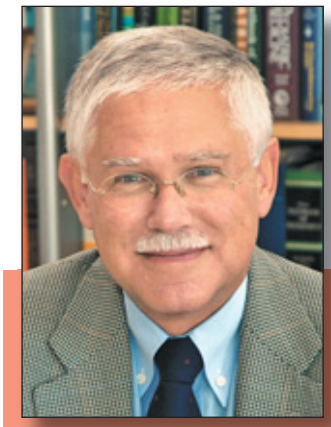
Segerer SE, Martignoni F, Bogdan A, Müller N, Kapp M, Dietl J, Rieger L, Kämmerer U. (2013) Thrombopoietin modulates the proliferation, migration and cytokine profile of decidual cell subsets during early gestation. Mol Hum Reprod. 19:361-8.

Palige K, Linde J, Martin R, Böttcher B, Citiulo F, Sullivan DJ, Weber J, Staib C, Rupp S, Hube B, Morschhäuser J, Staib P. (2013) Global transcriptome sequencing identifies chlamydospore specific markers in Candida albicans and Candida dubliniensis. PLoS One 8:e61940.

Hahne JC, Meyer SR, Kranke P, Dietl J, Guckenberger M, Polat B, Hönig A. (2013) Studies on the role of osteopontin-1 in endometrial cancer cell lines. Strahlenther Onkol. 189:1040-8.

3.10 Department of Pediatrics

CONTACT DETAILS



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Mission and Structure

The Children's Hospital of the University of Würzburg (staff: 67 MD's, 152 nurses, 47 technicians / administrative staff) comprises of 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 patients 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

Surfactant replacement has become a milestone in the treatment of neonatal respiratory distress syndrome (RDS) and has significantly decreased acute pulmonary morbidity and mortality of preterm infants worldwide. Besides improving lung function, surfactant acts as a key modulator of pulmonary innate and acquired immunity thereby regulating lung inflammatory processes. In different studies the effect of new synthetic surfactant preparations on RDS and their immunomodulatory role is characterized. In addition, the role of caffeine on the surfactant system and on airway remodelling processes is analysed (1). Furthermore, translational research involving various animal models has been helpful to answer basic questions concerning the effect of chorioamnionitis on maturation and development of the foetal lung and immune system.

Pediatric Oncology, Hematology and Stem Cell Transplantation:
Cellular immunity and immunmodulation in patients with malignant diseases

The immune system is capable of destroying 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.
Moreover requirements for efficient T-cell priming are analyzed in a robust, antigen-specific in vitro model and the influence of immune response modifiers is studied. As demonstrated for the clinically widely used src-kinase inhibitor dasatinib, interaction of drugs with different players in the immune system can lead to completely disparate effects (Ref. 2, Fig. 1).
We strive to develop new immunotherapies for patients with malignant diseases (dendritic cell vaccination, antigen-specific T-cells), and – in collaboration with the Comprehensive Cancer Center Mainfranken – aim to implement these techniques in clinical studies. A clinical study on tumor-lysate loaded autologous dendritic cells is set to recruit glioblastoma patients in 2014. Within the area of hematopoeitic stem cell transplantation, several multicenter studies are performed, focusing on engraftment after haploidentical stem cell transplantation using new methods for graft manipulation. These studies are part of our translational approach to get novel treatment strategies into the clinic (3).

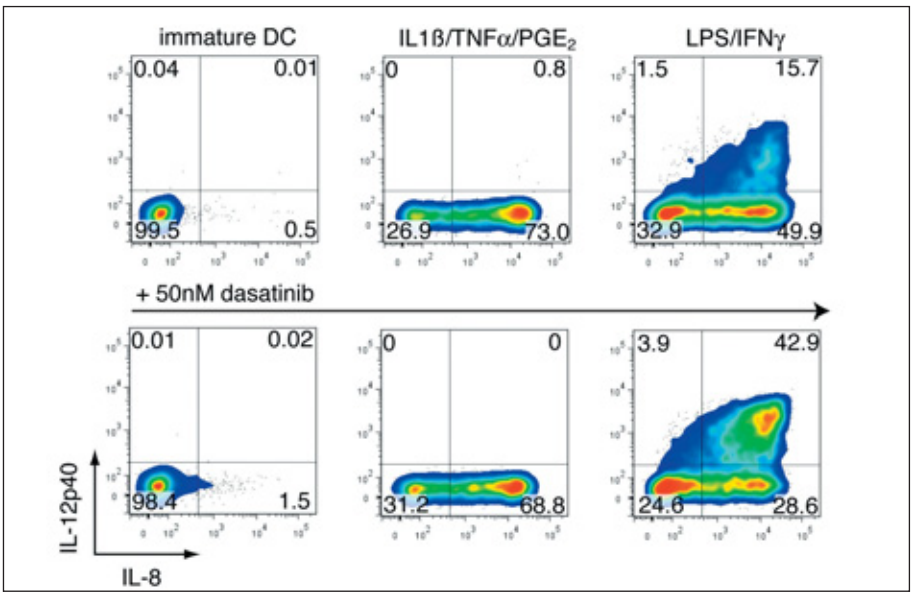

Fig. 1: Intracellular cytokine production in dendritic cells (DC). Stimulation of DC with LPS and interferon-γ combined with the src-kinase inhibitor dasatinib synergistically leads to IL-12 production (right). No such synergy is observed with cytokine-matured DC (middle) (Ref.2).

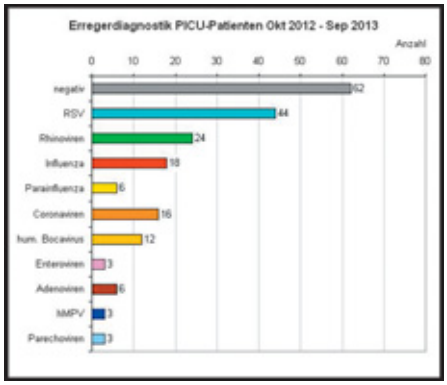

Fig. 2: Frequency of viral pathogens causing acute respiratory infection in184 patients from paediatric intensive care units (PICU) in Bavaria, identified by multiplex PCR (PICU study, October 12 - September 13). Numbers indicate individual cases.

Pediatric Infectious Diseases:
Epidemiology and prevention of infectious diseases

The burden of pediatric infectious diseases and the effects of vaccination programs on their epidemiology in children and adolescents are evaluated in several prospective studies (main research projects 2012/2013: varicella, pneumococcal disease, influenza, RSV and other viral respiratory infections (see figure 2)). Laboratory samples and clinical data on patient characteristics and severity of disease are collected from a network of hospital and practice pediatricians. Viral and bacterial pathogens types and subtypes are identified, using different molecular-biological methods in collaboration with the Institutes of Virology (Würzburg, Jena) and Hygiene and Microbiology (Würzburg), as well as the National Reference Center for streptococci (Aachen). Adaptations of pathogens, e.g. serotype replacement of pneumococci in pleural empyema under current vaccination programs are investigated.

Osteology:
Hypophosphatasia – pathophysiology and new treatment options

Hypophosphatasia is a rare disease of the bone characterized by reduced phosphatase activity. 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

An imbalance between inflammatory T cells and regulatory T cells is characteristic for T-cell mediated autoimmune disorders. The activation of inflammatory T cells can be modulated by in vitro polarization using various cytokines, by epigenetic modifications and interaction with mesenchymal stem cells. Using these approaches novel therapeutic targets may be identified for the treatment of Juvenile Idiopathic Arthritis and other autoimmune disorders.
Another project is aimed to investigate the role of immunosuppressive/immunomodulatory therapy on effector mechanisms against latent virus infections and on the humoral and cellular immune response to vaccine antigens to improve vaccination schedules for immunocompromised patients.

Pediatric Pulmonology / Cystic Fibrosis / Sports Medicine:
Physical activity and conditioning in healthy children and those with chronic lung diseases
Mesenchymal stem cells might be involved in pulmonary tissue repair processes and could thus mediate positive effects of exercise in chronic lung diseases. Therefore, two research projects addressed the question whether acute exercise can trigger a release of mesenchymal stem cells into the blood stream, comparing patients with cystic fibrosis or asthma to healthy controls. One additional study assessed the physical activity behavior in people with cystic fibrosis and healthy individuals. Two projects evaluated new concepts to improve patient care in cystic fibrosis. In one of these studies, the quality of expert answers to lay questions was determined in a European web-based system (ECORN-CF) (5). In another, still ongoing nationwide project, the effects of introducing case managers plus additional psychological support and exercise counseling into standard therapy are evaluated.

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 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 hematology and oncology, neuropediatrics, and pediatric pulmonology are qualified to train MDs in their respective subspecialties. The Children's Hospital regularly organizes 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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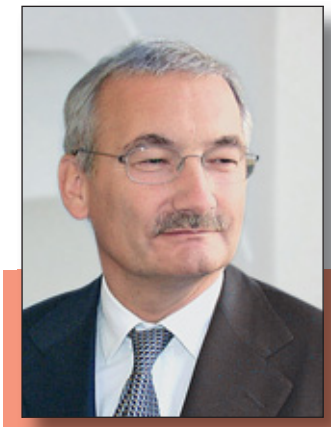
3.11 Department of Internal Medicine I

CONTACT DETAILS



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Mission and Structure

The Department of Internal Medicine I (DIM I) includes six specialities in research, teaching, and patient care: Endocrinology, Emergency- and Intensive Care, Cardiology/ Angiology, Nephrology, and Pneumology.

Endocrinology is in charge of a ward specialized in endocrinology/ diabetology as well as outpatient clinics for metabolism/ obesity and endocrinology caring for more than 5000 outpatients annually. Since 2003, Endocrinology has become the international reference centre for adrenal carcinoma.

Cardiology performs more than 3300 invasive procedures per year including percutaneous coronary interventions, catheter based implantations of closure devices in patients with atrial septal defects and persistently open foramen ovale, high frequency and cryo ablations in arrhythmias and hypertension. In cooperation with the Department of Cardiac Surgery, more than 250 minimally invasive stent-based aortic valves and mitraclips, 200 pacemakers and 200 ICDs/ CRTs were implanted per year. A cardiac transplantation program is established. Since August 2012 a modern cardiac research MRT is available.

The ZIM includes a state of the art intensive care ward with 24 beds and an emergency ward / chest pain unit 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.

Nephrology performs more than 6000 hemo- and peritoneal dialyses per year. The focus of inpatients lies on the treatment of acute renal failure and preparation of living donation for AB0 incompatible kidney transplantation. Outpatient departments provide care for chronic kidney disease, especially rare diseases like vasculitis, transplantation, hereditary diseases (Fabry, cystic kidney diseases), etc.

Pneumology cares for inpatients with bronchial carcinoma, severe pneumonia, severe COPD, pulmonary hypertension, or interstitial lunge disease and has more than 4.000 outpatient contacts for rare diseases like interstitial lung disease, sarcoidosis, pulmonary hypertension, and alpha-1-antitrypsin-deficiency.

Major Research Interests

Our research is characterized by interdisciplinary projects and coordination or participation in research consortia like the Collaborative Research Center SFB 688 “Mechanisms and imaging of cardiovascular cell-cell interactions” (see 5.2.3, page 160, deputy speaker Professor Ertl), the Comprehensive Heart Failure Center (CHFC, speaker Professor Ertl, see 5.1.7, page 142), the Cardiovascular Center, the Interdisciplinary Center for Clinical Research, the Comprehensive Cancer Center, Center for Infectious Disease, and the Interdisciplinary Training and Simulation Center (INTUS).

Endocrinology
(B. Allolio, M. Fassnacht)

The focus lies on translational and clinical studies in adrenocortical carcinoma. Since 2003, the German Adrenocortical Carcinoma Registry has been headed by Würzburg, now being developed to a European registry. The first, international randomized and largest (over 300 patients) trial in adrenocortical carcinoma (FIRM-ACT) was coordinated in Würzburg. It was recently published in the NEJM. Since 2011, endocrinology coordinates an EU supported phase III trial with adrenocortical carcinoma (ADVIO study)

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 imaging and treatment in adrenocortical carcinoma. This new method is currently evaluated in a multicentre trial (FAMIAN) supported by the German Research Council (DFG)
Moreover, several phase II and III studies on thyroid carcinoma, obesity, as well as prospective, in part multicentre national studies on hyponatremia and adrenal insufficiency are currently carried out partially in cooperation with the DZHI.

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

Cardiovascular research is involved in several research consortia. In 2010, the Comprehensive Heart Failure Center (CHFC) was founded (speaker G. Ertl). The CHFC initiated a faculty wide biobank concept supported by the BMBF (see page 142). Furthermore, cardiology is actively involved in the National Competence Network Heart Fai-

lure and the Collaborative Research Center 688. In general, research is centred on molecular mechanisms, imaging, and treatment of heart failure with *in vitro* and *in vivo* methods.

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

The focus is: MRI-Imaging of the heart and cardiac biophysics in rodents and humans, modelling of cardiac microcirculation, cellular and molecular processes in the vascular system (W. Bauer). Heart failure: ischemia reperfusion injury, healing after myocardial infarction, 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, nNOS and nuclear Ca^{2+} in heart failure (O. Ritter); cardiac metabolism, gender aspects (T. Pelzer).

Translational projects
(O. Ritter, R. Jahns)

Therapeutic cyclopeptides are being developed in autoimmune mediated heart failure (BMBF, GoBio, R. Jahns) and a preclinical lead substance (Calportin) for heart failure treatment (BMBF VIP, m4 award, O. Ritter).

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

Clinical cohorts exist for rare diseases like M. Fabry and M. Friedreich (F. Weidemann). Clinical trials deal with MR compatible pace maker leads and electrophysiology catheters (W. Bauer/ O. Ritter, first in man application), innovative echocardiographic methods (F. Weidemann), Interdisciplinary Network Heart Failure (C. Angermann/ S. Störk; INH), ETiCS R. (R. Jahns), role of beta1-autoantibodies for heart failure, RECODE (S. Störk, prognosis of heart failure patients followed by general practicioners), MOOD-HF (C. Angermann/ S. Störk, prognostic effect of the serotonin reuptake inhibitor escitalopram in patients with heart failure). Würzburg manages the national lead offices of 2 mega-trials: REVEAL (C. Angermann, G. Ertl, C. Wanner, 30.000 subjects); COMPASS (G. Ertl/ S. Störk, 21,000 subjects).

Nephrology
(C. Wanner, C. Drechsler, V. Krane)

The clinical topic is the identification of predictors for heart failure and sudden cardiac death in type 2 diabetics with chronic kidney disease. The questions are answered in large multicentre randomized trials and cohort studies (4D trial, genetic analyses, M. Fabry, etc.). Mainly immunomodulatory treatments are investigated in the studies of the transplantation unit. The coordinating centre of the KfH foundation of preventive medicine is responsible for 5 large national cohorts with up to 10 years of follow up. The European dialysis registry (based in Amsterdam) is chaired by Würzburg. In preclinical studies, pathomechanisms of damage and recovery of ischemic acute renal failure are studied.

Pneumonology
(M. Schmidt, T. Pelzer)

Oncologic studies are carried out in cooperation with the Comprehensive Cancer Center with novel molecular treatments for bronchial carcinoma (e.g. SELECT, ELDERTAC). Furthermore, pneumonology participates in studies of idiopathic lung fibrosis (PASSPORT, PANORAMA) or pulmonary hypertension (IMPRES). In basic science the pathogenesis and treatment of chronic thromboembolic pulmonary hypertension (CTEPH) is investigated.

Teaching

About 650 undergraduate clinical students participate in courses of Internal Medicine each semester including the main lecture, practical training of physical examination, bedside teaching, 2 weeks elective, and internship. With about 3,000 hours of teaching per semester, Internal Medicine is number one in teaching responsibilities in the medical curriculum. In 2013, new teaching modules for Clinical Sciences were implemented in cooperation with the Institute of Clinical Epidemiology and Biometry (P.U. Heuschmann) and the Comprehensive Heart Failure Center (S. Störk) including a Master and a PhD course Clinical Sciences at the Graduate School of Life Sciences.

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3.12 Department of Internal Medicine II

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General information and structure

The Department of Internal Medicine II (DIM II) includes six divisions 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 in the Center of Internal Medicine (Zentrum Innere Medizin, ZIM).

The **Division of Gastroenterology** (M. Scheurlen) is in charge of a specialized ward and the gastrointestinal outpatients clinic. More than 5000 endoscopic procedures are performed per year (specific focus on chronic inflammatory bowel disorders, tumors of the gastrointestinal tract (hereditary neoplastic disorders, neuroendocrine tumors, PNET center and gastric and pancreatic carcinoma). Since 2007 a "Darmzentrum" is established and since 2011 a modul pancreatic carcinoma.

In 2012 the **Division of Hepatology** (A. Geier): treatment of all stages of liver disorders including a liver transplant program (specialized inpatient and outpatient facilities). In the clinical focus are metabolic liver disorders, viral hepatitis B and C as well as malignant tumors of the liver (hepatocellular carcinoma, cholangiocarcinoma). For non-alcoholic fatty liver disease a national clinical network program has been established which is coordinated by our center.

A completely new and state of the art **Stem Cell Transplantation Unit** (G. Grigoleit, S. Mielke) 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 to improve infection and tumor control. In the division of hematology 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 the largest trial center in Germany including a phase I/II trial and offers the largest treatment and research program for patients with multiple myeloma in Germany as well as innovative clinical programs for patients with lymphomas and acute leukemia.

The **Division of Medical Oncology** (V. Kunzmann) runs a special ward but also a large interdisciplinary oncological outpatient clinic in which more than 11.000 patients with a broad spectrum of oncological disorders are treated. 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. gastric, pancreatic, hepatocellular and cholangiocarcinoma, but also sarcomas.

In the **Division of Psychosomatics** 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 psychiatry daycare of patients with psychosomatic disorders is offered. Specific research activities are the care of patients undergoing stem cell transplantation.

In the **Division of Clinical Immunology/ Rheumatology** (H.-P. Tony), patients with vasculitis and specific forms of rheumatoid arthritis, scleroderma and sjögren's syndrome are cared for. On the special ward 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.
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. 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** (A. Ullmann, H. Klinker) was certified as one of the first centers in Germany by the Deutsche Gesellschaft für Infektiologie as a center of infectiology. Patients with infectious disorders are cared for in the special ward for infectious disorders but also in a large outpatient clinic. The clinical focuses of the division are HIV-infections and chronic virus hepatitis, opportunistic infections in immunocompromised, esp hematological patients.

Interdisciplinary projects
The co-chair of the TR/CRC124 FungiNet (H. Einsele) and 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). H. Einsele is the coordinator of AspBioMICS and a WP leader in the FP7 funded Nano II. H. Einsele is the co-speaker of the EU FP7 program OPTATIO and coordinator of the newly funded EU FP7 consortium T-Control.

Research in Gastroenterology
With the support of the IZKF and BMBF a tumor bank with focus on stomach cancer and colorectal carcinoma was established and treatment concepts in gastric cancer and pancreas carcinoma are developed with new innovative combinations of tyrosine kinase inhibitors and new cytotoxic agents.

Research in Hepatology
Clinical research projects in Hepatology (A. Geier, T. Kudlich, O. Götze, J. Schmitt, M. Rau, D. Jahn), address the pathophysiology and treatment of chronic liver disorders, specifically metabolic liver disorders, viral hepatitis B and C as well as liver cancer including prospective cohort studies for non-alcoholic fatty liver disease and liver cancer. A translational research project on intratumoral drug-uptake has been established within the international *TRANSFER* study group. Additional research projects address: role of the microbiome, enterohepatic signalling and hepatic micro-RNAs in the pathophysiology of human fatty liver disease, therapeutic anti-cytokine strategies in murine models. Projects in the field of viral hepatitis C address genetic markers and metabolic host factors of disease progression and therapy response, especially the role of bile acids. Functional studies using 13C breath testing (methionin, methacetin) in chronic liver disease have been newly established.

Research in Hematology/Oncology
Research groups address the genetic, pathophysiology and therapeutic approaches in multiple myeloma in *in vitro* and *in vivo* models and other lymphoid malignancies. 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). H. Einsele is the speaker, R. Bargou the chair of the clinical research group (CRU) 216 “Oncogeneic signaling in multiple myeloma”. The Deutsche Studiengruppe Multiples Myelom is chaired by H. Einsele and S. Knop since 14 years. In addition a therapeutic treatment unit Multiple Myeloma is funded by the Carreras Foundation. In addition 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 (H. Einsele, co-chair). 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 These research programs are funded by the EU (FP7 T-Control, coordinator H. Einsele), BMBF and José Carreras Foundation. A third research focus is the development of immunotherapeutic strategies based on novel antibody constructs (bi-specific, trispecific antibodies and gene modified redirected T cells (T. Bumm, M. Topp, R. Bargou, H. Wajant and L. Rasche). 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) supported by grants from the BMBF, EU and the Deutsche Krebshilfe.

Research in Immunology/Rheumatology
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.

Research in Infectiology
New treatment strategies in HIV-infection are evaluated in early and phase III trials (clinical study center in the international HIV-study network of the Institute of Health USA). 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 internationally recognized (the pharmacokinetic of Ribavirin, drug monitoring of innovative antiviral agents). An additional research focus are infections in the immunocompromised patients with therapeutic drug monitoring (W. Heinz).

The group of J. Löffler develops new diagnostic strategies, risk stratification, biomarker determinations and new therapeutic approaches for patients with invasive fungal infections. The research is funded by the BMBF, Wilhelm Sander-Stiftung, BayImmuNet, EU FP7 T-Control, EU, EraNet PathoGenoMICs – AspBioMICS and the new established SFB/TR124 (co-chair: H. Einsele).

Teaching

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

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3.12.1 Division of Molecular Internal Medicine

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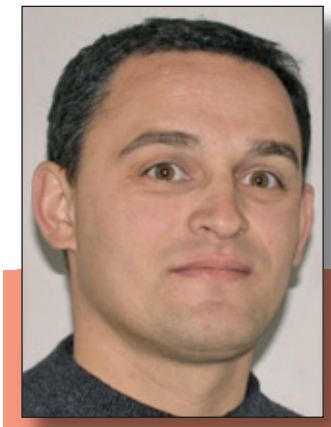

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Mission and Structure

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

- the German Research Foundation
- the Mildred Scheel Foundation for Cancer Research
- the German José Carreras Leukaemia-Foundation e.V.
- the Interdisciplinary Centre for Clinical Research of the University of Würzburg

Major Research Interests

The main 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 tissue homöostasis. The division is organized in three research groups engaged in the investigation of clinically relevant aspects of TNF receptor signal transduction and in the development of therapeutic useful recombinant TNF ligand variants and anti-TNF receptor antibodies.

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 TNF receptors locally in the tumor areal. In one approach, the fact is exploited that a subset of TNF receptors (e.g. 4-1BB CD27, CD95, OX40, TNFR2, TRAILR1/2) is naturally activated by membrane-bound TNF ligands, but not by soluble, still receptor binding-competent variants derived from these molecules. However, if such inactive soluble TNF ligands are artificially anchored on the cell surface, they acquire the same TNF receptor-stimulating activities as their natural occurring membrane-bound counterparts. Now, the activating effect of 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 which 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, already activating 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-associated proteases, it is again possible to localize the TNF receptor-stimulating ligand activity to the tumor area. It is also possible to overcome the poor responsiveness of TNF receptors to binding of soluble TNF ligands by secondary oligomerization of the ligand molecules. Against this background this group also develops and evaluates various scaffolds for multimerization of TNF ligands and agonistic TNF receptor-specific antibody fragments. Primary aim is here the development of potent TNFR2- and CD40 specific agonists for activation of regulatory T-cells and dendritic cells.

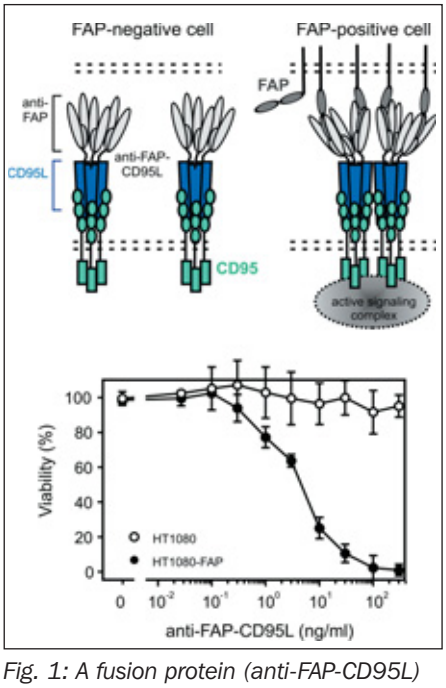

Fig. 1: A fusion protein (anti-FAP-CD95L) of soluble CD95L with an antibody domain specific for the tumor stroma marker FAP (fibroblast activation protein) interacts on FAP-negative tumor cells with CD95, but fails to trigger apoptotic signaling via this death receptor (open symbols). The same protein,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

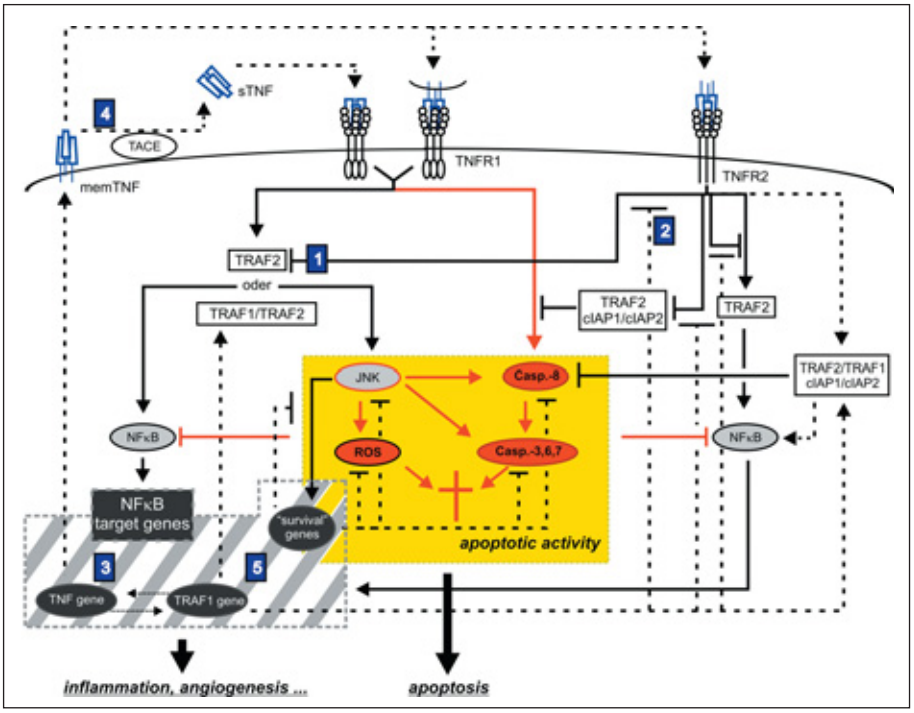

Fig. 2: TNFR1 and TNFR2 are functionally linked in a highly complex manner. Activation of TNFR2 by transmembrane TNF leads to degradation of the adapter protein TRAF2 (1). Because this protein is important for TNFR1-induced activation of the pro-inflammatory transcription factor NF-kappaB and recruitment 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.

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 apoptosis inducing activity which relies on the ability of these receptors to trigger activation of the protease caspase-8. Over the last years, we and others could show, however, that death 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. General research efforts of this group are thus aimed to characterize precise conditions, where stimulation of death receptors leads to enhanced metastasis and aggressive tumor growth. In tumor cells which are resistant to apoptosis due to mechanisms acting downstream of caspase-8 activation, this group identified various substrates of caspase-8 that become cleaved under these non-apoptotic conditions. The main activities of this group are therefore currently focused on the evaluation of the relevance of processing of caspase-8 substrates for the pro-tumoral activities of death receptors.

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). Moreover, the crosstalk mechanisms used by TNFR2 to control the quality and activity of TNFR1 signaling can also be triggered by TNFR2-related TNF receptors, e.g. Fn14. As a consequence, such TNFR2-related receptors can modulate the activity of the TNFR1-TNFR2 system and adjust so TNF responsiveness. The major concerns of this group are the investigation of the regulatory principles that cause the exceptional complexity of TNF signaling and evaluation of the relevance of these crosstalk mechanisms for tumor metastasis.

Teaching

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

SELECTED PUBLICATIONS

Salzmann S, Lang I, Rosenthal A, Schäfer V, Weisenberger D, Carmona Arana JA, Trebing J, Siegmund D, Neumann M, Wajant H. (2013) TWEAK inhibits TRAF2-mediated CD40 signaling by destabilization of CD40 signaling complexes. J. Immunol. 191:2308-2318.

Salzmann S, Seher A, Trebing J, Weisenberger D, Rosenthal A, Siegmund D, Wajant H. (2013) Fibroblast growth factor inducible (Fn14)-specific antibodies concomitantly display signaling pathway-specific agonistic and antagonistic activity. J. Biol. Chem. 288:13455-13466.

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Lang I, Fick A, Schäfer V, Giner T, Siegmund D, Wajant H. (2012) Signaling active CD95 receptor molecules trigger cotranslocation of inactive CD95 molecules into lipid rafts. J. Biol. Chem. 287: 24026-24042.

Fick A, Lang I, Schäfer V, Seher A, Trebing J, Weisenberger D, Wajant H. (2012) Studies of Binding of Tumor Necrosis Factor (TNF)-like Weak Inducer of Apoptosis (TWEAK) to Fibroblast Growth Factor Inducible 14 (Fn14). J. Biol. Chem. 287:484-495.

3.13 Institute of Clinical Biochemistry and Pathobiochemistry

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Professor Dr. rer. nat. Elke Butt
(Provisional head from 01. 01. 2012 until 31. 12. 2013)
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Professor Dr. rer. nat. Michael Zimmer
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Mission and Structure

The institute was founded in 1995 at the conclusion of a DFG-funded Clinical Research Unit (1989–1995) by Prof. Dr. Ulrich Walter. From 2001-2011 the Institute merged with the Central Diagnostic Laboratory. In 2012, institute and laboratory medicine demerged and Prof. Dr. Elke Butt became provisional head of the institute. In 2014, directorate will pass over to Prof. Dr. Alma Zernecke.

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), the BMBF, foundations, and industry.

Protein Biochemistry and LASP-1
(E. Butt)

The group of Prof. Butt 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 DFG and the "Stiftung Pathobiochemie".

A further topic is the role of LASP-1 in adhesion, aggregation and secretion of murine thrombocytes using the LASP-1 knockout mouse.

A second research domain is the characterization of cyclic nucleotides and their effector proteins. At www.cyclic-nucleotides.org side effects of the used cGMP-and cAMP-analogs can be looked up.

Clinical Biochemistry and Laboratory Medicine
(S. Gambaryan, J. Geiger)

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 is part of the SFB 688 and will be prolonged until end of 2013.

The BMBF network project SARA (System biology of prostaglandin and ADP P2Y12 receptor signaling pathways) was funded until 2012 within the framework of the BMBF research initiative "system biology in medicine" The goal of the BMBF project is to obtain a comprehensive understanding of platelet function regulation in healthy as well as diseased states.

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.

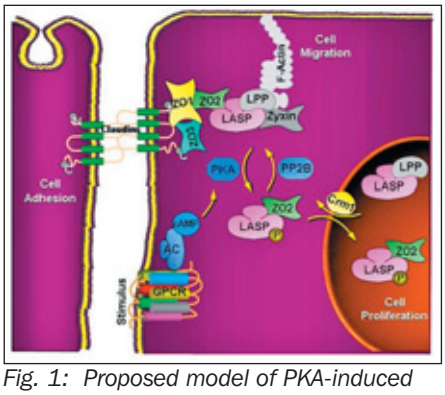

Fig. 1: Proposed model of PKA-induced LASP-1 translocation. Under basal conditions, LASP-1 is associated with F-actin, zyxin and ZO-2 at the plasma membrane. Upon LASP-1 phosphorylation by PKA via activation of G-coupled receptor (GCRP), LASP-1 binding to F-actin and zyxin is impaired and the protein detaches from the plasma membrane, forms a complex with ZO-2, and translocates into the nucleus. In return, nuclear export is regulated by reversible binding to the exportin Crm-1. Activation of protein phosphatase PP2B by PKA results in the dephosphorylation of LASP-1 and return of the protein to the plasma membrane.

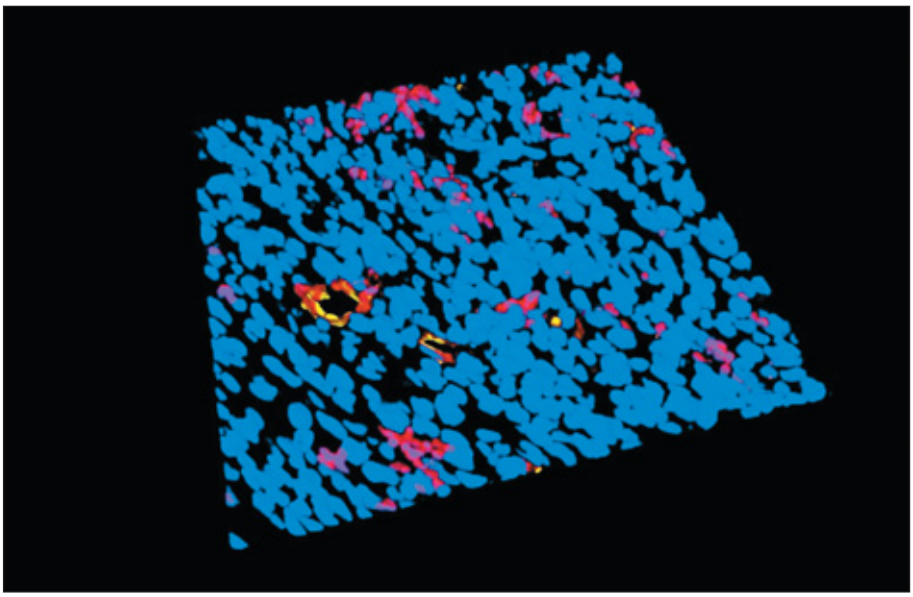

Fig. 2: Targeted delivery of a tumour vessel specific agent. The distribution of a vessel specific agent within the tumour is shown in green. Enrichment is observed in the blood vessels (red immuno staining), while the tumour cells themselves (blue counter stain) and blood cells (magenta) show only minor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

Angiogenesis and Tumour
(E. Henke)

Dr. Erik Henke 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.

Immune pathogenesis of atherosclerosis
(A. Zernecke)

In January 2014 Prof. Dr. Alma Zernecke, formerly heading the Vascular Biology Division at the Department of Vascular Surgery of the Technical University Munich, was appointed as new director of the institute. Her research centers on vascular diseases with its main focus on the involvement of immune responses and the migration of immune cells during the development of atherosclerosis and vascular remodeling after injury.

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).

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Mihlan S, Reiß C, Thalheimer P, Herterich S, Gaetzner S, Kremerskothen J, Pavenstaedt H, Lewandrowski RS, Sickmann A, Butt E. (2013) Nuclear Import of LASP-1 is regulated by Phosphorylation and Dynamic Protein-Protein Interactions. Oncogene 18:2107-2113.

Subramanian H, Zahedi RP, Sickmann A, Walter U, Gambaryan S. (2013) Phosphorylation of CalDAG-GEFI by protein kinase A prevents Rap1b activation. J. Thromb. Haemost. Epub.

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Döring Y, Manthey HD, Drechsler M, Lievens D, Megens RTA, Soehnlein O, Busch M, Manca M, Koenen RR, Pelisek P, Daemen MJ, Lutgens E, Zenke M, Binder CJ, Weber C, Zernecke A. (2012) Auto-antigenic protein-DNA complexes stimulate plasmacytoid dendritic cells to promote atherosclerosis. Circulation 125:1673-1683.

3.14 Department of Dermatology, Venereology and Allergology

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Professor Dr. med. Henning Hamm
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Professor Dr. rer. nat. Marc Schmidt
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Mission and Structure

The Department of Dermatology, Venereology and Allergology offers the entire spectrum of conservative dermatology, allergology, dermatologic surgery and dermato-oncology in patient care, research and teaching. Residents can obtain a full specialization in dermatology and venereology; additional board certifications 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*. In 2013, the Interdisciplinary Center for Allergic Diseases *(Allergiezentrum Mainfranken)* was founded. Apart from the department head, 3 professors of dermatology or molecular dermatology and 3 associate professors have been working in research and education during the period under report. Ten attendings, 7 further specialists in dermatology and 15 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:

- Outpatient clinic
- consultations for specific skin diseases (e.g. pediatric dermatology, autoimmune disorders, hair diseases, proctology)
- Inpatient clinic for conservative dermatology and dermato-surgery
- Skin Cancer Center with inpatient clinic for dermato-oncology
- Interdisciplinary therapy unit for dermato-oncology
- day clinic (leg ulcers/wounds, general dermatology, dermato-oncology)
- Outpatient clinic for allergology
- Outpatient clinic for phototherapy and photodynamic therapy
- Division of dermatohistopathology and autoimmune diagnostics
- Laboratory for dermatologic infectiology (mycology, serology)
- Research laboratories with focus on dermato-oncology, immunology and inflammation

Focuses of Clinical Interest

- Dermatooncology (A. Gesierich, A. Kerstan, M. Wobser)
- Allergology (A. Trautmann, A. Kerstan, J. Stoevesandt)
- Autoimmune and inflammatory skin diseases (M. Goebeler, S. Benoit, J. Stoevesandt)
- Hair diseases (H. Hamm, A. Kerstan)
- Dermatologic surgery (G. Weyandt, D. Presser, A. Gesierich)
- Phlebology (D. Presser) and proctology (G. Weyandt)
- Paediatric dermatology (H. Hamm, S. Benoit, M. Wobser)
- Dermatologic infectiology (A. Kolb-Mäurer)

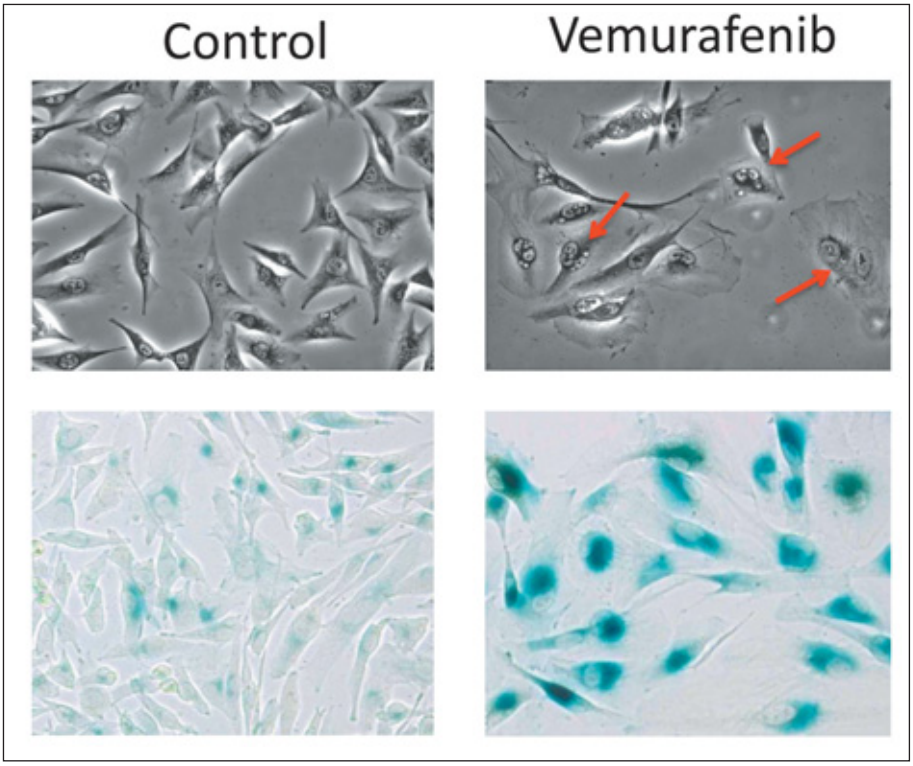

Fig. 1: Appearance of senescence features in melanoma cells in response to BRAFV600E inhibition. The V600E mutation in the protein kinase BRAF is frequently present in melanoma. Vemurafenib is a highly specific BRAFV600E inhibitor. Here we demonstrate that treatment of BRAFV600E melanoma cells with Vemurafenib induces several characteristics of senescence, a tumor suppressor mechanism. Phase contrast images demonstrate increased cell size and appearance of bi- or multi-nucleated cells. Activity of the senescence-associated-β-galactosidase (blue staining) is increased in Vemurafenib-treated BRAFV600E melanoma cells.

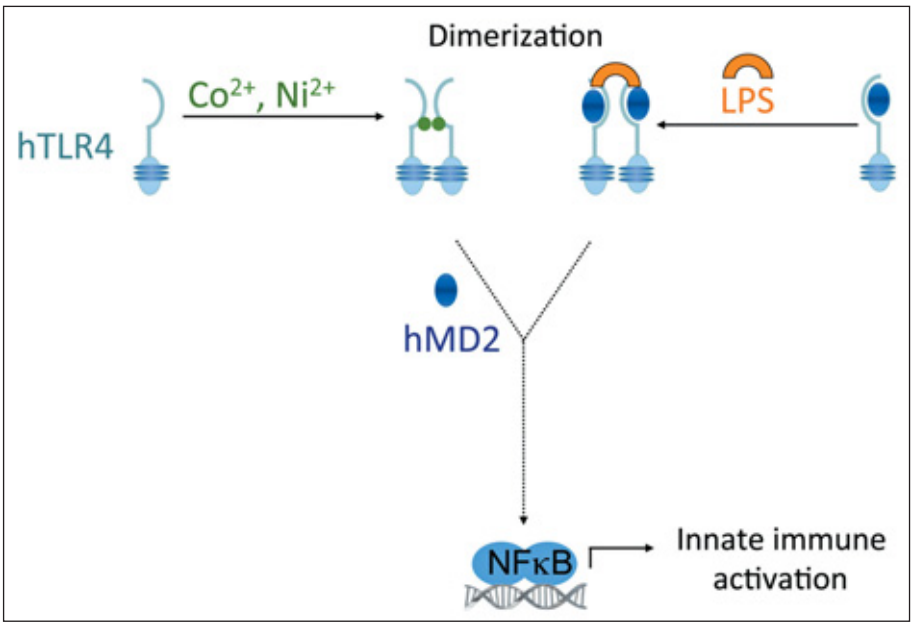

Fig. 2: Activation of TLR4, a receptor of innate immunity, by contact allergens nickel and cobalt. Metal allergens nickel and cobalt (green spheres) bind to non-conserved histidines (H456 and H458) in human toll-like receptor 4 (TLR4, light blue), the natural receptor for bacterial lipopolysaccharide (LPS), thereby triggering an innate immune response. Mechanistically, metal ion-binding to histidines of two opposing TLR4 molecules results in receptor homodimerization, which presumably facilitates recruitment of the TLR4 co-receptor MD2 (dark blue) that is required for further activation of downstream proinflammatory signalling cascades such as the NF-κB pathway. Unlike metal-induced TLR4 dimerization, which can occur in the absence of MD2, LPS-induced receptor dimerization strictly requires MD2 as ligand binding is mediated by interaction with hydrophobic residues in both TLR4 and MD2. The differential requirement of MD2 for LPS- and metal-induced TLR4 dimerization may allow the development of specific inhibitors of metal-induced contact dermatitis without affecting bacterial responses.

- Dermatohistopathology (H. Kneitz, A. Kerstan, M. Wobser)

Major Research Interests

Tumor biology and tumor immunology

Many patients are referred to the Dermatology department because of skin cancers. A main field of research therefore addresses aspects of the biology of cutaneous tumors. Focuses during the period under report were:

- signal transduction in Merkel cell carcinoma
- viral carcinogenesis
- tumor senescence
- small molecule inhibitors of the MAP kinase pathway in melanoma
- tumor suppressor proteins in skin cancer
- melanoma immunology
- melanoma genetics
- apoptotic signalling pathways in epithelial cutaneous tumors
- cell migration and neoangiogenesis
- pathogenesis of primary cutaneous B- and T-cell lymphoma
- phenotypic and molecular characterization of rare cutaneous lymphoma subtypes (peripheral T-cell lymphoma, NOS)

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.

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Haferkamp S, Borst A, Adam C, Becker TM, Motschenbacher S, Windhövel S, Hufnagel AL, Houben R, Meierjohann S. (2013) Vemurafenib induces senescence features in melanoma cells. J Invest Dermatol. 133:1601-1609.

Houben R, Adam C, Baeurle A, Hesbacher S, Grimm J, Angermeyer S, Henzel K, Hauser S, Elling R, Bröcker EB, Gaubatz S, Becker JC, Schrama D. (2012) An intact retinoblastoma protein-binding site in Merkel cell polyomavirus large T antigen is required for promoting growth of Merkel cell carcinoma cells. Int J Cancer. 130:847-856.

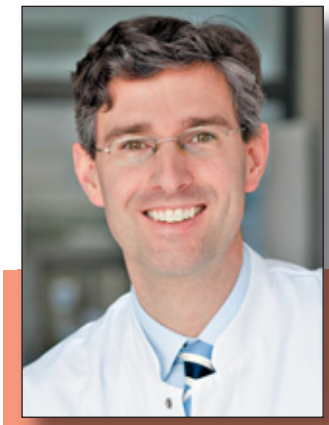
Kerstan A, Beyersdorf N, Stoevesandt J, Trautmann A (2012). Wasp venom immunotherapy expands a subpopulation of CD4(+)CD25+ forkhead box protein 3-positive regulatory T cells expressing the T-cell receptor V 2 and V 5.1 chains. J Allergy Clin Immunol. 130:994-6.e3.

Raghavan B, Martin SF, Esser PR, Goebeler M, Schmidt M. (2012) Metal allergens nickel and cobalt facilitate TLR4 homodimerization independently of MD2. EMBO Rep. 13:1109-111.

Willmes C, Adam C, Alb M, Völkert L, Houben R, Becker JC, Schrama D. (2012) Type I and II IFNs inhibit Merkel cell carcinoma via modulation of the Merkel cell polyomavirus T antigens. Cancer Res. 72:2120-2128.

3.15 Department of Diagnostic and Interventional Radiology

CONTACT DETAILS



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Mission and Structure

The Department of Diagnostic and Interventional Radiology provides the complete spectrum of modern radiological services at the University Hospital of Würzburg. 34 physicians and eight scientists, as well as 44 technicians work together to ensure state-of-the-art diagnostics and interventional radiology.
Over 23.250 patients are scanned each year with four MRI systems (2 x 1,5T and 2 x 3T) and three Spiral-CT scanners that are available for emergency patients 24 hours a day. A main topic in diagnostic imaging and preventive medicine is the assessment of breast lesions, using mammography, sonography and MR-mammography. In order to rule out or assess breast cancer each year about 8.000 women undergo examinations at the Department of Diagnostic and Interventional Radiology. A field of valued expertise for in- and outpatients at the University Hospital is the treatment of diseases of the vascular and the biliary system. Modern interventional radiology performs dilations of 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 Department of Diagnostic and Interventional Radiology offers a postgraduate training in Radiology including the subspecialties of Pediatric Radiology and Neuroradiology.

Major Topics of Research

Intervention

(R. Kickuth, A. Dierks, N. Hassold, A. Sauer, F. Wolfschmidt)

Among others, the effectiveness and clinical outcome of iliac artery embolisation prior to EVAR utilizing Amplatzer Vascular Plug I or coils is evaluated. Another task is to test I-Flow measurements for better diagnosis of endoleaks during thoracic aortic stent graft implantations. The effectiveness and clinical outcome of Hematrix Active Patch for postinterventional hemostasis after use of large volume catheter sheaths (6 – 8 French) is under current trial in the interventional suite.

Novel MR Methods

(W. Kenn, H. Köstler, C. Ritter, T. Wech, A. Weng)

The interdisciplinary team develops novel MR imaging techniques. Major aims include rapid imaging techniques for real-time evaluation of the human heart, for rapid evaluation of MR relaxation parameters, accelerated 3D MR-cholangiography and dynamic imaging of the pelvis with high temporal and spatial resolution. Novel reconstruction techniques for 2D and 3D rea-time imaging with parallel acquisition and compressed sensing are developed. Furthermore, dedicated k-space read-out techniques and dynamic sodium imaging with short echo times are tested for increased image quality.

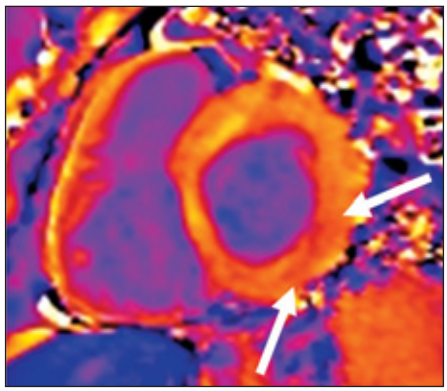

Fig. 1: Basal short axis view of the heart in a patient with Fabry disease. Myocardial T1-mapping utilizing modified Look-Locker-Inversion-Recovery (MOLLI) at 3 Tesla reveals intramural fibrosis of the posterolateral wall (arrows).

Cardiovascular Imaging

(Th. Bley, H. Köstler, C. Ritter, J. Donhauser, N. Hassold, S. Herz, T. Gassenmaier, J. Kunz, B. Petritsch, D. Stäb, A. Weng)

The cardiovascular research activities are jointly performed with specialists from cardiology, cardiac surgeons and basic scientists.
The main focus of cardiac high field MR imaging lies on functional and metabolic imaging, as well as tissue characterization. The impact of myocardial edema, myocardial perfusion and myocardial necrosis in myocardial infarct patients is studied. Techniques for visualization of myocardial hemorrhage and quantitative perfusion analysis are developed. High field sodium MR imaging for quantification of sodium content in skeletal muscle and myocardium in patients with hyperaldosteronism is scrutinized. MR proton spectroscopy techniques are applied for assessment of myocardial and hepatic steatosis as negative prognostic parameters within the Würzburg Adipositas Study (WAS) and as routine imaging in patients with Fabry disease.
Special focus is placed on identification and quantification of diffuse myocardial fibrosis utilizing T1-mapping techniques.
Absolute quantification of myocardial perfusion of endothelium based vasoreaction is studied utilizing the Cold Pressor Test (CPT) in various systemic diseases.
Ultrahigh resolution 17,6 Tesla MRI in mice models are utilized for evaluation of aortic elasticity and pulse wave velocity with nanoparticle contrast material in arteriosclerosis.
High resolution MR imaging of the superficial temporal artery in giant cell arteritis is applied for evaluation of extent of the di-

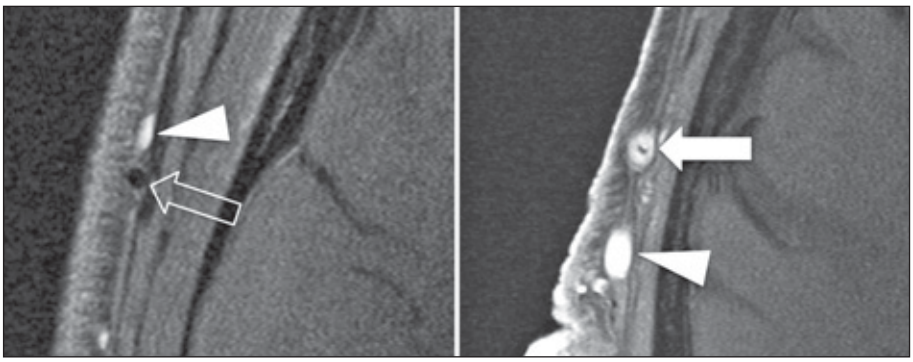

Fig. 2: 3 Tesla MRI of the superficial temporal artery in a healthy volunteer (open arrow in left image) and of the inflamed temporal artery in a patient with giant cell arteritis (arrow in right image). The arrowhead points at the superficial temporal vein.

sease in the vasculature from head to toe. Sex- and age-specific changes of the aortic root in patients with aortic stenosis are studied with cardiac CT imaging. The value of cardiac CT for interventional planning of Transarterial Aortic Valve Implantation (TAVI) is assessed.

Pediatric Radiology
(H. Köstler, H. Neubauer, C. Wirth, S. Veldhoen, A. Sauer, D. Stäb, A. Thurner)

Interdisciplinary projects study whole body MR techniques including diffusion weighted imaging in inflammatory and oncological diseases. The relationship between lung function and morphological changes in patients with mucoviscidosis are examined by MRI in free breathing without contrast agents. Ultrasound-based tissue elastography is analyzed in diseases of the thyroid gland. Further interdisciplinary focuses include longitudinal studies on safety of ultrasound contrast media and on morphological changes in hypophosphatasia with enzyme replacement therapy.

MR mammography of pathologies of the female breast
(T. Pabst, U. Schedelbeck, E. Schmid, A. Thurner)

While only the conventional mammography is authorized for breast cancer screening in Germany, it is known that MR mammography achieves a higher detection sensitivity especially for smaller breast cancer and avoids radiation exposition.
While using high temporal resolution 3T MR techniques in MR mammography studies for visualization and quantification of the contrast agent passage, a fat saturation method (DIXON) and diffusion weighted imaging (DWI) are performed to improve specificity for characterization of pathologies.

MRI of the lung
(Th. Bley, H. Köstler, T. Pabst, C. Ritter, C. Wirth A. Fischer, S. Sauer, D. Stäb, S. Veldhoen)

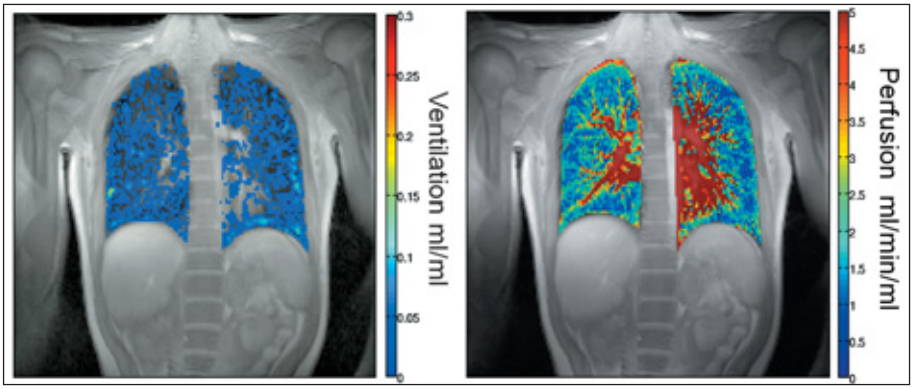

Fig. 3: Time resolved quantitative parameter maps of the lung of a healthy volunteer. Left: Ventilation as a function of a respiratory cycle; Right: perfusion as a function of a heart cycle.

The aim of this research project is to determine perfusion and ventilation of the human lungs simultaneously by means of MRI in free breathing without contrast agent using SENCEFUL (SElf-gated Non-Contrast-Enhanced FUnctional Lung imaging) and to display both in semi-quantitative maps. Clinical studies assess whether tissue pathologies can be detected and differentiated from healthy tissue in cystic fibrosis, chronic obstructive lung disease and bronchial carcinoma by means of perfusion and ventilation changes.

Teaching

Physicians of the Department of Diagnostic and Interventional Radiology hold lectures for medical students on radiology techniques and image interpretation and offer continuing medical education regularly for physicians from other Departments of the University Hospital, surrounding hospitals or private practice.

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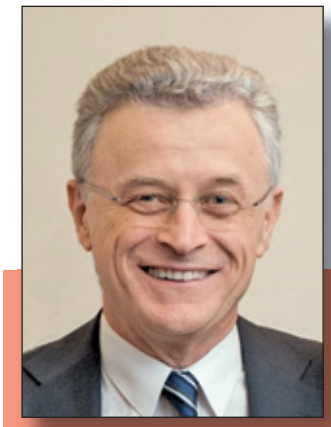
3.15.1 Division of Neuroradiology

CONTACT DETAILS



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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 and one 1.5T MR scanner operated exclusively by the department plus one 1.5T MR scanner operated in alternation with the Pediatric Radiology.

Staff: 3 senior physician positions, 7 residents, 11 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) are the top priorities 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)

As part of the Comprehensive Heart Failure Center (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 Research Center for Magnetic Resonance Bavaria (MRB) we explore quantification of MR relaxation times for improved diagnosis of neurodegenerative disorders.

Neurooncology
(M. Warmuth-Metz, B. Bison)

The neuroradiological reference site of HIT-Studies is located in the Department of Neuroradiology and serves all German multi-centric, pediatric neurooncological studies. Classification of different stages of the disease is the basis for treatment recommendations. Reference staging is an inclusion criterion for most of the pediatric brain tumor studies. New methods and treatment concepts are permanently discussed, explored and designed with the national and international reference centers, ensuring standardized guidelines for the imaging of children with brain tumors. Third-party funded by the German Child Cancer Foundation (Deutsche Kinderkrebsstiftung).

Pediatric Neuroradiology
(M. Warmuth-Metz)

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

Experimental MR Imaging
(G. Homola)

Exploration of new in vivo imaging methods of vascular diseases in close cooperation with the Department of Neurology. Special coils, optimized MR sequences und cont-

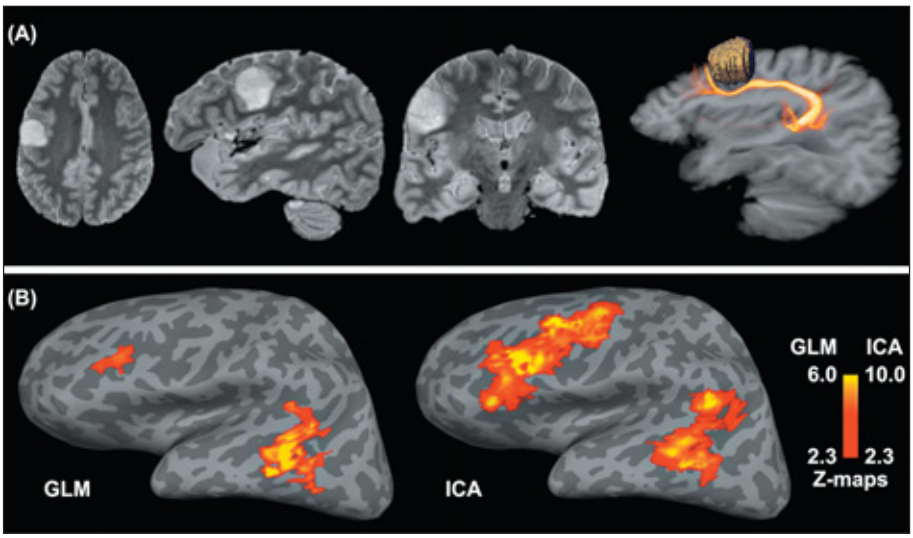

Fig. 1: (A) On the left: axial, sagittal and coronal view of a left frontal oligodendroglioma (T2/FLAIR). On the right: wireframe model of the tumor in proximity to the arcuate fasciculus as volume rendering on a projection view. (B) fMRI activations evoked in Broca's and Wernicke's areas by auditory detection of words vs. non-words. Data driven Independent Component Analysis (ICA) tends to be more sensitive and specific than the General Linear Model (GLM) and helps to prevent false-negative results in a clinical context.

rast agents with altered molecular structure are applied. Furthermore, the impact of metabolic disorders on the CNS is examined by multimodality imaging techniques. Plasticity of the auditory system related to vestibular schwannoma is analyzed by diffusion tractography and diffusion tensor imaging (DTI) in collaboration with the Department of Neurosurgery.

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

Joint research projects with the Department of Neurosurgery, the Department of Neurology and the Clinic for Psychiatry as well as the Department 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. We relate fMRI activation probabilities and structural connectivities in presurgical language mapping to assist intraoperative neuronavigation with the view to preserve functionally vital cortical areas and fiber tracts from surgical damage. (cf. Fig. 1) Characterization and quantification of neuronal resting-state networks by fMRI. Improving in vivo magnetic resonance spectroscopy (MRS) and quantified perfusion techniques 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.

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

Improvement of the effectiveness of vessel recanalization. Examination of pharmacological and mechanical recanalization. Interventional treatment of acute strokes with new stent-based methods. Diagnostics and interventional treatment of vasospasms after subarachnoidal hemorrhages. Research on effective therapeutic approaches on large cerebral aneurysms.

Teaching

The Department of Neuroradiology offers students of the University of Würzburg a wide range of lectures and courses within the radiological and neuroradiological teaching. The head of the department is authorized to full neuroradiological training (3 years). The department is actively engaged in the education of Bachelor, Master and PhD students.

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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 16,000 examinations are performed annually. In addition, more than 850 in-patients are treated with radioactive isotopes. Approximately 150 out-patients receive treatment for chronic inflammation of joints. The Division of Experimental Nuclear Medicine and Radiochemistry, headed by Prof. Samnick, operates a cyclotron to produce the PET-radioisotopes ^{18}F, ^{11}C, ^{15}O, ^{13}N and ^{123}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
(S. Samnick, A. Schirbel)

Translational research is supported by the Radiochemistry Department, providing innovative imaging biomarkers for molecular imaging with PET/CT and SPECT/CT as well as radionuclide based therapies. After successful implementation of a novel cyclotron and validation of radiotracer production, first radiotracers could be produced from July 2011. In the past 3 years, the following research projects could be initiated or supported: SFB688 “Mechanisms and imaging of cell-cell interactions in the cardiovascular system” (DFG), “FDG-PET and iodometomidate imaging for adrenocortical tumors (FAMIAN)” (DFG), Comprehensive Heart Failure Center Würzburg “Prevention of heart failure and its complications” (BMBF), “Integrated therapy unit multiple myeloma” (Wilhelm Sander- Stiftung), “Novel recombinant vaccinia viruses and radiotracers for molecular PET imaging and tumor treatment (MoBiVir)” (BMBF), „Imaging dyskinesia in people with Parkinson’s disease” (The Michael J. Fox Foundation for Parkinson’s Research), „Imaging of molecular biomarkers for clinical heterogeneity and disease progression in Parkinson´s disease” (IZKF Würzburg), and further projects funded by the IZKF Würzburg.

Pre-clinical imaging/Cardiology
(T. Higuchi)

Imaging biomarkers provided by the radiochemistry unit will be used in a translational working program using preclinical PET and SPECT scanners. 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 α 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.

Diagnosis and therapy of thyroid disorders
(P. Schneider, J. Biko)

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.

Medical Physics/Radiation Safety
(M. Lassmann)

The main scientific research areas comprise radiation protection, internal dosimetry in nuclear medicine and the combination of biodosimetric methods and physical dosimetry as well as improvement of dosimetric methods for isotope based therapies. In collaboration with a Norwegian company, initial data on the dosimetry of a CD37-specific antibody have been collected. The beta-emitter labeled construct (177Lu-antiCD37) will be used in a clinical phase I-trial recruiting patients with Non-Hodgkin’s-Lymphoma. From June 2011 to the end of 2013, the BMBF sponsored project NUKDOS has been performed together with the University of Ulm and the BfS (Bundesamt für Strahlenschutz). This project developed novel methods suitable to standardize dosimetry of radionuclide based therapies.

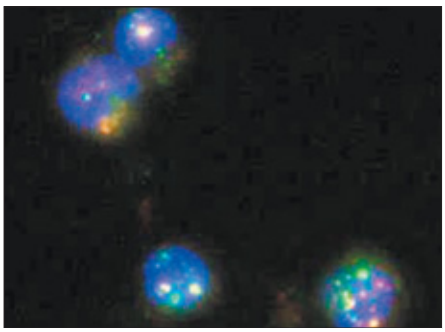

Fig 1: Gamma-H2AX-Foci (green) und 53BP1-Foci (red) within the nucleus (blue) of leucocytes after in-vitro radiation using iodine-131.

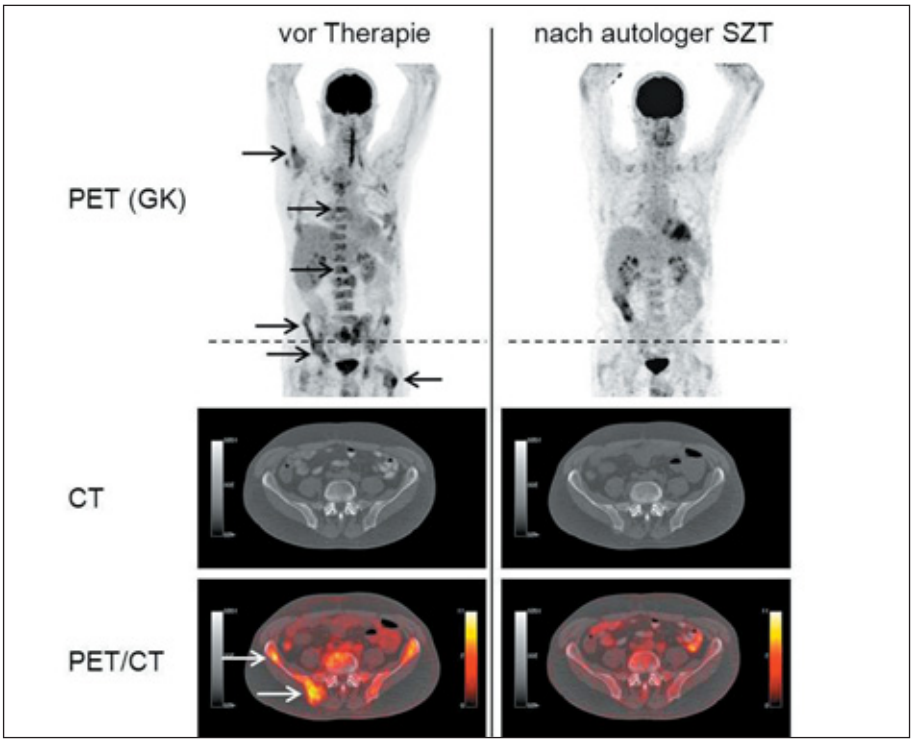

Fig. 2: Molecular imaging allows the early detection of response to anticancer treatment. In the figure, a PET/CT follow-up study is shown indicating viable bone lesions of multiple myeloma (arrows) prior to treatment. After autologous stem cell transplantation, molecular imaging shows a complete remission.

Oncology
(A. Buck, K. Herrmann)

The range of radiopharmaceuticals has been broadened, including also innovative imaging biomarkers such as radiopeptides (^{68}Ga-PSMA, ^{68}Ga-CPCR4-2). There is a close collaboration to members of the Comprehensive Cancer Center, invasive and non-invasive disciplines of the UKW and regional hospitals as well as basic scientists. Patients with tumors of the adrenal gland are more frequently examined with the radiopharmaceutical 123I-iodmetomidate, allowing specific detection of tumors arising from the adrenocortical region based on specific 11ß-hydroxylase activity. A research program recently submitted together with colleagues from the Dept. of Endocrinology focusing on the clinical evaluation of the radiotracer (FAMIAN) was recently granted by the DFG. Within the coordinated program "integrated therapy unit multiple myeloma", funded by the Wilhelm Sander-Stiftung, innovative and more established radiotracers are used for characterizing the individual tumor heterogeneity. In a translational project, suitable biomarkers were selected in in-vitro experiments. At present, these tracers are further characterized in preclinical animal models. The regulatory hurdles to perform a clinical trial are already fulfilled.

Neurology/Psychiatry
(I. Isaias)

The research area "neuroimaging" is headed by Prof. Isaias. He is also chairing the IZKF sponsored research program "Imaging of molecular biomarkers for clinical heterogeneity and disease progression in Parkinson's disease". In cooperation with the Department of Neurology, dopamine transport scintigraphy is currently examined in patients with Parkinson's and atypical Parkinson's disease and compared to clinical/neurological parameters. The research group is funded also by the Michael J. Fox foundation for Parkinson's disease.

Neuromusculo-skeletal system
(P. Schneider)

Biomechanical research of the musculoskeletal system is further strengthened by two novel patents: „Ergometer, Laufschuh und Fahrradpedal" (Pat.-Nr. 10 206 032 081) and „Kraftauswertevorrichtung und Kraftauswerteverfahren zur Bestimmung von Gleichgewichtskenngrößen" (Pat.-Nr. EP 1 763 656 B1). A prospective controlled, 3-arm cohort study has recently shown that medication with thyroid hormones has no effect on the muscular-skeletal system.

WHO REMPAN-Center
(C. Reiners, R. Schneider)

The major research interest of the collaboration center REMPAN (Radiation Emergency Medical Preparedness and Assistance Network), recently re-accredited by the WHO, includes protection of inhabitants in case of radiation emergencies. In cooperation with the Belarus partner institution ARNICA, the WHO REMPAM Center (www.rempan.ukw.de) evaluates the incidence of breast cancer in patients with radiation induced thyroid carcinoma.

Teaching

In addition to lectures performed within the program "imaging techniques, radiation treatment and radiation protection", the Department of Nuclear Medicine participates in interdisciplinary lectures (e.g. "Interdisciplinary Oncology", "Communication in Oncology"). Lectures at a technical school are performed as well as dedicated programs for assistant medical doctors (workshop "thyroid ultrasound). Since 2012, the scientific program "Forum Nuklearmedizin Würzburg" is offered to medical doctors and scientists in the field. Since 2013, the program "Dialogue between Radiology and Nuclear Medicine" exists.

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3.17 Department of Radiation Oncology

CONTACT DETAILS

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General Information

The clinic for radiotherapy (stuff: 18.5 physicians, 12 medical physicists, 19 radiographers, 16 nurses) uses 5 linear accelerators (including IGRT by means of cone beam CT and an afterloading unit for remote controlled inserts of radioactive sources. Patients are treated in a policlinic department, in a ward with 20 beds and in a day ward with 10 treatment places. The ward for palliative care of the university hospital with additional 10 beds is linked to our department. Spiral-CT, ultra sound, as well as examinations with MR-tomography in co-operation with the Institute of diagnostic radiology and PET-CT scans at the nuclear medicine department provide the anatomical and physical data base for the computerised treatment planning. Radiation planning, dose calculations and the calibration and quality assurance of the treatment units are carried out by the section of medical physics. About 2200 patients are treated annually. By means of the day ward it is possible to avoid hospitalisation even in more intensive parts of the treatment, e.g. during concurrent chemotherapy. In addition to the typical spectrum of radiation therapy, intra- and extra-cranial 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, mamma and of the extremities are conducted.
Major Research Interests

Development of highly conformal treatment techniques

The optimisation of the temporal and spatial dose distribution, aiming to concentrate the impact at the tumour tissue and concurrently sparing nearby organs at risk is the general objective of our research.
Further developments of stereotactic treatments in the region of the body, of inverse planning techniques and the integration of temporal and spatial uncertainties are undertaken.

Medical Physics
(O. Sauer)

For Medical Physics this demands the development and implementation of increasingly complex technics, calculation and measurement of complex dose distributions with high accuracy, plus quality assurance at a high level for every irradiation. Therefore research concerns image guided radiotherapy (IGRT), optimisation and adaptation of intensity modulated radiation therapy (IMRT) and dosimetry of ionising radiation. Topics are: - computation of tomographic images with the patient in treatment position, image registration, - tracking of moving targets and movement compensation, - 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 non-coplanar techniques for the body region, - dose measurement and dose calculation under non-equilibrium conditions, especially for small fields and online dosimetry.

Radiation Biology
(T. Djuzenova)

Our radiobiological laboratory (4 scientists, 3 technicians, 1 grant position) is appropriately equipped to carry out basic research of the biological effects of ionizing radiation (IR) in human tumour and normal cells. During the last 2 years we further intensified our experiments on the Heat-Shock-Protein 90 (Hsp90) inhibition in combination with IR. The new data show that, simultaneous Hsp90 inhibition and irradiation may induce cell-type specific radiosensitisation as well as cytotoxicity against

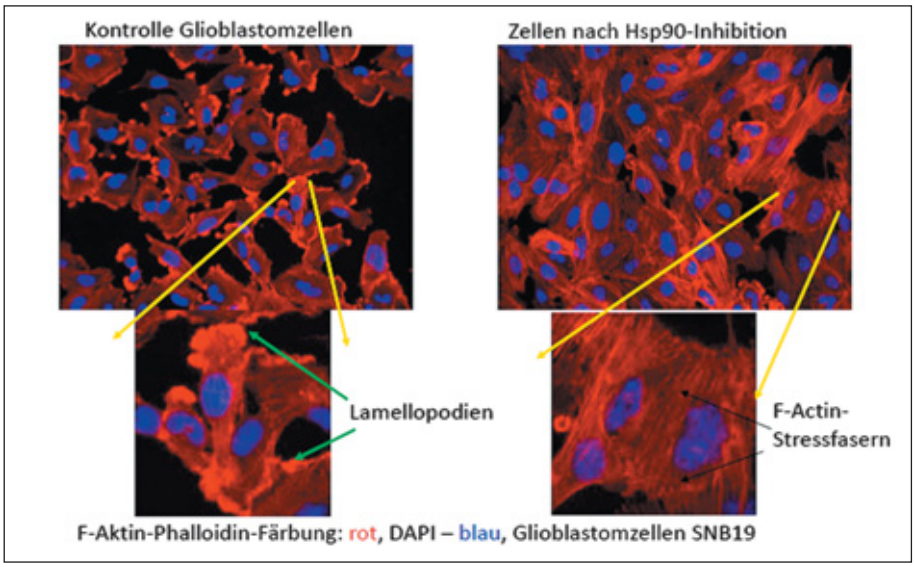

Fig. 1: Representative microphotographs of F-actin (phalloidin, in red) and nuclear (DAPI, in blue) co-staining of NVP-AUY922-treated and control SNB19 cells. Magnification, 400x. As seen from the images, Hsp90 inhibition with NVP-AUY922 (right-hand image) reduced the appearance of filopodia and lamellipodia but strongly increased the number of actin stress fibers [Hartmann et al., 2013].

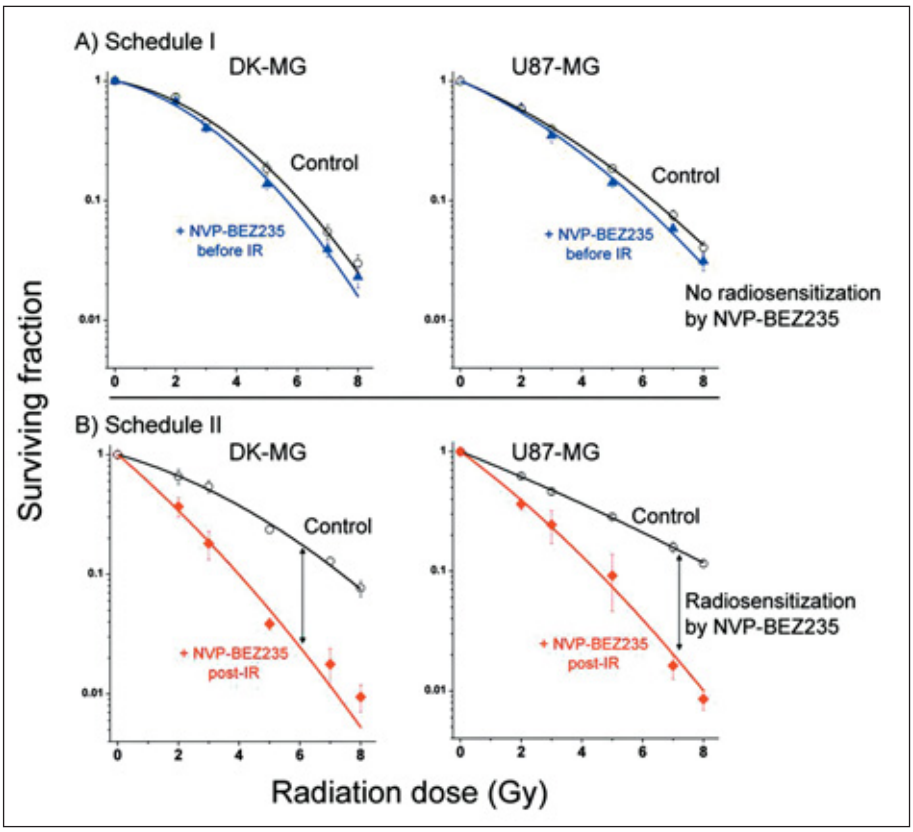

Fig. 2: Clonogenic survival of glioblastoma cell lines treated with NVP-BEZ235 and irradiated either in schedule I (top row) or schedule II (bottom row). Irradiated cells were plated for the colony-forming test either immediately after IR (top row) or 24 h post-IR (bottom row). After 2 weeks, colonies containing at least 50 cells were scored as survivors. Data derived from at least four independent experiments for each cell line and schedule were pooled together and fitted by a linear quadratic equation. The SD values are indicated by error bars.

tumour cells (Niewidok et al., 2012).
In addition, we found that treatment with Hsp90 inhibitor NVP-AUY922 reduced the appearance of filopodia and lamellipodia but strongly increased the number of actin stress fibers (Fig. 1, right-hand image) in glioblastoma SNB19 cells (Hartmann et al., 2013) under normoxia or hypoxia (0.1% O_2). Besides this, three independent *in vitro* migration/invasion assays revealed a striking ability of the Hsp90 inhibitors to decrease by 3-10 times the migration and invasivity of the tested tumor cell lines.
Besides Hsp90 targeting, during the report period we explored the possibility to combine IR with the inhibition of PI3K pathway which is often upregulated in tumour tissue. To this end, we studied the impact of inhibitor and IR schedule on the radiosensitizing ability of dual PI3K and mTOR inhibitor NVP-BEZ235 in four human glioblastoma cell lines (Kuger et al., 2012). We found that, depending on the drug-IR schedule, the NVP-BEZ235 can act either as a strong radiosensitizer or as a cytostatic agent in glioblastoma cells (Fig. 2).

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.
Two randomized multicentre trials, one for organ preservation in Larynx/Hypo-pharynx Cancer (Delos 2) and one about concurrent radio-chemotherapy in advanced lung cancer (GILT-CRT) were successfully finished in 2012. Respective publications are under preparation. The department is leading national and international consortia on dose escalation studies through precision radiation therapy (Spine, Synergy Consortium, WG stereotaxis of DEGRO). The department head is also heading the Ärztliche Stelle § 83 StrlSCHV of the Bavarian State Medical Chamber and is member of the Radiation Protection Commission at the federal ministry of environment.
An additional activity is palliative radiation oncology. In 2013 the results on prognosis adapted radiation therapy for lung cancer have been published. Currently a project concerning adequate access to specialized palliative care is conducted.

Teaching

Except the obligatory courses on radiology the working groups give classes and hold seminars for residents, medical physicists and biologists. PhD, MD, master and bachelor thesis are supervised.

SELECTED PUBLICATIONS

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

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Mission and Structure

The clinic of Otorhinolaryngology, plastic and aesthetic surgery (28 physicians, 5 scientists, 8 research fellows) has 92 regular beds including 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. Development of coated electrodes for medical treatment of middle and inner ear.

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. Intraoperative monitoring of transfer function of active middle ear implants.

Inner ear biology
(K. Rak, J. Völker, S. Frenz, R. Mlynski in Zusammenarbeit mit dem Institut für klinische Neurobiologie, M. Sendtner)

Evidence and functional properties of neuronal stem cells in the rat cochlear nucleus. Dynamic changes of the neurogenic potential in the rat cochlear nucleus during postnatal development. Effects of defined gene mutations (TBCE gene) on inner ear structure in the pmn/pmn mouse. Interactions of neuronal structures with semiconductor materials.

Therapeutic use of stem cells in the damaged cochlea
(A. Radeloff, P. Schendzielorz)

Improvement of survival of ganglion cells following experimental deafening by local stem cell application in the cochlea of the guinea pig. Development of a stem cell coating on inner ear electrodes for optimization of functional linkage in cochlear implants.

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

Development of new objective testing procedures for frequency specific screening in newborns. Analysis of prespeech sounds in babies to objectify early speech development in pedaudiology.

Cochlear- and brain stem implants
(R. Mlynski, W. Shehata-Dieler, A. Radeloff, S. Brill, S. Kaulitz, in cooperation with the department for neurosurgery, C. Matthies, 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 electrostimulation 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 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. Objectivication of binaural hearing in persons with normal and impaired hearing.

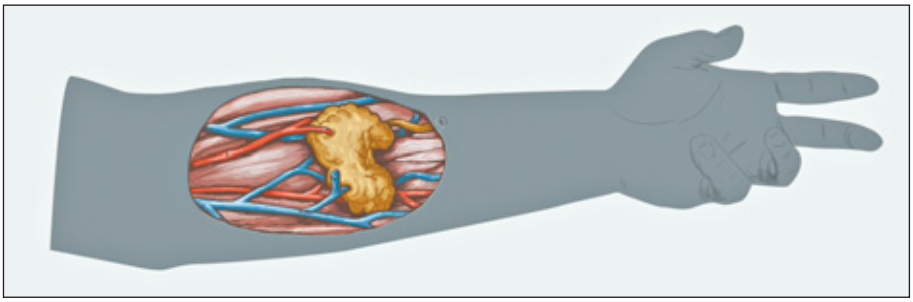

Fig.1: Schematic drawing of a transplanted submandibular gland in a patient´s forearm.

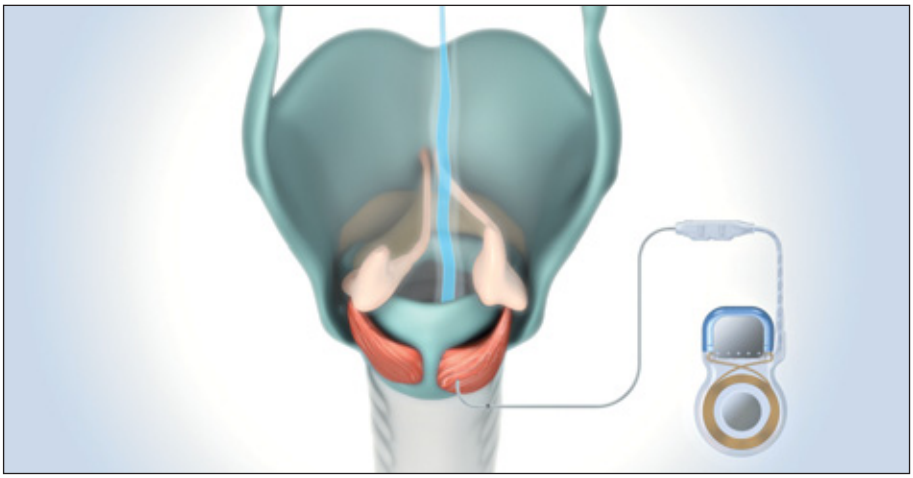

Fig. 2: Schematic drawing of the new Medel laryngeal pacemaker.

Hearing research
(M. Vollmer, A. Wiegner, in cooperation with the University of California, R. Beitel, and the Ludwig-Maximilians University Munic, B. 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, C. Köhler, C. Ginzkey, S. Hackenberg, G. Steussloff)

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
(K. Frölich, A. Scherzad, N. Kleinsasser, M. Burghartz in cooperation the the department of orthopedics, U. Nöth)

Establishment of stabile cartilaginous structures with different scaffold materials. Functionality of stem cell engineered tissue in an animal model.

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, department of dermatology, R. Houben, Fraunhofer Institute for silicate research, C. Gellermann)

Establishment of an interdisziplinary research group “use of nanomaterials in oncology“.

Compensatory saliva production following radiotherapy
(M. Burghartz, N. Kleinsasser, R. Hagen in cooperation with the institute for tisse engineering and regenerative medicine, H. Walles)

Development of cellbased compensatory saliva production in decellularized pig intestine (BioVasc®). Pilote study for a two staged autotransplantation of submandibular gland in humans.

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.

SELECTED PUBLICATIONS

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Schmidt M, Polednik C, Roller J, Hagen R. (2013) Cytotoxicity of herbal extracts used for treatment of prostatic disease on head and neck carcinoma cell lines and non-malignant primary mucosal cells. Schmidt M, Polednik C, Roller J, Hagen R.Oncol Rep 29:628-636.

Hackenberg S, Scherzed A, Technau A, Frölich K, Hagen R, Kleinsasser N. (2013) Functional responses of human adipose tissue-derived mesenchymal stem cells to metal oxide nanoparticles in vitro. J Biomed Nanotechnol 9:1-10.

Rak K, Völker J, Frenz S, Scherzed A, Radeloff A, Hagen R, Mlynski R. (2013) Dynamic changes of the neurogenic potential in the rat cochlear nucleus during post-natal development. Exp Brain Res. 226:393-406.

Ginzkey C, Scheich M, Harnisch W, Bonn V, Ehrmann-Müller D, Shehata-Dieler W, Mlynski R, Hagen R.(2013) Outcome on hearing and facial nerve function in microsurgical treatment of small vestibular schwannoma via the middle cranial fossa approach. Eur Arch Otorhinolaryngol. 270:1209-16.

3.19 Department of Ophthalmology

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Mission and Structure

A staff of 36 physicians and 89 nurses, technicians and scientists cares for approx. 20.000 outpatients and more than 5.700 inpatients annually. In 2012, about 6.900 surgical procedures and about 1.600 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 vitroretinal diseases and ocular trauma. Specialized teams care for eyelid affections, conjunctival, corneal and orbital diseases. Another main focus of the department is the section 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 been established in 2013. 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

Glaucoma and anterior segment of the eye

New strategies are developed to treat ocular surface disease, recent methods of cornea transplantation are studied, new surgical strategies to lower intraocular pressure in juvenile glaucoma (e. g., 360° trabeculotomy, 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.. 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.
Measurement of the peripapillary nerve fiber layer has become a standard procedure in glaucoma diagnostics. High resolution spectral domain OCT allows to separate the retinal ganglion cell layer from other retinal layers, thus helping to advance glaucoma diagnostics and follow-up.

Retinology and imaging methods of the posterior segment of the eye

The optical coherence tomography (OCT) is a well-established non-invasive method for the diagnosis of different diseases of the central retina like macular edema, vitreomacular traction syndrome or age related macular degeneration. OCT measurements provide optical slices through the retina, similar to B-scan images from ultrasonography, but with an improved spatial resolution by a factor of more than 20.

Basic Research

Cell Biology

Today there are two main research projects at the ophthalmic cell biology lab: Ocular scarring and cellular regeneration.
Scarring reactions take a central role in the pathophysiology of many ocular diseases such as contracture of the retina or postoperative conjunctival scarring after penet-

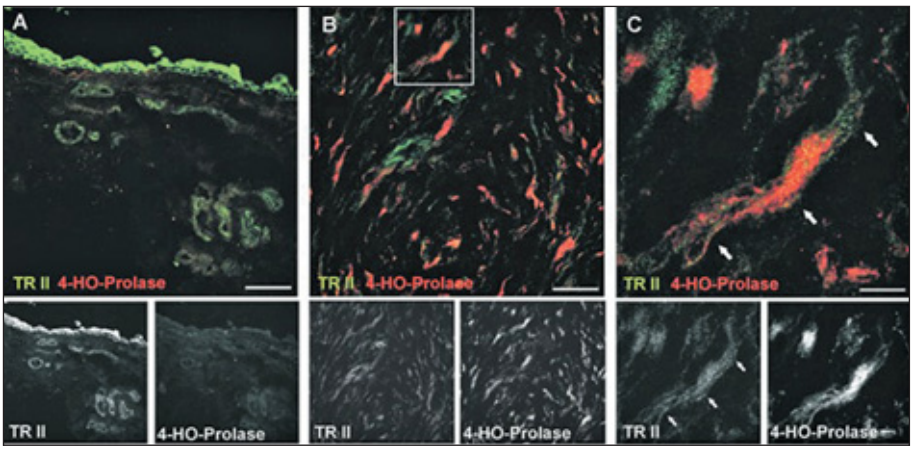

Fig 1: In contrast to native conjunctiva specimen postoperative scarred conjunctiva show many 4-HO-prolase positive fibroblasts with enhanced co expression of TGF-b- receptor type II (double immunofluorescence stain). (Figure by Dr. T. Meyer-ter-Vehn and Dr. D. Kampik, Research group for cell biology).

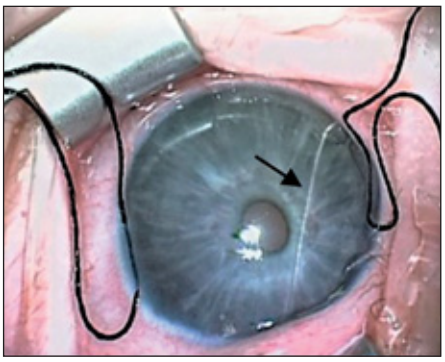

Fig. 2: Surgical field during a 360° trabeculotomy, a modern surgical method to treat congenital glaucoma. A microcatheter that had been inserted circumferentially via Schlemm's canal is used to open the trabecular meshwork 360°. In that illustration the catheter has already opened the trabecular meshwork by about 270°. (Figure by Prof. Dr. T. Klink, Research group for innovative glaucoma surgery).

rating glaucoma surgery. We established a cell culture model for conjunctival scarring using primary human tenon fibroblast (Fig. 1) enabling us to study biochemical and cell biology steps in the transdifferentiation of fibroblasts to myofibroblasts. We observed specific intracellular signaling events – inhibition of individual cell signaling molecules resulted in modulation of the scarring reaction. The most promising substances are now test in an animal model for postoperative ocular scarring.

Various cell types essential for maintaining vision do not regenerate in vivo but degenerate with age. Under certain conditions, however, some cells retain their capacity to undergo cell division. Our aim is to initiate mechanisms of cellular regeneration in otherwise quiescent cells. We test this in retinal pigment epithelial cells by activating or overexpressing cell cycle regulating transcription factors to trigger proliferation. In cooperation with the Würzburg Eye Bank and the Institute for Tissue Engineering, this is also applied to corneal endothelial cells.

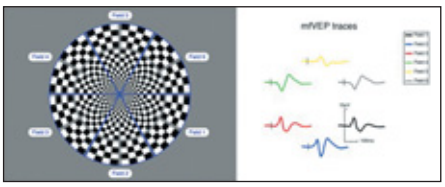

Fig. 3: Multifocal techniques allow to simultaneously record cortical mfVEP responses to inverting checkerboard patterns (left) from different parts of the visual field (right). Due to the complex surface of the visual cortex mfVEP signals from the upper and lower parts of the visual field show opposite polarities (Figure by Dr. Th. Meigen, Electrophysiology Lab).

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. Recently, these techniques were adapted (a) to study retinal ganglion cell function using pattern ERG recordings, which allows an early diagnosis of glaucoma, (b) to record retinal and cortical signals with multifocal techniques where the responses from different parts of the visual field can be recorded simultaneously (Fig. 3), and (c) 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.

SELECTED PUBLICATIONS

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Haigis W. (2012) Intraocular lens calculation after refractive surgery. Eur Oph Rev. 6:21-24.

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 out-patients and emergencies. Over the passed 2 years (2012-2013) 3,300 patients were treated surgically and 12,000 patients in the outpatient department. The outpatient 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
(M. Löhr, C. Hagemann, C. Matthies, R.-I. Ernestus)

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. Large regular outpatient clinics for patients with skull base tumours, sporadic and genetically based vestibular schwannomas and meningiomas (neurofibromatosis types 1 and 2) are the basis for these laboratory investigations and for clinical studies focusing on long-time functional outcome and quality-of-life. In cooperation with the Department for Tissue Engineering (Prof. Walles, Dr. Nietzer) culture models are developed to study tumour growth and invasion and for testing of pharmacological agents for future individualized adjuvant therapies.

Functional Microsurgery & Neurostimulation
(C. Matthies, V. Sturm)

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.
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 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 le-

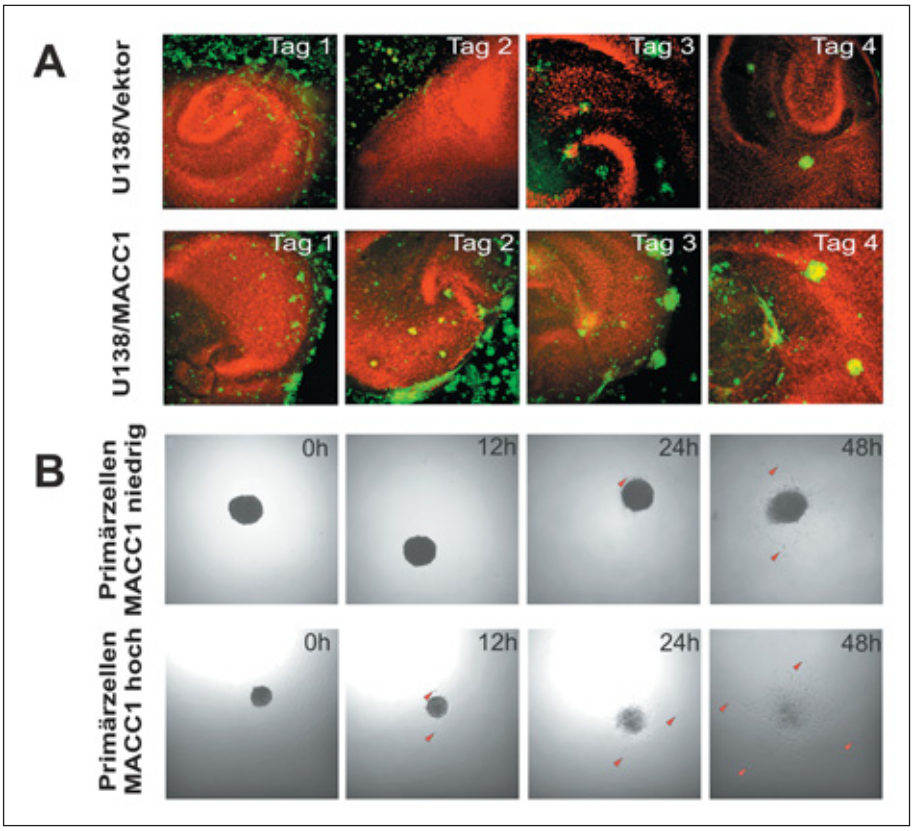

Fig. 1: MACC1 Overexpression promotes tumor formation and invasion and migration of glioblastoma cells. A) Transient overexpression of MACC1 in the glioblastoma cell line U138 promotes cell invasion and tumor formation in a mouse brain slice culture model (modified from Hagemann et al., Neuro-Oncol. 15, 2013). B) Primary cells isolated from patient glioblastoma material show high level of MACC1 expression and earlier and faster migration from cell sphaeroids as compared to cells with low endogenous MACC1 expression (unpublished data).

sions and life threatening dystonic storms. A developing topic is the combination of neuroprotective and regenerative factors.

Neurovascular Disease
(J.-Y. Lee, E. Kunze, C. Stetter, 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.

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. The inpatient service has 86 beds including an 8 bed Stroke Unit, a 10 bed Neurological Intensive Care Unit and a neurological emergency room, serving over 4,500 inpatients per year. The outpatient department provides for over 9,000 out-patient visits per year (including emergency admissions) and additionally runs an extensive in-house consulting service (2,500 consultations). 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 neuromuscular 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) and electron microscopy. The Department of Neurology in addition runs an interdisciplinary neuro-geronto-psychiatric outpatient clinic ("day care clinic") in collaboration 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 multimodal treatment of patients with advanced Parkinson´s (plus-) disease.
The Department has 36 full time academic members, 93 nursing staff members, 23 technicians and 10 staff members in administration and special services. Additional 13 academic positions are supported by extramural grants. In 2013 a junior research group „Imaging for molecular biomarkers for clinical heterogeneity and disease progression in Parkinson´s disease" headed by Dr. Dr. Ioannis Isaias and supported by the Würzburg Interdisciplinary Center for Clinical Research was established in cooperation with the Department of Nuclear Medicine. The Department of Neurology contributes to the Sonderforschungsbereich (Cooperative Project Center Grant) #688, joint projects within the FP7 Programme of the European Community 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, C.W. Ip, I.U. Isaias in cooperation with C. Matthies, Department of Neurosurgery, and A. Buck, Nuclear Medicine)

Deep brain stimulation: Clinical and experimental neurophysiological investigations on underlying mechanisms; acute and chronic ("brainradio") recordings in movement disorders; development of improved stimulation procedures. Kinematic laboratory: Evaluation of treatment effects in movement disorders, pathophysiology of gait disturbances; pathogenesis of dystonia in rodent models; skin as a histological marker for Parkinson´s disease; molecular imaging (PET, SPECT) of movement disorders; genetics of rare movement disorders.

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

Neuroimaging: Development and evaluation of new methods for in-vivo imaging of neuroinflammation by magnetic resonance imaging and PET (cooperation with Prof. P. Jakob, Department of Physics V, and Prof. S. Samnick, Nuclear Medicine). Pathogenesis of multiple sclerosis and polyneuritis (experimental autoimmune encephalomyelitis and neuritis); molecular mechanisms of disturbances of the blood brain barrier; molecular biomarkers in multiple sclerosis; international treatment trials; role of autoreactive antibodies in neurological disorders.

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 ("thromboinflammation"); development of novel antiplatelet 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, Department of Neurosurgery); functional and cellular stroke imaging using ultrahigh field MRI (coo-

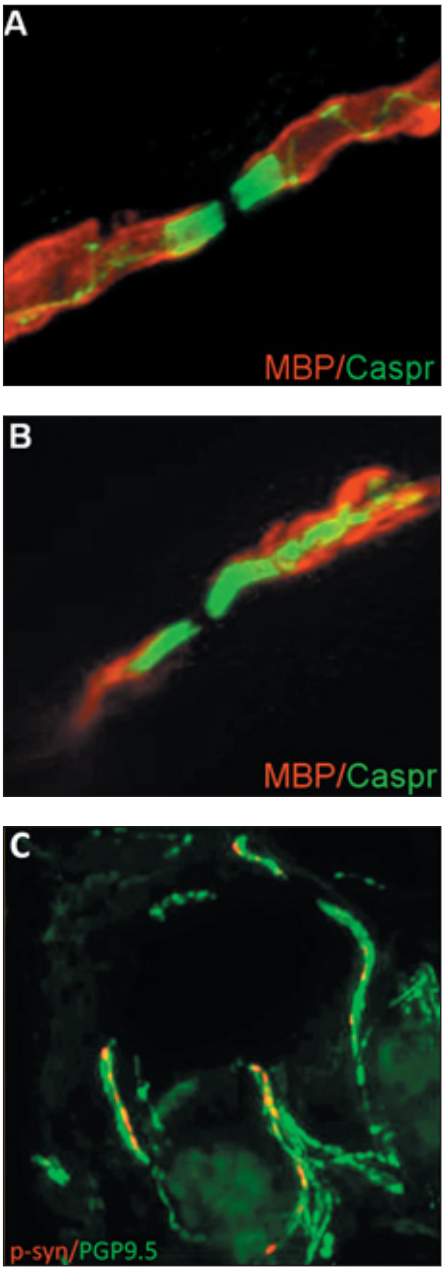

Fig. 1: Skin biopsies as diagnostic tool in neurology. (A,B) Immunostaining of human myelinated nerve fibres from skin punch biopsies for myelin basic protein, a myelin component (red), and caspr, a paranodal protein (green). (A) shows the strictly paranodal and mesaxonal location of caspr in a normal human subject. Note the pathological extension of caspr staining beyond the paranodal region in a patient with a demyelinating neuropathy. (C) shows pathological alpha-synuclein deposits (red) in skin nerves stained by the axonal marker PGP9.5 (green) in a patient with Parkinson´s disease (By Courtesy of Doppler/Sommer).

peration Department Physics V); studies on cognitive decline and interactions between heart and brain function during heart failure and stroke (Chronic Heart Failure Center, Würzburg); establishment of a supraregional stroke telemedicine network (starting in 2014) and an interdisciplinary neurovascular board; cerebrovascular outpatient clinic, international treatment trials.

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

Pathophysiology of neuropathic and generalized chronic pain with focus on neuro-immune interactions and their molecular regulation; skin biopsies as a diagnostic tool in neurology (neuropathies, M. Parkinson); pathophysiology of neurological complications in M. Fabry; pathophysiology of antibody-associated disorders of the CNS and PNS; international trials on treatment of pain and neuropathies.

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, D. Zeller, S. Klebe, 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 Musculoskelettal 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); genetics of neuromuscular disorders.

Teaching

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

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3.22 Institute for Clinical Neurobiology

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Mission and Structure

The Institute for Clinical Neurobiology was founded in 2000 as an independent institute at the University Hospital. The Institute is mostly working in basic science, but it is also involved in sustaining the special unit for motoneuron diseases at the Department of Neurology, in order to allow and ensure the transfer of scientific knowledge into clinical applications. Since 2010, the institute is situated in laboratories of the former Institut für Medizinische Strahlenkunde in building E4.

Major Research Interests

Central research focus are studies on the mechanisms of neuronal cell death, the establishment and analysis of animal models for motoneuron diseases, and the development of new therapies for the treatment of amyotrophic laterals sclerosis and spinal muscular atrophy, the most common forms of motoneuron disease in children and adults.

Further lines of research focus on the mechanisms how neural stem cells differentiate into neurons and functional neural circuits. Investigation of the signal transduction pathways by which neurotrophic factors influence differentiation, survival and axonal growth of neurons are of central interest. The generation and analysis of gene knockout mice allows investigating which signal molecules are involved in mediating these cellular effects of neurotrophic factors. Recently, it was shown that activation of the Trk-B receptor is involved in migration of newly generated nerve cells in the subcortical zone of the embryonic cerebral cortex. However, the receptor is not activated by its ligand, but transactivated via the activation of the epidermal growth factor receptor. We are currently investigating whether this mechanism plays a role in migration and metastasis of tumor cells.

Another research focus is the analysis of the pathophysiology of spinal muscular atrophy, the most common form of motoneuron disease in children. This disease is characterized by axonal defects and defects of neurotransmission at neuromuscular synapses. These defects are due to a defect in transport of mRNAs and also of non-coding RNAs (ncRNAs) in axonal projections in motoneurons. This finding correlates with clinical observations in patients with spinal muscular atrophy. On the basis of these experiments, new therapeutic strategies for this disease can now be developed.

In 2012, a new research group headed by Prof. Carmen Villmann was founded at the Institute. This group is interested in the molecular pathomechanisms of motor dysfunction caused by defects in glycinergic neurotransmission. Mutations in the human *GLRA1* gene, which codes for the alpha 1 subunit of the glycine receptor, are responsible for hyperekplexia (Startle Disease, Stiff-Baby Syndrom, OMIM #149400). Tactile or acustic stimuli cause a typical startle reaction that leads to loss of control on muscle tone and posture. Mouse models with corresponding mutations in the glycine receptor subunits and similar symptoms have been established (spastic, spasmodic and oscillator). These mouse lines can be used to study these diseases and the underlying mechanisms of altered motor control.

The Institute for Clinical Neurobiology is also involved in the patient care within a special unit for motoneuron diseases (Dept. of Neurology, Prof. Volkmann), in order to ensure the transfer of basic science into clinical applications.

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

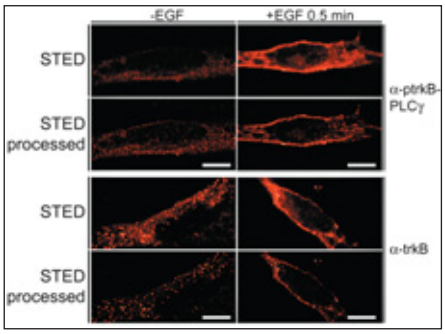

Fig. 1: Translocation of the Trk-B receptor from the endoplasmatic reticulum to the cell surface is stimulated by epidermal growth factor. This translocation mechanism regulates the subcellular distribution and thus the migration of young neurons from the subventricular zone to the cortex, which can then form networks in different the layers of the brain (taken from Pühringer et al., Nat. Neurosci. 2013).

Teaching

The Institute for Clinical Neurobiology is involved in the training of students in clinical neurobiology as well as the training of biology students (Bachelor and MSc Courses) with focus on neurobiology. Another focus is the training of students in biomedicine and participation in training programs for the class Neuroscience of the Graduate School of Life Sciences 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 Center of Mental Health, Department of Psychiatry, Psychosomatics and Psychotherapy with Division of Forensic Psychiatry

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Mission and Structure

The department of Psychiatry, Psychosomatics and Psychotherapy (PPP) as part of the Center of Mental Health 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 anxiety disorders and adult attention deficit/hyperactivity disorder. Specialized out-patient services as part of the outpatient clinic as well as 51 day-care therapy slots for psychiatric, psychosomatic and neurogeroton-psychiatric disorders complement the 144 in-patient therapy slots with two intensive care units and units specialized on affective disorders (bipolar depression and treatment-resistant depression), substance abuse therapy and psychotherapy. Specialized diagnostic and therapeutic options are provided by the laboratory of therapeutic drug monitoring and the laboratory of psychophysiology. The integrated department of forensic psychiatry provides expert opinions on legal aspects of mental disorders.

Major research interests

The research activities of the clinic are characterized by their interdisciplinarity with research groups of psychiatrists, psychologists and biologists and their internationality which is reflected not only by its cooperations, but also by its researchers who come from the Netherlands, Estonia Spain, Italy, Bosnia, Turkey, Brasil, Japan and China. Close ooperations at the level of the UKW exist in the context of the the SFB 581, the GK 1253, the GSLS, the IZKF and the DHZI, 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, ADHD and Frontotemporal Lobe Dementia, the SHIP study and the TRR SFB 58 on Fear, Anxiety and Anxiety Disorders which was extended into a 2nd funding period. At the international level, the PPP participates in cooperations with the NIMH 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 as well as EU networks on suicidality, anxiety disorders and impulsivity. Funding agencies include the DFG, the BMBFand the EU

The interdisciplinarity and internationality was recently formalized by the foundation of the Center of Mental Health with members of the University Hospital and the University of Würzburg as well as a scientific advisory board (Fig. 1).

Methodological approaches on the basis of differentiated clinical and neuropsychological diagnostic procedures cover a broad range from psychopysiological and modern imaging approaches such as near infrared spectroscopy and functional magnetic resonance tomography (in cooperation with the Department of Neuroradiology and the research center Magnet-Resonanz-Bayern e.V. as well as the Institute of Psychology I) over modern methods of genomics and proteomics such as high throughput genotyping (Core Facility Genetics in cooperation with the Institute of Clinical Biochemistry, the IZKF and the institute of human genetics, (Fig. 2) and their combination in the context of imaging genomics up to cell culture and animal models, in particular knockout and transgenic mouse models (in cooperation with the Institute of Clinical Neurobiology, the ZEMM and the Biocenter).

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

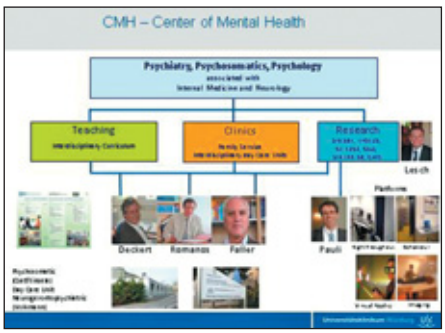

Fig. 1: Center of Mental Health of the University Hospital and the University of Würzburg.

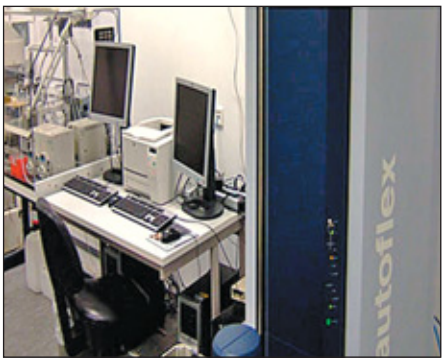

Fig. 2: Highthroughput Genotyping via MALDI-ToF (photo provided by A. Reif).

Herrmann) with the clinical research groups of the department 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 including psychotherapy 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, regulatory mRNAs, neuronal plasticity, adult neurogenesis and induced pluripotent stem cells.

This research focus on anxiety and affective disorders in the context of the SFB TR 58, the GK1253 and the DZHI was further strengthened after the nomination of KP Lesch as Chair of Molecular Psychiatry by the nomination of K. Domschke as replacement for A. Fallgatter (who became chair of psychiatry at Tübingen) and L. Hommers as head of a IZKF junior group.

The main research topics thus are:

- Markers for early diagnosis and innovative therapeutic approaches in affective disorders, anxiety disorders, adult ADHD, psychoses of the schizophrenia spectrum and dementias (J. Deckert, K.-P. Lesch, K. Domschke, B. Warrings, S. Unterecker, A. Reif, C. Jacob, G. Stöber, B. Pfuhlmann, T. Polak, M. Lauer).
- Identification of morphological and neurochemical pathological processes in psychoses of the schizophrenia spectrum and neurodegenerative disorders (H. Heinsen, A. Schmitt, P. Riederer, E. Grünblatt, M. Fischer).
- Identification of genetic factors in affective disorders, psychoses of the schizophrenia spectrum, anxiety disorders and ADHD (K.-P. Lesch, J. Deckert, K. Domschke, A. Reif, L. Hommers, G. Stöber, M. Gawlik).
- Imaging of emotional and cognitive processes in adults, adolescents and children (M.J. Herrmann, K.-P. Lesch, A. Reif, K. Domschke, J. Deckert).
- Gene-environment-interactions, neuronal plasticity, adult neurogenesis and induced pluripotent stem cells in humans and in rodent models (K.-P. Lesch, J. Deckert, A. Reif, K. Domschke, A. Schmitt, S. Kittel-Schneider).

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. In cooperation with medical psychology and psychology I a seminar on efficient exam preparation for all students was developed. J. Deckert contributed to the development of the Orpheus-AMSE-WMFE Guidelines for MDPD programs.

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Williams NM, Franke B, Mick E, Anney RJ, Freitag CM, Gill M, Thapar A, O'Donovan MC, Owen MJ, Holmans P, Kent L, Middleton F, Zhang-James Y, Liu L, Meyer J, Nguyen TT, Romanos J, Romanos M, Seitz C, Renner TJ, Walitza S, Warnke A, Palmason H, Buitelaar J, Rommelse N, Vasquez AA, Hawi Z, Langley K, Sergeant J, Steinhausen HC, Roeyers H, Biederman J, Zaharieva I, Hakonarson H, Elia J, Lionel AC, Crosbie J, Marshall CR, Schachar R, Scherer SW, Todorov A, Smalley SL, Loo S, Nelson S, Shtir C, Asherson P, Reif A, Lesch KP, Faraone SV. (2012) Genome-wide analysis of copy number variants in attention deficit hyperactivity disorder: the role of rare variants and duplications at 15q13.3. Am J Psychiatry. 169:195-204.

3.24 Center of Mental Health, Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy

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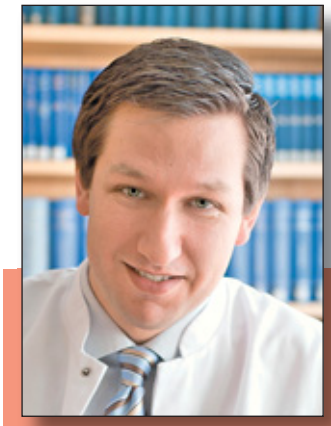

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Mission and Structure

The Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy provides care for patients up to the age of 18 years who are affected by mental disorders across the whole range of psychiatry and psychosomatics. The department consists of 2 open in-patient units, each with 16 beds, an out-patient unit, a closed ward (12 beds), the „Klinik am Greinberg“ (15 beds), and a day clinic (14 beds). In addition, there is a „parent pavilion“ and the therapy house „Sternstunden“, which will be completed by mid 2014. The department cooperates with the Wichern school for ill children. A neurobiological laboratory and a laboratory for therapeutic drug monitoring have been set up for research as a joint institution with the Department of Psychiatry, Psychosomatics and Psychotherapy. Therapeutic measures comprise such therapies as systemic family therapy, cognitive behavioural therapy, occupational therapy, physiotherapy, exercise therapy, speech therapy, music therapy, curative pedagogy, art therapy, and animal assisted therapy. The staff consists of a total of 140 persons, of which 24 are medical physicians, 14 psychologists, 6 medical technicians, 13 therapeutic practitioners, 11 secretaries, and 72 nurses. In all sections of the department, the department´s capacity is above 100%.

Research Projects

Anxiety Disorders
(M. Romanos, J. Oechsner)

Within the SFB TRR 58, subproject Z02 serves two major purposes. First of all, it is a service facility, providing other subprojects of the SFB with healthy volunteer samples; secondly it constitutes a genuine scientific project: 500 healthy children between 8 and 12 years undergo a differential fear-conditioning and generalization paradigm. While examining the influence of psychometric characteristics and genetic variants, physiological data (such as skin conductance and heart rate) are recorded.

Autism Spectrum Disorder
(R. Taurines, T. Jans, J. Geissler, B. Martin)

Core symptoms of autism spectrum disorder are attributed to a neural maldevelopment, although no markers have been identified with diagnostic or therapeutic value so gar. In our studies, we have determined the mRNA expression of candidate genes in full blood. On the protein level, we have assessed the plasma oxytocin by a standardized and validated radioimmunoassay. We have applied proteomics to identify potential novel pathophysiological candidates. Furthermore, the impact of gene variants on peripheral mRNA and protein concentrations of candidates have been determined. Our projects were realized in cooperation with the Department of Psychiatry and Psychotherapy, University of Rostock, the Department of Child and Adolescent Psychiatry, University of Zurich, the Institute of Life Science, Swansea, and the Department of Functional Proteomics, Medizinisches Proteom-Center, Ruhr-Universität Bochum.

Attention-Deficit /Hyperactivity Disorder (ADHD)
(M. Romanos, J. Geissler, M. Gerlach, T. Jans)

In our clinical research unit (KFO 125) numerous scientific studies on the neurobiology and molecular genetics of ADHD have been conducted. In order to pursue our research projects, we are currently seeking for funding. Alongside our neurobiological focus on ADHD, our department is committed to psychotherapy research (see the research report on our BMBF joint project: Effects and Mechanisms of Psychotherapy in the Treatment of ADHD).

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

A “biological marker” is defined as a characteristic feature, which, after validation, serves to measure normal biological and pathogenic processes. It can also serve to measure the pharmacological responsiveness to therapeutic interventions. Using different methods (such as real-time PCR, proteomics, olfactory tests, transcranial sonography) potential measurement parameters are evaluated as biomarkers in order to achieve a significant improvement in the diagnosis and personalized treatment of psychiatric diseases.

Depression
(M. Gerlach, K. Gellner, M. Romanos)

Depression in adults is a well-established risk factor for the development and exacerbation of cardiovascular diseases, for child-

ren and adolescents, however, this relationship has not yet been specifically investigated. Our research group has assumed that the activation of the sympathetic nervous system is responsible for the impaired regulation of heart rate variability. For this reason, we have been examining heart rate variability using 24h-ECG recording and changes in the „stress axis“ by measuring cortisol levels under conditions of rest and during stress in children and adolescents presenting with depression compared with healthy and ADHD controls. This research project is being carried out in cooperation with DZHI and the department for clinical epidemiology at UKW.

Developmental Psychopharmacology
(K. Egberts, M. Romanos, S.-Y. Dang, S. Reichert, R. Taurines, M. Gerlach)

Increasing prescription numbers of psychotropic drugs in children and adolescents are contrasting with the uncertainties of safety and efficacy issues due to the lack of clinical (authorization) trials. A multicentre clinical trial on pharmacovigilance in children and adolescents (“TDM-VIGIL”) under the guidance of our department and funded by the German Federal Institute for Drugs and Medical Devices (BfArM- number: 73.05/3832- 397285/12) collects epidemiological prescription and safety data of psychotropic drugs to evaluate the benefit-risk-ratio as well as minimize and prevent adverse effects by therapeutic drug monitoring.

Neurobiology of Attention Networks in Anxiety and Anxiety disorders (IZKF N262)
(S. Neufang)

In the IZKF-funded (starting 7/2014) collaboration project with the Department of Psychiatry, Psychosomatics and Psychotherapy (Prof. Dr. Dr. Katharina Domschke) and the Department of Neuroradiology (Dr. György Homola) the efficiency of the attention network and its neurotransmitter-related neuronal correlates is examined using the attention network test via a combination of neuropsychological and neuroimaging techniques in patients with panic disorder and healthy controls. Furthermore, in an imaging (epi)genetic approach, genetic/epigenetic variants will be examined for their potential as biomarkers of a dysfunctional attention network and/or predictors or even neurobiological correlates of therapy response.

Developmental Neuroimaging
(S. Neufang, J. Geissler, A. Akrif)

The Developmental Neuroimaging Lab focuses on the examination of brain maturation processes in combination with the development of cognitive skills. We use mr-based functional imaging techniques, e.g. fMRI (task- and resting-state fMRI), and structural MRI (morphometry, DTI). We examine healthy subjects and patients with affective disorders in order to investigate how emotional stimuli interfere with attentional processing (so-called emotion regulation) in children, adolescents and young adults, and what is the role of oestrogen, a puberty hormone, and serotonin genes in emotion regulation. In a further study we investigate the pathophysiological role of iron in dopamine-associated movement disorders.

Developmental Psychiatric Neurobiology
(C. Drepper)

With this newly established working group the development of biological models of neuropsychiatric disorders should be further promoted. Due to the increasing identification of disease-associated gene variants in humans, the functional characterization of these variants in model organisms will be essential for the understanding of the involved pathomechanisms. Priorities will be on the establishment and functional characterization of *in vitro* models (cell culture), zebrafish models and mouse models. From molecular changes in individual cells to larger restructuration of projections between different brain areas a wide range of different techniques will be used.

Teaching

In its role as interface study programme, our department is involved in the training of medical doctors, psychologists, educators, biologists, and medical and nursing professions. The interdisciplinary curricular lectures for physicians are carried out jointly by representatives of adult psychiatry, our department, medical psychology and the departments of internal medicine. For medical students elective courses, a work experience block or semester internships are offered. Furthermore, there is an extensive teaching export in the form of curricular lectures, offering the German Diploma or the initial Bachelor and Master´s degree, the German state exam for the courses psychology and special education as well as at the University of Applied Sciences for social work students. The clinic participates in the establishment of the new Master’s program in “Translational Neuroscience” from the winter semester 2014/15. Similarly, an elective course for biomedical students is newly introduced.

SELECTED PUBLICATIONS

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3.25 Chair of Experimental Biomedicine – Vascular Medicine

CONTACT DETAILS

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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 for Experimental Biomedicine (RVZ), 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. Large parts of the research projects are integrated into the Collaborative Research Center 688 (SFB 688) 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.

Platelets are anuclear organelle-rich cell fragments derived from bone marrow megakaryocytes (MKs) that safeguard vascular integrity. 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 subsequent formation of fibrin-rich thrombi that seal the wound. These processes are crucial to prevent excessive blood loss (haemostasis), however, in diseased vessels they can lead to complete occlusion and thus to ischaemic 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 ischaemic 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*.

Platelet α-granules are critical mediators of haemostasis, thrombosis and thrombo-inflammation

The major platelet organelles, α-granules, release proteins thought to participate not only in thrombus formation and haemostasis, but also inflammation and wound healing, although their functional significance *in vivo* is unknown. Mutations in *NBEAL2* have been linked to gray platelet syndrome (GPS), a rare bleeding disorder characterized by macrothrombocytopenia with platelets lacking α-granules. We have generated mice with a genetic deficiency in *Nbeal2* and could show that they display the characteristics of human GPS with defective α-granule biogenesis in MKs and their absence from platelets. Nbeal2-deficiency did not affect MK-differentiation and proplatelet formation *in vitro* or platelet lifespan *in vivo*. Nbeal2-deficient platelets displayed impaired adhesion, aggregation and coagulant activity *ex vivo* that translated into defective arterial thrombus formation and protection from thrombo-inflammatory brain infarction following focal cerebral ischaemia (Deppermann *et al., J Clin Invest* 2013). This study thus revealed for the first time that platelet α-granule constituents are critically required not only for haemostasis, but also thrombosis and acute thrombo-inflammatory disease states.

Role of Rho GTPases in platelet production

Platelets are produced by bone marrow MKs, which extend protrusions, or so-called proplatelets, into bone marrow sinusoids. Proplatelet formation requires a profound reorganization of the MK actin and tubulin cytoskeleton. Rho GTPases, such as RhoA, Rac1, and Cdc42 are important regulators of cytoskeletal rearrangements in platelets but their role during platelet production has not been established. We analyzed the *in vitro* and *in vivo* consequences of MK- and platelet-specific RhoA gene deletion in mice. We found a pronounced macrothrombocytopenia in RhoA-deficient mice and the mutant cells displayed an altered shape but only a moderately reduced life span. RhoA was required for efficient secretion of α- and dense granules and integrin-mediated clot retraction *in vitro* and normal haemostasis and occlusive thrombus formation *in vivo* (Pleines *et al., Blood* 2012). In a separate study, we could show that Rac1 and Cdc42 possess redundant roles in platelet production and function. In contrast to a single-deficiency of either protein, a double-deficiency of Rac1 and Cdc42 in MKs resulted in macrothrombocytopenia, abnormal platelet morphology, and impaired platelet function. Double-deficient bone marrow MKs matured normally *in vivo* but displayed highly abnormal morphology and uncontrolled fragmentation. Consistently, a lack of Rac1/Cdc42 virtually abrogated proplatelet formation *in vitro*. Strikingly, this phenotype was associated with severely defective tubulin organization,

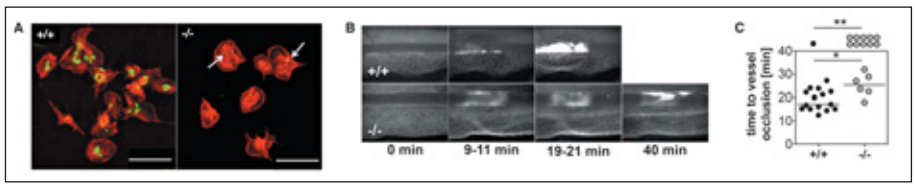

*Fig. 1: (A) Fluorescence microscopy of spread wild-type and Nbeal2-/- platelets (actin: red; vWF: green). Note the almost complete absence of the α-granule marker protein von Willebrand factor (vWF). Arrows indicate residual vWF in Nbeal2-/- platelets. Bar: 7.5 µm. (B) Nbeal2-deficient mice display impaired thrombus stability in FeCl3-injured mesenteric arterioles. Platelets were fluorescently stained in vivo and thrombus formation was monitored using intravital microscopy. Representative images are shown. (D) Time to stable vessel occlusion is depicted. Each symbol represents one arteriole. *, $p < 0.05$; **, $p < 0.01$.*

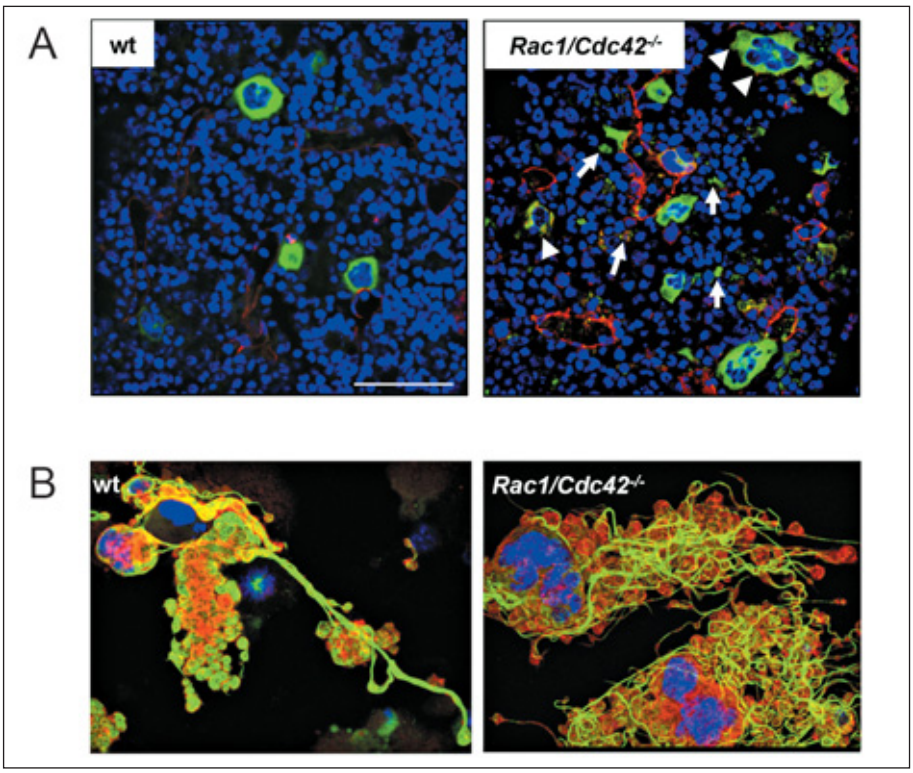

Fig. 2: Increased MK numbers in bone marrow of Rac1/Cdc42-/- mice and altered tubulin structure of Rac1/Cdc42-/- MKs. (A) Determination of MK number and morphology within the bone marrow. MK (green); endothelial cells (red); nuclei (blue). (B) Analysis of actin and tubulin structure in early proplatelet forming MKs by confocal microscopy demonstrates that tubulin structure is altered and virtually absent in most proplatelet tips. Stained are: tubulin (green); actin (red); nuclei (blue).

whereas actin assembly and structure were barely affected. Together, these results suggest that the combined action of Rac1 and Cdc42 is crucial for platelet production, particularly by regulating microtubule dynamics (Pleines *et al., Blood* 2013).

Mechanisms of Ca^{2+}-Signalling

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 the Ca^{2+} channel TRPC6 in the regulation of platelet activation and could reveal a cooperative action of Orai1 and TRPC6 in these cells.

Regulation and function of the platelet receptors GPVI and CLEC-2

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 and the only recently discovered CLEC-2 receptor can be depleted in circulating platelets in mice by injection of an anti-GPVI antibody (JAQ1) or anti-CLEC-2 antibody (INU1), respectively, resulting in long-term antithrombotic protection but only moderately increased bleeding times. We could now demonstrate that the deletion of both receptors results in a severe bleeding defect suggesting that the two receptors have partially redundant functions. Further studies have provided novel insights into the molecular mechanisms of GPVI/CLEC-2 downregulation. These findings may serve as a basis for the development of new antithrombotic therapies.

Teaching

The Chair of Experimental Biomedicine - Vascular Medicine is 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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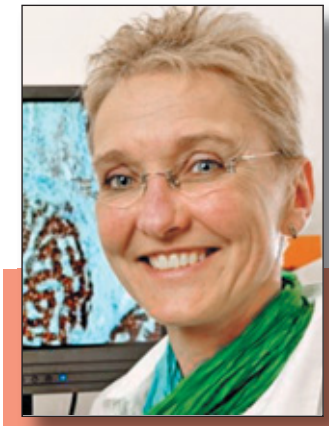
3.26 Chair Tissue Engineering and Regenerative Medicine (TERM)

CONTACT DETAILS



Prof. Dr. human. biol. Heike Walles
(Chair)

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Mission and Structure

At the chair *TERM* implants of endogenous cells are engineered by **T**issue **E**ngineering methods which minimize the body´s implant rejection. The hereby activated self-healing mechanisms result in tissue regeneration (**R**egenerative **M**edicine).
Prior to market authorization new drugs and substances are to be tested regarding their quality, efficacy and safety. Testings in animals, however, are not convincing due to species-specific differences or laws. Consequently, we develop human test systems as alternative tissue models which reflect the body´s complex characteristics and which allow tests according to the ADME criteria (Absorption, Distribution, Metabolism, Excretion). Tissue specific bioreactors (Fig. 1) culture conditions of the cell´s natural microenvironment in the body are created to ensure the in vitro functionality of the used cells. A biological vascularized scaffold, the BioVaSc, is applied to generate vascularized tissue in vitro (Fig. 2). Tissue models as well as models for various diseases like tumors or infectious diseases are set up with the BioVaSc. Accordingly, in vitro mechanisms can be studied and regenerative therapies can be developed. These already successfully applied models have become a basis for numerous cooperations with teams from the university hospital and from the university Würzburg.

Major Research Interests

In vitro test systems
(F. Baur, G. Dandekar, C. Göttlich, S. Kurdyn, C. Lotz, M. Metzger, J. Nickel, S. Nietzer, A. Rossi, M. Schweinlin, M. Steinke, A. Stratmann, C. Tripp, S. Wilhelm)

Cornea
In this ex vivo test system substances in corneas from slaughter pigs can get non-animal tested according to the OECD direction 405. The ramification of chemical substances or mechanic irritations on the surface or on the deep cornea is also analyzed regarding chronicle changes and tissue regeneration. A special bioreactor has been developed to optimize culture conditions.

Skin
An already patented 3D skin equivalent (EP 1 290 145B1) is combined with the BioVaSc to engineering complex vasularised skin tissue models consisting of the subcutis and the epidermis. This model qualifies for testing the penetration of substances and their impact on irritations and corrosions. In cooperation with the hemato-oncology mechanisms of rejections from implants are analyzed.

Trachea
The human airway mucosa is imaged by this this system consisting of .respiratory epithel cells and the underneath human bronchus tissue. The biological scaffold BioVaSc is used in combination with primary epithel cells and fibroblasts. In this complex test system studies on infections of human obligate microorganisms such as Bordetella pertussis (whopping cough bacteria) are carried out in collaboration with a priority program of the university Würzburg.

Intestine
Meanwhile both ogranoid tissue cultures and intestinal barrier models from primay murine and human cells are available as intestinal testsystems. Human cells are taken from biopsies and applied on the BioVaSc scaffold. Cell cultivation in bioreactors improves the differences of cells and the formation of the physiological barrier function. In the BMBF projects PeTrA and LipoTrans a human intestinal testsystem is applied to develop nanomaterial-based formulations for an improved agent transport (e.g. anesthetics, tumor vaccines).

Lung tumor
In the lung tumor model invasion could be induced with TGF and subsequently, testing in advanced tumor stages could be simulated. In the IZKF funded project BD-247an in silico model with essential signal cascades and its networks was developed in cooperation with the Chair Bioinformatics. A targeted clinical therapy in vitro and in silico has already been successfully simulated.

Biomaterials
(A. Appelt-Menzel, D. Fecher, S. Graiff, S. Kress, J. Reboredo, A. Schwab, H. Walles)

Under the EU project HydroZONES an osteochondral test system is developed for testing biomaterials. Inducing defects in an osteochondral plug cell-biomaterial-interactions can be examined. Furthermore, different organs (e.g. lung, bowel, heart) are decellularized in the laboratory and then used as scaffold for engineering 3D tissue replacement models or for electrospinning. The electrospinning method allows the engineering of fibre scaffolds with adapted properties such as fibre alignment or pore size. As a result of a layered matrix tissue structures can be imitated which stimulate stem cells to differentiate into tissue specific cells.

Fig. 1: Tissue specific bioreactors and incubators in the lab of the chair TERM.

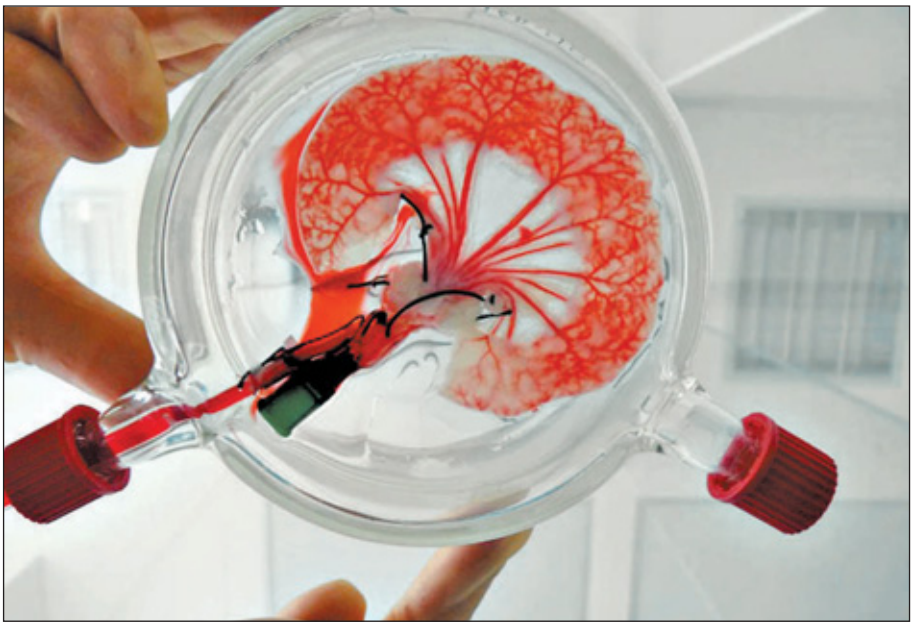

Fig. 2: Biological vascularized scaffold BioVaSc used for the engineering of autologous implants and test systems.

Bioreactors
(J. Hansmann, M. Jannasch, S. Krziminski, H. Walles)

Computer-guided perfusion bioreactors for the simulation of the physiological blood flow, the aspiration or the peristaltic of the intestine are available cultivating systems at TERM. Parallel to this, periphery systems have been designed for an improved and simpler operability of the bioreactor systems which significantly increase in complexity due to growing demands of the cultivating conditions. These systems also comprise incubators for implant engineering under GMP conditions to facilitate an optimal integration of bioreactors.

Implants
(C. Amrehn, C. Beck, M. Haddad-Weber, M. Leistner, M. Metzger, C. Moll, M. Mühlemann, S. Murawicki, O. Pullig, J. Reboredo, C. Rücker, M. Steinke, H. Walles)

On the basis of BioVaSc technologies (autologous) cell-matrix-products are developed to produce implants. So complex tissues with a preserved tissue structure and improved integration capacity can be established in vitro, and projects can be processed on different (pre-) clinical development levels. In the EU project IDEA analogue vascularized tissue models are exploited to examine in vitro the impact of cell labeling on the function and homing of stem cells. Under a DZHI start-up project G, different adult tissues are examined as a source for the generating of functional cardiomyocytes. After isolation, proliferation, and differentiation they are implanted to produce 3D heart muscle tissue.

Junior Research Group ETFace
Since October 2013 the Junior **Research Group ETFace** has been established under a funded proposal NanoMatFutur in charge of Jan Hansmann dealing with the **interaction process** of cells and implants.

Project Group »Regenerative Technologies in Oncology«
(M. Metzger, T. Schwarz, M. Steinke, H. Walles)

On the BioVaSc scaffold in vitro tumor test systems for the lung, colon, and mamma carcinoma as well as for the neurofibromatosis are established by various tumor cell lines as well as by primary isolated cells. Quantitative exploitation methods have been established to judge the efficacy of a test substance. These include division rate, apoptosis, cell invasion onto the matrix, and the activation state of various signal cascades. Additionally, novel therapy strategies which target at *the interaction process between* stroma and tumor are examined with co-cultures of tumor stroma cells (tumor environment). In the project Skinheal established methods are used to characterize a vascularized human skin melanoma model and to implant for examine metastasis and circulating tumor cells.

Teaching

The engineer-oriented course “Functional Materials“ (FUN; until SS 2011 TEC-FUN: Technology of Functional Materials) covers all areas for developing modern functional precursor material: from the chemical syntheses to the definition of physical properties, up to the functionalizing of surfaces applicable also for regenerative therapies. This interdisciplinary study course includes the Medical Faculty (Walles H, Jakob F, KLH), the Faculty of Physics and Astronomy, the University of Applied Sciences Würzburg-Schweinfurt, the Fraunhofer Institute for Silicate Research ISC, the Center for Applied Energy Research (ZAE) and the South German Kunststoffzentrum (SKZ). The classes may be elected by Biology, Biomedicine and Biochemistry students; medical students are offered an integrative seminar (optional).

SELECTED PUBLICATIONS

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Jakob F, Ebert R, Ignatius A, Matsushita T, Watanabe Y, Groll J, Walles H. (2013) Bone tissue engineering in osteoporosis. Maturitas 75:118-24.

4. Center for Dental and Maxillofacial Health

4.1 Introduction

There are five separate departments or clinics, which are comprised under the name of “Center for Dental and Maxillofacial Health”:

- Department of Conservative Dentistry and Periodontology
  (Head: Professor Dr. Bernd Klaiber)
  Division of Periodontology (Head: Professor Dr. Ulrich Schlagenhauf)
- 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), and
- Department for Functional Materials in Medicine and Dentistry
  (Head: Professor Dr. Jürgen Groll)

All the different heads of the departments form the Board of Directors of the “Center for Dental and Maxillofacial Health”, headed by the acting chairman (at present: Prof. Dr. Angelika Stellzig-Eisenhauer).

At this Center there are scarcely 600 students of dental medicine, approximately half of them working in the clinical section. As far as formation and research is concerned, as well as medical specialist care of sick people we have 171,65 positions at our disposal. By means of Extra-budgetary Funds and half-time employment however, the number of employees is around 265, 70,42 of them are working as active researchers. 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 2012 about 29500 persons got outpatient treatment and about 1720 were treated as in-patients.

Prof. Dr. Angelika Stellzig-Eisenhauer
(acting Chairman)

4.2 Department of Orthodontics

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Professor Dr. rer. nat. Kathleen Wermke
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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 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 Pediatric 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.

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. This project was honored with the first prize of the German Society of Orthodontics (DGKFO) in 2011.
In a further externally funded research project (German Society of Orthodontics) the longitudinally growth of the infants' skull has been analyzed. The objective is to build

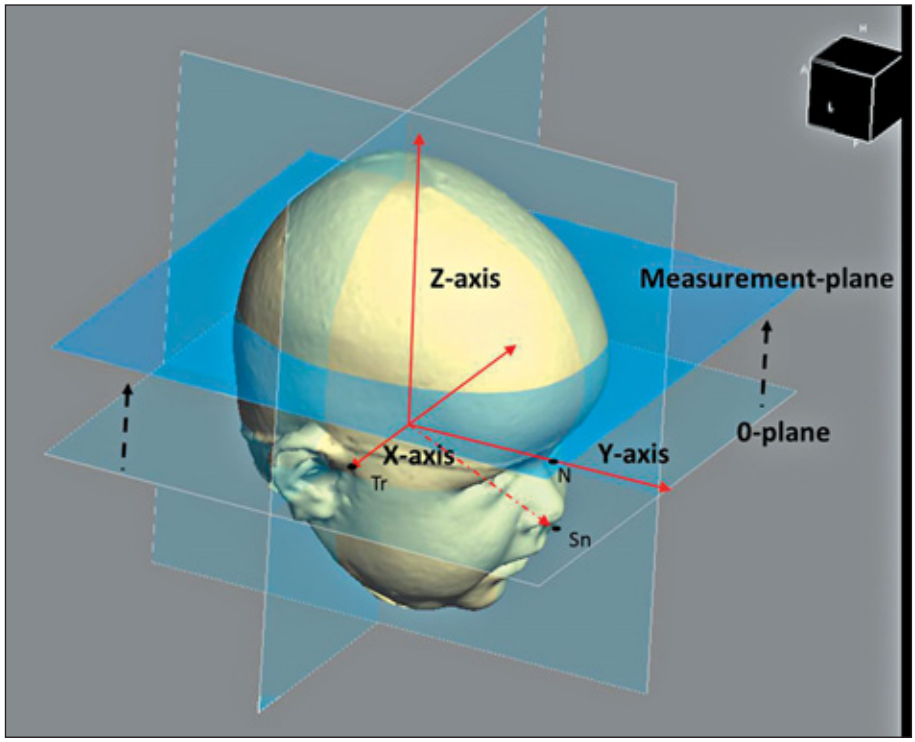

Fig. 1: 3D-Analysis of an infant's head.

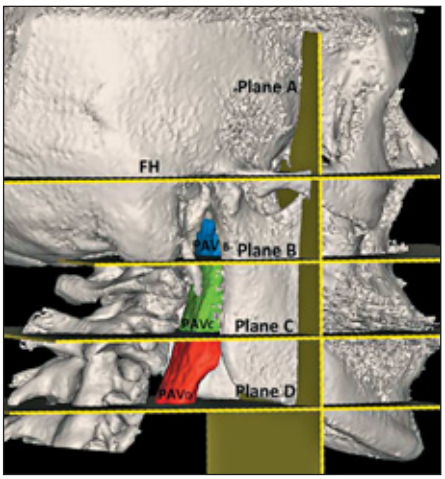

Fig. 2: 3D-reconstruction of DVT-data with anaylsis of the nasopharynx.

up a database of three-dimensional, morphometric, longitudinally recorded data from baby and infant skulls. Therefore with morphometric 3D-data standardized physiological data can be established.

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 previous studies by the Department of Orthodontics three-dimensional soft tissue imaging was successfully integrated into orthodontic diagnostics and treatment. Additionally the analysis of facial asymmetries before and after the interdisciplinary treatment of patients with a severe dysgnathia was performed.

In further research projects the skeletal analysis of the face and the nasopharynx in all three dimensions has been established in dysgnathia patients.

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).

Clinical analysis of the TMJ in patients with juvenile idiopathic arthritis (JIA) in compared to imaging techniques with ultrasonography and MRI
(Meyer-Marcotty P, Rieckert M, Stellzig-Eisenhauer A, Neubauer H, Holl-Wieden A, Prelog M.)

In cooperation with the Children's Hospital and Polyclinic for Children, the Institute of Radiology, the Department of Oral, Maxillary and Plastic Facial Surgery and the Department of orthodontics the pathology of the TMJ in patients with juvenile idiopathic arthritis (JIA) is being investigated. The aim of this project is the classification of a TMJ-pathology in patients with JIA and the early diagnosis of patients with TMJ-pathology.

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.

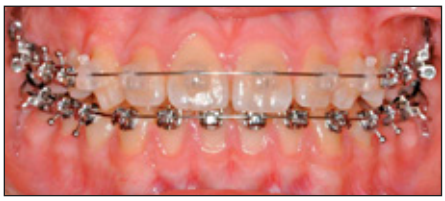
Fig. 3: Full Multi-braces appliance in situ with esthetic white braces in the visible area.

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 development of innovative biocompatible and bioactive materials for applications in biomedical basic research and applications in humans with focus on regenerative materials and therapies. Accordingly, an interdisciplinary team of biologists, chemists, pharmacists, and physicists 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 (mico-) 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

Metallic implant materials for load-bearing applications interact with the biosystem primarily via their physico-chemical properties. The ideal implant surface should provide excellent biocompatibility and at the same time have antimicrobial potential to reduce the risk of postoperative infection and to support rapid osteointegration of the implant. In the work group for biointerface engineering two key methods of functional surface coating are being investigated: By means of electrochemically assisted and electrophoretic deposition refractory metal surfaces are being provided with ceramic coatings on the basis of calcium and magnesium phosphates, which are additionally doped with biologically active respectively bactericidal metal ions. Furthermore, magnetron sputtering – a physical vapor deposition technique – is being applied for the fabrication of multiphasic coating systems of refractory metals and their oxides and nitrides. Further functionalization of these coatings takes place by doping with metal ions (e.g. silver, see Figure 1), by electrochemical nanostructuring as well as by oxygen diffusion hardening for the improvement of surface properties.

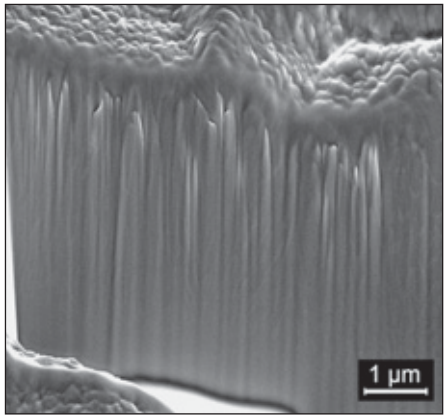

Fig. 1: FIB cut across a silver-doped titanium coating.

Bioactive Inorganic Scaffolds

The development of ceramic scaffold materials for bone regeneration at FMZ occurs from reactive cement powders based on calcium and magnesium phosphates that set after addition of an aqueous phase and form a stable implant without further sintering. The bone cements are processed in novel application forms, characterized regarding their chemical, physical, and biological properties, and optimized for the desired form of therapy. Depending on the application area, the presentation of biodegradable bone replacement materials in the form of pastes, simple molds or granulates is advantageous. The transfer of the cement systems to 3D powder printing allows the fabrication of patient-specific implants. All application forms result in microporous cement structures, which significantly contributes to the biocompatibility of the material. In addition, the processing at room temperature provides the possibility to incorporate organic modifications like antibiotics or proteins into the material. The local release of the agents from the cement matrix into the bone allows controlled release of pharmacologically active doses without systemic side effects. Besides the application of protein-based growth factors also the equipment of the ceramics with bioactive ions like Sr^{2+} or Cu^{2+} is being investigated. A further field of research is the fabrication of spherical granulates from bioresorbable cement pastes by means of an emulsion technique, resulting in particles with significantly reduced inflammatory potential.

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.

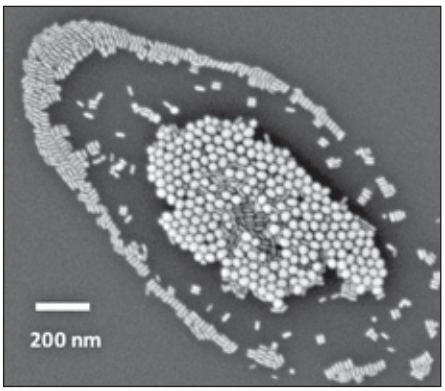

Fig. 2: Scanning electron micrograph of spherical and rod-shaped gold nanoparticles

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 (Figure 2). Our results demonstrate that rather simple changes in surface chemistry of nanoparticles can significantly affect the behavior of human immune cells. This may be used to influence inflammation and healing processes for example after implantation. A particular research focus is put on colloidal hydrogels, so-called nanogels. They combine characteristics of hydrogels like biocompatibility, high-water content as well as tunable chemical and mechanical properties with the features of nanoparticles such as high-surface area and overall sizes in the range of cellular compartments. These properties make them intriguing candidates for entrapment of hydrophilic bioactive molecules to provide a hydrophilic environment and protect them from degradation. Oxidative 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

Within their natural surrounding cells are supported by an extracellular matrix (ECM) that enables their survival and determines their adhesion, growth, proliferation, migration, differentiation and function. Main components of all ECMs are hydrogels and insoluble protein fibers that serve as binding sites and mechanical scaffold for the cells as well as source of reversibly bound soluble factors, which control their growth and differentiation. Besides the 3D matrix of a specific tissue, thin layers of basal membranes control structural properties of our body and provide a basis for an unidirectional growth, as for example in skin.
Core activities at FMZ are the synthesis, formulation and evaluation of biodegradable materials to create structures that mimic the natural ECM as close as possible. For this approach modified biopolymers as well as biocompatible functional polymers are used to prepare coatings, hydrogels and nanofibrous constructs. To generate a structural hierarchy, methods such as electrospinning of solutions and melts and rapid-prototyping techniques are currently applied. In this field of activity, a novel and internationally unique method was further developed to prepare fibrous scaffolds with a controlled fiber deposition to control cell growth

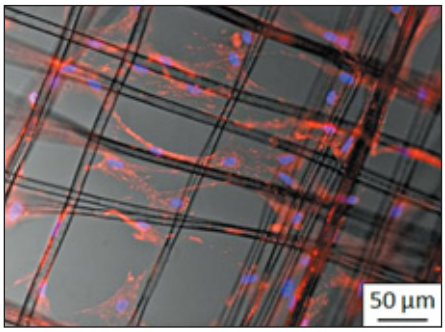

Fig. 3: Cell growth on melt electrospun fibers.

on a micrometer scale. Further modifications of the fibers with new polymeric additives towards biomimetic *in vitro* cell cultures and clinical applications are at the moment an intensive research focus (Figure 3).

(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. The microbiology section deals with testing of newly developed antimicrobial surface modifications like Ti(Ag)N coatings on metal substrates. Cell biology focuses on cell-surface interactions in 2D and 3D culture systems including matrices like gels and fibres. Additional key aspects are the interaction of cells with nanomaterials as well as co culture systems.
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 materials developed in the department as well as 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 and polymer chemistry. 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 “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 1.600 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, A. Seher, 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 are characterised to establish new concepts for personalised tumor therapy. A further project is the identification of microRNAs in oral squamous cell carcinoma to individualise tumor therapy. The screening of microRNAs via affymetrix array technology using bioinformatical analysis results in the identification of prognostic or stage descriptive biomarkers.

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
(C. Linz, A. Seher, U. Müller-Richter)

The therapy unit „multiple myeloma“ of the „Sander Stiftung“ is an interdisciplinary concept that summarize the clinical and scientific expertise of many institutes of the university hospital würzburg. The focus of our group is the analysis of bisphosphonate-associated necrosis of the jaw in multiple myeloma patients to identify important clinical markers or biological factors which are responsible for the induction of heavy bone destruction or bone necrosis in the mandible. So far it is unknown which conditions lead to this extreme phenotype in 1 to 3% of bisphosphonate treated patients.

Research team for tissue regeneration of oral mucosa
(U. Müller-Richter, C. Linz, A. Fuchs, A. Kübler, J. Groll (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 co-cultures (dermal equivalents plus keratinocytes) with dermal equivalents alone tends to reveal insights about dermal-epithelial interaction. A further topic is the investigation of the vascularisation capability using this

model. The mechanical forces affecting a transplant in the oral cavity are emulated and 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, C. Linz, 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. growing factors).

Research Team Modern Imaging
(C. Linz, C. Blümel (Nuklearmedizin), U. Müller-Richter, A. Kübler)

The diagnostic specifity and sensitivity of neck lymph knot staging can be increased via FDG-PET/CT. Aims of this study are diagnostic improvement, early identification of relapses or metastasis and the reduction of radiation exposure. In addition we use 3D-based sentinel lymph node diagnostic for head and neck tumors. The illustration of sentinel lymph nodes allows displaying the first draining lymph node stations. The declipseSPECT-System is a radioactive based imaging technology for three dimensional orientation in real time during the tumor operation. The visualization is achieved via an infrared signal transmitted by an acustic gamma sonde that allows the illustration of the complete operation room per infrared sensitive video camera. The goal is a drastic reduction of the morbidity and mortality through a high selective elimination of the lymph nodes.

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 51 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 syndroms is offered.

Major Research Interests

Clinical field studies and experimental research in the field of dental implantology are prominent research topics. Department staff are working with temporary – and since one year – short implant designs with focus on handling and fracture properties of these implants. For many years research has also focussed on the concept of “strategic” and angulated implants in conjunction with removable dentures with special attention on the aspect of superstructure wear.

A workgroup in cooperation with other faculties (Department of Experimental Physics 5 under supervision of Prof. Dr. Jakob) 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 and introducing therapeutic modalities. 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.
Protocols for high and ultra-high resolution MRI that have been under development since 2004 have been further refined. Especially replacement of VIBE- by TSE-sequences sequences yielded a simplyfied and therefore faster dataset segmentation by clearer depiction of compact bone (Figure 1).
An improved modality for digital impression reduces the likelihood of negative interaction between soft tissue and prepared teeth when the patient’s anatomy is less favourable.
As motion artefacts decrease quality of MR imaging a marker based method was developed which allows quasi-prospective motion correction and also post-processing. This method is currently being evaluated in 3D-TSE measurements.
Whole-body MR scanners are expensive to purchase and maintain due to their capabilities and infrastructural requirements. To circumvent this hurdle a cooperation between the Department of Prosthodontics and the University of Sheffield examined the possibilities for a dedicated MR dental scanner. At the centre of this device is a 0.2T permanent magnet that brings the cost down to 15% of that of a current scanner equipped with a superconducting magnet. Measurements were carried out to determine cardinal parameters such as SNR, resolution of a given volume in a certain measurement time.
The requirement for a process of age determination that can be used in a court of law has led to an interdisciplinary cooperation with the Ludwig-Bolzmann-Institute in Graz, Austria. In this study, key parameters are deduced from magnetic resonance imaging and conventional x-ray pictures of a given patient and are then interpreted statistically. To present, over 250 datasets have been examined.

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 to December 2013 almost 400 of these cores

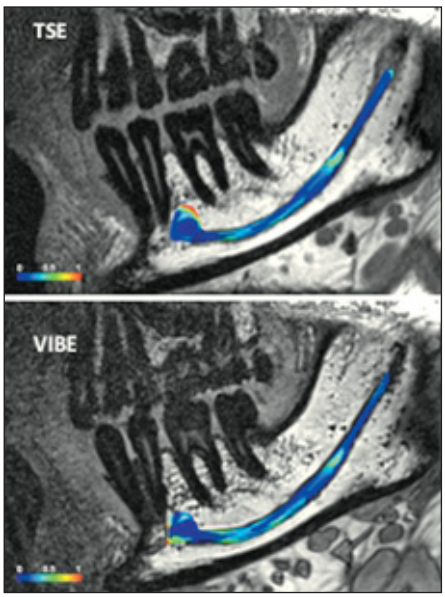

Fig. 1: MRI of the mandibular nerve canal, the newer measurement protocol is depicted on top, the older on the bottom. Despite two different measurement and segmentation methods the inferior alveolar nerve is depicted clearly.

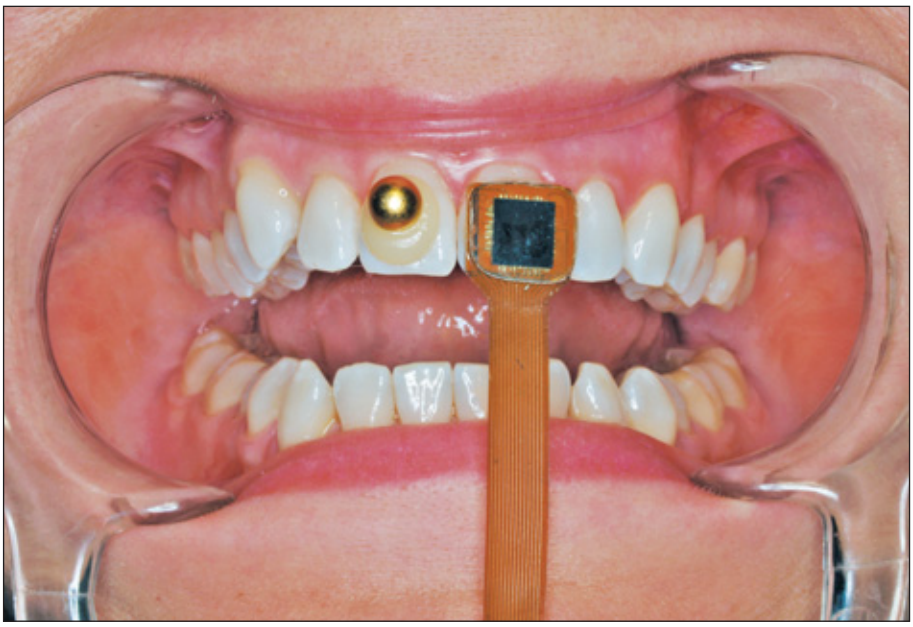

Fig. 2: Novel tooth mobility setup. A spherical magnet is affixed to the left tooth, on the right a hall sender is glued to the incisor thus making measurement of relative motion possible.

have been placed in fractured teeth. The design has proven to be competitive in clinical application to "classic" post-and-cores and has established a position in which it has become standard therapy for fractured telescopes.

Measuring tooth mobility is one further field of research. The older method of placing a light source on one tooth and a CCD camera on the other has been replaced by another setup that makes use of a spherical magnet and an application specific integrated circuit (ASIC) developed by the Fraunhofer Insititute for Integrated Circuits. With this hall-sensor setup, relative motion can be captured in high spatial and temporal resolution (Figure 2).

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 ca. 360 students participated in the medical courses, 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. Beginning 2010, a supplementary eLearning project has been created 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. Ca. 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. P. Pospiech). Both lectures span two semesters.
On average, each student performs between two and three restorations which are subject to individual grades. In 2013 this equated to almost 600 prosthetic restorations which were made per class, as well 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, whom 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 equipped with 10 dental chairs - 3 of them in the section of periodontology-, 2 working centres for the dental technicians and facilities for taking radiographs. For the practical part of the students´ education 24 dental chairs are available, 40 working stations for dental technicians as well as 55 dummies for preclinical traning.

The area of responsibility of the Department of Operative Dentistry and Periodontology covers 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 outpatients are treated. 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 placed on minimally invasive cavity preparation and on adequate restoration of these cavities using adhesive techniques: Due to micro-mechanical bonding of restorative materials to conditioned enamel and dentine, the preparation of macro-mechanical cavities - with further loss of healthy tooth-substance - can be avoided. Further emphasis is based on Esthetic Dentistry: adjustments of contour-, colour- and position-anomalies with non-invasive or minimally-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 full crowns. Preserving healthy tooth substance and dispensing with 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

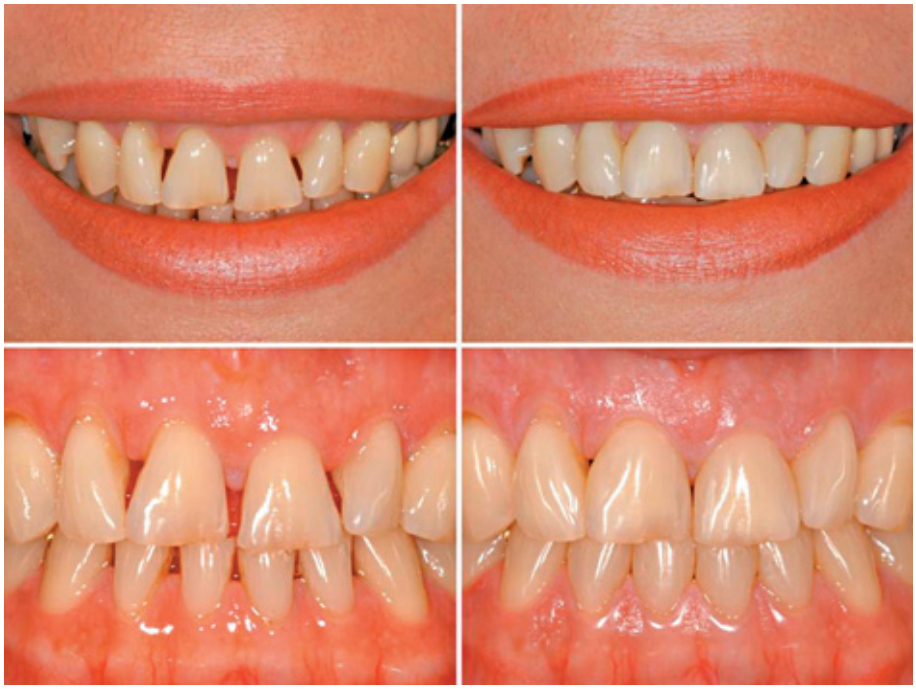

Fig. 1: Restoration of „black triangles“ (dark interproximal spaces) in front teeth using non-invasive direct composite resin restorations.

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.
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 the majority of data published so far.

Another clinical study evaluates an improved dental resin composite, which will be mainly used in the anterior region. The duration of this study will be four years.

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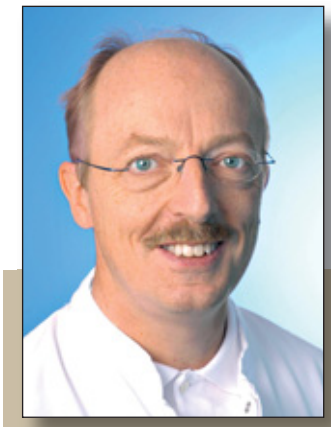
4.6.1. Division of Periodontology

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 Deutsche 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 per-

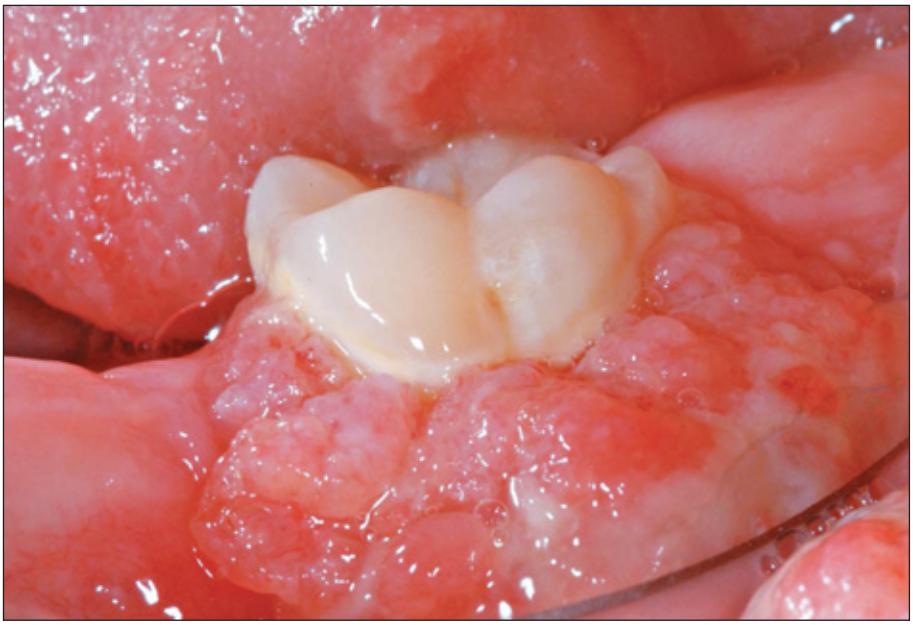

Fig. 1: Periodontal inflammation in a patient suffering from hereditary plasminogen deficiency.

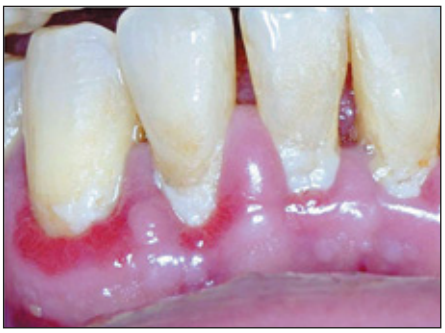

Fig. 2: Pronounced plaque-induced gingival inflammation in a patient with insufficently controlled diabetes type I.

iodontal 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)

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 three Collaborative Research Centers (Sonderforschungsbereiche), five Transregios, one Clinicial Research Unit and three Graduate Colleges which are performed together with institutions of other faculties, especially of the Biological Faculty. Furthermore, in total twelve Research Centers and Centers for Research and Treatment, as well as eleven national and international Research Alliances and the Graduate School of Life Sciences (GSLS) are described.

5.1 Research Centers and Centers for Research and Treatment
5.1.1 Rudolf Virchow Center for Experimental Biomedicine

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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 (DFG) 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 received funding as the DFG Research Center for Experimental Biomedicine for 12 years until June 2013; it is now being continued as a Central Research Institution of the University of Würzburg with funds of the State of Bavaria, the University and the Medical Faculty.

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“, which 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 with 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 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 supported by the State of Bavaria and the University of Würzburg as basic funding, who study 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 Masters Program in Biomedicine, initiated in the winter term 2001/02 at the University of Würzburg, and is now coordinating the Program. It is also involved in the more recently established programs in Biochemistry (BSc/MSc), the MSc-program in Experimental Medicine, and the FOKUS Program “Life Sciences”. A Graduate School for Biomedicine was de-

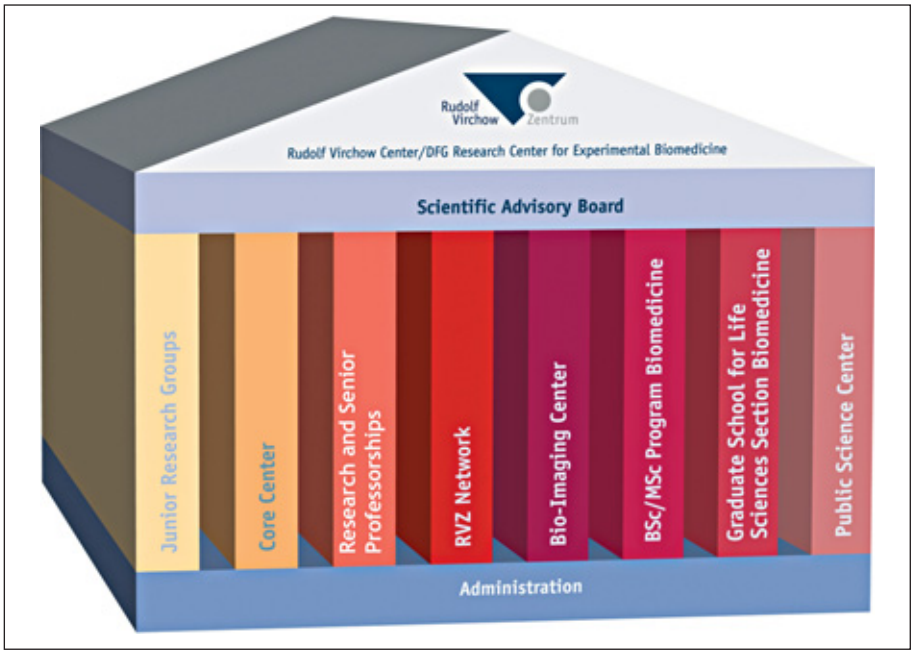

Fig. 1: Structure of the Rudolf Virchow Center.

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veloped that has become the nucleus for a large-scale reform of graduate training at the University and culminated in the foundation of the "Graduate School of Life Sciences". This school won approval in the context of the national "Excellence Initiative" in the fall of 2006. Finally, the "Public Science Center" organizes events for the general public, in particular several courses and projects for pupils.

Major Research Interests

At the time of reporting 15 research groups are established at the Rudolf Virchow Center. Research groups work on "target proteins". The research pursued at the Center can therefore be grouped into four Research Fields: (1) Protein Structure and Function, (2) Proteins in Cellular Signaling, (3) Nucleic Acid Binding Proteins, and (4) Proteins in Cell-Cell Interactions and Motility. The main projects reflect the focus on cell surface proteins and their signaling proteins, and on nucleic acid binding proteins.

Membrane Biophysics
(R. Benz)

The group studies the effects of membrane active prokaryotic toxins and the transport of bacterial toxins into eukaryotic target cells. Here, the interactions of cytolytic bacterial toxins with biological and artificial membranes are of particular interest. These toxins form membrane pores, leading to a collapse of membrane structure and to the dissipation of membrane potential. The processes involved in toxin transport across artificial lipid bilayers and cell cultures are the topics of our research, together with studying membrane active molecules with artificial lipid bilayer membranes.

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.

HAD Phosphatases
(A. Gohla)

HAD-type phosphatases are an emerging class of enzymes with essential functions for transcription, cellular metabolism and cytoskeletal dynamics. We aim to understand the regulation as well as the physiological and pathological roles of Chronophin and AUM, two novel mammalian HAD phosphatases that we have discovered. Building on the important role of chronophin for cofilin-dependent actin remodeling, our research has a strong focus on signaling to the cytoskeleton. Altered cytoskeletal dynamics play crucial roles in the pathogenesis of cardiovascular diseases and malignant tumors, and we now know that chronophin and AUM are deregulated in some of these diseases.

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 multi-molecular 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.

G Protein-Coupled Receptors
(C. Hoffmann)

In order to transduce a signal of a hormone or prescription drug across the plasma membrane G-protein-coupled receptors (GPCRs) need to undergo conformational changes. The focus of our research is to investigate such conformational changes during GPCR activation and deactivation. Therefore we develop FRET-based probes for GPCRs to image the conformational change in living cells and millisecond time resolution. The use of such FRET-based sensors allows us to study receptor ligand interaction directly at the level of the receptor itself. Thus we are able monitor the effects of potential future drugs at the protein level and can correlate the observed data with effects on different signalling pathways triggered by receptor activation.

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.

Immune Tolerance
(S. Kissler)

While our immune system is tightly regulated and usually recognizes only harmful antigenes like pathogens, a significant number of people react to self-antigens and develop autoimmune diseases. The group seeks to understand the genetic polymorphisms that predispose individuals to autoimmunity and the regulatory pathways that fail during onset of disease. The main approach is the genetic manipulation of model organisms by RNA interference (RNAi). Therefore lentiviral transgenesis is used to generate animals in which target genes are constitutively silenced by RNAi. After pioneering this strategy in the model for type 1 diabetes, the group is now refining lentiviral technology to make its application for the study of immune tolerance more versatile and specific.

Signaling Processes of Receptors
(M. Lohse)

Cyclic nucleotides – cyclic AMP (cAMP) and cyclic GMP (cGMP) – belong to the most ubiquitous intracellular messengers. Both are produced in response to multiple stimuli, act on several intracellular targets, and regulate a vast array of biological functions. However, in spite of the fundamental importance of these signaling systems, very little is known about the temporal and spatial patterns of their production and action. To gain an insight into these dimensions, the group develops methods to create images of these second messengers in intact cells, and to resolve these intracellular signals in space and in time.

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 posttraumatic 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.

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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 and Parkinson.

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

The main focus of our research is analyzing posttranslational modifications (PTMs) by mass spectrometry (MS). MS is an excellent technique for analyzing protein modifications and many advances in this area have been made over the last few years. However, the enormous potential of this technique for analyzing 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, etc. This involves developing new methods for protein cleavage, peptide separation, fractionation and enrichment, chemical modification, optimizing peptide fragmentation (CDI and ETD), as well as developing new software tools for data analysis.

Hormonal Regulation of Metabolism
(G. Sumara)

Adaption to changes in nutrient availability is pivotal for survival of living organisms. Specific responses to fasting and feeding in different organs are regulated by a complex array of hormonal cues. Deregulation of nutrient sensing leads to development of metabolic diseases including type 2 diabetes. We combine genetic and biochemical approaches to understand the complex signaling events occurring in different organs (e.g. liver and adipose tissue) during fasting, feeding and other physiological conditions.

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.

Membrane Biology
(A. Wehman)

Throughout life, cells communicate to coordinate the organism's response to stimuli. Cells release extracellular vesicles that can carry signals to alter fate decisions or the immune response. The goal of our research is to discover how vesicles bud from the surface of cells and to determine how similar it is to viral budding. Defining how vesicles form is an essential first step to designing strategies to induce or suppress their formation and thereby monitor or influence disease severity.

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.

Teaching

All groups offer internships and lectures for students of the Bachelor and Masters Program in Biomedicine as well as other programs. Annual symposia and conferences are held for scientists from medicine and the natural sciences. Graduate students at the Center are members of the in the graduate program "Virchow Graduate Program " that belongs to the Section Biomedicine of the "Graduate School of Life Sciences".

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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) is a cross-faculty and interdisciplinary institution at the University of Würzburg that is dedicated to research of several infectious diseases that severely impact human health. The center is structured in a manner that facilitates interdisciplinary cross-faculty communication, initiation of joint research activities and recruitment of extramural funding, as well as the joint organisation of international conferences and meetings. It includes researchers from four institutes within the medical faculty, the department of internal medicine II of the university hospital as well as five departments from the faculties of biology, chemistry, and pharmacy. An important element of the centre is the four independent young investigator groups, whose work focuses on current emerging topics in microbiology and infectious diseases. These Young Investigator groups are associated with and physically located within the Institute for Molecular Infection Biology (IMIB). Notably, this Young Investigator programme has been identified as a means to successfully promote the research and careers of junior scientists throughout Germany and on the international level. Based on the high scientific output and international reputation of the ZINF, in 2009 it became a central and permanent institution of the University.

Research focus

Regulatory RNAs in Helicobacter pylori and Campylobacter jejuni
(C. M. Sharma, since 2010)

The Gram-negative Epsilonproteobacterium Helicobacter pylori colonizes the stomach of about 50% of the world's population leading to gastritis, ulcers, and even gastric cancer. The related pathogen, Campylobacter jejuni, is currently the most common cause of bacterial gastroenteritis in humans and it is also associated with several secondary autoimmune disorders. Using deep-sequencing technology we have previously analyzed the transcriptomes of these prevalent human pathogens on a global scale and identified many small regulatory RNA (sRNAs) candidates, an emerging class of post-transcriptional gene expression regulators in bacteria. Research in our lab currently focuses on the functional characterization of abundant sRNAs and the underlying molecular mechanisms of post-transcriptional gene regulation. In particular, we

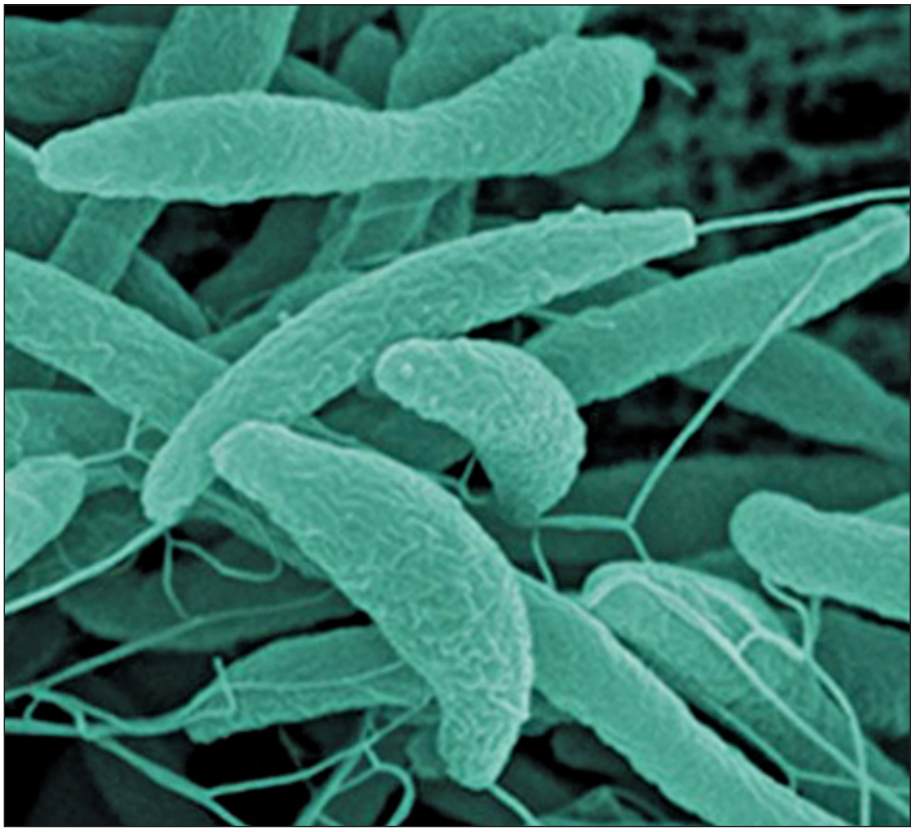

Fig. 1: Scanning electron microscopy image of Campylobacter jejuni.

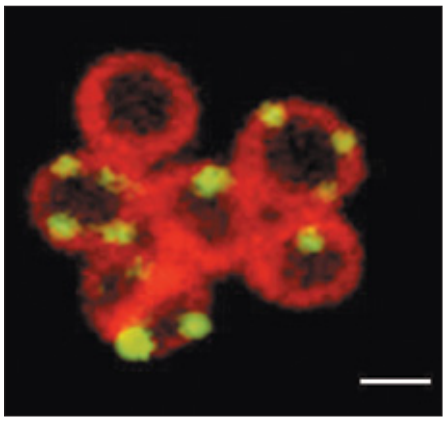

Fig. 2: Localization of lipid rafts in S. aureus cells using GFP-tagged flotilllin (Green). Membranes stained in red. Scale bar is 1μm.

are interested in the roles of sRNAs in pathogenesis and stress response of Helicobacter and Campylobacter. Moreover, since Epsilonproteobacteria lack a homolog of the RNA chaperone Hfq, a key player in sRNA-mediated regulation in enterobacteria, we are also interested in identifying and characterizing of auxiliary protein factors. Furthermore, we are applying and developing deep sequencing approaches for transcriptome analyses (RNA-seq). Our overall goal is to establish Helicobacter and Campylobacter jejuni as new model organisms for RNA-mediated regulation in pathogenic bacteria and to obtain new insights into the mechanisms of post-transcriptional gene regulation and virulence control.

Bacterial cell differentiation
(D. Lopez, since 2010)

Biofilms are surface-associated microbial communities that play an important role in many chronic infections. They are composed of multiple subpopulations of cells with specialized roles in the community, for example, the bacteria are encased in an extracellular matrix that is produced by a subpopulation of specialized cells, while other subpopulations remain motile and others even benefit from the community by secreting proteases or antibiotics. The same situation also occurs during infections, where subpopulations of cells differentiate into specific states that express the distinct virulence factors required to trigger an infective process.
We are using pathogenic bacterial models to study the molecular mechanisms involved in the differentiation process of the distinct subpopulations of specialized cells, which are required to establish successful infection. Specifically, we have identified that specific receptor proteins are spatially organized into lipid microdomains within bacterial membranes, in an analagous manner to the lipid rafts found in eukaryotic cells. Importantly, we have found that disruption of these microdomains leads to the deregulation of several bacterial-signalling pathways involved in pathogenesis such as biofilm formation. We are currently establishing how these microdomains are assembled, their molecular role in the functional organisation of important cellular processes and as a potential new mode of intervention against bacterial infections.

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

Trypanosomes are small unicellular eukaryotic parasites of insects, birds, fish, and mammals that have been around for more than 300 million years. Most species of trypanosomes are non-pathogenic but infamous exceptions exist: *Trypanosoma brucei* causes sleeping sickness in Sub-Saharan Africa and *Trypanosoma cruzi* causes Chagas in Central and South America. Yet, many aspects of trypanosome biology are still not well understood, including the regulation of gene expression – which is the research interest of our group.

Using the protazoan parasite *T. brucei*, we are studying the epigenetic mechanisms involved in establishing transcriptional permissive and repressive chromatin structures. One key question is how changes in chromatin structure can help the parasite to evade the host immune response via antigenic variation. Our group is interested in how epigenetic factors such as posttranslational histone modifications, histone variants and ncRNA interact to form chromatin structures that modulate transcription. Central to this work is the use of deep sequencing technology to determine the genome-wide distribution of the various epigenetic factors.

Teaching

ZINF members participate in practical courses and lectures for undergraduate students of biology, medicine and biomedicine and supervise Bachelor and Masters students' theses projects. In addition, members of the centre are also members of the Graduate School of Life Sciences (GSLS) and involved in graduate student supervision and training. The centre also regularly organises seminars, workshops and conferences covering current topics in medicine and microbiology.

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5.1.3 Interdisciplinary Center for Clinical Research (IZKF)

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Assignments and Structure

The IZKF Würzburg organizes the Medical Faculty's internal funding for research. Its major goal is the strengthening of clinical research through interdisciplinary cooperation between clinical research and basic research in biomedical sciences. In 2013, its funding volume was approx. 5 Mio. Euro.

Three main instruments characterize the IZKF's work:

- The support of interdisciplinary aligned research projects within its scientific emphases (project grants).
- The extension of a systematic promotion of young researchers in medicine.
- The establishment of Core Facilities and flexible funding instruments in order to improve local structural conditions (structural development).

Peer review methods and a transparent fund management are the preconditions for the center's internal research management. It has three assertive organs

- The general assembly („Zentrumskonferenz"),
- The executive board which is responsible for coordinating all instruments and which decides on every promotion
- The External Scientific Advisory Board, who accompanies the center's activities and who participates on the assessment of every project proposal.

The IZKF Würzburg was founded in 1996 within the federal advancement program "Health Research 2000" of the Federal Ministry of Education and Research. It is entirely funded by the Free State of Bavaria since 2004. The statues, which have been revised in 2010/2011, are documenting the progress of the center's aims, duties, funding and decision-making structures in the area of new structural and scientific challenges in the Medical Faculty.

Main research – Project Grants

The main research is particularly represented in the IZKF-project grants. The aim of this issue-focused promotion is a stronger factual consolidation of the faculty's scientific emphases and to seize and enhance new topics. A condition for a grant is the cooperation between clinical researchers and basic researchers in biomedicine. After up to three years of an IZKF-promotion it is expected to transfer the projects into external third-party funding. All IZKF-projects are selected through internal and external peer reviews. In 2011, the triennial review cycle was changed to an annual review in order to allow access to the IZKF in shorter intervals while having the same competitive conditions. For the 2012 call for proposals, the center received 31 project proposals. 15 projects received a grant and started their work in 2013. Altogether, in 2013, the IZKF promoted **30 research projects in 6 project areas. 43 different departments of the University and the University clinic** were involved.

Project area A: Pathophysiology of inflammatory response

A project of the Institute for Virology and Immunobiology and the Department of Internal Medicine II is concerned with the question of how the control of the transcription factor C/EBPß effects the activation of B cells and their differentiation to a plasma cell for infection defense and in inflammatory rheumatic diseases. The functional role of the interleukin receptor crosstalk in the pathogenesis of steatohepatitis is investigated by researchers from the Department of Neurology and the Department of Internal Medicine II. Further research projects investigate

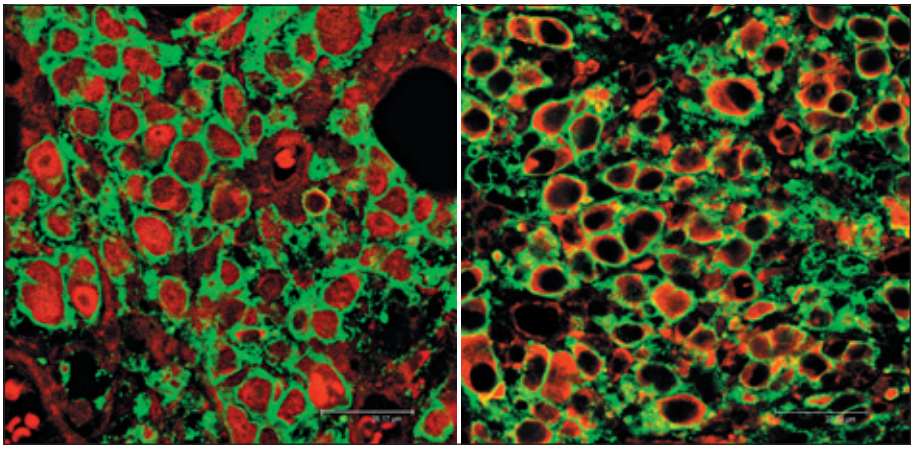

Fig.1: A (left): Confocal micrograph of an iliac crest trephine biopsy with a dense infiltration of malignant plasmacytes (CD138; green). Moreover, the tumor cells show a strong, aberrant nuclear reactivity for cMYC (red). B (right): Confocal micrograph of an iliac crest trephine biopsy shows broad infiltrates of a multiple myeloma. (CD138; green). Furthermore, the tumor cells are cytoplasmic positive for YB-1 (red). Project B-188, Cooperation of Mottok, Rosenwald (Pathology) and Chatterjee, Steinbrunn (Department of Internal Medicine II).

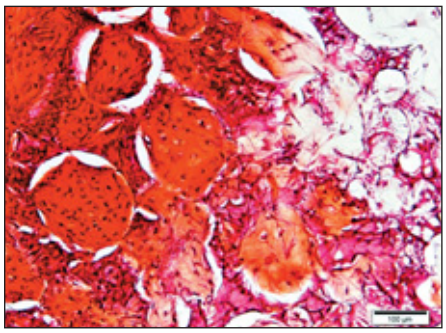

Fig. 2: Growing of living cartilage for tissue replacement – A spongy scaffold (round pore structure) is colonized with stem cells. The stem cells are stimulated so that they overtake the function of the chondrocytes. (Production of extracellular matrix, red) Project D-218/D-219, Cooperation of Blunk, trauma surgery, and Meinel, pharmaceutical technology, Photo: Martin Krähnke).

the improvement of the biocompability of alloplastic materials through a coating with biotechnical-made spun silk, the pathogenesis of autoimmune diseases like multiple sclerosis and the pathophysiological role of T cells in craniocerabral trauma. Seven projects were promoted in this area.
Participating facilities (8): Gynecological Clinic, Institute for Virology and Immunobiology, Chair for Tissue Engineering & Regenerative Medicine, Department of Internal Medicine II, the Neurosurgical Department, and the Rudolf Virchow Center.

Project area B: Malignant Transformation and Tumor/Host-Interaction

The main focus lies on a better understanding of molecular mechanisms in malignant diseases in order to develop novel therapeutic strategies. Inter alia, the scientists research the relevance of the heat shock protein HSP90 for the radiosensitivity of malignant cells, the synthetic lethality in APC- or FBW7-mutated colon cancer to identify novel molecular target structures, or they evaluate oncogenes as prognostic markers in multiple myeloma. Furthermore, they examined Chlamydia trachomatis as a potential risk factor for endometrial ovarian cancer and characterized the principles of Senescence Escape after oncogene stimulation and cytostatic drug treatment. Six projects were promoted in this area.
Participating facilities (10): Biocenter, Gynecological Department, Surgical Department I, Dermatology Department, Department of Radiation Oncology, Cardiothoracic Surgery, Chair for Tissue Engineering & Regenerative Medicine, Department of Internal Medicine II, Pathology and the Chair of Bioinformatics.

Project area D: Transplantation and Tissue Engineering

These cooperation projects focus on the development of specific stem cell therapies. In the area of Tissue Engineering they examined the effect of vascularized meniscal tissue with a novel biomatrix. Further projects looked at the Neurogenesis and regenerative potential of induced pluripotent stem cells, a stem cell-based therapeutic strategy for vocal cord-augmentation and the reconstruction of laryngeal defects, as well as the expression of tumor antigens during pregnancy. Ten projects were promoted in this area.
Participating facilities (14): Institute of Clinical Radiology and Cell Biology, Institute of Pharmacy and Food Chemistry, Surgical Department I and II, Cardiothoracic Surgery, Department for Functional Materials in Medicine and Dentistry, Chair for Tissue Engineering & Regenerative Medicine, Department of Internal Medicine II, Neurosurgical Department, Orthopaedic Clinic König-Ludwig-Haus, Pathology, Chair of Bioinformatics and the Research Center for Infectious Diseases.

Project area E: Vasculopathies und Myocardial Diseases

The three projects investigate the pathophysiological relevance of depolarizing transporters in the S3-segment of the proximal tubulus for kidney damage after ischemia, Isoprostanes and cardiac blood vessel growths, and with the comorbidity in ischemic stroke.
Participating facilities (4): Institute of Anatomy and Cell Biology, Department of Internal Medicine I, Department of Neurology and the Rudolf-Virchow-Center.

Project area F: Novel Diagnostic and Imaging Devices

This area covers the whole range of biological imaging. Our scientists work mainly with MR- and PET-imaging devices in order to understand pathophysiological processes and to improve diagnostic and therapeutic approaches. They examine the acute brain damage after subarachnoid haemorrhage as well as the subcellular localization of antibodies. Moreover, they develop functional 3D MR-based diagnostics of intestinal obstruction. Five projects were promoted in this area.
Participating facilities (9): Surgical Department I, Department of Mathematics, Institute of Diagnostic Radiology, Clinic for Oral and Facial Surgery, Neurosurgical Department, Department of Neurology, Department of Nuclear Medicine, Department of Physiology and the Department of Radiation Oncology.

Project Area N: Clinical and experimental Neurobiology

Here, we have a total of seven projects with psychiatric, neurological and neurophysiological focus. They examine the plasticity after experimental traumatic brain injury, the axonal mechanism of deep brain stimulation and the effects of positive environmental influences during pregnancy on resilience.
Participating facilities (12): Department of Aneasthesia and Critical Care, Institute of Anatomy and Cell Biology, ENT Clinic, Institute of Human Genetics, Institute for Clinical Neurobiology, Institute of Clinical Radiology and Cell Biology, Neurosurgical Department, Department of Neurology, Pathology, Department of Physiology, Department of Psychiatry and Psychotherapy and Institute of Forensic Medicine.

Junior Career Programs

The IZKF-Junior Career Program is a specific facilitation that offers a research oriented additional qualification. Its aim is a dovetailing of clinical and biomedical research at the earliest possible stage at every level of one's medical career. Alongside the direct Junior Career Programs, the IZKF supports young and motivated scientists of the Medical Faculty with IZKF-research grants.

A special focus in this area should be placed on the IZKF-research groups.

The IZKF-research groups are part and parcel in the IZKF's portfolio for career enhancement. By giving novel scientific and structural impetus they also provide a long-term and sustainable enhancement of research in our clinical departments. Thus, they contribute significantly to the profile formation of the faculty's main research. In 2010, the executive board decided to rename the IZKF-junior research groups as IZKF-research groups in order to stress the possibility for experienced scientists to re-

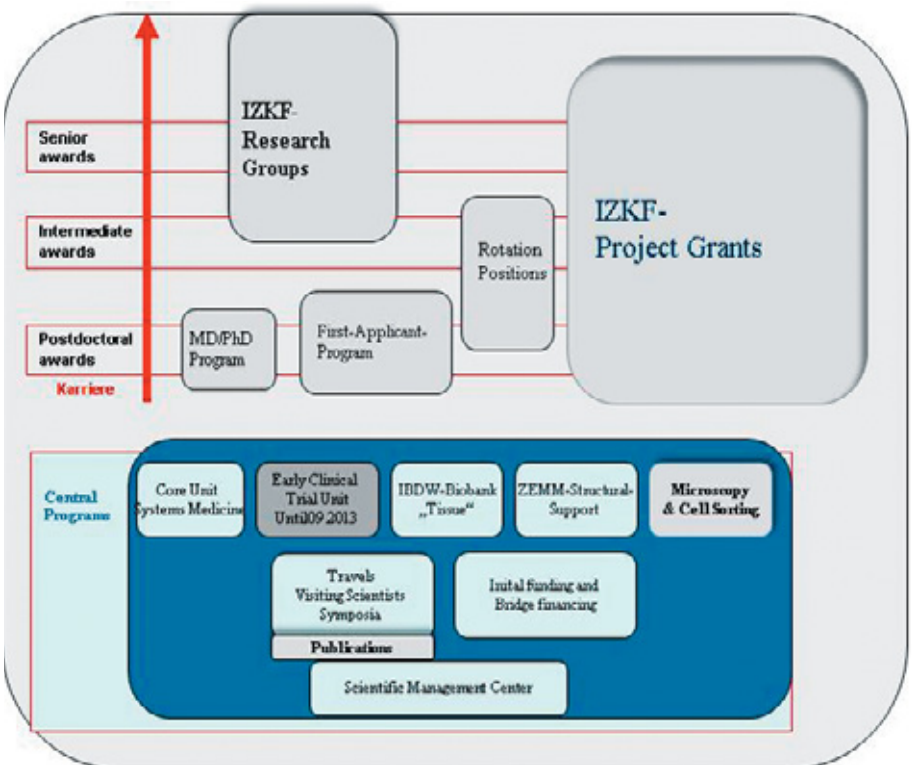

Fig. 3: Diagram of the IZKF-research funding.

ceive the funding, e.g. connected to a research professorship (following the Heisenberg-professorships). A main focus is the compatibility of research and clinic through creative solutions. In total, the groups are funded for up to five years. The group leader position is internationally tendered; the candidates are surveyed and approved by our external board. The first three IZKF-research groups with collaborations of Psychiatry and the Department of Internal Medicine I, the pediatric clinic and the Department of Internal Medicine II as well as Neurology and Nuclear Medicine have already started.
The fourth group collaborates with the Research Center of Infectious Diseases (ZINF) and will start shortly.

The research groups in detail:
Research Group I

„Common pathways of Cardiovascular and Neuropsychiatric Diseases", promoted as a joint group of the IZKF, DZHI, Psychiatrical Clinic and the Department for Internal Medicine I.

Group leader: Dr. Leif Hommers; approved in August 2012
Cardiovascular diseases and psychiatric diseases with organic causes (neuropsychiatric diseases) are currently one of the most common reasons for lost disease-free years of one's life, especially if they occur in combination. The IZKF/DZHI-research group „Common pathways of Cardiovascular and Neuropsychiatric Diseases" explores basic molecular processes in order to extend the knowledge of similarities and cardiovascular and neuropsychiatric diseases and to obtain new perspectives in the development of therapeutic approaches.

Research Group II

„In vivo Imaging in preclinical models to develop, establish and validate novel concepts in immune- and tumor therapies", Department of Internal Medicine II and the Pediatric Clinic

Group leader: Dr. Andreas Beilhack; approved in April 2012. The research group's scientific focus is on the areas of tumor immunology, infection immunology and transplantation immunology. In order to illuminate complex immune processes, the IZKF-research group develops new imaging and microscopy techniques. The aim is the development, establishment, and validation of novel concepts in immuno- and cancer therapy.

Research group III
"Imaging for molecular biomarkers for clinical heterogeneity and disease progression in Parkinson's disease", Neurology and Nuclear Medicine

Group leader: Dr. Ioannis Isaias; approved in May 2013
After Alzheimer's disease, Parkinson is the second most common neurodegenerative disease and affects approximately a percentage of 0,3 of the total population with about 8-18 incidences in 100.000 persons/ year. Dr. Isaias' research group studies the pattern of neurodegeneration, compensatory mechanisms and biomarkers for disease progression in clinically defined subgroups of patients with Parkinson disease.

Carreer programmes for young physicians

- Würzburg's MD/PhD Program was founded in 1997. It is intended for physicians who already completed their experimental doctoral thesis. The aim of the program is the establishment of an excellent, postgraduate subject-specific qualification for young physicians by acquiring the Dr. rer. nat. / PhD in accordance with the Doctoral Graduation Regulations of the International Graduate School of Life Sciences (GSLS). Until 2013, the program has had 34 alumni. Since 2012, the MD/PhD program is fully integrated into the GSLS and since 2013, the awardees also have the possibility to spend the last year in a clinic, which is pro rata financed by the corresponding clinical department.
- The First-time Applicant Program (EAST) facilitates young physicians, with a doctorate, to enhance their own scientific approaches within two years in a working group that is specifically arranged for this purpose, and to transfer them into an external third party funding with the support of a mentor. The EAST invites tenders bi-yearly. In the first round in 2008, seven physicians received a promotion. In 2010, there were three women and five men selected, in 2012 five women and three men.
- The IZKF-Rotation Program enables young resident physicians to get exempted from patient care in order to do re-

search. The IZKF provides five rotation positions in each year. In 2012 and 2013 12 physicians from 11 clinical departments got promoted.

Other activities – Structural support and infrastructure

In order to enhance the local infrastructure, the IZKF supported four Core Facilities:

- The support for the Early Clinical Trial Unit, an in 2007 approved, highly specialized unit for experimental tumor therapy, ended in August 2013. The facility conduces the catalysis of the translational oncological research and the development of new drugs and therapy approaches under optimized conditions. The ECTU remains as an integral part of the Comprehensive Cancer Center Mainfranken and is therefore in close cooperation with every CCC-associated clinical department and institute. The ECTU is now financed by the Chair of Translational Oncology.
- The Core facility "Microarray-Unit" was established in 2001 and broadened the spectrum of services as the "IZKF-Service Unit for Microarray applications and bioinformatic analysis of high throughput methods". In 2013, it passed into the Core Unit "Systems Medicine" which is co-financed by the Medical Faculty. It is a service partner for high throughput measures for researchers at the University and the University Clinic. The Core Unit currently consists of the units "Genome and Transcriptome Sequencing" and the "Microarray-Unit" with the affiliated Bioinformatics. Further units, like "Single Cell Analysis" and "RNAi/ Chemical Screening" will be launched soon.
- The IZKF extended the support of the "Center for experimental molecular medicine (ZEMM)" which allows access to the ZEMM's central animal management for the IZKF members
- The Biobank (tissue) is supported since 2011. The IZKF-financed Biobank is integrated into the CCC Mainfranken and is an integral part of the BMBF-promoted "Interdisciplinary Bank of Biomaterials and Data Würzburg (IBDW)"
- New is the "Service Unit for confocal microscopy and flow cytometry-based cell sorting". The Unit provides both methods with a high standard and with operator-assistance for interested people. Therewith, a long-term and efficient technology platform was established for the IZKF's and the faculty's scientists.

The IZKF considers itself as the internal instrument for research funding of the Medical Faculty. Research projects, that have a short- or medium-term potential for an external third-party funding, are supported with initial funding and bridge financing. Furthermore, the IZKF promotes visiting scientists, supports the planning and implementation of seminars and symposia and enables its members to visit meetings. Since 2011, the IZKF also provides advice for scientists in external third party funding with its service "Scientific Management". In the UKW's newly established department 3.4 „Internal and External Management of Research Funds (FoMM)", consisting of the department 3.4.1 "Matters of Third Party Funding" and the department 3.4.2 „IZKF/ Internal Research Funds", all matters concerning internal and external research funding are coordinated and administrated under the supervision of Dr. Andrea Thelen-Frölich. With this redeployment, internal and external-financed projects will be supported and seen through from the first planning to the final report, and is therefore a useful complement to the service „Scientific management".

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5.1.4. Interdisciplinary Bank of Biomaterials and Data Würzburg (ibdw)

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General Information

Medical research based on human biochemical, histological or genetic data analysed in conjunction with (longitudinal) clinical information is essential to foster improvements in the detection, diagnosis, treatment, and prevention of multi-factorial diseases.

Embedded in the National Biobank Initiative of the Federal Ministry of Education and Research (BMBF) the *Interdisciplinary Bank of Biomaterials and Data Würzburg* (ibdw) has been set up as one (out of five) centralized National Biobanks aiming to systematically collect and quality-controlled store both liquid (blood/DNA/urine) and solid bio-materials (tissues, biopsies) donated by patients and study participants of the Medical Campus Würzburg for medical research.

In the developmental concept of the ibdw as an *independent central service unit* of the Medical Faculty priority has been set towards a concerted establishment and sharing of resources for medical research comprising clinical data, human biological samples, and biochemical, histological and/or genetic information derived from their analysis. In this aim the ibdw currently puts stepwise into practice a systematic, simultaneous and (in the future) sequential collection of both liquid and solid BM from patients and study participants of all departments of the University Hospital.

To secure integrity and long-term quality of the collected biomaterials, as one of its paramount tasks the ibdw has implemented (and will department-wise release) highest quality standards according to the current OECD- and ISBER-recommendations. Because there are no restrictions with respect to storage-duration and/or the purpose of (medical) research, all bio-materials and data hosted by the ibdw must strictly adhere to the legal framework (including privacy protection) and all current ethical principles. For each collected human bio-sample the ibdw provides the corresponding annotation (basic) data and, if required, access to expandable (harmonized) disease-specific clinical datasets in accordance with current data protection and safety regulations (multi-level data access model).

Structure, aims, and major research interests of the ibdw

The ibdw is composed of a central database and two central bio-sample repositories, one for liquid and the other for solid/tissue biomaterials, and a limited number of specialized decentralized biobanks, all adhering to ibdw standards and rules. The Medical Faculty, that is, the Julius-Maximilians-University and the University Hospital together hold full responsibility for the ibdw which is governed by its own steering committee. Each central and decentralized collection of data and biomaterials meets highest quality standards according to the current OECD/ISBER recommendations.

Implementation of the ibdw concept is currently achieved jointly with the Service Centre Medical Informatics (SMI) by a establishing an uniform IT-structure across all departments and institutes of the Medical Research Campus (also linked with e.g., the pathology information system and the tumour databank of the CCCM) tracking the ibdw-conform labelled and processed individual liquid and/or solid bio-samples in order to correlate them with the patient-specific pseudonymized clinical data sets collected along the patient management paths. However, clinical information and/or information derived from the analysis of the patients' bio-samples will be accessible only on request by a specified data and privacy protecting regulation.

To secure high automation and thus high quality of ibdw-hosted biomaterials (BM) for liquid bio-samples there is tight cooperation with the Hospital's Central laboratory, for tissue samples tight collaboration with all surgical departments present in the Centre for Operative Medicine (COM); therefore, the tissue-bank of the ibdw/CCCM under guidance of the Institute of Pathology has been installed next door to the operation

Fig. 1: Tissue-bank of the ibdw/CCCM situated in the Centre of Operative Medicine (ground plan, floor -1) under guidance of the Institute of Pathology. Photos show (in counter-clockwise direction) the novel cryotom, transport of (fresh frozen) tissue-samples, and the online-temperature monitored -80°C freezers of the tissue-bank.

theatres and, of course, also next to the rapid section laboratory directly in the COM, floor -1 (Figure 1).
Pre-existing high quality bio-sample collections within the University Hospital have been identified to be step-by-step integrated into the ibdw. In addition, the ibdw manages and operates human bio-materials as well as access to corresponding clinical and laboratory (analytical) data provided by existing national and international publicly funded basic and clinical research programs at the University and the University Hospital of Würzburg that have been successfully executed in the past years. These include - but are not limited to - the Interdisciplinary Center for Clinical Research (IZKF), the Comprehensive Cancer Center Mainfranken (CCCM), the Comprehensive Heart Failure Center (CHFC), and the Rudolf Virchow Centre (RVZ), DFG Research Center for Experimental Biomedicine.
The official grand opening of the ibdw was in June 2013 with the hand-over of the keys for the new building A8, which besides a Bio II-laboratory contains two automated cryostores each having a capacity of about 0.5 Mio of liquid bio-samples. On the day after, the resident population was invited to visit the ibdw and to get some information on the scope and aims of a disease-oriented biobank (panel discussion, Figure 2). In addition, since December 2013 the ibdw participates as work package WP4 leader in the BMBF-funded implementation of the German Biobank Node (GBN) as a "bridge head" to the European Biobank Infrastructure (BBMRI-ERIC). Aims of the GBN are to coordinate and harmonize national biobank-activities comprising –amongst others– harmonization of data-acquisition and -exchange (to achieve biobank-interoperability), standardization of quality-criteria and rules for the certification of biobanks, but also to develop a joint (national) strategy regarding ethical, legal and social matters of biobanks (including public visibility and public involvement). These ibdw 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 for medical research purposes);
- Long-term storage for more than 10 years (-140°C, gas phase liquid nitrogen) for pre-specified liquid BM;
- Implementation of a multi-level data storage and access concept ensuring consistency of data and bio-sample identity adopting all current data and privacy protection regulations;
- Implementation of hierarchical pseudonymized clinical data sets (basic annotation data, and harmonized disease-specific/study-specific datasets);
- Participation in the German Biobank Registry and the German Biobank Node (GBN, Berlin);
- Project-based cooperation with the biobank of the Bavarian Blood Donors (Bio-KEP project, since 09/2013 granted by the TMF);
- Project-based cooperation and networking on a national, European and global level.

Fig. 2: Panel discussion on consent-management and how to secure donors' privacy at the „open house" presentation of the ibdw 2013.

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5.1.5 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 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.

Transgenic Technology

The mouse is the most important mammalian model system in basic and translational research. Genetically engineered mice are indispensable tools for basic functional genomics as well as for applied biomedical research and the design of models for human disease.
Research with genetically engineered mouse models is dependant on the availability of specific techniques, highly specialized laboratory equipment and skilled staff. The Transgenic Technology provides the lab infrastructure for the maintenance and generation of transgenic mouse models and the complete set of gene targeting and transgenesis technologies in the setting of specific pathogen free (SPF) animal housing of the ZEMM. The facility offers support, advice and counselling for non-specialists in recombinant embryonic stem (ES) cell technology, *de novo* establishment of mouse ES cell lines and gene targeting experiments.
As a scientific service the Transgenic Technology performs the following experimental techniques:

1. Mouse rederivation
2. Generation of mouse models by gene targeting/injection of recombinant ES cells into host embryos for the formation of chimeric mice
3. Generation of mouse models by additive gene transfer/pronuclear injection
4. Lentiviral infection of oocytes
5. Cryopreservation of mouse lines

Mouse rederivation

Any mouse line imported to the SPF or breeding facilities of the ZEMM is rederived to ensure and maintain the high local hygiene level. Upon arrival, the animals are housed in the open facility. In 2014 a separate quarantine station will be set up for this purpose. The males are mated with superovulated donor females; embryos are collected and washed and are transferred into pseudopregnant foster mothers under SPF conditions. Before transfer to the final SPF housing room they undergo control hygiene monitoring.
A similar adopted protocol is used for the rederivation of cryopreserved embryos imported from external sources.
Cryopreserved sperm are rederived in a two-step protocol: *in vitro* fertilization and transfer of fertilized 2-cell embryos into foster mothers under SPF-conditions.

Generation of mouse models by gene targeting

The generation of chimeric mice via injection of recombinant embryonic stem cells

Fig. 1: View into an animal husbandry area.

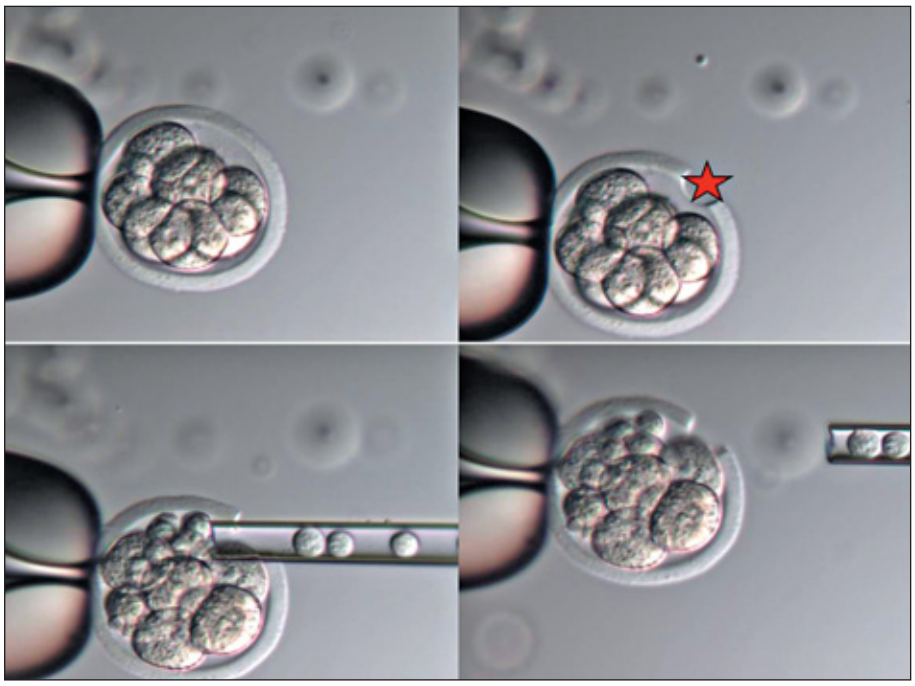

Fig. 2: Laser-assisted injection of recombinant ES cells into 8-cell embryos.

into host blastocysts is the key intermediate step in gene targeting experiments to transform a designed mutant allele from the molecular biology and embryonic stem cell level into the complexity of the living mouse model and demands highly specialized equipment and skills. Our lab is equipped with a new laser-assisted microinjection setup that was installed in 2013 at the ZEMM. Laser assisted micromanipulation of embryos not only facilitates standard ES cell injection procedures into blastocysts, but is particularly useful for injections into 8-cell embryos. 8-cell injection has the advantage of showing less interdependence of host embryo and ES-cell background. Our lab uses this technique successfully to inject recombinant embryonic stem cell clones of the C57BL/6 background into albino outbred host embryos. By utilizing recombinant ES clones from the International Mouse Knockout Consortium we increasingly benefit from this valuable scientific resource.

Generation of mouse models by additive gene transfer/pronuclear injection

The classical approach of additive gene transfer via pronuclear injection of DNA constructs is still an indispensable tool for mouse modelling. A new micromanipulation setup adjusted for pronuclear injection of transgene constructs was bought and installed in 2013. As standard oocyte donor strains FVB/N, F1-hybrids and C57BL/6N are available.

Generation of mouse models by lentiviral infection

As an alternative to pronuclear injection the infection of oocytes with recombinant lentiviruses is giving rise to multiple integrations in the genome which will segregate in the subsequent generations. A highly concentrated virus lysate is injected into the perivitelline space to infect the oocytes. A micromanipulation setup is available within the SPF area under S2 specification.

Cryopreservation of mouse lines

Cryopreservation of mouse lines is the method of choice to ensure a backup system that protects against loss due to colony contamination (health or genetic) and for the long term maintenance of lines that are no longer in scientific use and characterization to avoid breeding costs and animal consumption. The golden standard for valuable lines is still the cryopreservation of embryos which is time and material consuming, but allows rapid rederivation by simply thawing the embryos and transferring them into foster mothers. A robust, slow rate freezing protocol is established.
A faster and less expensive alternative is the cryopreservation of sperms. However, the rederivation of cryopreserved sperms by in vitro fertilization is more complex and its success rate is strongly influenced by the genetic background of the mouse line with low rates in the commonly used C57BL/6 background. Therefore an improved protocol is presently adopted that yields higher success rates with the problematic C57BL/6 strain and a sperm analyser was just recently purchased in order to assess the quality of sperm preparations and its suitability for *in vitro* fertilization.

5.1.6 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 physician scientist program, which aims at providing a structured, science-based training for physician-scientists oriented towards clinical immunology. Under the direction of Dr. Andreas Beilhack (Department of Medicine II) and Prof. Dr. Jörg Wischhusen (Department of Obstetrics and Gynecology) the Else-Kröner-Forschungskolleg Würzburg is funded by the Else-Kröner-Fresenius-foundation since 2012.

The Else-Kröner-Forschungskolleg Würzburg has been designed to provide optimal support for the careers of young physicians at the interface between patient care and clinical and experimental research. Within the program the eight selected fellows receive an optimized training in medical skills of their respective specialty. Furthermore, the Else-Kröner-Fellows participate in a special research training program, including a 12 month research period, integration into a clinical trial program, and a mentoring program. The eight Else-Kröner-Fellows are introduced to new methods of biomedical research within the eight participating departments and institutes and gained a comprehensive insight into the immunobiological basics of medicine through this new curriculum.

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. Since the immunological training of young researchers should not be limited to a medical school curriculum it should be also integrated into continuous clinical training.
The Else-Kröner-Forschungskolleg Würzburg recognizes the demand of patient-oriented personalization in 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 the same coin. Thus, all these topics are included in the curriculum of the Else-Kröner-Forschungskolleg Würzburg. The Else-Kröner-fellows get acquainted with the broad impact of immune function on common diseases beyond conventional disciplinary borders.
Although it is a comparatively new program the Else-Kröner-Forschungskolleg turned out to be highly successful in supporting long-term interdisciplinary cooperation. For example, this offers the unique opportunity to promote the translation of therapeutic approaches that have been proven to be successful in some immune related diseases towards new, not yet explored, disease conditions.

Patient-oriented immunological research

To guarantee an ideal interaction between experimental immunological and clinical re-

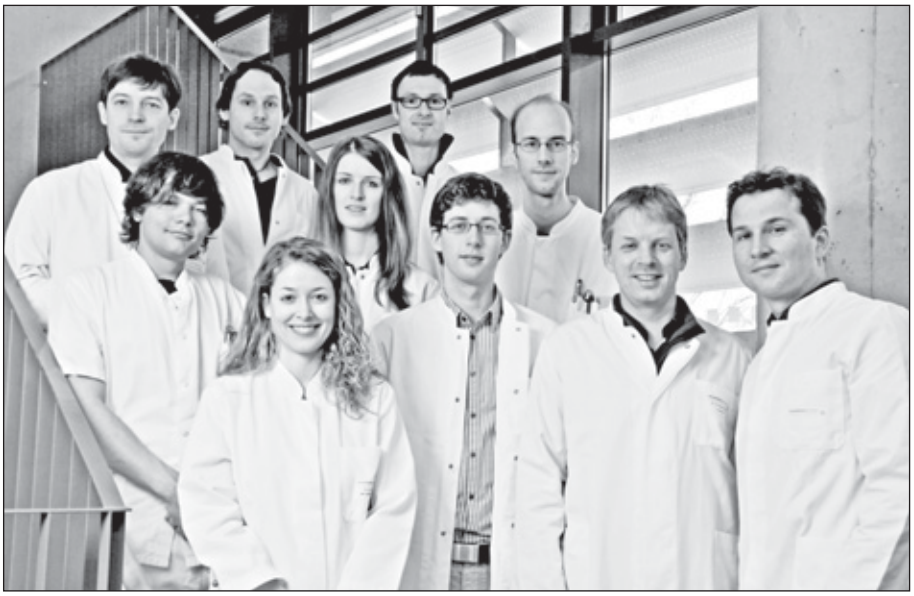

Fig. 1: The fellows of the Else-Kröner-Forschungskolleg for Interdisciplinary Translational Immunology.

Fig.2: In March 2012 the Else-Kröner-fellows organized the first Else-Kröner-Symposium "Translational Immunology – From Target to Therapy" in which leading international scientists participated.

search, eight different clinical departments and institutes from the Würzburg University Hospital and the Würzburg University joined to collaborate in the Else-Kröner-Forschungskolleg.

State-of-the-art individualized immunotherapy inevitably begins with the identification of target genes. These are analyzed at the Institute of Pathology Würzburg, an internationally recognized center for lymph node pathology with a 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 Internal Medicine I it was demonstrated that autoantibodies against ß1/2-adrenergic receptors can play a major role in the pathogenesis of cardiac insufficiency. The clinical concepts emerging from this research is further explored and developed at the new founded German Center for Heart Failure (DZHI), which is connected to the Department of Internal Medicine I.

The Department of Internal Medicine II focuses on innovative immunotherapies for hematological malignancies and has initiated the nationwide 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 IZKF-research group for Experimental Stem Cell Transplantation, established in 2012, is testing new immunological therapeutic concepts for leukemia, solid tumors, infections and graft-versus-host disease after stem cell transplantation in preclinical models.

Adoptive immunotherapies may benefit from novel protocols for efficient generation of tumor-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. The scientists are testing novel concepts for the regulation of 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, Venereology and Allergy has investigated tumor microenvironments as modulator and target structure of anti-tumoral immune reactions. It has successfully carried out trials in 2011 of peptide based vaccination against tumor-stroma-antigens. With the appointment of Prof. Goebeler as the new department chair the field of Allergy research was strengthened.

At the Department of Obstetrics and Gynecology 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 section for Experimental Tumor Immunology develops clinically relevant strategies for the immunotherapeutic "targeting" of tumor stem cells. Based on mRNA-profiles in the peripheral blood lymphocytes new diagnostic approaches have been developed.

Structured training for physician scientists

The actual participation of the selected fellows in the training program of the Else-Kröner-Forschungskolleg lasts 3 years. This time frame allows a personalized program in order to suit the individual interests and talents of each participant. Thus, 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 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 facilitated the rapid acquisition of a program overview and has also created personal contacts with experts in various disciplines.

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

Together with their supervisors, each fellow designed her/his individual program that should offer her/him 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, ensured that both clinical and scientific needs are considered.

An external faculty mentor provides personal guidance to each fellow's individual career development. This policy of external mentors limits potential conflicts of interest between the faculty and the supervisors. Although the fellows had the possibility to divide their lab rotation into shorter time intervals, all of them chose to complete their secured research time in one cycle.

One fellow further added a 6 month research stay at Stanford university to extend his scientific formation. This was jointly supported by the Else-Kröner- Forschungskolleg and the host clinic.

Because each fellow could pick the lab of their choice, it was ensured that the principal investigators of these laboratories had to accommodate the particular needs of the fellows. During this protected laboratory research period, the fellows were freed from all clinical obligations.

During the three-year training program we had and have 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 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 has offered 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.

5.1.7 Comprehensive Heart Failure Center (CHFC)

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General Information

Since November 2010 the Comprehensive Heart Failure Center (CHFC) has been funded as one of eight Integrated Centers for Research and Treatment by the Federal Ministry of Education and Research in Germany. The CHFC aims to prevent heart failure and its complications.

Heart failure is a rapidly growing health care problem. The syndrome affects approximately one 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 existing clinical study unit was transformed into the central clinical research facility of the CHFC, and is complemented by a Center for Biometry, Study Coordination and Study Management (ZBSS). Longstanding and very successful collaborations exist with the Collaborative Research Centers (SFBs), the Research Center for Experimental Biomedicine of the DFG (Rudolf Virchow Center), the Interdisciplinary Center for Clinical Research (IZKF) of the BMBF, Institute for Clinical Epidemiology and Biometry, and the International Graduate School of Life Science (Excellence Initiative) as well as with the national Competence Network Heart Failure (CNHF) whose main office was moved to Würzburg in 2012.

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. In cooperation with the Graduate School for Life Sciences the study course “Clinical Sciences” that may be extended into a masters degree shortly after finishing medical

Fig. 1: CHFC Members and staff.

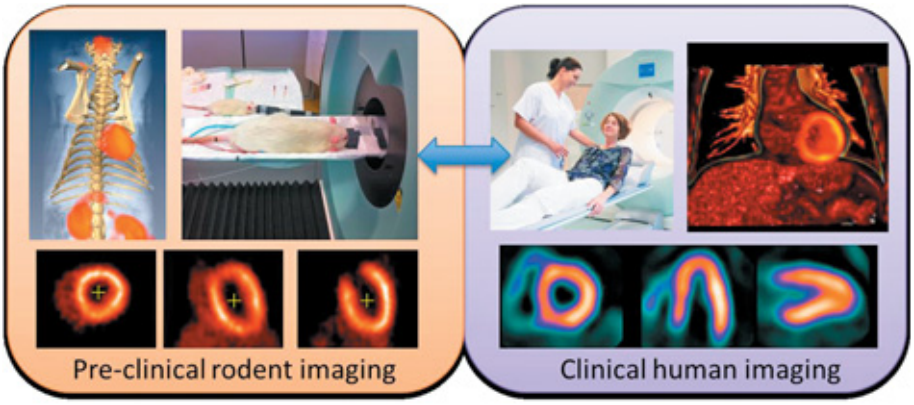

Fig. 2: Translational Cardiovascular Molecular Imaging.

studies, a curriculum in clinical research for physicians, and a PhD track "Clinical sciences" which started first in 2013, have been established. The start of the master course "Clinical Sciences and Epidemiology" is scheduled for the year 2015.
In the summer of 2013 a new CHFC's research building was granted by the German Research Foundation with support of the Bavarian State Ministry of Education, Science and the Arts. The ground-breaking ceremony will take place in January 2014.

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 multi-disciplinary interventions for heart failure patients ("management"), which were successfully tested in real world settings. On the basis of Project A1 (Characteristics and course of heart failure (stage A-D), and determinants of progression) the STAAB Cohort Study investigates frequency and factors influencing the early course of heart failure (A and B) in a population of Würzburg.
Biomaterials and standardized data sets are contributed by the prospective cohort study "Rheuma und Herz" (Associated Project A3) and the "Handheld BNP Studie" (Associated Project A4). Additionally, Project A2 focuses on effector kinases as target proteins of cardiac hypertrophy. The three rotational positions do research in the field of aortic valve replacement and cardiac surgery.

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

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. This includes the crucial role of clotting factor XIII for infarct healing (Project B1), the importance of the local, cardiac actions of C-type natriuretic peptide (project B11, start November 2013) as well as the correlation between oxidative stress and the development and progression of chronic heart failure (project B12).

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

Project Area C addresses basic pathophysiological principles, clinical progression, and new approaches for prevention and therapy of orphan cardiac diseases. New cardiotoxic cancer drugs are investigated in clinical studies. Project C6 focuses on the kinetics of myocardial inflammatory and autoimmune processes in the development of heart failure in animal studies and in a first human pilot study.

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

Obesity is linked with diastolic and systolic heart failure. For the first time clinical researchers investigate the effect of a bariatric operation on cardiac function and quality of life in an interdisciplinary randomized clinical trial (Project D1). Project D11 investigates in animal models the biochemical, molecular and hemodynamic parameters of this intervention. Project D12 establishes in a prospective cohort study a registry of obesity and heart failure in order to identify prognostic factors which can predict cardiac symptoms and function in obese patients.

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).

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Fig. 3: New research building as of 2016.

Patients with chronic kidney disease reveal a disproportionally high risk due to a high incidence and prevalence of cardiovascular disease. To identify new risk factors concerning heart failure and cardiovascular complications in patients with kidney disease are investigated by genome-wide association analyses in patients of the German Diabetes Dialysis Study (4 D Study, project E 5).
The rotational position in this project area also deals with the chronic cardiac and renal insufficiency by analysis of prevalence and risk factors of these diseases with data from the EUROASPIRE IV study. In the start-up project (E6) the correlation between COMT enzyme activity and clinical endpoints after cardiac surgery will be investigated in a pilot study

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. The consequence of heart failure on function of the brain is topic of project F2. Besides the human studies there are animal studies in mice and rats testing the influence of chronic heart failure on the brain morphology. Project F5 investigates the interdependency between cardiac diseases and stroke in human and animal studies.

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 (ICD Forum). The project will provide empiric data on the effect of a prevention program. Project G6 plans the development of new methods and technologies for the induction of neoangiogenesis in three-dimensional collagen scaffolds as well as the generation of functional vascular, autologous myocardial patches.

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

The Core Facility Imaging develops advanced morphologic, functional and metabolic imaging techniques to support the Project Areas. Further, researchers of the Core Facility develop in start-up projects model-based magnetization transfer contrast imaging for cardiac MRI (CF 1.8), investigate myocardial sodium content in patients with hyperaldosteronism (MyStIC Study CF 1.9), and develop a new approach for coronary magnetic resonance angiography.

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5.1.8 Comprehensive Cancer Center Mainfranken

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General Information

The CCC Mainfranken (CCC MF) has evolved from the "Interdisziplläres Tumorzentrum der Universität Würzburg", which founded in 1983. In 2008 the "Tumorzentrum" was transformed into the Comprehensive Cancer Center Mainfranken. In 2011, the German Cancer Aid awarded the CCC Mainfranken the status "Onkologisches Spitzenzentrum". Today, the CCC MF is the central forum for basic, translational and clinical cancer research as well as for cancer care at Würzburg University, the University Hospital and the region of Mainfranken. Thus, the CCC organizes three areas: multi-disciplinary care, translational and clinical research, and the regional cancer care network (outreach). In 2010 the clinical part of the CCC MF was certified as "Oncology Center" by the Deutsche Krebsgesellschaft and successfully passed re-evaluation in November 2013. In addition seven organ cancer centers as well as the center for stem cell transplantation, the interdisciplinary center for hereditary breast and ovarian cancer, and the interdisciplinary palliative care center have been established under the roof of the CCC and the Oncology Center:

(1) Breast Cancer Center (Speaker: Prof. J. Dietl)
(2) Gynecological Cancer Center (Speaker: Prof. J. Dietl)
(3) Colorectal Cancer Center (Speaker: Prof. C.-T. Germer)
(4) Pancreas Cancer Center (Speaker: Prof. C.-T. Germer)
(5) Skin Cancer Center (Speaker: Prof. M. Göbeler)
(6) Neuro-oncological Center (Speaker: Prof. R.-I. Ernestus)
(7) Head & Neck Cancer Center (Speaker: Prof. R. Hagen, Prof. A. Kübler)
(8) Stem Cell Center (Speaker: Prof. H. Einsele, Prof. P.G. Schlegel)
(9) Palliative Care Center (Speaker: Dr. B. v. Oorschot, Prof. M. Flentje)
(10) Center for Hereditary Breast and Ovarian Cancer (Speaker: Prof. T. Grimm, Prof. J. Dietl)

Multi-disciplinary Care

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. All cancer patients entering the CCC MF are discussed in 15 weekly interdisciplinary tumour conferences and are treated by multi-disciplinary teams. Furthermore, multidisciplinary outpatient facilities and counselling hours have been established in the field of GI-cancer, endocrine Tumors, prostate cancer, lung cancer and head & neck cancer. The central building of the CCC (C16) houses the central quality assurance team, the central cancer registry, the CCC trial office and the interdisciplinary outpatient facility for clinical trials, the interdisciplinary outpatient chemotherapy ward, and counselling hours for psycho-oncological and palliative care.

Additional multi-disciplinary offers for patients, health care professionals, and the community:

- Social service
- Information about self-help groups, meetings of self-help groups
- Sport courses and nutrition counselling hours for cancer patients
- Information seminars for patients, their relatives and the public about topics in the fields of cancer therapy and cancer prevention.
- Outpatient pain Center
- Counselling of patients and their families with hereditary cancer

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- Numerous training and education programs for physicians, clinician scientists, nurses and other health care professionals

Currently, a concept for a full-fledged central entry port located in one building is being developed for all cancer patients entering the CCC MF.

Outreach/Regional Cancer Care Network

Cooperating partners of the CCC Mainfranken are the academic teaching hospitals (Julius-Spital and Medical Mission Hospital) in Würzburg and other hospitals and specialists in private practices of the region Mainfranken (Aschaffenburg, Schweinfurt, Lohr, Bad Mergentheim, Bad Neustadt, Bad Kissingen, Coburg, Rothenburg, Kitzingen).
In order to better serve patients' needs for high-quality medical care within the vicinity of their residence the CCC MF actively supports the certification of general oncology and organ-specific centres in the regional area (in total: 2 centres for oncology, 5 for gastro-intestinal cancer, 5 for breast cancer, 2 for pancreatic cancer, 2 for gynecological cancer, 1 for prostate cancer). The CCC MF assures a high standard of medical care in the region by organizing joint tumor board activities, a regional trial network, central quality assurance, training and education programs, and the cancer registry services. In 2013 more than 10,000 cancer patients of the region of Lower Franconia were discussed in tumor boards of the regional cancer care network, 3,700 of these patients were discussed in joint cross-institutional tumor boards.

Translational Research

Clinicians 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 cooperations are also established with other faculties of the University.
The main focus of translational research at the CCC MF is to identify molecular targets and to develop therapeutic strategies for genetically complex and heterogeneous tumors. Between 2009 and 2013, the CCC MF therefore developed translational research programs focusing on (A) the identification of critical regulators of tumor cell physiology that can serve as molecular targets for targeted therapies, (B) on immunotherapy and (C) on targeted radiotherapy and molecular imaging. In addition, tumor genome sequencing has grown in importance and has therefore been developed into a fourth research program (D).
During the past few years preclinical research from the major research programs has been successfully translated into the clinic. For example, seminal work from scientists of the CCC MF has demonstrated the first clinical proof-of-concept that T cell-based immunotherapy has the potential to eradicate bulky tumor masses and to cure patients with chemo-resistant disease (program B, Figure 1).
Another highlight is the identification of new target structures making as yet non-druggable key oncogenes accessible to a targeted approach (program A). This research has in parts already progressed to a stage where the concepts are being tested in clinical trials.
The genome-sequencing program (D) led to the identification new pathogenetic pathways and might lay the foundation for the development of personalized and targeted therapies in a series of different cancer entities potential new targets in non-Hodgkin lymphoma, multiple myeloma, Wilm´s tumors, melanoma, brain tumors and endocrine tumors.
Research from program C (targeted radiotherapy and molecular imaging) led to the development of novel therapies in the field of endocrine tumors and in lung cancer.

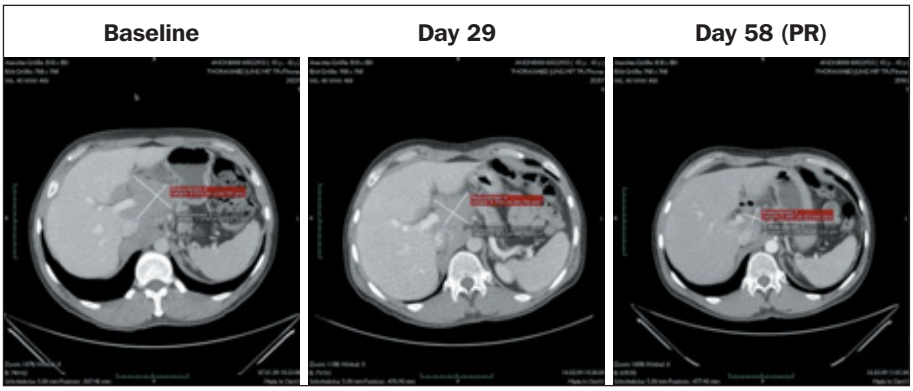

Fig. 1: Tumor regression of a bulky abdominal tumor in a patient with relapsed mantle cell lymphoma treated with a T cell-engaging BiTE antibody in a phase I trial.

Clinical Research

In addition to the translational research programs, the CCC MF has initiated a series of clinical research projects aimed at the improvement and further development of health care standards. The program includes studies on supportive care, psychosocial and palliative care, health care and outcome research, and predictive and prognostic factors.

Outcomes research and the clinical cancer registry

The 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 outcomes and healthcare research. For example, analysis of the cancer register follow-up data show that the survival probability of patients with rectum cancer treated at the CCC MF has markedly improved over the past few years (Fig. 2).
Other projects identify risk factors for development of peritoneal carcinomatosis in colorectal cancer and in gastric cancer with the aim of changing practice in aftercare. In addition, the CCC MF runs a program on biomarkers and prognostic factors in a number of cancer entities. Recently, projects in high-risk prostate and bladder cancer led to important clinical results with potential practice changing impact.

Clinical Trials

The central trial office of the CCC MF 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 sup-

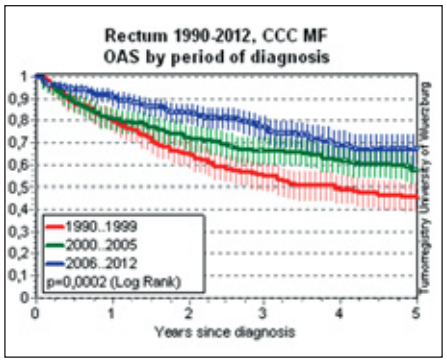

Fig. 2: Monitoring of outcome at the CCC MF – OAS of patients with rectum cancer for three time periods (95% confindence limits).

port, 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 interdisciplinary 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). The ECTU is one of the country´s largest phase-I units and was the first of its kind in Germany. Since its start in 2007 more than 30 phase-I and I/II trials have been initiated, many of them based on preclinical research of scientists of the CCC MF. Novel therapies tested in the ECTU include cellular and targeted therapies with novel antibodies, tyrosine kinase inhibitors heat shock protein inhibitors, radionuclides, HDAC inhibitors and other small molecules. Thus, the ECTU is an important structural element for the translation of basic research into the clinic.

In addition, in 2013 the CCC MF has established a central interdisciplinary outpatient unit for clinical trial activities in solid tumors (IOCT). The new trial unit focuses on large multi-disciplinary phase II and phase III trials, thus complementing the activities of the well-established Early Clinical Trial Unit (ECTU). The new trial unit has established a multi-disciplinary trial program with a multi-institutional investigator team comprising gyneco-oncology, uro-oncology, lung cancer, gastro-intestinal cancer and head & neck cancer.

Another important step in the field of clinical research was to integrate external physicians and community hospitals of the regional catchment area into the clinical research programs of the CCC Mainfranken and to establish a regional trial network. This has strongly enhanced accrual of patients of the regional area into clinical trials.

In 2012 more than 1000 cancer patients of the region Lower Franconia were in clinical trials.

Based on this infrastructure the CCC MF has initiated a comprehensive program of investigator-initiated studies aiming at the improvement and further development of health care standards. Studies are currently running in various fields of clinical oncology. Key trials, chaired and initiated by Würzburg PIs, have led to results with practice changing impact in psycho-oncological care, adrenocortical cancer (ACC), hemato-oncology, radio-therapy and lung cancer. In addition, investigators of the CCCMF contributed to practice changing IITs in the field of colorectal cancer and pancreatic cancer.

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5.1.9 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).

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, R. Hagen)

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

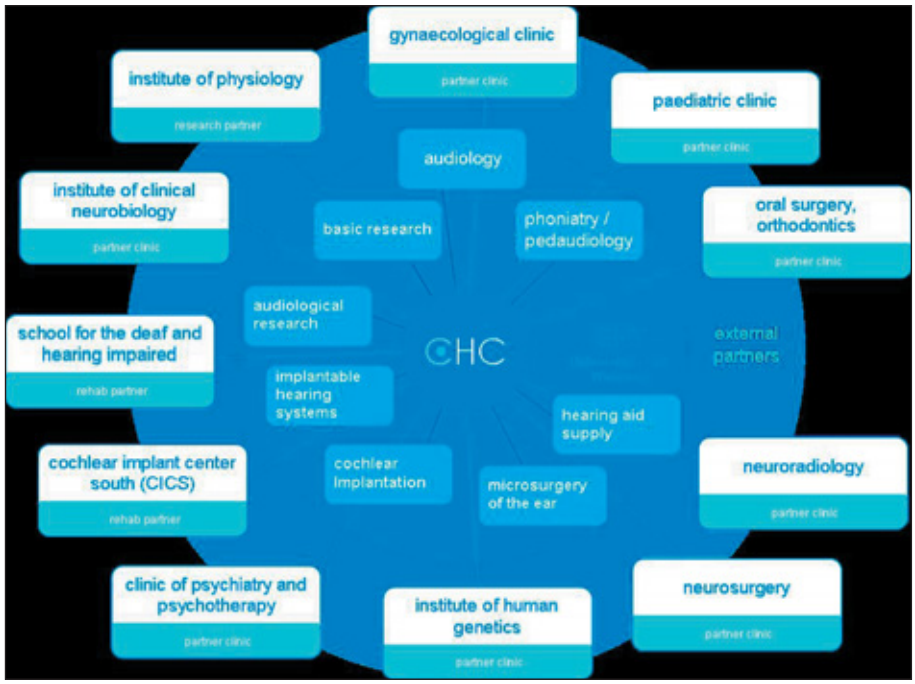

Fig. 1: Structure of the CHC.

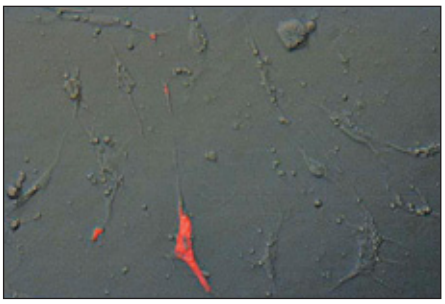

Fig. 2: Neuronal differentiation of adult stem cells for application in the inner ear (guinea pigs).

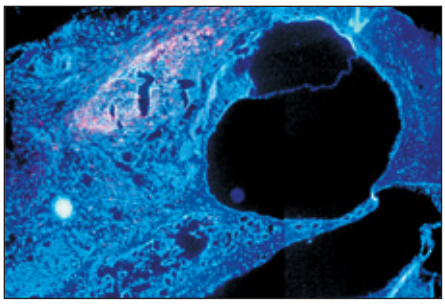

Fig. 3: Active migration of stained stem cells (pink) from basal cochlear turn (guinea pigs).

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. Intraoperative monitoring of transfer function of active middle ear implants.

Inner ear biology
(K. Rak, J. Völker, S. Frenz, R. Mlynski in Zusammenarbeit mit dem Institut für klinische Neurobiologie, M. Sendtner)

Evidence and functional properties of neuronal stem cells in the rat cochlear nucleus. Dynamic changes of the neurogenic potential in the rat cochlear nucleus during post-natal development. Effects of defined gene mutations (TBCE gene) on inner ear structure in the pmn/pmn mouse. Interactions of neuronal structures with semiconductor materials.

Therapeutic use of stem cells in the damaged cochlea
(A. Radeloff, P. Schendzielorz)

Improvement of survival of ganglion cells following experimental deafening by local stem cell application in the cochlea of the guinea pig. Development of a stem cell coating on inner ear electrodes for optimization of functional linkage in cochlear implants.

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

Development of new objective testing procedures for frequency specific screening in newborns. Analysis of prespeech sounds in babies to objectify early speech development in pedaudiology.

Cochlear- and brain stem implants
(R. Mlynski, W. Shehata-Dieler, A. Radeloff, S. Brill, S. Kaulitz, in cooperation with the department for neurosurgery, C.Matthies, 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 electrostimulation 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 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. Objectivication of binaural hearing in persons with normal and impaired hearing.

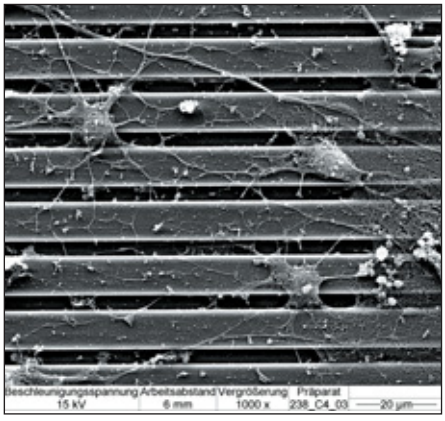

Fig. 4: Collateral sprouting of neuronal cells on semiconductor-material.

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

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5.1.10 Musculoskeletal Center Würzburg (MCW)

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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 of the elderly. 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, especially internal medicine, nuclear medicine, pediatrics, surgery, neurology and the institutes for radiology, pathology and genetics.
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 center is supported by the cooperation with the Interdisciplinary Center for Clinical Research IZKF, the Center for Experimental and Molecular Medicine ZEMM, the Institute for Bioinformatics, the faculties for biology, biophysics as well as theology and law jurisdiction for ethical and legal issues. The consortium is embedded into local, national and international research networks. 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.
Rapid translation of basic science results into clinical applications is facilitated by the upcoming Fraunhofer Translational Center, which is supported by the Bavarian government. The aims of this institution are Networking between Basic Science and Clinical Medicine, Education and Support of Clinician Scientists and education of personnel for clinical studies for good clinical practice GCP competence, seconded by close cooperations with the Chair for Biometry and Clinical Epidemiology. Intensive research in the interface between research, development and industrial production helps founding of new companies and feeds the close cooperation with Fraunhofer Society.

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, epigenetics 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 networks, e.g. the Sander-Stiftung Treatment Unit for Multiple Myeloma, DFG-Research Units FOR 793 and 1586, SFB630, BMBF-Consortia Osteopath and DIMEOs, the binational German-French consortium OBELICS, the EU-Consortia ADIPOA, VASCUBONE, HydroZONES and STEP and in the Bavarian Sarcopenia Network FORMOsA

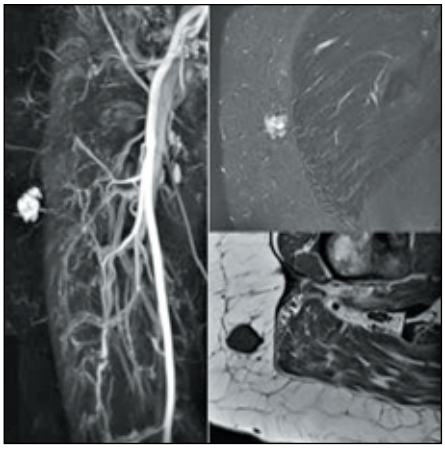

Fig. 1: Imaging of a mesenchymal mixed tissue tumor in the adipose tissue of the thigh, which by overproduction of FGF-23 produced a phosphate wasting syndrome and ouvert clinical oncogenic osteomalacia in a 51 year old female. This patient was cared for in close cooperation between the outpatient clinic for osteology, the orthopedic clinic König-Ludwig-Haus, the clinic for nuclear medicine and the Institutes for Radiology and Pathology (Lapa et al., JCEM 2013).

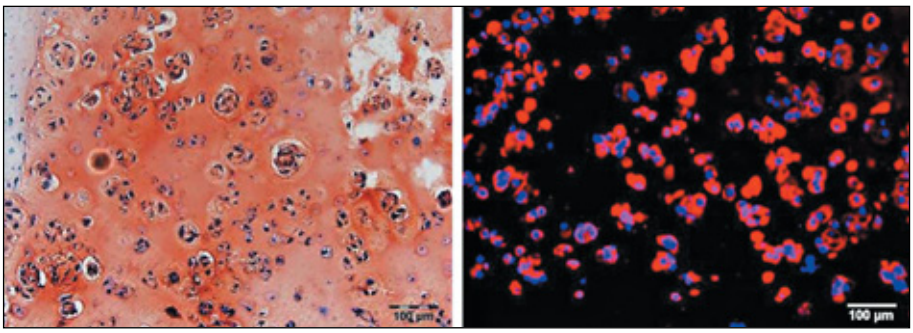

Fig. 2: Tailored hyaluronic acid-based hydrogels for cartilage regeneration. Hydrogels are seeded with mesenchymal stem cells from bone marrow. Following chondrogenic commitment cartilage specific components of the extracellular matrix are expressed (left panel: Glycosaminoglycans (Safranin-O-staining, red); right panel: collagen II immunohistichemical staining (red staining COLII, blue DAPI staining of nuclei). In this project hydrogels will be additionally functionalized by adding biomimetic peptide sequences. It is the aim of this project to optimize chondrogenic differentiation and to refine the clinical potential of the materials and constructs (Interdisciplinary MCW cooperation between the chair for functional materials in Medicine and Dentistry J. Groll, the head of research in the Department of Trauma, Hand, Plastic and Reconstructive Surgery T. Blunk and the Head of the Translational Ortthopedics team A. Steinert, funded by the IZKF. Image: Thomas Böck.).

supported by the Bavarian Research Foundation. Prof. Jürgen Groll was awarded an ERC Consolidator Grant in 2013 by the European Research Council.

Teaching

The main issues of teaching activities are curricular teaching of the core disciplines in medicine and dentistry and the relevant contributions of chairs and associated professors in modern interdisciplinary trans-faculty studies such as „Technology of functional materials“, „Biomedicine“ and „Life Science“ (e.g. within the Wuerzburg Graduate School of Life Sciences). MCW institutions are tightly involved in hosting and mentoring bachelor and master theses of the respective courses of studies as well as doctoral theses of graduate students.

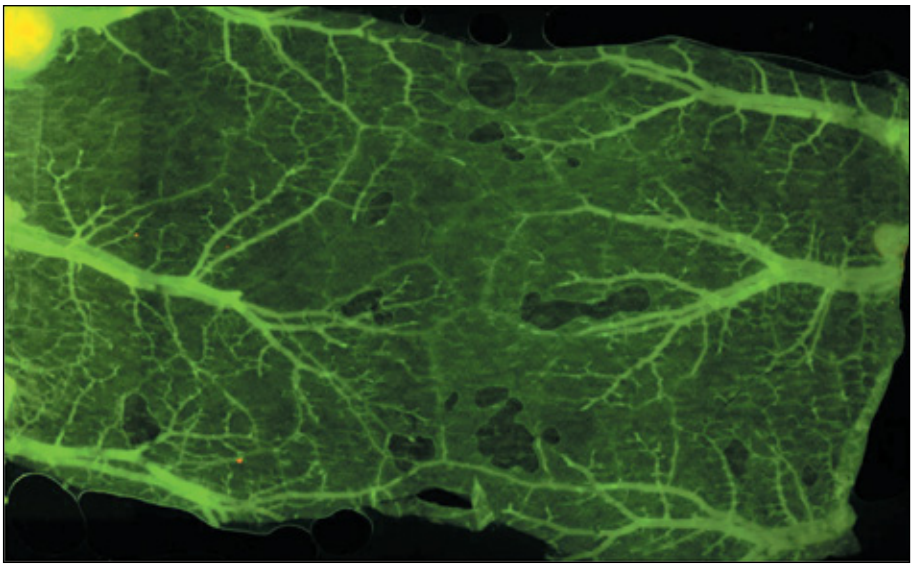

Fig. 3: Preparation of a BioVaSc (mBioVaSc). The de-cellularized vasculature structure was reendothelialised with human dermal microvascular endothelial cells. This mBioVaSc was established as a 3D structure at the Chair for Regenerative Medicine and Tissue Engineering within the Bavarian Sarcopenia Network FORMOsA. The image shows an overlay of vital (green staining) and dead (red staining) cells.

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5.1.11 Transplant Center (TPZ)

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Clinical Transplantation

The Transplant Centre Würzburg (TPZ) is one of several German transplant centres. The kidney transplant program oversaw a steady rate of 35-49 kidney transplants a year until 2012. Following the German liver allocation scandal, there was a dramatic decrease in organ donations nationwide, which negatively affected the kidney transplant rate in Wuerzburg as well. The living donation program could not fully compensate for this effect. By the end of 2013, 106 living kidney-transplants of related and unrelated donors had been performed. In addition, 866 postmortal kidneys were transplanted. Both programs are conducted in close cooperation between the Division of Nephrology and the Department of Urology since the start of the program in 1984. Furthermore, 13 combined kidney-pancreas-transplantations and two combined kidney-liver-transplantation were performed in collaboration with the Department of Surgery. Currently, 248 patients are waiting for a kidney graft in Wuerzburg.

Since 2008, 24 heart transplantations (three in 2013) have been conducted by the Department of Thoracic and Cardiovascular Surgery in collaboration with the Department of Internal Medicine I. At present 10 patients are on the waiting list for heart transplantation.

The liver transplantation program is managed via a collaboration between the Department of Surgery I and the Department of Internal Medicine II. Between 1991 and 2007 (when the program was temporarily discontinued), 69 liver transplants were performed. In 2012 the Divisions of Hepatology and Hepatobiliary and Transplant Surgery were formed and the liver transplantation program was re-launched together with the newly created Liver Center. Since the relaunch, 27 livers have been transplanted. Both the one-year patient and graft survival rate are currently 96%. In May 2013, following audits by the Assessment and Monitoring Commission (Prüfungs- und Überwachungskommission) of the German Medical Association (BÄK) and the State Government of Bavaria (led by Professor Mühlbacher, Vienna), the University of Wuerzburg's liver transplantation program was chosen as one of three future liver transplant programs in the Federal State of Bavaria. Currently, there are 33 patients on the waitlist for liver transplantation.

All patients of the programs mentioned above are served by the respective outpatient departments, most (in cooperation with local resident practitioners.) of them together with resident practitioners in the vicinity. Also involved is the Department of Dermatology, which offers 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 hospitals in Aschaffenburg, Schweinfurt, Coburg and other hospitals in the region, the registration of potential organ donors has been 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, San Francisco / USA, Seattle / USA, Sydney / Australia and the Ludwig Maximilian University in Munich.

Further Activities

Every two years the kidney transplant program organizes a regional transplantation workshop (Franconian Transplant Workshop) focusing on the operative and conservative aspects of kidney transplantation, the next meeting will take place in winter 2014 for the 13th time. Earlier in the year a seminar for patients and relatives ("fit for transplantation") is arranged with great success; in 2013 more than 250 participants attended.

SELECTED PUBLICATIONS

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Panther F, Strasen J, Czolbe M, Lazariotou M, Burkard N, Williams T, Lange V, Otto C, Ritter O. (2011) Inhibition of nuclear translocation of calcineurin suppresses T-cell activation and prevents acute rejection of donor hearts. Transplantation 91:597-604.

5.1.12 Clinical Trial Center Würzburg (CTCW)

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Mission statement and structure

The Clinical Trial Center Würzburg (CTCW) of the University Hospital Würzburg (UKW), originally founded in 2003 was restructured in 2012. The CTCW is the academic clinical research organization (ACRO) of the UKW for providing clinical trial support, implementing standards for the conduct of clinical studies and guaranteeing the high quality of patient-oriented research. The CTCW supports clinical trials of the phases I to IV comprising its planning, coordination, management, and analyses of following ICH-GCP guidelines.
The CTCW focuses specifically on the conduct of academically oriented investigator initiated clinical studies. By a close cooperation and continuous dialogue with the investigators, our services can be customized according to the individual requirements covering the spectrum of providing a full-service solution or also a support of specific aspects, e.g. data management or biometry. The CTCW is also part of the sponsor quality management of the UKW providing comprehensive standard operating procedures (SOPs) for all aspects of clinical studies.
The CTCW cooperates closely with other clinical research facilities at the UKW and the University Würzburg, such as the Comprehensive Heart Failure Center (CHFC), the Comprehensive Cancer Center Mainfranken (CCC MF), the Nephrological Study Center Würzburg (NSZ), the Service Center Medical Informatics (SMI), as well as the Institute for Clinical Epidemiology and Biometry (ICE-B).
The CTCW is offering regular education activities together with other experienced cooperation partners such as the CCC MF, the NSZ or CHFC research organisations for local clinical investigators in the form of courses for principal investigators, training to become a study assistant as well as lectures and seminars on clinical research.
In the following section, the clinical service portfolio of the CTCW is introduced.

Clinical Services

Our Clinical services consist of:
- Protocol development
- Submission to Ethics Committee and Regulatory Agencies
- Project Management & Site Management
- Clinical Monitoring
- Data Management and Biostatistics
- Regulatory Services

Clinical Project & Site Management

The Project Manager is the primary CTCW contact and works with all project team members involved in the conduct of the trial to ensure problem identification and resolution and adherence to study timelines, e.g. supporting protocol development, identify and select study sites, create and manage executive, steering and data safety monitoring committees, create educational tools and reference materials, engage in proactive and routine communication to sites, conduct investigator meetings and coordinator conference calls.

Clinical Data Management (CDM)

The CDM includes the collection, cleaning and management of patient data in compliance with regulatory standards. The primary objective of the CDM processes is to provide high-quality data by keeping the number of errors and missing data low as possible

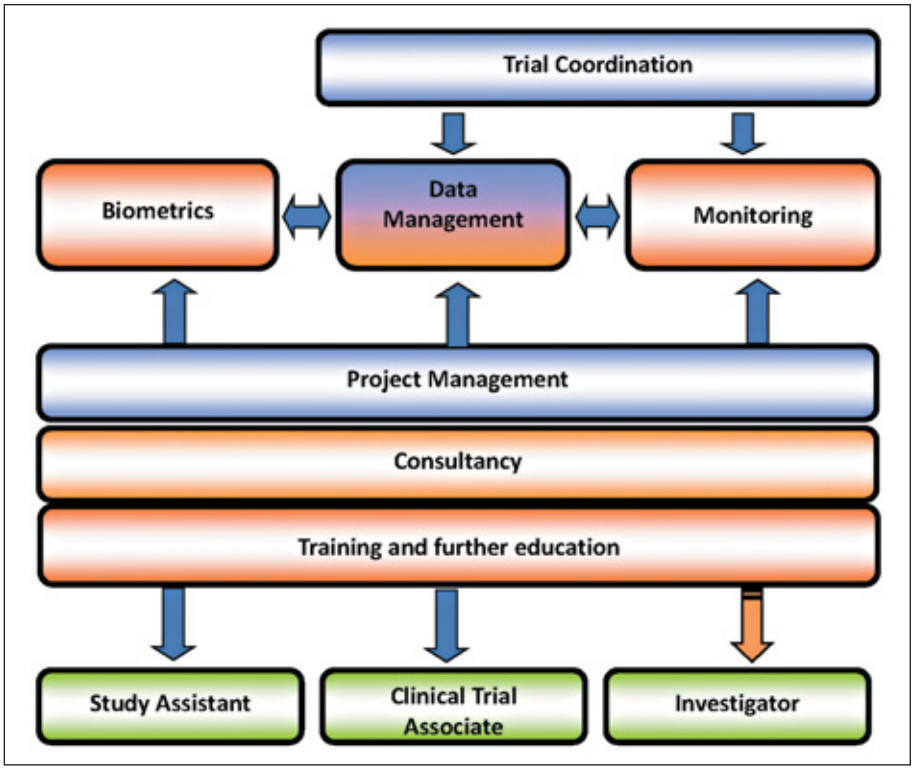

Fig. 1: Functional areas of the CTCW.

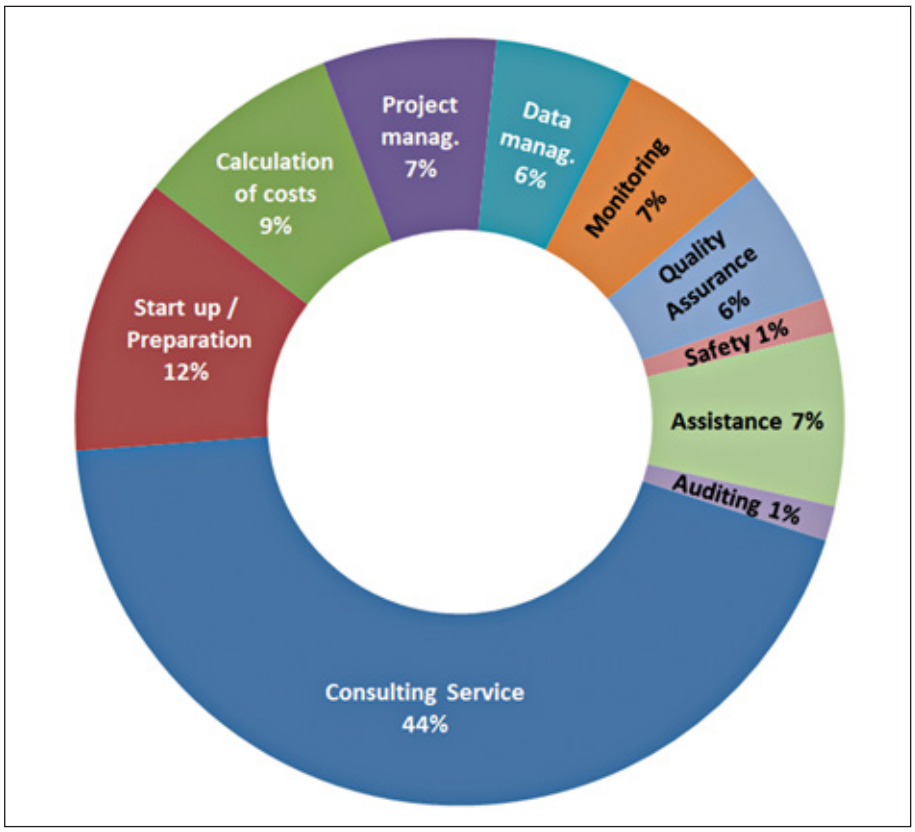

Fig. 2: CTCW clinical services 2012/2013.

and gather best data for analysis. Data management tools are provided at the CTCW to meet specific needs of different types of clinical studies – both for paper-based and Electronic Data Capture. The data management platform, SOPs and staff will provide the clinical researcher with cost-effective, secure, regulatory-compliant and efficient data management services.
Our panel of services of Clinical Data Management includes:

- Case Report Form (CRF) designing
- Development of project documentation: Data Management Plan, Data Cleaning/ Validation Plan
- Generation of annotated CRF
- Database designing and validation
- Data Cleaning: checks programming, query management, quality control
- Medical coding (MedRA, WHOdrug)
- SAE Reconciliation between the safety database and the clinical database.

Biostatistics

The CTCW biostatistical team supports clinical projects and provide assistance beginning at the initiation of a clinical trial. The statistics team collaborates with investigators on the analysis of trial data and prepares the statistical part of the primary manuscript at the conclusion of the trial.

Biostatistics services:

- Sample size and power calculations
- Statistical protocol development
- Statistical analysis plan
- Statistical report
- Statistical advices

Clinical Trial Monitoring

The CTCW provide also clinical monitoring services for different therapeutic areas across drug and medical device trials for building and maintaining sustainable relationships with investigative sites to ensure successful clinical trial progress.

Clinical Trial Monitoring services include:

- Site Qualification and Initiation
- Regulatory Documents Preparation and Collection
- Subject Enrolment/Retention Strategy Enhancement
- Site Personnel Training
- Monitoring Visits (pre-study visits, initiation visits, interim visits, closure visits)

Quality Assurance Services

- Standard Programs (GCPs, Validation, and 21 CFR Part 11 compliance) review
- Pre-Audit Readiness Resources
- Audit Participation and Handling

Clinical Operations

- Clinical Study Management
- Vendor Management
- Pharmacovigilance Service
- Project feasibility evaluation
- Regulatory authorities Liaison

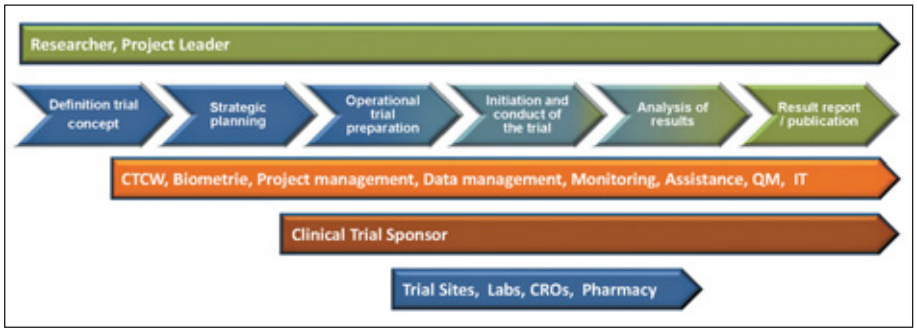

Fig. 3: Clinical trial process summary.

5.2. Collaborative Research Centers and Clinical Research Units

5.2.1 Collaborative Research Center 581, Molecular Models for Diseases of the Nervous System

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Speaker board
Professor Dr. Esther Asan
Professor Dr. Klaus V. Toyka
Professor Dr. Manfred Heckmann
Professor Dr. Rudolf Martini
Professor Dr. Utz Fischer
Professor Dr. Klaus-Peter Lesch

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(Office)
Phone: 0931/201-44001

General Information

The "Collaborative Research Center" SFB 581 „Molecular models for diseases of the nervous system" was established in 2000 at the University of Würzburg. In 2009, it was reviewed and funded for a final round of support until June 2012. It comprised groups from the faculties of medicine (clinical and theoretical institutes), biology and chemistry. The central goal was to investigate how gene mutations ultimately lead to the specific phenotypes in disorders of the nervous system, to identify contributions of reactive cells and neural activity to pathomechanisms and thus to contribute to a better understanding of the underlying disease processes. For that purpose two main focuses were set: the projects of part A focussed on mechanisms of inflammatory diseases, whereas the projects in part B dealt with molecular mechanisms of degenerative diseases. These two project parts were supplemented by two central projects on morphology/electron microscopy and modern light microscopic techniques (confocal and 2-photon-microscopy).

Major Research Interests

The SFB 581 had set the goal to investigate the complex course of primary and secondary pathophysiological processes in disorders 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 still difficult 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 collaboration with clinical researchers, investigates the cell biological cascade of disease development using suitable disease models. Thus the main emphasis in the SFB 581 was put on mouse and drosophila models. These models were used to study both the direct effect of signal transduction mechanisms on cellular structures and functions in the nervous system and the pathophysiological processes underlying the interactions of different cell types in neuroimmunological and neurodegenerative diseases.

The SFB connected molecular cell biologically oriented fundamental research to the understanding of the complex course of disease processes. In an interdisciplinary approach, the SFB 581 linked groups working with different methods on model systems for neurodegenerative and neuroimmunological disease processes.

This collaborative research center contributed significantly to training programs for students in the fields of Biology, Biomedicine as well as Experimental Medicine. Since the SFB was established, bachelor and master students participated actively in the projects. For this purpose the Deutsche Forschungsgemeinschaft and the University provided a considerable budget for student and graduate assistants. Members of the SFB 581 were actively involved in courses within the training programs for these students. The SFB 581 was also involved in the training of graduate students in the class "Neuroscience" of the International Graduate School (GSLS) at the University of Würzburg.

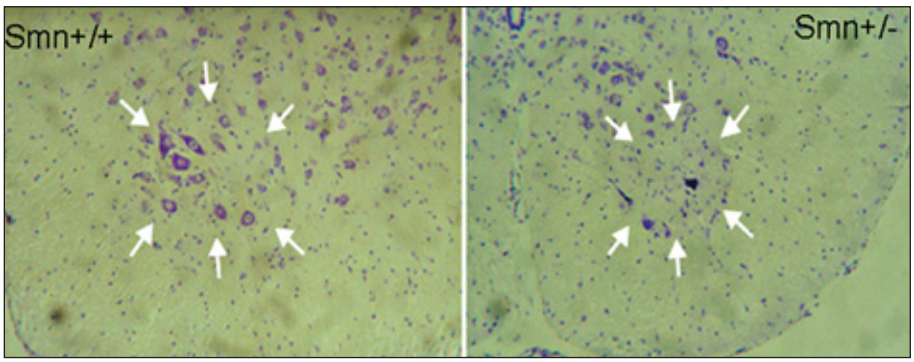

Fig. 1: Degeneration of spinal motoneurons in a mouse model for spinal muscular atrophy (Smn+/- right side). The area where motoneurons degenerate is labelled with white arrows.

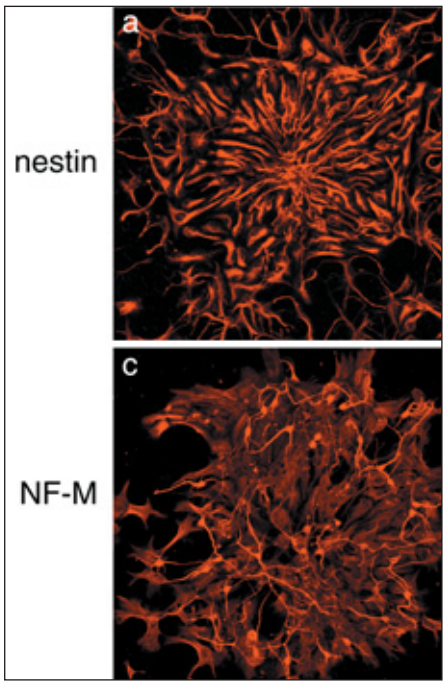

Fig. 2: Differentiation of neural stem cells in cell culture. Immature stem cells are labelled with an antibody against Nestin (panel a), 24 hrs after plating on Laminin, differentiated neurons that grow long neurites can be identified by labelling with antibodies against Neurofilament-N (lower panel).

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

A9 Lutz (Virologie und Immunbiologie): Präsentation cerebraler Glycolipide durch dendritische Zellen an NKT-Zellen und persistierende ZNS-Virus-Infektionen bei der Auslösung der EAE

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 Charlotte Förster (Neurobiologie/Genetik): 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 center 581:

July 3-4, 2009: International symposium, CRC 581 in Würzburg

December 1st, 2009: International symposium “Latrophilin-2”

April 2012: International Meeting CRC 581 in Würzburg

June 2012: NGF 2012 International Conference in Würzburg

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

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General Information

Infections by bacteria and parasites cause major health concerns - now, but also for the future. Due to the failure of antibiotic development to keep pace with the evolution of pathogens, novel infections emerge and well-known pathogens become resistant against all available classes of antibiotics. In low-income countries, infections caused by bacteria, fungi, parasites and viruses are still the leading cause of death. In May 2013, the WHO adopted a comprehensive resolution aimed at accelerating the efforts for overcoming the neglected, because poverty-associated tropical diseases – a measure that shows the utmost urgency of the topic.

Since 2003, the SFB 630 has been committed to the identification and development of novel anti-infectives. Currently 13 groups of four different faculties of the University of Wuerzburg and the Medical Mission Institute are successfully working together to reach this goal. According to the process of anti-infective development itself, the network is divided into three research areas. Area A is responsible for the preparation and characterization of compounds - by all state-of-the-art means of chemical synthesis and isolation from natural sources. All compounds are tested for their anti-infective potential against clinically relevant bacteria, fungi and parasites in the Central Laboratory supported by the rules of a quality management. The cellular and molecular interactions of active compounds with the respective pathogens are analyzed in Area B, including the determination of the target protein structure. Theoretical calculations, virtual screening and modelling are performed in Area C to characterize the molecular mode of action of the anti-infectives and to predict strategies for their optimization. The identified hits are further analyzed regarding their pharmacokinetic behavior in the Central Laboratory aiming to support the efficiency studies in animal models that also take place in Project Area B.

Major Research Interests

The research in the SFB focuses on the development of new drugs against infections caused by trypanosomes, *Leishmania*, plasmodia, Staphylococci, especially methicillin resistant *S. aureus* (MRSA), mycobacteria, *Candida, Neisseria,* and *Chlamydia*.

A severe problem in mycobacteria therapy is to overcome the bacterial cell wall, which is largely impermeable for small molecules. In a knowledge-driven approach, a novel algorithm was developed to predict the permeability probability of small organic compounds. This prediction permits the virtual screening and the synthesis to focus on potentially active compounds. The cell wall of mycobacteria is composed of long-chain fatty acids that are essential for the survival of the pathogen. Hence, the fatty-acid synthesis is one major target for anti-mycobacterial drug research. The mode of action of KasA, a condensing enzyme involved in this pathway, was analyzed by consecutive structural snapshots along the reaction coordinate of the enzyme. Even deeper insight into the mechanism of the reaction is provided by quantum mechanical calculations, which now may form the basis for a fine-tuning of inhibitors.

The fatty acid biosynthesis is also under investigation in *Staphylococcus* infection, es-

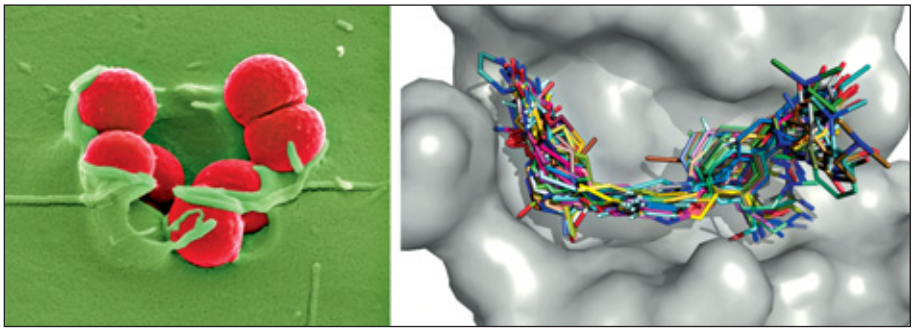

Fig. 1: Left: Bacterial Invasion. S. aureus bacteria (shown in red) penetrate a human embryonal kidney cell (shown in green). (K. Ohlsen). Right: The active site of S. aureus FabI. Based on our crystal structure new potential inhibitors were designed which are shown in different colors in the S. aureus FabI substrate binding pocket (shown in gray). The most promising compounds are currently synthesized and will be evaluated. (J. Schiebel, C. Kisker).

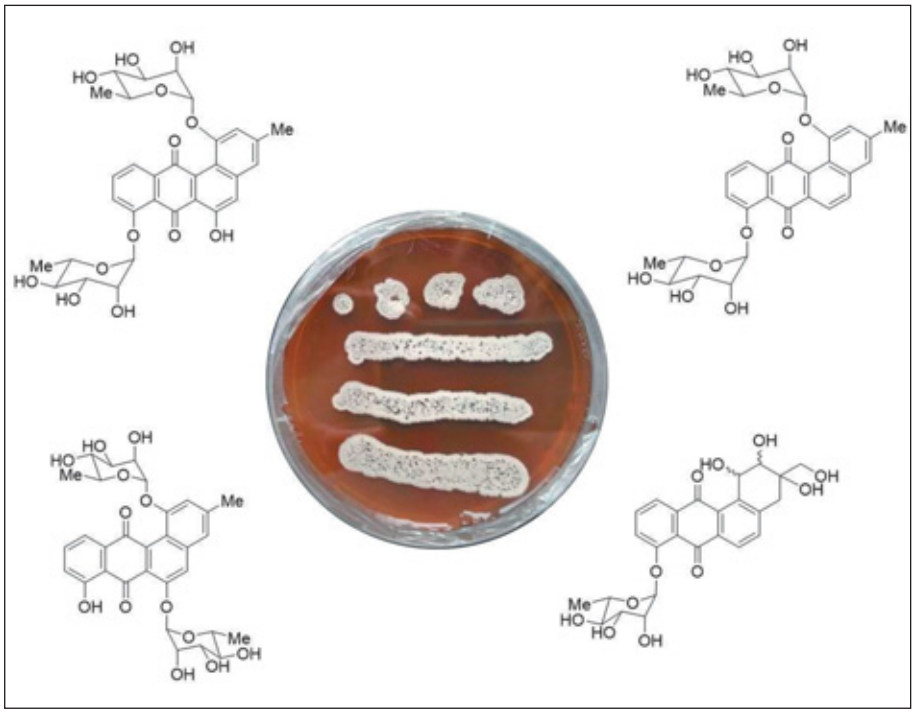

Fig. 2: New actinosporins A-D from sponge-associated bacterium Actinokineospora sp. strain EG49 (U. Abdelmohsen, U. Hentschel).

pecially MRSA. The structure of the enoyl-ACP reductase FabI, essential in this pathway of *S. aureus*, reveals key differences in ligand binding and recognition compared to homologous proteins - which is a necessary prerequisite to develop selective inhibitors. To elucidate the efficiency of such compounds, powerful, non-invasive imaging technologies provide information about the course and gravity of *S. aureus* infections in several *in vivo* model systems. Moreover, these methods may allow to reduce the number of animals needed for research evaluation of new antibiotics in the future.

Drug resistance is also a problem regarding the fungi *Candida albicans*, a commensal that can cause systemic infections in immune-compromised persons. One resistance mechanism is the constitutive expression of transcription factors that regulate efflux pumps and ergosterol biosynthesis. Analyzing the fitness of resistant strains by defined gain-of-function mutants of these transcription factors revealed a cost of resistance under conditions lacking the selective pressure. The additional mutations that compensate for the loss of fitness in vivo are now under investigation.

Another major target in several pathogens are proteinases that are essential for invasion, development and nutrition. Of special interest are the parasite proteinases of trypanosomes, leishmania and plasmodia, which are thoroughly investigated regarding the activity and selectivity of inhibitors. Moreover, the cysteine proteinase ChlaDuB1 of *Chlamydia trachomatis* was shown to be responsible for regulation of *Chlamydia*-mediated apoptosis resistance of their host cells. Inhibition of this enzyme sensitizes the infected cells for apoptosis and might be a way for anti-chlamydial therapy.

In addition, Ligand-based approaches without knowing the molecular target also led to potent anti-infective hits.

The design of a novel screening method targeting the clinically relevant, intracellular stage of *Leishmania major* allowed the identification of a new class of anti-leishmanial quinolines with excellent selectivities toward the pathogen.

Beside synthetic and recombinatoric chemistry, also plant extracts and Sponge-associated actinomycetes are used as a rich source for antimicrobial compounds. Several compounds purified from these bacteria show inhibitor activities against parasite proteinases.

Potent hit structures identified and characterized during these studies are further analyzed for their drug-like behavior and optimized to become lead molecules. The physicochemical characterization of anti-trypanosomal quinolones, as an example, led to a formulation that demonstrated already efficiency in an animal model.

Overall, the success of this research network that relies on the integrative and interdisciplinary cooperation of the power and creativity of the individual scientists is an example of highly productive drug development in an academic environment.

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 Biochemistry, University of Mainz)
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 2012
Joint PhD-student meetings of the SFB 630, SFB 766 and FOR854
"New Trends in Infectious Disease Research"
14. – 16.11.2012

3rd International Symposium
"Novel Agents against Infectious Diseases – an Interdisciplinary Approach"
20. – 22.11.2013

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5.2.3 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 fatalities worldwide. The SFB 688 collaborative research center founded in 2006 and recently extended until 2017 creates a unique 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 secondary events leading to damage and failure of the 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 is put 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 as well as advanced fluorescence-microscopy-based imaging methods in animal models of thrombosis, myocardial infarction and stroke shall allow the better surveillance of heart, brain 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:
We have generated mice deficient in NBEAL2 which reproduce all important aspects of the *Gray Platelet Syndrome*, a rare inherited bleeding disorder in humans characterized by the absence of α-granules from platelets. The *in vivo* analysis of these animals then provided the first direct evidence that platelet α-granules are of fundamental

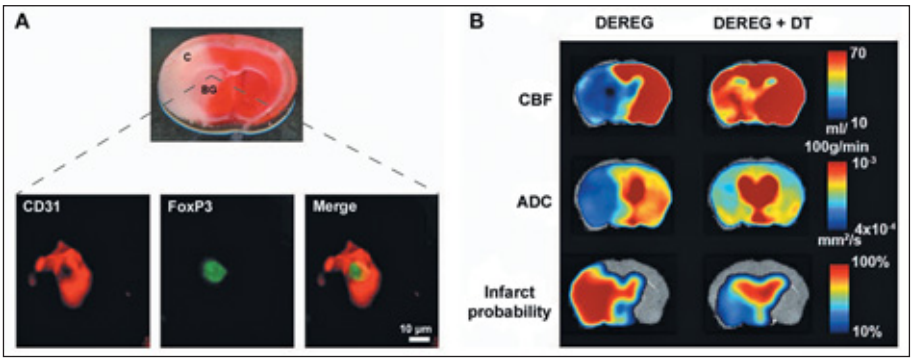

Fig. 1: (A) Regulatory T cells (Treg) (FoxP3-stain, green) are mainly located within the intracerebral vessel lumina (CD31 stain, red) on day 1 after stroke in mice. Upper panel: triphenyltetrazoliumchloride (TTC) coronal brain slice stained 24 h after stroke. The ischemic infarction appears in white, vital brain tissue appears in red. (B) Less thrombi are formed in the brain vasculature after stroke following depletion of Treg in DEREG mice with Diphtheria toxin (DT). As a consequence cerebral blood flow (CBF) is improved and the extent of stroke (apparent diffusion coefficient, ADC) or the infarct probability are reduced. Ultrahigh field MRI (17.6 Tesla) are depicted on day 1 after stroke. (modified from Kleinschnitz et al., Blood 2013).

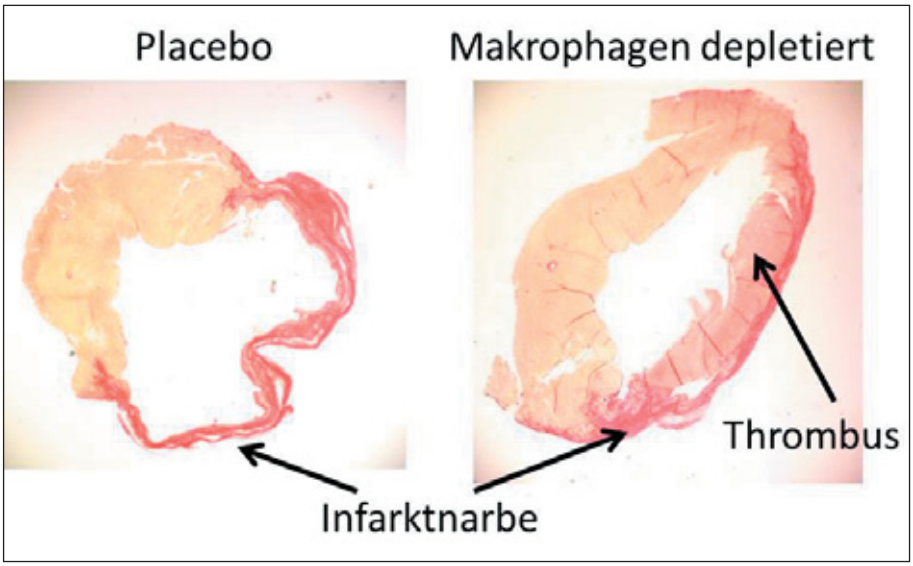

Fig. 2: Depicted is a crossection of a heart several weeks after myocardial infarction stained with picrosirius red. Collagen (scar) is stained red. A large ventricular thrombus is visible on the scar of macrophage depleted, but not on placebo treated mice (Frantz et al., FASEB J 2013).

importance of haemostasis and thrombosis but also in the pathogenesis of ischaemic stroke and in the initiation of wound healing (Deppermann *et al., J Clin Invest* 2013). Furthermore, we have established the Platelet Web Knowledgebase as a web-based repository on all human platelet proteins described so far as well as their interactions, modifications and available knowledge on these from literature, software predictions or databases (Boyanova *et al., Blood* 2012).

Because we had already shown that the interplay between T cells and members of the blood coagulation cascade massively promotes stroke development we in a follow-up study asked which of the different T cell subpopulations would be of particular relevance for ischaemic neurodegeneration. In doing so we very unexpectedly found that above all regulatory T cells (Treg) and their interaction with endothelial cells and platelets promote infarct growth (Kleinschnitz *et al. Blood* 2013). Depletion of Treg reduced intracerebral thrombus formation after stroke which in parallel improved cerebral blood flow (Fig. 1). Conversely and in full accordance with the concept of 'thrombo-inflammation', the depletion of kininogen, a member of the kallikrein/kinin-system and the plasmatic coagulation, significantly ameliorated the local inflammatory response in the brains of stroked mice (Langhauser *et al*., Blood 2012).

Various projects in the SFB 688 investigate the roles of the endothelial barrier and of tissue inflammation after ischaemia. The response to ischaemic injury can be separated into multiple overlapping phases. Following an acute inflammatory response, an initial reparative response takes place involving immune cells that will both terminate the initial inflammatory response and initiate repair. This is followed by a more prolonged phase of continued remodelling that involves both destruction and replacement of tissue. Studies of experimental myocardial infarction (MI) in different genetic mouse models showed that within the innate immune system, monocytes/macrophages and the coordinated activation of the complement system are of central importance for healing after MI (Fig. 2) (Frantz *et al., FASEB J* 2013). However, a role for adaptive immunity has also been suspected. Indeed, we identified the cardiac draining lymph nodes in the mediastinum as the site of adaptive immune response and showed the effects of antigen-presenting dendritic cells (DC) resulting in an increase in regulatory T cells after MI. This specific subset of T cells, which possibly becomes activated by recognition of cardiac autoantigens exposed by MI, facilitates collagen formation. In doing so regulatory T cells, together with components of the innate immunity, contribute to wound healing of the postischaemic myocardium (Hofmann *et al., Circulation* 2012).

Other projects of the SFB investigate the role of specific kinases in growth and mechanical functions of cardiomyocytes. Extracellular signal-regulated kinases 1 and 2 (ERK1/2) are central mediators of cardiac hypertrophy and are discussed as potential therapeutic targets. However, direct inhibition of ERK1/2 leads to exacerbated cardiomyocyte death and impaired heart function. We have previously identified ERK(Thr188) autophosphorylation as a regulatory phosphorylation of ERK1/2 that is a key factor in cardiac hypertrophy. Our present studies demonstrate that interference with ERK(Thr188) phosphorylation selectively attenuates ERK1/2-mediated cardiac hypertrophy without affecting antiapoptotic ERK1/2 signaling or overall physiological cardiac function (Ruppert *et al., PNAS* 2013). As compared to ERKs, the role of cGMP-dependent protein kinase I (cGKI) in the heart is less well characterized. Here, cGKI mediates signalling by different cGMP-synthesizing guanylyl cyclases: membrane-bound receptors for natriuretic peptides and intracellular receptors for nitric oxide/NO. Activation of cGKI located in the submembrane compartment phosphorylates and regulates sarcolemmal proteins, such as RGS2 and TRPC3/C6 channels, and attenuates pathological calcium entrance. Cytosolic cGKI phosphorylates proteins of the sarcoplasmatic reticulum (phospholamban) and within the contractile machinery (troponin I), ultimately enhancing inotropy and lusitropy. The role of these signalling pathways in cardiac homeostasis is emphasized by the phenotype of mice with cardiomyocyte-restricted inactivation of cGKI, which develop severe dilatative cardiomyopathy in response to enhanced cardiac afterload.

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.

Macrophage imaging was one key topic addressed. Nuclear techniques as 68Ga-DOTATATE PET were validated for imaging of inflammatory cells in atherosclerotic vessels and in a translational step also in pa-

tients, in whom they were correlated with other markers of atherosclerosis (Li *et al., EJNMMI Res* 2012). In reperfused myocardial infarcts ^{19}F-MRT imaging was applied to monitor macrophage invasion and this was correlated with specific patterns of disruption of myocardial microcirculation. Severe disruptions were associated with a reduced density of inflammatory cells and a poorer prognosis of cardiac remodeling (Ye *et al., Circulation* 2012).

Another issue addressed was the correlation between functional, morphological and molecular alterations of vessels during different stages of atherosclerosis. A new MRI method for determination of the local pulse wave velocity was established. In a mouse model of atherosclerosis it was shown that the local elasticity, as determined by the local pulse wave velocity, was reduced prior to the development of plaques or its precursors (Gotschy *et al. Circ Cardiovasc Imaging* 2013). This MRI approach demonstrated for the first time that functional parameters precede morphological alterations in the early phase of atherosclerosis. In the field of molecular MRI of atherosclerosis, the expression of the (early marker) adhesion molecule VCAM-1 was detected by functionalized iron nanoparticles in different tissue components of the vessel wall and validated by immune-histochemical techniques (Michalska et al., *ATVB* 2012). In the field of microstructural MRI we were the first who solved analytically the paradigm of spin dephasing in the pericapillary magnetic field (Ziener et al. Phys Rev E 2012). For susceptibility weighed imaging techniques, this will be decisive step towards quantitative imaging of the microcirculation.

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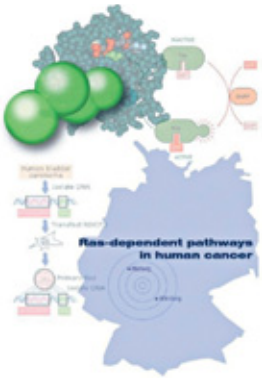
5.2.4 Transregio-Collaborative Research Center 17, Ras-Dependent Pathways in Human Cancer

CONTACT DETAILS



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General Information

The Transregio 17 is formed by researchers at the universities of Marburg and Würzburg and is co-ordinated by Martin Eilers and Andreas Neubauer. The Transregio started in 2004. In total there are about 20 project leaders and within each project there are diploma and PhD students working on their theses. All PhD students are members of an integrated Graduate College, organized by the members of the Transregio. The projects are subdivided into three areas distributed over the two participating universities. There is a very close interaction between all areas and projects. A special focus of the Transregio is the integration of clinical and translational research and the establishment of key technologies through central facilities and co-operativ projects.

Major Research Interests

The Transregio aims at understanding how critical cellular properties of tumor cells, such as deregulated proliferation, apoptosis, chemoresistance and metastasis emerge from the interaction between deregulated signaling pathways and the genetic status of the tumor cells. Cancer is most often defined as a disease of aberrant cell signaling. While the individual molecules that constitute signal transduction pathways, their biochemical functions and the way they are mutated in human cancers are increasingly well understood, we know very little about how deregulated signal transduction translates into those cellular and clinical phenomena that ultimately dictate the course of the disease in the patient. This is particularly true for the Ras pathway, which has emerged as a key signal transduction pathway that contributes to the genesis of a wide variety of human tumors.

The striking observation underlying much of the work in this Transregio is that the outcome of deregulated signaling through the Ras pathway is not stereotype, but is dictated by the genetic status of the cell. Humans harbor protective mechanisms that prevent tumor induction by a single mutation of a proto-oncogene such as Ras. As a result, multiple mutations have to accumulate in a single cell before it develops into a tumor. Therefore, it is necessary to understand in molecular detail how the genetic

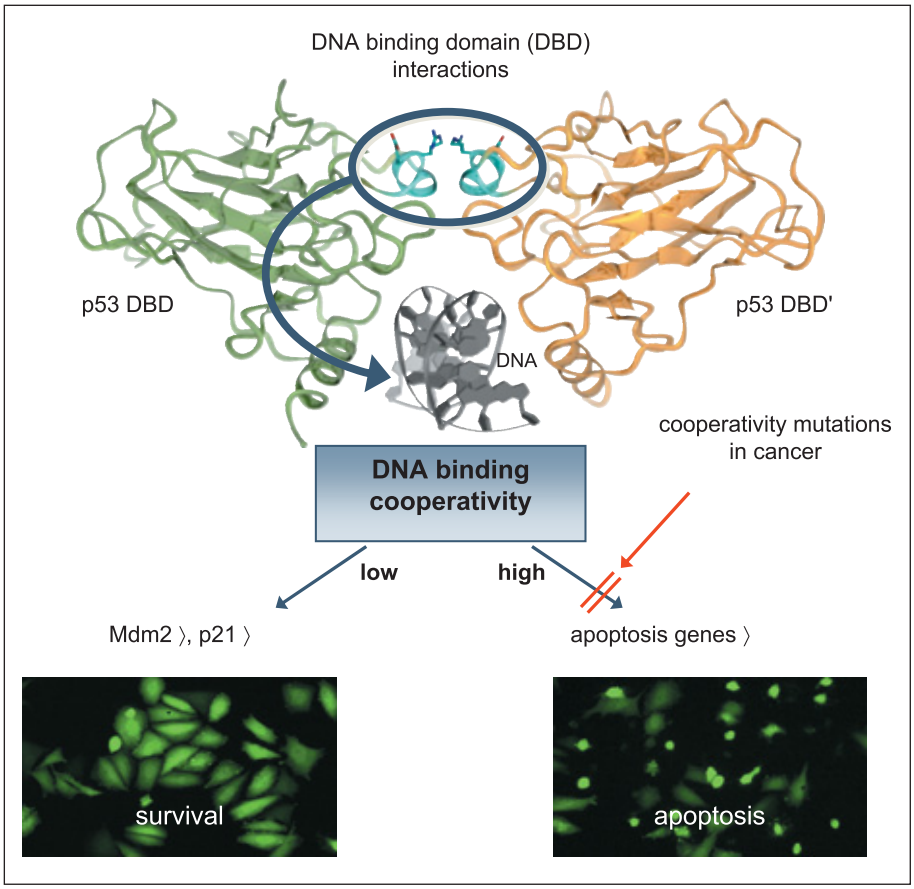

Fig. 1: Structure of the p53 tumor suppressor protein.

status of a cell affects the outcome of deregulated signaling through the Ras pathway. This does not solely apply to cellular phenotypes, but also to the clinical phenomena that we ultimately need to understand, like invasion, metastasis and the response to therapy.

To approach these questions, the research program concentrates on the elucidation of signal transduction through the Ras pathway (project area A), the analysis of cellular responses to Ras and their genetic control (project area B), and investigation of Ras-dependent signaling in human tumors (project area C). Key technologies supplied by members of the Transregio are the development of animal models for understanding Ras dependent pathways in human cancers, gene expression profiling, high-throughput RNAi screening using high-content microscopy, tissue-based pathology and mass-spectrometry assisted protein analysis.

The research teams from the Medical Faculty of Würzburg include Physiological Chemistry (Stefan Gaubatz, Svenja Meierjohann, Manfred Schartl), Biochemistry and Molecular Biology (Martin Eilers) and Internal Medicine II (Ralf Bargou).

Meeting of the Transregio

Internal Retreat of the Integrated Graduate College Transregio 17 (25.09.-27.09.2013)
Schloss Pommersfelden

SELECTED PUBLICATIONS

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5.2.5 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. T. Rudel (C6, 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

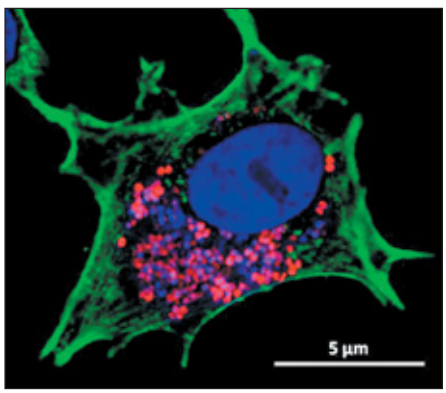

Fig. 1: Invasion of S. aureus into epithelial cells. S. aureus (red) has invaded a lung epithelial cell isolated from a cystic fibrosis patient. The size of the epithelial cell is indicated by the actin cytoskeleton in green, and DNA is stained in blue.

emerging field that is becoming the increasing focus in model bacteria such as *E. coli and B. subtilis* is the role of small regulatory RNAs in cell physiology. These RNAs are significantly involved in stress adaptation of bacteria, and it can be expected that these crucial molecules also play a role in the control of virulence. This novel problem is being addressed in project part B4. Specifically, a sRNA was found that is encoded upstream of the *ica*-operon in *S. epidermidis* which is probably involved in the regulation of the *ica*-expression. This small RNA could thus influence pathogenicity via production of PIA (polysaccharide intercellular adhesin), synthesized by enzymes encoded by the ica-operon, and therefore constitutes a good starting point for the analysis of the role of regulatory RNAs. In 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 (Fig. 1). The aim is to generate a first, integrated view of the intracellular behavior of *S. aureus*.

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 ion fluxes between mitochondria, endoplasmatic reticulum and cytosol will be determinerd to investigate the role of individual proteins in calcium signaling and their role in cell death induction. 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 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 detect infection foci and to prevent staphylococcal diseases (Fig. 2). Overall, these data will provide an overview on the dynamics of bacterial spread in the host and its 3D distribution.

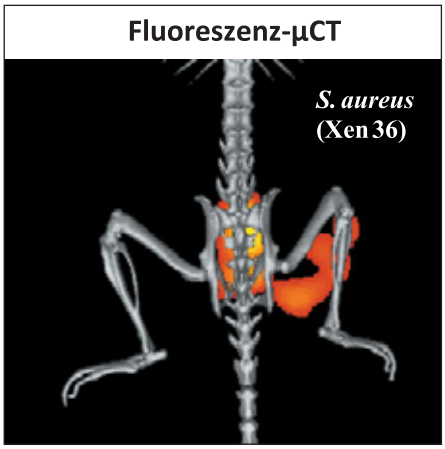

Fig. 2: Detection of S. aureus infection by using fluorescently labeled vancomycin.

Symposia

2nd International Symposium "Pathophysiology of Staphylococci in the Post-Genomic Era", Kloster Banz, 11.-14.11.2012

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5.2.6 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 – was established 2008 by the DFG and started its scientific activities on July 01, 2008. The support of the TR52 by the DFG finished at the end of 2013. The major research aim of the TR52 was to gain new scientific insights into the function of T-lymphocytes. This was achieved through the intensification and concentration of scientific research on the transcriptional control of gene expression in this vital population of lymphoid cells. Thereby, the aim was 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.

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 take 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-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 it-

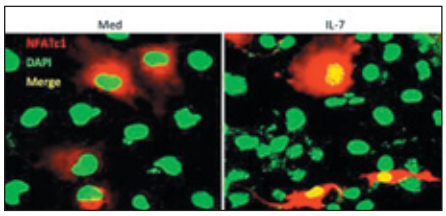

Fig. 1: IL-7 mediated nuclear translocation of transcription factor NFATc1 (from Patra, A.K. et al., Nature Immunology 2013). Vectors expressing IL-7Rα, IL-2Rγ, Jak3 and NFATc1 were transfected into COS-7 tissue culture cells. 44 h after transfection the cells were either cultured in medium (Med) or stimulated with 10 ng/ml IL-7 for 2 h. Cells were counter stained with NFATc1 (red) and DAPI (green) for nuclear staining. The yellow staining (right) indicates the nuclear localisation of NFATc1 whose activity controls a large number of genes which orchestrate the function of our immune system.

self. 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 was to unravel the complexity of these processes. A further aim was to introduce these findings achieved into the causal treatment of human autoimmune and allergic disorders.
In Würzburg, four projects were 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

Highlights of scientific communication between the projects of the TR52 were the biannual retreats of the TR52 which were organized in each of the three TR cities. To these events 2-3 outstanding scientists were invited to give keynote lectures about themes in which almost all members of the TR were interested. Such keynote lectures were given about the last progress in creating transgenic and gene-deficient mice, in next generation DNA sequencing (NGS) techniques and in the latest progress in protein sequencing approaches. Each project of the TR had to present once per year it latest progress on its own work, and in particular students were stimulated to present or, at least, to take part actively in the discussions at the retreats. In addition, there were a lot of discussions between individual projects before and after each retreat to streamline the own research work. – In this context we also want to remind on the International Workshop on "Transcriptional Programming in the Immune System" which was organized by the TR52 from 17th to 20th October 2010 in Würzburg and assembled more than 200 scientists. A detailed report about this workshop was given 2011 in the Eur.J. Immunology (see Berberich-Siebelt, F., A. Avots and E. Serfling, Eur. J. Immunol. 41: 885-888, 2011).

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5.2.7 Transregio-Collaborative Research Center 58, Fear, Anxiety, Anxiety Disorders

CONTACT DETAILS

Fear, Anxiety, Anxiety Disorders
Furcht, Angst, Angsterkrankungen
SFB / TRR 58

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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 after the end of the first funding period and review in 2012 was extended until 2016. It 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 80 scientists collaborate in 18 subprojects of the SFB-TRR 58 in an interdisciplinary way and numerous graduates and Ph.D. students undergo research training in structured Ph.D. programs, at Würzburg in the context of the GSLS and the GK1253.
Fear and anxiety, the two phylogenetic oldest emotions, are the focus of the 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 anxiety disorders in a translational approach. While in the first funding period mechanisms of conditioning and extinction were in the center of interest, the projects of the second funding period focuse on the mechanisms of sustained fear and fear generalization. To do so, neurobiologists and neurophysiologists, physicists and psychologists, neurologists and psychiatrists closely work together in an interdisciplinary manner. Results from model organisms like knock-out mice are validated in humans by innovative experimental approaches *(imaging genomics, epigenomics)*. Genetic findings in humans are in turn be experimentally verified in animal models *(reverse genetics)*. To achieve these aims, the TRR-SFB 58 consists of three closely connected areas of research with participation of scientists from Würzburg in 9 of the 18 subprojects:

Research area A - **basic science** - explores the molecular mechanisms of the development of fear in animal models (figure 1). Studies of serotonin-transporter knockout mice as best-established animal model of fear exploring the mismatch hypothesis and the role of epigenetic programming (A01 and A05; Lesch, Schmitt) are complemented by studies on the role of hippocampal BDNF and NOS1-dependent 5HT1A-transmission in the context regulation of fear and anxiety (A09 and B06; Blum, Sendtner, Reif).

In research area B – **behavioural science** - healthy subjects are investigated on multiple levels with experimental psychophysiological paradigms for fear and anxiety. In each subproject, the role of genetic modulation of the behavioural response is scrutinized. Studies on cue versus context fear conditioning and generalisation in virtual reality (B01; Pauli) are applied as well as studies on anticipation and perception of somatic symptoms employing neurophysiological and functional magnetic resonance imaging (B05; Wieser).

Research area C – **translational science** - focuses on the investigation of pathomechanisms which are differentially relevant for phasic/specific and sustained/generalized anxiety disorders and their treatment (figure 2). Epigenetic experimental designs (C02; Domschke, Lesch, Deckert) as well as electrophysiological and functional magnetic resonance imaging experimental designs (C06; Herrmann) are employed. The role of genetic variants is again under investigation in both subprojects.

The large (n=1643) cohort with ex ante phenotypically and genetically well defined control subjects for the studies of areas B

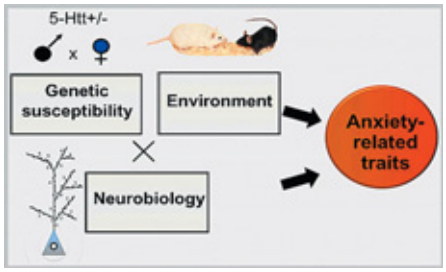

Fig. 1: Experimental approaches of research area A.

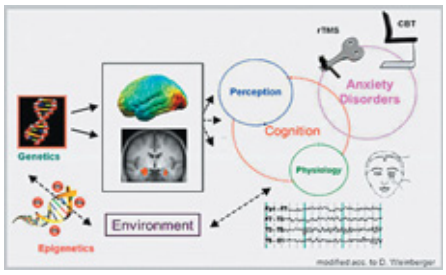

Fig. 2: Experimental approaches of research area C.

and C made available by the **central project Z02** (Deckert, Reif, Pauli) is extended in the 2nd funding period by a cohort of probands (n=1500) which in addition are experimentally characterized for fear generalization. It will be complemented by a cohort (n=500) of children and adolescents (Romanos). As in the 1st funding period, the cohort will provide probands for subprojects of areas B and C and by the analysis of the complex genetics of fear-and anxiety-relevant behaviours will provide new candidate molecules for research area A.

A paradigmatic example for the interdisciplinary and synergistic research of the 1st funding period 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 15 publications so far.

At the University of Würzburg, the following institutions currently are involved:
Medical Faculty, Center of Mental Health, Department of Psychiatry, Psychosomatics and Psychotherapy (project leaders: J.Deckert, K.Domschke, K.P.Lesch, M.J.Herrmann, A.Reif, A.Schmitt), Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (M.Romanos), Institute of Clinical Neurobiology (R.Blum, M.Sendtner) and Institute of Phyiology (associated member: E.Wischmeyer);
Faculty of Philosophy, Institute of Psychology I (project leaders: P.Pauli, M.Wieser);
A.Fallgatter (with A.C. Ehlis), B.Gerber and A.Mühlberger left for W3 chairs at Tübingen (Department of Psychiatry and Psychotherapy), Leipzig (Institute of Biology, Genetics) and Regensburg (Institute of Psychology) 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
3rd International Symposium on Fear, Anxiety, Anxiety Disorders; Hamburg, 11.-13.10.2013

SELECTED PUBLICATIONS:

Glotzbach-Schoon E, Andreatta M, Reif A, Ewald H, Tröger C, Baumann C, Deckert J, Mühlberger A, Pauli P. (2013) Contextual fear conditioning in virtual reality is affected by 5HTTLPR and NPSR1 polymorphisms: effects on fear-potentiated startle. Front Behav Neurosci 7:31.

Karabeg MM, Grauthoff S, Kollert SY, Weidner M, Heiming RS, Jansen F, Popp S, Kaiser S, Lesch KP, Sachser N, Schmitt AG, Lewejohann L. (2013) 5-HTT deficiency affects neuroplasticity and increases stress sensitivity resulting in altered spatial learning performance in the Morris water maze but not in the Barnes maze. PLoS One 8:e78238.

Tupak SV, Reif A, Pauli P, Dresler T, Herrmann MJ, Domschke K, Jochum C, Haas E, Baumann C, Weber H, Fallgatter AJ, Deckert J, Ehlis AC. (2012) Neuropeptide S receptor gene: Fear-specific modulations of prefrontal activation. Neuroimage 66C:353-360.

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5.2.8 Transregio-Collaborative Research Center 124, Pathogenic Fungi and their Human Host: Networks of Interaction

CONTACT DETAILS

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General information

The Transregio CRC124 Jena-Würzburg was initiated and established in 2013 by the Deutsche Forschungsgemeinschaft (DFG) and began its work on October 1st, 2013. The CRC/Transregio aims to combine state-of-the-art research in mycology and immunology to gain novel insights into the pathophysiology of invasive mycoses, a clinical entity of growing importance. In the long-term perspective, it is the explicit aim of this initiative to use modern sophisticated high-throughput tools in basic research to generate knowledge, which can be used to improve diagnosis and treatment of these infections. As this requires large-scale and project overarching data interpretation, project area B integrates systems biology and structured bioinformatical approaches to data processing, management and interpretation to connect the experimental project areas A and C and foster the translational approach. Furthermore, translational research is strongly supported by existing infrastructure at both sites, so in Jena, the Center for Sepsis Control and Care, and the Early Clinical Trial Unit and the interdisciplinary GMP facility in Würzburg.

Major research interests

Project Area A – Aspergillus fumigatus: From environmental microorganism to pathogen

Project area A aims at the characterization of the infection-relevant networks of *A. fumigatus* (biology of the pathogen) and host cells upon confrontation with *A. fumigatus* (host response). Methods of functional genome analysis such as proteome and transcriptome analyses both of the pathogen and the host, e.g. different morphotypes of the pathogen, various host cell types, directly from tissue etc., will be employed. Both technologies were established by PIs involved in the proposed project area.
Aims of the project area A are: (1) to systematically investigate all levels of infection biology starting with the pathogen, via its interaction with single cell types (epithelial cells, DCs, alveolar macrophages, neutrophils, natural killer (NK) cells), more complex infection models involving several cell types at the same time, mouse models up to clinical samples, (2) to elucidate the regulatory circuits in both the pathogen and the host cells using methods of functional genome analysis, (3) to clarify the relevance of single genes / proteins in this process by applying functional analyses (generation of knock-out mutants, biochemical analysis, cell culture and animal models, RNAi), (4) to analyze material from patients based on these data, to prove the hypotheses generated in experimental (primary cells, cell cultures, animal models) and computational models.
We will not only elucidate pathogenicity mechanisms, but also identify diagnostic biomarkers and potential targets for new antimycotic approaches, including the development of protocols for GMP-grade generation of DCs, NK and Treg cells suitable for clinical use.

Project Area B – Bioinformatics / Computational systems biology of infection

Project area B interlinks the project areas A and C and is essential for the comparative approach of this CRC/Transregio. In project area B data of different origin and structure will be analyzed to construct dynamic network models and, finally, to compare the networks representing both pathogens in interaction with the host. Additionally, the project INF will contribute to and guarantee a standardized acquisition and management of data from the pathogenic fungi and host cells. This standardization will be supported using both an already established data warehouse and Standard Operating Procedures until now, access only *via* password by the members from Würzburg and Jena).

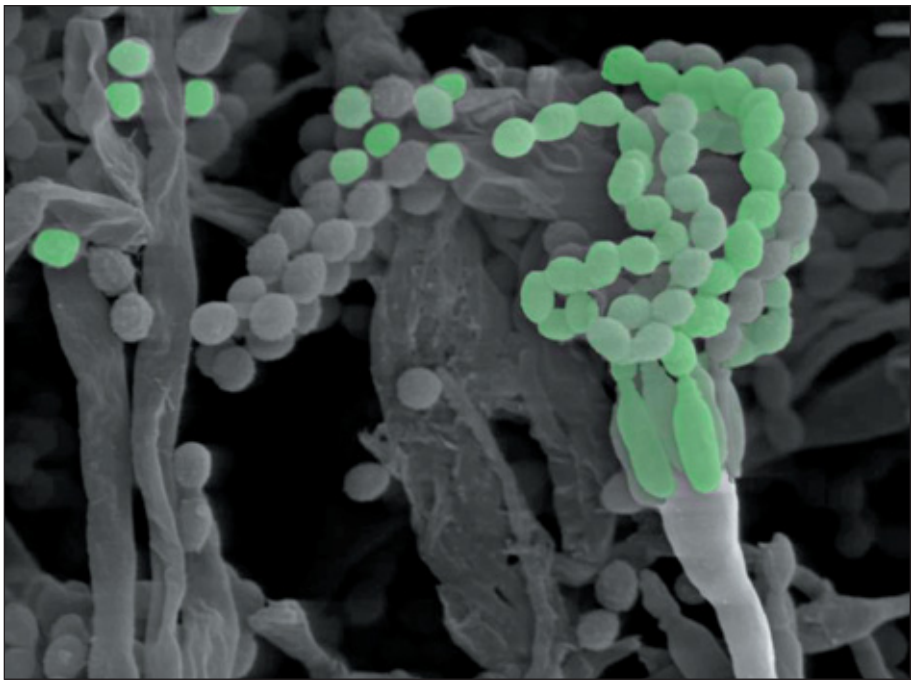

Fig. 1: Aspergillus fumigatus conidia (in green).

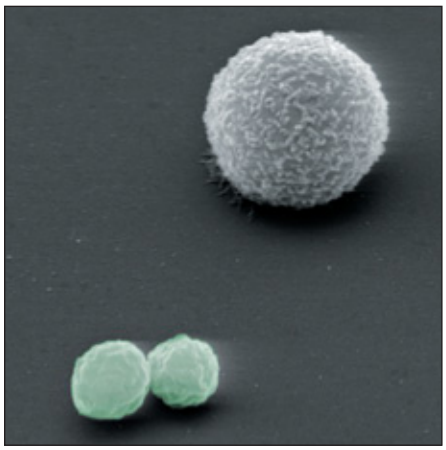

Fig. 2: Aspergillus fumigatus conidia (in green) and human plasmacytoid dendritic cell.

The standardization of experiments for the pathogenic fungi, immune cells and their interaction ensures the generation of comparable and thus valuable data sets that will allow to draw significant conclusions and to construct models with high predictive power with the perspective to assist the diagnosis and personalized therapy of fungal infectious diseases. The aim is to construct network models followed by network model analysis, to support the optimal and standardized design of further experiments and to draw predictions for novel strategies for diagnostics (biomarker design) and therapy.

The aims of the TR124 are: (1)Transcriptome data obtained from immune effector cells and host tissues as well as from the pathogenic fungi with the aim to investigate niche- and stage-specific expression profiles. (2) Proteome data acquired from host and pathogens. (3) Besides the aforementioned genome-wide data, also genetic, microbiological and biochemical data as well as data from clinical investigations will be received and analyzed. (4) Data will be also generated in a spatiotemporal resolution to describe and model the infection process in both time and space. This will be achieved by using techniques already established by the project partners, such as confocal laser scanning microscopy (several partners), timelapse fluorescence microscopy, *in vivo* imaging and also MALDI-imaging.

Complementary bioinformatic methods to understand host-pathogen interactions are the metabolic reconstruction, game theory, Bottom-up: signaling molecules, knowledge-based networks, Boolean, Top-down: reconstruction of dynamic gene regulatory networks and Image data analysis and agent-based spatial modeling.

Project Area C – Candida albicans: From commensal to pathogen

Project area C focuses on the transition of *C. albicans* from commensal growth to the early stages of severe, life-threatening infections. Key aspects will be the investigation of regulatory networks governing translocation of *C. albicans* from the gut as the main reservoir to the bloodstream and consequent responses of human innate and adaptive immunity. In addition to high throughput tools for proteome and transcriptome analysis, mutant libraries partially generated by FungiNet PIs and modern imaging technologies will be used to analyze networks of pathogen-host interplay.

Aims of the project area C are (1) to identify the molecular networks enabling and regulating tissue invasion of *C. albicans* by systematically analyzing the stepwise processes preceding dissemination of the fungal pathogen, (2) to use high-throughput methods and advanced imaging tools to elucidate and functionally analyze mechanisms of the host response during interaction of different host cells and tissues (epithelium, neutrophils, monocytes, macrophages) with *C. albicans* in a range of models from infection of cell lines to more complex setups integrating primary human cells and *in vivo* models, (3) to characterize the mutual communication between *C. albicans* and the human host, focusing on the role of mediators secreted by both pathogen and host cells in triggering, modulating or enhancing antifungal immune-responses, (4) to allocate data and information for future translational approaches to diagnosis and therapy of fungal infection, using clinical material from local biobanks to evaluate the potential of identified markers for clinical application.

The following projects of Würzburg are included in the CRC/TR124:

A2 Prof. Dr. Hermann Einsele und Prof. Dr. Jürgen Löffler, Internal Medicine II, University Hospital Würzburg

A3 Dr. Andreas Beilhack, Internal Medicine II, University Hospital Würzburg, und Dr. Katrin Heinze, Rudolf-Virchow-Center, University Würzburg

A4 Prof. Dr. Max Topp, Internal Medicine II, University Hospital Würzburg

B1 Prof. Dr. Thomas Dandekar, Center for Infectious Diseases, Dept. of Bioinformatics, University Würzburg

B2 Prof. Dr. Thomas Dandekar, Dr.Dr. Marcus Dittrich, both Center for Infectious Diseases, Dept. of Bioinformatics, University Würzburg

C2 Prof. Dr. Joachim Morschhäuser, Center for Infectious Diseases, Institute for Molecular Infection Biology, University Würzburg

C6 Prof. Dr. Thomas Hünig, Dr. Niklas Beyersdorf, both Center for Infectious Diseases, Institute for Virology and Immunobiology

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5.2.9 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 and successfully passed international re-evaluation in 2013. 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 incurable cancer of the hematopoietic system. The ultimate goal of this research is to identify molecular target structures for the development of novel therapies. Within the framework of this Clinical Research group 18 scientists from 7 different institutes of Würzburg University cooperate in 6 subprojects and 3 core facilities (z projects). This includes the Department for Internal Medicine II, the Institute of Pathology, the Department of Biochemistry II, the Rudolf-Virchow-Center, the Institute of Pharmacy and Food Chemistry, and the Institute of Organic Chemistry. There is also a close cooperation with physicians and scientists from the Department of Internal Medicine III 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 Würzburg University. Thus, the CRU is an important element of the Comprehensive Cancer Center Mainfranken (CCCMF), 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 CCCMF, which facilitates rapid translation of knowledge in basic research into clinical trials.

Scientific Program

The underlying hypothesis for the CRU 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 CRU to attempt an extensive functional characterization of the *oncogenic signaling 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 aid 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-κB-, and stress-response-pathways. 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 order to identify critical nodes and protein-protein interactions of the oncogenic signaling network we have established novel technologies in proteomics and masspectrometry. In a complementary approach we plan to screen for still unknown signaling 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 1: Steinbrunn/Chatterjee/ Bargou
Aim of this project is the analysis of Ras-dependent pathways and the interaction of these pathways with the oncogenic signaling network in myeloma cells. This work will clarify whether Ras-dependent signaling pathways are relevant therapeutic targets.

Subproject 4: Bommert/ 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. One aim of this project is to analyze the role of YB-1 within the oncogenic signaling network *in vivo* in various transgenic mouse models, another aim is to elucidate the molecular mechanism how YB-1 contributes to the malignant phenotype of MM.

Subproject 6: Chatterjee/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 7: Holzgrabe/Sotriffer/Bringmann
Previous work of this project has demonstrated that the heat-shock-protein pathway is frequently activated in myeloma cells and critically contributes to the maintenance of the oncogenic signaling network. Aim of this project is therefore to develop novel pharmacological inhibitors of the heat-shock-protein pathway. This project focuses on HSP90, HSP70, and the transcription factor HSF-1 (heat-shock-stimulating-factor-1).

Subproject 8: Stühmer/Wajant/Siegmund
There is increasing evidence that the NF-κB system is a central regulator of the oncogenic signaling network in multiple myeloma that integrates the signals of various other

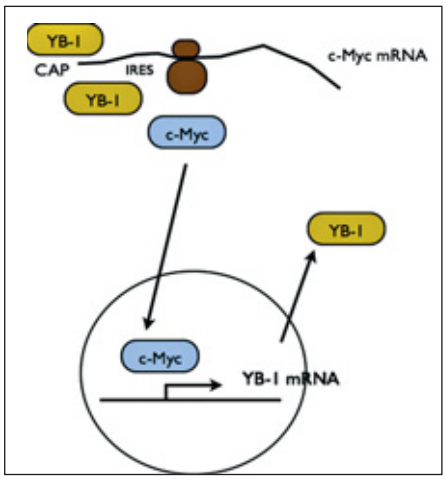

Fig. 1: Oncogenic feed-forward loop: YB-1 regulates c-Myc mRNA translation and c-Myc is a transcription factor for the YB-1 gene.

pathways. Aim of this project is therefore to analyze the interaction of NF-κB with other signaling pathways.

Subproject 9N: Leich/Rosenwald
This project is based on results from the whole exome sequencing project of the 1st funding period showing that MM is affected by multiple and heterogeneous somatic mutations in adhesion- and receptor tyrosine kinase signaling molecules. Aim of this project is to characterize the functional relevance of these newly identified mutations and to lay the foundations for the development of novel targeted and personalized therapies.

Subproject 10N: Eilers
Results of the 1st funding period have shown that mutated Ras mediates its oncogenic effect at least in parts via still unknown downstream pathways. Aim of this project is therefore to identify therapeutically relevant targets in Ras-mutated myelomas by an unbiased shRNA screening approach. First results suggest that Ras is involved in the regulation of proteins, which play a critical role in energy metabolism of MM cells.

Z Project 1 Rosenwald/Einsele/Beilhack
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 and the development of MM mouse models.

Z 2 Project Langer/Bullinger
This z-project performs a comprehensive genetic analysis of primary myeloma samples by FISH, SNP Chip Arrays and high-throughput sequencing for the different subprojects. Another aim of this z-project is to correlate genetic data with clinical data in order to identify novel prognostic biomarker.

Z 4N Project Schlosser
Aim of this z-project is the development and implementation of new proteomics and mass-spectrometry technologies for the identification of critical protein-protein interactions of the oncogenic signaling network.

Research Milestones

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 death in a subgroup of MM patients.
Besides Ras-dependent pathways, we could identify different stress response proteins of the heat shock protein (HSP) system, including HSP90, HSP70 and HSF-1, as potential therapeutic targets *in vitro* and could characterize their function in MM mouse models. Furthermore, a series of novel pharmacological inhibitors of the heat shock protein pathway have been developed and are currently being tested in preclinical models. Thereby, combined blockade of different HSPs leads to enhanced anti-tumor effects.
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 (Figure 1).
Finally, we found that only parts of the NF-κB 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 have led to the identification of novel therapeutic targets in MM. For example, whole exome sequencing of primary tumor samples from MM patients revealed a pronounced genetic heterogeneity in MM, but also revealed clustering of these mutations within cell adhesion genes and genes of the RTK/Ras network. These finding might lay the foundations for the development of targeted and personalized therapies in MM.

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5.3. Research Training Groups
5.3.1 Research Training Group 1048, Molecular Basis of Organ Development in Vertebrates

CONTACT DETAILS

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General Information

One of the most important goals of the Research Training Group was to reach a better understanding of the molecular basis of organ development in vertebrates. In all areas the RTG1048 contributed considerably to the advancement of knowledge. The research of the doctoral students did significantly contribute to the further development of the scientific projects. Under the paradigm that normal and pathological development often use the same molecules and pathways the topic of the RTG1048 is of immediate relevance to medicine. Consequently, several projects addressed questions that are directly linked to disease development or understanding stem cell development for regenerative medicine. The aim of the Research Training Group 1048 was to contribute to a better understanding of the molecular mechanisms which underlie the establishment of a fully functional, healthy organism. The RTG1048 also aimed at providing a structured PhD research and training environment in Developmental Biology. After 9 years funding of the Deutsche Forschungsgemeinschaft (DFG) the Research Training Group 1048 has now been successful completed.

Major Research Interests

The researchers of the RTG1048 are members of the Faculties of Medicine, Biology, Chemistry and Physics. Since many of the participating labs had a strong background in biomedical research and worked on vertebrate model organisms we had selected organ development in vertebrates as the focus of this research programme. The participating labs covered all major vertebrate model organisms that are currently used in Developmental Biology and made students familiar with all aspects of cell biology, biochemistry, genetics and transgenic technologies. One major concept in the RTG1048 was to study common mechanisms of development and disease. Therefore a special focus was the development of the adult organs rather than the early process of embryonic development.
The research program focused on the role of key molecules or molecular complexes (signaling molecules, transcription factors, splicing factors, micro RNAs) in organogenesis of vertebrates. Major topics included neurogenesis, cardiovascular development and germ cell development. Experiments were done in four model organisms (mouse, frog, zebrafish and medaka) and covered a wide range of techniques. An important methodological aspect of the GRK 1048 was the inclusion of modern imaging techniques such as confocal microscopy and SPIM.

Teaching

The participating research groups represented various fields ranging from stem cell biology to single molecule microscopy. This had its positive impact on the breadth of the teaching program. Structures of supervision such that each student had a Thesis Advisory Committee that mentors her/him during the entire training period had been established. On an annual basis the project of each student was evaluated and restructured as necessary to guarantee a successful completion. The Research Training Group was part of the “Graduate School of Life Science (GSLS)”. The qualification program of the RTG1048 offered 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 combined seminars, lectures and retreats with workshops, soft skills and practical training modules. The participants were 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 ensured that students will be well equipped for an independent and successful scientific career in biomedicine.

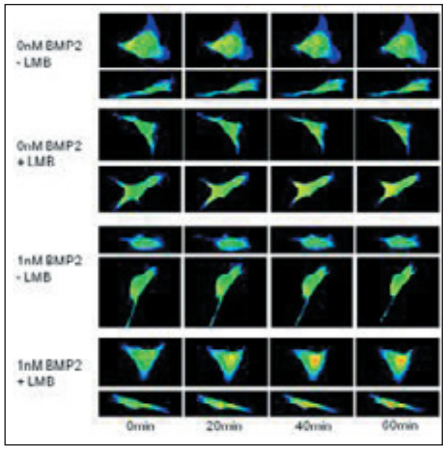
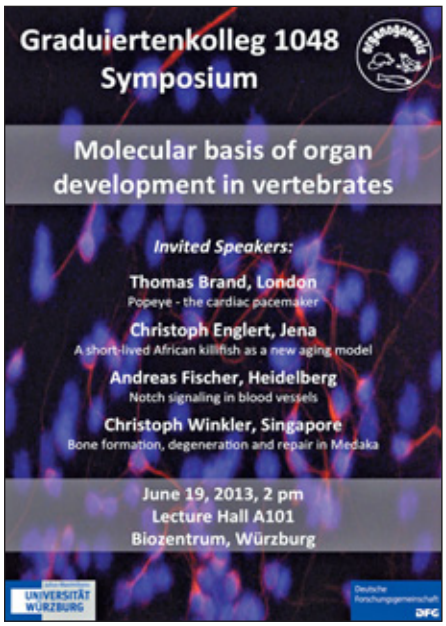


Fig. 1: Live recording of Smad1 movement in a single cell.



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5.3.2 Research Training Group 1253, Emotions

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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.

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.

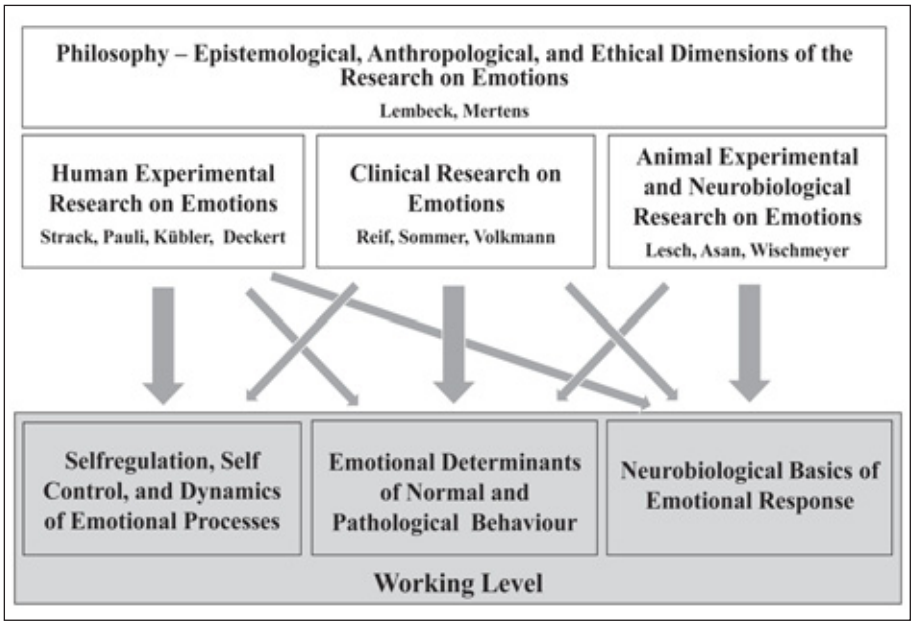

Fig. 1: Principal Investigators and structure of the RTG.

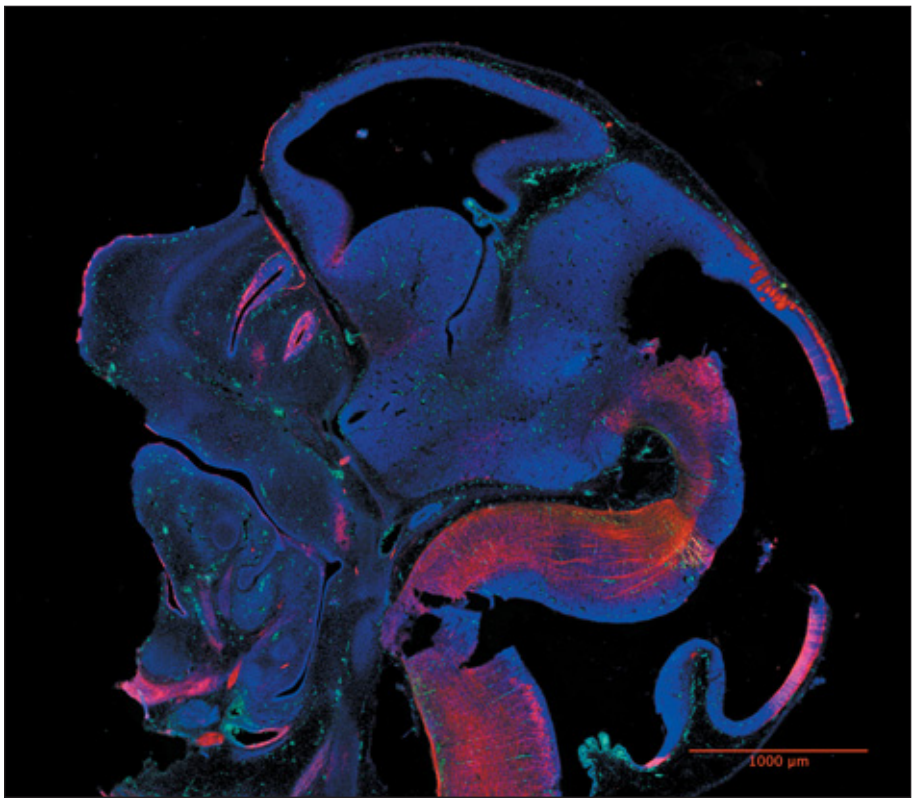

Fig. 2: Combining modern microscopic techniques with fluorescence immunolabeling, it is possible to visualize the distribution and localization of different structures and molecules in tissue and cell culture. Due to the use of different dyes researchers can distinguish between several different targets in the same sample. This picture has been taken from the midsection of a sagitally sliced mice embryo during the 13 gastational day. Fluorescence antibodies against 1) CDH13 (red), a cell-adhesion molecule which is expressed in neurons during development, 2) Serotonin (green), a very important neurotransmitter involved in numerous behavioral and physiological processes and 3) DNA (blue) which is primarily located in the nucleus of cells, made several fiber tracts and structures visible. With these methods the development of neuronal tissue and ultimatly the formation of the brain can be investigated. (Picture: D. Kiser & A. Forero)

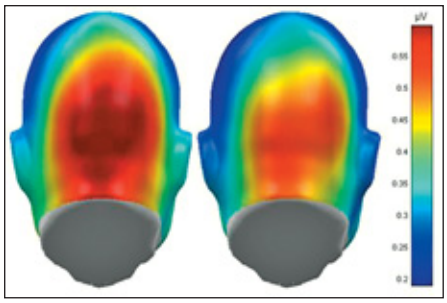

Fig. 3: Steady-state visually evoked potentials elicited by flickering stimuli during differential context conditioning. In one context an unpleasant noise was presented unpredictably (left), a second context was never paired with the noise (right).

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5.3.3 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

To strengthen the collaborative links between the University of Würzburg and universities on the African continent, the DFG supported form 2008 to 2013 the International Research Training Group (IRTG1522) on "HIV/AIDS and associated infectious diseases in Southern Africa" with two Universities in Cape Town and the close by Stellenbosch. At Würzburg University 11 PhD student plus 2 MD student stipends financed by the DFG and complementary 12 PhD student stipends financed by the NRF (National Research Foundation) at the Universities of Stellenbosch and Cape Town were created. Thematically divided in three areas 12 research projects on infectious diseases were conducted. South Africa supplied patient samples that could not be obtained in Germany and the samples can be investigated by methods available in Würzburg but rarely, if at all applied in South Africa. The IRTG fully acknowledged that the Republic of South Africa as the most developed country of whole Africa had an infrastructure that allows biomedical research to be conducted on the same level with Germany so that enormous synergies were created. The main corner stone of this IRTG is a student exchange programme between the participating universities that permitted students from Würzburg to spend some research time in Cape Town and *vice versa*.
Questions on clinical virology and basic questions on HIV and virus-induced immunosuppression were investigated in Area one. In area two some HIV-associated infectious agents were investigated. And in area three questions on the immunology of infectious agents were followed. Numerous connecting aspects bridged the research fields of different areas. The speaker on the South African side of this IRTG was Prof. Wolfgang Preiser from the „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

5.4 Research Alliances
5.4.1 Bavarian Immunotherapy Network (BayImmuNet): Generation of Clinical Grade Antigen-specific T-cells with an Early Effector Phenotype for Adoptive T-cell Immunotherapy

CONTACT DETAILS

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Professor Dr. med. Paul-Gerhardt Schlegel
(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. The funding period ended in 2013.

SELECTED PUBLICATIONS

Wölfl M, Schwinn S, Yoo YE, Reß ML, Braun M, Chopra M, Schreiber SC, Ayala VI, Ohlen C, Eyrich M, Beilhack A, Schlegel PG. (2013) Src-kinase inhibitors sensitize human cells of myeloid origin to Toll-like-receptor-induced interleukin 12 synthesis. Blood 122:1203-13.

Chapuis AG, Ragnarsson GB, Nguyen HN, Chaney CN, Pufnock JS, Schmitt TM, Duerkopp N, Roberts IM, Pogosov GL, Ho WY, Ochsenreither S, Wölfl M, Bar M, Radich JP, Yee C, Greenberg PD. (2013) Transferred WT1-reactive CD8+ T cells can mediate antileukemic activity and persist in post-transplant patients. Sci Transl Med. 5:174ra27.

Wölfl M and Greenberg PD. (2014) Antigen-specific Activation and Cytokine-facilitated Expansion of naïve, human CD8+ T-cells (ACE-CD8). Nature Protocols, (in press).

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.

Eyrich M, Rachor J, Schreiber SC, Wölfl M, Schlegel PG. (2013) Dendritic Cell Vaccination in Pediatric Gliomas: Lessons Learnt and Future Perspectives. Front Pediatr. 1:12.

5.4.2 German Research Foundation: Priority Program 1356, Pluripotency and Cellular Reprogramming

CONTACT DETAILS

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www.spp1356.de

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?
- 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.

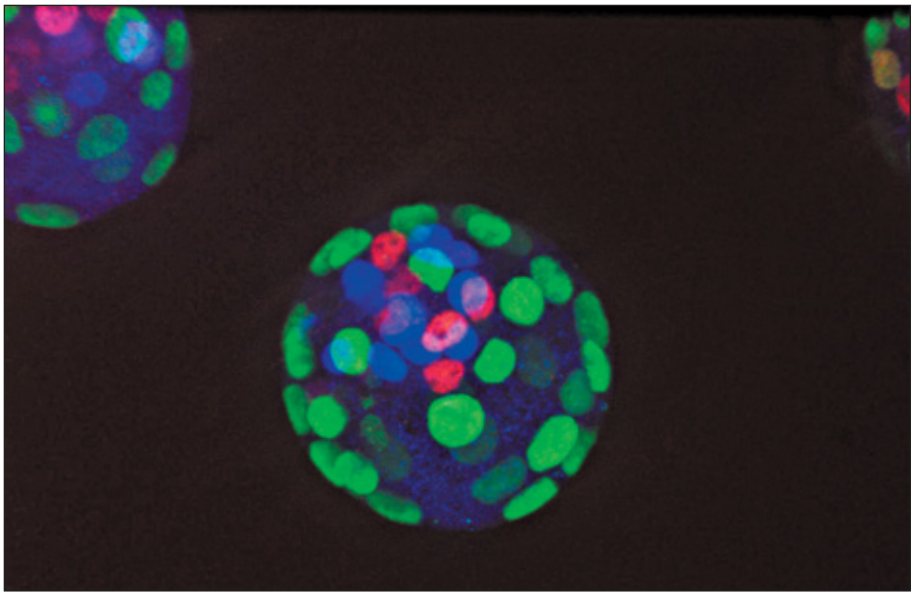

Fig. 1: Mouse blastocyst after confocal immunofluorescence (Cdx2, green; Nanog, blue; Sox17, red) (Picture: M. Bioani, MPI Münster).

5.4.3 German Research Foundation: Research Unit 2123, Sphingolipid Dynamics in Infection Control

CONTACT DETAILS

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Structure

RU2123 is funded through the Deutsche Forschungsgemeinschaft since december 2013. It unifies research groups of the universities of Würzburg and Duisburg-Essen and is headed by the speaker Prof. Dr. Sibylle Schneider-Schaulies, Institute for Virology and Immunobiology University of Würzburg and as vice speaker Prof. Dr. Erich Gulbins, Institute for Molecular Biology, University of Dusiburg-Essen. It is the general scientific topic of RU2123 to reveal the importance of sphingolipid dynamics in uptake, but also immunological control of medically relevant pathogens in their respective host cells and/or organisms. In addition to providing novel insights into basic scientific concepts, the understanding of the interactions of the respective pathogen with membrane domains and their consequences for both the pathogen and its host may well pave the way for novel targets for therapeutic interventions. The establishment of principles specific to or extending beyond the individual pathogen and the development of novel biological test systems mandates close collaboration of research groups internationally renowned in their respective fields which are supported by innovative analytical and technological platforms. Within the RU2123 this was achieved by incorporation of eight scientists from five different institutions of the University of Würzburg and two scientists of the University of Duisburg-Essen. In Würzburg, the Institutes for Virology and Immunobiology and for Hygiene and Microbiology (Medical Faculty), the Departments for Microbiology and for Biotechnology and Biophysics (Biological Faculty, Biocenter), and the Institute for Organic Chemistry (Chemical Faculty) have projects within the RU2123. These are run by 5 infectiological research groups which receive support by two service projects, one administrative, the other studying membrane dynamics by high resolution microscopy and implementing novel protocols and compounds that are developed in collaboration with the RU2123 research groups. As required to meet its central goals, the RU2123 has access to a highly advanced analytical platform (providing proteomics, lipidomics and MALDI Imaging to the RU) within external collaboration with the ‚Potsdam-Essen Center for Mass spectrometry and MALDI Imaging (CMSMI)' newly founded by Prof. Erich Gulbins and Prof. Burkhard Kleuser.

Scientific focus

Initially considered as abundant, yet inert structural components of cellular membranes, the ability of sphingolipids to regulate cellular signaling was only recognized in the early 80s of the last century. The following decades clearly revealed the importance of sphingolipid metabolism in the regulation of cell viability and identified it as a promising target for therapeutical intervention (for instance Fingolimid and Amitriptyline in multiple sclerosis or cystic fibrosis, respectively).
Sphingomyelin breakdown into phosphocholin and ceramide by acid or neutral sphingomyelinases (ASM and NSM, respectively) has been associated with the formation of ceramide enriched membrane microdomains (Fig. 1). These compartimentalize receptors and associated signalosomes but also alter biophysical properties of the membrane thereby affecting fluidity and curvature. Though activation of sphingomyelinases and consequences thereof have been intensely studied in the context of cellular stress or ligation of death receptors, studies addressing their induction by pathogens and their role in regulating pathogen-host interactions were anecdotal. Because they can compartimentalize receptors and signalosomes, and modulate the activity of the actin cytoskeleton and, by altering membrane properties, efficiencies of membrane fusion and endo-exocytosis, it appeared more than likely that sphingolipids and their metabolites induced by pathogens are essential regulators in infections and their control by host immune responses. From the ankle of the pathogen, this may include adhesion, internalization, trafficking, interaction with compartments important for replication, or release, from that of the host, induction of cell autonomous (for instance apoptosis), innate (for instance generation of reactive oxygen intermediates) or adaptive (for instance compartimentalization of the T cell receptosome) responses, to name only examples) might be subject to modulation by sphingolipid breakdown. Basic studies published by the RU speakers lended strong support to this hypothesis, and these were the basis for the establishment of flourishing collaborations among the RU participating research groups. These all established the importance of sphingolipid breakdown as an essential step of infection with their respective, medically relevant pathogen in its relevant host cells/model organisms. Both synergistic (for instance with regard to sphingomyelinase activation by individual pathogens) and complementary approaches (for instance the role of sphingolipid breakdown in pathogen uptake) are extensively represented within the RU2123 (Abb. 2). The highly advanced technical/analytical platform is doubtlessly another unique selling point of the RU. This includes in addition to standard and advanced cell culture systems the availability of a collec-

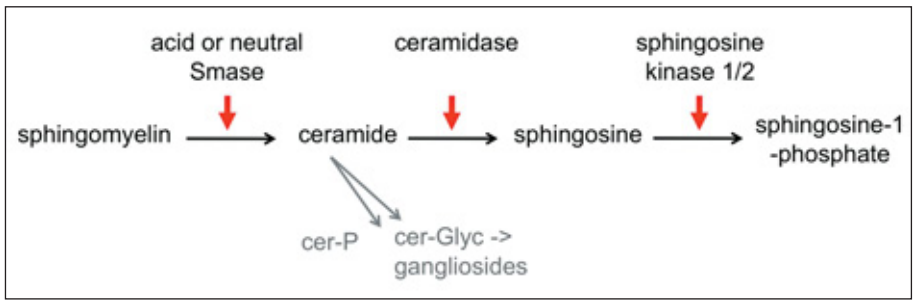

Fig. 1: Schematic illustration of essential components of the sphingomyelin breakdown pathway.

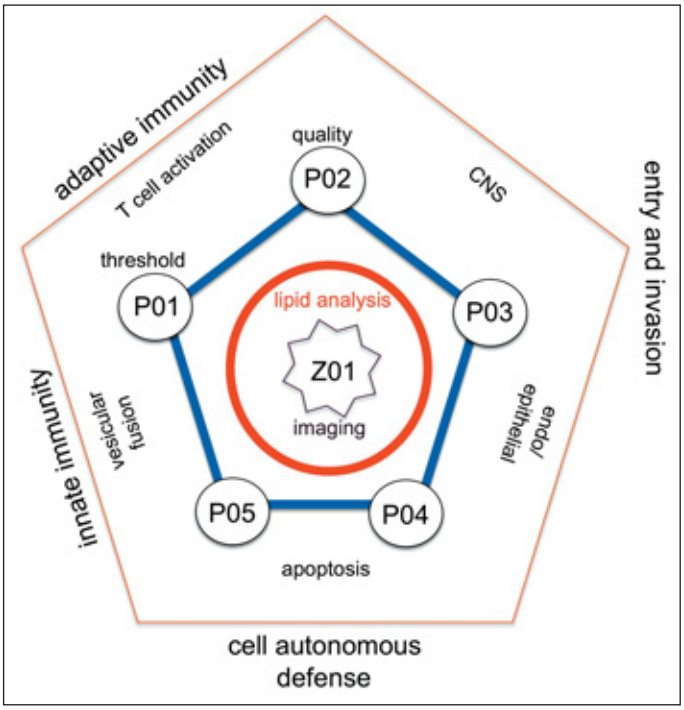

Fig. 2: Schematic illustration of major scientific foci and interactions within RU2123

tion of transgenic/knockout mouse strains some of which are alreday used for infection experiments, more are being generated within the RU. The service project will be instrumental in monitoring the composition and dynamics of sphingolipid-containing membrane domains and associated protein complexes at high resolution at a subcellular level, while the collaboration with the CMSMI will enable the RU research groups to measure and/or visualize accumulation and dyanimcs of sphingolipid metabolites at a cellular and organ level.

TP1: S. Schneider-Schaulies/N. Müller

Preliminary results of the project revealed that contact mediated T cell paralysis induced by measles virus (MV) is associated with the activation of NSM and ASM. The project aims to identify the relevant receptor structure and molecular targets of sphingomyelinase activation in T cells as well as the general role of sphingomyelin breakdown in the activity of the immunological synapse (Fig. 3)

TP2: N. Beyersdorf/J. Schneider-Schaulies

Preliminary data obtained within this project revealed that expansion and effector functions of regulatory T cells are subject to ASM mediated regulation. Therefore, the project addressed the role of ASM in modulating differentiation, expansion and effector functions of subpopulations of the T cell compartment as well as the role of its activity in an experimental measles virus CNS infection model which is controlled by regulatory and CD8+ T cells.

TP3: A. Schubert-Unkmeir

Preliminary data obtained within this project supported an important role of the ASM activated by *Neisseria meningitidis* in the formation of ceramide enriched membrane domains which were important for uptake of especially invasive strains into brain endothelial cells. In addition to unraveling mechanisms of pathogen mediated ASM activation, the project addresses the role of the enzyme in compartimentalization of receptors and subsequent activaton of signaling pathways as relevant for uptake.

TP4: T. Rudel

Preliminary data obtained within this project revealed that SREC-I dependent uptake of disseminating *Neisseriae gonorrhoeae* into epithelial cells relies on pathogen induced NSM activation, and thus substantially differs from the known ASM-dependent invasion of epithelial cells and macrophages. Consequently, mechanisms of NSM activation and the role of the enzyme in formation of the invasion complex as well as in the induction of cell autonomous responses will be studied within this project.

TP5: H. Grassmé/E. Gulbins

Preliminary data obtained within this project revealed an essential role for the NSM in controlling experimental Mycobacterium *Bacillus Calmette-Guérin* infections. Central questions addressed in this project are mechanisms of NSM induction in macrophages by BCG, as well as the role of the enzyme in intracellular compartimentalization of the pathogens and in regulating macrophage effector functions *in vitro* and *in vivo*.

Z1: M. Sauer/J. Seibel

The service projects supports the RU by synthesizing modified sphingolipids for efficient and specific labeling of subcellular domains as well as establishment of tools allowing for high resolution imaging of sphingolipid-containing membrane domains, tracking and quantitative data analyses.

Z2: S. Schneider-Schaulies
Administration

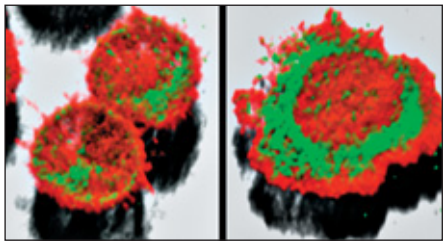

Fig. 3: Detection of f-actin (red) and ceramide (green) on human T cells seeded onto poly-L-lysin (left) or anti-CD3/CD28 coated slides. 3D reconstruction after deconvolution.

SELECTED PUBLICATIONS

Grassmé H, Jendrossek V, Riehle A, von Kürthy G, Berger J, Schwarz H, Weller M, Kolesnick R, Gulbins E. (2003) Host defense against Pseudomonas aeruginosa requires ceramide-rich membrane rafts. Nat Med 9:322-330.

Grassmé H, Kirschnek S, Riethmueller J, Riehle A, von Kürthy G, Lang F, Weller M, Gulbins E. (2000) CD95/CD95 ligand interactions on epithelial cells in host defense to Pseudomonas aeruginosa. Science 290:527-530.

Zhang Y, Li X, Carpinteiro A, Goettel JA, Soddemann M, Gulbins E. (2011) Kinase suppressor of Ras-1 protects against pulmonary Pseudomonas aeruginosa infections. Nat Med 17:341-346.

Gassert, E, Avota, E, Harms, H, Krohne, G, Gulbins, E, Schneider-Schaulies, S. (2009) Induction of Membrane Ceramides: A Novel Strategy to Interfere with T Lymphocyte Cytoskeletal Reorganisation in Viral Immunosuppression. PloS Path. 5: e1000623.

Avota E, Gulbins E, Schneider-Schaulies S. (2011) Ceramide generation is essential for enhancement of viral uptake in dendritic cells. Plos Pathogens 7:e1001290.

5.4.4 BMBF Joint Project, CB-HERMES: Expansion of Cord Blood Stem Cells

CONTACT DETAILS

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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 allogeneic CB-HSCs transplantation for elderly patients suffering from haematopoietic disorders.
Overall goal: to broaden the therapeutic application of CB-HSCs by developing robust means that allow significant HSC expansion and better engraftment.

Major Research Interests

Specific aims: 1) to develop rational and robust means of *ex vivo* CB-HSC expansion: by novel growth factor cocktails, nano-structured 3D surfaces, modification of inhibitory pathways, induced epigenetic modifications and by specific stroma environments; 2) development of clinically applicable standard operating procedures for CB-HSC expansion using CD34+ cells isolated from umbilical cord blood; 3) eludicate molecular pathways and intercellular networks operating in HSC *ex vivo* expansion cultures; 4) exploring genetic, epigenetic and functional integrity of expanded cells *in vivo*.

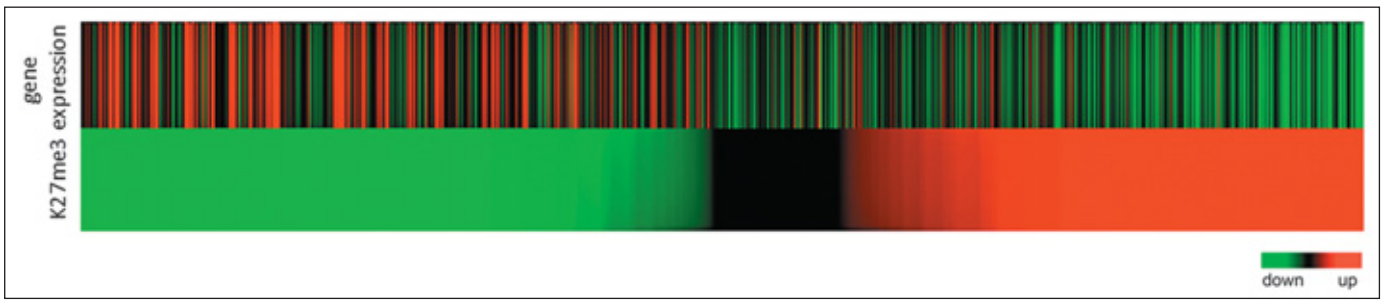

Fig. 1: Global modification of the genome with H3K27me3 and gene expression.

No.	Head of the project	Institution	Title of the subproject
1	Dr. Bernd Schiedlmeier, Professor 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 E-mail: experimental.hematology@mh-hannover.de	Pathway discovery and protocol development
2	Dr. Sabine Neuß-Stein, Dr. Thomas Hieronymus, Professor Dr. Martin Zenke	RWTH Aachen University Institute of Pathology Pauwelsstraße 30 52074 Aachen Phone: +49 241 8080622 Fax: +49 421 8082439 E-mail: 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 E-mail: Thomas.hieronymus@ewth-aachen.de E-mail: martin.zenke@rwth-aachen.de	Biomaterial scaffolds for CB-HSC expansion
3	Professor Dr. Albrecht Müller	University Würzburg Institute of Medical Radiation and Cell Research Versbacher Straße 5 97078 Würzburg Phone: +49 931 - 201 45848 (office) Phone: +49 931 - 201 45478 / 45146 (secr.) Fax: +49 931 - 201 45147 E-mail: albrecht.mueller@uni-wuerzburg.de	Epigenetic characterisation of CB-HSCs
4	Professor 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 E-mail: wwagner@ukaachen.de www.ukaachen.de/sites/lfg/stammzellbiologie	Expansion of CB-HSCs with human MSCs
5	Professor Dr. Arnold Ganser, Professor 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 E-mail: mischak-weissinger.eva@mh-hannover.de E-mail: Ganser.Arnold@mh-hannover.de	Clinical Application of CB-HSCs

5.4.5 BMBF Joint Project, Effects and Mechanisms of Psychotherapy in the Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in Children and Adults

CONTACT DETAILS

Network on Psychotherapy research

ADHD - net

Professor Dr. med. Andreas Warnke
(Speaker: 2006 to 2012)

Professor Dr. A. Philipsen
University Hospital Freiburg
(Speaker since 2012)

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www-i.klinik.uni-wuerzburg.de/deutsch/einrichtungen/kliniken/kjp/forschung/ADHD/ForschungsverbundPsychotherapieADHS/content.html

General Information

This national network is part of a research program on psychotherapy in the treatment of psychiatric disorders founded by the German Ministry of Education and Research. The need for a more intense study of psychotherapy in Germany had been stressed by the advisory committee for evidence based psychotherapy (Wissenschaftlicher Beirat Psychotherapie) of the German Psychotherapeutic Association (Bundespsychotherapeutenkammer) and the German Medical Association (Bundesärztekammer). Our network focuses on the treatment of ADHD. ADHD in adults has long been unrecognized and underestimated. Randomized controlled clinical trials including morphological and genetic variables are still missing worldwide.

The aims of the present network are:

- to evaluate the effects of a structured disorder specific psychotherapy (group setting) in adult ADHD in a randomized, placebo-controlled multi-centre study comparing the outcome of psychotherapy, psychopharmacological treatment (methylphenidate) and the combination of both;
- to analyse whether the developed psychotherapy manual can be successfully transferred to the setting of child and adolescent psychiatry: does ADHD parent (i.e. adult) treatment reinforce parent (i.e. mother) training outcome in the treatment of ADHD children;
- to examine whether there are specific neurobiological markers (such as striatal morphology and neurochemistry and genetic variations), which can differentially predict therapeutic response to pharmacotherapy, psychotherapy or a combination of both.

The structure of the national network is interdisciplinary and multicentre. 4 projects are established in 13 study centres: recruiting and manualized therapy are provided by clinics for adult psychiatry and psychotherapy (APP) and clinics for child and adolescent psychiatry and psychotherapy (CAPP) in Wuerzburg (APP, CAPP), in Freiburg (APP, CAPP), Mannheim central institute (APP, CAPP), Homburg (forensic psychiatry, CAPP), Berlin (APP, CAPP), Essen (APP), Mainz (APP) and Rostock (APP). The multimodal imaging studies will be conducted by the recently established South German Brain Imaging Center (APP Freiburg). Genetic data will be collected and analyzed in Wuerzburg (EPP). Data management, statistical analysis and monitoring will be provided by the Centre for Clinical Trials and LabConsult in Freiburg. An advisory board is supervising the projects. Treatment integrity is assured by randomized videotaping and external supervision. The consideration of scientific and ethical criteria based on the GCP document of the International Conference on Harmonization (ICH) is supervised by a Data Monitoring Committee (DMC). Our research program is strengthened by the cooperation with the Clinical Research Group ADHD (KFG 125, founded by the German Research Association, DFG) in Wuerzburg and international cooperation.

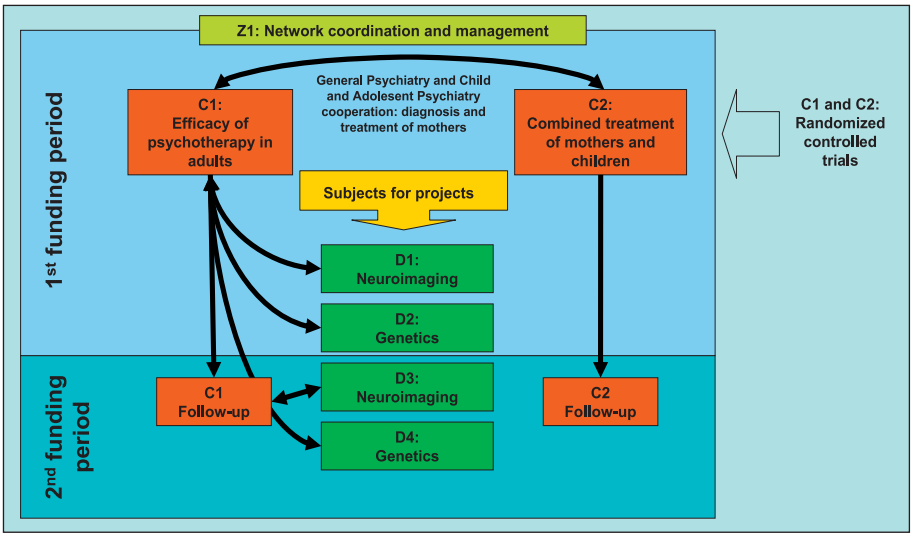

Fig. 1: Network structure.

Major Research Interests

Main issue of the child psychiatric study groups (principal investigator: A. Warnke, since 2012: T. Jans, 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.

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 were conducted in 2012. Results on clinical outcomes and associated neurobiological findings have successively been published since 2012.

SELECTED PUBLICATIONS

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5.4.6 BMBF Joint Project, SARA: Systems Biology of PGI2 and ADP P2Y12 Receptor Signaling

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General Information

The SARA project consortium was supported by the research initiative „Medical Systems Biology - MedSys“ in the framework of the BMBF program „Biotechnology”.
The SARA project funding lasted from February 2009 until January 2012 with an extension until December 2012. The project aimed at a comprehensive understanding of prostaglandin and ADP stimulated signaling of human platelets.
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 (PGI_2), play a particular role in physiology and pathophysiology by maintaining the equilibrium of platelet activation and inhibition. Though ADP is regarded a rather weak platelet agonist in recent years it became evident that a complete platelet aggregation is only possibly by activation of ADP stimulated pathways. Sole inhibition of one of the three ADP receptors known for platelets is sufficient to prevent thrombus formation. PGI_2 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 aimed 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 were investigated. By innovative mass-spectrometry techniques the whole platelet proteome could be characterized and aligned to transcriptome data by elaborate data analysis. Protein phosphorylation time-courses were determined qualitatively by means of the sophisticated SH2-profiling technique – and quantified by the newly developed technique of quantitative phosphoproteomics. Extensive pharmacological and functional analysis of platelet signal transduction completed the data resource for the generation and modeling of the signaling network. Based on the data models of platelet function regulation were successfully implemented and tested.
Overall, the project provided a wealth of new and important data and by means of the signaling models new insights into the thrombotic event. The knowledge furnished by the SARA project forms the basis for an improved understanding of the physiology and pathophysiology of platelet aggregation. Thus future development in diagnosis and therapeutics of atherothrombosis will be rendered possible.

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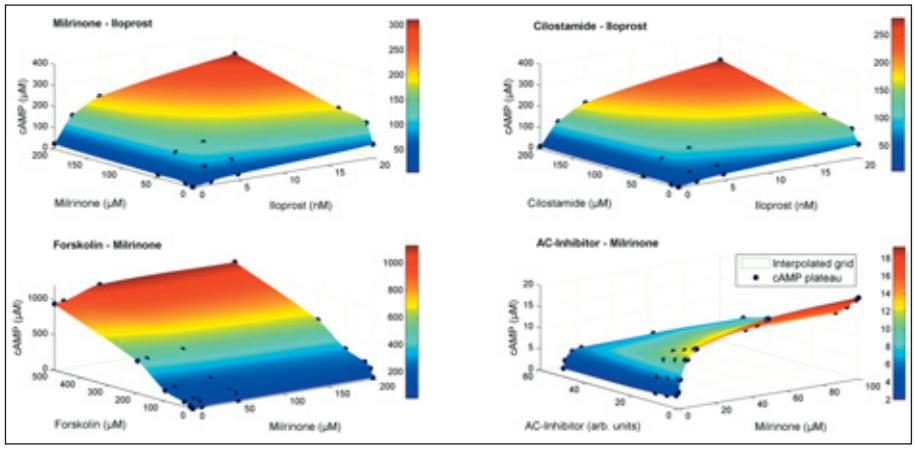

Fig. 1: Experimental (dots) and predicted cyclic-AMP concentrations in human platelets under adenylyl-cyclase stimulation and/or phosphodiesterase inhibition.

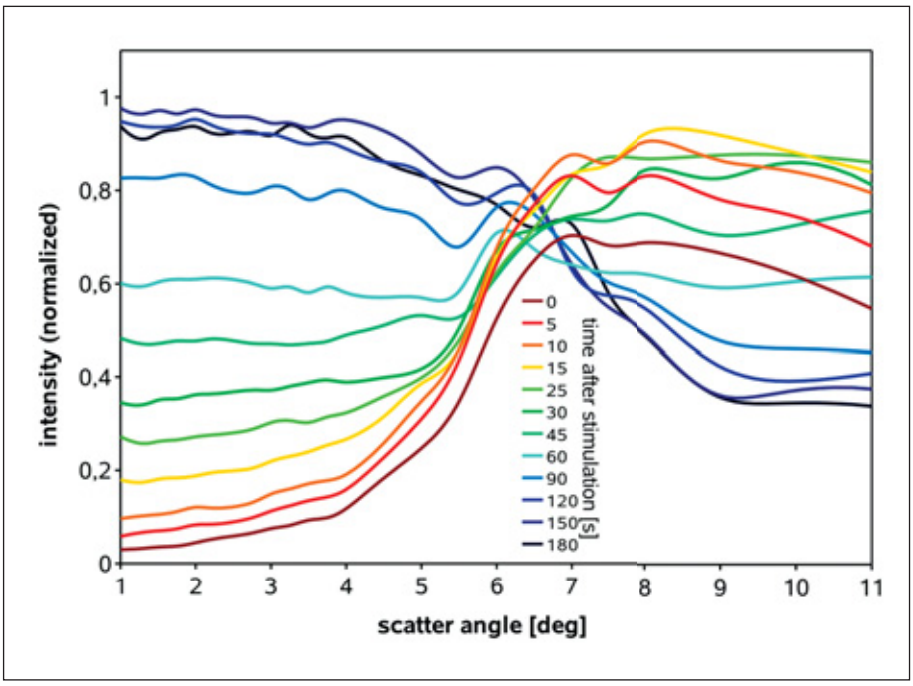

Fig. 2: Changes in the angle-dependent scatter profile of a platelet suspension during the activation process as observed with the LASCA (low angle light scatter analysis) setup.

Project C: Functional analysis of platelets

Aim of the project was a comprehensive definition and description of the role of P2Y12 ADP receptor and prostaglandin receptor mediated pathways in platelets.
Any biochemical and pharmacological experiment required for the generation of samples or data employed to further processing or analysis by other partners in this consortium was designed, validated, carried out and analyzed in this project. The demand for high quality and reproducible preparations of human platelets of defined functional state prompted for optimized and quality controlled methods. Meanwhile the newly developed protocols serve as blue print for a harmonized platelet preparation technique in international collaborations. For the dynamical models of signal transduction and regulation of human platelets reliable and accurate data were generated. Due to lack of appropriate methods several novel techniques had to be developed. Time resolved and quantitative simultaneous monitoring of platelet shape change and aggregation was enabled with a method based on the analysis of laser scatter profiles. A solid-phase assay for reliable quantitative determination of protein phosphorylation and a liquid chromatographic technique for the exact quantification of platelet nucleotide content and release were developed and implemented as well. Subsequently the bioinformatical models generated by the collaboration partners were validated biochemically. In close collaboration with vasopharm and Roche Diagnostics, two industrial partners, we evaluated novel potential phosphoprotein markers suitable for monitoring human platelet function and inhibition in health and disease.
The project was finished in December 2012.

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5.4.7 BMBF Joint Project, Medical Infection Genomics – Genome Research on Pathogenic Bacteria

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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.

The participating groups of the Medical Infectious Genomics network focus on human pathogenic bacteria that are of high socio-economic relevance for the public health system in Germany due to their wide dissemination in, e. g., hospitals or that pose a particular threat for the 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 in involved 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 in parallel the gene expression profiling of the bacterial pathogen and the eukaryotic host 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 project employs 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 Prof. Dr. Susanne Engelmann from the Helmholtz Centre for Infection Research in Braunschweig. The research groups want to get 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.

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5.4.8 ERA-NET, aspBIOmics: Invasive Aspergillosis – Biomarkers for Prevention, Diagnosis and Treatment Response

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General Information

The Consortium aspBIOmics is funded since April 2011 within the ERANET PathoGenoMics programme (Bundesministerium für Bildung und Forschung).

Invasive aspergillosis (IA) is the most detrimental infection in patients with haematological malignancies. Although, IA may be perceived to be an uncommon disease with an incidence of 10,000 patients annually in Europe, there is increasing evidence that IA is affecting a broader range of patients. In addition, IA is the most expensive opportunistic infection in immunosuppressed patients; the annual cost in Europe is >100 million Euro.

A major problem in the management of IA is the poor diagnosis. Therefore, within aspBIOmics, we develop and evaluate a battery of *in vitro* assays for a comprehensive multimodality analysis, combining the detection of *Aspergillus fumigatus* elements (DNA, RNA, polysaccharides, proteins), host factors and the individual genetic susceptibility of the patients. The advance of this combined approach is the availability of a panel of biomarkers incorporated into rapid and sensitive *ex vivo* assays. For the first time, a multi-parameter diagnostic strategy is undertaken to target IA. This strategy has the potential to identify patients who are at highest risk of IA before the infection occurs. In consequence, effective tailored prophylaxis can be given and the success of antifungal therapy can be monitored.

Major Research Interests

In a multi-centre approach, serum and whole blood samples (n=3.170) from 417 haematological patients with a high risk for IA were collected and analyzed for the presence of galactomannan (by ELISA) and fungal DNA (by PCR). One proven, 22 probable and 45 possible cases of IA were diagnosed according to revised EORTC classification. Two commercial prototype assays for *A. fumigatus* nucleic acid detection in human specimens using semi-automated procedures and the real-time PCR format have been developed. The first allows the detection of fungal DNA with a sensitivity of 10 genomes/ml and a false positive rate of 0%. The second concerns fungal RNA detection. Both prototypes are currently under analytical validity studies
By applying immunoproteomics, the antibody response of patients with IA was characterized identifying secreted proteins. They were used to generate a mouse monoclonal antibody for new immunoassays. Additionally, a camelid antibody fragment interacting with a cell wall polysaccharide was selected and several small secreted proteins (SSP, 10 kDa) have been identified. The production of antibodies in rabbits is on-going to detect SSP in patients. Furthermore, the *in vitro* volatome of *A. fumigatus* has been analysed. Multiple volatile compounds have been defined and evaluated for their suitability as biomarkers in patient breath condensates.

As regularly observed in bacteria and yeast, *A. fumigatus* develops resistance against

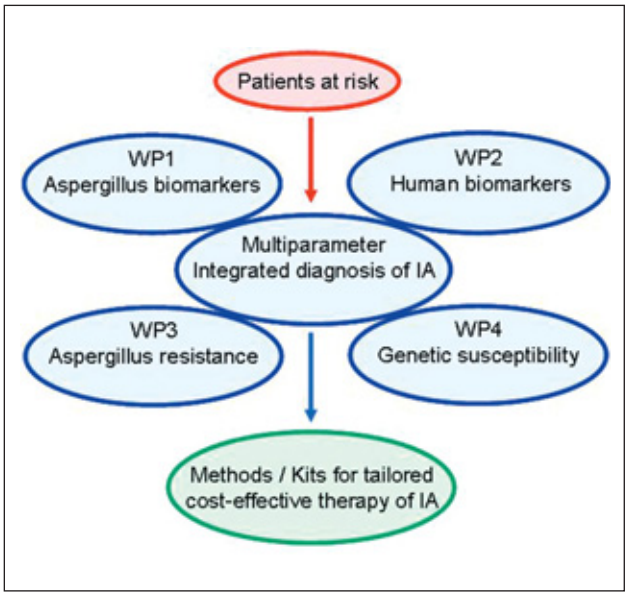

Fig. 1: Overview of the structure of aspBIOmics and its subsequent Work Packages (WP).

antifungal drugs. In order to better understand the low environmental dispersion of some of the *A. fumigatus* triazole resistant strains, the fitness *in vivo* and *in vitro* of strains carrying different mutations (Cyp51A gene: M220K or G54W) were analysed. No significant differences quantified by real-time PCR between *wild type* (WT) and mutant strains were found, suggesting that the mutants grew comparably to the WT *in vitro* or in lungs of immunosuppressed mice. Also no difference was found in growth on minimal or rich solid mediums at 37 or 50°C. Mutations Cyp51A G54W or M220K did not modify the fitness of the strains carrying them.

The Consortium works also on the definition of new human biomarkers in IA. Thereby, sera from patients with IA were screened by multiplex ELISA assays for the presence of defined cytokine and chemokine patterns. Furthermore, immune cells from these patients were stimulated with either *A. fumigatus* germlings or ß-glucan (TruCulture™, Myriad) to identify potential deficiencies in their cytokine and chemokine release (readout by multiplex ELISA assays).

To identify new human loci associated with IA, a genome-wide association study in 544 haematological patients at high-risk for IA was performed. Genotyping was carried out using the Immunochip® (Illumina) containing 140.000 SNPs for fine mapping. Our preliminary analysis identified several new polymorphisms (on 10 different chromosomes) to be associated with an increased risk for IA. To improve the statistical power of this study, we are currently genotyping a second cohort of haematological patients.

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5.4.9 EU-Project, HydroZONES: Bioactivated Hierarchical Hydrogels as Zonal Implants for Articular Cartilage Regeneration

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General Information

HydroZONES is a collaborative large project funded by the European Union within the 7th framework programme under grant agreement no. 309962. It was initiated January 1st 2013 with a runtime of 5 years and an overall EC funding of 9,75 Mio Euro. The consortium is organized in 9 Workpackages and comprises 16 partners from Germany, Netherlands, United Kingdome, Spain, Portugal and Australia, including 6 small and medium enterprises. Overall aim of HydroZONES is to sustainably heal articular cartilage defects.

Major research interests

Background

Articular cartilage is a load-bearing tissue that covers the surface of bones in joints and functions as a low-friction surface and a mechanical damper. Even in a harsh mechanical environment, it demonstrates excellent resiliency. Articular cartilage is a hydrogel-like, matrix-rich tissue without vasculature and neuronal component that contains only 5 – 10 % of specialised cells, so called chondrocytes, which maintain the structural and functional integrity of the matrix. This matrix is organised into characteristic depth zones, each with distinct physicochemical and biological properties and functions, that work together to impart low-friction, wear-resistant behaviour to diarthrodial joints (Fig. 1). Articular cartilage lacks a sufficient intrinsic repair response and cannot heal. Hence the zonal structure and function are commonly and irreversibly lost following trauma and in disease. As a result, cartilage defects are prone to develop into osteoarthritis, the predominant cartilage disease. Osteoarthritis is characterised by a loss of cartilage, typically progressing from superficial fibrillation to complete erosion down to the underlying subchondral bone.

Cartilage damage is a major cause of chronic pain, decreased mobility and a reduced quality of life, with more than 151 million affected people worldwide. It can be caused by sport accidents, but can also result from normal wear and tear due to aging. It often starts with a small defect which grows over time. When large areas of the cartilage layer are destroyed, a surgical intervention is usually unavoidable. Despite intensive research, no clinical therapy is available today that leads to true healing of hyaline cartilage. Current clinical attempts to repair cartilage only result in temporary pain reduction and the formation of functionally insufficient repair tissue that does not resemble the layered structure of healthy hyaline cartilage. This newly formed tissue is mechanically insufficient, and only delays the ultimately still necessary full joint replacement by prosthesis. Hence, none of the current therapies for cartilage repair provide a consistent and durable long-term solution.

Generally, cartilage implants used in the clinic today do not resemble and cannot reestablish the hierarchical tissue organisation that appears critical for normal cartilage function. HydroZONES is based on the

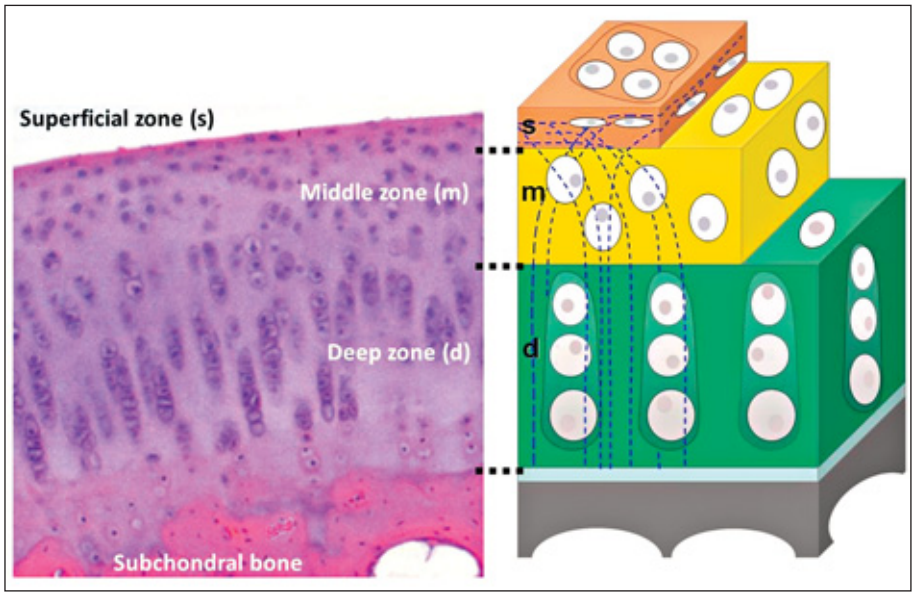

Fig. 1: Histology of hyaline cartilage (left image) and schematic drawing of the hierarchical zonal organisation with at least three biochemically different chondral layers.

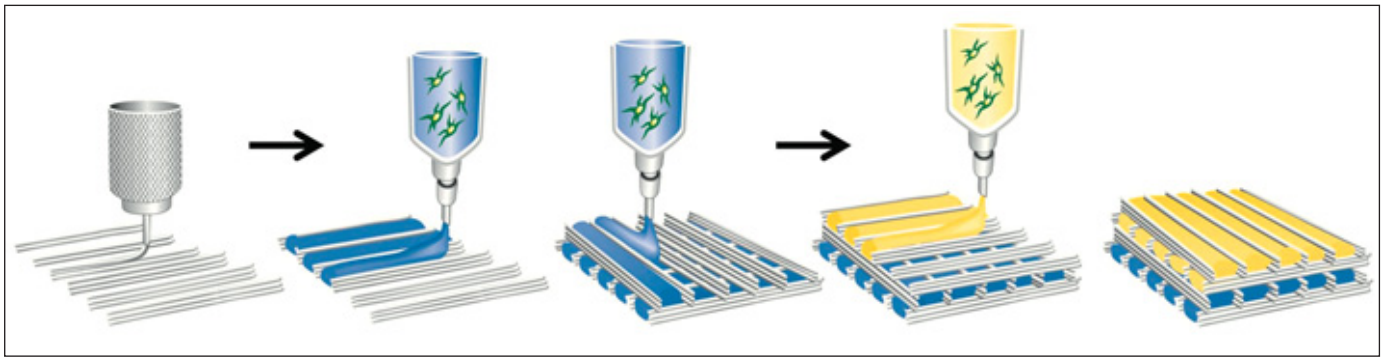

Fig. 2: Scheme of the technological approach that relies on printing of a thermoplast scaffold for initial mechanical stability (left) and successive co-printing of cell-loaded hydrogels with biochemical cues that correspond to the respective chondral layer (middle, right).

hypothesis that the development of zonal properties is critical for the long-term stability and functionality of tissue-engineered cartilage, and that a biomimetic zonal organisation of the implants themselves is critical to induce native tissue hierarchy and thus achieve regeneration of functional hyaline cartilage.

Objectives and research approach of HydroZONES

As cartilage is a hydrogel-like matrix rich tissue, one promising regenerative approach is the use of (cell-laden) hydrogel matrices to fill cartilage defects. Hydrogels are water swollen three-dimensional (3D) networks of hydrophilic polymers that allow encapsulation of cells and diffusion of nutrients. They are thus especially attractive for cartilage repair as they recapitulate several features of the natural cartilage matrix. Additionally, hydrogels allow for efficient and homogeneous cell seeding, can provide biologically-relevant chemical and physical signals and can be formed in various shapes. Whilst advances have been made in the development of hydrogels for enhanced cell survival and chondrogenesis, little attention has been paid to recapitulating the zonal structure and function of native cartilage.

The first and most important objective of HydroZONES is to develop a hierarchically structured hydrogel based but mechanically stable scaffold that recapitulates the zonal distribution of the native articular cartilage. For hydrogel development, three leading internationally recognised European laboratories in biomaterials development and hydrogel technology provide established but innovative hydrogel technology comprising usability in printing devices, specific functionalisation with peptides, Glycosaminoglycans and growth factors and finally the option to load the hydrogels with cells during printing due to cytocompatible cross-linking reactions. Scaffolding will be addressed in HydroZONES by the application and development of 3D bioprinting technologies (Fig. 2). Degradable and clinically used thermoplastic polymers will be applied for mechanical reinforcement of the hydrogels to ensure stability of the constructs for handling during operation and minimum initial stability in the patient. HydroZONES will follow and compare cell-free and cell-loaded hydrogels, comparing chondrocytes and bone marrow derived mesenchymal stem cells for their efficacy. Human chondrocytes from OA patients and human bone marrow derived stem cells will be tested for initial in vitro assessment of the scaffolds. Detailed studies will be performed with these cells as well but also with the respective porcine and equine cells for correlation with the in vivo experiments. Advanced bioreactors will be employed for in vitro testing of the constructs and results will be used as input for realistic in silico modelling. Scaffolds that pass our stringent and well-documented in vitro and in vivo screening will undergo long-term pre-clinical in vivo testing, which will set a new international standard for pre-clinical testing of cartilage implants. HydroZONES will install a thorough testing and selection procedure through in vitro testing (conform to ISO 10993-5), biocompatibility and biofunctionality screening and evaluation in long-term pre-clinical models. Establishment of a consortium wide quality and regulatory affairs management system according to EN ISO 13485:2007 (QM/RAM) will allow setting up a new internationally acceptable standard for pre-clinical testing of (osteo-) chondral implants.

Second major aim of HydroZONES is the development of a predictive 3D in vitro assay for chondral implants, validated against our in vivo results, together with the hardware to perform the assay. Bioreactors will be tailored for dynamic recapitulation of the natural stimuli of cartilage tissue, with the aim to minimize the necessary number of in vivo tests during future implant development.

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5.4.10 EU-Project, OPTATIO: Optimizing Targets and Therapeutics in High Risk and Refractory Multiple Myeloma

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General information and research interests

OPTATIO is an EU project under Framework Programme 7 and brings together the expertise from 12 partner institutions from Austria, Germany, the Czech Republic, Italy, Hungary, and Spain.
The concept of OPTATIO is that adhesive or cytokine interactions of. These cells with the bone marrow microenvironment (BMM), which render neoplastic cells resistant to the effect of chemotherapeutic agents. These are the underlying cause for MM treatment failure characterized by the primary or secondary resistance to drugs. This concept is based on the observation that the development of MM is a complex multistep process involving both early and late genetic changes in the tumor cell as well as selective supportive conditions by the bone marrow microenvironment. Notably, despite the presence of a variety of common chromosomal abnormalities, mutations and translocations in essential tumor growth and suppressor genes in MM cells, oncogenomic studies have identified only subtle differences distinguishing MM from monoclonal gammopathy of unknown significance (MGUS), an obligate high incidence premalignant phase of the disease. In order to target the essential components of this interactive network with the aim of developing a principally new and innovative MM treatment strategy, there is a strong need to establish preclinical *in vitro* and *in vivo* models of MM that include functionally relevant components of the BMM to enable effective drug development and drug-related biomarker development.
Therefore, it is the overall objective of the OPTATIO research consortium to exploit the importance of MM-BMM interactions for the transition of MGUS to overt MM, for intrinsic therapy resistance in high risk MM and for disease relapse due to the development of acquired drug resistance. This innovative way of exploiting the cancer microenvironment network for therapeutic interference may well serve as a transposable model system for all types of malignancies.

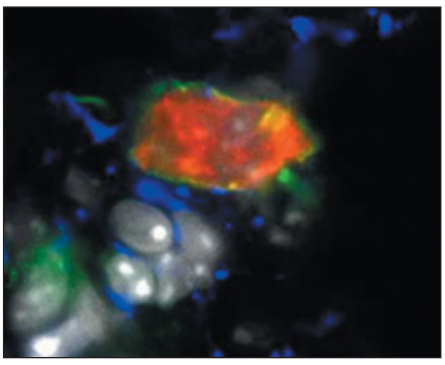

Fig 1: Metastatic multiple myeloma cell. Riedel et al., 2012.

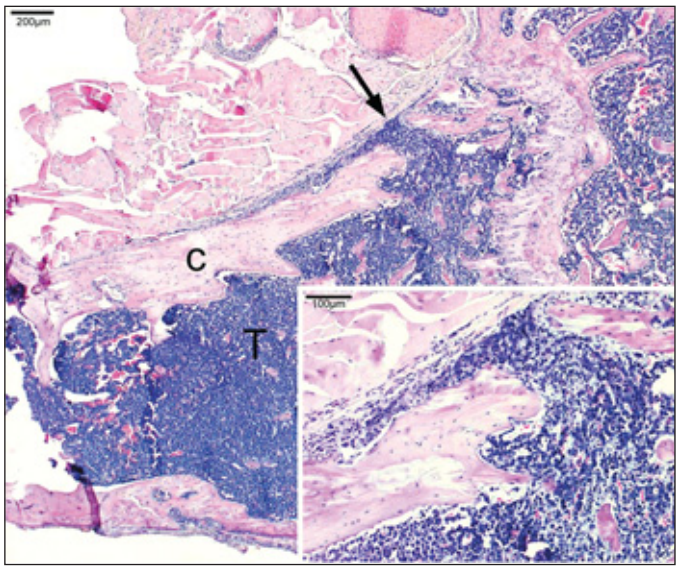

Fig 2: Bone destruction (arrow) caused by multiple myeloma cell proliferation. Riedel et al., 2012.

The specific objectives are:

1. Analysis of clinical data and tissue specimens from MM patients to search for novel prognostic and/or predictive biomarkers of MM-BMM interactions at the cellular and molecular level.
2. Development of new diagnostic methods suitable for the prediction of individual patients' response to the established treatment.
3. Development of new lead compounds for targeting the MM-BMM interference using innovative drug discovery approaches.
4. Pre-clinical testing of newly developed lead compounds in improved animal models

If this project turns to be successful, chemical compounds that prove effective in vitro and in animal models will eventually be clinically tested and biomarkers will be validated with respect to their relevance for patient selection, monitoring and response/outcome prediction in a personalized fashion in the follow-up projects.

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Heimberger T, Andrulis M, Riedel S, Stühmer T, Schraud H, Beilhack A, Bumm T, Bogen B, Einsele H, Bargou RC, Chatterjee M. (2013) The heat shock transcription factor 1 as a potential new therapeutic target in multiple myeloma. Br J Haematol 160:465-76.

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5.4.11 EU-Project, T-Control: Donor T Cells for Immune Control

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General information and research interests

'T-Control' – a EU-FP7 Collaborative Project to combat hematologic malignancies

In T-Control, 4 outstanding research partners from Germany, the UK and the Netherlands are joining forces to combat the most common forms of leukemia and lymphoma. The consortium brings together the expertise of 3 academic institutions – University of Würzburg, GER; Leiden University, NED; and Anthony Nolan Trust, UK; and one partner in the emerging biotech industry (Stage Cell Therapeutics, GER). Adoptive immunotherapy, in the setting of allogeneic hematopoietic stem cell transplant (alloHSCT), is the only established, potentially curative treatment for high-risk hematological malignancies (e.g. leukemia, myelodysplastic syndromes, advanced myeloproliferative disorders, high-risk lymphomas and multiple myeloma), and is currently applied in more than 15,000 patients per year in Europe. The number of patients undergoing this procedure is rapidly increasing, but the risk of treatment failure and life-threatening complications is still high. For example, in patients with high-risk leukemia receiving an alloHSCT, mortality due to relapse or treatment complications, e.g. infections and Graft-versus-host disease (GvHD) can exceed a rate of 50%. Thus, the development of strategies to reduce the risk associated with alloHSCT would enable physicians to offer this procedure to a much larger number of patients that are in desperate need of potentially effective treatment options.

Joint forces from 3 European countries in 'T-Control'

Each of the 3 academic partners in T-Control has key expertise in the diagnosis and management of the three main complications of alloHSCT – i.e. relapse, viral infection and GVHD, and will make unique contributions to the work program. The partners have worked together successfully in the FP6 project ALLOSTEM, thus sharing a common track record in translational research in hematology/oncology. Stage, which has a proven track record in the development of cell therapeutics, will coordinate the T-Control project and bundle all efforts into a unified and directed development program with the aim to commercialize the anticipated cell products. The Stage Streptamer technology was selected by T-Control to provide a common cell purification and selection platform. Streptamers provides unique technical and economic advantages over other cell selection procedures including complete removal of the selection reagents from the purified cell population, providing minimally manipulated non-ATMP cell products, and will be utilized to generate all cell products in this project.

The aims in T-Control - enhance potency and reduce complications in alloHSCT

The therapeutic effect of alloHSCT is mediated to a major extent by T cells from the stem cell donor that recognize tumor associated antigens (TAA) or polymorphic antigens (minor histocompatibility antigen - MiHA) and eradicate the malignant leukemic cells. However, donor T cells may not only mediate this beneficial Graft-versus-Tumor (GVT) effect, but may also recognize MiHA on non-hematopoietic cells from the recipient, resulting in GVHD. Strategies to separate GVT from GVHD after alloHSCT are essential for further enhancing patient eligibility and cure rates, and minimizing the risk of this procedure in the treatment of hematological tumors. Potential strategies have been investigated by physicians and researchers for several decades – many concepts have been proposed, yet the ultimate breakthrough to separate GVT from GVHD remains to be accomplished. At present, several approaches are being taken clinically to reduce the incidence and severity of GVHD, including complete removal of T cells from the stem cell graft which can prevent the onset of severe, high-grade GVHD, but is associated with impaired resistance to infections and compromises the GVT effect. Systemic suppression of GVHD with immunosuppressive drugs either alone, or in conjunction with T cell depletion can be attempted, but is toxic (nephrotoxicity, neurotoxicity, microangiopathy etc.) and associated with reduced resistance to infections and a higher incidence of tumor relapse. In the unfortunate case of tumor relapse after alloHSCT, the remaining treatment options are limited and the prognosis typically poor – the use of donor lymphocyte infusions (DLI) obtained from the stem cell donor can induce remissions in a subset of patients but is often associated with induction of severe GVHD. Thus, at present, physicians and patients alike are facing a significant clinical challenge, i.e. that there is presently no established strategy that can reproducibly separate anti-tumor/anti-pathogen (i.e. GVT and graft versus infection – GVI) reactivity from GVHD after alloHSCT. The team of investigators in T-Control has therefore joint efforts to make a major leap forward in accomplishing this goal and is proposing to select only T cells with defined antigen specificity and with defined function to be part of the stem cell graft in order to obtain maximum GVT and GVI reactivity, with minimal GVHD. To prevent severe GVHD, the investigators will first remove all T cells from the stem cell graft and then:

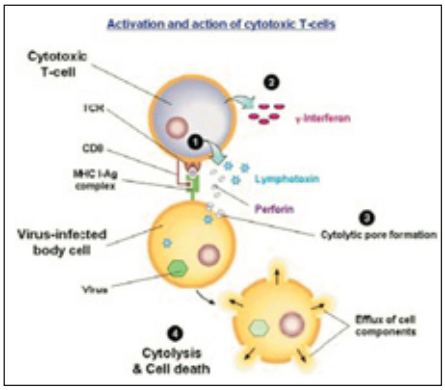

Fig.1: Function of Cytotoxic T cells: Cytotoxic T cells (CTL) recognize virus-infected cells (and tumor cells) via major histocompatibility complex (MHC) I presented antigens on target cells and release lytic enzymes and induce apoptosis to destroy the infected or malignant cell. Streptamer reagents contain MHC I molecules (green) to select CTL (blue) via its T cell receptor. The multispecific T-cell product is a defined mixture of CTLs directed against different viral and tumor antigens selected with a mixture of MHC I Streptamer reagents.

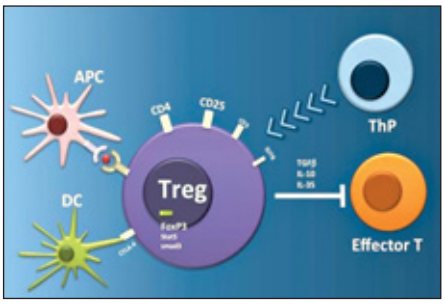

Fig. 2: Function of Tregs: Tregs inhibit effector T cells that causing GVHD or autoimmune diseases either by cell-cell contact or the release of soluble factors such IL-10 and TGFβ. The concomitant expression of CD4 and CD25 can be used to select Tregs with streptamer reagents and obtain a Treg product with immune-suppressive function.

1. Select and add back tumor specific/ MiHA specific T cells to combat the tumor
2. Select and add back virus specific T cells to combat infections
3. Select and administer T cells with suppressive activity (Tregs) to mitigate residual GVHD

Reversible streptamer reagents will be used as the common cell selection methodology to purify minimally manipulated effector and suppressor T cells for all therapeutic applications.

Aim 1&2: Isolating tumor- and virus-specific T cells to combat the tumor and infections

CMV- or EBV-specific T cells can be used to treat patients with resistant CMV or EBV infection after alloHSCT or organ transplantation, but *in vitro* culture methods are required to isolate or generate and then expand antigen specific T cells for clinical application. The successful implementation of such therapeutic strategies into routine clinical practice was complicated by the laborious and expensive GMP production process, and the need for a strong expertise in cell cultivation and release testing. An alternative strategy pursued in T-Control utilizes reversible Streptamer reagents to isolate T cells specific for viral pathogens which takes only one day for completion, thus minimizing the labor, time and cost of cell production, and provides a non-ATMP cell product which alleviates much of the burden associated with product validation and release. Moreover, the T-Control investigators will compose in a simultaneous selection procedure with multiple Streptamers, a virus-, MiHA- and TAA-specific T cell product derived from the memory and naive T cell repertoire from healthy (stem cell) donors that will be used therapeutically or prophylactically to treat viral infections and tumor relapse after alloHSCT. Based on the genetic differences between donor and recipient, target antigens include hematopoiesis-associated MiHA or TAA that are aberrantly or overexpressed on malignant but not normal tissues. Streptamer selection reagents against a variety of MiHA and TAA are being developed and validated for GMP-manufacturing in T-Control to generate a tumor-/pathogen-reactive T cell product that is tailored for each individual patient. The methodologies and protocols developed in T-Control are paving the way to a new area of individualized medicine in hematology and oncology that will incorporate strategies of T-cell engineering such as modification with tumor-reactive chimeric antigen receptors (CARs) to further enhance anti-tumor efficacy in the near future.

Aim 3: Regulatory T cells to mitigate residual GVHD

The T-Control investigators had already provided preliminary evidence in the FP6 ALLOSTEM project that regulatory T cell products (Tregs) can be manufactured and used in a clinical setting to treat GVHD. GVHD is the most severe complication after allogeneic HSCT leading to high morbidity and mortality, and is unpredictable due to the high genetic variability between donors and recipients. The incidence of GVHD may already be substantially reduced by our strategy of T cell depletion and subsequent transfer of Streptamer-purified virus-specific and/or tumor-specific T cells (Aim 1&2) but still, effective long-term control and prevention of GVHD is of major importance and may be accomplished by preventive or therapeutic adoptive transfer of Tregs. It has been shown that Tregs are capable of controlling severe GVHD in animal models and early clinical studies demonstrated Treg infusion to be safe. T-Control will focus on Streptamer selected, minimally manipulated Tregs derived from third party umbilical cord blood (UCB). UCB has the attraction that it may be obtained "off-the-shelf" from already established, clinically accredited sources (UCB banks). However, at present, no rapid and highly reproducible method to purify UCB Tregs is available. The Streptamer technology has the potential to allow high yield isolations from cryopreserved units and, therefore, allow for sufficient cell numbers to be obtained from a single UCB unit. We will therefore develop a rapid and highly reproducible Streptamer-based selection method to purify Tregs from UCB to prevent or treat severe GVHD following allogeneic HSCT. In a clinical trial, the investigators will focus on deriving insights on the optimal timing and dosing of Treg administration – both are presumed to be critical parameters for clinical efficacy. In addition, it is likely that primary Treg products as proposed in T-Control which are only selected and not expanded *in vitro*, will expand and persist significantly better compared to *in vitro* expanded cell products that have been used in previous clinical trials. If successful, this technology could be extended to the treatment of a variety of autoimmune diseases.

In summary, T-Control will develop two novel T cell products using the Streptamer-based isolation method, which generate minimally manipulated T cells approved as non-ATMPs: tumor-reactive/virus-specific T cells to treat and prevent relapse and infection after alloHSCT; and Tregs to prevent or treat GVHD in patients undergoing alloHSCT. The Streptamer selection method allows rapid isolation of highly purified T cell products, which will be tested in two clinical trials allowing the development of cell products for the European market.

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5.5 Graduate School of Life Sciences (GSLS)

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(Director, UWGS; Vice Dean, GSLS)

Professor Dr. rer. nat. Dr. med. habil. Heidrun Moll
(Vice Dean)

Dr. rer. nat. Gabriele Blum-Oehler
(GSLS office)
Phone: 0931/31-81474

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 the MD/PhD program, which was initiated by the Faculties of Biology and Medicine in 1996/7 as the first such program in Germany. Discussions within the entire university to improve graduate training led to the foundation of the "International Graduate School" (IGS) by the University Senate in December 2003. The IGS was initiated to cover the academic spectrum of the entire university, with separate graduate schools catering towards the specific scientific and training needs and cultures of its diverse disciplines.

Section Biomedicine

As a first step, the Section 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 unified program. Since then, several generations of basic and clinical scientists have successfully completed this program. 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 were founded: Infection and Immunity, Neuroscience and Integrative Biology.

The growing Graduate School

Increases in size and scope resulting from the progressive integration of further programs and 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 an umbrella organization of the independent graduate schools in 2006 and was renamed as the 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.
All four Graduate Schools cater towards the needs of their different broad fields of science, uniting research in the Life Sciences, the Humanities, the Natural Sciences and Social Sciences (see Fig. 1). Each school manages their day-to-day business independently.

The umbrella organization, 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 for the individual schools. The core principles laid down in the graduation regulations remain those that were originally established in the Section Biomedici-

Fig. 1: Structure of the University of Würzburg Schools.

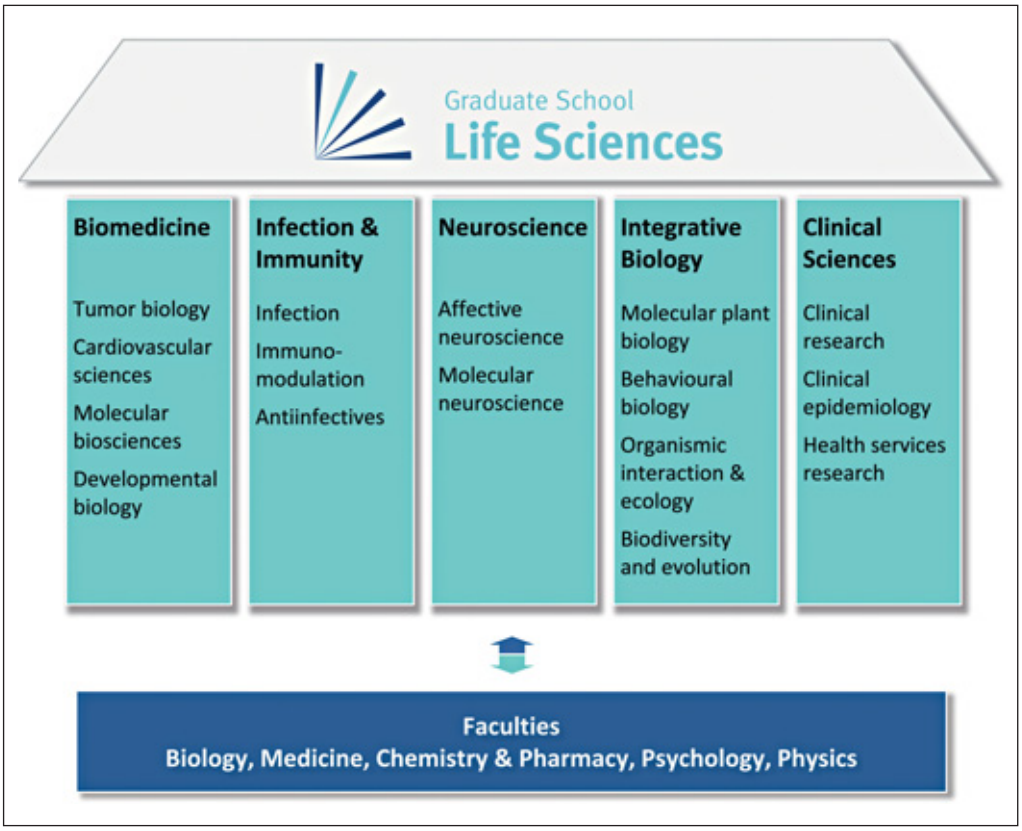

Fig. 2: Structure of the Graduate School of Life Sciences.

ne, 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 for the GSLS were set forth in the successful application to 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 in 2011. 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).

GSLS fellowship program: A special fellowship program of the GSLS comprises the core element of the funding by the Excellence Initiative. The eighth round

Key elements of training in the Graduate Schools

- The traditional single supervisor ("Doktorvater bzw. Doktormutter") is replaced by a thesis committee with three principal investigators (PIs).
- A wide range 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 common quality standard is assured through the set of requirements.

Mentoring System
Each doctoral researcher is matched with 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 on 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.

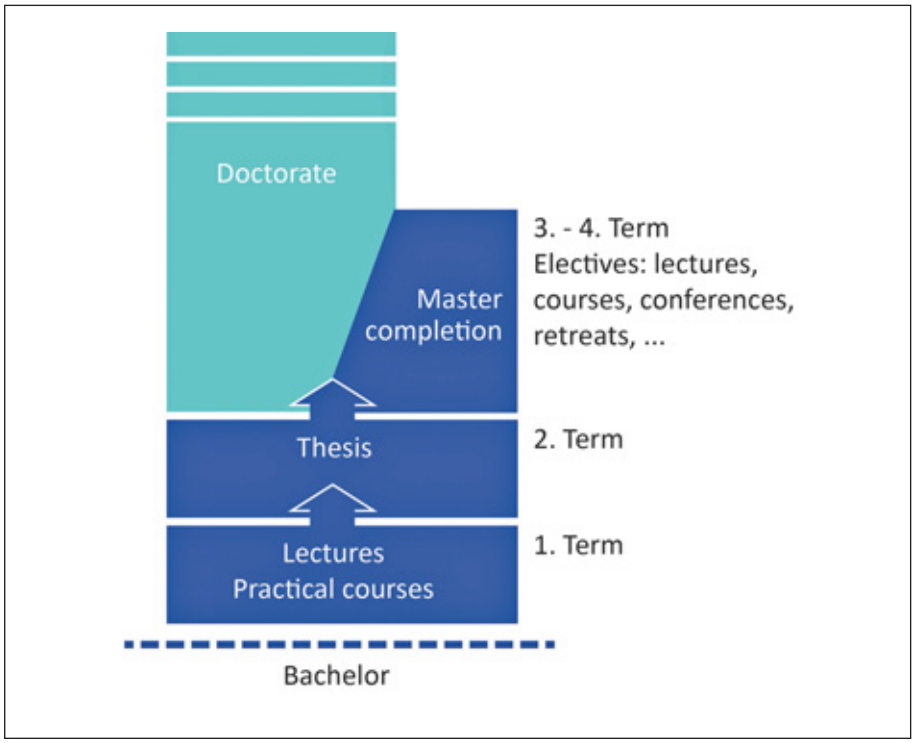

Fig. 3: The study program FOKUS Master Life Sciences: Through the fast track option, students with a bachelor degree can already begin their doctoral studies after only one year. In order to be eligible for this fast track, students must pass all exams in the first two semesters with outstanding grades. Students who do not qualify for the fast track option can complete their master degree within the normal time frame of four semesters.

of international recruitment began in the fall of 2013. To date more than 2000 standardized written applications were evaluated in the recruitment rounds, and interviews with more than 350 candidates were performed by the GSLS admission board in Würzburg, by means of video conferencing and abroad. So far 88 fellows from 21 different countries, underscoring the international character of the GSLS, have been supported by the GSLS.
To date, the number of formal members of the GSLS has risen to more than 200 principal investigators from all participating faculties. In 2013 the number of doctoral researchers registered in the doctoral study program "Life Sciences" rose to more than 340.

Excellence Program for Medical Doctoral Researchers: In July 2012, the renewal proposal of the GSLS in the framework of the second phase of the Excellence Initiative was approved. 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 has been envisaged, addressing the top ~20% of the medical students

Since March 2013, 19 MD students have registered in the structured doctoral training program of the GSLS. For registration the following criteria have to be fulfilled:

- Receipt of an MD fellowship from the Medical Faculty or the GSLS
- The thesis entails an experimental or clinical epidemiological research project
- Successful completion of the First State Exam in medicine is required
- A dedicated phase towards the thesis of at least nine months
- The establishment of a thesis committee with three PIs.

Two application rounds for MD fellowships will be offered each year, starting on 15th April and 15th October, respectively.
All requirements for MD students will amount to a third of those for the natural sciences GSLS doctoral researchers, as the program is expected to last a maximum of one year. The program consists of seminars, journal clubs, methods courses, workshops, retreats and the active participation in at least one international conference. MD students can also choose from a great variety of transferable skills courses in the GSLS. An additional requirement is to obtain at least one co-authored peer-reviewed original research publication prior to completion of their thesis.

The Study Program FOKUS Master Life Sciences: The usual admission requirement for the doctoral study program of the GSLS is a Master of Science degree or a diploma. Previously, students holding a BSc degree could only enter the GSLS after a one-year qualification phase consisting of a mini thesis and three oral exams. To attract excellent international research-minded candidates directly after their BSc, the GSLS and the Faculty of Biology, in cooperation with the other constituent faculties of the GSLS, designed the fast track course FOKUS Life Sciences. Created in 2012 and accredited in 2013, the study program has attracted excellent students from around the world. Candidates go through a rigorous selection process during the application before being admitted to the program. In the class of 2013/2014, out of 165 applicants only the top eleven students were accepted. In the first semester, the students are prepared for active life science research through two specially designed lecture series and a multitude of lab-based internships. Only students succeeding in the first semester with excellent grades remain on the fast track and can pursue their master thesis in the second semester (see Figure 3). The thesis ideally sets the foundation for a following PhD project which the students can immediately start if the master thesis is excellent. The remaining ECTS points required for the MSc degree will be earned during the PhD phase. With the option to work towards a PhD within a year of a BSc degree and to obtain a master degree parallel to the PhD study, the FOKUS Life Sciences course attracts internationally excellent students to Würzburg.

6. The Medical Faculty: Basic Data

1. Collaborative Research Centers, Clinical Research Units, Research Training Groups

Collaborative Research Centers:

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

Transregio-Collaborative Research Center 124, Pathogenic Fungi and their Human Host: Networks of Interaction

Clinical Research Units:

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

International 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

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
2012 Prof. Dr. Kurt Kochsieck
Würzburg

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
2013 Elterninitiative leukämie- und tumorkranker Kinder e.V
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

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 Juvenile 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. E.-B. Bröcker, Professor Dr. H. Hamm, Professor Dr. J.C. Becker, Professor Dr. A. Trautmann, Department of Dermatology, Venereology and Allergology
Autumn 2010	Professor Dr. R. Jahns, Department of Internal Medicine I
Spring 2011	Dr. B. van Oorschot, Department of Radiation Oncology – Center for Palliative Medicine Dr. S. Neuderth, Division of Medical Psychology, Medical Sociology, and Rehabilitation Research Professor Dr. Dr. A. Kübler, Director of the Department of Oral and Maxillofacial Surgery
Autumn 2011	Professor Dr. R. Meffert, Director of the Department of Trauma-, Hand-, Plastic and Reconstructive Surgery
Spring 2012	Professor Dr. J. Volkmann, Director of the Department of Neurology
Autumn 2012	PD Dr. S. Knop, Department of Internal Medicine II Professor Dr. B. Klaiber, Director of the Department of Conservative Dentistry and Periodontology
Spring 2013	PD. Dr. U. Dietz, Department of General, Visceral, Vascular and Pediatric Surgery Dr. R. Wagner, Department of Trauma, Hand, Plastic and Reconstructive Surgery
Autumn 2013	Professor Dr. A. Friebe, Institute of Physiology

7. Habilitations

2012

Clinical

Dr. med. Briegel, Wolfgang	Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy
Dr. med. Krockenberger, Mathias	Obstetrics and Gynecology
Dr. med. Ritter, Christian Oliver	Radiology
Dr. med. Dr. med. dent. Klammert, Uwe	Oral and Maxillofacial Surgery
Dr. med. Thomas, Wolfgang	Paediatrics and Adolescent Medicine
Dr. med. Weyandt, Gerhard	Dermatology and Venerology
Dr. med. Lopau, Kai	Internal Medicine
Dr. med. Geis, Christian	Neurology
Dr. med. Goltz, Jan Peter	Radiology
Dr. rer. nat. Schmitt, Angelika	Molecular Psychiatry
Dr. med. Segerer, Sabine	Obstetrics and Gynecology
Dr. med. Jakubietz, Rafael G.	Plastic and Aesthetic Surgery
Dr. med. Jakubietz, Michael G.	Plastic and Aesthetic Surgery
Dr. med. Zeplin, Philip H.	Plastic and Aesthetic Surgery

Preclinical

Dr. rer. nat. Bodem, Jochen	Virology
Dr. rer. nat. Nikolaev, Viacheslav	Pharmacology and Toxikology
Dr. rer. nat. Ebert, Regina	Experimental Osteology

2013

Clinical

Dr. med. Sommer, Sebastian-Patrick	Cardiovascular Surgery
Dr. med. Neubauer, Henning	Radiology
Dr. med. Ip, Chi Wang	Neurology
Dr. med. Kredel, Markus	Anaesthesiology
Dr. med. Vollmer, Maike	Neurophysiology
Dr. med. Hofmann, Ulrich	Internal Medicine and Cardiology
Dr. med. Frey, Sönke Percy	Trauma Surgery
Dr. med. Redel, Andreas	Anaesthesiology
Dr. med. Brede, Elmar-Marc	Anaesthesiology
Dr. med. Hackenberg, Stephan	Otorhinolaryngology
Dr. med. Heinz, Werner Johannes	Internal Medicine
Dr. med. Jansen, Hendrik A.	Trauma Surgery
Dr. med. Jurowich, Christian Ferdinand	Surgery
Dr. med. Schmidt, Kasten	Plastic and Aesthetic Surgery

Preclinical

Dr. med. Beyersdorf, Niklas	Immunology
Dr. med. Elias, Johannes	Medical Microbiology

8. Registration numbers

Human medicine and dentistry

	human medicine/ thereof female	dentistry / thereof female
WS 2011/12	167 / 108	61 / 38
SS 2012	170 / 115	53 / 29
WS 2012/13	167 / 107	53 / 33
SS 2013	170 / 94	53 / 34
WS 2013/14	170 / 93	55 / 33

Bachelor- and master courses

	biomedicine Bc. / thereof female	biomedicine Ma. / thereof female	experimental medicine Ma. / thereof female
WS 2011/12	30 / 27	13 / 11	1 / 0
SS 2012	0	1 / 0	0
WS 2012/13	31 / 28	11 / 11	1 / 0
SS 2013	0	0	0
WS 2013/14	26 / 19	18 / 12	0

Accompanying courses

	experimental medicine / thereof female	clinical research and epidemiology / thereof female
WS 2011/12	3 / 0	-
SS 2012	0	-
WS 2012/13	6 / 2	3 / 2
SS 2013	2 / 1	2 / 1
WS 2013/14	6 / 4	4 / 2

9. Graduations

Human medicine and dentistry

	human medicine / thereof female	**dentistry / thereof female**
Spring 2012	127 / 61	48 / 36
Autumn 2012	107 / 61	52 / 42
Spring 2013	141 / 83	56 / 28
Autumn 2013	125 / 79	50 / 32

Bachelor- and master courses

	biomedicine Bc. / thereof female	**biomedicine Ma. / thereof female**	**experimental medicine Ma. / thereof female**
Spring 2012	19 / 16	16 / 12	-
Autumn 2012	0	0	-
Spring 2013	23 / 16	11 / 9	1 / 0
Autumn 2013	1 / 1	1 / 0	0

Doctorates (without doctorates in natural sciences)

	preclinical	**clinical**	**total**
2012	35	132	167
2013	44	165	209

10. The deans of the medical faculty since 1945

1945 to 1947	Professor Dr. med. Dankwart ACKEMANN
1947 to 1948	Professor Dr. med. Jürg ZUTT
1948 to 1949	Professor Dr. med. Max MEYER
1949 to 1951	Professor Dr. med. Curt SONNENSCHEIN
1951 to 1952	Professor Dr. med. Werner WACHSMUTH
1952 to 1953	Professor Dr. med. Hans SCHEUERMANN
1953 to 1954	Professor Dr. med. Hermann WOLF
1954 to 1955	Professor Dr. med. Dr. phil. Wilhelm NEUMANN
1955 to 1957	Professor Dr. med. Heinrich SAAR
1957 to 1958	Professor Dr. med. Georges SCHALTENBRAND
1958 to 1959	Professor Dr. med. Kurt NEUBERT
1959 to 1960	Professor Dr. med. Hans FRANKE
1960 to 1961	Professor Dr. med. Erich BAUEREISEN
1961 to 1962	Professor Dr. med. Ernst WOLLHEIM
1962 to 1963	Professor Dr. med. Horst WULLSTEIN
1963 to 1964	Professor Dr. med. Hans-Werner ALTMANN
1964 to 1965	Professor Dr. med. Horst SCHWALM
1965 to 1966	Professor Dr. med. dent. Rudolf NAUJOKS
1966 to 1967	Professor Dr. med. Wolfgang SCHWERD
1967 to 1968	Professor Dr. med. August RÜTT
1968 to 1969	Professor Dr. med. Erich BAUEREISEN
1969 to 1970	Professor Dr. med. Helmut RÖCKL
1970 to 1971	Professor Dr. med. Theodor Heinrich SCHIEBLER
1971 to 1973	Professor Dr. med. Karl Heinz WEIS
1973 to 1975	Professor Dr. med. Johannes LANG
1975 to 1977	Professor Dr. med. Erich BAUEREISEN
1977 to 1979	Professor Dr. med. Otto SCHRAPPE
1979 to 1981	Professor Dr. med. Karl-Heinrich WULF
1981 to 1983	Professor Dr. med. Karl-August BUSHE
1983 to 1985	Professor Dr. med. Volker ter MEULEN
1985 to 1987	Professor Dr. med. Gerhardt NISSEN
1987 to 1989	Professor Dr. med. Stefan SILBERNAGL
1989 to 1991	Professor Dr. med. Kurt KOCHSIEK
1991 to 1994	Professor Dr. med. Hans Konrad MÜLLER-HERMELINK
1994 to 1996	Professor Dr. med. Klaus WILMS
1996 to 1998	Professor Dr. med. Klaus TOYKA
1998 to 2002	Professor Dr. med. Volker ter MEULEN
2002 to 2004	Professor Dr. med. Stefan SILBERNAGL
2004 to 2006	Professor Dr. med. Georg ERTL
since 2006	Professor Dr. med. Matthias FROSCH

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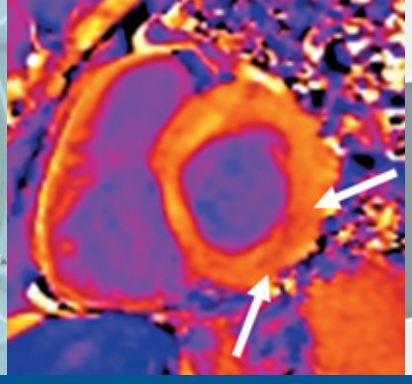
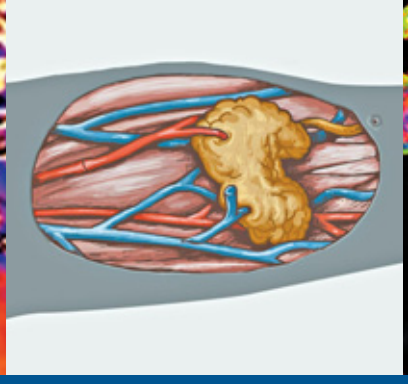
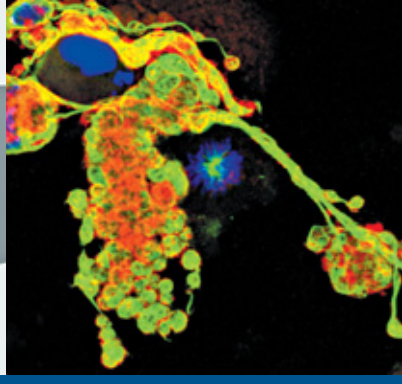

University of Würzburg

Uniklinikum Würzburg

Medical Faculty

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