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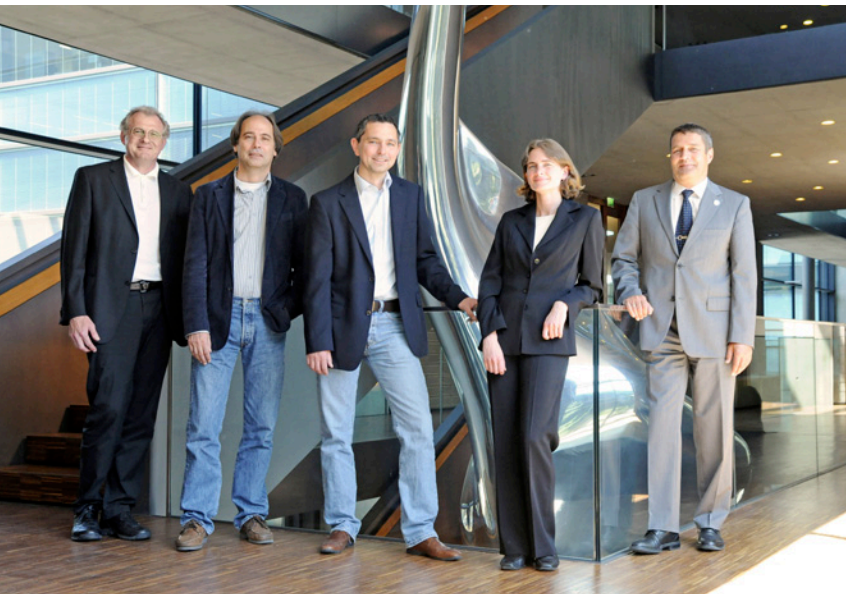
International Graduate School in Molecular Medicine Ulm
Biannual Report 2013

Funded by the Excellence Initiative of the German federal and state governments

IGradU



Former Board of Directors: B. Böhm, D. Brockmann, M. Kühl, T. Weil, P. Bäuerle

Welcome to the information brochure of the International Graduate School in Molecular Medicine Ulm!

This is the third biannual report published by the International Graduate School in Molecular Medicine Ulm (IGradU) since its foundation in 2006. The last two years have been very exciting. First of all, IGradU applied for a second round of funding within the framework specified by the Excellence Initiative of the German federal and state governments. We are thus very pleased to announce that our concepts of training, our scientific programs, our mentoring and gender activities as well as our financial programs (such as the Mobility Program and Key Competence seminars) were decisive in convincing the international review panel at a hearing in Bonn in January, 2012. On June 15, 2012, we were officially informed that IGradU will be funded as one out of 45 Graduate Schools until September 2017. We would like to take this opportunity to say a very warm *Thank You* to all those who have helped to make IGradU such an outstanding success and above all to all our PhD students, the PIs and supervisors, the Coordination Office as well as the boards of Ulm University and the Medical Faculty.

As of June 2013, 177 PhD students from the life sciences and 24 medical PhD students are being trained at the Graduate School by 77 primary supervisors. PhD students perform their thesis work in 46 institutes and departments of Ulm University. This number of students attests to the wide recognition of the high quality of our standards at Ulm University.

When talking about successful PhD training, there are always those questions regarding the length of time that students will need to finalize their thesis work and how many papers they will publish as well as what kind of career opportunities will be available to them following graduation. On average, our PhD students require 44 months to complete their PhD work and publish 3.5 papers in peer review journals until their disputation. Most of our graduates pursue their scientific careers as postdocs abroad in high ranking international universities and institutions such as Harvard, Cambridge (USA), Stanford, California (USA), McGill University, Montreal (Canada), the University of Lund (Sweden) and the University of Liège (Belgium). The alumni of these universities meet on a regular basis at Ulm University both to discuss their scientific projects with our students and also to offer them advice for their future careers.

Which programs are new at IGradU? The most important of these is a new Research Training Group funded by the German Research Council (DFG) that was established in 2013. The topic of this Research Training Group is *CEMMA: Cellular and Molecular Mechanisms in Aging* (Speaker: Prof. Dr. H. Geiger, Department of Dermatology and Allergology). This is an important module that is ideally suitable for enhancing our training in the research area of *Development, Aging and Degeneration*.

Our research topic, *Signaling Networks in the Hematopoetic System and Oncology*, has been significantly strengthened by the new DFG-funded Collaborative Research Center topic entitled *Experimental Models and Clinical Translation in Leukemia* (Speaker: Prof. Dr. H. Döhner, Department of Internal Medicine III). Based on the success of our joint PhD Programme with the University of Padua in Italy, we have also established a second joint PhD Programme with the BioCenter Oulu in Finland on the topic of tissue homeostasis: *Development, Aging and Regeneration*. The first PhD students will enter this program in the summer semester of 2013. In addition, a new Guest Professor Programme has been introduced for scientists invited to the university. Finally, we have also established a Junior Faculty Programme in order to assist junior scientists who have already received funding to accept PhD students but are not yet allowed to be the primary supervisor due to a lack of a higher teaching allowance (Habilitation). As members of the Junior Faculty, these scientists can actively participate in the Thesis Advisory Committees supervising their students. Moreover, members of the Junior Faculty are trained for their future career either in academia or industry by being provided with additional training opportunities. Seminars on offer include: Leadership - Managing and Motivating Teams; Project and Time Management; Managing Laboratories; and Conflict Management.

Finally, we would like to thank two members, who have since left the Board of Directors of IGradU, for their enthusiastic support during their term of office, namely, Prof. Dr. Peter Bäuerle, Head of the Institute of Organic Chemistry II, and Prof. Dr. Bernhard Böhm, Department of Internal Medicine I. Prof. Dr. Bäuerle has been replaced by Prof. Dr. Axel Groß, Head of the Institute of Theoretical Chemistry, as the new representative of the Presidium of Ulm University on the Board of Directors of the Graduate School. Prof. Dr. Böhm accepted a dual appointment from London and Singapore. Nevertheless, as a result of his new position at the Nanyang Technological University in Singapore, we are hoping that IGradU can now closely cooperate with this internationally renowned university by offering student exchanges and training. Prof. Dr. Böhm's replacement is Prof. Dr. Bernd Knöll from the Institute of Physiological Chemistry. We are looking forward to working effectively and productively with our new board members in order to further enhance the profile, training concepts and the international reputation of the International Graduate School in Molecular Medicine Ulm.

On behalf of the Board of Directors

Prof. Dr. Michael Kühl
Chairman

PD Dr. Dieter Brockmann
Managing Director

Current Board of Directors: M. Kühl, A. Gross, B. Knöll, D. Brockmann, T. Weil

The Graduate School

The second period of funding for IGradU from the Excellence Initiative of the German federal and state governments

The Excellence Initiative of the German federal and state governments was established in 2005. The Excellence Initiative aims to promote top-level research and to improve the quality of German universities and research institutions in general, thus making Germany a more attractive research location, making it more internationally competitive and focussing attention on the outstanding achievements of Germany universities and the German scientific community (www.dfg.de). The DFG is responsible for running the initiative together with the German Science Council.

Forty-five graduate schools serve to assure the quality of standards in promoting junior researchers and have been founded on the principle of training outstanding doctoral students within an excellent research environment (www.dfg.de). They are supported by the German Research Foundation (DFG) and create the ideal conditions for training doctoral students that include not only a stimulating research environment, but also a structured study program. The first funding period took effect in 2007 and lasted 2012 during which time IGradU was funded. Since October 2012, IGradU has been in its second funding period and this will continue until September 2017. For the further development of IGradU, we have defined a concept to help strengthen existing structures and to extend and develop new training opportunities for our PhD students.

Planned initiatives for the second funding period are:

- Guest Scientist Program
- Specific gender training programs and programs for clinician scientists (e.g. Else Kröner Science College and the Hertha Nathorff Program)
- A Junior Faculty
- Alumni Days
- Research Training Group in cooperation with Biberach University of Applied Science in the field of Pharmaceutical Biotechnology
- Projects to further strengthen international cooperation with Wuhan/China, Padua/Italy, Oulu/Finland, Chapel Hill/USA

We expect IGradU to train more than 200 students in 2014 in the fields of the life sciences at Ulm University and our partner institutions. In June 2013, the number of PhD students already totals 158 students.

Molecular Medicine – the challenge of the 21st Century

What is Molecular Medicine?

The discovery of microorganisms as the cause of infectious diseases and penicillin as an effective weapon to combat them revolutionized the field of medicine in the last century. Today, medicine is again going through a phase of radical change. It has become clear that the causes of many human diseases reside in the cells, namely, the genes and the proteins they produce. To broaden this knowledge and use it for the well-being of patients is the aim of the new interdisciplinary scientific subject of *Molecular Medicine*. Scientists working in the field of Molecular Medicine analyze the molecular mechanisms of the origin of diseases with the long-term goal of developing innovative diagnostic and therapeutic concepts and strategies. Their experimental findings are highly relevant for society since cardiovascular diseases, cancer and metabolic disorders, to name but a few, are deemed to be the major causes of death worldwide. Moreover, dementia, such as Alzheimer's Disease and other diseases linked to aging, will increase the costs for our health systems dramatically, especially in view of the dramatic demographic changes in population structure. Because of the significance of Molecular Medicine for modern society, the need to provide highly trained scientists is of immense importance.

PhD training in Molecular Medicine at Ulm University

Modern concepts in Molecular Medicine utilize interdisciplinary approaches that combine methods from the areas of molecular biology and genetics with those from informatics, mathematics, physics and engineering. In the past, PhD studies in Germany lasted many years and were marked by a strong dependency on one scientific supervisor. Today's training concepts are based on a well-structured and defined schedule with a broader approach to supervision. In October 2005, the Medical Faculty of Ulm University launched a three year doctoral training program entitled *International PhD Programme in Molecular Medicine*. The major aims of this program are:

- to improve graduate training by creating an active and motivating research environment
- to encourage graduates to perform independent scientific research by adopting a multi-level supervision and mentoring approach
- to steer graduate education by establishing a definitive program structure
- to advance graduate career opportunities in the academic world and in industry.

Our *International PhD Programme in Molecular Medicine* leads to the international degree of *Doctor of Philosophy* or the German degree of *Doctor rerum naturalium*. Each PhD student is assigned an interdisciplinary Thesis Advisory Committee (TAC) consisting of scientists from Ulm University and abroad to offer scientific advice from a wide range of perspectives. The graduates perform their research in the different institutes and departments of Ulm University, and come together for common training activities and to attend optional courses organized by the Graduate School. During the three year program, the students complete two intermediate examinations before their TAC to ensure appropriate progress in their scientific project.

Training in clinical research

To strengthen the training of medical students in clinical research, the Graduate School also runs the program *Experimental Medicine*. In order to participate in this program, students of human medicine are obliged to interrupt their course of studies for nine months to work full time in a laboratory. During this period, students are supported by a fellowship of the Medical Faculty or the Graduate School and receive €500 per month. Besides their lab work, doctoral students must attend seminars, prepare literature reports and give progress reports. It is expected that the quality of medical dissertations will increase significantly by means of this structured program designed for MD thesis work. At the same time, medical students are thus ideally prepared for PhD training.

Proven excellence

In 2006, the *Molecular Medicine* study programs at Ulm University were integrated into the newly founded *International Graduate School in Molecular Medicine Ulm*. One year later, the school's training concept received official recognition of its excellence through funding from the *Excellence Initiative* of the German federal and state governments amounting to €1 million per annum for a period of five years. We have been able to secure this funding up to the year 2017 with an additional €1.4 million per year. The *Excellence Initiative* was founded in 2005 to grant competitive awards to the best performing German universities and has subsequently proved to be greatly beneficial for the success of our Graduate School, the Medical Faculty and Ulm University. Our Bachelor, Master and PhD programs were accredited by the Central Evaluation and Accreditation Agency Hannover (*ZevA, Zentrale Evaluations- und Akkreditierungsagentur Hannover*). This is yet another endorsement of the high scientific and educational quality of the programs we offer.

Leitmotif of IGradU

It is the vision and declared objective of IGradU to train PhD and MD students in an international context and to the highest standards in order to strengthen the scientific performance of Ulm University in the field of Molecular Medicine and to further develop its national and international reputation.

Promotion of Junior Scientists

The Graduate School is committed to the promotion of junior scientists and offers a variety of compatible programs that serve to support and actively encourage these scientists.

The *International PhD Programme in Molecular Medicine*

Speaker: Prof. Dr. M. Kühl, Institute of Biochemistry and Molecular Biology; www.uni-ulm.de/mm

In October 2005, the Medical Faculty of Ulm University launched a three year doctoral training program entitled *International PhD Programme in Molecular Medicine*. This postgraduate course offers a structured doctorate in English. The course was accredited in March 2009. During their postgraduate course, doctoral candidates are monitored by the three members of a Thesis Advisory Committee (TAC). The TAC consists of scientists from Ulm University and abroad, and offers scientific advice from a wide range of perspectives. A member of the Junior Faculty can act as a fourth member of the TAC. This provides an opportunity for Junior Faculty members to gain

their first experience in advising PhD students. The graduates perform their research in the various institutes of Ulm University and come together for common training activities and courses organized by the Graduate School. Each student's coursework is calculated and accredited according to the European Credit Transfer and Accumulation System (ECTS). After having successfully defended their thesis, graduates opt to receive either the international academic title of PhD or the German academic title Dr. rer. nat. The opportunity for graduates to obtain the academic title of Dr. rer. nat. or PhD is a unique feature of the Medical Faculty and the Graduate School at Ulm University. This aspect will continue to make Ulm more attractive in the future and to strengthen its importance on an international level.

GRK 1041 Molecular Diabetology and Endocrinology in Medicine

Speaker: Prof. Dr. Bernhard O. Böhm, Department for Internal Medicine I; www. uni-ulm.de/grk1041

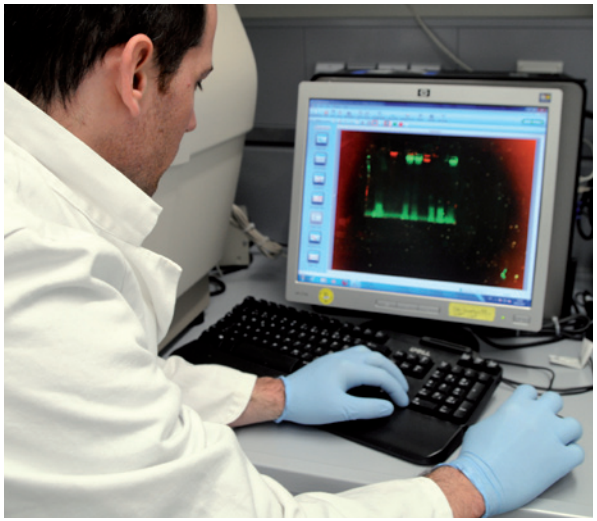
The German Research Foundation set up the Research Training Group of Molecular Diabetology and Endocrinology in Medicine at Ulm University in July 2004. GrK1041 is run under the direction of the International Graduate School in Molecular Medicine Ulm. The aim of this multi-faculty research/training program is to convey theoretical and practical knowledge in the field of molecular diabetology and endocrinology for both students of human medicine and qualified natural scientists. This research/training program represents an outstanding platform for further training in clinical/experimental medicine with the main emphasis on endocrinology, diabetology and metabolic diseases, while at the same time allowing students to conduct an individual research project under the guidance of a qualified person.

The research projects carried out in the research/training group 1041 include epidemiologically important and highly relevant problems in the fields of diabetology and endocrinology:

- Chronic hyperglycemia and its vascular complications
- Diabetes as an autoimmune disease
- Metabolic diseases and advanced aging
- Genetic basis of Type 1 and Type 2 diabetes and rare variants

"I am very grateful to the Graduate School in Ulm for giving me the opportunity to study there and for helping to shape my career. IGradU is unique in offering multi-member supervision and financial support as well as a congenial and collaborative atmosphere in which I could pursue my scientific and academic goals. I was impressed by the caliber and diversity of the students and faculty members. Now that I am a postdoc at the Center for Regenerative Medicine, MGH, Harvard University, my intention is to advance the understanding of lung stem cell biology and develop new therapies for lung disorders."

Tata Purushothama Rao has a postdoctoral position at Harvard Medical School in Boston. He graduated in spring 2011.



GRK 1789 Cellular and Molecular Mechanisms in Aging

Speaker: Prof. Dr. Hartmut Geiger, Department of Dermatology and Allergology

CEMMA is a research training program for graduate students with a focus on aging research. Demographic development has led to the prediction of a significant increase in age-associated diseases. Thus, age-associated diseases and their prevention will become one central aspect of medicine, business and social studies. An improved and in-depth knowledge of the basic molecular and cellular mechanisms of aging will allow the formulation of rational approaches and therapies that are ultimately aimed at achieving healthy aging. The research training program, Cellular and Molecular Mechanisms in Aging (CEMMA), will recruit and train the next generation of scientists in aging research and this will be a very critical task in light of anticipated demographic developments. The qualification program in the field of aging research includes specific teaching modules centered on model systems in aging research and on the theories of molecular aging. In addition, there are also modules analyzing aging with respect to general medicine and social studies. Research projects within CEMMA focus on aging and cancer, stem cells, DNA-repair, age-related changes in immune cells, and inflammation and neurodegenerative diseases.

Cooperative PhD Training Group – Pharmaceutical Biotechnology (PBT)

Speakers: Prof. Dr. Peter Dürre, Institute of Microbiology and Biotechnology;
Prof. Dr. Jürgen Hannemann, University of Applied Sciences in Biberach

The region around Ulm is the second largest pharmaceutical industrial area within Germany. Prominent members are Boehringer Ingelheim Pharma GmbH in Biberach, Rentschler Biotechnologie GmbH in Laupheim, and Ratiopharm/Teva Pharmaceutical Industries in Ulm. The field of Pharmaceutical Biotechnology is an interdisciplinary research topic both in natural science and in medicine and is therefore optimally suited for a cross-university cooperative PhD training group. The cooperative PhD training group includes research projects which cover the whole value added chain in the field of pharmaceutical biotechnology. Through a specifically designed program, PBT makes possible a highly specialized degree that allows intensive cooperation and an interlinking of the two universities in the field of the life sciences. The PhD-training group of Ulm/Biberach is one of eight cooperative PhD training groups being funded by the State of Baden-Württemberg. Scholarship holders are chosen based on a common selection procedure with the International Graduate School in Molecular Medicine Ulm and participate in its program. There are currently five PhD-students taking part in this cooperative PhD training course.

Study Programme Experimental Medicine

Speaker: Prof. Dr. Th. Wirth, Institute of Physiological Chemistry;
www.uni-ulm.de/med/med-molmed/promotionsprogramm-experimentelle-medizin.html

In 2005, in order to combat deficiencies in the supervision and quality of medical theses, the Medical Faculty implemented a structured training program entitled *Study Programme Experimental Medicine*, which was subsequently adopted by the Graduate School in 2009. The requirement for entry is an above-average intermediate examination (part one of the national medical licensing exam). Doctoral candidates must interrupt their studies in medicine for nine months in order to concentrate fully on their experimental work. The Medical Faculty and the Graduate School support this program with approximately 30 stipends yearly (€500 per month over ten months). Doctoral candidates submit reports on their research work in the program's seminars in addition to giving presentations of up-to-date scientific literature in a *Journal Club*. As an option, students may attend part of the training programs offered by the International Graduate School in Molecular Medicine Ulm.

The Junior Faculty at Ulm University

The Junior Faculty (JF) at IGradU is a newly established program for junior researchers working at Ulm University or Ulm University Medical Center. "Junior researchers" are those who have recently completed their (PhD) studies and are in the process of establishing their own junior research group and of becoming junior professors with the intention of eventually receiving habilitation.

The overall aim of the Junior Faculty is to promote the careers of junior scientists by means of an active interaction with the university, the faculty boards and society. Joining the Junior Faculty has the following benefits:

- The opportunity to conduct PhD-supervision as a member of a TAC (Thesis Advisory Committee)
- The support of supervisors
- Opportunities to receive financial support for further/continuing education
- Mentoring (gender programs, dyadic mentoring, peer-to-peer mentoring)

"Looking back, there are three aspects that supported my scientific development during my time in the PhD Programme. Firstly, the frequent progress reports and intermediate examinations were an excellent means of summarizing the data that I had collected and, from this perspective, they helped me to establish my future objectives and strategies. Secondly, the interdisciplinary nature of communicating with my PhD colleagues was a source of inspiration for me and helped me to overcome various obstacles in the methods that I used. And last but not least, the Program provided the funding to allow me to attend a number of international meetings that have given me invaluable insights into my own particular scientific field as well as being of great benefit to me in planning my future. I personally think that the International Graduate School in Molecular Medicine is an ideal place for PhD students who prefer to think originally and outside the box."
Manuel Lüdeke has a postdoctoral position in the Department of Urology at Ulm University. He graduated in Fall 2012.

To become a member of the Junior Faculty, a grant or secured extramural funding is required, e.g. BMF, DFG, EU-programs, programs provided by the Medical Faculty of Ulm University or such state programs as the Margarete von Wrangell Habilitation Program for women etc.

Activities of the Junior Faculty comprise continuing education courses according to the wishes of participants, e.g. lab management courses, support for pedagogic workshops (e.g. the teaching certificate awarded by the state of Baden-Württemberg), and participation in the annual science fairs and JF-meetings.

Else Kröner-Forschungskolleg Ulm – Support for the Scientific Career Development of Junior MDs (Clinician Scientist Program)

Since the spring of 2011, the Else-Kröner-Fresenius-Stiftung (Else Kröner-Fresenius Foundation) in cooperation with the International Graduate School in Molecular Medicine Ulm supports a research college on the topic of "Stem Cells, Aging and Malignant Transformation- from experimental model to clinical application" in the context of a structured educational program for outstanding junior doctors. This clinician scientist program comprises:

- Rotation positions (100% free from clinical obligations)
- Experimental work focused on stem cells, aging and malignant transformation
- Dedicated mentoring and training concepts
- Individualized support for a combined scientific and clinical career as a "physician-scientist"

The college is headed by Professor Dr. Stephan Stilgenbauer of the Department of Internal Medicine III, Prof. Dr. Hartmut Geiger of the Department of Dermatology and Allergology (in close cooperation with the Division of Research) and PD Dr. Dieter Brockmann of the Dean's Office of the Medical Faculty. The main aims of the program are training in and the development of experimental laboratory techniques and approaches, transfer of clinical problems into research concepts, development of a distinct research profile and group, and translation of research results into improved diagnostic procedures and therapies.

The Else Kröner-Fresenius Foundation is currently supporting five outstanding and talented junior doctors from Ulm University.

Hertha Nathorff Program of the Medical Faculty – New Impetus for Funding Junior Female Scientists in Biomedical Research

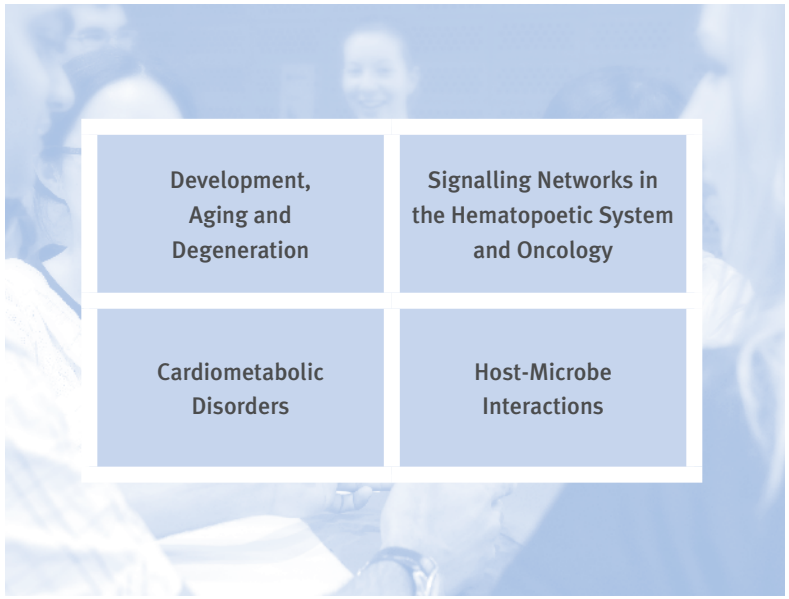
Since May 2013, the Medical Faculty of Ulm University in cooperation with the International Graduate School in Molecular Medicine Ulm supports five talented junior female doctors as part of the Hertha Nathorff funding program.
This program enables the scientific career development of junior female scientists who have gained a PhD but lack the qualification of a university lecturer. Due to a 100% release from clinical obligations, these junior female scientists can conduct research, preferably in the area of experimental investigations although this does not exclude clinical investigations. At the same time, medical technical assistants, who have secured part-time work arrangements on behalf of applicants who are pregnant or breastfeeding, can also be funded. Furthermore, finance is available for individual initiatives aimed at acquiring further qualifications, e.g. conference visits and network exchanges etc.
This structured program for the scientific and vocational qualification of junior female doctors is named after the Jewish doctor Hertha Nathorff (née Einstein) who was born in Laupheim and, prior to her emigration to the USA in 1938, had been persecuted by the National Socialists.
The criteria for receiving a grant consist of a completed doctorate and research on an original topic that is preferably integrated into the research focus of the medical university.

"I value my education at the International Graduate School in Molecular Medicine Ulm. This program provided me with experience, friendships and many opportunities that helped to build my confidence in finding and enjoying my work at HMS. It was a wonderful time in my life and one of the best experiences that I have ever had."
Aleksandra Tata has a postdoctoral position at the Harvard Medical School in Boston in the Department of Neurobiology. She graduated in Fall 2011.

The Graduate School's Research Training Groups

From the beginning of their PhD studies, doctoral students are organized and trained in smaller, thematically focused Research Training Groups in order to concentrate on specific research areas in Molecular Medicine. These Research Training Groups, based on the scientific topics particular to Ulm University, are defined by the Board of the Graduate School and implemented at the International Graduate School in Molecular Medicine Ulm. For each of the four Research Training Groups, two persons are responsible for organizing retreats, seminars and activities within their respective Training Group.

The four Research Training Groups are:



Graduates are actively integrated into the international scientific community.

Each year the Graduate School organizes international meetings where students deliver poster presentations and talks while at the same time having the opportunity to seek advice for their work from professional international scientists. We also hold scientific retreats where graduates can exchange ideas among themselves and with senior scientists within a relaxed atmosphere. Furthermore, our PhD students have the chance to attend meetings and conferences abroad with the financial support of travel grants from the Graduate School.

In order to prepare our doctoral candidates for the job market, we offer a variety of key competency seminars in such subjects as project management, bioethics, and patent law. In addition, we regularly organize career workshops and excursions to pharmaceutical companies.

"The Program offers students a varied range of scientific education that accompanies their own laboratory studies and this is an excellent way of gaining insight into other research areas as well as broadening one's own horizons. I personally appreciated the generous financial support to attend various international conferences and also the numerous social events organized by the Graduate School. In addition, the professional training courses in such areas as project management were exceedingly useful in preparing me for a career in industry. I am currently working in the Development Department at Rentschler Biotechnology that focuses on downstream processing of recombinant proteins."
Matthias Kron is now working at the Zeiss GmbH in Oberkochen. He studied at the Department of Gene Therapy and graduated in Spring 2012.

Alumni

The Graduate School's alumni reflect the excellence and caliber of its students. Our alumni are part of a broad and diverse network that includes students from all disciplines and from all over the world.

Our alumni are invited to attend science meetings and seminars organized by the Graduate School. It has always been our aim to bring together former and current students in order to promote an enthusiastic doctoral culture at the Graduate School and, to achieve this, our first IGradU Alumni Meeting was held on July 3, 2013. At these meetings, our alumni give a presentation on their current occupation and visit their former labs. There is plenty of time to meet up and chat with old colleagues and new students either at the university or during the summer party in the afternoon.

Careers

Our Alumni work in a variety of sectors. Below is a sample list of places where our former students have found a new occupation:

- Cleveland Clinic, Department of Pathobiology, Cleveland, Ohio, USA
- Harvard Medical School, Immune Disease Institute and Children's Hospital Boston, Boston, USA
- Harvard Medical School, Regenerative Medicine Section of Harvard Stem Cell Institute, Boston, USA
- McGill University, Department of Biochemistry, Montreal, Quebec, Canada
- Stanford University School of Medicine, Psychiatry & Behavioral Science, Stanford, USA
- Stanford University School of Medicine, Department of Biochemistry, Stanford, USA
- University of Liège, Coma Science Group, Cyclotron Research Centre, Liège, Belgium
- University of Lund, Lund Center for Stem Cell Biology and Cell Therapy, Lund, Sweden
- Deutsches Krebsforschungszentrum DKFZ, Heidelberg, Germany
- ETH Zürich, Institut für Pharmazeutische Wissenschaften, Zürich, Switzerland
- Baltech AG, Hallbergmoos/Munich
- Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany
- Roche Deutschland Holding GmbH, Penzberg, Germany

Our free services include:

- Invitation to events at the Graduate School and Ulm University
- Use of the Career Service of Ulm University – free of charge for graduates up to two years after the completion of their studies
- Alumni email address for life

The Graduate School's Gender Equality Programs

At present, 67% of our doctoral candidates are female. To maintain this standard, special initiatives have been adopted for the benefit of female doctoral students, single parent doctoral students, doctoral students with children, and doctoral students during pregnancy.

Childcare Programs

In order to enable PhD students with children to pursue their work, the Graduate School offers various childcare programs. Our childcare programs provide financial support for childcare during meetings and conferences, stays abroad and for childcare services outside the regular business hours of daycare centers. We can also offer practical help in finding the right daycare center.

Technical Assistance

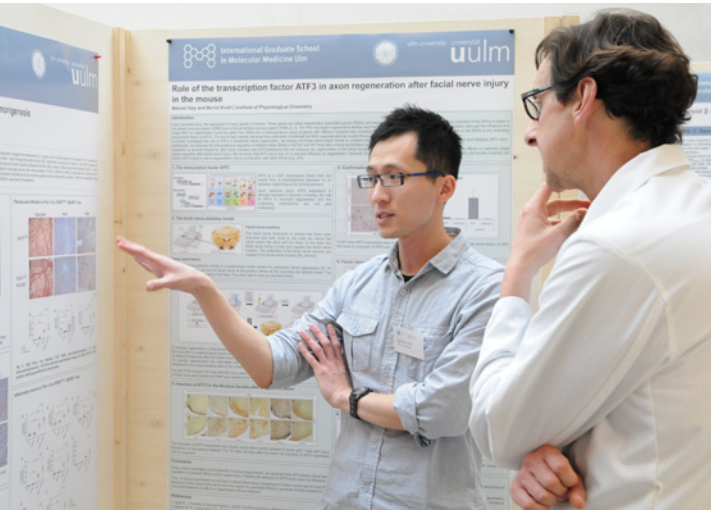
The Graduate School finances the employment of technical assistants to conduct experiments for students during pregnancy and maternity leave as regulated by law. This enables female students to continue their PhD work during and after pregnancy without the loss of valuable time. This financing of technical assistants by the Graduate School is possible for a maximum period of one year

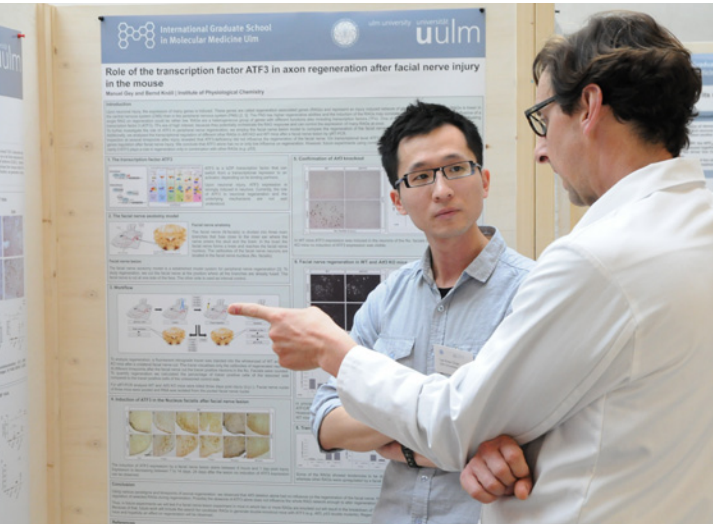
Female Mentoring

A Mentoring and Training program *(MuT)* enables our highly qualified female scientists to become acquainted with the ways and means of successfully tapping their career potential and exploring the opportunities available to them. It is there to support their personal development and assist in planning their careers.

Scholarships

Many institutions offer a varietyof scholarships for female students and those with children. The Graduate School provides information regarding the possibilities of financial support and assists students in receiving these scholarships in order to alleviate the conflicting demands of studying and family life. These numerous female scholarships have helped to increase the number of future female professors. To contribute to this development, the Graduate School provides re-entry fellowships for doctoral students who may have had to interrupt their work due to maternity leave.





The Graduate School's Mentoring Programs

Scientific Mentoring

The training of outstanding researchers is the key task of the International Graduate School in Molecular Medicine Ulm. As mentioned before, our major aims in this respect are:

- Cutting-edge research training of junior scientists
- Scientific independence and the self-responsibility of PhD students
- Improvement of employability through training in key competencies.

Each doctoral student is supervised by a Thesis Advisory Committee (TAC) which is involved in ensuring interdisciplinary training and mentoring in research.
Each TAC consists of three members:

- The group leader of the laboratory where the thesis work is performed
- A scientist from another institute of Ulm University
- An external reviewer, either from industry or from a research institute

Furthermore, a member of the School's Junior Faculty (see page 15) can be integrated into the TAC as an additional member.

The TAC supervises PhD students in their daily laboratory work to help them with formal or technical problems, and to evaluate oral examinations and their written dissertation. This multiple supervision approach supports the independence of our PhD students as junior researchers.

Social Mentoring

Apart from their scientific training, our doctoral students are offered mentoring on different levels to facilitate their stay in Ulm and to help them concentrate fully on their academic performance in their chosen field of scientific research. Our Coordination Office assists graduates with the organization of their studies within the *International PhD Programme in Molecular Medicine*, and of their study life in general. This office is the first point of contact and assists applicants before they are even accepted into the program, as well as throughout the period of their PhD studies up to their final graduation. It also advises on issues concerning visas, contracts, work permits, accommodation and health insurance etc.

Each year the graduates elect three students to represent their interests on the various boards and committees of the Graduate School and to act as their official contact concerning student issues.

M4M – Mentorship for Molecular Medicine – is a social mentoring program that brings together doctoral students and senior mentors living in Ulm for mutual exchange and support. The idea behind the program is to give our international students a positive impression of everyday German culture through a variety of social activities such as excursions, intercultural workshops and themed evenings. This personal contact and individual support gives students the opportunity to participate more easily in German society. Senior mentors support doctoral students even before their arrival in Ulm and help them to find their way during their first days and weeks in a new country. Regular meetings and personal contact between PhD students and senior mentors help to develop an atmosphere of confidence and familiarity.

Female Mentoring

The Graduate School supports participation in the MuT-Program, (Mentoring and Training Program) for junior female academics. MuT enables highly qualified female scientists to become acquainted with the ways and means of successfully tapping their career potential and of exploring the opportunities available to them. It is designed to support their personal development and assist in planning their careers.

Mentorship for
Molecular Medicine
PhD Students

Additional Benefits for Students

Our program offers additional benefits for students. The most frequently requested programs include:

Mobility Program

In order to enhance the integration of our students into the international scientific community, the Graduate School offers a mobility program awarding financial support to students wishing to participate in meetings and to engage in practical training. Students can obtain funding for short visits to national and international conferences and for long-term stays at laboratories lasting up to several months. The Mobility Program also covers the Joint PhD program offered with Padua and Oulu.

Doctoral Student Award

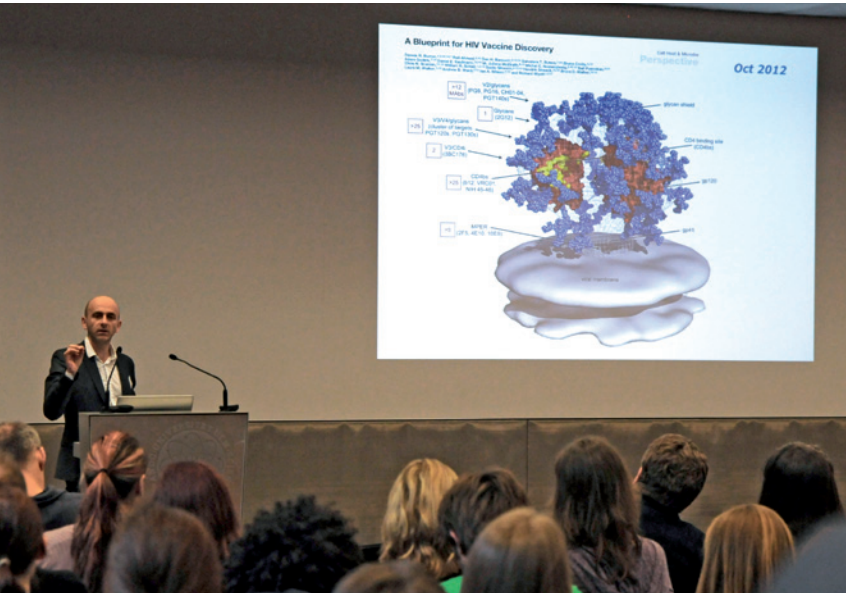
To motivate doctoral students and to honor extraordinary achievements, the Doctoral Student Award is presented once a year by the Graduate School. Awards are conferred for exceptional research, either as documented in publications or as talks given at international scientific conferences, and for the development and implementation of innovative novel methods. Interdisciplinary projects are given preferential consideration. Students are free to use this award for any purpose that helps to promote their career in the field of science.

Postdoc Fellowships and Programs

The Graduate School provides postdoctoral fellowships for a period of three to six months for outstanding doctoral students planning to apply for a postdoctoral academic position abroad. This is an important benefit since applications for postdoctoral fellowships are normally evaluated over a period of up to six months. Key competency courses also offer assistance in writing grant applications or managing the laboratory, e.g. EMBO courses, and have proved useful for those beginning a new postdoctoral career.

Social Activities

The Graduate School organizes regular social activities, e.g. summer and Christmas parties or sport activities (basketball, soccer and table tennis games etc.), to create a friendly atmosphere and to foster a team spirit between doctoral students and supervisors. Each year many PhD-students and their supervisors take part in the biggest marathon in Ulm known as the “Einstein-Marathon.” In 2012, a small team also participated in the “Dragon Boat” run.



The Graduate School's International Networking

Scientific excellence not only depends on the outstanding performance of talented young researchers but also on the close cooperation with a worldwide network of renowned partner institutions. Consequently, the Graduate School is continually developing and maintaining scientific and research relations between Ulm and other higher educational and research institutes worldwide. Currently, the Graduate School closely cooperates with several international institutions, such as: the Tongji Medical School in Wuhan, China; Medical School of Southeast University in Nanjing, China; the University of North Carolina at Chapel Hill, USA; the University of Padua in Italy; the Universities of Oxford, Cambridge and London; MRC Harwell, UK; BioCenter Oulu, Finland; Bart's and Queen Mary's College, London; the Campus Bio-Medico University, Rome; and the Universitat Autònoma de Barcelona.

One of the central elements of our strategy in developing the international character of the School is the annual spring and fall meetings attended by speakers whose reputation is recognized internationally. Another important aspect is the promotion of international cooperation by means of various exchange programs and double-degree agreements. In 2011, the Graduate School and the Universities of Oxford, Cambridge and London, together with MRC Harwell, agreed to collaborate on the OXION Ion Channels and Disease Initiative with the aim of promoting joint training activities for PhD students. A joint PhD program with the University of Padua in Italy has also been established. A second joint PhD program with the BioCenter Oulu in Finland will be initiated in 2013 at a launch meeting in Oulu involving all relevant participants.

Moreover, in 2010, the Graduate School was able to award a visiting professorship to Professor Hiromitsu Nakauchi, an internationally renowned scientist in the field of stem cell research, from the University of Tokyo, Japan. He will be a Guest Professor until the end of September 2013 and already had a Junior-Research Group in Ulm. The success of this venture with Professor Nakauchi led to the idea of extending our international network and of launching our Guest Professor and Guest Scientist Programs.

Guest Professor and Guest Scientist Programs

The Guest Professor Program consists of two modules: (1) the first module is funded annually to the amount of €50,000 by the state of Baden-Württemberg with the aim of attracting the best and most renowned experts to Ulm. The Guest Professorship has been awarded for five years. This program has included the founding of a Junior Research Group in Ulm. The Guest Professor is expected to visit Ulm frequently and to contribute to the research and teaching at the Graduate School; (2) the second module is financed by IGradU and guest professors visit Ulm University for a period of two to four weeks.The aim of the Guest Scientist Program is to invite junior researchers from abroad for a period of 10 to 14 days to visit the institutes and departments of Ulm University in order to establish and develop closer cooperation. We plan to invite at least five guests each year. All visiting researchers are expected to work in the labs, give presentations and offer courses to our students.

Since its foundation in 2006, the Graduate School has worked in close cooperation with the following partner institutions:

Padua

In 2010, a joint PhD program with the University of Padua in Italy was set up. Doctoral students taking part in this joint program are supervised by Thesis Advisory Committees consisting of scientists from Ulm and Padua. The students spend a part of their studies in both Germany and Italy to achieve a double diploma that is recognized by both universities.

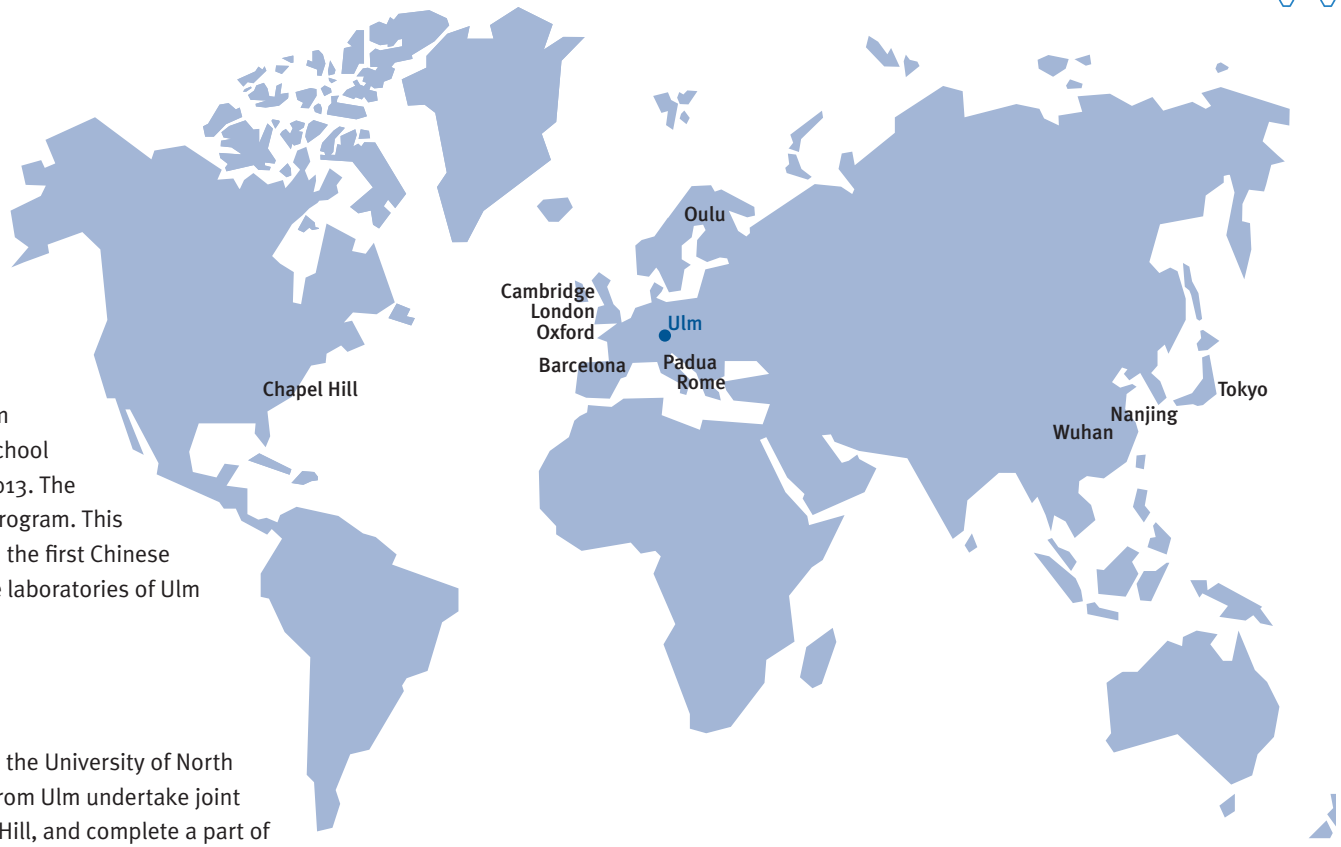
Oulu

The Biocenter Oulu in Finland represents our most longstanding international relationship and regularly invites students from the Graduate School to summer schools in Finland. Likewise, the Graduate School shares the insights of its research in Germany to graduates in Finland by inviting them to attend meetings and visit our laboratories. Students in Germany and Finland also have the possibility of participating in practical training courses at either institution. Just recently, a range of joint PhD projects was agreed upon. A meeting to launch these co-tutelage programs offered by the Universities of Oulu and Ulm will take place in Ulm in September 2013.

Wuhan

Each year the Graduate School organizes summer schools abroad with the ultimate goal of presenting Ulm-based research in order to increase the international visibility of the school and to recruit highly qualified PhD candidates. The first Summer School to be held at Houazhong University of Science and Technology/Tongji Medical College in Wuhan, China, took place in August 2007. The chosen topic of the seventh Summer School in Wuhan in 2013 is *Lung Development and Disorders: From Molecules to Disease*.

In June 2013, a new cooperation contract between Ulm University and Tongji Medical College was signed. The aim is to further strengthen the scientific cooperation between scientists and students, especially in connection with the International Graduate School.



Nanjing, China

A delegation from the Medical Faculty of Ulm University and IGradU visited the Medical School of Southeast University in Nanjing in May 2013. The aim was to establish a scientific exchange program. This program will begin in September 2013 when the first Chinese students will start their practical work in the laboratories of Ulm University.

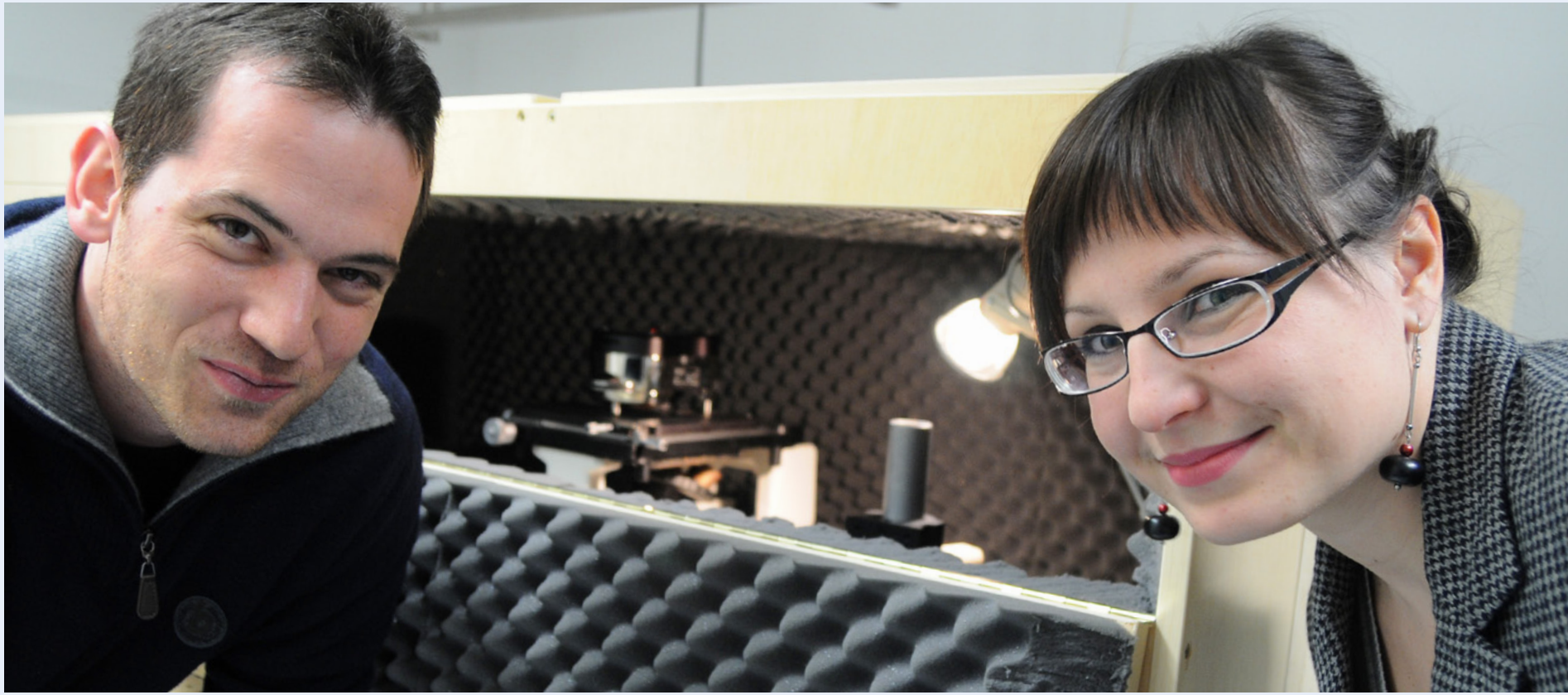
Chapel Hill

The Graduate School has a partnership with the University of North Carolina at Chapel Hill, USA. PhD students from Ulm undertake joint scientific projects between Ulm and Chapel Hill, and complete a part of their studies at Chapel Hill.

Universities of Oxford, Cambridge and London, and MRC Harwell

Collaboration involving joint training activities for PhD students between the Graduate School and the OXION Ion Channels and Disease Initiative at the Universities of Oxford, Cambridge and London, and MRC Harwell, began in 2011. Activities include joint lab courses and lab visits to learn novel techniques and to foster joint projects. In addition, students in both Germany and the UK are able to participate in retreats and meetings.

A tri-national PhD Programme in Endocrinology has been established in collaboration with Bart's and Queen Mary's College (London), the Università Campus Bio-Medico di Roma (Rome) and the Universitat Autònoma de Barcelona (Barcelona).



Participating Institutes and Departments of Ulm University

The Graduate School collaborates with 12 institutes, 8 clinical-theoretical institutes and 15 medical departments and institutes of Ulm University. The institutes and departments are described on the following pages.

Institutes

Clinical-theoretical Institutes

Medical Departments and Institutes

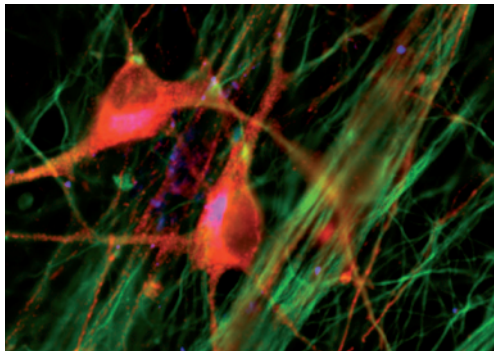
The Team:
Head of Institute: T. M. Böckers
Professor: N. Golenhofen
Group Leaders/Postdocs: St. Liebau (GL), B. Bartelt-Kirbach, A. Böckers, J. Bockmann, U. Fassnacht, Ch. Pröpper, M. Schmeisser, M. Schön,
PhD Students: N. Kanwal, A.L. Janssen, M. Schmeisser, P. Udvardi, S. Halbedl, M. Klingenstein, L. Linta, St. Pfänder, St. Raab, M. Bertolessi
Study Programme Experimental Medicine Student: T. Weiss
Additional Members of Thesis Advisory Committees: E. Gundelfinger (Magdeburg), A. Ludolph (Ulm), W. Robberecht (Leuven), M. Kreutz (Magdeburg), J. Kremerskothen (Münster), HJ Kreienkamp (Hamburg), C. Sala (Mailand), A. Storch (Dresden), F. Edenhofer (Würzburg), H. Lerche (Tübingen), C. Kubisch (Ulm), M. Karsak (Ulm), J. Fehling (Ulm)

Institute of Anatomy and Cell Biology

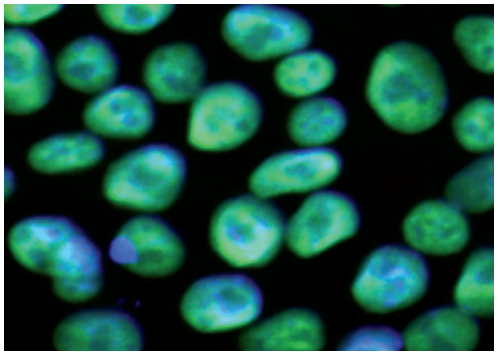
Stem Cell Biology and Proteins of Synaptic Contacts: Functional Characterization of iPS Cells and Synapses in the Context of Neuropsychiatric Diseases

Head: Tobias M. Böckers

Stem cells are considered a very valuable tool for dissecting developmental aspects and investigating pathomechanisms, and can be used for cell-based therapies. Stem cells are characterized by their abilities of symmetrical cell division and their potential to give rise to different cells in organisms. Pluripotent, embryonic stem cells of the blastocyst's inner cell mass can even generate all the cells of an organism. Since the first generation of the so-called induced pluripotent stem cells (hiPS) by Yamanaka, pluripotent stem cells can be reprogrammed from several kinds of somatic cells. This offers the chance of investigating stem cells and their differentiated progeny in disease-specific settings. In this respect, we generated iPS cells from patients with defined genetic defects that either lead to developmental defects in the central nervous system or cause neurodegeneration. In our



Neuron derived from a human induced pluripotent stem cell (iPS-cell). iPS cells were generated from hair keratinocytes. The cell is immunostained for thyrosin hydroxylase (red), tubulin (magenta), the synaptic protein synaptophysin (green) and nuclei are labeled by DAPI (blue). (Photo by Stefan Liebau)



Plucked Hair Keratinocyte-derived induced human pluripotent stem cells expressing the stem cell marker Oct4 (green). Nuclei are stained with DAPI (blue). (Photo by Stefan Liebau)

studies including stem cell biology, we are investigating human and patient-specific iPS cells of several neurological disorders such as ProSAP/SHANK-related autism spectrum disorders (Leonhard Linta), LRRK2-related M. Parkinson (Stefanie Raab), developmental defects of the nervous system related to dysfunctional translation initiation (Maira Bertolessi), developmental disorders related to mutations in an RNA Polymerase (Moritz Klingenstein) as well as neurodegeneration (ALS).

In addition, we concentrate on glutamatergic synapses of the central nervous system that are specific cellular junctions characterized by an electron-dense web underneath the postsynaptic membrane known as the postsynaptic density (PSD). PSDs are composed of a dense network of several hundred different proteins that creates a macromolecular complex serving a wide range of different functions. Prominent PSD proteins, such as members of the MaGuk or ProSAP/Shank family, build up a dense scaffold that creates an interface between clustered membrane-bound receptors, cell adhesion molecules and the actin-based cytoskeleton. The synaptic rearrangement (structural plasticity) is a rapid process and is believed to underlie learning and memory formation. The characterization of synapse/PSD proteins is especially important in light of recent data suggesting that several mental disorders have their molecular defect at the synapse/PSD level. Anna-Lena Jansen, Michael Schmeisser and Noreen Kanwal's projects concentrate on the role of ProSAP/Shank molecules and interacting proteins within the PSD. The self-assembly of these proteins is zinc dependent and zinc seems to play a key role in the local rearrangement of structural PSD components. This is followed up by Stefanie Pfänder in human neurons derived from induced pluripotent stem cells (iPS). In addition, we are working on drugs influencing synapse number and maturity (Patrick Udvardi) as well as on neuronal heat shock protein expression.

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Selected Publications:

- *Schmeisser MJ, Baumann B, Johannsen S, Vindedal GM, Jensen V, Hvalby Ø, Sprengel R, Seither J, Lattke M, Oswald F, Boeckers TM and Wirth T (2012): IKK/NF-κB signaling dynamically regulates synapse formation and spine maturation via Igf2/Igf2R. J Neurosci 32(16):5688-5703.*
- *Leblond CS, Heinrich J, Delorme R, Proepper C, Betancur C, Huguet G, Konyukh M, Chaste P, Ey E, Rastam M, Anckarsäter H, Nygren G, Ståhlberg O, Gillberg IC, Melke J, Toro R, Regnault B, Fauchereau F, Mercati O, Lemière N, Skuse D, Poot M, Holt R, Curran S, Collier D, Bolton P, Chiocchetti A, Klauck SM, Poustka F, Freitag CM, Bacchelli E, Minopoli F, Maestrini E, Mazzone L, Ruta L, Sousa I, Vicente A, Oliveira G, Pinto D, Scherer S, Zelenika D, Delepine M, Lathrop M, Guinchat V, Devillard F, Assouline B, Mouren MC, Leboyer M, Gillberg C, Boeckers TM and Bourgeron T (2012): Genetic and functional analyses of SHANK2 mutations provide evidence for a multiple hit model of autism spectrum disorders. Plos Genetics 8, 2; e1002521.*
- *Schmeisser MJ, Ey E, Wegener S, Bockmann J, Stempel AV, Kuebler A, Janssen AL, Udvardi PT, Shiban E, Spilker C, Balschun D, Skryabin BV, Dieck St, Smalla KH, Montag D, Leblond CS, Faure P, Torquet N, Le Sourd AM, Toro R, Grabrucker AM, Shoichet SA, Schmitz D, Kreutz MR, Bourgeron T, Gundelfinger ED, Boeckers TM (2012): Autistic-like behaviours and hyperactivity in mice lacking ProSAP1/Shank2. Nature, 486: 256-260.*
- *Linta L, Stockmann M, Kleinhans KN, Böckers A, Storch A, Zaehres H, Lin Q, Barbi G, Böckers TM, Kleger A, Liebau S (2012): Rat embryonic fibroblasts improve reprogramming of human keratinocytes into induced pluripotent stem cells. Stem Cells Dev. 10;21(6):965-76 (2012).*
- *Stockmann M, Linta L, Föhr KJ, Boeckers A, Ludolph AC, Kuh GF, Udvardi PT, Proepper C, Storch A, Kleger A, Liebau S, Boeckers TM (2011): Developmental and Functional Nature of Human iPSC Derived Motoneurons. Stem Cell Rev.*
- *Proepper C, Steinestel K, Schmeisser M, Heinrich J, Langer J, Bockmann J, Liebau S and Boeckers TM (2011): Heterogenous nuclear ribonucleoprotein K (hnRNPK) binds Abi-1 at synaptic sites. Plos One 6,(11), e27045.*

Institute of Biophysics

Molecular Mechanisms of Transcription and Gene Regulation in Eukaryotes

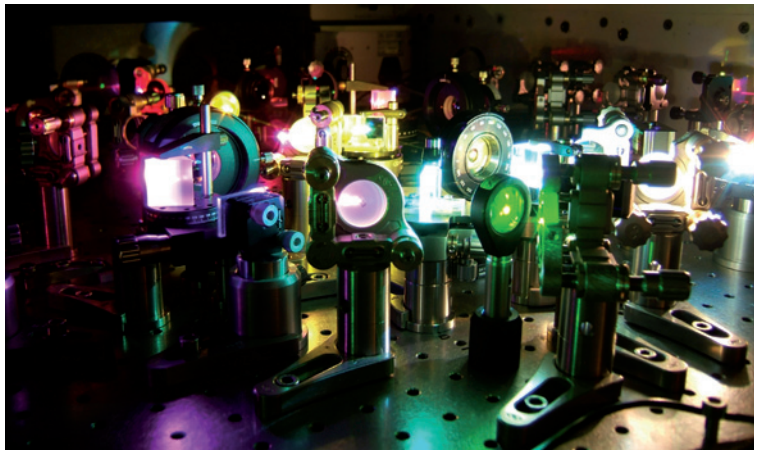
Head: Jens Michaelis

Gene expression in eukaryotes is a complicated and highly regulated dynamical process. By looking at the key steps of this process in real time and at the level of single molecules, we are able to obtain mechanistic insight. Using single-molecule fluorescence resonance energy transfer (smFRET) and related techniques, we were able to obtain structural and dynamic information about one of the key enzymes of gene expression, RNA polymerase II. During this process we had to improve the methodology for such measurements in order to gain access to the quantitative information required for building models elucidating structure-function relationships. To achieve this, we developed the so-called Nano Positioning System (NPS) and applied it to open questions in the areas of transcription initiation, transcription elongation and, most recently, nucleosome remodeling.

The Team:
Head of Institute: J. Michaelis
Group Leaders/Postdocs: C. Röcker, W. Kügel, S. Ude
PhD Students: M. Budde, T. Dörfler, M. Holzner, K. Krzemien, J. Nagy, C. Osseforth, K. Paul, J. Reichel, M. Schwarz
Study Programme Experimental Medicine Student: K. Krzemien
Additional Members of Thesis Advisory Committees: T. Weil (Ulm), M. Otto (Ulm), R. Beckmann (Munich)

Rather than just looking at the structure and dynamics of single complexes, the intra cellular movement of complexes is also of interest for understanding the spatio-temporal regulation. We perform such experiments using single-molecule tracking techniques, thereby focusing on specific aspects, such as the position and mobility of certain factors during the cell cycle. By attaching fluorescent particles or even single dye molecules to such complexes, we can obtain position information on length scales down to a few nanometers in real time.

With the growing amount of information about gene expression available, the questions that are developing have also become more and more complex and, as a result, there is often the wish to study ever larger complexes and transient architectures. For this reason, we are also developing super-resolution optical fluorescence microscopy techniques in which the resolution limit of optical microscopy is overcome by turning fluorescent molecules on and off. By using these techniques one can bridge the length scale from that of single molecules to standard microscopy approaches covering the cellular level. Thus, we now have the complete toolbox for answering mechanistic questions regarding gene expressions in vitro as well as in living cells.



Setup of a super-resolution optical fluorescence microscope based on the principle of stimulated emission depletion (STED). The microscope was developed in the institute and now allows for the super-resolution imaging of two colors simultaneously with a resolution of about 30nm in x and y and about 80 nm in z.

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Selected Publications:

- *Torrano AA, Blechinger J, Osseforth C, Argyo C, Reller A, Bein T, Michaelis J, Bräuchle C (2013): "A fast analysis method to quantify nanoparticle uptake on a single cell level," Nanomedicine, doi: 10.2217/nnm.12.178.*
- *Bönisch C, Schneider K, Pünzeler S, Wiedemann S, Bielmeier C, Bocola M, Eberl C, Kuegel W, Neumann J, Kremmer E, Leonhardt H, Mann M, Michaelis J, Schermelleh L, Hake S (2013): "H2A.Z.2.2 is an alternatively spliced histone H2A.Z variant that causes severe nucleosome destabilization," Nucleic Acids Research, 40, 5951-5964.*
- *Treutlein B, Muschielok A, Andrecka J, Jawhari A, Buchen C, Kostrewa D, Cramer P, Michaelis J (2012): Dynamic architecture of the RNA polymerase II open promoter complex, Molecular Cell 46, 136-146.*
- *Grohmann D, Nagy J, Chakraborty A, Klose D, Fielden D, Ebright RH, Michaelis J, Werner F (2011): "The initiation factor TFE and the elongation factor Spt4/5 compete for binding to the RNAP clamp during transcription initiation and elongation," Molecular Cell 43, 263-274.*
- *Moffitt J, Osseforth C, Michaelis J (2011): "Time gating improves the spatial resolution of STED microscopy", Optics Express 19, 4242-4254.*
- *Muschielok A, Andrecka J, Brückner F, Jawhari A, Cramer P, Michaelis J (2008): "A Nanopositioning system for macromolecular structural analysis," Nature Methods 5, 965-971.*

The Team:
Head of Institute: K. Otte
Professors: B. Burghardt, S. Gaisser, H. Frühwirth, H. Grammel, J. Hannemann, F. Hesse, H. Kiefer, C. Mavoungou, K. Otte, A. Schafmeister, C. Schips, U. Traub-Eberhard, K. Zimmermann
Head of Laboratory: R. Handrick
PhD Students: S. Fischer, J. Lauber, A. Paul, M. Stützle, A. Wagner, F. Bickel, O.O. Oyetayo, K. Schwab, F. Stiefel, Y. Zang
Students Study Programme Experimental Medicine: S. Fischer, M. Stützle, F. Stiefel
Additional Members of Thesis Advisory Committees: G. Grillari (Vienna), M. Fändrich (Ulm), T. Noll (Bielefeld)

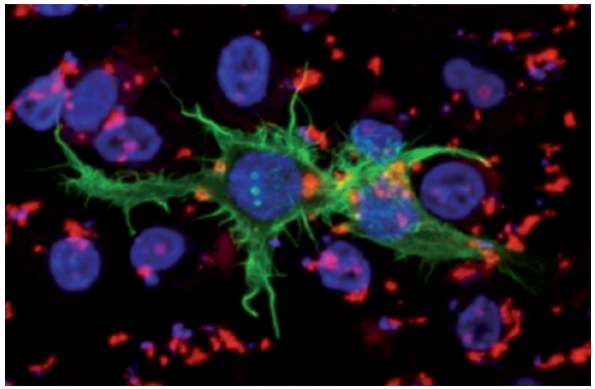
Institute of Applied Biotechnology

Pharmaceutical and Industrial Biotechnology

Head: Kerstin Otte

Research and development at our laboratories are focused on the production processes for products of pharmaceutical and industrial biotechnology. The production process includes cell line establishment, fermentation of eukaryotic and prokaryotic cells, protein purification and protein analytics. The focus of our various research projects ranges from upstream and cell line development for biopharmaceutical production to crystallization of biopharmaceutical proteins and protein aggregation in the production process. Industrial biotechnology deals with synthetic multienzyme systems for multiple step reactions.

Biopharmaceuticals are medicines mainly produced by animal cells. Among conventional cell and process engineering to improve productivity, the potential of microRNAs is still unexplored. MicroRNAs are short single-stranded and evolutionary conserved RNA molecules that play a central role in many cellular processes. They influence gene expression by interaction with mRNAs and are able to modify cellular pathways. Two PhD projects focus on the use of microRNAs in the production process for biopharmaceuticals. The PhD project of Fabian Stiefel aims at identifying microRNAs, which are relevant



Confocal laser scanning micrographs illustrating the cellular localization of fluorescent labeled small double-stranded RNA (red) in CHO DG44 suspension cells transiently transfected with a cationic polymer. A Lifeact-GFP encoding plasmid was co-transfected to indicate the actin cytoskeleton (green). Cell nuclei were counterstained with DAPI (blue). Images were obtained at 63x magnification.

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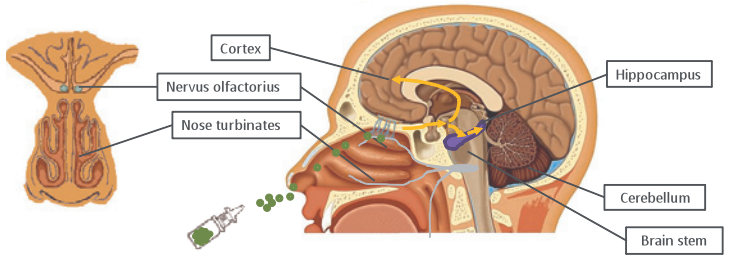
for the production process in production cell lines, and at investigating their potential for process control. Simon Fischer focuses in his PhD project on the modification of microRNAs in CHO cells for the optimization of the production process for biopharmaceutials. A large scale microRNA screen will identify a number of targets to improve production in order to avoid translational burden of the cell (Fig. 1).

The development and testing of the intranasal application of CNS active antibody formats is the PhD project of Martina Stützle (Fig. 2). Therapeutic antibodies are important for many indication areas. Antibodies are usually not able to pass the blood-brain barrier although small peptides can be delivered by intranasal application. In this project, different antibody formats are developed and delivered by means of aerosols, and are tested for potency, safety and quality.

The PhD project of Fabian Bickel aims at understanding mAb aggregation mechanisms and the systematic development of additives to avoid aggregation. Certain substances like osmolytes are known to protect organisms against different kinds of stress such as temperature, pH shifts, high salt concentrations or high pressure. Based on the properties of these compounds, new molecules will be developed with the aid of chemometrics.



Intranasal application of a CNS-active antibody aerosol

Selected Publications:

- *Park SH, Das BB, Casagrande F, Tian Y, Nothnagel HJ, Chu M, Kiefer H, Maier K, De Angelis AA, Marassi FM, Opella SJ (2012): Structure of the chemokine receptor CXCR1 in phospholipid bilayers. Nature 2012 Nov 29;491(7426):779-83. doi: 10.1038/nature11580. Epub*
- *Boubeva R, Reichert C, Handrick R, Müller C, Hannemann J and Borchard G (2012): New Expression Method and Characterization of Recombinant Human Granulocyte Colony Stimulating Factor in a Stable Protein Formulation. CHIMIA. Vol. 66, (5): 281-285.*
- *Carius L, Hädicke O, Grammel H (2012): Stepwise reduction of the culture redox potential allows the analysis of microaerobic metabolism and photosynthetic membrane synthesis in Rhodospirillum rubrum. Biotechnol Bioeng. doi: 10.1002/bit.24734.*
- *Thaisuchat H, Baumann M, Pontiller J, Hesse F, Ernst W (2011): Identification of a novel temperature sensitive promoter in CHO cells. BMC Biotechnol. 11(1):51. doi: 10.1186/1472-6750-11-51.*
- *Zang Y, Kammerer B, Eisenkolb M, Lohr K, Kiefer H (2011): Towards protein crystallization as a process step in downstream processing of therapeutic antibodies: screening and optimization at microbatch scale. PLoS One. 6(9):e25282. Epub 2011 Sep 22.*
- *Schindowski K, von Bohlen, Halbach O, Strelau J, Ridder DA, Herrmann O, Schober A, Schwaninger M, Unsicker K (2011): Regulation of GDF-15, a distant TGF-β superfamily member, in a mouse model of cerebral ischemia. Cell Tissue Res. 343(2):399-409.*

Institute of General Physiology

Cellular and Molecular Lung Physiology

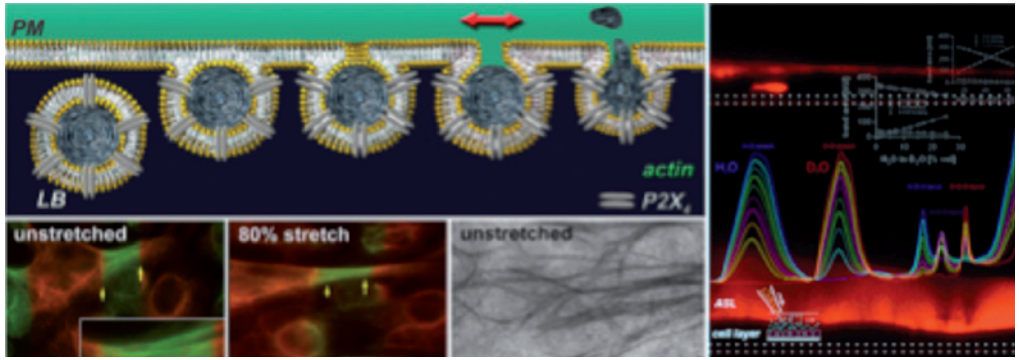
Head: Paul Dietl

Understanding the molecular physiology of the lung is essential for understanding disease and developing new treatment strategies. Within the institute, we focus on fundamental cellular mechanisms that are crucial for lung function. Employing a range of high-resolution imaging techniques compared with molecular biology and biochemistry, we study surfactant secretion, epithelial fluid transport and mechanical forces affecting cellular function.

The Team:
Head of Institute/Professor: P. Dietl
Group Leaders/Postdocs: M. Frick, E. Felder, O. Wittekindt, P. Miklavc
PhD Students: K. Thompson, K. Ehinger, K. Neuland
Additional Members of Thesis Advisory Committees: R. Tarran (Chapel Hill), P. Gierschik (Ulm)

a) Exocytosis and secretion (Dr. Frick/Dr. Miklavc)
Surfactant, a lipid-rich and lipoprotein-like substance, is the secretory product of type II pneumocytes stored in vesicles called lamellar bodies (LBs). Surfactant secretion is essential for life and occurs through regulated exocytosis of LBs. In addition, LB exocytosis is a good model for studying the exocytotic process using life cell imaging techniques.

We have recently developed several new microscopy techniques to study essential steps during this process. Combining live cell imaging techniques (darkfield microscopy, fluorescence microscopy, LSM, FRET, FRAP, TIRF etc.) with molecular and biochemical tools, we aim to elucidate cellular and molecular



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mechanisms of hemifusion, fusion pore formation, fusion pore expansion and content release. These experiments aim to improve mechanistic insights into membrane merger, lipid and content mixing, signaling and trafficking, and to understand basic pathogenic mechanisms of pulmonary disease.

b) Transepithelial transport (Dr. Wittekindt)
Transepithelial transport along the conducting and respiratory epithelium is essential for lung function. Its deregulation is a major pathomechanism in many inflammatory lung diseases like bronchitis, asthma and chronic obstructive pulmonary disease (COPD). We recently developed a new technique to study water transport and apical volume homeostasis in respiratory epithelia. This technique, in combination with electrophysiological measurements (impedance, Ussing-Chamber), enables us to investigate the effect of noxae on epithelial transport function in order to understand basic pathomechanisms in lung diseases.

c) Intermediate filaments in stretched cells (Dr. Felder)
Mechanical forces can modify cellular functions in various ways. Obviously, only limited levels of mechanical stress can be tolerated by a cell and intermediate filaments (IF) play a crucial role in protecting the cell from tensile strain. However, surprisingly little is known about the behavior of IF in stretched living cells. The lack of information about mechanical effects of IF crosslinks with other cytoskeletal components further complicates our understanding.

We are addressing these questions by stretching cells on elastic silicone membranes with different stretch devices. This allows life cell imaging experiments, preparation of stretched cells for electron microscopy as well as harvesting the cells for biochemistry or molecular biology. A particular focus of our work is the role of IF phosphorylation, the best studied modification of IF. Despite the drastic effects of phosphorylation on the IF in static cell cultures, our studies are among the very few that also demonstrate an effect on their mechanical properties.

Selected Publications:

- *Thompson K, Korbmacher J, Hecht E, Hobi N, Wittekindt O.H, Dietl P, Kranz C, Frick M (2013): FACE (fusion-activated Ca2+-entry) in alveolar type II epithelial cells couples surfactant secretion and lung fluid homeostasis. FASEB J.; 27(4):1772-83.*
- *Fois G, Weimer M, Busch T, Felder ET, Oswald F, von Wichert G, Seufferlein T, Dietl P, Felder E (2013): Effects of keratin phosphorylation on the mechanical properties of keratin filaments in living cells. FASEB J.; 27(4):1322-9.*
- *Neubauer D, Korbmacher J, Frick M, Kiss J, Timmler M, Dietl P, Wittekindt OH and Mizaikoff B (2013): Deuterium Oxide Dilution: A Novel Method to Study Apical Water Layers and Transepithelial Water Transport. Anal. Chem.; April 5.*
- *Miklavc P, Hecht E, Hobi N, Wittekindt OH, Dietl P, Kranz C and Frick M (2012): Actin coating and compression of fused secretory vesicles are essential for surfactant secretion: a role for Rho, formins and myosin II. J Cell Sci.; 125(11):2765-74.*
- *Miklavc P, Mair N, Wittekindt OH, Haller T, Dietl P, Felder E, Timmler M. and Frick M (2011): Fusion-activated Ca2+entry via vesicular P2X4 receptors promotes fusion pore opening and exocytotic content release in pneumocytes. Proc. Natl. Acad. Sci.; 108(35):14503-8.*
- *Miklavc P, Frick M, Wittekindt OH, Haller T, Dietl P (2010): Fusion-activated Ca2+ entry: an "active zone" of elevated Ca2+ during the postfusion stage of lamellar body exocytosis in rat type II pneumocytes. PLoSOne. 5:e10982.*

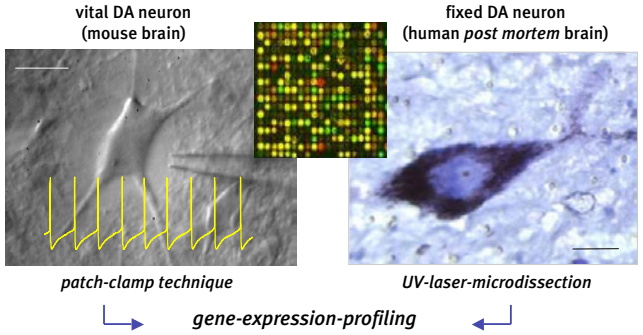
Institute of Applied Physiology

Work Group: Molecular Neurophysiology

Head: Birgit Liss

Our research is focused on the dopamine midbrain system. This system – and the activity of dopamine releasing (DA) midbrain neurons – is not only involved in motor control and movement disorders like Parkinson's disease, but also plays a crucial role in emotional and cognitive brain functions, and in related disorders such as schizophrenia, drug addiction, or attention-deficit-hyperactivity-disorders (ADHD).

Our main research goal is to define functional and molecular mechanisms of different types of DA midbrain neurons with defined projections, which define their distinct physiological roles and their selective transitions to disease states. By combining brain-slice in vitro electrophysiology and UV laser microdissection with molecular quantitative gene expression profiling at the single cell level, we aim to define the pathophysiological signaling pathways that control DA neuron activity as well as selective activation of disease pathways, in particular in Parkinson's disease.



Schematic overview for analyzing electrophysiological function and gene expression of individual dopamine (DA) neurons from vital mouse brains (left) and post mortem human brains (right), combining brain slice patch-clamp technique (yellow trace: typical spontaneous activity of a DA neuron) or UV-laser microdissection (LMD) with gene-expression profiling (quantitative PCR after reverse transcription of mRNA, or microarray-based analysis). Scale bars: 15 µm

To address these issues, we analyze cellular function as well as gene expression of individual DA neurons from controls and from respective disease mouse models as well as from postmortem human brains. We focus on the role of ion channels and receptors, since their cell-specific activity directly defines neuronal activity in health and disease states.

The Team:
Head of Institute: B. Liss
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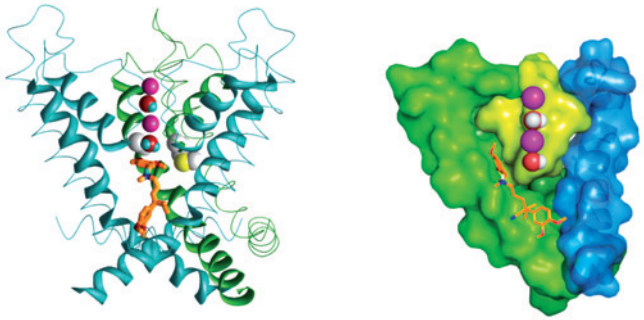
Group Leaders/Postdocs: Z. Andronache, E. Dragicevic, M. Fauler, W. Melzer
PhD Students: J. Duda, M. Janbein, M. Orynbayev, C. Poetschke



Docking of verapamil in the inner pore of the voltage-gated potassium channels hKv1.3.

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Work Group: Ion Channel Structure/Function

Head: Stephan Grissmer

We are interested in the properties, modification and modulation of ion channels in cell membranes. We would like to clarify the physiological role of ion channels in cellular responses and in diseases. Lately, we have used molecular biological techniques in combination with electrophysiology to study structure-function relationships of potassium channels with the goal of rationally designing drugs for the modification/modulation of ion channel function. To aid this endeavor we used different blockers of potassium channels, such as tetraethylammonium, verapamil or peptide toxins, to identify the binding site of those blockers and, with the known three-dimensional structure of the blockers, to obtain a negative imprint on the channel's surface. This newly uncovered structure of each different potassium channel will guide rational drug design to be specific for each potassium channel type. Furthermore, we are also searching for endogenous proteins that can interact with ion channels and thereby possibly modulate their function.

Selected Publications:

- *Schiemann J, Schlaudraff F, Klose V, Bingmer M, Seino S, Magill PJ, Zaghloul KA, Schneider G, Liss B, Roeper J (2012): K-ATP channels in dopamine substantia nigra neurons control bursting and novelty-induced exploration. Nat Neurosci. 2012 Sep;15(9):1272-80.*
- *Gruendemann J, Schlaudraff F, Liss B (2011): UV-laser microdissection and gene expression analysis of individual neurons from post mortem Parkinson's disease brains. Methods Mol Biol. 755:363-74.*
- *Kuras Z, Grissmer S. (2009): Effect of K+ and Rb+ on the action of verapamil on a voltage-gated K channel, hKv1.3: implications for a second open state? British Journal of Pharmacology 157(5):757-768.*
- *Andronache Z, Hamilton SL, Dirksen RT, Melzer W. (2009): A retrograde signal from RyR1 alters DHP receptor inactivation and limits window Ca2+ release in muscle fibers of Y522S RyR1 knock-in mice. Proc Natl Acad Sci USA. 106(11):4531-6.*
- *Gründemann J, Schlaudraff F, Haeckel O, Liss B (2008): Elevated alpha-synuclein mRNA levels in individual UV-laser-microdissected dopaminergic substantia nigra neurons in idiopathic Parkinson's disease. Nucleic Acids Research, 6(7):e38.*
- *Lammel L, Hetzel A, Haeckel O, Jones I, Liss B, Roeper J (2008): Unique properties of mesoprefrontal neurons within a dual mesocorticolimbic dopamine system. Neuron, 57(5):760-73.*

Institute of Physiological Chemistry

Molecular Pathways Regulating Differentiation and Disease

Head: Thomas Wirth

We use conditional mouse genetics to investigate the functions of transcriptional regulators and key components of signaling pathways in normal differentiation processes as well as in animal disease models. In addition to Cre-loxP-based gene deletion, we use tetracycline-regulated gene expression systems to activate or block specific signaling pathways in transgenic mice. This type of approach has provided a deep insight into both developmental as well as pathophysiological processes.

A large part of our work deals with the IKK/NF-κβ signaling pathway. This pathway is activated in many cell types in response to stress and inflammatory signals and is itself not only a prime regulator of inflammation but also of cell proliferation and apoptosis.

Recent work focuses on the role of NF-κβ for efficient neuronal differentiation, its contribution to various types of heart and liver disease, and the analysis of the NF-κβ system for in vivo progression of pancreatic carcinoma. Lap Kwan Chan in his PhD project is trying to uncover the role of oxidative stress and inflammation in pancreatic diseases, such as pancreatic carcinoma, pancreatitis and diabetes.

We identified IKK/NF-κβ signaling in astrocytes as a major regulator of neuroinflammation. Notably, we demonstrated that NF-κβ activation in astrocytes impairs ciliogenesis and links neuroinflammation to hydrocephalus formation. Currently, we are analyzing the function of neuroinflammation in the development of neurodegenerative diseases, e.g. the PhD project of Alexander Magnutzki addresses Alzheimer's disease. He is also establishing a novel Alzheimer model allowing temporal and spatial regulation of neurotoxic Aβ forms. Christine Schurr studies the consequences of neuroinflammatory

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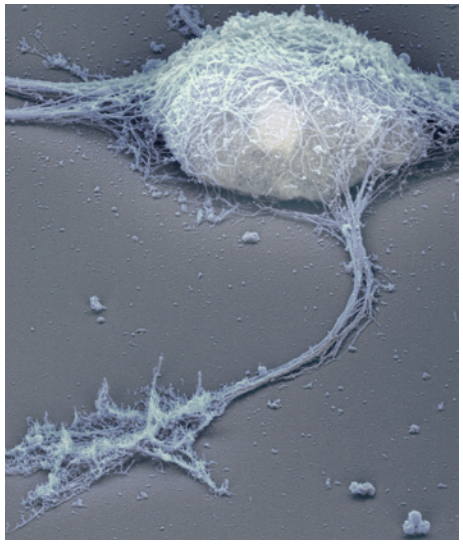
processes for the onset and progression of Amyothropic Lateral Sclerosis. She also addresses the question whether in Multiple Sclerosis neuroinflammation is initiated by an autoimmune process or represents secondary consequences to axonal degeneration and myelin degradation.
Cellular and tissue homeostasis are regulated by the FoxO transcription factors downstream of the insulin receptor signaling. We generated transgenic mice to allow cell type-specific modulation of FoxO3 activity. The role of FoxO3 in the liver is investigated in the PhD project of Sarah Gul. She found that FoxO expression blunts the insulin feedback to the liver and results in induction of hyperglycemia.

In our work on lymphomagenesis, we identified FOXO1 as a tumor suppressor in classical Hodgkin lymphoma (cHL). Marion Vogel tries to identify the role of FOXO1 repression in cHL pathogenesis and to identify tumor suppressor mechanisms deregulated by FOXO1 repression. Given that deregulation of miRNA expression plays a critical role in FOXO1 repression, as we have found recently, the MD project of Franziska Herrmann is dedicated to the investigation of the role of miRNA in block of terminal differentiation in CHL.

The PhD project of Manuel Gey investigates the role of the gene regulator ATF3 in facial nerve regeneration. In addition, the MD student Stephanie Haverkamp is analyzing transcriptional regulation of peripheral nerve regeneration. Further projects focus on gene regulatory programs provided by the serum response factor (SRF). Here, work by the PhD student Sofia Anastasiadou and MD student Sophie Liebenehm addresses potential roles of SRF in myelination and demyelination processes. Pascal Lösing, a PhD student in the laboratory, is analyzing SRF's contribution in neurodegenerative conditions elicited by epileptic seizures. Finally, the PhD student Christopher Meyer zu Reckendorf is trying to uncover and characterize novel cofactors interacting with SRF.



Electron microscopical image of a mouse hippocampal neuron grown in cell culture. The nucleus, center of gene activity, is highlighted in yellow. Cytoskeletal filaments are labelled in blue.

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Selected Publications:

- *Maier HJ, Schips TG, Wietelmann A, Krüger M, Brunner C, Sauter M, Klingel K, Böttger T, Braun T, Wirth T (2012): Cardiomyocyte-specific Iκβ kinase (IKK)/NF-κβ activation induces reversible inflammatory cardiomyopathy and heart failure. PNAS 109, 11794-9.*
- *Sunami Y, Leithäuser F, Gul S, Fiedler K, Güldiken N, Espenlaub S, Holzmann KH, Hipp N, Sindrilaru A, Luedde T, Baumann B, Wissel S, Kreppel F, Schneider M, Scharffetter-Kochanek K, Kochanek S, Strnad P, Wirth T (2012): Hepatic activation of IKK/NFκβ signaling induces liver fibrosis via macrophage-mediated chronic inflammation. Hepatology 56, 1117-28.*
- *Xie L, Ushmorov A, Leithäuser F, Guan H, Steidl C, Färbinger J, Pelzer C, Vogel MJ, Maier HJ, Gascoyne RD, Möller P, Wirth T (2012): FOXO1 is a tumor suppressor in classical Hodgkin lymphoma. Blood 119, 3503-3511.*
- *Beck H, Flynn K, Lindenberg KS, Schwarz H, Bradke F, Di Giovanni S, Knöll B (2012): Serum Response Factor (SRF)-cofilin-actin signaling axis modulates mitochondrial dynamics. Proc Natl Acad Sci USA 109, 2523-32.*
- *Lattke M, Magnutzki A, Walther P, Wirth T, Baumann B (2012): Nuclear factor κβ activation impairs ependymal ciliogenesis and links neuroinflammation to hydrocephalus formation. J Neurosci 32, 11511-23.*
- *Guan H, Xie L, Leithäuser F, Flossbach L, Möller P, Wirth T and Ushmorov A (2010): KLF4 is a tumor suppressor in B-cell non-Hodgkin lymphoma and in classical Hodgkin lymphoma. Blood 116, 1469-1478.*

Institute of Biochemistry and Molecular Biology

Tissue Homeostasis: Development, Aging and Regeneration

Head: Michael Kühl

We at the Institute of Biochemistry and Molecular Biology investigate the molecular basis of tissue and organ development during embryogenesis. We also wish to learn more about how different tissues and organs are maintained during aging and how they regenerate after injury. To tackle these questions, we use different model organisms such as *Mus musculus, Xenopus laevis, Danio rerio, Drosophila melanogaster* as well as murine embryonic stem cells.

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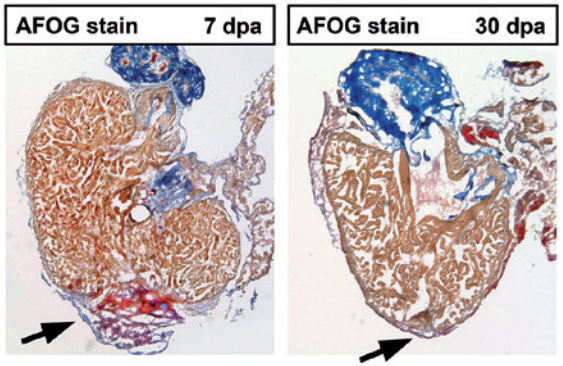
Different groups of the institute study heart development (Kühl, Pandur and Philipp Labs). The heart is the first functional organ during vertebrate development. Defects during cardiac development result in congenital heart diseases occurring in approximately 1% of all newborns and are estimated to be the cause of 10% of stillbirths and spontaneous abortions. Defects in regulatory molecules that function in early heart development have been linked to congenital cardiovascular malformation. Detailed analyses of normal heart development at the molecular level will help us to understand the pathological changes that occur in congenital heart diseases. Moreover, the recent identification of adult cardiac stem cells that can differentiate into functional cardiomyocytes opens up a new perspective in the long-term therapy of heart diseases and reinforces the need to understand the process of normal cardiac development. For similar reasons, we study pronephros development in *Xenopus* (Kühl lab). The pronephros represents the functional embryonic kidney in this species.

Another focus of the institute is to uncover cellular and molecular mechanisms underlying the elevated regenerative capacity of lower vertebrates. In contrast to mammals, fish and amphibians can completely restore many internal organs and their appendages after injury. A detailed understanding of the mechanisms regulating this naturally occurring regeneration will aid the development of regenerative



Zebrafish can fully regenerate their hearts after injury. Histological staining of heart sections at seven days post amputation of the apex of the ventricle shows fibrin-rich wound tissue in red, and resolution of the wound and absence of a collagen-rich scar which stains blue, at 30 days post amputation.

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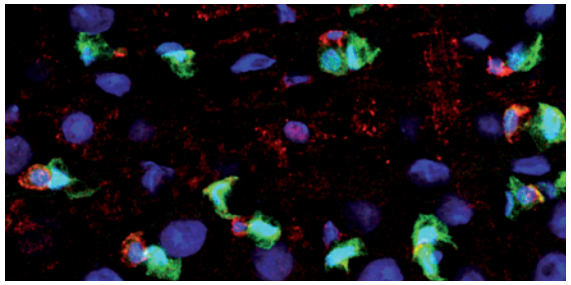
therapies in humans. The Weidinger Lab studies heart and appendage regeneration in the zebrafish model. We focus on the role of extracellular signaling pathways and use systems biology approaches to uncover regulatory networks controlling regeneration, and study the mechanisms inducing cellular plasticity during regeneration.

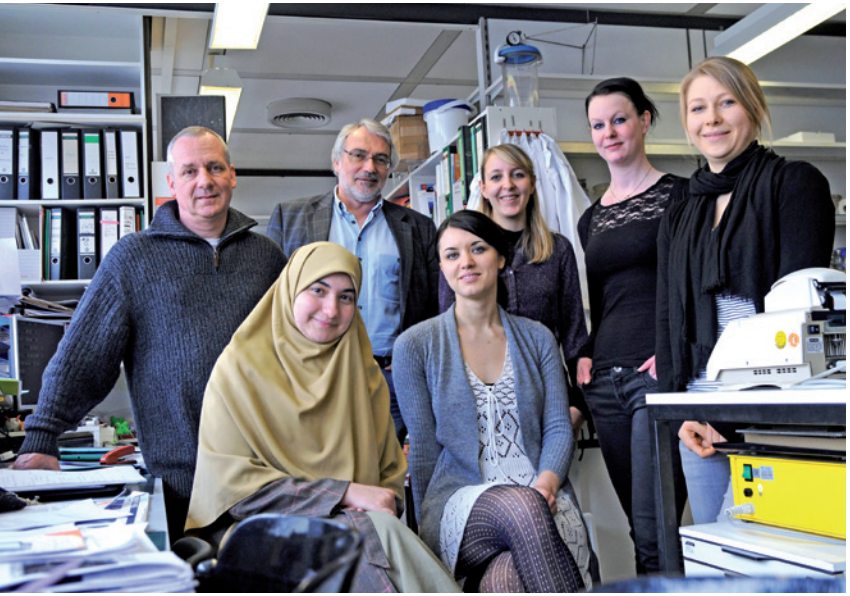
We also study molecular changes underlying the aging process using intestinal stem cells in *Drosophila* (Pandur lab) and hematopoetic stem cells in the mouse (Kühl lab, in cooperation with the group of K.L. Rudolph, Jena) as model systems. Finally, the molecular design and the regulation of the Wnt signaling network are analyzed by the Kühl and Weidinger labs. We use a combination of signaling assays in fish and frog embryos and cultured cells, biochemical approaches and mathematical modeling to uncover novel molecular regulators of this important signaling network. This modeling is performed in collaboration with H. Kestler (Ulm). For this purpose, we use quantitative models based on ordinary differential equations and qualitative models. For both models, hypotheses will be generated by computer-based simulations that can either be verified or falsified by experimental means in cell-based assays.



The image shows cells of the *Drosophila* midgut. Intestinal stem cells are positive for the GFP-reporter and the Notch ligand Delta (red).

Selected Publications:

- *Herrmann F, Groß A, Zhou D, Kestler HA, Kühl M (2012): A boolean model of the cardiac regulatory network determining first and second heart field identity. PLOS One, 7, e46798.*
- *Tauc HM, Mann T, Werner K, Pandur P (2012): A role for Drosophila Wnt-4 in heart development. Genesis, 50, 466-481.*
- *Bugner V, Tecza A, Gessert S, Kühl M (2011): Peter Pan functions independent of its role in ribosome biogenesis during early eye and craniofacial cartilage development in Xenopus laevis. Development, 138, 2369-78.*
- *Kagermeier-Schenk B, Wehner D, Ozhan-Kizil G, Yamamoto H, Li J, Kirchner K, Hoffmann C, Stern P, Kikuchi A, Schambony A, Weidinger G (2011): Waif1/5T4 inhibits Wnt/beta-catenin signaling and activates noncanonical Wnt pathways by modifying LRP6 subcellular localization. Dev. Cell. 21, 1129-1143.*
- *Knopf F, Hammond C, Chekuru A, Kurth T, Hans S, Weber CW, Mahatma G, Fisher S, Brand M, Schulte-Merker S, Weidinger G (2011): Bone regenerates via dedifferentiation of osteoblasts in the zebrafish fin. Dev. Cell. 20, 713-724.*
- *Knopf F, Schnabel K, Haase C, Pfeifer K, Anastassiadis K, Weidinger G (2010): Dually inducible TetON systems for tissue-specific conditional gene expression in zebrafish. PNAS. 107, 19933-19938.*



Institute of Microbiology and Biotechnology

Anaerobic Pathogens: Acne and Cancer Therapy

Head: Peter Dürre

Major projects involve spore formation, regulation of solvent formation in clostridia, development of gas fermentation by anaerobes as a novel biotechnological production platform, construction and application of recombinant clostridial endospores for cancer treatment, and identification of acne-causing enzymes in *Propionibacterium acnes* for selective inhibition and disease therapy. In molecular medicine, two projects are pursued. Clostridial endospores germinate only under hypoxic conditions found in mammals in the vicinity of tumors. Therefore, these endospores are ideally suited for targeting solid cancer structures. Apathogenic clostridia are provided with genes that encode tumor-attacking proteins, and the application of recombinant spores and their selective germination at the tumor allow multiplication there and specific therapy. *P. acnes* is a normal skin inhabitant and as an opportunistic pathogen it is also a major cause of acne vulgaris. This skin disease affects more than 85% of all teenagers. The complete genome of *P. acnes* has been sequenced and the annotation of the genome now opens the possibility of identifying factors responsible for pathogenesis and of looking for agents that specifically inhibit them. Another intention is to identify genes by encoding potential pathogenic factors transcribed in vivo. The aim is to classify acne-patients via expression analysis of genes by encoding potential pathogenic factors into the clinical classification of acne: acne vulgaris, comedonica and papulopustulosa.

Regulation of Carbon Metabolism in *Mycobacteria*

Head: Bernhard Eikmanns

Mycobacterium tuberculosis, the causative agent of tuberculosis, is able to persist within hosts for decades. It must adapt its carbon (C-) metabolism to tissue environments. It is assumed that the organism mainly subsists on fatty acids rather than on carbohydrates within the host. The aim of the project is to identify and analyze regulation of the genes by encoding the key enzymes of the central C-metabolism and to come to a better understanding of the coordination of the metabolism in *M. tuberculosis* and *M. bovis* BCG. We found the orf Rv0465c of *M. tuberculosis* in order to encode a protein with 56% identity to the transcriptional regulator RamB from *Corynebacterium glutamicum*, a well-studied organism used in the production of amino acids. We hypothesized that Rv0465c is an

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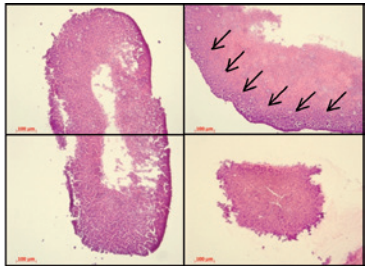
orthologue of *ramB* and involved in the regulation of the glyoxylate cycle genes, and possibly also in the regulation of other genes involved in fatty acid metabolism. We found that Rv0465c has a more specific regulatory function in *M. tuberculosis* than RamB in *C. glutamicum*. We now focus on other regulators involved in control of key enzymes in the C-metabolism of *M. bovis* BCG and *M. tuberculosis*.

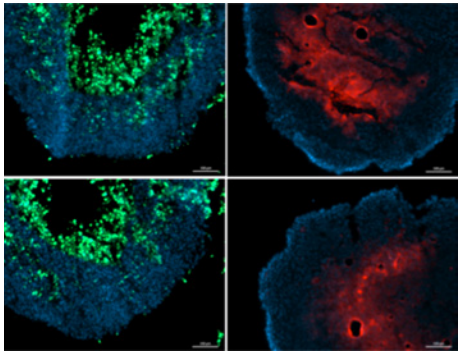
Tumor-Targeting with Bifidobacteria by Using Three-dimensional Tumor Models

Head: Christian Riedel

Bifidobacteria are Gram-positive, anaerobic bacteria of the normal human intestinal microbiota. They are able to colonize and replicate in hypoxic or necrotic regions of solid tumors following oral, intravenous or intratumoral application in animal models. Due to their non-pathogenic nature, genetically engineered bifidobacteria are promising candidates as life vectors for delivery and expression of therapeutic genes to inhibit tumor growth. We developed three-dimensional in vitro tumor models. Cryo-sections of three-dimensional tumors were stained and analyzed by microscopy for morphological and histological tumor characteristics. We could show that bifidobacteria survived in these three-dimensional in vitro tumors. In a first attempt to generate recombinant bifidobacteria for tumor therapy, cytosine deaminase was expressed in *B. bifidum* and *B. longum/infantis*. The recombinant strains metabolized the prodrug 5-fluorocytosine into the toxic substance 5-fluorouracil which inhibits DNA synthesis. Culture supernatants of the recombinant bifidobacterial strains showed an inhibitory effect on the growth of tumor cell lines.



H&E staining of cryo-sections of three-dimensional in vitro HT-29 tumors. The arrows indicate the outer layers of the tumors consisting of actively proliferating cells. This area is distinct from the inner core of the tumor consisting of necrotic tissue.



Apoptosis (TUNEL, green) and hypoxia staining (Pimonidazole, red) of cryo-sections of in vitro generated three-dimensional HT-29 tumors. Both stains label the inner core of the tumors indicating that hypoxia and apoptotic areas inside these tumors largely overlap and suggest that these areas especially may allow the survival of anaerobic bifidobacteria.

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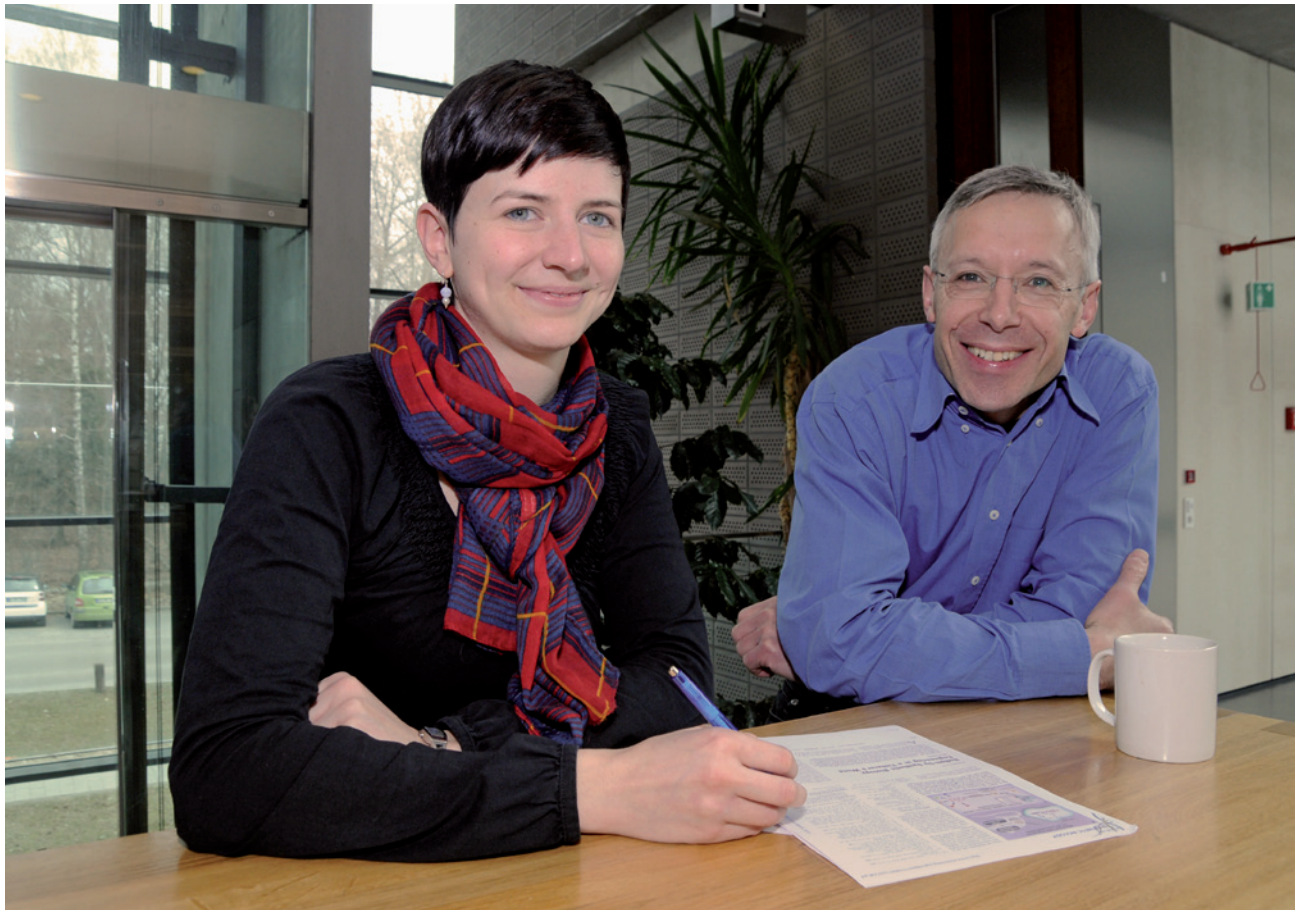
Selected Publications:

- *Brüggemann H, Henne A, Hoster F, Liesegang H, Wiezer A, Strittmatter A, Hujer S, Dürre P, Gottschalk G (2004): The complete genome sequence of Propionibacterium acnes, a commensal of human skin. Science 305: 671-673.*
- *Theys J, Pennington O, Dubois L, Landuyt W, Anné J, Burke P, Anlezark G, Dürre P, Wouters BG, Minton NP, Lambin P (2006): Repeated systemic treatment cycles of Clostridium-directed enzyme prodrug therapy results in sustained anti-tumour effects in vivo. Br J Cancer 95: 1212-1219.*
- *Köpke M, Held C, Hujer S, Liesegang H, Wiezer A, Wollherr A, Ehrenreich A, Liebl W, Gottschalk G, Dürre P (2010): Clostridium ljungdahlii represents a microbial production platform based on syngas. Proc Natl Acad Sci USA 107: 13087-13092.*
- *Micklinghoff JC, Breitinger KJ, Schmidt M, Geffers R, Eikmanns BJ, Bange FC (2009): Role of transcriptional regulator RamB (Rv0456c) in the control of the glyoxylate cycle in Mycobacterium tuberculosis. J Bacteriol 191:7260-7269.*
- *Gleinser M, Grimm V, Zhurina D, Yuan J, Riedel CU (2012): Improved adhesive properties of recombinant bifidobacteria expressing the Bifidobacterium bifidum-specific lipoprotein BopA. Microb Cell Fact 11:80.*
- *Sun Z, Baur A, Zhurina D, Yuan J, Riedel CU (2012): Accessing the inaccessible: molecular tools for bifidobacteria. Appl Environ Microbiol 78:5035-5042.*



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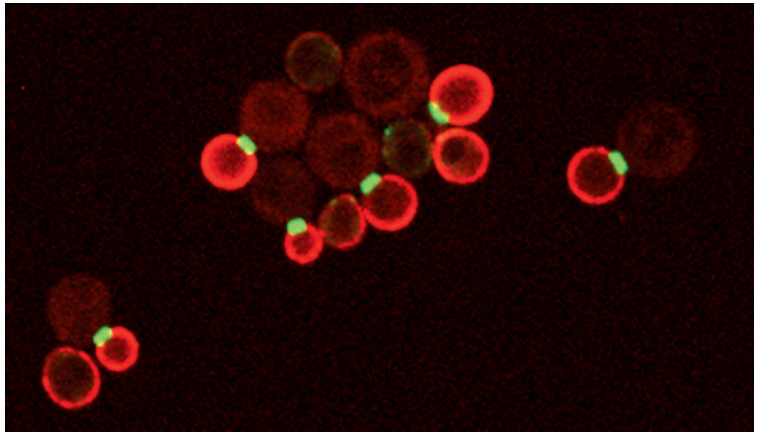
PhD Students: J. Chollet, H. Gregorius, J. Neller, C. Renz, R. Rösler, L. Rieger, C. Tian, Y. Wu
Additional Members of Thesis Advisory Committees: B. Knöll (Ulm), R. Wedlich-Söldner (Munich)

Institute of Molecular Genetics and Cell Biology

The Organization of the Polar Cortical Domain in Yeast

Head: Nils Johnsson

The small GTPase Cdc42p defines through its localized activation the polarity of a growing yeast cell. In its GTP bound state ($Cdc42_{GTP}$), $Cdc42_{GTP}$ will stimulate downstream effector proteins that organize the asymmetric formation of cellular structures and the directed transport of molecules to the site of polarization. To initiate and maintain



Co-expression of two fluorescently labelled polarity proteins in budding yeast cells. The red staining marks regions of active GTPase Cdc42p. Green staining decorates the border between mother and daughter cell and the site of future cell separation. (Photo by Julian Chollet)

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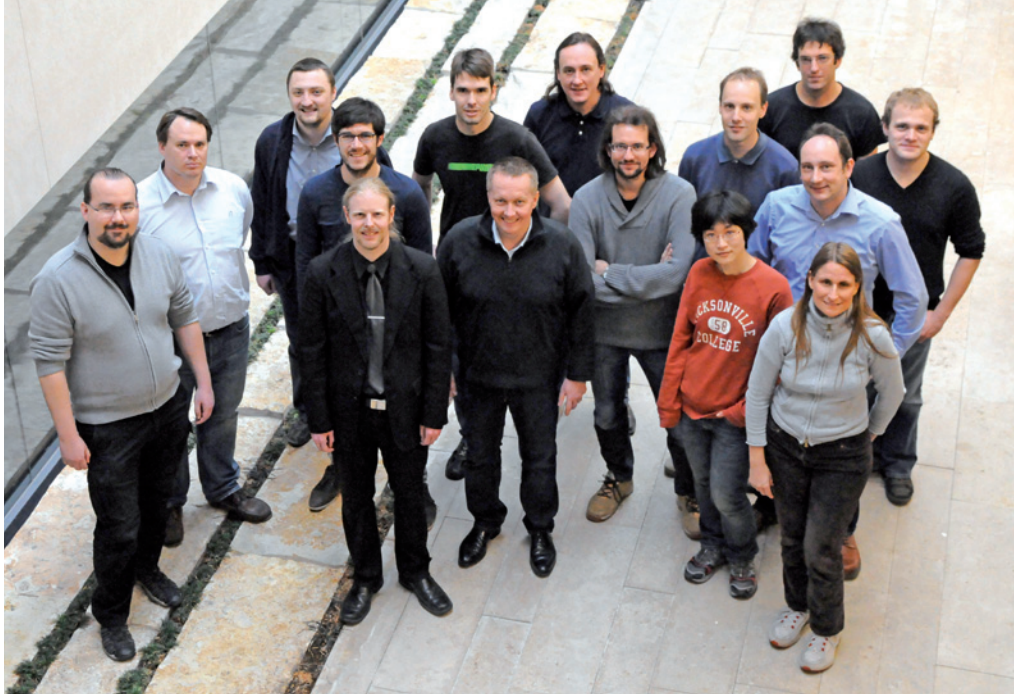
polarization, Cdc42p and its effectors are assembled at the bud tip until the polarity axis is redirected during the late G2 phase and mitosis. The organization of the proteins and lipids at the bud tip is highly dynamic and maintained through a constant exchange of its constituents. The forces that determine the structure of this so-called polar cortical domain (PCD) are interactions of the core components with $Cdc42_{GTP}$, the interactions among the proteins of the PCD, and the interactions between components of the PCD and the membrane. We are interested in two main questions concerning the structure and function of the PCD. Can we understand the dynamic structure of the PCD through the self-assembly and self-organization of critical protein-protein and protein-membrane interactions? How do certain protein members of the PCD perform their role as hinges between the GTPase Cdc42p and its effectors?

Selected Publications:

- *Moreno D, Neller J, Kestler HA, Kraus J, Dünkler A and Johnsson N (2013): A fluorescent reporter for measuring cellular protein-protein interactions in time and space. Mol Syst Biol. 9, 647.*
- *Gronemeyer T, Wiese S, Ofman R, Bunse C, Pawlas M, Hayen H, Eisenacher M, Stephan C, Meyer HE, Waterham HR, Erdmann E, Wanders RJ, Warscheid B (2013): The proteome of human liver peroxisomes: Identification of five new peroxisomal constituents by a label-free quantitative proteomics survey. PLoS-ONE 8; e57395*
- *Labedzka K, Tian C, Nussbaumer U, Timmermann S, Walther P, Müller J, Johnsson N (2012): Sho1p connects the plasma membrane with proteins of the cytokinesis network via multiple isomeric interaction states. J Cell Sci. 25, 4103-4113.*
- *Dünkler A, Müller J and Johnsson N (2012): Detecting protein protein interactions with the Split-Ubiquitin sensor. Methods Mol. Biol. 786, 115-130.*
- *Hruby A, Zapatka M, Heucke S, Rieger L, Wu Y, Nussbaumer U, Timmermann S, Dünkler A, Johnsson N (2011): A constraint network of interactions: Protein Protein-protein interaction analysis of the yeast type II phosphatase Ptc1p and its adaptor protein Nbp2p. J Cell Sci. 124, 35-46.*



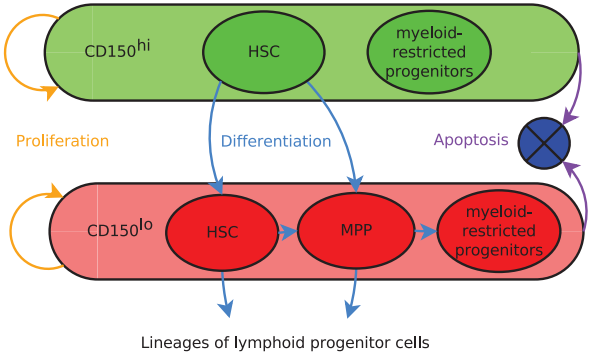
Core Facility Medical Systems Biology

Bioinformatics and Systems Biology

Head: Hans Armin Kestler

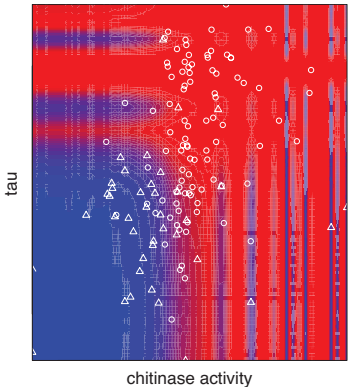
Biology and molecular medicine increasingly focus on the behavior of whole systems. Examples are metabolic, signal transduction or gene regulatory networks. Even small networks exhibit complex responses. Building models can aid the understanding of these systems and guide experiments to verify hypotheses. Modeling these networks mathematically requires the generation and formalization of knowledge on different levels, including the establishment of links between genes and cell status, and the characterization of co-regulated genes or associating gene changes to pathways or networks. The methods used for these investigations largely stem from the field of machine learning and statistics. Boolean networks are one type of model that can also be used to represent gene regulation. In this regard, we were recently able to find generalization error bounds that can be used for this type of model selection. Currently, we are investigating this topic further as it also has a strong impact on biomarker discovery with the aid of transductive algorithms (projects Florian Schmid, Ludwig Lausser). In these settings, feature selection and knowledge integration are paramount. To this end, we are also investigating the visualization and aggregation of knowledge from different platforms and across different species with regard to common denominators of stem cell aging (projects Sebastian Behrens, André Burkovski).

The Team:
Head of Core Facility: H. A. Kestler
Group Leader/Postdoc: M. Maucher, A. Groß, E. Sträng
PhD Students: J. Kraus, L. Lausser, M. Grieb, M. Müssel, A. Burkovski, S. Behrens, A. Fürstberger, G. Völkel, S. Wang, T. Schnattinger, F. Schmid
Students Study Programme Experimental Medicine: Computer Science
Additional Members of Thesis Advisory Committees: Kühl (Ulm), P. Frasconi (Florence), J. Hoheisel (Heidelberg), M. M. Comin (Padua), M. Buchholz (Marburg)



A model for irradiation-induced differentiation: A differentiation checkpoint limits hematopoietic stem cell self-renewal in response to DNA damage. Cell populations with defined expression levels of CD150 surface markers contain hematopoietic stem cells (HSCs) and myeloid-restricted progenitor cell subpopulations, populations with low CD150 levels additionally multi-potent progenitors (MPP). All cell types can undergo proliferation (orange arrows) or apoptosis (purple arrows). HSCs and MPPs may undergo differentiation (blue arrows).
Using a mathematical model based on delay-differential equations, we were able to show that differentiation across subpopulations of HSCs provides an explanation of the cell counts observed after irradiation.

Another aspect is how to arrive at these Boolean variables, i.e. how to binarize data from gene expression values in a well-defined way (project Markus Maucher). This is also directly linked to modeling signal transduction and gene regulation with Boolean functions either directly from literature and/or via reverse engineering or the direct inclusion of expert knowledge on known dynamics (projects Christoph Müssel, Melanie Grieb, Shuang Wang). Other approaches being investigated are models based on differential equations or probabilistic rules which usually require the inclusion of more global knowledge (projects Alexander Groß, Johann Kraus, Eric Sträng).
Other projects are concerned with sequence analysis and optimization algorithms (affiliated group members Axel Fürstberger, Thomas Schnattinger and Gunnar Völkel).



Biomarker discovery of Alzheimer's disease: Combination of the markers tau and chitinase activity enables estimation of decision regions to discriminate between Alzheimer's Disease (red) and no dementia (blue). Regions were estimated using a naive Bayes classifier on data from individuals with Alzheimer's Disease (circles) or no dementia (triangles). (Research Highlight: Nature Reviews Neurology 8, 178, 2012 and Watabe-Rudolph, M. et al. Neurology 78(8):569-77, 2012).

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Selected Publications:

- *Herrmann F, Groß A, Zhou D, Kestler HA*, Kühl M (2012): A Boolean Model of the Cardiac Gene Regulatory Network Determining First and Second Heart Field Identity. PLOS ONE, 7(10):e46798, *corresponding author*
- *Wang J, Sun Q, Morita Y, Jiang H, Groß A, Lechel A, Hildner K, Guachalla LM, Gompf A, Hartmann D, Schambach A, Wuestefeld T, Dauch D, Schrezenmeier H, Hofmann W, Nakauchi H, Ju Z, Kestler HA, Zender L, Rudolph KL (2012): A Differentiation Checkpoint Limits Hematopoietic Stem Cell Self-Renewal in Response to DNA Damage. Cell, 148(5):1001–1014.*
- *Hopfensitz M, Müssel C, Wawra C, Maucher M, Kühl M, Neumann H, Kestler HA: Multiscale binarization of gene expression data for reconstructing Boolean networks (2012): IEEE/ACM Transactions on Computational Biology and Bioinformatics, 9(2):487–498.*
- *Maucher M, Kracher B, Kühl M, Kestler HA (2011): Inferring Boolean network structure via correlation. Bioinformatics, 27(11):1529–36.*
- *Meyer LH*, Eckhoff SM*, Queudeville M, Kraus JM, Giordan M, Stursberg J, Zangrando A, Vendramini E, Moericke A, Zimmermann M, Schrauder A, Lahr G, Holzmann K, Schrappe M, Basso G, Stahnke K*, Kestler HA*, te Kronnie G*, Debatin KM (2011): Early Relapse in Pediatric ALL is identified by Time To Leukemia in NOD/SCID mice and is characterized by a gene signature in- volving survival pathways. Cancer Cell, 19(2):206-17. * equal contribution*
- *Kraus JM, Kestler HA (2010): A highly efficient multicore algorithm for clustering extremely large datasets. BMC Bioinformatics, 11(1):169.*

Division of Neurophysiology

Translational Research on Channelopathies

Head: Frank Lehmann-Horn

Channelopathies are diseases caused by dysfunction of ion channels, which are expressed in many cell types, tissues and organs, hence explaining the wide phenotypic diversity of their clinical manifestations. In voltage-gated cation channels, a recurrent pattern for mutations is the neutralization of positively charged residues in the voltage-sensing S_4 transmembrane segments. These mutations cause dominant ion channelopathies affecting many tissues such as brain, heart and skeletal muscle (Groome et al. 2011). Recent studies suggest that the pathogenesis of associated phenotypes is not limited to alterations in the gating of the ion-conducting alpha pore. Instead, aberrant so-called omega currents facilitated by the movement of the mutated S_4 segments during activation and during recovery contribute to symptoms (Fig. 1A). Surprisingly, these omega currents display uni- or bi-directionality and conduct cations with varying ion selectivity. Additionally, the voltage sensitivity enables the channels to conduct omega currents that are activated in either a hyperpolarized or a depolarized voltage range (Jurkat-Rott et al. 2012).

One of these channelopathies with mutant voltage sensors, hypokalemic periodic paralysis (HypoPP), is clinically characterized by paroxysmal episodes and late-onset muscle dystrophy. The weakness spells are triggered by hypokalemia. The disease is caused by neutral replacements of the first arginine of S_4 segments of calcium and sodium channel of skeletal muscle. The mutations form an omega pore conducting an inward Na^+ omega current at normal resting membrane potential and at hyperpolarization (Fig. 1B). The omega current shows an above-linear increase with hyperpolarization (Fig. 1C) although the electrical field is focused to a single amino acid (Ohm resistor) and not constantly increasing within the membrane (constant field theory). The non-linearity of the omega current reflects the stochastic process of a voltage-dependent open probability and follows a Boltzmann distribution.

In addition, we have shown that the resting membrane potential of excitable cells is distributed around two electrically stable values and the membrane is therefore electrically bistable (Fig. 2A, Jurkat-Rott et al. 2009). In weak HypoPP patients, the fraction of fibers in the depolarized state (P2) is large (Fig. 2B, right panel). Due to the sustained depolarization, the sodium channels are inactivated (Fig. 2C). Therefore, the fibers cannot generate an action potential (Fig. 2D) and are paralyzed. Substances such as carbonic anhydrase and aldosterone inhibitors can shift the fibers in the P2 state in the normal P1 state (Fig. 2B, left panel).

Lowering extracellular K^+ aggravates the omega-induced depolarization, which is in contrast to the predictions of the Goldman equation (Fig. 2E). Due to the permanent Na^+ influx, HypoPP muscle fibers accumulate intracellular Na^+ and water. The edema is cytotoxic and causes muscle degeneration in the periodic paralysis (Amarteifio et al. 2012) and also in the more frequent Duchenne muscle dystrophy (Weber et al. 2011, Lehmann-Horn et al. 2012).

The Team:
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Senior Research Professor of the non-profit Hertie-Foundation
Head of Division: K. Jurkat-Rott
Guest-Professor: J. Groome
Group Leaders/Postdocs: R. Schleip
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Additional Members of Thesis Advisory Committees:
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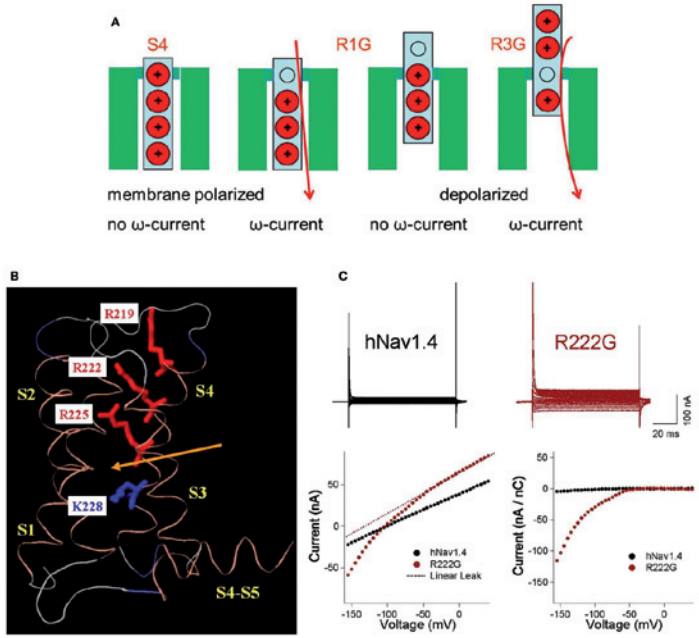

Fig. 1: Omega pores and currents dependent on the position within the S4 segment, the voltage sensor. A. Replacement of the outermost arginine (red) by a neutral amino acid (grey) such as glycine (R1G) opens a conductive pathway through the polarized membrane, resulting in an omega current (red). At depolarized potentials at which the S4 segment moves outward, the conductive pathway is closed by a deeper arginine and the omega current ceases. In contrast, the replacement of a deeper arginine (R3G) only opens the omega pore if the membrane is depolarized. B. Homology model of domain I in hNav1.4 based on crystal structure of NavAb (activated-closed; crystal structure at 0 mV), using Modeller. The positions of arginine and lysine residues of S4 are shown, relative to the putative gating pore constriction (arrow). C. Comparison of current-voltage (I/V) traces for wild type hNav1.4 and R222G, with plots of raw I/V, linear leak, and normalized current (linear leak subtracted from IV and normalized to gating current at 40 mV). The mutation R222G causes HypoPP type 2. External solution contained 120 mM K^+ and 1 µM TTX.

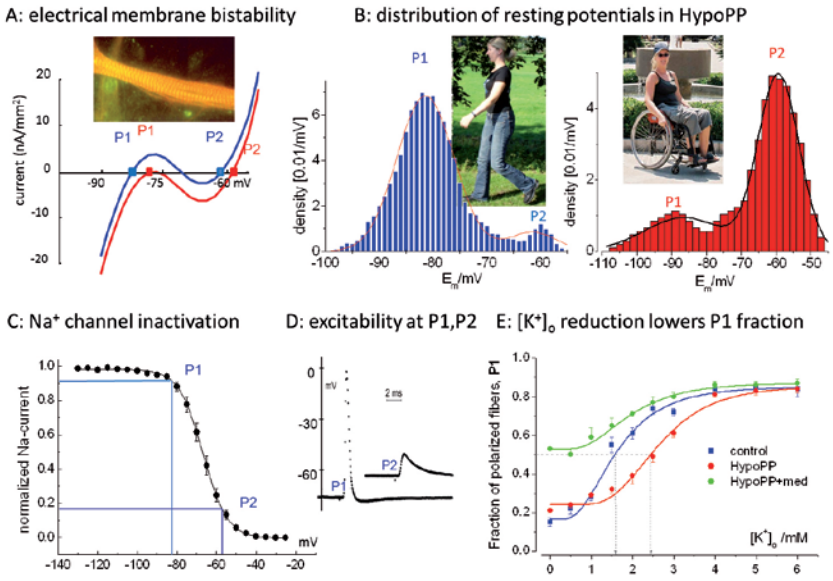

Fig. 2: A. the membrane of muscle fibers (insert) is electrically bistable. B. the fraction of fibers in the depolarized state (P2) is large in weak HypoPP patients before (right panel) and after treatment (left panel). C. the inactivation curve of voltage-gated sodium channels shows highly negative P1 values and less negative P2 values. D. in contrast to fibers in the P1 state, fibers in P2 state cannot generate an action potential and are paralyzed. E. at lowered extracellular K^+, HypoPP fibers (red) are shifted to the right compared to control fibers (blue); medication shifts the HypoPP curve to the left (green).

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Selected Publications:

- *Groome J, Lehmann-Horn F, Holzherr B (2011): Open- and closed-state fast inactivation in sodium channels: Differential effects of a site-3 anemone toxin. Channels 5, 65-78.*
- *Jurkat-Rott K, Weber MA, Fauler M, Guo XH, Holzherr BD, Paczulla A, Nordsborg N, Joechle W, Lehmann-Horn F (2009): K+-dependent paradoxical membrane depolarization and Na+ overload, major and reversible contributors to weakness by ion channel leaks. Proc Natl Acad Sci USA 106, 4036-41.*
- *Amarteifio E, Nagel AM, Weber MA, Jurkat-Rott K, Lehmann-Horn F (2012): Hyperkalemic Periodic Paralysis and Permanent Weakness: 3-T MR Imaging Depicts Intracellular ^{23}Na Overload. Radiology 264, 154-63.*
- *Weber MA, Nagel AM, Jurkat-Rott K, Lehmann-Horn F (2011): Sodium (^{23}Na) MRI detects elevated muscular sodium concentration in Duchenne muscular dystrophy. Neurology 77, 2017-24.*
- *Lehmann-Horn F, Weber MA, Nagel AM, Meinck HM, Breitenbach S, Scharrer J, Jurkat-Rott K (2012): Rationale for treating oedema in Duchenne muscular dystrophy with eplerenone. Acta Myol 31, 31-9.*
- *Jurkat-Rott K, Groome J, Lehmann-Horn F (2012): Pathophysiological role of omega pore current in channelopathies. Front Pharmacol 3, 112.*

Institute of Orthopedic Research and Biomechanics, Center of Musculoskeletal Research

Work Group: Cellular and Molecular Regulation of Bone Remodeling and Regeneration

Head: Anita Ignatius

The Team:
Head of Institute: A. Ignatius
Professors: L. Dürselen, H.-J. Wilke
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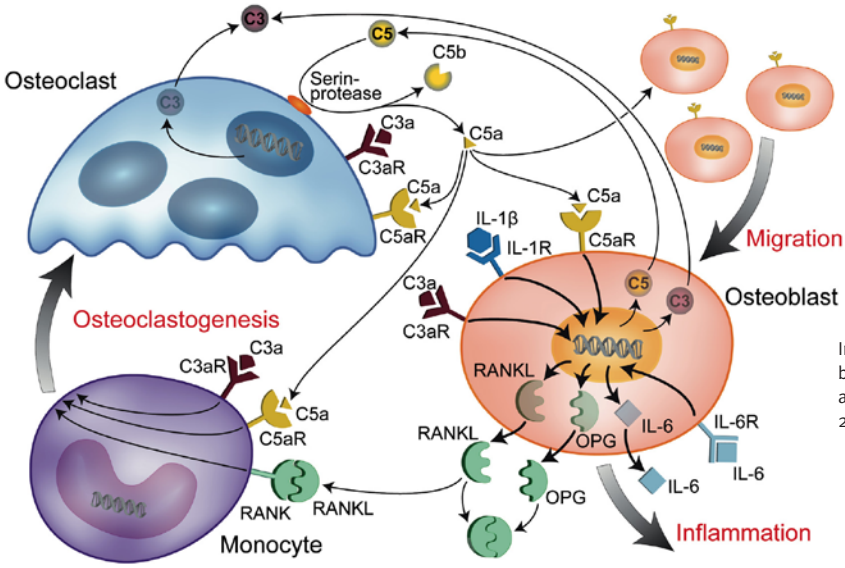
Students Study Programme Experimental Medicine: M. Haffner, J. Kemmler, E. Wehrle
Additional Members of Thesis Advisory Committees: M. Huber-Lang (Ulm), P. Radermacher (Ulm), M. Amling (Hamburg), F. Jakob (Würzburg), M. van Griensven (Munich)

The overall goal of the research activities at this interdisciplinary research institute is to better understand the reasons for degeneration and diseases of the musculoskeletal system and to develop improved therapeutical strategies. The various research groups of the institute deal with basic and applied research projects which are related to bone metabolism and regeneration in healthy, diseased and injured patients, mechanotransduction in bone, intervertebral disc regeneration and biomechanics of the spine and joints.

One of our research teams focuses on fracture healing in osteoporotic bone. Osteoporosis is one of the most prevalent diseases in the aged population. It predominantly affects postmenopausal women, but also older men, and is characterized by an imbalance between bone formation and resorption. The resulting bone loss leads to fragility fractures. Fracture healing is often associated with complications due to the reduced regenerative capacity of the osteoporotic bone. The underlying



Influence of complement on bone cells (Schöngraf P. et al. Immunobiology, 2013, 218:1-9)

pathomechanisms might be complex and are poorly understood so far. Important factors might be sex hormone deficiency, advanced age, immobilization, altered mechanotransduction, and deficiencies in important regulatory pathways, such as Wnt signaling. Wnt signaling is a key pathway controlling bone formation. Polymorphisms in Wnt-related genes are associated with osteoporosis. We therefore investigate in particular the role of Wnt signaling in bone regeneration and fracture healing using a broad spectrum of methods (specific mouse models with modifications in the Wnt pathway, histology, micro computed tomography, cell culture, molecular biology). Furthermore, we are interested in the role of estrogen in bone regeneration, the interaction of estrogen receptor signaling and the Wnt pathway in mechanotransduction in bone. Our current results indicate that both pathways are important for bone regeneration and mechanically induced bone formation, and interact both in vitro as well as in vivo. The results of these studies might help to identify crucial pathomechanisms of impaired bone regeneration in osteoporotic patients.

Another focus of our research is the investigation of the influence of systemic inflammatory conditions, such as posttraumatic systemic inflammation, on bone regeneration. A severe tissue trauma is associated with an extensive activation of the complement system, a crucial part of the innate immunity. Our present data suggest an important role of complement in delayed bone healing. We investigated the effects of activated complement on osteoblasts and osteoclasts and found that the complement anaphylatoxins could modulate important bone cell functions, such as osteoblast migration, cytokine release and osteoclast formation and activity. These data help to understand the interaction of posttraumatic inflammatory conditions on bone regeneration.

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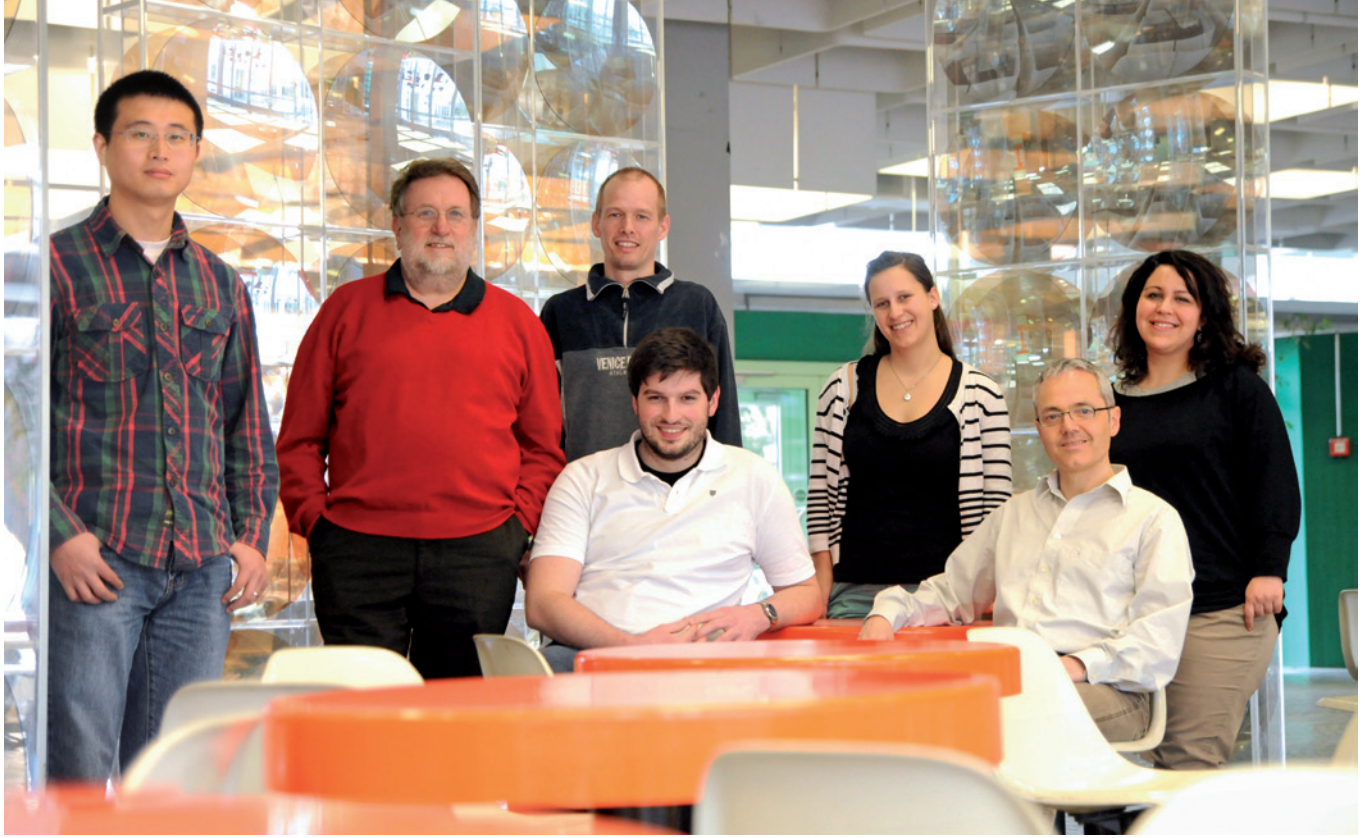
Selected Publications:

- *Recknagel S, Bindl R, Kurz J, Wehner T, Schoengraf P, Ehrnthaller C, Qu H, Gebhard F, Huber-Lang M, Lambris JD, Claes L, Ignatius A (2012): C5aR-antagonist significantly reduces the deleterious effect of a blunt chest trauma on fracture healing. J Orthop Res. 30:581-6.*
- *Ignatius A, Ehrnthaller C, Brenner RE, Kreja L, Schoengraf P, Lisson P, Blakytny R, Recknagel S, Claes L, Gebhard F, Lambris JD, Huber-Lang M (2011): The Anaphylatoxin Receptor C5aR Is Present During Fracture Healing in Rats and Mediates Osteoblast Migration In Vitro. J Trauma. 71:952-960.*
- *Ignatius A, Schoengraf P, Kreja L, Liedert A, Recknagel S, Kandert S, Brenner RE, Schneider M, Lambris JD, Huber-Lang M (2011): Complement C3a and C5a modulate osteoclast formation and inflammatory response of osteoblasts in synergism with IL-1β. J Cell Biochem. 112:2594-2605.*
- *Recknagel S, Bindl R, Kurz J, Wehner T, Ehrnthaller C, Knoferl MW, Gebhard F, Huber-Lang M, Claes L, Ignatius A (2011): Experimental blunt chest trauma impairs fracture healing in rats. J Orthop Res. 29:734-739.*
- *Liedert A, Mattausch L, Rontgen V, Blakytny R, Vogele D, Pahl M, Bindl R, Neunaber C, Schinke T, Harroch S, Amling M, Ignatius A (2011): Midkine-deficiency increases the anabolic response of cortical bone to mechanical loading. Bone. 48:945-951*
- *Liedert A, Wagner L, Seefried L, Ebert R, Jakob F, Ignatius A (2010): Estrogen receptor and Wnt signaling interact to regulate early gene expression in response to mechanical strain in osteoblastic cells. Biochemical and biophysical research communications. 394:755-759.*



Institute of Virology

Work Group: Morphogenesis, Pathogenesis and Therapy in Human Cytomegalovirus (HCMV) Infection, as well as Interaction of the Virus with the Adaptive and Innate Immune System and Molecular Mechanisms of Cell Tropism

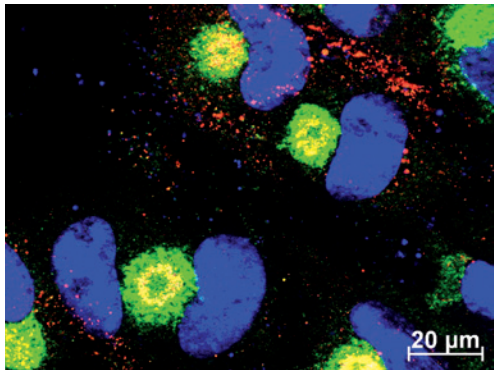
Head: Thomas Mertens

Human Cytomegalovirus (HCMV), a member of the Herpes virus family, is a highly relevant and threatening pathogen for individuals with an immature or compromised immune system (e.g. transplant recipients, intrauterine children, preterm babies, AIDS patients). Serious infections can occur following primary infection or reactivation from lifelong latent infection. Our group characterizes HCMV genes and their gene products with respect to viral morphogenesis, cell tropism, pathogenesis and antiviral therapy.

The Team:
Head of Institute: Th. Mertens
Professors: D. Michel, C. Sinzger
Group Leaders/Postdocs: J. von Einem, G. Frascaroli, D. Lieber, B. Reinhardt, A. Schubert
PhD Students: I. Brock, I. Cappadona, D. Hochdorfer, Z. Wu
Additional Members of Thesis Advisory Committees: W. Brune (Hamburg), S. Jonjic (Rijeka), G. Palù (Padua)

Therefore, we investigate the consequences of viral infection for the host cells and the interaction of viral and cellular proteins as well as the impact of HCMV infection on the immune functions of monocytes, macrophages and NK cells.

In cooperation with the Central Unit of Electron Microscopy, we are investigating intracellular viral transport and egress mechanisms by focusing on the interactions of HCMV tegument proteins with cellular proteins. The scope is also to clarify what cellular machineries are hijacked by the virus and if new targets for antiviral intervention can be characterized. Another focus of our work concerns the interaction of the virus with the innate immune system and the role of NK cells in protecting against severe HCMV disease in humans. The latter work is done in cooperation with the BMT unit of the pediatric clinic at the University Hospital Ulm.



Localization of viral proteins (red and green) in HCMV-infected cells (cell nucleus – blue)

The impact of antiviral therapy and viral resistance is constantly increasing. We are analyzing the two genes, UL97 and UL54, known to be responsible for HCMV antiviral resistance. We are also compiling a database for the correlation of resistant pheno- and genotypes in collaboration with the Department of Neuroinformatics. This database, which is the first for HCMV, has been made available through the internet and is currently being used worldwide.

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- *Wu Z, Sinzger C, Frascaroli G, Reichel J, Bayer C, Wang L, Schirmbeck R, Mertens T (2013): HCMV induced NKG2ChiCD57hi natural killer cells are effectors depending on humoral antiviral immunity. J Virol. Epub ahead of print*
- *Brock I, Krüger M, Mertens T, von Einem J (2013): Nuclear Targeting of Human Cytomegalovirus Large Tegument Protein pUL48 Is Essential for Viral Growth. J Virol. 87(10):6005-19.*
- *Schauflinger M, Villinger C, Mertens T, Walther P, von Einem J (2013): Analysis of human cytomegalovirus secondary envelopment by advanced electron microscopy. Cell Microbiol. 15(2):305-14.*
- *Bayer C, Varani S, Wang L, Walther P, Zhou S, Straschewski S, Bachem M, Söderberg-Naucler C, Mertens T, Frascaroli G (2013): Human cytomegalovirus infection of M1 and M2 macrophages triggers inflammation and autologous T-cell proliferation. J Virol. 87(1):67-79.*
- *Schuessler A, Sampaio KL, Straschewski S, Sinzger C (2012): Mutational mapping of pUL131A of human cytomegalovirus emphasizes its central role for endothelial cell tropism. J Virol. 86(1):504-12.*
- *Chevillotte M, Ersing I, Mertens T, von Einem J (2010): Differentiation between polymorphisms and resistance-associated mutations in human cytomegalovirus DNA polymerase. Antimicrob Agents Chemother. 54(12):5004-11. Epub 2010 Sep 27. PubMed PMID: 20876378; PubMed Central PMCID: PMC2981283.*

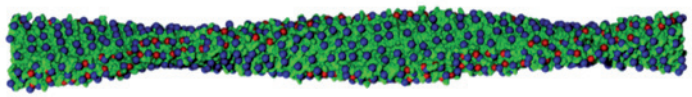
Institute of Molecular Virology

HIV-1 and AIDS

Head: Frank Kirchhoff

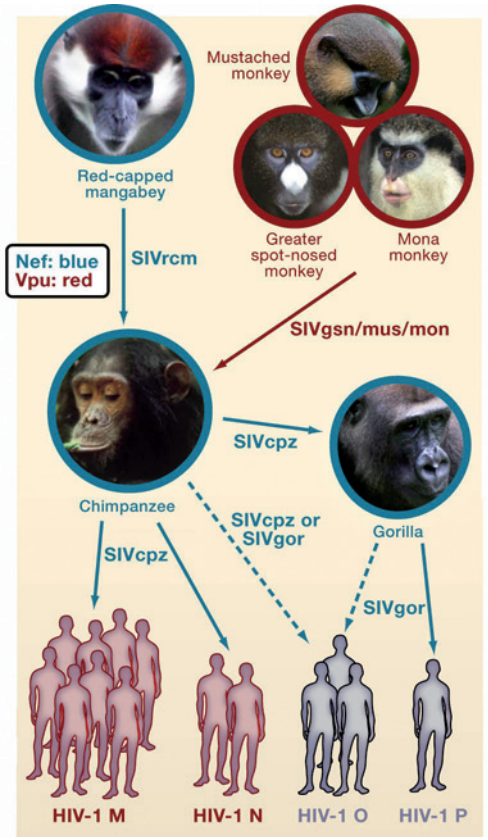
One of our major research interests is to clarify why only one of at least four independent zoonotic transmissions of SIVs found in chimpanzees or gorillas to humans is responsible for the AIDS pandemic. Our results showed that only pandemic HIV-1 M strains evolved a fully functional Vpu that counteracts tetherin (a cellular factor that blocks virus release) and degrades CD_4 (the primary receptor of HIV) to promote the release of fully infectious viral particles. Vpus from non-pandemic HIV-1 O and P strains are poor tetherin antagonists, whereas those from the rare group N viruses do not degrade CD_4 (1) although they seem to be in the process of adapting to humans (2). We also found that primate lentiviruses can rapidly reacquire accessory gene functions that are lost after cross-species transmission (3). Our findings may explain why group M viruses are almost entirely responsible for the global HIV/AIDS pandemic.

Our second major focus is the characterization and optimization of novel inhibitors or enhancers of HIV-1 and other viral pathogens. To achieve this, we screen complex peptide-protein libraries from natural sources, such as hemofiltrate, semen, spleen, saliva and breast milk, for natural compounds affecting HIV-1 infection. These studies have led to the discovery of several HIV-1 inhibitors. One of them, VIRIP, blocks HIV-1 entry by direct binding to the gp41 fusion peptide. Mono-therapy with an optimized VIRIP variant reduces the viral loads by about 1.3 orders of magnitude without causing severe side effects (4). We also used this approach to identify endogenous factors involved in sexual transmission of HIV-1 and found that fragments of the abundant semen marker prostatic acidic phosphatase (PAP) form amyloid fibrils, termed Semen-derived Enhancer of Virus Infection (SEVI), that capture HIV virions and enhance their infectious



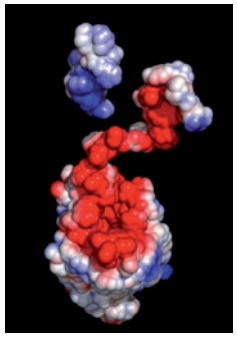
Refined molecular model of an EF-C fibril (N in blue, O in red, backbone in green)

The Team:
Head of Institute: F. Kirchhoff
Professor: J. Münch
Group Leaders/Postdocs: C. Goffinet, D. van der Merwe, D. Sauter, A. Specht, S. Usmani, H. Yu
PhD Students: F. Arnold, A. Gawanbacht, N. Götz, J. Heilmann, D. Hotter, S. Kluge, C. Krapp, V. Lodermeyer, K. Mack, K. Mohr, J. Müller, Palesch, C. Stürzel, D. E. Varga, S. Xu, O. Zirafi
Additional Members of Thesis Advisory Committees: R. Swanstrom (Chapel Hill)



Evolution of HIV-1. SIVcpz represents a recombinant of the precursors of viruses nowadays found in Red-capped mangabeys and *Cercopithecus* monkeys and was subsequently transmitted to humans and gorillas. Nef-mediated tetherin antagonism is indicated by green and Vpu-mediated tetherin antagonism by red lines or contours, respectively. As indicated by the dashed line it is unknown whether HIV-1 group O strains originated from chimpanzees or gorillas. Photos of nonhuman primates are courtesy of M.L. Wilson, Cecile Neel and Martine Peeters.

virus titer by several orders of magnitude. Thus, SEVI may play an important role in sexual transmission of HIV and represents a new target for its prevention. Recently, we developed analogous amyloidogenic peptides for the enhancement of retroviral gene delivery in basic research and clinical approaches (5). In our ongoing studies we identified, among others, novel inhibitors and enhancers of HIV in breast milk, and also an as-yet unknown CXCR4 antagonist that blocks X4-tropic HIV-1 strains (6).



Model of the docking of a naturally occurring peptide to the CXCR4 receptor

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Selected Publications:

- *Yolamanova M, Meier C, Shaytan AK, Vas V, Bertoncini CW, Arnold F, Zirafi O, Usmani SM, Müller JA, Sauter D, Goffinet C, Palesch D, Walther P, Roan NR, Geiger H, Lunov O, Simmet T, Bohne J, Schrezenmeier H, Schwarz K, Ständker L, Forssmann WG, Salvatella X, Khalatur PG, Khokhlov AR, Knowles TP, Weil T, Kirchhoff F, Münch J (2013): Peptide nanofibrils boost retroviral gene transfer and provide a rapid means for concentrating viruses. Nat Nanotechnol. 8(2):130-6*
- *Sauter D, Unterweger D, Vogl M, Usmani SM, Heigele A, Kluge SF, Hermkes E, Moll M, Barker E, Peeters M, Learn GH, Bibollet-Ruche F, Fritz JV, Fackler OT, Hahn BH, Kirchhoff F (2012): Human tetherin exerts strong selection pressure on the HIV-1 group N Vpu protein. PLoS Pathog. 8(12):e1003093.*
- *Götz N, Sauter D, Usmani SM, Fritz JV, Goffinet C, Heigele A, Geyer M, Bibollet-Ruche F, Learn GH, Fackler OT, Hahn BH, Kirchhoff F (2012): Reacquisition of Nef-mediated tetherin antagonism in a single in vivo passage of HIV-1 through its original chimpanzee host. Cell Host Microbe. 12(3):373-80.*
- *Forssmann WG, The YH, Stoll M, Adermann K, Albrecht U, Barlos K, Busmann A, Canales-Mayordomo A, Giménez-Gallego G, Hirsch J, Jiménez-Barbero J, Meyer-Olson D, Münch J, Pérez-Castells J, Ständker L, Kirchhoff F, Schmidt RE (2010): Short-term monotherapy in HIV-infected patients with a virus entry inhibitor against the gp41 fusion peptide. Sci Transl Med. 2(63):63re3*
- *Sauter D, Schindler M, Specht A, Landford WN, Münch J, Kim KA, Votteler J, Schubert U, Bibollet-Ruche F, Keele BF, Takehisa J, Ogando Y, Ochsenbauer C, Kappes JC, Ayouba A, Peeters M, Learn GH, Shaw G, Sharp PM, Bieniasz P, Hahn BH, Hatziioannou T, Kirchhoff F (2009): Tetherin-driven adaptation of Vpu and Nef function and the evolution of pandemic and nonpandemic HIV-1 strains. Cell Host Microbe. 6(5):409-21.*
- *Kim K-A et al.: Discovery and characterization of an endogenous CXCR4 antagonist. (submitted)*

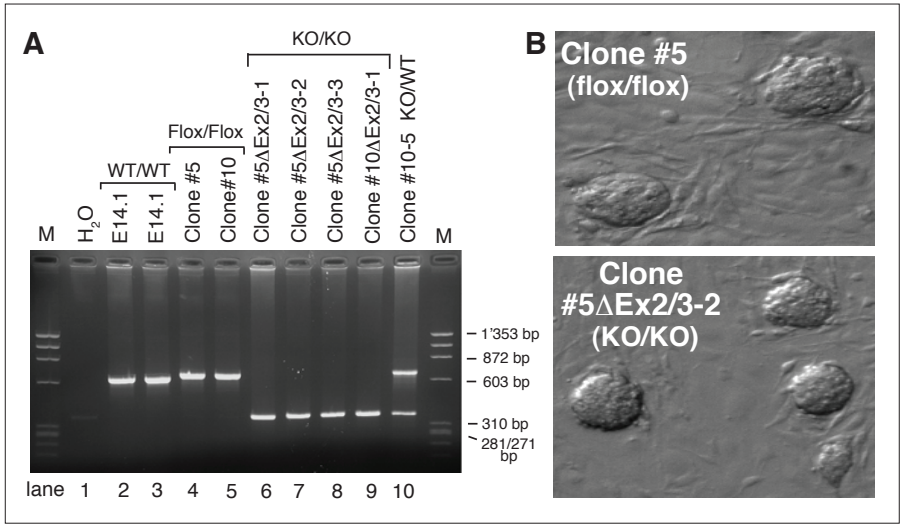
The Team:
Head of Institute/Division: H.J. Fehling (temporary)
Group Leader/Postdoc: V.C. Martins
PhD Students: A. Tasdogan, S. Kumar
Additional Members of Thesis Advisory Committees:
C. Buske (Ulm), A.F. Stewart (Dresden)

Institute of Immunology/Division of Molecular Immunology

Dissecting Phenotypic Defects in *Mixed-Lineage-Leukemia-5 (Mll5)*-Deficient Mice and Cell Lines: Towards a Molecular Understanding of Mll5 Function

Head: Hans Jörg Fehling

Gene targeting in embryonic stem (ES) cells is a key expertise of the Molecular Immunology group. We use this approach for sophisticated genetic manipulations of the mouse genome to create mouse models of human diseases, but also simply to assess unknown functions of novel genes. *Mixed-Lineage-Leukemia-5 (Mll5)* is a member of the MLL/Trithorax family of epigenetic regulators. The human gene is located in a genomic region frequently deleted in myeloid malignancies, which has led to speculation about potential tumor suppressor activities. To get a first idea about the physiological role of *Mll5*, we have generated and characterized knockout mouse mutants (Madan V. et al. 2009). These animals exhibit a variety of phenotypic abnormalities, including partial neonatal lethality, impaired fertility, retarded growth, defective lymphopoiesis, radiation sensitivity due to bone marrow failure, and numerical, functional and cell-cycle defects of specific hematopoietic stem/progenitor cell populations. The major goal of Alpaslan Tasdogan's PhD project was to obtain first insights into the molecular mechanisms underlying the described hematopoietic phenotypes. Towards this goal, Alpaslan has followed several lines of investigation. For instance, he has established stable cell lines, including embryonic stem (ES) cells, from our constitutive *Mll5*-deficient mouse mutants as well as from newly bred mice in which *Mll5* can be inactivated in an inducible or tissue-specific fashion (Fig.1). Detailed molecular and biochemical characterization of these cell lines has revealed striking molecular abnormalities which were subsequently shown to explain most of the hematopoietic defects in *Mll5*-knockout mice. In



Generation of *Mll5*$^{flox/flox}$, *Mll5*$^{KO/KO}$ and *Mll5*$^{KO/WT}$ embryonic stem (ES) cell lines.
A. Characterization of *Mll5* alleles in blastocyst-derived and Cre-recombinase-treated ES cell clones by genomic PCR. E14.1 ES cells (lanes 2 + 3) served as wild-type controls.
B. Phase contrast microscopy of a representative *Mll5*$^{flox/flox}$ ES clone (#5, derived from *Mll5*$^{flox/flox}$ mice) and a representative *Mll5*$^{KO/KO}$ clone (#5ΔEx2/3-2), documenting typical ES cell morphology.

another approach, Alpaslan has generated epitope-tagged *Mll5* alleles via gene targeting in ES cells. These genetically modified ES cells are currently used for in vitro differentiation studies and to generate corresponding knockin mouse strains. Mll5-epitope-tagged cell lines and mice will be invaluable tools for a number of molecular and biochemical analyses, including reliable quantification of Mll5 protein during specific phases of the cell cycle in synchronized cells, the detection of interacting partner proteins by co-immunoprecipitation and the identification of physiological target genes by chromatin immunoprecipitation (ChIP). The epitope-tagging experiments are done in collaboration with the laboratory of Prof. Dr. A.F. Stewart, Technical University Dresden.

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Selected Publications:

- *Luche H, Tata Nageswara R, Kumar S, Tasdogan A, Beckel F, Blum C, Martins VC, Rodewald H-R, Fehling HJ (2013): In vivo fate mapping identifies pre-TCRalpha expression as an intra- and extra-thymic, but not prethymic, marker of T lymphopoiesis. J Exp Med. 210,699-714.*
- *Teupser D, Weber O, Rao NT, Sass K, Thiery J, Fehling HJ debatin(2011): No reduction of atherosclerosis in C-reactive protein (CRP)-deficient mice. J Biol Chem. 286, 6272-9.*
- *Schlenner SM, Madan V, Busch K, Tietz A, Läufle C, Costa C, Blum C, Fehling HJ, Rodewald H-R (2010): Fate mapping reveals separate origins of T cells and myeloid lineages in the thymus. Immunity 32, 426-36.*
- *Madan B, Madan V, Weber O, Tropel P, Blum C, Kieffer E, Viville S, Fehling HJ (2009): The pluripotency-associated gene Dppa4 is dispensable for embryonic stem cell identity and germ cell development but essential for embryogenesis. Mol Cell Biol. 29, 3186-203.*
- *Madan V, Madan B, Brykczynska U, Zilbermann F, Hogeveen K, Doehner K, Doehner H, Weber O, Blum C, Rodewald HR, Sassone-Corsi P, Peters AFM, Fehling HF (2009): Impaired function of primitive hematopoietic cells in mice lacking the Mixed-Lineage-Leukemia homolog Mll5. Blood 113, 1444-54.*
- *Luche H, Weber O, Rao TN, Blum C, Fehling HJ (2007): Faithful activation of an extra-bright red fluorescent protein in "knock-in" Cre-reporter mice ideally suited for lineage tracing studies. Eur J Immunol. 37, 43-53.*

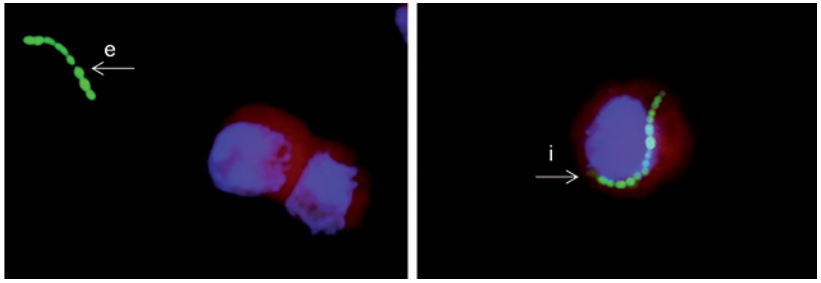
Institute of Medical Microbiology and Hygiene

Work Group: MyTB-Lab

Head: Steffen Stenger

The successful defense against an infection with *Mycobacterium tuberculosis* requires the innate as well as the adaptive immune system. In this context, our group focuses on infection immunology aspects important in mycobacterial host interactions. The goal is to elucidate the details of known immunity mechanisms and to identify novel mycobacterial clearance mechanisms. The overall goal lies in improving prevention strategies against tuberculosis and to contribute to novel therapeutic approaches. For this purpose, we use clinically relevant specimens in our experimental approaches, such as human blood, pulmonary cells and tissue samples from tuberculosis patients. Stephanie Kallert is enrolled as a graduate student in IGradU and pursues the design and evaluation of strategies to optimize Lipid-specific T cell responses against *Mycobacterium tuberculosis*. Hydrophobic molecules, such as lipids and lipoproteins, are a new class of antigens which can activate cytotoxic T cells and therefore play an important part in protection from infectious disease. For optimal use of this characteristic, it is important to bring the hydrophobic antigens efficiently into antigen-presenting cells, e.g. macrophages. The goal of this project is to develop methods for the introduction of hydrophobic molecules through the eukaryotic cell wall into macrophages in order to reach an optimal activation of the immune system resulting in the elimination of pathogenic microorganisms.

The Team:
Head of Institute: S. Stenger
Professor: B. Spellerberg
PhD Students: D. Asam, M. Busch, C. Florindo, S. Kallert, A. Sagar, S. Shabayek
Study Programme Experimental Medicine Students: J. Dick, H. Unger



Depicted are streptococci *(S. agalactiae)* following the incubation with human monocyte-derived cells. Bacteria are fluorescently labeled with EGFP. On the left, bacteria are located extracellularly (e), while on the right, bacteria are found intracellulary (i) in the cytoplasm of the eukaryotic cell.

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Work Group: Molecular Mechanisms of Streptococcal Pathogenicity

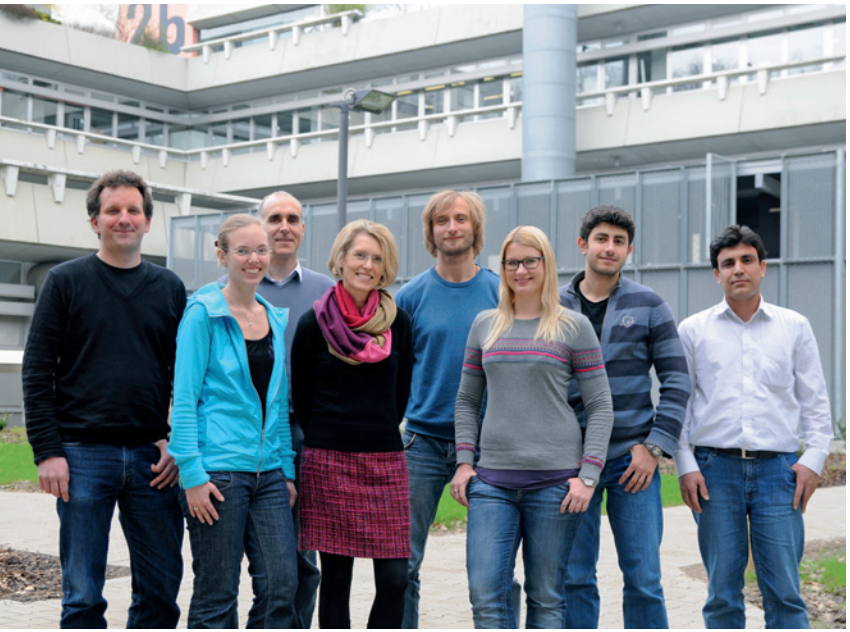
Head: Barbara Spellerberg

The work of our group focuses on molecular mechanisms of streptococci that are important for human infections. Bacterial pathogenicity represents a complex multifactorial interaction between microbial pathogens and their hosts. Innate immunity mechanisms play an important role in the defense against invasive bacterial infections. To survive in human blood, invasive microbial pathogens interfere with the humoral and cellular innate immunity of the host. Many bacterial virulence factors play an important and specific role in this interaction. One of the main goals of our group is to elucidate the molecular details of these encounters. Within this context, we were able to elucidate different streptococcal virulence factors that are crucial for human infections. These include the pyruvate oxidase of *Streptococcus pneumoniae*, the genetic background of *Streptococcus agalactiae* hemolysin production and a composite transposon of *S. agalactiae* harboring genes that are involved in adhesion to host extracellular matrix structures and interference with the human complement system.

At the Graduate School, we pursue two projects. One investigates the role of bacterial cell wall structures for human streptococcal infections. While CRP has been detected and named for its ability to bind to the cell wall of *S. pneumoniae*, the molecular details of this interaction are not completely understood. Especially puzzling is the fact that, while CRP has been shown to interact with the phosphorylcholine in the pneumococcal cell wall, streptococci and other bacteria lacking this molecule in their cell walls still cause massive CRP rises. Within the second project, we were able to elucidate the genetic background of *Streptococcus anginosus* ß-hemolysin production. While *S. anginosus* strains are often isolated from various abscesses and are regarded as an emerging pathogen in cystic fibrosis patients, very little is known about the molecular mechanisms of pathogenicity in *S. anginosus*. The identification of the ß-hemolysin genes by our group will allow us to investigate their specific role in *S. anginosus* infections.

Selected Publications:

- *Aymanns S, Mauerer S, van Zandbergen G, Wolz C, Spellerberg B (2011): High level fluorescence labeling of gram-positive pathogens. PLoS ONE 6, e19822.*
- *Brandt CM, Spellerberg B (2009): Human infections due to Streptococcus dysgalactiae subspecies equisimilis. Clin Infect Dis. 49, 766-72.*
- *Bruns H, Meinken C, Schauenberg P, Härter G, Kern P, Modlin RL, Antoni C, Stenger S. (2009): Anti-TNF immunotherapy reduces CD8+ T cell-mediated antimicrobial activity against Mycobacterium tuberculosis in humans. J Clin Invest. 119, 1167-77.*
- *Bruns H, Stegelmann F, Fabri M, Döhner K, van Zandbergen G, Wagner M, Skinner M, Modlin RL, Stenger S (2012): Abelson tyrosine kinase controls phagosomalacidification required for killing of Mycobacterium tuberculosis in human macrophages. J Immunol. 189, 4069-78.*
- *Gleich-Theurer U, Aymanns S, Haas G, Mauerer S, Vogt J, Spellerberg B (2009): Human serum induces streptococcal C5a peptidase expression. Infect Immun. 77, 3817-25.*
- *Nickel D, Busch M, Mayer D, Hagemann B, Knoll V, Stenger S (2012): Hypoxia triggers the expression of human β defensin 2 and antimicrobial activity against Mycobacterium tuberculosis in human macrophages. J Immunol. 188, 4001-7.*



The Team:
Head of Institute: C. Kubisch
Professor: H. Kehrer-Sawatzki
Group Leader/Postdoc: G. Borck
PhD Students: N. Kakar, N. Sowada, J. Vogt, R. Yilmaz
Additional Members of Thesis Advisory Committees:
H.J. Fehling (Ulm), L. Kluwe (Hamburg),
J. Weishaupt (Ulm), B. Wollnik (Köln)

Institute of Human Genetics

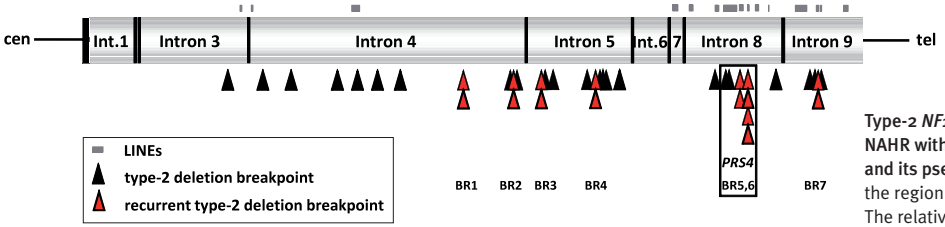
Characterization of Molecular Mechanisms Underlying Human Genetic Diseases

Head: Christian Kubisch

The Institute of Human Genetics offers genetic counseling as well as molecular and cytogenetic diagnostics. Additionally, basic research on various inherited human disorders is performed by different research groups.

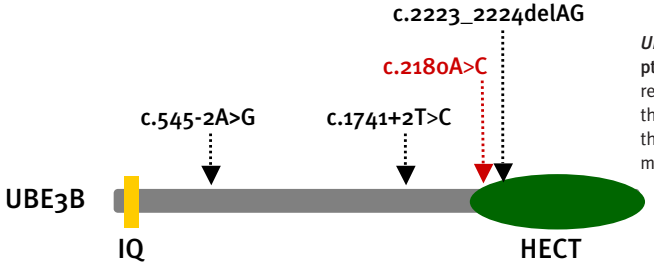
Several aspects of the hereditary cancer syndrome Neurofibromatosis type-1 are investigated by the working group of Prof. Dr. biol. hum. H. Kehrer-Sawatzki. As a member of this group, M. sc. Julia Vogt investigated in her PhD thesis the mutational mechanisms underlying large *NF1* microdeletions which are observed in 5% of all patients with NF1. Four types of *NF1* microdeletions (type-1, type-2, type-3 and atypical) were identified which differ with respect to the extent of the deleted region, the location of the respective breakpoints and the underlying mechanisms. Julia Vogt's work revealed that *NF1* microdeletions with recurrent breakpoints are mediated by nonallelic homologous recombination (NAHR), whereas atypcial *NF1* deletions do not exhibit recurrent breakpoints and are mostly caused by non-homologous end joining and microhomology-mediated replication-dependent recombination. In the course of her PhD thesis, Julia Vogt developed different techniques, including customized Multiplex Ligation-dependent Probe Amplification (MLPA), as well as customized array techniques to improve the identification of *NF1* microdeletion breakpoints at high resolution. By means of these approaches, she found that not only the breakpoints of *NF1* microdeletions mediated by meiotic NAHR but also those mediated by mitotic NAHR cause somatic mosaicism with normal cells in the affected patients cluster within specific regions and encompass only a few kilo-base pairs (Fig.1). Some of these preferred regions of recurrent genomic breakage are located within the *SUZ12* gene and its pseudogene *SUZ12P*. A combination of open chromatin conformation and short non-B DNA-forming repeats is likely to predispose to recurrent mitotic NAHR mediating *NF1* microdeletions with breakpoints located within the *SUZ12* sequences (PhD project, Julia Voigt).

The research group led by Prof. Dr. med. Christian Kubisch focuses on the identification and characterization of novel disease genes underlying monogenic and complex genetic disorders such as hearing impairment, neurodegenerative diseases, migraine, progeroid syndromes and syndromes



Type-2 *NF1* microdeletions are mediated by mitotic NAHR with breakpoints located in the *SUZ12* gene and its pseudogene *SUZ12P*. Exon-intron structure of the region of homology between *SUZ12* and *SUZ12P*. The relative positions of the 40 type-2 *NF1* deletion breakpoint regions are indicated by black triangles. Recurrent breakpoint regions (BR1-BR7) are denoted by red triangles. The rectangular box highlights the NAHR hotspot PRS4, which is located within intron 8.

associated with congenital malformations and intellectual disability. The group recently described a novel human genetic syndrome characterized by facial dysmorphic features, intellectual disability, short stature, microcephaly and low cholesterol levels (blepharophimosis-ptosis-intellectual disability syndrome). This syndrome is caused by biallelic mutations of the *UBE3B* gene which encodes an E3 ubiquitin ligase of unknown function. Ubiquitin ligases transfer ubiquitin on target proteins which will consequently be degraded by the proteasome. The PhD project of MSc Rüstem Yilmaz aims at a functional characterization of UBE3B missense mutations located in the HECT domain of the protein. We will generate constructs containing the *UBE3B* wild-type sequence and several mutations identified in our lab and in others, and will test the ubiquitination capacity of the mutants in in vitro assays. We will also characterize the brains of *Ube3b*$^{-/-}$ mice with respect to histological brain anomalies, anomalies of the morphology and number of synapses, and distribution of synaptic marker proteins. Finally, we will investigate patients with features of the blepharophimosis-ptosis-intellectual disability syndrome but no *UBE3B* mutation in order to identify novel genes implicated in syndromic forms of intellectual disability (PhD project, Rüstem Yilmaz).



***UBE3B* mutations identified in a blepharophimosis-ptosis-intellectual disability syndrome.** Schematic representation of UBE3B with the N-terminal IQ and the C-terminal HECT domain and the positions of three truncating mutations (black) and one missense mutation (red; p.Gln727Pro).

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Selected Publications:

- *Kehrer-Sawatzki H, Vogt J, Mußotter T, Kluwe L, Cooper DN, Mautner VF (2012): Dissecting the clinical phenotype associated with mosaic type-2 NF1 microdeletions. Neurogenetics 13:229-236.*
- *Vogt J, Mussotter T, Bengesser K, Claes K, Högel J, Chuzhanova N, Fu C, van den Ende J, Mautner VF, Cooper DN, Messiaen L, Kehrer-Sawatzki H (2012): Identification of recurrent type-2 NF1 microdeletions reveals a mitotic nonallelic homologous recombination hotspot underlying a human genomic disorder. Hum Mutat 33:1599-1609.*
- *Roehl AC, Mussotter T, Cooper DN, Kluwe L, Wimmer K, Högel J, Zetzmann M, Vogt J, Mautner VF, Kehrer-Sawatzki H (2012): Tissue-specific differences in the proportion of mosaic large NF1 deletions are suggestive of a selective growth advantage of hematopoietic del(+/-) stem cells. Hum Mutat 33:541-550.*
- *Szakszon K, Salpietro C, Kakar N, Knegt AC, Oláh E, Dallapiccola B, Borck G (2013): De novo mutations of the gene encoding the histone acetyltransferase KAT6B in two patients with Say-Barber-Biesecker/Young-Simpson syndrome. American Journal of Medical Genetics A 161:884-888.*
- *Basel-Vanagaite L, Dallapiccola B, Ramirez-Solis R, Segref A, Thiele H, Edwards A, Arends MJ, Miró X, White JK, Désir J, Abramowicz M, Dentici ML, Lepri F, Hofmann K, Har-Zahav A, Ryder E, Karp NA, Estabel J, Gerdin AKB, Podrini C, Ingham NJ, Altmüller J, Nürnberg G, Frommolt P, Abdelhak S, Pasmanik-Chor M, Konen O, Kelley RI, Shohat M, Nürnberg P, Flint J, Steel KP, Hoppe T, Kubisch C, Adams DJ, Borck G (2012): Deficiency for the ubiquitin ligase UBE3B in a blepharophimosis-ptosis-intellectual disability syndrome. American Journal of Human Genetics 91:998-1010.*
- *Borck G, Shin B-S, Stiller B, Mimouni-Bloch A, Thiele H, Kim J-R, Thakur M, Skinner C, Aschenbach L, Smirin-Yosef P, Har-Zahav A, Nürnberg G, Altmüller J, Frommolt P, Hofmann K, Konen O, Nürnberg P, Munnich A, Schwartz CE, Gothelf D, Colleaux L, Dever TE, Kubisch C, Basel-Vanagaite L (2012): eIF2γ mutation that disrupts eIF2 complex integrity links intellectual disability to impaired translation initiation. Molecular Cell 48:641-646.*

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Head of Institute: P. Gierschik
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Study Programme Experimental Medicine Students: H. Christow, J. Rausch
Additional Members of Thesis Advisory Committees: R. Marienfeld (Ulm), R. Wetzker (Jena), T. Böckers (Ulm), T. Wieland (Mannheim), K.D. Spindler (Ulm), M. Thelen (Bellinzona), S. Kochanek (Ulm), M. Schwarz (Tübingen), C. Montecucco (Padua), G. Fischer (Halle)

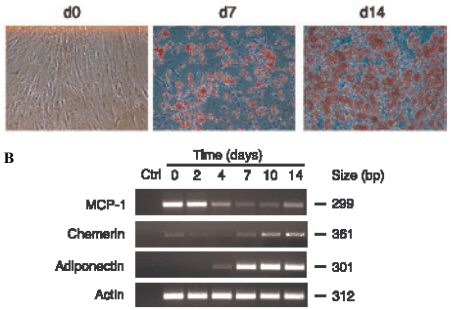
Institute of Pharmacology and Toxicology

Signal Transduction Mediated by Heterotrimeric and Rho GTPases

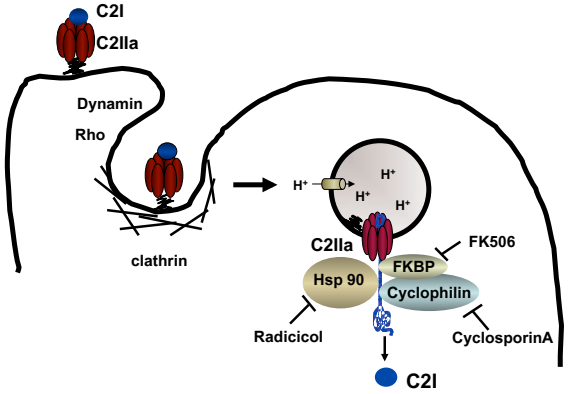
Head: Peter Gierschik

GTPases bind and hydrolyze GTP and are members of a large family of proteins involved in collecting, integrating, processing and distributing extracellular and intracellular information to regulate and orchestrate many fundamental aspects of cell function, such as cell proliferation, migration, differentiation and apoptosis, as well as multiple specialized cell functions, including secretion, contraction, phagocytosis and various sensory and neuronal as well as immune cell functions. Aside from their central role in cell biology and physiology, GTPases are of paramount clinical importance for contributing to the pathogenesis of human diseases and to the action of a major portion of the drugs currently used in clinical practice.

Three doctoral projects pursued at the institute are concerned with the structure-function relationships of GTPases, two of which have been completed recently. Mariana Pfreimer investigated the mode of Rho GTPase activation by chemokine receptors through heterotrimeric GTPases (G proteins) and the **l**eukemia-**a**ssociated **R**ho **g**uanine nucleotide exchange factor (RhoGEF) LARG. Carolin König explored the impact of G-protein-coupled receptors on terminal differentiation and trafficking of human adipocytes and/or their interaction with monocytes/macrophages and other cell types in the adipose tissue. Anja Bühler studies the mechanisms of phospholipase C-γ_2 (PLCγ_2) activation by the Rho GTPase Rac2 and the molecular mechanisms of PLCγ_2 activation in mutants found in human hereditary autoinflammatory diseases and in animal models of such disorders.



Expression of chemokines and adipokines in human adipose lineage cells during terminal adipocyte differentiation. *A*, Simpson-Golabi-Behmel (SGBS) preadipocytes, cultured cells capable of differentiating *in vitro* into mature white adipocytes were subjected to a 14 day differentiation process, which was controlled by Oil Red O staining of the cellular lipid content. Cells of day 0 *(d0)*, day 7 *(d7)*, and day 14 *(d14)* are shown. *B*, Reverse transcriptase polymerase chain reaction expression analysis of mRNAs encoding the human CC chemokine monocyte chemoattractant protein 1 (MCP-1) or the adipokines chemerin and adiponectin in SGBS cells at days 0 through 14 of the differentiation protocol. *Ctrl*, control sample without single-stranded template cDNA. Adapted from Koenig et al. (2013) Mol. Cell. Endocrinol. 369:72.



Role of host cell chaperones in uptake of the binary C2 toxin from *Clostridium botulinum*. (modified from Barth H, Aktories K (2011) E J Cell Biol 90:944-950)

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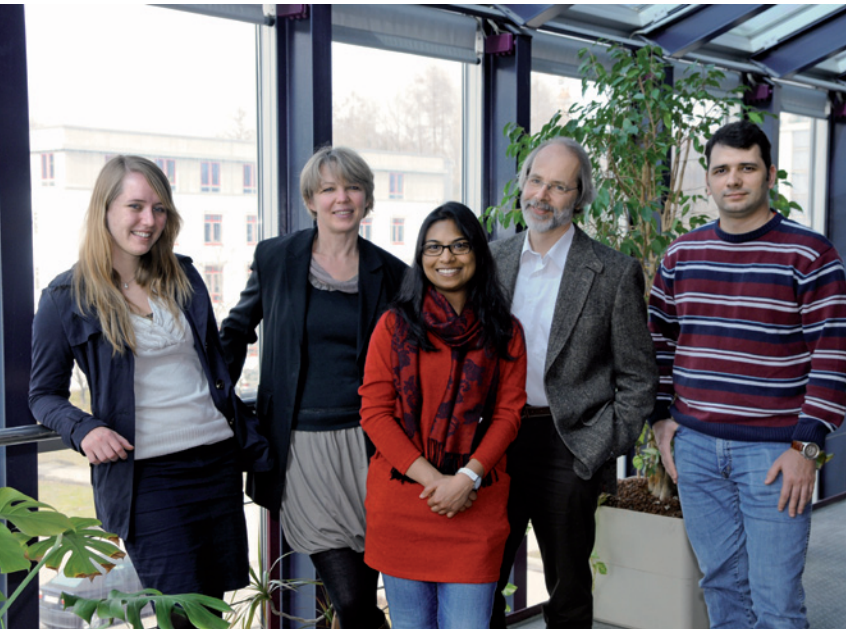
Cellular Uptake of Bacterial Exotoxins and Their Use as Molecular Trojan Horses for Drug Delivery

Bacterial exotoxins are proteins which enter mammalian cells and enzymatically modify specific substrates in their cytosol. This results in cell damage and the symptoms of severe diseases such as diphtheria, anthrax or botulism. For cell entry, a binding/translocation domain mediates the transport of an enzyme domain into the cytosol. This unique mode of action makes exotoxins ideal transporters for targeted delivery of macromolecules into cells. We investigate the molecular mechanisms underlying the toxin transport into target cells and develop tailor-made transporters based on enzymatic inactive toxin fragments thereof to deliver pharmacologically active molecules into the cytosol of monocytes/macrophages.

Maren Lillich and Hannes Christow constructed toxin-based transporters to deliver mammalian proteins into cells by coupling the binding/transclocation moieties of clostridial toxins to streptavidin, either by genetic fusion and expression of the recombinant protein or by chemical crosslinking in vitro. Biotin-labeled molecules bound to the streptavidin domain are delivered by the fusion toxins into various cell types including tumor cells. Katharina Ernst studies the role of host cell chaperones in mediating the uptake of bacterial toxins into the host cell cytosol. She demonstrated that various peptidyl prolyl *cis/trans* isomerases specifically facilitate the intracellular membrane transport of ADP-ribosylating toxins by directly interacting with their catalytic domains. Lydia Dmochwitz develops and characterizes recombinant fusion toxins based on an enzymatically inactive variant of C3 toxin from *Clostridium botulinum*, which is selectively taken up into monocytes/macrophages. Since C3-based transporters serve the selective delivery of enzymes into cultured monocytes/macrophages, the vision behind this approach is their therapeutic use in monocyte/macrophage-associated diseases.

Selected Publications:

- *Pfreimer M, Vatter P, Langer T, Wieland T, Gierschik P, Moepps B (2012): LARG links histamine-H1-receptor-activated Gq to Rho-GTPase-dependent signaling pathways. Cell. Signal. 24:652-663.*
- *Koenig C, Fischer-Posovszky P, Rojewski MT, Tews D, Schrezenmeier H, Wabitsch M, Gierschik P, Moepps B (2013): Absence of CC chemokine receptors 2a and 2b from human adipose lineage cells. Mol. Cell. Endocrinol. 369:72-85.*
- *Lillich M, Chen X, Weil T, Barth H, Fahrer J (2012): Streptavidin-conjugated C3 protein mediates the delivery of mono-biotinylated RNAse A into macrophages. Bioconjug. Chem. 23: 1426-1436.*
- *Christow H, Lillich M, Sold A, Fahrer J, Barth H (2013): Recombinant streptavidin-C3bot for delivery of proteins into macrophages. Toxicon, in press.*
- *Dmochewitz L, Förtsch C, Zwerger C, Väth M, Felder E, Huber-Lang M, Barth H (2013): A recombinant fusion toxin based on enzymatic inactive C3bot1 selectively targets macrophages. PLoS One 8:e54517.*
- *Kaiser E*, Böhm N*, Ernst K*, Langer S, Schwan C, Aktories K, Popoff MR, Fischer G, Barth H (2012): FK506-binding protein 51 interacts with Clostridium botulinum C2 toxin and FK506 blocks membrane translocation of the toxin in mammalian cells. Cell. Microbiol. 14:1193-1205. (*contributed equally)*



Institute of Pharmacology of Natural Products and Clinical Pharmacology

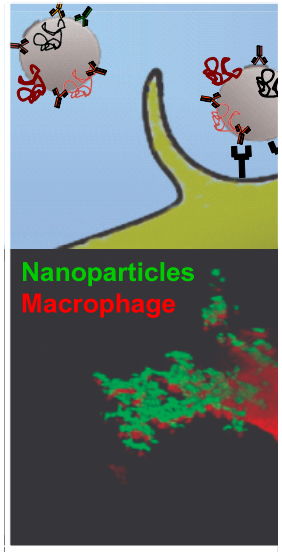
Work Group: Molecular Pharmacology and Biophysics

Head: Thomas Simmet

Modulation and Remote Control of Cell Function by Functionalized Nanosized Particles

Nanosized particles have a rapidly increasing number of industrial and medical applications. Macrophages are phagocytes that act as a first line of defense by internalizing particulate matter, including nanoparticles. Nanosized particles are capable of biasing relevant functions of immune cells, including those of macrophages. However, despite the frequent use of nanosized materials, the interactions of nanoparticles with phagocytosing immune cells remain poorly understood. Our goals are: i) to learn in greater detail how distinct surface properties and functionalizations of nanoparticles affect their interaction with cellular membranes; ii) to address cellular consequences that might be induced by distinct nanosized materials; and iii) to investigate how nanotechnology could be exploited for the remote control of cell functionality and eventually for therapeutic purposes. A wide variety of cell and molecular biological as well as biophysical methods and techniques, including advanced imaging, will be applied to address these questions.

This project is performed in collaboration with the Max Planck Institute for Polymer Chemistry (Prof. K. Landfester), Mainz, the Institute of Applied Physics (Prof. G.U. Nienhaus), KIT, Karlsruhe, and the Czech Academy of Sciences (Prof. A. Dejneka, Prof. V. Zablotskii).



Interaction between nanoparticles and macrophages

The Team:
Head of Institute: T. Simmet
Professors: J. Stingl, T. Syrovets
Group Leaders/Postdocs: O. Lunov, B. Büchele, C.Q. Schmidt, S. Hafner
PhD Students: M. El Gaafary, O. Efimkina, C. Loos, T. Paul, K. Stiebel, Z. Schmidt
Additional Members of Thesis Advisory Committees: V. Mailänder (Mainz), J. Brockmöller (Göttingen), T. Seufferlein (Ulm), H. McLeod (Chapel Hill), K. Scharffetter-Kochanek (Ulm)

Dr Oleg Lunof started his PhD in April 2009 and, having completed it successfully at the Institute of Pharmacology of Natural Products and Clinical Pharmacology in August 2011, he was awarded summa cum laude. Due to his outstanding performance, he also received the Doctoral Student Award in 2011.

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Work Group: Clinical Pharmacology

Head: Julia Stingl

Individual Mechanisms of Cytarabine Toxicity

Bone marrow suppression and hematological toxicity are frequent problems related to drug therapy with cytarabine (AraC). It would therefore be valuable to have predictive markers for the individual probability and severity of AraC-associated adverse effects. The aim of this project is to evaluate the role of genetic factors in individual drug toxicity to find predictive markers for the occurrence of AraC-related side-effects. As a model for the AraC toxicity, lymphocytes from healthy volunteers are used to examine the inter-individual differences in AraC toxicity and to correlate these findings with genetic factors.

Biomarkers for skin toxicity and response to EGFR inhibitors in keratinocytes and fibroblasts

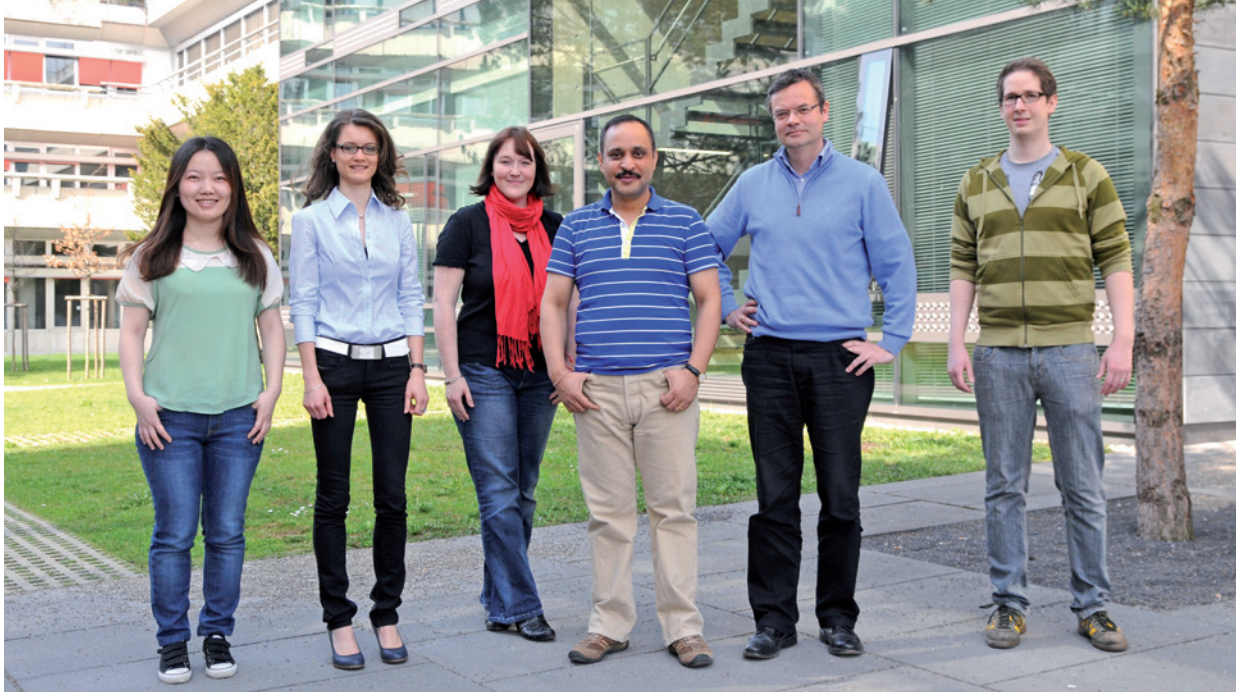
For EGFR inhibitory anticancer drugs, it has been shown that the follicular epidermal growth signaling pathway is critical for both the frequently occurring skin toxicity mediated by effects of the EGFR-inhibitors on the keratinocytes as well as for the therapeutic response of tumor cells to the drug. Primary human keratinocytes serve as a model to understand individual genetic differences in the molecular drug action of the important new class of EGFR inhibitors.

Gene expression and activity of the EGFR signaling pathway will be characterized in keratinocytes and fibroblasts in order to study the genetic modulation of the EGFR inhibiton in these cells.

This project is performed in collaboration with the Institute for Pharmacogenomics and Individualized Therapy, University of North Carolina, Chapel Hill, NC, USA (Prof. H. McLeod). The PhD student T. Paul will spend about one year of his PhD studies in Chapel Hill and the remaining time in Ulm.

Selected Publications:

- *Lunov O, Syrovets T, Loos C, Nienhaus GU, Mailänder V, Landfester K, Rouis M, Simmet TH (2011): Amino functionalized polystyrene nanoparticles activate the NLRP3 inflammasome in human macrophages. ACS Nano 5:9648-9657.*
- *Lunov O, Syrovets T, Beil J, Delacher M, Tron K, Nienhaus GU, Musyanovych A, Mailänder V, Landfester K, Simmet TH (2011): Differential uptake of functionalized polystyrene nanoparticles by human macrophages and a monocytic cell line. ACS Nano 5:1657-1669.*
- *Lunov O, Zablotskii V, Syrovets T, Röcker C, Tron K, Nienhaus GU, Simmet Th (2011): Modeling receptor-mediated endocytosis of polymer-functionalized iron oxide nanoparticles by human macrophages. Biomaterials 32:547-55.*
- *Parmar S, Schuhmann C, Rüdiger S, Boeck S, Heinemann V, Kächele V, Seeringer A, Paul T, Seufferlein T, Stingl JC (2013): Pharmacogenetic predictors for EGFR-inhibitor-associated skin toxicity. Pharmaco-genomics, in press.*
- *Fuerst D, Parmar S, Schuhmann C, Rüdiger S, Boeck S, Heinemann V, Kaechele V, Stiebel K, Paul T, Seufferlein T, Mytilineos J, Stingl JC (2012): HLA polymorphisms influence the development of skin rash arising from treatment with EGF receptor inhibitors. Pharmacogenomics 13: 1469-76.*
- *Morag A, Pasmanik-Chor M, Oron-Karni V, Rehavi M, Stingl JC, Gurwitz D (2011): Genome-wide expression profiling of human lymphoblastoid cell lines identifies CHL1 as putative SSRI antidepressants response biomarker. Pharmacogenomics, 12:171-84.*



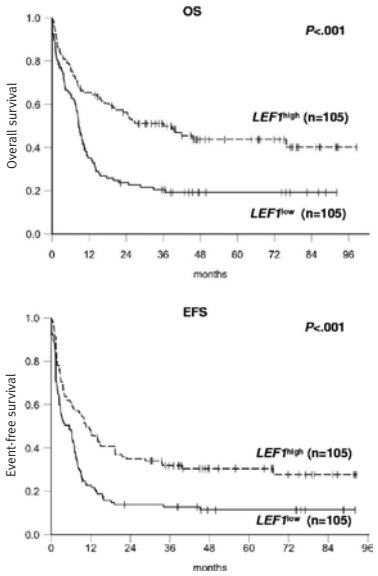
Institute of Experimental Cancer Research

Characterization of the Molecular Biology of Normal and Leukemic Hematopoiesis

Head: Christian Buske

The Team:
Head of Institute: C. Buske
Professor: V.P.S. Rawat
Group Leaders/Postdocs: A. Muranyi, A. Mulaw, N. Vegi, M. Feuring-Buske (Internal Medicine III), F. Kuchenbauer (Internal Medicine III)
PhD Students: S. Bamezai, D. Daria, K. Edmaier, S. Ihme, T. Mandal, K. Stahnke, J. Huang, F. Mohr, E. Gentner, L. Ferruzzi
Study Programme Experimental Medicine Students: A. Grunenberg, E. Panina, A. Bootz
Additional Members of Thesis Advisory Committees: S. Fulda (Frankfurt), H. Glimm (Heidelberg), H. Geiger (Ulm), S. Bohlander (Munich), H. Döhner (Ulm), A. Koul (Belgium)

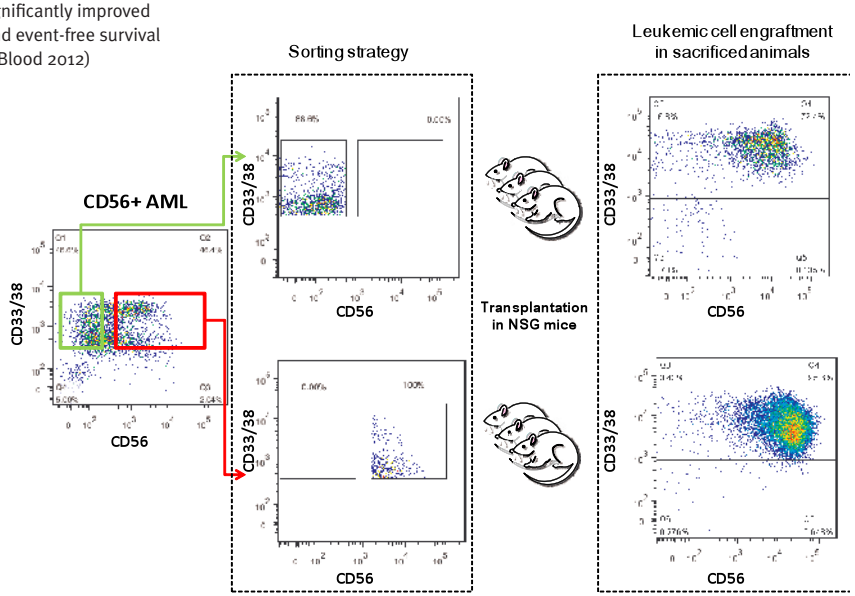
It is well accepted that leukemia originates from normal hematopoietic stem or progenitor cells which have acquired critical genetic alterations leading to uncontrolled self-renewal and impaired differentiation of the leukemic cells. The institute focuses on characterizing key molecular events which cause malignant transformation of normal hematopoietic stem cells into leukemic stem cells using a wide panel of different murine models that mimic human leukemias. Using murine bone marrow transplantation assays and retroviral gene transfer, we were able to identify several novel regulators of normal and leukemic stem cells, such as *VENTX* or *CDX2*. Furthermore, we could demonstrate that genetic alterations have to collaborate to induce acute myeloid leukemias (AML), such as the fusion gene *AML1-ETO* and the *FLT3* length mutation. In addition, we used murine leukemia models to profile leukemic stem cells and to identify differences between normal and leukemic stem cells, and could thus show that in acute myeloid leukemia characterized by



We identified LEF1 as a novel independent prognostic factor in human AML patients with normal karyotype. High expression of LEF1 is associated with a significantly improved overall survival (OS) and event-free survival (EFS). (Metzeler et al., Blood 2012)

the fusion gene CALM-AF10 the leukemic stem cell differs from its normal counterpart by the expression of the lymphoid-associated antigen B220. Currently, the group focuses on the relevance of lymphoid antigen expression in acute myeloid leukemias (J. Huang*, M. Feuring-Buske), the role of the LEF1 in human AML (K. Edmaier*, C. Buske), the identification of novel regulatory genes of leukemic stem cells (E. Gentner*, C. Buske), the function of the TET protein family in normal and malignant hematopoiesis (F. Mohr*, VPS Rawat), the role of non-coding RNAs in human leukemogenesis (S. Ihme, M. Mulaw), and the biology of NPM1 mutated leukemias (A. Muranyi, C. Buske). For this research program, the institute has access to state-of-the-art FACS technology as well as to next generation sequencing technology.

**Students of the International Graduate School*



Leukemic subfractions isolated from patients with acute myeloid leukemia (AML) harbor leukemic stem cells and engraft into NSG mice.

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Selected Publications:

- *Metzeler KH, Heilmeier B, Edmaier KE, Rawat VP, Dufour A, Döhner K, Feuring-Buske M, Braess J, Spiekermann K, Büchner T, Sauerland MC, Döhner H, Hiddemann W, Bohlander SK, Schlenk RF, Bullinger L, Buske C (2012) High expression of lymphoid enhancer-binding factor-1 (LEF1) is a novel favorable prognostic factor in cytogenetically normal acute myeloid leukemia. Blood. 120(10):2118-26.*
- *Rawat VP, Humphries RK, Buske C (2012): Beyond Hox: the role of ParaHox genes in normal and malignant hematopoiesis. Blood. 120(3):519-27.*
- *Eppert K, Takenaka K, Lechman ER, Waldron L, Nilsson B, van Galen P, Metzeler KH, Poeppl A, Ling V, Beyene J, Canty AJ, Danska JS, Bohlander SK, Buske C, Minden MD, Golub TR, Jurisica I, Ebert BL, Dick JE (2011) Stem cell gene expression programs influence clinical outcome in human leukemia. Nat Med. 17(9):1086-93.*
- *Rawat VP*, Arseni N*, Ahmed F, Mulaw MA, Thoene S, Heilmeier B, Sadlon T, D' Andrea RJ, Hiddemann W, Bohlander SK, Buske C*, Feuring-Buske M* (2010): The vent-like homeobox gene VENTX promotes human myeloid differentiation and is highly expressed in acute myeloid leukemia. Proc Natl Acad Sci U S A. 107(39):16946-51. * both authors contributed equally*
- *Petropoulos K, Arseni N, Schessl C, Stadler CR, Rawat VP, Deshpande AJ, Heilmeier B, Hiddemann W, Quintanilla-Martinez L, Bohlander SK, Feuring-Buske M, Buske C (2008): A novel role for Lef-1, a central transcription mediator of Wnt signaling, in leukemogenesis. J Exp Med. 205:515-522.*
- *Deshpande AJ, Cusan M, Rawat VP, Reuter H, Krause A, Pott C, Quintanilla-Martinez L, Kakadia P, Kuchenbauer F, Ahmed F, Delabesse E, Hahn M, Lichter P, Kneba M, Hiddemann W, Macintyre E, Mecucci C, Ludwig WD, Humphries RK, Bohlander SK, Feuring-Buske M, Buske C (2006): Acute myeloid leukemia is propagated by a leukemic stem cell with lymphoid characteristics in a mouse model of CALM/AF10-positive leukemia. Cancer Cell. 10:363-374.*

Department of Internal Medicine I

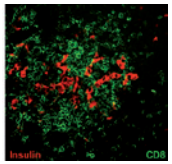
Development and Maintenance of Malignant and Inflammatory Phenotypes in Gastrointestinal Diseases

Head: Thomas Seufferlein

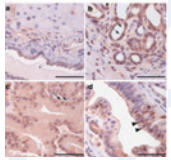
At the Department of Internal Medicine I, the focus of our research addresses primarily key signaling pathways and principles of cell biology that initiate and maintain malignant transformation in gastrointestinal cancer. These signaling events are closely linked to embryonic development and stem cell biology. Our second focus is autoimmunity and immune responses in the gut, pancreas and the liver. We aim to identify and delineate molecular pathways responsible for early events in cancer development, the tumor host interaction as well as metastasis and disease progression. In this context, we use genetically engineered animal models and state-of-the-art techniques in cell biology and biochemistry in order to identify the contribution of subcellular compartmentalization as a regulatory principle in tumor biology. Projects in our department address angiogenesis, growth control, secretion, transcriptional regulation and epigenetics in cancer, migration and metastasis as well as the identification and targeting of tumor stem cells. We further develop vaccination strategies for the specific control of chronic Hepatitis-B virus (HBV) infection and autoimmune type 1 diabetes.

The Team:
Head of Department: T. Seufferlein
Professors/Group Leaders: M. Dollinger, A. Kleger, A. Lechel, F. Oswald, R. Schirmbeck, M. Wagner, G. von Wichert
Postdocs: M. Armacki, N. Azoitei, T. Eiseler, S.-F. Katz, P. Riedl, G. Román Sosa, A. Illing
PhD Students: A. Becher, M. Hohwieler, P. Klöble, H. Müller, C. Münzberg, R. Qin, M. Raiwa, V. Rossini, R. Russel, J. Schroer, R. Sroka, A. Staab, K. Stifter, V. Thiel, C. Weidgang, C. Wille
Additional Members of Thesis Advisory Committees: Dr. Arnold (Freiburg), Prof. Borggrefe (Gießen), Prof. Ellenrieder (Marburg), Prof. Ignatius (Ulm), Dr. Kaether (Jena), Prof. Seckl (London), Prof. de Vos (Sheffield)

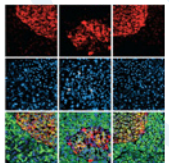
The findings of our research projects will be useful for elucidating the patho-mechanisms of gastrointestinal cancer, liver diseases and diabetes, and will be used to identify novel therapeutic strategies for these diseases. Besides these efforts in basic research, the Department of Internal Medicine I is the coordinating institution for many clinical multicenter studies addressing the prevention and treatment of gastrointestinal cancers.



Autoimmunity
- Autoantigens
- DNA-based vaccination
- Murine diabetes models
- CD8 T-cells
- Regulatory T-cells



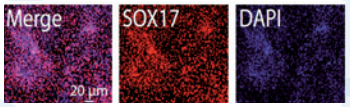
Mouse Models of Cancer
- Pancreatic cancer, HCC
- Carcinogenic mechanisms
- Evaluation of therapeutic strategies



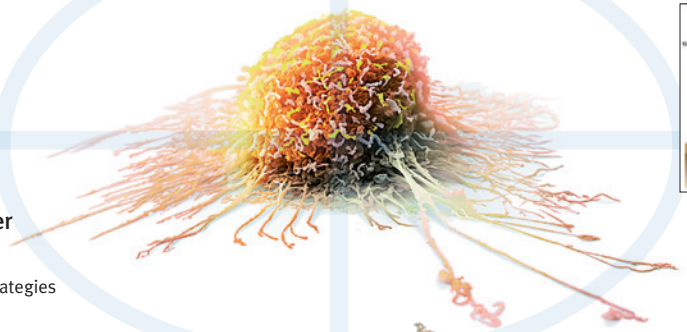
Cytoskeleton
intermediate filaments
- Resistance to treatment
- Disease related function
- Transformation

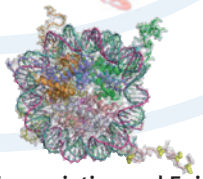
Clinical trials
IITs
Phase I/II
Phase III
CCCU

Translational research
- Prognostic markers
- Predictive markers
- Identification of subgroups

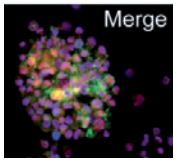


Embryonic Development and Stem Cells
- Pancreas Development
- Disease modelling
- Tissue engeering

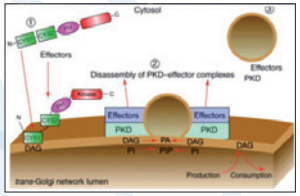




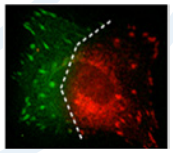
Transcription and Epigenetics
- Notch Signalling in Development and Cancer
- Transcription complexes
- Histone marks



Angiogenesis
- Novel angiogenic signals
- Function of oncogenes
- Response to treatment



Protein Transport
- Protein complexes at the TGN
- Vesicle shedding
- Apoptosis and cytokinesis
- Nucleo- cytoplasmic shuttling



Migration and Invasion
- Role of oncogenes
- Metastasis and protein kinases
- Regulation of EMT

The research groups at our department use a broad spectrum of animal models and state-of-the-art techniques. We aim to address key signaling pathways and molecular mechanisms that initiate and maintain malignant transformation in gastrointestinal cancer as well as autoimmunity and immune responses in the gut, pancreas and the liver.

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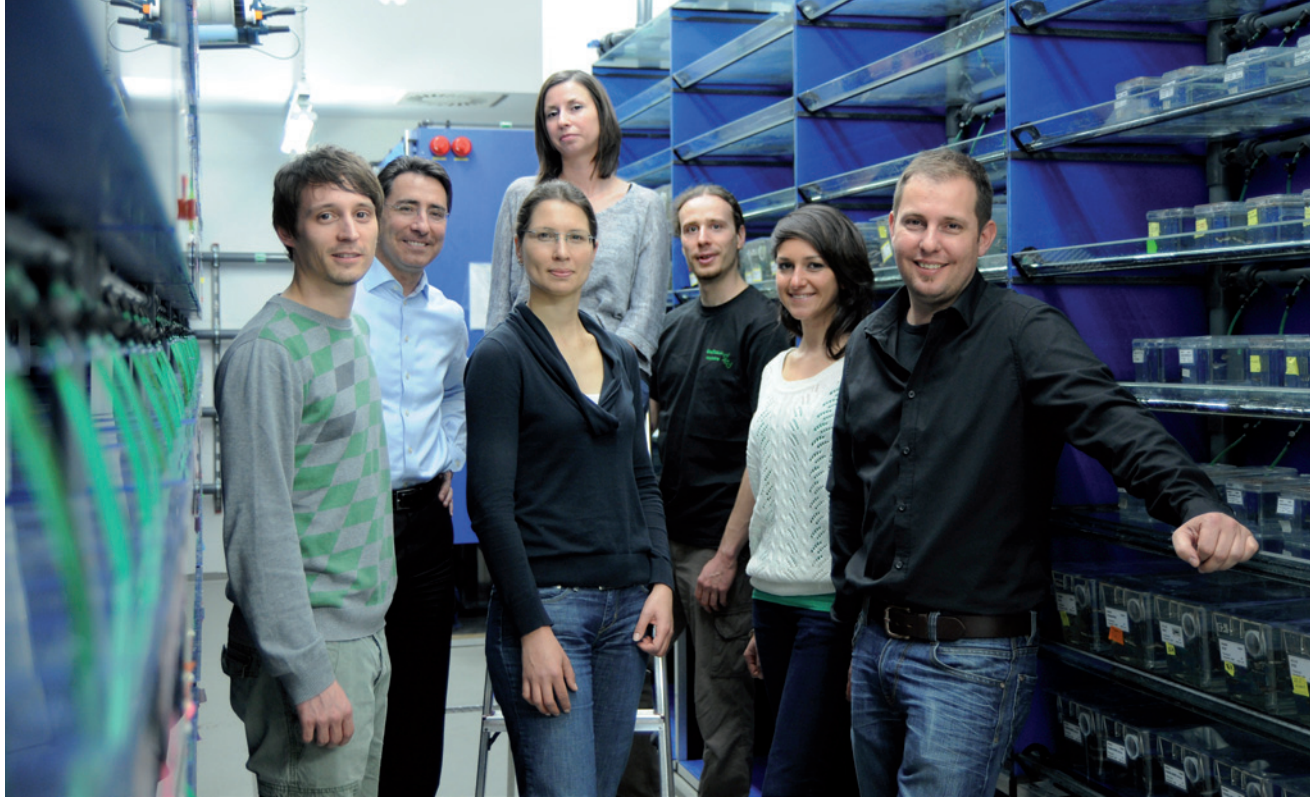
Selected Publications:

- *Wacker SA, Alvarado C, von Wichert G, Knippschild U, Wiedenmann J, Clauß K, Nienhaus GU, Hameister H, Baumann B, Borggrefe T, Oswald F (2011): RITA, a novel modulator of Notch signalling, acts via nuclear export of RBP-J. EMBO J.*
- *Krndija D, Münzberg C, Maass U, Hafner M, Adler G, Kestler HA, Seufferlein T, Oswald F, von Wichert G (2012): The phosphatase of regenerating liver 3 (PRL-3) promotes cell migration through Arf-activity-dependent stimulation of integrin alpha 5 recycling. J Cell Sci.*
- *Eiseler T, Koehler C, Nimmagadda SC, Jamali A, Funk N, Joodi G, Storz P, Seufferlein T (2012): Protein Kinase D1 mediates anchorage-dependent and independent growth of tumor cells via the zinc-finger transcription factor Snail1. J Biol Chem.*
- *Busch T, Armacki M, Eiseler T, Joodi G, Temme C, Jansen J, von Wichert G, Omary MB, Spatz J, Seufferlein T (2012): Keratin 8 phosphorylation regulates keratin reorganization and migration of epithelial tumor cells. J Cell Sci.*
- *Pusapati GV, Eiseler T, Rykx A, Vandoninck S, Derua R, Waelkens E, Van Lint J, von Wichert G, Seufferlein T (2012): Protein kinase D regulates RhoA activity via rhotekin phosphorylation. J Biol Chem.*
- *Armacki M, Joodi G, Nimmagadda SC, de Kimpe L, Pusapati GV, Vandoninck S, Van Lint J, Illing A, Seufferlein T (2013): A novel splice variant of calcium and integrin-binding protein 1 mediates protein kinase D2-stimulated tumour growth by regulating angiogenesis. Oncogene.*



Department of Internal Medicine II

Dissecting the Molecular Pathology of Heart and Skeletal Muscle Disease

Head: Wolfgang Rottbauer

The Team:
Head of Department: W. Rottbauer
Group Leader: S. Just
Postdoc: I. Berger
PhD Students: J. Bührdel, S. Hirth, S. Rudeck, J. Segert
Study Programme Experimental Medicine Students: T. Zimmermann, M. Rattka
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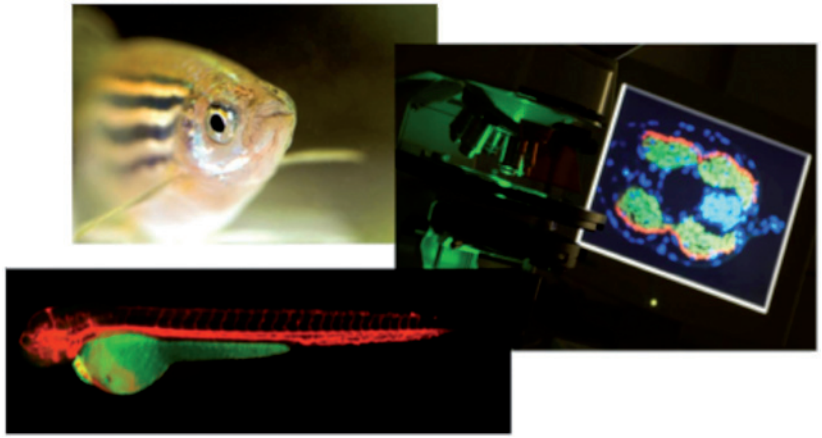
Molecular Cardiology

The main focus of the laboratory is to dissect novel genetic and molecular pathways of pathological cardiac and skeletal muscle development and growth using state-of-the-art forward and reverse functional genomics approaches in animal models (e.g. zebrafish, mouse). The long-term goal of our research is to identify novel therapeutic targets for cardiac and skeletal muscle diseases (in vivo high-throughput small compound screens). Currently, at the International Graduate School in Molecular Medicine Ulm, the following experimental PhD and MD projects are being pursued.
To develop targeted treatment strategies for human myofibrillar myopathies (MFM), the PhD project

of John Bührdel aims to elucidate the genetic basis and the precise molecular mechanisms that translate known MFM mutations into the myopathic phenotype using functional genomics in zebrafish. In a second PhD project, Steven Rudeck aims to dissect the molecular pathways leading to myofibril assembly and to identify new candidate genes such as SMYD1 and UNC-45 involved in human cardiac and skeletal muscle myopathies. Furthermore, in an attempt to develop novel molecular treatment strategies for heart failure, the PhD project of Sofia Hirth aims to further elucidate the role of ILK-signaling in cardiac stretch sensing and mechanotransduction. The main goal of the PhD project of Julia Segert is to unravel the precise genetic and molecular mechanisms that translate Nexilin mutations into the cardiomyopathic phenotype using in vivo and in vitro model systems.

The experimental MD research project of Tobias Zimmermann aims to decipher the molecular and cellular mechanisms that control cardiomyocyte proliferation and heart regeneration in zebrafish. To dissect the functional role of DCM-associated genes and disease modifying SNPs derived from GWA studies, the MD student Manuel Rattka uses state-of-the-art in vivo reverse genetics approaches.



The zebrafish is an excellent model to study cardiovascular and muscle development and function using forward and reverse functional genomics approaches.

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Selected Publications:

- *Just S, Berger IM, Meder B, Backs J, Keller A, Marquart S, Frese K, Patzel E, Rauch GJ, Katus HA, Rottbauer W (2011): Protein kinase d2 controls cardiac valve formation in zebrafish by regulating histone deacetylase 5 activity. Circulation. 124:324-334.*
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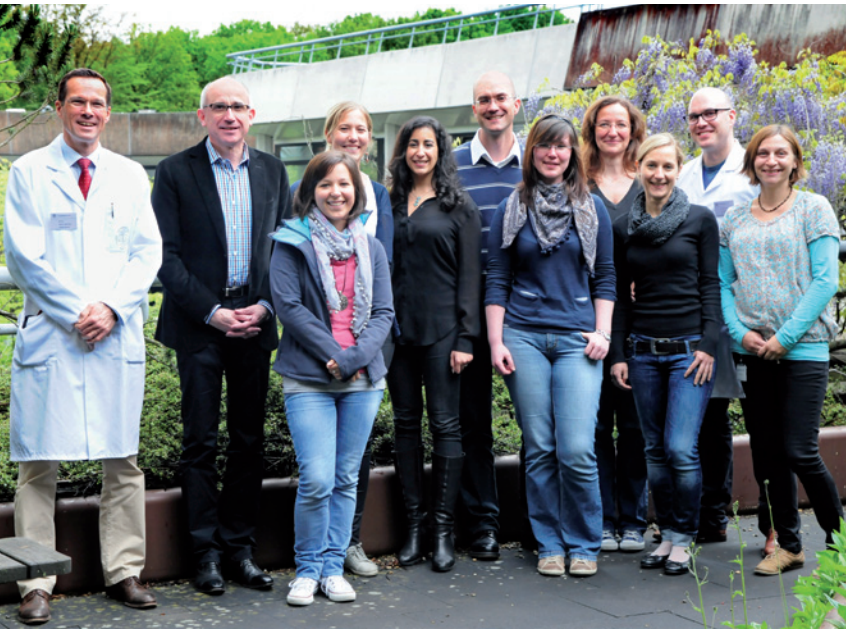
- *Hassel D, Scholz EP, Trano N, Friedrich O, Just S, Meder B, Weiss DL, Zitron E, Marquart S, Vogel B, Karle CA, Seemann G, Fishman MC, Katus HA, Rottbauer W (2008): Deficient zebrafish ether-a-go-go-related gene channel gating causes short-qt syndrome in zebrafish reggae mutants. Circulation. 117:866-875.*



The Team:
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Professors: L. Bullinger, J. Greiner, K. Döhner, S. Stilgenbauer
Group Leaders: F. Kuchenbauer, D. Mertens, C. Scholl
Postdocs: A. Dolnik, B. Jebaraj, S. Kugler, A. Rouhi
PhD Students: S. Cocciardi, K. Faber, S. Grasedieck, H. Kiryakos, K. Krowiorz, E. Schneider, V. Schneider, B. Stolze
Study Programme Experimental Medicine Students: S. Häbe
Additional Members of Thesis Advisory Committees: H. Geiger (Ulm), S. Fröhling (Heidelberg), K. Rippe (Heidelberg), P. Lichter (Heidelberg), T. Kindler (Mainz), H.J. Fehling (Ulm), K. Spiekermann (Munich), S. Fulda (Frankfurt)

Department of Internal Medicine III

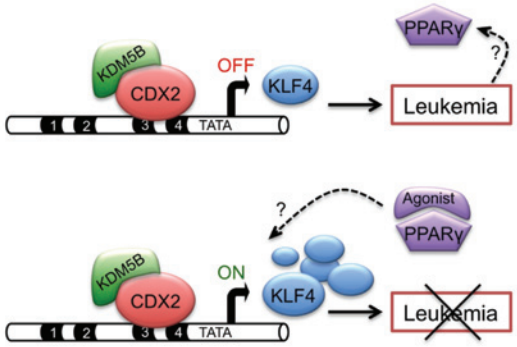
Characterization of Pathogenic Lesions and Development of Novel Therapies in Patients with Hematopoietic Malignancies and Solid Tumors.

Head: Hartmut Döhner

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the Western world, but the underlying pathomechanism remains unclear. Billy Jebaraj focuses on: (i) mutations in signaling pathways in CLL; and (ii) the pathogenic link between telomere attrition in a genetically related disease known as mantle cell lymphoma (MCL). Telomere length was found highly variable in MCL, and telomere dysfunction in MCL was evident from a comparison with normal B-cells but had no significant association with any biological or clinical feature. This was in contrast to CLL where a significant correlation of short telomeres with poor prognostic subgroups was confirmed. This indicates that, as opposed to CLL, telomere length is not of prognostic relevance in MCL (Jebaraj, Blood 2012).

Recently, we have aimed to elucidate the biological basis of Acute Myeloid Leukemia (AML) by means of gene expression profiling (GEP), SNP microarray analysis, DNA methylation profiling, and next generation sequencing (NGS) approaches. Currently, we are following up selected newly identified leukemia-associated gene mutations, such as cohesion factor complex aberrations, in order to investigate their functional relevance. Furthermore, by whole exome sequencing within a longitudinal study of paired diagnostic and relapse AML samples, we are focusing our efforts on genomic aberrations associated with treatment resistance and clonal evolution (PhD project Sibylle Cocciardi).

Several projects of the department are centered on the identification of molecular abnormalities in hematopoietic and epithelial malignancies that are important for the initiation and/or maintenance of the transformed phenotype Katrin Faber has used transcriptional profiling followed by functional hit validation to search for genetic vulnerabilities in specific subtypes of AML. She was able to identify the tumor suppressor KLF4 as a target of the leukemogenic oncogene CDX2, which is aberrantly expressed in 90% of patients with AML. In addition, she could show that PPARg agonists derepressed KLF4 and were preferentially toxic to $CDX2^{+}$ leukemic cells, thus opening a new route for drugging AML through modulation of PPARg signaling (Faber et al., JCI 2012). Britta Stolze



Model of CDX2 actions in AML development. Top panel: Aberrant CDX2 expression leads to downregulation of KLF4 ("OFF") through binding to distinct sites in the KLF4 regulatory region and recruitment of the H3K4 demethylase KDM5B, thereby contributing to leukemogenesis. Aberrant CDX2 expression also causes deregulated PPARγ signaling via an unknown mechanism. The bottom panel shows that PPARγ agonist treatment upregulates KLF4 expression ("ON"), thereby inhibiting the viability and proliferation of AML. Further studies are required to elucidate the mechanism whereby aberrant CDX2 expression and loss of KLF4 cause deregulated PPARγ signaling (dashed arrows).

is applying large-scale proteomic and phospho-proteomic strategies to determine the mechanism underlying the selective requirement for the serine/threonine kinase STK33 in cancers driven by mutations in KRAS, the most frequently mutated human oncogene with a high prevalence in lung, colon and pancreatic cancer.

Much evidence implicates non-coding RNAs, such as microRNAs (miRNAs), as contributing factors in the pathogenesis of hematological neoplasms. Based on a microfluidics screen and identifying characteristic miRNAs in hematopoietic subpopulations, we centered on multiple functional screens to identify the functional role of candidate miRNAs in normal and malignant hematopoiesis (PhD Project Kathrin Krowiorz). In parallel, we further investigate epigenetic mechanisms regulating the expression of miRNAs during leukemogenesis (PhD project Edith Schneider).

Recently, circulating miRNAs were discovered in blood and were found to reflect the presence of malignant and non-malignant diseases. Therefore, we explore the potential of circulating miRNAs as biomarkers in leukemias and investigate their functional role in cell-to-cell communication (PhD project Sarah Grasedieck).

Another key aspect in leukemia treatment strategies is the immune system. We have been focusing on leukemia-associated antigens such as epitopes derived from $NPM1^{mut}$, PRAME, RHAMM or WT1. We analyzed their expression in sorted cell populations of fresh AML patient cells using CD34 and CD38 markers. Gene expression analyses (Affymetrix/Taq-Man) have been performed that show significant expression differences in the leukemic stem cell, such as fraction, the hematopoietic stem cell fraction and the bulk, for different LAAs. We have been validating these results using functional assays, such as CFUs and chromium release assays, to define one target structure that might be suitable for an immunotherapeutic approach (PhD project Vanessa Schneider).

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Selected Publications:

- *Dolnik A, Engelmann JC, Scharfenberger-Schmeer M, Mauch J, Kelkenberg-Schade S, Haldemann B, Fries T, Krönke J, Kühn MWM, Paschka P, Kayser S, Wolf S, Gaidzik VI, Schlenk RF, Rücker FG, Döhner H, Lottaz C, Döhner K, Bullinger L (2012): Commonly altered genomic regions in acute myeloid leukemia are enriched for somatic mutations involved in chromatin-remodeling and splicing. Blood. 120(18):e83-92.*
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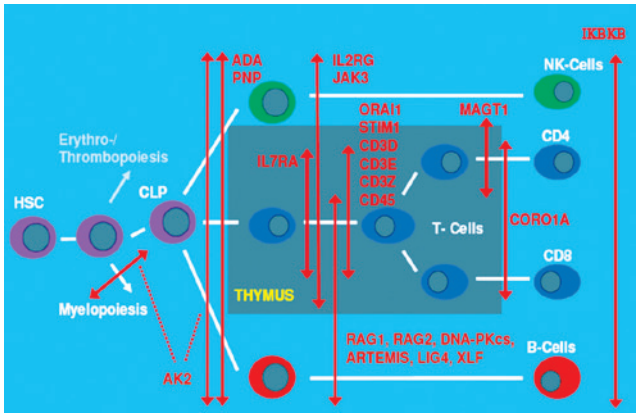
Institute of Transfusion Medicine

Genetics and Molecular Pathophysiology of Immunodeficiencies

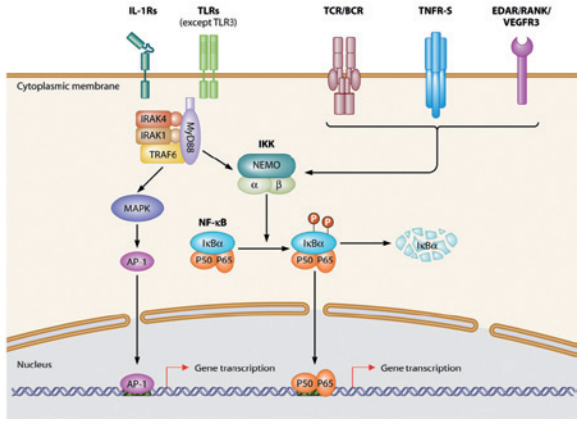
Head: Hubert Schrezenmeier

Severe combined immunodeficiency (SCID) refers to a genetically and clinically heterogeneous group of disorders with defective cellular and humoral immune functions. Patients with SCID present in infancy with recurrent, persistent infections by opportunistic viral and fungal organisms. The common characteristic of all types of SCID is the absence of T cell-mediated cellular immunity due to a defect in T cell development or function. If present, B cells can be either primarily defective or merely deprived of adequate T cell signals. Without treatment, the disease is invariably lethal within the first year of life. The most common classification of SCID cases relies on immunophenotyping according to the presence or absence of T, B and NK cells. Recent progress in the molecular characterization of SCID defects allows the definition and follow-up of more homogeneous cohorts according to the underlying genetic defect. The elucidation of the molecular defects in SCID patients has contributed to the understanding of very basic cellular mechanisms such as purine metabolism (ADA-, PNP-defect), signaling cascades (CD3 components, interleukine receptors and respective downstream factors), transcription factor behavior (MHCII-defects), Ca-channels (ORAI and STIM-deficiency), mitochondrial energy metabolism (AK2 defect), thymic T cell egress (CORO1A-defect), antigen receptor structure (TRAC-defect) and DNA repair (V[D]J recombination and NHEJ factors) (Fig.1).

The Team:
Head of Institute: H. Schrezenmeier
Head of Department: K. Schwarz
Group Leaders/Postdocs: M. Lorenz, D. Niewolik, U. Pannicke, F. Radecke
PhD Student: M. Führer
Additional Members of Thesis Advisory Committees: S. Ehl (Freiburg), H.J. Fehling (Ulm)



Development of B and T lymphocytes and NK cells from hematopoietic stem cells to mature, functional immune cells. Some genes which are required during the differentiation or activation process are depicted in red; red arrows indicate the developmental block associated with the particular gene defect.



(Picard et al., Clin. Microbiol. Rev., 2011)

Signal transduction pathways which involve IKKbeta.

Very recently, we elucidated the molecular defect and part of the molecular pathophysiology of a peculiar SCID entity: Unexpectedly, the patients exhibit normal numbers of lymphocytes which cannot be activated properly. Deficiencies in the nuclear encoded *IKBKB* gene are responsible for this SCID type. The protein IKKbeta encoded by *IKBKB* is involved in multiple signal transduction pathways including innate, inflammatory and antigen receptor stimulation (Fig. 2). Although many genetic defects in SCID patients have now been detected. About 30% of SCID variants still lack a genetic diagnosis.

In collaboration with the bone marrow transplantation unit of the Clinics for Pediatric- and Adolescent Medicine (University Hospital Ulm), in our group novel SCID cases are constantly identified on the basis of clinical and immunological data. The focus of our group is to analyze the underlying genetic defect of the SCID patients and to unravel the molecular pathophysiology of their lymphocyte defect. We make use of modern molecular tools, including loss of heterozygosity screens and candidate gene/transcriptome/exome sequencing, to identify the molecular basis of so far unresolved SCID cases. Functional complementation assays are performed with candidates from the molecular screen.

A better definition of the genetic, immunologic and phenotypic variability of these patients will help to define additional facets of the development and function of the human immune system and in addition will provide a faster road to diagnosis and potential therapy of this life-threatening disease.

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Selected Publications:

- *Kühl JS, Schwarz K, Münche A, Schmugge M, Pekrun A, Meisel C, Wahn V, Ebell W, von Bernuth H (2011): Hyperbillirubinemia, cholestatic hepatitis and fetal hepatic failure in TlowB-NK- Severe Combined Immunodeficiency caused by Adenosine Deaminase Deficiency (ADA-SCID). Klinische Pädiatrie, 2011; 223: 85-89.*
- *Pannicke U, Hönig M, Schulze I, Rohr J, Heinz G, Braun S, Janz I, Rump EM, Seidel MG, Matthes-Martin S, Soerensen J, Greil J, Stachel DK, Belohradsky BH, Albert MH, Schulz AS, Ehl S, Friedrich W, Schwarz K (2010): The most frequent DCLRE1C (ARTEMIS) mutations are based on homologous recombination events. Human Mutation, 2010; 31: 197-207.*
- *Rohr J*, Pannicke U*, Döring M, Schmidt-Graeff A, Wiech E, Busch A, Speckmann C, Müller I, Lang P, Handgretinger R, Fisch P, Schwarz K, Ehl S (2010): Infant-onset chronic inflammatory bowel disease can be caused by hypomorphic mutations in the gene encoding Artemis. J ClinicImmunol. 30: 314-320. *Equal contribution.*
- *Pannicke U, Hönig M, Hess I, Holzmann K.H, Friesen C, Rump EM, Barth TF, Rojewski MT, Schulz A, Boehm T, Friedrich W, Schwarz K (2009): Reticular dysgenesis (aleukocytosis) is caused by mutations in the gene encoding mitochondrial adenylate kinase 2. Nat Genet. 41:101-105.*
- *Schütz C, Gudowius S, Schneider DT, Huck K, Manfras B, Pannicke U, Megahed M, Willemze R, Göbel U, Schulz A, Debatin KM, Friedrich W, Schwarz K, T. Niehues, T (2008): A novel type of combined immunodeficiency caused by hypomorphic RAG mutations. N Engl J Med. 358:2030-2038.*
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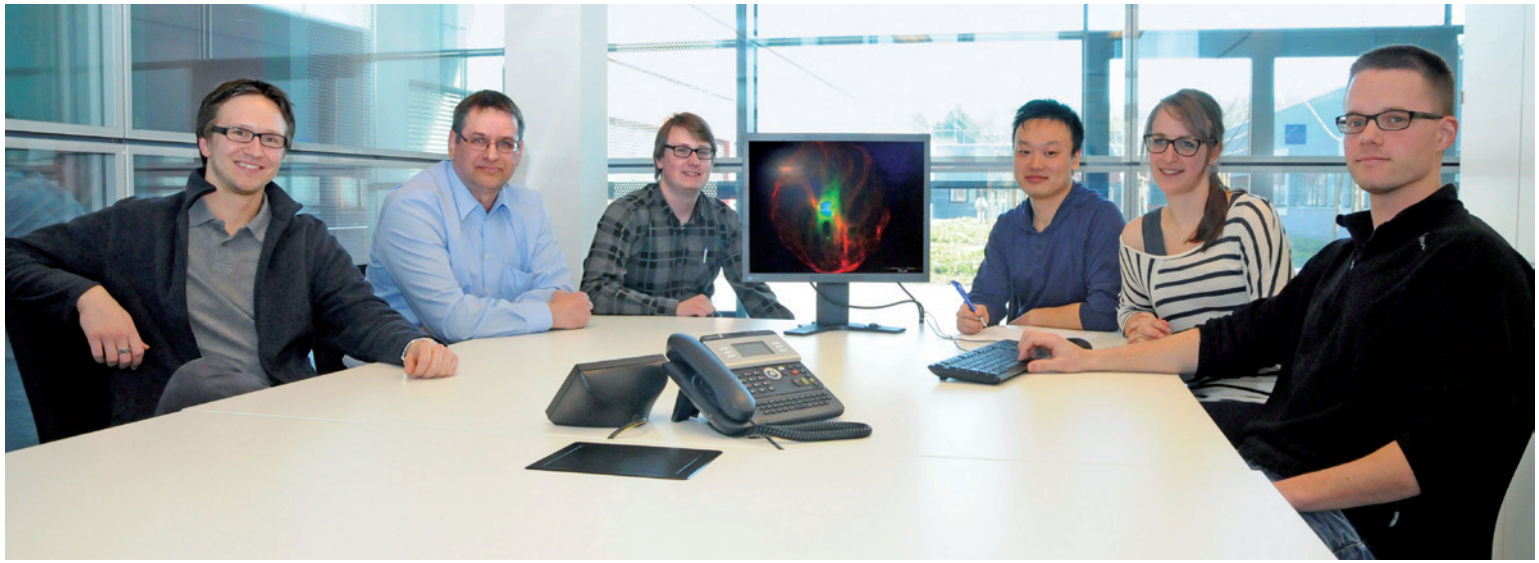

Department of General and Visceral Surgery

Regulation and Functions of Members of the Casein Kinase 1 (CK1) Family and Especially of CK1δ

Head: Doris Henne-Bruns

Research in the Department of General and Visceral Surgery is concentrated on malignant diseases and obesity-related research. Cancer research is focused on basic and translational research projects, including the characterization of alterations in signal transduction pathways, and the identification of new target molecules and prognostic factors, especially for pancreatic, colorectal and gastrointestinal stroma tumors.

Our group is interested in the validation of CK1 isoforms to gain detailed information regarding their functions and regulation. Members of the highly conserved CK1 family are ubiquitously expressed in all eukaryotes. Mammalian CK1 isoforms (α, β, γ, δ, ε) and their splice variants are involved in

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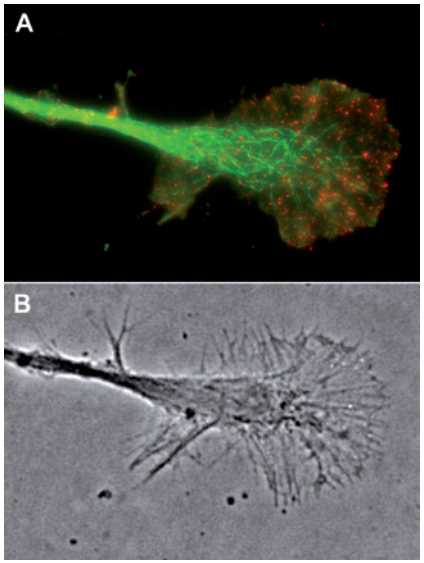

Localization of CK1δ expression in RGCs
Immunofluorescence staining (A) and phase contrast image (B) of the neurite growth cone of a retinal ganglion cell (RGC) using the CK1δ-specific monoclonal antibody 128A (red) and the βIII-tubulin-specific monoclonal antibody RB-9249-Po (green). Epifluorescence microscopy of RGCs revealed that CK1δ is located in granular particles aligned at microtubules all over the growth cone.

diverse cellular processes, including membrane trafficking, circadian rhythms, cell cycle progression, chromosome segregation, apoptosis, differentiation and regeneration processes. Mutations and deregulation of CK1 expression and activity have been linked to various diseases, including neurodegenerative disorders, as in Alzheimer's and Parkinson's diseases, sleeping disorders, and proliferative diseases such as cancer. Consequently, recent interest in its role in carcinogenesis and degenerative diseases, and in developing CK1-specific inhibitors, has enormously increased.

Within the last two years, Joachim Bischof has concentrated on: (i) the identification of cellular kinases which influence CK1δ activity by phoshorylating CK1δ within its C-terminal regulatory domain; (ii) the role of CK1δ in the regeneration of retinal ganglion cells after optic nerve injury; and (iii) the identification of new CK1 isoform-specific small inhibitors. At the same time, Julia Richter has focused on the characterization of the role of CK1δ in tumorigenesis and the progression of colorectal cancer.

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Selected Publications:

- *Kornfeld JW, Baitzel C, Könner A, Nicholls H, Vogt M, Herrmanns K, Scheja L, Haumaitre C, Wolf AM, Knippschild U, Seibler J, Cereghini S, Heeren J, Stoffel M, and Brüning JC (2013): Obesity-Induced Overexpression of miR-802 Impairs Glucose Metabolism Via Posttranscriptional Silencing of Tcf2/Hnf1β. Nature 494:111-5. doi: 10.1038/nature11793.*
- *Hirner H, Gunes C, Bischof J, Wolff S, Grothey A, Kuhl M, Oswald F, Wegwitz F, Bosl MR, Trauzold A, Henne-Bruns D, Peifer C, Leithauser F, Deppert W, and Knippschild U (2012): Impaired CK1 delta activity attenuates SV40-induced cellular transformation in vitro and mouse mammary carcinogenesis in vivo. PLoS One 7, e29709.*
- *Bischof J, Leban J, Zaja M, Grothey A, Radunsky B, Othersen O, Strobl S, Vitt D, and Knippschild U (2012): 2-Benzamido-N-(1H-benzo[d]imidazol-2-yl)thiazole-4-carboxamide derivatives as potent inhibitors of CK1delta/epsilon. Amino Acids 43, 577-591. Epub 2012.*
- *Bischof J, Muller A, Fander M, Knippschild U and Fischer D (2011): Neurite Outgrowth of Mature Retinal Ganglion Cells and PC12 Cells Requires Activity of CK1delta and CK1epsilon. PLoS One 6, e20857.*
- *Giamas G, Man YL, Hirner H, Bischof J, Kramer K, Khan K, Lavina Ahmed SS, Stebbing J and Knippschild U (2010): Kinases as targets in the treatment of solid tumors. Cellular Signalling. 22(7):984-1002. doi: 10.1016/j.cellsig.2010.01.011. Epub 2010 Jan 21.*
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Department of Orthopedic Trauma, Hand, Plastic and Reconstruction Surgery

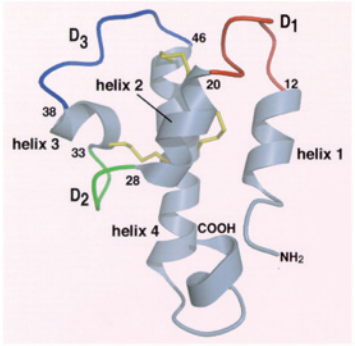
Research in the Department of Orthopedic Trauma, Hand, Plastic and Reconstruction

Head: Florian Gebhard

The Team:
Head of Department: F. Gebhard
Professor: M. Huber-Lang
Study Programme Experimental Medicine Student:
B. Schäfer

Surgery mainly focuses on the inflammatory response after severe tissue injury by using various clinically relevant ex vivo and in vivo trauma models. In a retranslational approach from clinical “damage control surgery” of polytrauma patients, our group is especially interested in the “molecular damage control” and management after polytrauma, which is also a main topic of the Center of Musculoskeletal Research (ZMFU) and DFG Research Unit KFO 200, Ulm University.

Sampling of serum from polytrauma patients in the Trauma-Laboratory for analyses of the immune response.



Complement activation product C5a as a main target molecule for immune-modulation after severe tissue injury.

After polytrauma, the human body is exposed to numerous danger- and pathogen-associated molecular patterns (DAMPS/PAMPS). These molecular patterns are detected by the innate immune system and specific danger messages are transmitted to the cellular defense system ("first line of defense"). In parallel, an early activation of various protein kinase cascades occurs, especially of the complement system and coagulation system. The resulting fluid phase and cellular inflammatory reaction is accompanied by a complex neuro-endocrine stress reaction, which all intend to clear the "molecular danger." In the clinical setting, this inflammatory response is known as systemic inflammatory response syndrome (SIRS), which can end in multi-organ failure and death.

In this context, the project of Berndson Schäfer investigates the early DAMP/PAMP sensing of trauma-released subcellular structures, such as dsDNA, ssRNA, mitochondria, mtDNA, histones and membrane fragments, and their potency to activate the coagulation and complement cascade as an early "master alarm" system to trigger the systemic inflammatory response. Furthermore, using in vivo models of multiple injury, the capacity of complement modulating therapeutic strategies (inhibition of C5a-C5aR interaction) are evaluated for beneficial local and systemic immune effects and their capacity to control the molecular danger response and to improve organ function and clinical outcome.

The studies are supported by DFG HU823/3-2 and KN-475/5-2.

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www.uniklinik-ulm.de/unfallchirurgie

Selected Publications:

- *Kanse SM, Gallenmueller A, Zeerleder S, Stephan F, Rannou O, Denk S, Etscheid M, Lochnit G, Krueger M, Huber-Lang M (2012): Factor VII-activating protease is activated in multiple trauma patients and generates anpahylatoxin C5a. J Immunol 188:2858-65.*
- *Burk AM, Martin M, Flierl MA, Rittirsch D, Helm M, Lampl L, Bruckner U, Stahl GL, Blom AM, Perl M, Gebhard F, Huber-Lang M (2012): Early complementopathy after multiple injuries in humans. Shock 37:348-54.*
- *Amara U, Flierl MA, Rittirsch D, Klos A, Chen H, Acker B, Brückner UB, Nilsson B, Gebhard F, Lambris JD, Huber-Lang M (2010): Molecular intercommunication between the complement and coagulation systems. J Immunol. 185, 5628-36.*
- *Amara U, Kalbitz M, Perl M, Flierl MA, Rittirsch D, Weiss M, Schneider M, Gebhard F, Huber-Lang M (2010): Early expression changes of complement regulatory proteins and C5A receptor (CD88) on leukocytes after multiple injury in humans. Shock. 33(6):568-75.*
- *Rittirsch D, Flierl MA, Nadeau BA, Day DE, Huber-Lang M, Mackay CR, Zetoune FS, Gerard NP, Cianflone K, Kohl J, Gerard C, Sarma JV, Ward PA (2008): Functional roles for C5a receptors in sepsis. Nat Med. 14, 551-557.*
- *Huber-Lang M, Sarma JV, Zetoune FS, Rittirsch D, Neff TA, McGuire SR, Lambris JD, Warner RL, Flierl MA, Hoesel LM, Gebhard F, Younger JG, Drouin SM, Wetsel RA, Ward PA (2006): Generation of C5a in the absence of C3: a new complement activation pathway, Nat Med. Jun12(6), 682-7.*

www.schirinkretschmann.de/You-may-have-a-Pink-Cadillac

Breathing life into an artwork by Schirin Kretschmann, "You may have a Pink Cadillac, 2011," a permanent installation at the Center for Biomedical Research, Ulm.

The Team:
Head of Department: S. Kochanek
Professor: S. Kochanek
Group Leader: PD Dr. F. Kreppel
Postdocs: S. Espenlaub, A. Hoffmeister, B. Huang, T. Lucas
PhD Students: V. Emmerling, R. Kratzer, L. Krutzke, J.-M. Prill
Study Programme Experimental Medicine Student:
M. Scheitenberger
Additional Members of Thesis Advisory Committees:
H.J. Fehling (Ulm), H. Geiger (Ulm), M. Hörer (Laupheim), M. Ogris (Munich), P. Ng (Houston), R. Schirmbeck (Ulm), K. Ulbrich (Prague)

Department of Gene Therapy

Viral Vectors for Therapeutic Applications

Head: Stefan Kochanek

We are strongly interested in the development of new therapeutic procedures for diseases, for which there is currently no treatment. We use viral and non-viral gene transfer to introduce genes into cells, cell culture and also in vivo. Vectors loaded with specific genes may either help to treat certain diseases (somatic gene therapy) or, in the case of infectious diseases, to prevent them (genetic vaccination). Complex hurdles must be overcome before safe and successful gene therapy can be possible. This can only be achieved by means of a close cooperation of various scientific and medical disciplines. A strong scientific focus is on the development of gene transfer vector technology by genetic and chemical engineering and the use of improved vectors for selected inborn or acquired disorders as well as new vaccine strategies in preclinical models.

Viruses as a Delivery Vehicle for Genes

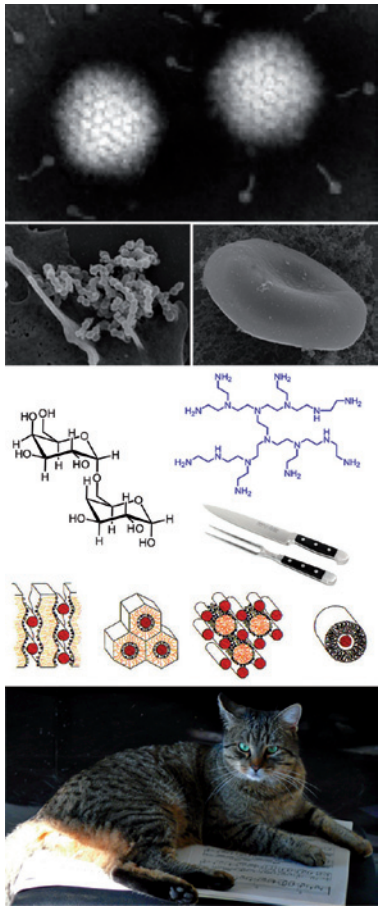
Since viruses have evolved together with their host, they are by nature very efficient delivery vehicles for their genes. By removing one or several essential genes, they can then be used for efficient gene transfer in vitro and in vivo to specific cell types. Adenoviruses have been studied for many years and are very well understood from a molecular point of view. Several projects in our laboratory thus relate either to the improvement of adenovirus vectors or to their use in different genetic and non-genetic diseases.

Overcoming Barriers in Gene Therapy

So far, in vivo gene therapy has only been successful in a few cases. The main reason for this is the lack of efficient gene transfer in vivo due to the interaction of vector particles with barriers in the blood and in tissues. In two separate PhD projects, Jan-Michael Prill and Lea Krutzke use chemical and genetic modification of adenovirus vectors to identify and overcome barriers imposed by human blood in order to achieve targeted gene delivery to specific tissues.

Vectors for Genetic Vaccination

Genetic vaccination shows considerable promise as a solution to overcome the limitations of classical vaccines. However, neither the mechanisms of induction nor the persistence of adaptive immune responses, when the antigen is expressed following gene transfer, are completely understood. In the past, we have observed that the immunogenicity of adenovirus vectors limits the multispecificity of T cell



Some of our tools for gene transfer: we are flexible... and we also like arts and music.

responses raised against vector-encoded antigens and we design experiments with the aim of better understanding basic mechanisms. Such studies will likely open avenues for an improved vector design based on a better understanding of the basic principles of the induction of immune responses in the context of gene transfer. In her PhD project, Ramona Kratzer, uses adenovirus as a vaccine vector and attempts to improve the immunogenicity of encoded antigens by optimizing the coding sequence, with a special focus on antigen glycosylation.

Oncolytic Vectors for Tumor Therapy

A new focus of the laboratory is the development of oncolytic viruses for the treatment of solid cancers and the testing of these vectors in improved models of pancreatic cancer. These studies take into account the complex composition of solid tumors that, in addition to neoplastic cells, contain many other cell types, such as stromal cells and endothelial cells, and also an extracellular matrix.

Primary Cell Immortalization and Vector Production

One of our long-standing interests is also the immortalization and characterization of primary human cells from amniotic fluid (MD project of Marina Scheitenberger) with the aim of generating cell lines that are suitable for industrial production of viral vectors.

Industrial Production of Adeno-Associated Virus (AAV) Vectors

In her PhD project conducted at Rentschler Biotechnology GmbH, Laupheim, and supervised by Dr. Markus Hörer, Director Virus-based Biologics, Verena Emmerling will generate improved production cell lines for a high titer production of AAV vectors.

Neurodegenerative Diseases

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder that is caused by the expansion of a CAG triplet repeat in exon 1 of huntingtin, a very large protein that is located in the cytoplasm of many, including neuronal, cell types. In our work we try to improve our understanding of the function of normal and mutant huntingtin either by recombinant production of full-length huntingtin or by using adenovirus vectors as a tool for functional studies with the long-term goal of contributing to the development of a treatment for HD.

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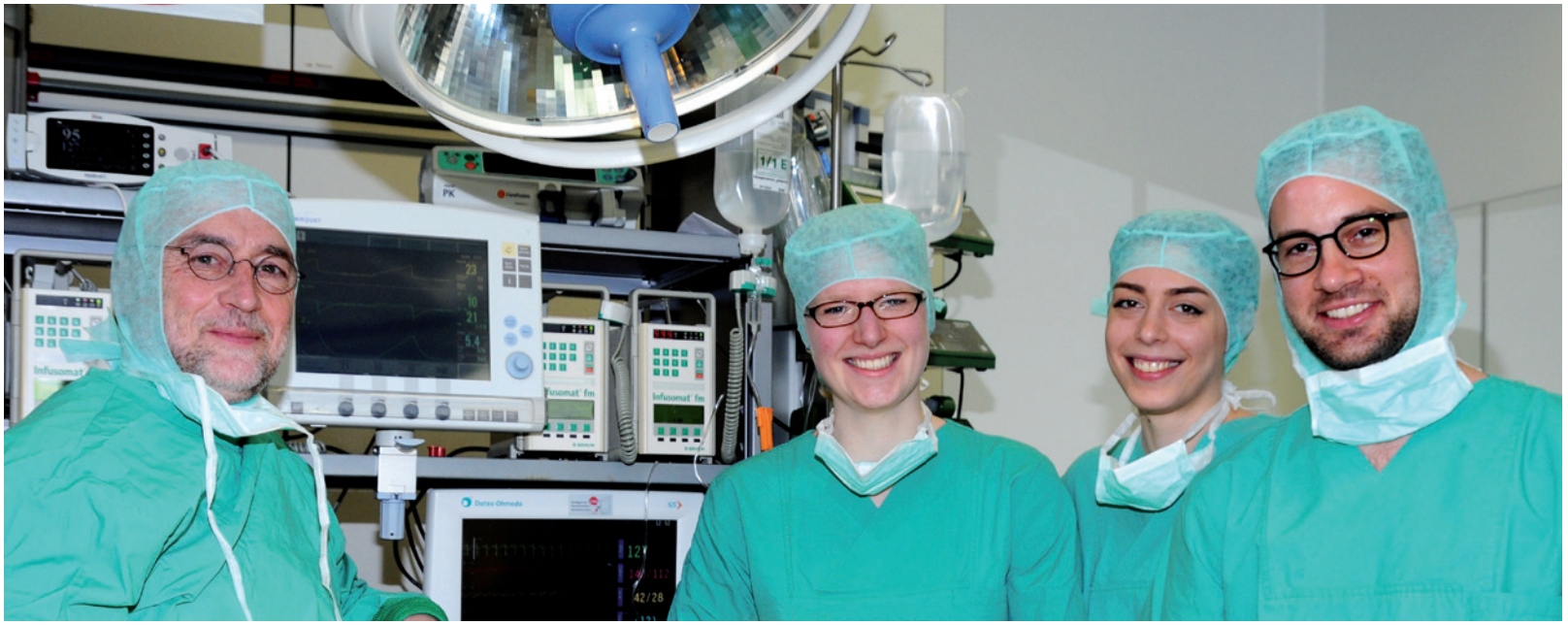
Selected Publications:

- *Kreppel F, Kochanek S (2008): Modification of adenovirus gene transfer vectors with synthetic polymers: a scientific review and technical guide, Mol Ther 16, 16-29.*
- *Kron MW, Engler T, Schmidt E, Schirmbeck R, Kochanek S, Kreppel F (2011): High-capacity adenoviral vectors circumvent the limitations of ΔE1 and ΔE1/ΔE3 adenovirus vectors to induce multispecific transgene product-directed CD8 T-cell responses. J Gene Med. 13(12):648-57.*
- *Prill JM, Espenlaub S, Samen U, Engler T, Schmidt E, Vetrini F, Rosewell A, Grove N, Palmer D, Ng P, Kochanek S, Kreppel F (2011): Modifications of adenovirus hexon allow for either hepatocyte detar-geting or targeting with potential evasion from Kupffer cells. Mol Ther. 19:83-92.*
- *Zong S, Kron MW, Epp C, Engler T, Bujard H, Kochanek S, Kreppel F (2011): ΔE1 and high-capacity adenoviral vectors expressing full-length codon-opti-mized Merozoite surface protein 1 for vaccination against Plasmodium falciparum. J Gene Med. 13:670-9.*
- *Dong X, Zong S, Witting A, Lindenberg KS, Kochanek S, Huang B (2012): Adenovirus vector-based in vitro neuronal cell model for Huntington's disease with Human disease-like differential aggregation and degeneration. J Gene Med. 14, 468-81.*
- *Laakkonen JP, Engler T, Romero IA, Weksler B, Couraud PO, Kreppel F, Kochanek S (2012): Transcellular targeting of fiber- and hexon-modified adenovirus vectors across the brain microvascular endothelial cells in vitro. PLoS One. 7(9):e45977.*



Department of Anesthesiology

Effects of the PPAR-β/δ Agonist GW0742 During Resuscitated Porcine Septic Shock

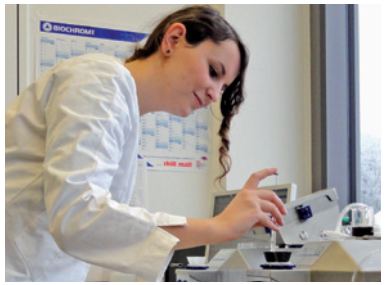
Head: Michael Georgieff

The scientific focus of the department is the development of new strategies to prevent multiple organ failure after circulatory shock resulting from trauma and hemorrhage, sepsis or ischemia/reperfusion-injury. Particular attention is paid to the clinical relevance of the protocol design, i.e. the integration of standard intensive care measures (e.g. mechanical ventilation, invasive hemodynamic monitoring, circulatory support etc.) into experimental setup in order to mimic the clinical scenario as far as possible. Innovative interventions studied target the systemic inflammatory response, the interplay of oxidative and nitrosative stress as well as antioxidant defense mechanisms, the cellular energy metabolism and the activity of the mitochondrial respiratory chain.

The Team:
Head of Department: M. Georgieff
Professors: P. Radermacher, M. Schneider
Group Leaders/Postdocs: E. Calzia, K. Föhr, J. Vogt, M. Weiss
PhD Students: B. Eilts, F. Gottschalch, J. Matallo, F. Tillmans, U. Wachter
Study Programme Experimental Medicine Students: M. Reize, S. Riedesser
Additional Members of Thesis Advisory Committees: E. Calzia (Ulm), M. Huber-Lang (Ulm)

In unresuscitated rodent models of septic shock activation of the peroxisome proliferator activator, receptor-β/δ (PPAR-β/δ) improved visceral organ function. All the existing data, however, originate from rodent models, which did not integrate standard therapy aimed at maintaining adequate systemic hemodynamics. In addition, all these experiments were performed in young and healthy animals, which is in sharp contrast to the clinical scenario of patients with pre-existing co-morbidities such as atherosclerosis and/or chronic obstructive pulmonary disease. Therefore, our group focuses on the clinical potential of the newly PPAR-β/δ agonist GW0742 in a porcine model of long-term, fully resuscitated, fecal peritonitis-induced septic shock. In order to mimic the clinical scenario we use animals with familial hypercholesterinemia, which, due to a special diet, develop the typical symptoms of a "metabolic syndrome" that causes ubiquitous vascular atherosclerosis and ultimately results in chronic renal dysfunction and histopathological alterations of the kidney tissue. The present data suggest that in contrast to the existing literature, the therapeutic efficacy of exogenous PPAR-β/δ agonists is nearly completely blunted under conditions of pre-existing kidney disease, most likely due to the markedly reduced tissue PPAR-β/δ-receptor expression associated with the increased oxidative stress and reduced endogenous nitric oxide production which is typical for this disease.

Student analyzing an immune histochemistry staining of the kidney for the PPAR-β/δ-receptor expression.



Student performing the measurement of the mitochondrial activity of kidney parenchyma cells using "high resolution respirometry."

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Selected Publications:

- *Bracht H, Scheuerle A, Gröger M, Hauser B, Matallo J, McCook O, Seifritz A, Wachter U, Vogt JA, Asfar P, Matejovic M, Möller P, Calzia E, Szabó C, Stahl W, Hoppe K, Stahl B, Lampl L, Georgieff M, Wagner F, Radermacher P, Simon F (2012): Effects of intravenous sulfide during resuscitated porcine hemorrhagic shock. Crit Care Med. 40:2157-67.*
- *Gröger M, Matallo J, McCook O, Wagner F, Wachter U, Bastian O, Gierer S, Reich V, Stahl B, Huber-Lang M, Szabó C, Georgieff M, Radermacher P, Calzia E, Wagner K (2012): Temperature and cell-type dependency of sulfide-effects on mitochondrial respiration. Shock. 38:367-74.*
- *Simon F, Scheuerle A, Gröger M, Stahl B, Wachter U, Vogt J, Speit G, Hauser B, Möller P, Calzia E, Szabó C, Schelzig H, Georgieff M, Radermacher P, Wagner F (2011): Effects of intravenous sulfide during porcine aortic occlusion-induced kidney ischemia/reperfusion injury. Shock. 35:156-63.*
- *Wagner F, Wagner K, Weber S, Stahl B, Knöferl MW, Huber-Lang M, Seitz DH, Asfar P, Calzia E, Senftleben U, Gebhard F, Georgieff M, Radermacher P, Hysa V (2011): Inflammatory effects of hypothermia and inhaled H2S during resuscitated, hyperdynamic murine septic shock. Shock. 35:396-402.*
- *Simon F, Scheuerle A, Gröger M, Vcelar B, Möller P, Georgieff M, Calzia E, Radermacher P, Schelzig H (2011): Comparison of carbamylated erythropoietin-FC fusion protein and recombinant human erythropoietin during porcine aortic balloon occlusion-induced spinal cord ischemia/reperfusion injury. Intensive Care Med. 37:1525-33.*
- *Wagner F, Scheuerle A, Weber S, Stahl B, McCook O, Knöferl MW, Huber-Lang M, Thomas J, Asfar P, Szabó C, Möller P, Gebhard F, Georgieff M, Calzia E, Radermacher P, Wagner K (2011): Cardiopulmonary, histological and inflammatory effects of intravenous H2S after blunt chest trauma-induced lung contusion in mice. J Trauma. 71:1659-67.*

The Team:
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Professors: H. Geiger, J.M. Weiss
Labmanager: M. Wlaschek
Group Leaders/Postdocs: A. Basu, A. Brown, M.C. Florian, M. Gatzka, S. Iben, D. Jiang, P. Maity, T. Peters, A. Sindrilaru, R. Tiwari, N. Treiber, S. Vander Beken
PhD Students: R. Assfalg, J. de Vries, V. Farsam, F. Ferchiu, O.G. Gonzalez, A. Gregoryan, N. Guidi, S. Koch, S. Köllner, A. Kügler , P. Meyer, Y. Qi, Kamayani Singh, Karmveer Singh, B. Überle
Study Programme Experimental Medicine Student: B. Meier
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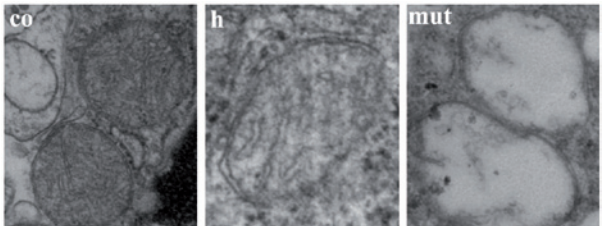
Department of Dermatology and Allergic Diseases

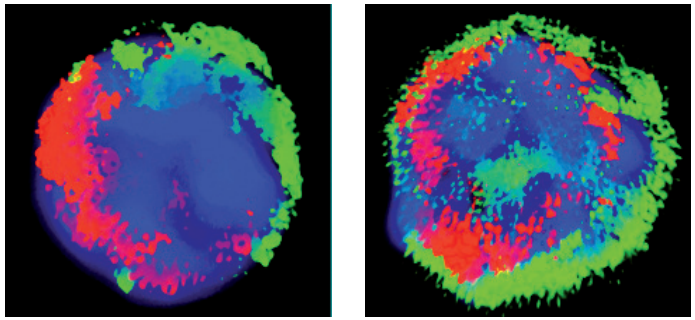
Work Group: Aging: Mechanisms and Novel Preventive Strategies

Head: Karin Scharffetter-Kochanek

Life expectancy has risen in developed societies and the mystery of aging has still not been resolved. The prevalence of infectious, autoimmune, endocrine and mental diseases and of connective tissue degeneration has sharply increased. We are testing the hypothesis whether oxidative stress and/or DNA damage pathways are of general relevance to the intrinsic and extrinsic aging of the connective tissue and life span. The connective tissue-specific SOD2 deficient mouse shows a complex aging phenotype. We are interested in the role of free radicals and its impact on signaling pathways involved in the organization of the extracellular matrix, organ maintenance, metabolic homeostasis and renewal capacities of stem cells (Karmveer Singh). The DNA damage response pathway (DDR) resulting in cellular senescence is addressed in dermal fibroblasts (Florentina Ferchiu). Stromal cells influence the tumorigenesis of skin tumors. The role of senescent fibroblasts in tumor progression is investigated on the cellular and organismic levels (Vida Farsam). The complex cellular interactions in aging are addressed in a systems biology approach with specific focus on NFkB (Patrick Meyer). The nucleolus is studied as stress sensor of DDR and related signaling pathways (Robin Assfalg) that possibly also affect ribosomal biogenesis (Sylvia Koch). The regenerative and repair effect of mesenchymal stem cells (MSC) and their mediators is analyzed in acute wound healing in mice (Yu Qi). Molecular and cellular mechanisms of wound repair by MSC in mouse models of impaired regeneration are analyzed (Andrea Kügler).



Electron micrograph of Sod2-deficient fibroblast mitochondria (mut) reveals a severely disturbed structure with loss of cristae and degeneration of structure compared to Sod2 heterozygous (h) and Sod2-competent fibroblasts (co).



The distribution of tubulin (green) and acetylated histone 4 lysine 16 (red) in hematopoetic stem cells shows polarity in a young cell (now left) that is lost in an older cell (now right). The nucleus (blue) has been rendered slightly transparent to allow for visualization of the distribution of acetylated histone 4 lysine 16 within the nucleus. The image was acquired and analyzed by M.C. Florian. Based on an idea from M.C. Florian, H. Geiger, and A. Ronchi.

Work Group: Hematopoiesis and Hematopoietic Stem Cells

Head: Hartmut Geiger

Hematopoiesis is the process by which mature blood cells are formed from hematopoietic stem cells (HSC). Research in our laboratory is centered on stem cell aging, leukemia and DNA damage responses. In mice and humans there is a successive decline in stem cell function from adulthood to old age. This decline has been associated with perturbed tissue homeostasis and impaired injury repair in aged individuals. HSCs from aged animals are impaired by their inability to self-renew, to contribute efficiently to hematopoiesis and to differentiate. Our hypothesis is that distinct molecular and cellular pathways contribute to stem cell aging. Our data supports the view that the elevated activity of small RhoGTPases found in hematopoietic cells in aged animals results in altered adhesion to stroma cells. We were able to demonstrate that aged stem cells are more active inside the bone marrow niche in vivo, which most likely results in less stable stem cell stroma interactions. Altered adhesion to the niche/stroma could be one underlying cause for phenotypes associated with aged HSCs. Altered DNA damage response pathways in aged HSCs might be critical for increased incidence of age-associated disease. We are developing molecular tools to determine DNA damage responses in HSCs (Bettina Überle). Aging in stem cells might contribute to an increase in leukemia with age. We are interested in determining whether the age of the stem cell niche/stroma influences leukemia development (Novella Guidi).

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Selected Publications:

- *Sindrilaru A, Peters T, Wieschalka S, Baican C, Baican A, Peter H, Hainzl H, Schatz S, Qi Y, Schlecht A, Weiss JM, Wlaschek M, Sunderkoetter C, Scharffetter-Kochanek K (2011): An unrestrained inflammatory M1 macrophage population induced by iron impairs wound healing in humans and mice, J Clin Invest 121, 985-997.*
- *Treiber N, Maity P, Singh K, Kohn M, Keist AF, Ferchiu F, Sante L, Frese S, Bloch W, Kochanek S, Sindrilaru A, Iben S, Högel J, Ohnmacht M, Claes LE, Ignatius A, Chung JH, Lee MJ, Kamenisch Y, Berneburg M, Nikolaus T, Braunstein K, Sperfeld AD, Ludolph AC, Briviba K, Wlaschek M, Scharffetter-Kochanek K (2011): Accelerated aging phenotype in mice with onditional deficiency for mitochondrial superoxide dismutase in the connective tissue, Aging Cell 10, 239-254.*
- *Singh K, Gatzka M, Peters T, Borkner L, Hainzl A, Wang H, Sindrilaru A, Scharffetter-Kochanek K (2013): Reduced CD18 levels drive Treg conversion into Th17 cells in the CD18hypo PL/J mouse model of psoriasis, J Immunol 190, 2544-53.*
- *Geiger H, Pawar SA, Kerschen EJ, Nattamai KJ, Hernandez I, Liang HP, Fernández JÁ, Cancelas JA, Ryan MA, Kustikova O, Schambach A, Fu Q, Wang J, Fink LM, Petersen KU, Zhou D, Griffin JH, Baum C, Weiler H, Hauer-Jensen M. (2012): Pharmacological targeting of the thrombomodulin-activated protein C pathway mitigates radiation toxicity, Nature Med 18, 1123-9.*
- *Florian MC, Dörr K, Niebel A, Daria D, Schrezenmeier H, Rojewski M, Filippi MD, Hasenberg A, Gunzer M, Scharffetter-Kochanek K, Zheng Y, Geiger H (2012): Cdc42 Activity Regulates Hematopoietic Stem Cell Aging and Rejuvenation, Cell Stem Cell 10, 520-530.*
- *Assfalg R, Lebedev A, Gonzalez OG, Schelling A, Koch S, Iben S. (2012): TFIIH is an elongation factor of RNA polymerase I, Nucleic Acids Res 40, 650-9.*

Department of Gynecology and Obstetrics

Head: Wolfgang Janni

Division of Gynecological Oncology

Head: Lisa Wiesmüller

DNA Repair, Tumor Suppression and the Aging Process: In Search of Mechanisms and Markers

Failure to repair DNA double-strand breaks (DSBs) causes immunodeficiencies, chromosome instability syndromes and progeria. Error-prone repair causes genomic instabilities that accelerate the multistep process of tumorigenesis. We developed assay systems for the analysis of all DSB repair pathways in immortalized and primary cells from different organs. The power of pathway-specific testing to detect even subtle DSB repair deficiencies was documented by testing cells derived from a series of *Ataxia telangiectasia*, Nijmegen breakage syndrome and Fanconi anemia patients as well as from a collection of breast cancer patients with mutations in *BRCA1*, *BRCA2* or *CHEK2*. Having identified a phenotypic signature that captures various defects resulting from breast-cancer-predisposing alterations, we performed the first case-control study for prospective evaluation of this potential biomarker in peripheral blood lymphocytes. The results showed that error-prone DSB repair activities were elevated in women with familial risk (Fig. 1) and in breast cancer patients of young age. Importantly, the risk-specific signature also captures synthetic lethal interactions with inhibition of PARP1, which has become an extremely promising target for therapies selectively eliminating repair-defective tumor cells.

Combined use of DSB repair testing, genomic PCR and quantitative analysis of nuclear structures indicative for DNA lesions, repair intermediates and/or enzyme complexes elucidated particular mechanisms underlying genetic destabilization in hematopoietic malignancies such as upon expression of BCR-ABL or constitutive NF-kB activation (Fig. 2). Further projects are aimed at the identification of novel disease-causing genes, synergies between cancer susceptibility and modifier genes through combination of functional testing (patient families/cohorts, mouse models) and genotyping (siRNA screen, whole exome sequencing) as well as the mechanistic characterization of the development of secondary, therapy-induced leukemias with implications for risk prediction.

Interestingly, recent literature has described the striking links between replicative senescence, telomere maintenance, aging and DSB repair. We characterized the role of and functional interactions

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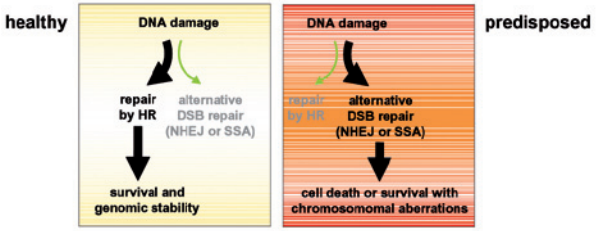
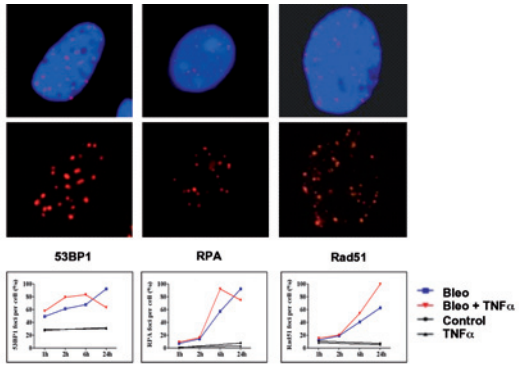
PhD Students: M. Volcic, I.C. Ireno, K.J. Obermeier
Additional Members of Thesis Advisory Committees:
M. Filipic (Lubljana), S. Fulda (Ulm), H. Geiger (Ulm), P. Gierschik (Ulm), M.E. de Lima Perez Garcia (Belo Horizonte), R. Winqvist (Oulu)

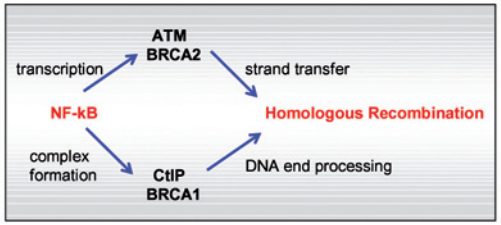


DSB repair substrate	High risk individuals n	Controls[b] n	Unit	OR[c] (95% CI)	P value[d]	Area under the ROC[e] curve
EJ-EGFP	35	144	0.45	1.71 (1.21-2.49)	0.0034	0.66
Δ-EGFP/3'EGFP	18	94	0.33	2.61 (1.57-4.84)	0.0007	0.71
HR-EGFP/3'EGFP	14	74	0.39	4.03 (1.86-11.92)	0.0045	0.72

Predictive power of error-prone DSB repair activities for discrimination between high-risk individuals versus controls. Our team previously showed that a shift from error-free HR to error-prone repair pathways using the DNA substrates EJ-EGFP, Δ-EGFP/3'EGFP, and HR-EGFP/3'EGFP can be detected in lymphoblastoid cells from individuals with breast-cancer-predisposing mutations. Consequently, we performed the first case-control study for prospective evaluation of this potential biomarker in peripheral blood lymphocytes from 35 individuals of high breast and ovarian cancer risk families, 175 sporadic breast cancer patients, and 245 healthy donors. We found increases of error-prone repair in women with familial risk versus controls particularly when applying substrate HR-EGFP/3'EGFP (Odds Ratio 4.05).

between different aging-related proteins in DSB repair such as ATM, Fanconi anemia gene products, SIRT1, p53 and PARP1. The challenge is now to understand the details of how DSB repair is regulated during the aging process in differentiated versus stem cells. Regarding DSB repair and its accuracy in hematopoietic stem cells, data are scarce and in part contradictory. Regarding DNA repair as a function of age in human beings, first data sets suggest that age exacerbates chromosome damage. However, the underlying mechanisms have remained enigmatic and emphasize the need for systematic investigations. Taken together, the purpose of our research is to understand the molecular details of DNA damage response mechanisms and their deregulation during aging, carcinogenesis and in chromosome instability syndromes. Our ultimate goal is to develop biomarkers to monitor/detect age-related processes, cancer risk, and therapeutic responsiveness.





Role of NFκB in DSB repair. DSBs were induced by exposure to the radiomimetic drug bleomycin (bleo) alone or in combination with the NFκB activator TNFα. To visualize various stages of DSB repair, cells were processed for immunolabeling of 53BP1 indicative of DSBs, for RPA indicative of single-stranded DNA, and Rad51 indicative of the HR machinery. Focal signals in the DAPI-stained nucleus were analyzed on an Olympus BX51 epifluorescence microscope and quantified by AnalySIS software including the mFIP module. From these and further data published in Volcic et al. 2012, a model of NFκB-dependent DSB repair regulation was proposed.

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www.uni-ulm.de/klinik/ufk/cms/html/forschung_gyn-onko.htm

Selected Publications:

- *Böhringer M*, Obermeier K*, Griner N, Waldraff D,Dickinson E, Eirich K, Schindler D, Hagen M, JerryDJ*, Wiesmüller L* (2013): siRNA screening identifies differences in the Fanconi anemia pathway in BALB/c-Trp53+/- with susceptibility versus C57BL/6-Trp53+/- mice with resistance to mammary tumors. Oncogene, in press.*
- *Keimling M*, Deniz M*, Varga D, Stahl A, Schrezenmeier H, Kreienberg R, Hoffmann I, Koenig J*, Wiesmüller L* (2012): The power of DNA double-strand break (DSB) repair testing to predict breast cancer susceptibility. FASEB J 26, 2094-2104.*
- *VolcicM, KarlS, BaumannB, Salles D, DanielP, FuldaS, Wiesmüller L (2012): NF-κB regulates DNA double-strand break repair in conjunction with BRCA1-CtIP complexes. NucleicAcids Res 40, 181-195.*
- *Keimling M*, Volcic M*, Csernok A*, Wieland B, Dörk T, Wiesmüller L (2011): Functional characterization connects individual patients' mutations in Ataxia Telangiectasia Mutated (ATM) with dysfunction of specific DNA double-strand break repair signalling pathways. FASEB J 25, 3849-3860.*
- *Salles D, Mencalha AL, Ireno IC, Wiesmüller L*, Abdelhay E* (2011): BCR-ABL stimulates mutagenic homologous DNA double-strand break repair via the DNA-end-processing factor CtIP. Carcinogenesis 32, 27-34.*
- *Gatz SA, Wiesmüller L (2006): p53 in recombination and repair. Cell Death Differ 13, 1003-1006.*

** equal contributions*

Department of Neurology

Molecular Mechanisms in Neurodegenerative Diseases

Head: Albert C. Ludolph

The Team:
Head of Department: A.C. Ludolph
Professors: C. von Arnim, H. Braak, K. Danzer, M. Otto, J. Weishaupt
Group Leaders/Postdocs: B. von Einem, J. Eschbach, A. Freischmidt, A. Grabrucker, C. Schnack, A. Witting
PhD Students: R. Chhabra, C.M. Eckert, R. Hesse, M. Leibinger, A. Wahler, C. Wandhoff, M. Feiler, L. Zondler, H. Bayer, N. Pasquarelli
Study Programme Experimental Medicine Students: L. Di Giorgio, S. Kirschmer, L. Campanelli, H. Tritschler, M. Büchsel, V.Roth, W.Ruf, N. Rizik, M. Schöpflin, D. Pasche
Additional Members of Thesis Advisory Committees: S. Kochanek (Ulm), J. Klucken (Erlangen), B. Ferger (Biberach), M. Karsak (Ulm), T. Böckers (Ulm), F. Gillardon (Biberach)

The Department of Neurology at Ulm University focuses its clinical and experimental work mainly on understanding the molecular mechanisms underlying such neurodegenerative diseases as Alzheimer's, Parkinson's and Huntington's disease, frontotemporal dementias, and amyotrophic lateral sclerosis/ motor neuron disease (ALS/MND). Structurally, it consists of a number of large outpatient clinics each serving their respective patient populations in addition to a clinical trial centre, which specializes in the clinical studies of selected groups of patients. There is also a gene and biobank, an inpatient clinic for acutely neurologically ill patients, and an experimental section in which more than fifty scientists work in ten basic neuroscience groups. These groups perform experimental research on the basic mechanisms of the diseases mentioned above.

The group of Prof. Dr. von Arnim conducts in vitro and in vivo experimental studies on Alzheimer's disease (AD) and is interested in the processing, sorting and signaling of the β-amyloid precursor protein (APP) and associated proteins (including motor proteins), and their subcellular compartimentalization. The work focuses on aspects of trafficking in AD by employing novel molecular imaging techniques (FLIM, TIRF). The ultimate goal of these studies is the translation of the findings into clinical therapeutic approaches which can be supported by imaging techniques in small animals and humans.

The group of Dr. Witting investigates the role of inflammation and its regulation by metabolic processes in neurodegenerative diseases, with a special focus on amyotrophic lateral sclerosis and Huntington's disease. The metabolic aspects of neurodegenerative diseases are further investigated in other tissues

and cells in collaboration with the groups of Dr. Dupuis, Dr. Weydt and Dr. Lindenberg. This integrated research might open new avenues of therapeutic interventions for these devastating diseases.
Studies on the etiology and pathogenesis of ALS/MND are the focal point of Prof. Dr. Ludolph's group. Experimental studies on etiology and pathogenesis center on resistance to hypoxia, neuritic transport and their associated proteins, and neuroinflammation, both in vitro and in vivo. The final goal of these experimental studies is the development of clinical interventions. This includes both preclinical intervention for the prevention of the disease and the development of therapies in the clinical phase to influence the human disease therapeutically.
The group of Jun. Prof. Dr. Danzer works on alpha-synuclein oligomer secretion from living neurons and transmission of oligomers in Parkinson's disease, which complements the immunohistopathological studies of Prof. Dr. Braak in this field of research. The work focuses on the identification of key players in the secretion process and deciphering the molecular mechanisms of initiation and propagation of neurodegenerative proteins both in vitro and in vivo. New in vivo models for Parkinson's disease built the basis for direct translation from basic research to clinics and will allow the identification of new pharmaceutical targets.
The group of Prof. Dr. Weishaupt works on cell and molecular biological aspects of ALS and Parkinson's disease. Members of the group are focused either on posttranslational modifications (specifically sumoylation) as regulators of pathological protein aggregation, the development of ALS protein aggregation assays for high-throughput screening or in vivo modeling of ALS-associated protein oligomerization and spreading of pathology. Further central topics of the Weishaupt team comprise the role of innate immunity as well as genetics and epigenetics in ALS, including next generation sequencing of genetic DNA or microRNA.

The group of Jun. Prof. Dr. Grabrucker investigates biometals in the brain, especially their influence on excitatory post synapses and specifically on scaffold proteins of the ProSAP/Shank family. These proteins play fundamental roles in the nascent assembly and function of glutamatergic synapses and are linked to Autism Spectrum Disorders, Alzheimer's disease and Schizophrenia. For this purpose, they use novel drug carriers, i.e. nanoparticles, and characterize them in regard to their potency to influence synapse formation, maturation and plasticity.

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Selected Publications:

- *Danzer KM, Kranich LR, Ruf WP, Cagsal-Getkin O, Winslow AR, Zhu L, Vanderburg CR, McLean PJ (2012): Exosomal cell-to-cell transmission of alpha synuclein oligomers. Mol Neurodegener. 7(1):42. Epub ahead of print*
- *Ingre C, Landers JE, Rizik N, Volk AE, Akimoto C, Birve A, Hübers A, Keagle PJ, Piotrowska K, Press R, Andersen PM, Ludolph AC, Weishaupt JH (2012): A novel phosphorylation site mutation in profilin 1 revealed in a large screen of US, Nordic, and German amyotrophic lateral sclerosis/frontotemporal dementia cohorts. Neurobiol Aging. Epub ahead of print*
- *Jesse S, Lehnert S, Jahn O, Parnetti L, Soininen H, Herukka SK, Steinacker P, Tawfik S, Tumani H, von Arnim CA, Neumann M, Kretzschmar HA, Kulaksiz H, Lenter M, Wiltfang J, Ferger B, Hengerer B, Otto M (2012): Differential sialylation of serpin A1 in the early diagnosis of Parkinson's disease dementia. PLoS One. 7(11). Epub*
- *Beyer A.-S., von Einem B, Schwanzar D, Thal DR, Ingelsson M, Makarova A, Deng M, Chhabra ES, Pröpper C, Böckers TM, Hyman BT, von Arnim CAF (2010): Engulfment adaptor PTB domain containing 1 interacts with and affects processing of the amyloid-beta precursor protein. Neurobiol Aging. 2012 Apr;33(4):732-43. Epub*
- *Lebedeva E, Stingl JC, Thal DR, Ghebremedhin E, Strauss J, Özer E, Bertram L, von Einem B, Tumani H, Otto M, Riepe MW, Ludolph AC, von Arnim CAF (2010): Genetic variants in presenilin genes and correlation to cerebrospinal β- amyloid 42 concentrations and diagnosis of Alzheimer's disease. Neurobiol Ageing. 2012 Jan;33(1):201.e9-201.e18. Epub*
- *Ferger AI, Campanelli L, Reimer V, Muth KN, Merdian I, Ludolph AC and Witting A (2010): The effect of mitochondrial dysfunction on the immunological properties of microglia, J. Neuroinflammation 7:45.*

Department of Otorhinolaryngology

Ear Tissue Regeneration Using Human Cells and Novel Nano-Cellulose Scaffolds

Head of Research: Nicole Rotter

Description of lab:
One focus of the research lab is regeneration of nasal and articular cartilage using stem cells and tissue engineering. The second focus is salivary gland regeneration and pathophysiology of radiogenic salivary gland damage. The lab has a significant expertise in culturing and characterizing chondrocytes from nose and auricle. We examine the potential of different biological materials such as different xenogenetic collagens and bacterial nanocellulose for regeneration of cartilage structures. We demonstrated that chondrocytes, isolated from auricle and nasal septum, can adhere, proliferate and even synthesize extracellular matrix on these scaffolds. In other studies of the laboratory, we search for an adequate source of cells for in situ cartilage regeneration. Different immunocompetent animal models for orthotopic transplantation of tissue-engineered nasal cartilage have been established. New biomaterials are evaluated and compared with regard to local inflammatory tissue reactions, their mechanical strength and stability. Aditionally, we establish a stem cell-based approach for salivary gland dysfunction following radiation therapy.

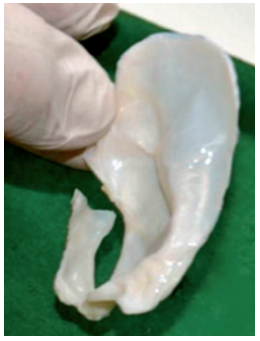
The Team:
Head of Research: N. Rotter
Head of Department: T.K.H. Hoffmann
Professor: N. Rotter
Group Leader/Postdoc: S. Schwarz
PhD Students: E-M. Feldmann, A. Elsässer
Additional Members of Thesis Advisory Committees:
A. Ignatius (Ulm), P. Gatenholm (Gothenburg)

Description of Project:

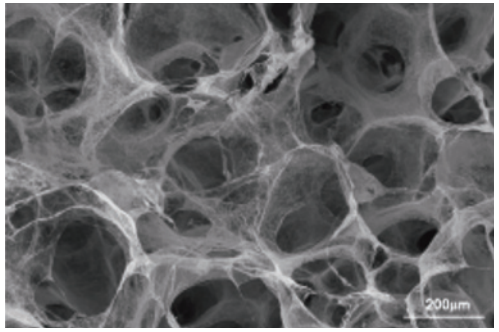
In western countries the incidence for the complete absence of the auricle is 1:17.500, whereas the frequency of minor dysplasia has an incidence of 1:6.800. In twenty percent of these cases both auricles are affected. In addition to these, the cases of traumatic or tumorous defects of the auricle need to be taken into account. Especially for children with major dysplasia of the auricle, an inconspicuous outer appearance is important for their psychological and emotional well-being as well as their psychosocial development. Without reconstructive surgery, many patients suffer from reduced self-confidence due to their obvious deformities. Despite donor-site morbidity, reconstructions of the auricle, usually performed with rib cartilage, have shown a significant psychosocial benefit in the majority of treated patients.

Due to the complexity of surgical reconstruction using rib cartilage, auricular reconstruction remains one of the greatest challenges within the field of reconstructive surgery. Despite the advances in stem cell technology and biomaterials, auricular cartilage engineering is still in an early stage of development. This is due to critical requirements such as mechanical properties of the scaffold material and the post-surgical long-term structure. Furthermore, the complex shape of the auricle adds another facet of complexity to the challenge of auricle reconstruction.

This project focuses on auricle reconstruction using a novel nano-biomaterial, bacterial cellulose, generated in dynamic culturing conditions using bioreactors, and co-culture of human chondrocytes and stem cells. The project is truly interdisciplinary since it combines engineering, such as bioimaging and biomechanics, for quantitative evaluation of requirements and outcomes, detailed material science expertise at the nanoscale for material development and manipulation, detailed biotechnology and cell biology proficiency for sophisticated replication of biological growth and development and clinical commitment for profiling existing clinical challenges, shortcomings and end goals. Our goal is to develop and evaluate a preclinical therapy for auricle reconstruction. Methods and results developed here will also be applicable in the regeneration of nose, trachea, spine and articular joints.



Bacterial nanocellulose in the shape of a human auricle



Porous bacterial nanocellulose (REM)

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Selected Publications:

- *Bermueller C, Schwarz S, Elsaesser AF, Sewing J, Baur N, von Bomhard A, Scheithauer M, Notbohm H, Rotter N (2013): Marine Collagen Scaffolds for Nasal Cartilage Repair: Prevention of Nasal Septal Perforations in a New Orthotopic Rat Model Using Tissue Engineering Techniques. Tissue Eng Part A. Epub ahead of print*
- *Feldmann EM, Sundberg JF, Bobbili B, Schwarz S, Gatenholm P, Rotter N (2013): Description of a novel approach to engineer cartilage with porous bacterial nanocellulose for reconstruction of a human auricle. J Biomat Appl. Epub ahead of print*
- *Schwarz S, Elsaesser AF, Koerber L, Goldberg-Bockhorn E, Seitz AM, Bermueller C, Dürselen L, Ignatius A, Breiter R, Rotter N (2012): Processed xenogenic cartilage as novel biomatrix for cartilage tissue engineering: effects on chondrocyte differentiation and function. J Tissue Eng Regen Med. Epub ahead of print*
- *Schwarz S, Koerber L, Elsaesser AF, Goldberg-Bockhorn E, Seitz AM, Dürselen L, Ignatius A, Walther P, Breiter R, Rotter N (2012): Decellularized Cartilage as a Novel Biomatrix for Cartilage Tissue Engineering Applications. Tissue Eng Part A. 18(21-22):2195- 209.*
- *Schuh E, Hofmann S, Stok K, Notbohm H, Müller R, Rotter N (2011): The influence of matrix elasticity on chondrocyte behavior in 3D. J Tissue Eng Regen Med. Epub Oct 28.*
- *Schuh E, Kramer J, Rohwedel J, Notbohm H, Müller R, Gutsmann T, Rotter N (2010): Effect of matrix elasticity on the maintenance of the chondrogenic phenotype. Tissue Eng Part A. 16(4):1281-90.*

The Team:
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Professors: C. Beltinger, G. Lahr, M. Wabitsch
Group Leaders/Postdocs: D. Fabricius, P. Fischer-Posovszky, L.H. Meyer, G. Strauss, M-A. Westhoff
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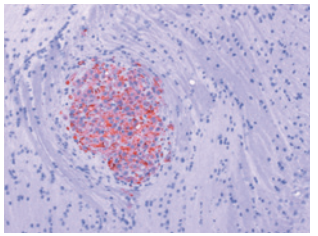
Department of Pediatrics and Adolescent Medicine

Apoptosis and Cancer Therapy

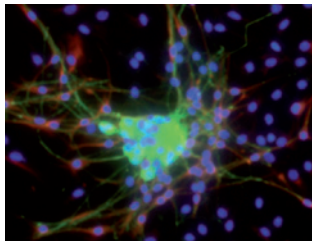
Heads: Prof. Dr. Klaus-Michael Debatin, Dr. Mike-Andrew Westhoff

The aim of our group is to understand how malignancies develop resistance to common cancer therapies and are thus able to avoid apoptosis and other forms of cell death.

We made key contributions to translational cell death research and have successfully developed combination approaches, whereby conventional therapy is paired with novel pharmacological substances that allow for the use of reduced amounts of chemotherapeutics, and thus reduced side effects, without the loss of potency, while concurrently enhancing tumor-specificity. Many of these approaches are currently being evaluated in vivo or are already being transferred to a clinical setting.



Microscopic section of a human Glioma growing in a mouse brain. Note the invasive phenotype which common in vivo approximations are unable to recapitulate.



Peripheral sympathetic progenitors (green), potential cells of origin of neuroblastoma and its stem cells.

Pathogenesis and Experimental Therapy of Pediatric Tumors

Head: Prof. Dr. Christian Beltinger

The Beltinger group investigates the pathogenesis of embryonic tumors and their stem cells and develops new preclinical therapies for these and other pediatric tumors. In the process, the molecular analysis of apoptosis and other types of cell death play an important role.

Leukemia

Heads: PD Dr. Lüder Hinrich Meyer, Prof. Dr. Klaus-Michael Debatin

The main aims of our group are to characterize features of leukemia biology reflecting patient outcome and to identify novel therapeutic strategies. Employing a previously established xenograft leukemia model, we are investigating mechanisms of leukemia development in different organ compartments and functionally evaluating aberrant signaling in leukemia cells as a target for directed treatment of pediatric leukemia.

Immunoregulation and GVHD

Head: PD Dr. Gudrun Strauss

T cells are the mediators of the cellular immune response. They eliminate invading pathogens and protect from diseases but they can also turn their reactivity against self and induce either autoimmunity or the deleterious graft-versus host disease (GVHD), the main complication after allogeneic bone marrow transplantation. A prerequisite for both processes is the specific activation of T cells by the cognate antigen. Our work focuses on the role of death receptors in antigenic T cell activation and the development of new treatment strategies for GVHD by interfering with death receptor pathways or by using myeloid-derived suppressor cells.

Experimental Obesity Research

Heads: PD Dr. Pamela Fischer-Posovszky, Prof. Dr. Martin Wabitsch

The excessive accumulation of adipose tissue in obesity leads to the development of severe co-morbidities such as type 2 diabetes mellitus and cardiovascular disease. Complementing our clinical studies in obese children and adolescents, our experimental research has centered on the biology and pathobiology of adipose tissue. Using a variety of molecular, cellular and in vivo approaches, we aim to understand the mechanisms controlling adipose tissue mass.

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Selected Publications:

- *Keuper M, Wernstedt Asterholm I, Scherer PE, Westhoff MA, Möller P, Debatin K-M, Strauss G, Wabitsch M, Fischer-Posovszky P (2013): TRAIL (TNF-related apoptosis-inducing ligand) regulates adipocyte metabolism by caspase-mediated cleavage of PPARgamma. Cell Death Dis. 4:e474.*
- *Hartmann N, Messmann JJ, Leithäuser F, Weiswange M, Kluge M, Fricke H, Debatin KM, Strauss G (2013): Recombinant CD95-Fc (APG101) prevents graft-versus-host disease in mice without disabling antitumor cytotoxicity and T-cell functions. Blood. 121(3):556-65.*
- *Schlitter AM, Dorneburg C, Barth TF, Wahl J, Schulte JH, Brüderlein S, Debatin K-M, Beltinger C (2012): CD57(high) neuroblastoma cells have aggressive attributes ex situ and an undifferentiated phenotype in patients. PLoS One. 7(8):e42025.*
- *Queudeville M, Seyfried F, Eckhoff SM, Trentin L, Ulrich S, Schirmer M, Debatin K-M, Meyer LH (2012): Rapid engraftment of human ALL in NOD/SCID mice involves deficient apoptosis signaling. Cell Death Dis. 3:e364.*
- *Meyer LH, Debatin K-M (2011): Diversity of human leukemia xenograft mouse models: implications for disease biology. Cancer Res. 71(23):7141-4.*
- *Hartmann N, Leithäuser F, Albers C, Duyster J, Möller P, Debatin K-M, Strauss G (2011): In vitro-established alloantigen-specific CD8+ CTLs mediate graft-versus-tumor activity in the absence of graft-versus-host disease. Leukemia. 25(5):848-55.*

The Team:
Head of Department: M. Schrader
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Group Leaders/Postdocs: C. Maier, M. Lüdeke
Study Programme Experimental Medicine Student:
A. Nottelmann-Mariné
Additional Members of Thesis Advisory Committees:
K. Spindler (Ulm), B. Wullich (Erlangen)

Department of Urology

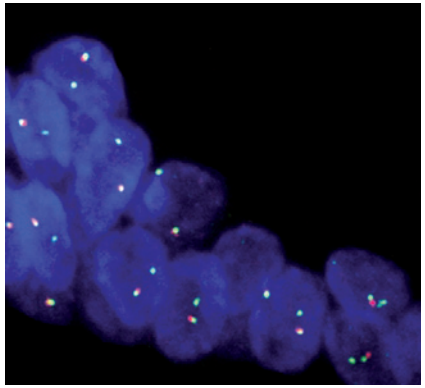
Molecular Genetics of Familial Prostate Cancer

Head: Mark Schrader

Familial clustering of prostate cancer has been known for a long time and the heritable component of this malignancy is expected to be stronger than for any other common cancer. Nevertheless, dissection of the responsible germline risk factors has proven difficult as various genes seem to be involved, each one hidden in a condition termed “complex inheritance.” The identification of high-risk genes remains especially challenging and is currently being approached by improved genome-wide research strategies.

The “Familial Prostate Cancer Project” established by the Institute of Human Genetics and the Department of Urology at Ulm University has its main study focus on sequencing whole exomes of prostate cancer patients. From the large prostate cancer study cohort available at Ulm, affected men are selected based on their family history and the most severe clinical manifestation of the disease. This project, as well as our efforts in genome-wide association studies, is integrated in large collaborative activities such as the International Consortium for Prostate Cancer Genetics (ICPCG) and the PRACTICAL consortium. Within the last two years, the networks have determined a series of 70 common variants associated with prostate cancer risk, and moreover, that the first tumor-specific high risk gene *HOXB13* is responsible for 3% of familial clustering.

In the presence of genetic heterogeneity, sample splitting for the generation of more homogeneous study samples is a promising strategy to facilitate disease gene identification. For this purpose, the research group has introduced the previously identified oncogene fusion *TMPRSS2-ERG* as a surrogate marker for a homogeneous pathomechanism to define a potentially distinct entity of prostate cancer. The occurrence of the chromosomal rearrangement *TMPRSS2-ERG* further links tumorigenesis to cellular DNA-repair capacity, a mechanism that is presumably involved in the susceptibility of this tumor. In his PhD study, Manuel Lüdeke has discovered and investigated DNA repair genes which appeared to harbor rare germline variants substantially associated with fusion positive prostate cancer. Intriguingly, not only rare variants (as candidates for higher risk mutations) but also common risk polymorphisms seem associated with *TMPRSS2-ERG* fusion status, strengthening the hypothesis of an etiologically distinct tumor subtype. A series of known prostate cancer risk variants have been investigated for correlations with *TMPRSS2-ERG* status and



TMPRSS2-ERG fusion positive prostate cancer. The dual color FISH break apart assay uses a green probe downstream of the *ERG* gene and a red probe mapping upstream, towards the 3 Mb distant *TMPRSS2* gene at chromosome 21. Colocalization of the signals indicate an intact chromosome 21. Absence or separation of a red signal indicates deletion of the intergenic region, suggesting the fusion of *TMPRSS2* to *ERG*.

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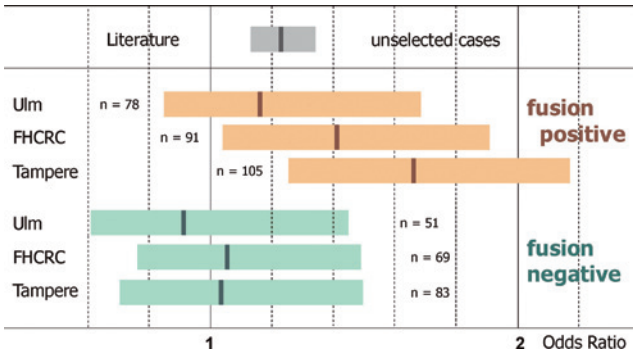
their influence on the individual DNA-repair capacity of carriers according to their genotypes (PhD work of Antje Rinckleb). Further experiments on candidate polymorphisms and genes are currently being processed by Andrea Nottelmann-Mariné in the Study Programme in Experimental Medicine.



Example of a common prostate cancer risk variant, rs10993994 at 10q11, which is specifically associated with the *TMPRSS2-ERG* fusion.

In three research groups (Ulm, FHCRC Seattle and University of Tampere) cases were split by *TMPRSS2-ERG* fusion status and separately compared to control groups of the referring study sites. Corresponding odds ratios appeared higher for the fusion positive subgroups (OR ≈ 1.5, red panel), while the SNP obviously does not have any effect in fusion negative cases (OR ≈ 1, green panel). Since unselected samples represent always a 50:50 mixture of fusion positive and negative cases, the effect size of rs10993994 known from literature lies intermediate (OR = 1.25, grey panel). Light bars denote 95% confidence intervals for the given odds ratios. The variant is also associated with DNA-repair capacity (data not shown).

Selected Publications:

- *Hofer MD*, Kuefer R*, Maier C*, Herkommer K, Perner S, Demichelis F, Paiss T, Vogel W, Rubin MA, Hoegel J (2009): Genome-wide linkage analysis of TMPRSS2-ERG fusion in familial prostate cancer. Cancer Res 69, 640-646. *equal contribution*
- *Luedeke M, Linnert CM, Hofer MD, Surowy HM, Rinckleb AE, Hoegel J, Kuefer R, Rubin MA, Vogel W, Maier C (2009): Predisposition for TMPRSS2-ERG fusion in prostate cancer by variants in DNA repair genes. Cancer Epidemiol Biomarkers Prev 18, 3030-3035.*
- *Luedeke M*, Coinac I*, Linnert CM, Bogdanova N, Rinckleb AE, Schrader M, Vogel W, Hoegel J, Meyer A, Dork T, Maier C (2012): Prostate Cancer Risk Is not Altered by TP53AIP1 Germline Mutations in a German Case-Control Series. PLoS One 7, e34128. *equal contribution*
- *Rinckleb AE*, Surowy HM*, Luedeke M, Varga D, Schrader M, Hoegel J, Vogel W, Maier C (2012): The prostate cancer risk locus at 10q11 is associated with DNA repair capacity. DNA Repair (Amst) 11, 693-701. *equal contribution*
- *Xu J, et al. (2013): HOXB13 is a susceptibility gene for prostate cancer: results from the International Consortium for Prostate Cancer Genetics (ICPCG). Hum Genet 132, 5-14.*
- *Eeles RA, et al. (2013) Identification of 23 novel prostate cancer susceptibility loci using a custom array (the iCOGS) in an international consortium, PRACTICAL. Nat Genet, in press.*

Department of Child and Adolescent Psychiatry/Psychotherapy

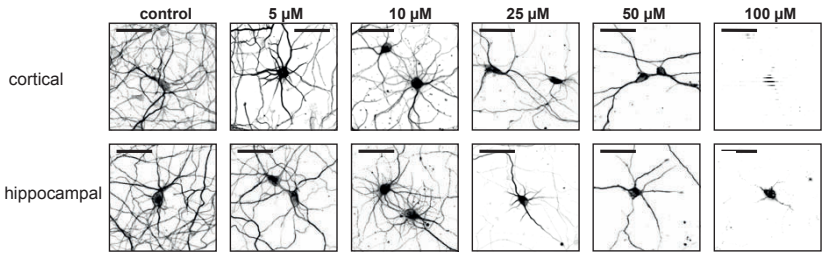
Age-dependent Cell Biological Effects of Psychotropic Substances in Maturing Neuronal Systems

Head: Jörg M. Fegert

If the prevalence of psychiatric disorders in childhood and adolescence is increasing, then this has been intensively debated for many years now. In contrast, it is undoubtedly true that the frequency of prescriptions of psychotropic medications for minors is significantly increasing. Most psychotropic substances are used “off-label” meaning there is a huge lack of knowledge about the cell biological effects of the prescribed compounds in the developing brain. Pediatric psychopharmacology can only be properly understood within the context of developmental neurobiology.

The Team:
Head of Department: J. M. Fegert
Group Leaders/Postdocs: A. G. Ludolph
PhD Student: P. T. Udvardi
Additional Member of Thesis Advisory Committee:
A. Storch (Dresden)

In a joint venture between the Clinic of Child and Adolescent Psychiatry and the Institute of Anatomy and Cell Biology, we are conducting in vitro studies in neuronal cell cultures and in vivo studies in rodents to assess the potential impact of psychotropic substances on cell development. We are interested in the effects of the substances most frequently used in child and adolescent psychiatry: methylphenidate, a psychostimulant and dopamine transporter inhibitor; atomoxetine, a selective norepinephrine transporter inhibitor (both compounds are used in the treatment of attention deficit hyperactivity disorder); and fluoxetine, a selective serotonin transporter inhibitor and antidepressant. Besides their well-known effects on the presynaptic monoaminergic transporter molecules, all three substances seem to have an impact on cell plasticity. Our working group was able to detect neuroprotective effects of methylphenidate. Fluoxetine and atomoxetine exerted a dose-dependent effect on cell viability and a reduction of neuronal arborisation and synaptic density. In collaboration with the Department of Anesthesiology, we were able to show that atomoxetine inhibits the NMDA-receptor, a mechanism that influences apoptosis in the developing brain. We are currently investigating a possible age-dependency of the effects of atomoxetine and fluoxetine not only on the expression of various monoaminergic transporters and subunits of the NMDA-receptor (PhD work Patrick Udvardi) but also, since the NMDA-receptor is embedded in a much larger complex of proteins associated with the post-synaptic density (PSD), on the expression of PSD scaffolding proteins.



Effect of atomoxetine on cortical and hippocampal neurons. The neuronal cells were treated on DIV 5 for 72 h with the indicated concentrations of atomoxetine. The neurons were immunolabeled with antibodies against MAP2 (microtubular-associated protein 2). Bar = 20 µm. Loss of sprouting emerged in cortical and hippocampal neurons dose-dependently. The impairment of the dendritic network starts at an atomoxetine concentration of 5 µM.

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Psychotherapy
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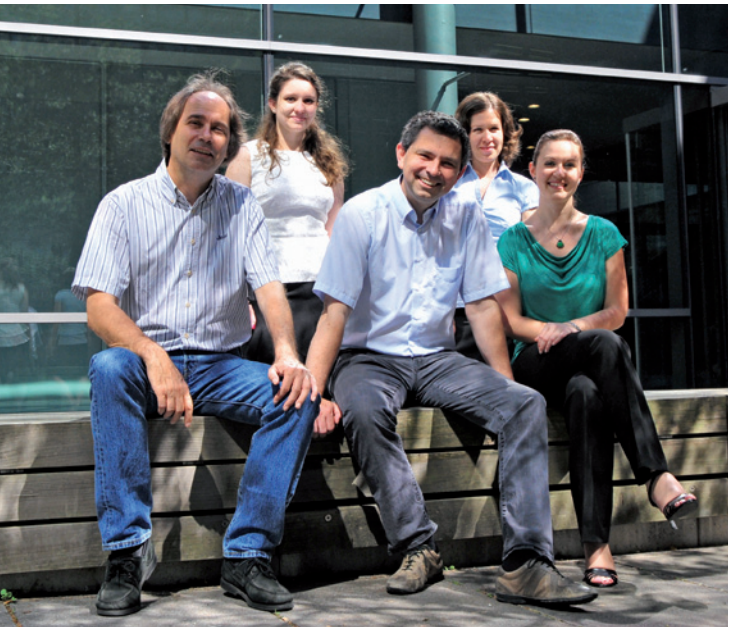
Selected Publications:

- *Ludolph AG, Schaz U, Storch A, Liebau S,Fegert JM, Böckers TM (2006): No neurotoxic but neuroprotective effects of Methylphenidate in primary mesencephalic cultures, J Neural Transm 113, 1927-34.*
- *Ludolph AG, Kassubek J, Schmeck K, Glaser C, Wunderlich A, Buck AK, Reske SN, Fegert JM, Mottaghy FM (2008): Dopaminergic dysfunction in attention deficit hyperactivity disorder (ADHD), differences between pharmacologically treated and never treated young adults: A ···3,4-dihdroxy-6-[18F]fluorophenyl-L-alanine PET study, NeuroImage 41, 718-727.*
- *Schaz U, Ludolph AG, Udvardi PT, Schaz U, Henes C, Adolph O, Weigt HU, Fegert JM, Boeckers TM, Föhr KJ: Atomoxetine acts as an NMDA receptor blocker in clinically relevant concentrations, Br J Pharmacol 160, 283-91.*
- *Schaz U, Föhr KJ, Liebau S, Fulda S, Koelch M, Fegert JM, Boeckers TM, Ludolph AG (2010): Dose-dependent modulation of apoptotic processes by fluoxetine in maturing neuronal cells: an in vitro study. World J Biol Psychiatry. 2010 Aug 24. Epub ahead of print*

Organization of the Graduate School



Who we are - Organization of the Graduate School

The International Graduate School in Molecular Medicine Ulm is a central interdisciplinary institution of Ulm University headed by a Board of Directors consisting of a chairman, a vice chairman, a representative of the presidency of Ulm University, a representative from the Faculty of Natural Sciences, and a managing director. The Board of Directors is responsible for the scientific profile of the Graduate School, the interdisciplinary training, the regulation of programs, the performance-based allocation of resources, and public relations. While the chairman acts as the representative of the Graduate School, the managing director is responsible for the school's administrative management. Both are official representatives of the Graduate School in financial affairs. The board decides on all financial issues concerning the Graduate School, such as work contracts, student scholarships and applications for the various social programs on offer.

The Board of Directors is supported by an International and Scientific Advisory Board which offers suggestions for the general development of the Graduate School and its PhD Programme. The Advisory Board includes scientists from Ulm University's various faculties, in addition to those from other international research institutes, as well as representatives from pharmaceutical companies. While the scientific members ensure the international compatibility of the PhD Programme and its compliance with international standards, the representatives from industry offer advice that is particularly relevant to the employability of our PhD graduates. The members of the faculties of Ulm University assist in identifying those interdisciplinary subjects that can improve the training of doctoral students.

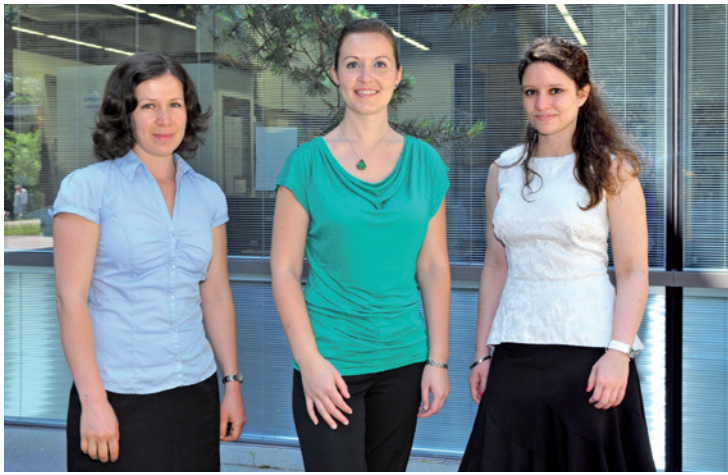
Members of the International and Scientific Advisory Board (June 2013):

Academic Representatives	Industrial Representatives	Representatives of Ulm University	Alumni of the Graduate School	Student Representatives
Y. Kloog, Tel Aviv	U. Bücheler, Boehringer Ingelheim	A. Böckers, Institute of Anatomy and Cell Biology	M. Chevillotte, USA	A. Hempel, Institute of Biochemistry and Molecular Biology
M. J. Lohse, Würzburg	N. Rentschler, BioRegionUlm	K. Dietmayer, Dean of the Faculty of Engineering and Computer Science	A. Lebedev, Canada	T. Hering, Department of Neurology
S. A. Moody, Washington D.C.	H. Wendt, Bayer	J. Ankerhold, Dean of the Faculty of Natural Sciences		Y. Koch, Department of Neurology
G. Nienhaus, Karlsruhe		D. Rautenbach, Faculty of Mathematics and Economics		
P. Pozzilli, Rome				
S. Vainio, Oulu				

The PhD Committee is in charge of the scientific monitoring and development of the International PhD Programme in Molecular Medicine right from the start of the application procedure through to the thesis defense. It is responsible for the assessment of applications in order to maintain the high standards of research required by the program. Furthermore, the PhD Committee supervises the school's compliance with the regulations of the program and constantly improves them. It also conducts the intermediate as well as the final evaluation of students. The PhD Committee consists of eight scientists from Ulm University and one student representative.

The Principal Investigators (PIs) are a group of 28 scientists from Ulm University responsible for the scientific profile and organization of the Graduate School as well as for the training of our PhD students. For instance, the PIs organize the four different Research Training Groups of the Graduate School. In addition to this, each Thesis Advisory Committee includes at least one PI to ensure equal and excellent standards of research training for all PhD students.

As mentioned previously, doctoral students are organized and trained in smaller **Research Training Groups** from the beginning of their PhD studies. The groups concentrate on different fields of Molecular Medicine and each group includes a number of Principal Investigators responsible for its coordination.
The four Research Training Groups are: 1) Development, Aging and Degeneration; 2) Signaling Networks in the Hematopoetic System and Oncology; 3) Cardiometabolic Disorders; and 4) Host-Microbe Interactions.



Moreover, highly proficient medical students are trained in clinical research by participating in the "Programme of Experimental Medicine."

Due to the increasing number of PhD students, the **Coordination Office** has also expanded. Three coordinators are now responsible for the administration and organization of the Graduate School. They are the principal contact point for all students, supervisors and applicants, and give advice and support concerning the policies and procedures of the Graduate School as well as answering questions concerning academic issues. The office also preselects applications and coordinates the selection procedure.
The organization of curricular and extracurricular activities in addition to meetings and examinations are part of the daily work of the office. The Coordination Office also deals with the Graduate School's public relations and assists in coordinating the interaction and cooperation between the large numbers of people and institutions involved at the Graduate School.

Three **Student Representatives** are appointed at the Graduate School. They are elected by the PhD Students and their appointment is for a duration of one year. The Student Representatives act as the voice of all the PhD Students attending the Graduate School. The regular meetings with the Board of the Graduate School serve as an opportunity to discuss the issues and wishes of the students. In addition, these representatives are responsible for organizing social activities and the Progress Report Seminar.

How to study the *International PhD Programme in Molecular Medicine*

During the three year period of PhD studies, students must take part in a number of compulsory activities amounting to 20 ECTS (European Credit Transfer System). Central teaching activities include the lecture series *Improve your Textbook Knowledge* for first-year PhD students as well as the participation in a Journal Club and the biweekly seminar *Progress Report*. The lecture series *Improve your Textbook Knowledge* allows graduates from different disciplines to refresh the basic knowledge needed to perform research in Molecular Medicine independently of their scientific background. In the seminar *Progress Report*, students are trained to communicate and present their own research data to their fellow students and to place it in a broader international context. Furthermore, graduates must attend a series of 30 lectures a year presented by external speakers. Another important compulsory course is the seminar *Good Scientific Practice* which takes place before the start of any practical work. Since the summer semester of 2013, all students must present a project plan within the first six months of their PhD studies. This helps both students and supervisors to structure the project to be undertaken while at the same time setting the objectives and establishing a personalized career plan.

In addition to curricular seminars and lectures, we offer PhD students a wide variety of optional activities. As one of our aims is to give students an insight into the work of industrial employers, we organize excursions to pharmaceutical and biotech companies. Summer schools and other scientific events in cooperation with partners from industry help to motivate students to deepen their knowledge of basic science and other practical applications. We also organize annual scientific retreats focusing on particular topics, e.g. the Hematology and Oncology Retreat held in Austria and the Molecular Medicine Retreat hosted by our partner university in Italy. Furthermore, there is a wide range of key competence seminars organized in order to improve the employability of our graduates. For instance, we offer courses in biosafety, bioethics, project management, funding, patent rights, scientific writing and presentation, team work and leadership skills, and career workshops. From this variety of optional activities, students must choose a minimum of two courses per year. Within the first two years of doctoral training, students are expected to attend three practical courses in different laboratories over a period of ten days. This practical training allows graduates to learn new and innovative techniques in Molecular Medicine.

Particular elements of our study concept are incorporated in two intermediate examinations. Students must pass examinations at the completion of their first and second years of study to ensure proper progress in their chosen scientific project. Both examinations take place within a public forum at our international meetings held in April and October each year. While the first intermediate examination consists of a poster presentation in front of the Thesis Advisory Committee (TAC), the second intermediate examination includes a scientific talk in addition to a poster presentation. Only those students who successfully pass their intermediate examinations may proceed to their second or third year of study.

Supervision Agreement

It is the mission of the Graduate School to provide excellent and guaranteed supervision for every PhD student participating in the program. Therefore, the Board of Directors has decided that each individual student, together with each member of the TAC, must sign a supervision agreement within the first six months of the PhD Programme. The purpose of the supervision agreement is to define the rights and duties of the students, the Thesis Advisory Committee and the Graduate School respectively. The aim is to protect each party in this supervision arrangement.

International PhD Programme in Molecular Medicine – Study Plan

Module number	Activity	Credit Points	Duration of examination (min)
First study year			
1.1	Lecture Series (30 optional talks)	1	
1.2	Journal Club* (1,5 hrs / 2 weeks)	2	
1.3	Seminar (Progress Report 1 h / 2 weeks)	1	
1.4	Lecture "Improve your textbook knowledge" and a Seminar "Good Scientific Practice"	2	
1.5	Project Plan (counts s one activity) + Other optional participation optional participation in 1 activitiy à 8 hrs (minisymposia, excursions, workshops etc.)	1	
	Sum 1st year	8	
	Intermediate examination 1		60
Second study year			
2.1	Lecture Series (30 optional talks)	1	
2.2	Journal Club* (1,5 hrs / 2 weeks)	2	
2.3	Seminar (Progress Report 1 h / 2 weeks)	1	
2.4	Compulsory optional practical training**	3	
2.5	Others (minisymposia, excursions, workshops etc.); optional participation in 2 activities à 8 hrs	1	
	Sum 2nd year	8	
	Intermediate examination 2		60
Third study year			
3.1	Lecture Series (30 optional talks)	1	
3.2	Journal Club* (1,5 hrs / 2 weeks)	2	
3.3	Seminar (Progress Report 1 h / 2 weeks)	1	
3.4	Others (minisymposia, excursions, workshops etc.); optional participation in 2 activities à 8 hrs	1	
	Sum 3rd year	5	
	Overall Sum	20	
	PhD project work	160	
	Overall sum	180	

* You should attend the journal club of your institute. In case that your institute does not offer a journal club, please attend the journal club in the institute of your second supervisor.

** The practical training has to cover 10 days in total in 3 different thematic fields till the end of the 2nd year (not in the own department).

According to the study plan, for the successful completion of the 1st year must be acquired 7 credit points, for the completion of the 2nd year 15 credit points (7 of the 1st + 8 of the 2nd year), and till the end of the 3rd year 5 credit points more must be acquired.

For the successful completion of the PhD programme, the PhD student must have acquired 180 credit points in total after the 3rd year (including the PhD thesis).

Please note: The legally binding version of the study plan is the one included in the study and examination regulations of the International PhD Programme in Molecular Medicine.

How to apply

Do you find the study concept of our international PhD program attractive? The following information will advise you about our application and selection procedures as well as the financing of PhD positions.

Our PhD Selection Procedure

The Graduate School accepts new students for the PhD Programme in April and October each year. The formal admission requirements are:

- A Master of Science degree, a German diploma, a German state examination or an equivalent degree in either the life sciences, physics, chemistry, informatics or a related field
- An overall grade of 2,0 or above according to the German grading system. Applicants who meet with our formal admission criteria are invited to our PhD Selection Days. During these days, applicants give an oral presentation in English on the topic of their master thesis and are personally interviewed by representatives of the school. They also have the opportunity to meet the project leaders of the PhD projects they have applied for.

Following our PhD Selection Days, applicants will be admitted to the PhD Programme on condition that:

- The candidate's oral presentation and the personal interviews have been evaluated with an overall grade of 2,0 or above according to the German grading system.
- The applicant has demonstrated above average English language skills during the presentation and the personal interviews.
- A potential supervisor has given a written statement accepting the applicant as a PhD student.

How to find a PhD Project

These are the most convenient ways to choose a PhD project at Ulm University:

- Respond to one of the advertisements on our homepage (http://www.uni-ulm.de/einrichtungen/mm/international-phd-programme-in-molecular-medicine/open-phd-positions.html) or to those published 2-3 times a year in the magazines *Nature* and *Die Zeit*.
- Establish contact with a professor from Ulm University who is willing to accept you for a vacant PhD position.

Application

If you wish to apply for our PhD Programme, please use our online-application form.
During the application process you will be asked to provide the following documents:

- Academic transcripts (bachelor certificate, master certificate, transcript of records, diploma supplements etc.)
- A curriculum vitae outlining your previous education and professional experience

Important remarks

- Submitted documents must be in pdf format.
- All submitted documents must be either in English or in German. If original documents are neither in English nor in German, certified translations are required.
- Applicants who are invited to our PhD Selection Days can request financial support to cover their travel costs.
- The presentation at Ulm University is part of our selection procedure and cannot be replaced by telephone interviews.
- Please note that applicants who succeed in our PhD Selection Days can only be accepted for the PhD Programme if they have been accepted for a PhD position by the Graduate School or by a supervisor from Ulm University.

How to finance a PhD position

Acceptance into our PhD Programme and securing a PhD position at Ulm University do not automatically mean that you will receive funding from the university. We ask that you determine in advance how your PhD position will be financed. The following options are proposed:

- Receive a work contract from the Graduate School
- Obtain a scholarship from the Graduate School
- Gain acceptance for a paid PhD position through a professor of the university
- You can also finance yourself either through a scholarship from your home country, from DAAD, or from any other funding organization

The Graduate School's work contracts and scholarships amount to a salary of pproximately €1,400 per month (before tax). If you are not funded by the Graduate School, your salary may differ from this amount due to an alternative way of financing. Please ask your supervisor or your funding organization about the monthly funding rate.

Please note:
There are no tuition fees for doctoral students at Ulm University.

Ulm University and Science City

Founded in 1967, Ulm University is the youngest university in the state of Baden-Württemberg. From the beginning, the *College of Medicine and Natural Sciences* had a clear focus on the disciplines the name suggests: biology, chemistry, physics, mathematics and medicine. This was how the original range of subjects looked. The founders explicitly attributed to this new institution of advanced education the character of a research university. The close contact among different subjects and the interdisciplinary character of research were encouraged and promoted. This concept of a “university under one roof” has been maintained over the years and has been exercised in the hiring of professors. Faculties have always ensured that the areas central to the work of new professors and of those who are already employed by the university continue to progress. This idea is the basis for concentrating on certain fields of research and the foundation of a series of collaborating research centers established at Ulm University over the years.

The university's excellent reputation is largely due to the high level of cooperation among the different disciplines. Many research awards and commissions for cooperation projects, whether in the fields of computer science, economics, engineering and mathematics, or the natural and life sciences, are proof of this. Since the university's foundation, the original range of disciplines has been enlarged. At present, Ulm University consists of four faculties: Natural Sciences; Engineering and Computer Science; Mathematics and Economics; and Medicine. It hosts more than 8,000 students. Ulm University is renowned for its personalized atmosphere and for the close working relationship existing between students and professors. Its research profile is characterized by a focus on the life sciences and medicine, information and communication technologies, nano- and biomaterials, as well as financial services and their mathematical methodology. Other specialized areas, such as pharmaceutical biotechnology as well as a Bachelor course of study in psychology, have recently been established.

The main university campus is located on a hill above the city of Ulm *(Eselsberg)* and houses a wide range of research and development centers as well as several hospitals that together comprise what is known as the Science City or *Wissenschaftsstadt*. This proximity of academic institutions and industrial R&D allows improved interaction between academic teaching and research on the one hand and industrial needs on the other.

Situated between woods and grain fields, the campus offers space for recreation and an outstanding view over the city. The art trail known as the *Kunstpfad* exhibits the artworks of internationally renowned and talented young artists distributed throughout the campus.

About the City of Ulm

Ulm/Neu-Ulm is an attractive twin city lying at the heart of southern Germany between Stuttgart and Munich. The 170,000 citizens of Ulm and Neu-Ulm are divided between the two states of Baden-Württemberg and Bavaria by the river Danube. The two municipal authorities cooperate and have grown into a common economic area. As the commercial and cultural heart of the region, they act in unanimity. Both cities have excellent traffic connections with the north-south and the east-west highways, six railway lines and five major state roads all intersecting here. Ulm's main train station is situated on an important rail route. The nearest airports are located in Stuttgart (approx. 80 km/50 miles) and Munich (approx. 145km/90 miles).

While Ulm is an ancient town, Neu-Ulm is relatively young. In Ulm, there are the charming Fisherman's and Tanners' Quarter with its old houses, alleyways and that air of medieval times. In Neu-Ulm, regularity in its architecture prevails since this was the only form considered to be stylish and elegant in the nineteenth century. Neu-Ulm was originally established as a counterpart to Ulm. Today, the two sister cities, though unlike, are both open to contemporary ideas of construction.

The city center of Ulm houses a mixture of stone monuments from its days as a free city of the Holy Roman Empire and more recently designed modern architecture, for example, the postmodern townhouse next to the gothic Münster and the historical market place with its city library in the form of a glass pyramid. Neu-Ulm has also come a long way with the modernization of its city center.

The twin city of Ulm/Neu-Ulm offers a wide variety of cultural events such as the *Museumsnacht* (Night of the Museums), *Internationales Donaufest* (International Danube Festival) and the *Ulmer Zelt*, one of many music festivals. There is a main theater as well as several other smaller theaters. Whether sociable or fashionable, there are bars, pubs, cafés and beer gardens to suit everyone's taste. The city's geographical proximity to the Allgäu, Lake Constance and the Alps offers the opportunity to enjoy sporting activities such as hiking, cycling, skiing and surfing. A survey by IHK Ulm (*Industrie- und Handelskammer Ulm*/Chamber of Commerce and Industry, Ulm) has shown that the region of Ulm has the highest economic growth in Germany. The local economy expanded by 41 per cent between 1998 and 2007. At the same time, the unemployment rate has been reduced by more than 40 per cent and a mere 3.6 per cent of Ulm's population are currently out of work. It is in this context that Ulm has been declared as Germany's *Wohlfühlregion* Nr. 1 (Feel-good-region no. 1) in a survey conducted by Deutsche Bank. In the *Prognos Future Ranking 2010*, Ulm has reached ninth place among 412 German districts in terms of its future potential. Its population is constantly growing and is the youngest in the state of Baden-Württemberg.

The Ulm region called *Stiller Star* (Silent Star) by the German newspaper Handelsblatt is an important center for the pharmaceutical industry and biotechnology. Large corporations, such as Boehringer Ingelheim, Rentschler Biotechnologie, Merckle, Cognis and Ratiopharm, are located here and attest to the close interaction between the world of science and the economy.

The City Hall of Ulm was built in 1370. The Renaissance wall painting (restored in 1900) depicts a traditional boat known as an *Ulmer Schachtel* sailing down the river Danube towards the Black Sea. The emblems decorating the gable show all the cities Ulm has traded with throughout the centuries.

Facts and Figures

Facts and Figures
(June 2013)

PhD Students,
International PhD Programme in Molecular Medicine

Total number of PhD students	177
Male	56
Female	121
International students	44
Parental students	7

PhD Students,
Programme in Experimental Medicine

Total number of PhD students	24
Male	16
Female	8
International students	3
Parental students	0

Doctorates conferred (2011-2013), *International PhD Programme in Molecular Medicine*

Name	Topic	Main supervisor (names)	Institute	Date of final examination	Degree
Kracher, Barbara	Towards a rule-based model for the Wnt signaling network	Prof. Dr. Kühl, Michael	Institute of Biochemistry and Molecular Biology	06/14/2011	Dr. rer. nat.
Hartmann, Natalie	Role of apoptosis-resistant T cells in allogeneic bone marrow transplantation	Dr. Strauss, Gudrun	Department of Pediatrics and Adolescent Medicine	07/04/2011	Dr. rer. nat.
Lück, Sonja Christine	Modulation of immune cell signaling and function by functionalized nanosized particles	Prof. Dr. Döhner, Konstanze	Department of Internal Medicine III	07/05/2011	Dr. rer. nat.
Lunov, Oleg	Modulation of immune cell signaling and function by functionalized nanosized particles	Prof. Dr. Simmet, Thomas	Institute of Pharmacology of Natural Products and Clinical Pharmacology	08/17/2011	PhD
Bangert, Annette	Sensitization of glioblastoma cells to apoptosis by histone deacetylase inhibitors	Prof. Dr. Fulda, Simone	Department of Pediatrics and Adolescent Medicine	08/25/2011	Dr. rer. nat.
Bugner, Verena	Characterisation of Xenopus Peter pan during eye and neural crest cell development	Prof. Dr. Kühl, Michael	Institute of Biochemistry and Molecular Biology	09/20/2011	Dr. rer. nat.
Schips, Tobias	Role of Foxo3 in cardiac disease	Prof. Dr. Wirth, Thomas	Institute of Physiological Chemistry	10/04/2011	Dr. rer. nat.
Allegra, Danilo	MicroRNA processing in Chronic Lymphocytic Leukemia	Prof. Dr. Stilgenbauer, Stephan	Department of Internal Medicine III	10/06/2011	PhD
Unterkircher, Thomas Andreas	Sensitization of glioblastoma to TRAIL	Prof. Dr. Fulda, Simone	Department of Pediatrics and Adolescent Medicine	10/12/2011	Dr. rer. nat.
Tata, Aleksandra	Characterization of potential non-canonical Wnt target genes during pronephros development in Xenopus laevis	Prof. Dr. Kühl, Michael	Institute of Biochemistry and Molecular Biology	11/10/2011	PhD
Naumann, Ivonne	Sensitization of neuroblastoma for apoptosis	Prof. Dr. Fulda, Simone	Department of Pediatrics and Adolescent Medicine	11/18/2011	Dr. rer. nat.
Laschak, Martin	Androgen dependent regulation of N-CoR in prostate cancer cell lines	Prof. Dr. Spindler, Klaus-Dieter	Institue of General Zoology and Endocrinology	12/02/2011	Dr. rer. nat.
Parmar, Sumit	Pharmacogenetic factors involved in cancer treatment	Prof. Dr. Stingl, Julia	Institute of Pharmacology of Natural Products and Clinical Pharmacology	12/15/2011	Dr. rer. nat.
Pfreimer, Mariana	Rho GTPases: role in cheomkine-chemokine receptor signaling	PD Dr. Möpps, Barbara	Institute of Pharmacology and Toxicology	12/22/2011	Dr. rer. nat.
Ruß, Annika	The role of microRNAs in acute myeloid leukemia	Prof. Dr. Döhner, Konstanze	Department of Internal Medicine III	01/03/2012	Dr. rer. nat.
Volcic, Meta	Role of the apoptosis-modulatory molecule NF-?B in DSB repair	Prof. Dr. Wiesmüller, Lisa	Department of Obstetrics and Gynecology	01/17/2012	PhD
Stadel, Dominic Kastja	Targeting IAPs in pancreatic cancer therapy	Prof. Dr. Fulda, Simone	Department of Pediatrics and Adolescent Medicine	02/02/2012	Dr. rer. nat.
Tuduce, Ioana Laura	The cross talk between RA (Retinoic Acid) and PCP (Planar Cell Polarity) signaling during neural tube closure	Prof. Dr. Kühl, Michael	Institute of Biochemistry and Molecular Biology	03/06/2012	PhD
Kron, Matthias	miRNA-regulated adenovirus vectors for genetic vaccination	Prof. Dr. Kochanek, Stefan	Deparment of Gene Therapy	05/03/2012	Dr. rer. nat.

Name	Topic	Main supervisor (names)	Institute	Date of final examination	Degree
Jennewein, Claudia Nora	Regulation of death receptor-induced apoptosis via NF-kappaB in glioblastoma cell lines	Prof. Dr. Fulda, Simone	Department of Pediatrics and Adolescent Medicine	05/22/2012	Dr. rer. nat.
Wagner, Liane	Smac Mimetic BV6 in Glioblastoma	Prof. Dr. Fulda, Simone	Department of Pediatrics and Adolescent Medicine	06/21/2012	Dr. rer. nat.
Zong, Shan	Characterization of Adenovirus vectors expressing optimized Plasmodium falciparum merozoite surface protein 1 (MSP-1) for genetic vaccination	Prof. Dr. Kochanek, Stefan	Department of Gene Therapy	07/24/2012	PhD
Herrmann, Franziska Erika Gertrud	Describing the gene regulatory network of early murine heart development	Prof. Dr. Kühl, Michael	Institute of Biochemistry and Molecular Biology	07/24/2012	Dr. rer. nat.
Lüdeke, Manuel	Predisposition for TMPRSS2-ERG Fusion in prostate cancer	PD Dr. Maier, Christiane	Department of Urology	09/04/2012	Dr. rer. nat.
Kuh, Georges Ful	Rodent p150 Mutant Characterization and the Novel Interaction of p150 with Tubuling Binding Cofactor B (TBCB)	Prof. Dr. Böckers, Tobias	Institute of Anatomoy and Cell Biologie	10/09/2012	PhD
Dong, Xiaomin	Primary neuron model of Huntington's disease by high capacity adenovirus mediated expression of full length huntingtin	Prof. Dr. Kochanek, Stefan	Deparment of Gene Therapy	09/24/2012	PhD
Katz, Sarah-Fee	P53 deletion leads to bilineal liver tumor formation and to prolonged self renewal, chromosomal instability and transformation of liver progenitor cells	Prof. Dr. Rudolph, Karl Lenhard	Institute of Molecular Medicine	12/03/2012	Dr. rer. nat.
Jain, Garima	Defining IKK as novel drug target to treat prostate cancer	Dr. Marienfeld, Ralf	Institute of Pathology	12/14/2012	PhD
Heinrich, Jutta	Synapto-nuclear transport mechanism	Prof. Dr. Böckers, Tobias	Institute of Anatomoy and Cell Biologie	12/14/2012	Dr. rer. nat.
Groß, Alexander	Inferring signal transduction pathway models	Dr. Kestler, Hans Armin	Institute of Neural Information Processing	02/12/2013	Dr. rer. nat.
Faber, Katrin	Identification of genetic vulnerabilities in AML using functional genomic screens	PD Dr. Fröhling, Stefan	Department of Internal Medicine III	02/19/2013	Dr. rer. nat.
Singh, Karmveer	Insulin-Like Growth Factor-1 Signaling Under High Oxidative Stress Conditions of the Connective Tissue Specific Sod2 Deficient Aging Mouse Model	Prof. Dr. Scharffetter-Kochanek, Karin	Department of Dermatology and Allergology	03/01/2013	PhD
Tao, Si	Wnt signaling in aging stem cells	Prof. Dr. Kühl, Michael	Institute of Biochemistry and Molecular Biology	04/16/2013	PhD
Leibinger, Marco	Neuroprotection and axonal regeneration in central nervous system	Prof. Dr. Fischer, Dietmar	Department of Neurology	04/25/2013	Dr. rer. nat.
König, Carolin Susanne	Molecular mechanisms of human CC chemokine receptor CCR2a and CCR2b action in an adipocyte-like environment	PD Dr. Mömpps, Barbara	Institute of Pharmacology and Toxicology	04/25/2013	Dr. rer. nat.
Jebaraj, Billy Michael Chelliah	Telomeres and chronic lymphocytic leukemia (CLL)	apl. Prof. Dr. Stilgenbauer, Stephan	Department of Internal Medicine III	05/28/2013	PhD
Singh, Kamayani	Resolving the pathogenesis of Psoriasis,in CD18 hypomorphic mice model	Prof. Dr. Scharffetter-Kochanek, Karin	Department of Dermatology and Allergology	05/15/2013	PhD

Workshops	Date	Organizer
Project Management for Research Projects – Advanced level	01/20/2012-01/21/2012	GSC 270
German course – German for Beginners	Every Monday, started: 01/23/2012	GSC 270
Communication & presentation in the academic context	03/08/2012-03/09/2012	GSC 270
Workshop on isolation of mouse hematopoietic stem cells and analysis	04/30/2012 - 05/14/2012	Y. Morita
Sicherheit in der Gentechnik	05/03/2012 - 05/04/2012	GSC 270
In vivo Imaging Methods from Preclinical to Clinical Research	05/04/2012-05/05/2012	UU
Good Scientific Practice	05/07/2012-05/08/2012	GSC 270
Good Manufacturing Practice	05/15/2012	UU
Teamwork & leadership competencies in academia and beyond	06/08/2012	GSC 270
Workshop Job Application Training for Foreign Students	06/21/2012	UU
Good Scientific Practice	07/09/2012-07/10/2012	GSC 270
Communication & presentation in the academic context	09/06/2012-09/07/2012	GSC 270
Academic Writing	09/21/2012	GSC 270
Identification of Claudin 2 as a putative paracellular water channel	10/01/2012	GSC 270
Intercultural Training Seminar	10/20/2012	M4M, ZAWiW
Stem Cell Seminar 2012	10/31/2012	GSC 270
Extramural Funding	11/15/2013-11/16/2012	GSC 270
Project Management for Research Projects – Basic Level	11/29/2012-11/30/2012	GSC 270
Project Management for Research Projects – Advanced level	01/24/2013-01/25/2013	GSC 270
Communication & presentation in the academic context	03/07/2013-03/08/2013	GSC 270
Powerful Presentations	03/08/2013	UU
Extramural Funding	03/18/2013-03/19/2015	GSC 270
Upward Leadership Seminar	04/19/2013	GSC 270
Good Scientific Practice	11/12/2012-11/13/2013	GSC 270
Sicherheit in der Gentechnik	04/25/2013-04/26/2013	GSC 270
German course – German for Advanced Beginners	Every Monday, started: 04/29/2013	GSC 270
Financial Planning for Doctoral Students	05/17/2013	GSC 270

Workshops	Date	Organizer
Microscopy Seminar (Zeiss AG)	05/28/2013-05/29/2013	GSC 270
“Germany-Welcome!”	05/31/2013	UU
Statistics seminar	06/10/2013-06/11/2013	GSC 270
Job Application Training for Doctoral Students	06/19/2013	GSC 270
Biotech Quality Manager	07/01/2013	GSC 270
PhD/MD and then Career Possibilities with a Start in Science!	07/15/2013-07/16/2013	GSC 270
Communication & presentation in the academic context	09/12/2013-09/13/2013	GSC 270
Academic Writing	09/25/2013-09/27/2013	GSC 270
Successful acquisition of funding for junior researchers (for members of the Junior Faculty only)	10/14/2013-10/15/2013	GSC 270
Good Scientific Practice	10/15/2013-10/16/2013	GSC 270
Statistics seminar	11/04/2013-11/05/2013	GSC 270
PhD/MD and then Career Possibilities with a Start in Science!	11/11/2013-11/12/2014	GSC 270
Extramural Funding	12/09/2013-12/10/2013	GSC 270
Good Scientific Practice	11/12/2012-11/13/2012	GSC 270

Excursions	Date	Organizer
Rentschler Biotechnologie GmbH	02/22/2012	GSC 270
Carl Zeiss AG	05/23/2012	GSC 270
Rentschler Biotechnologie GmbH	02/27/2013	GSC 270
Carl Zeiss AG	05/08/2013	GSC 270
Böhringer Ingelheim Pharma GmbH & Co. KG	06/26/2013	GSC 270

Symposia	Date	Organizer
International Conference: Bridging Disciplines - Evolution and Classification in Biology, Linguistics and the History of Sciences	06/24/2011 - 06/26/2011	H. Fangerau
Colloqium: New frontiers in Biophysics: From single molecules to super-resolution optical microscopy	10/17/2011	J. Michaelis
Symposium Core Facility Small Animal MRI	10/18/2011	Medical Faculty
Spring Meeting 2012	03/29/2012 - 03/31/2012	GSC 270
Tag der Molekularen Mediczin 2012	04/21/2012	Students
Uni Ulm goes International - Die Universität Ulm präsentiert ihre internationalen Studienprogramme und Betreuungsangebote	05/30/2012	UU
Fall Meeting 2012	10/04/2012 - 10/06/2012	GSC 270
Spring Meeting 2013	04/11/2013 - 04/13/2013	GSC 270
1st BIU Symposium	05/30/2013	Medical Faculty
2nd BIU Symposium	06/03/2013	Medical Faculty
Fall Meeting 2013	10/10/2013 - 10/12/2013	GSC 270
Bundeswehr Symposium	11/20/2012	Medical Faculty

Summer and Winter Schools	Date	Organizer
2011 Summer School: Metabolic Aspects of Chronic Brain Diseases	07/20/2011 - 07/26/2011	P. Weydt
Bregenz Summer School in Endocrinology 2011	07/242011 - 07/28/2011	GSC 270
GRK Winter School 2011	12/12/2011 - 12/15/2011	GRK 1041
6th Tongji-Ulm Summer School in Molecular Medicine: Heart Development and CardioMetabolic Diseases: From Molecules to Disease;	07/30/2012-08/04/2012	GSC 270
2013 German Chinese Summer School: Clinical and Molecular Aspects of Age-Related Brain Diseases	07/09/2013-07/26/2013	UU and Bejing Hospital, China
7th Tongji-Ulm Summer School in Molecular Medicine: Lung Development and Disorders: From Molecules to Disease	07/29/2013-08/03/2013	GSC 270

Retreats	Date	Organizer
Facs of Neuroscience Development, Plasticity & Disease	09/05/2011 - 09/09/2011	GSC 270
Topics in Molecular Medicine, Bressanone, Italy	01/13/2012-01/15/2012	GSC 270
Hematology and Oncology, Bregenz, Austria	06/22/2012-06/23/2012	GSC 270
Genetics and Molecular Biology, Myrtle Beach/USA	09/07/2012- 09/07/2012	Chapel Hill, USA

Social Activities	Date
Table Tennis Cup	08/18/2011
Visit of the Oktoberfest 2011	09/28/2011
Exkursion to castle Neuschwanstein, Linderhof palace and a "flying visit" to the church of Wies	10/22/11
Theatre Ulm: "La poesia dei piedi"	04/12/2011
Christmas Party	12/07/2011
Excursion to Paris	01/05-08/2012
Excursion to Augsburg	04/02/2012
Bowling	02/08/2012
Indian Afetrnoon	02/25/2012
Guided Tour through memorial "DenkStätte Weiße Rose"	04/25/2012
Excursion to Rothenburg ob der Tauber	04/28/2012
Chinese Afternoon	05/12/2012
Excursion to Regensburg	06/07/2012
Summer Party	07/18/2012
Trip to Europapark	07/07/2012
Excursion to Allgäu	08/19/2012
Einstein-Marathon	09/16/2012
Excursion: Oktoberfest, Munich	09/28/2012
Hike tour to "Weidacher Hütte"	10/07/2012
Excursion to the Hauff museum of prehistoric world	10/21/2012
Excursion to Strasbourg	11/24/2012
Christmas Party	12/05/2012
"60 years Baden-Württemberg" afternoon	02/02/2013
Night watchman tour through Ulm	04/24/2013
Excursion to Stuttgart - exhibition "Maya-Code"	05/18/2013
Dragon boat race	06/30/2013
Summer Party	07/03/2013
Excursion: Oktoberfest, Munich	09/25/2013
Einstein-Marathon	09/29/2013

Invited Speakers (2011-2013)

Topic	Speaker	Date	Organizer
Construction of the Kidney: Current Views & Future Visions	Seppo Vainio Oulu/Finland	07/18/2013	GSC 270
Challenges in Organogenesis & Bioengineering - the Kidney as a Model System	Seppo Vainio Oulu/Finland	07/15/2013	GSC 270
Human Cytomegalovirus binding to monocytes directs viral entry and the functional changes associated with viral persistence	Andrew Yurochko Lousiana/USA	07/02/2013	GSC 270
Fast Inactivation in Skeletal Muscle Sodium Channels: Countercharges in the Voltage Sensor Module	James Groome Idaho/USA	05/13/3013	GSC 270
Regulation of Hematopoiesis: Normal and Leukemia Stem cells	Michael Milyavsky Tel Aviv/Israel	04/25/2013	GSC 270
Structure and function of Notch transcription complexes	Rhett A. Kovall Cincinnati/USA	04/13/2013	GSC 270
Breast cancer malignancy is influenced by increased levels of HER1 adaptor protein Ruk/CIN85	Nina Kozlova Oulu/Finland	04/13/2013	GSC 270
Polo-like kinase 1and p22warf1 in oncology	Juping Yuan Frankfurt/Germany	04/13/2013	GSC 270
The PINK1-parkin mitophagy pathway: Relevance for Parkinson's disease pathogenesis	Jan-Willem Taanman London/UK	04/12/2013	GSC 270
Regulation of Shank proteins	Hans-Jürgen Kreienkamp Hamburg/Germany	04/12/2013	GSC 270
Cross talk between hypoxia and insulin signaling	Thomas Kietzmann Oulu/Finland	04/12/2013	GSC 270
Recognition of murine cytomegalovirus infected cells by activating an inhibitory Ly49 NK cell receptors	Stipan Jonjic Rijeka/Croatia	04/12/2013	GSC 270
HIV cell-to-cell transmission and innate response	Oliver Schwartz Paris/France	04/11/2013	GSC 270
Extracellular Space Travel by Wnt proteins	Michael Boutros Heidelberg/Germany	02/07/2013	SFB 1074
Lessons learned from characterizing structural variation in the cancer genome	Jan Korbel Heidelberg/Germany	01/24/2013	SFB 1074
Stem Cell Seminar 2012	Hiromitsu Nakauchi Tokyo/Japan	10/31/2012	GSC 270
Constitutive Mismatch-Repair Deficiency Syndrome: Phenotype and Mutational Spectrum of Biallelic Tumor-Suppressor Gene Mutation Carriers	Katharina Wimmer Innsbruck/Austria	10/06/2012	GSC 270

Topic	Speaker	Date	Organizer
The role of autophagy in cancer cells following FTS treatment	Eran Smuckler Tel Aviv/Israel	10/06/2012	GSC 270
Insight into new function of neurofibromin type	Lior Faigenbloom Tel Aviv/Israel	10/06/2012	GSC 270
The role of Hypoxia-Inducible Factors in Malignant Melanoma Invasion	Sara Hanna Chapel Hill/USA	10/06/2012	GSC 270
Players and mechanisms in hereditary predisposition to breast cancer	Robert Winqist Oulu/Finland	10/06/2012	GSC 270
RNA Therapeutics for Leukemia	H. Leighton Grimes Cincinnati/USA	10/06/2012	GSC 270
Chromatin Remodelling and DNA Methylation	Gernot Längst Würzburg/Germany	10/05/2012	GSC 270
Development of antigen reduced xenogeneic heart valve matrices for tissue engineering purposes	Robert Ramm Hannover/Germany	10/05/2012	GSC 270
Transcriptional Mechanisms of Axonal Regeneration	Julianne McCall Heidelberg/Germany	10/05/2012	GSC 270
Human hair follicle equivalents in vitro for transplantation and substance testing	Beren Atac Berlin/Germany	10/05/2012	GSC 270
Computer-Based Identification of a novel LIMK1/2 inhibitor that synergizes with FTS to destabilize the actin cytoskeleton	Roni Rack Tel Aviv/Israel	10/05/2012	GSC 270
Farnesylthiosalicylic Acid (Salirasib) Inhibits Rheb in TSC2-Null ELT3 Cells: A Potential Treatment for Lymphangioleiomyomatosis (LAM)	Victoria Makovski Tel Aviv/Israel	10/05/2012	GSC 270
Functional and Structural Characterization of the RNA Helicase DDX1	Julian Kellner Heidelberg/Germany	10/05/2012	GSC 270
Histone post-translational modifications promote DNA replication in Saccharomyces cerevisiae	Lindsay Rizzardi Chapel Hill/USA	10/05/2012	GSC 270
Proteomic screen reveals Fbw7 as a modulator of the NF-κβ pathway	Karim Ullah Oulu/Finland	10/05/2012	GSC 270
A functional SNP underlying association of the 11q13.4 locus with type 2 diabetes	Jennifer Kulzer Chapel Hill/USA	10/05/2012	GSC 270
Investigating the Role of HIF-prolyl hydroxylase 3 on the cell polarity	Fazef Moafi Oulu/Finland	10/05/2012	GSC 270
Antibacterial cytokine IL-22 goes antiviral	Tanel Mahlakoiv Freiburg/Germany	10/05/2012	GSC 270

Topic	Speaker	Date	Organizer
Host Clearance and Microbial Variation Determine that Invasive Pneumococcal Disease is Founded by a Single Bacterial Cell	Marco Oggioni Sienna/Italy	10/05/2012	GSC 270
Mechanisms of bicoid mRNA gradient formation in Drosophila	Stefan Baumgartner Lund/Sweden	10/04/2012	GSC 270
Regulation of cellular contractility downstream of Rho GTPase signalling	Perihan Nalbat Duisburg-Essen/Germany	06/29/2012	KFO 142
Genetic cell modification to enhance hematopoietic regeneration	Christopher Baum Hannover/Germany	06/25/2012	GSC 270
Head and tail of Wnt signalling in the beetle Tribolium	Reinhard Schröder Rostock/Germany	06/04/2012	GSC 270
GR dimers control JNK-mediated inflammation and cell-death via MKP-1 in an in vivo TNF model	Claude Libert Ghent/Belgium	05/23/2012	GRK 1041
Small molecules targeting p53 as prototype anticancer drugs and research tools to study p53 biology	Galina Selivanova Stockholm/Sweden	05/10/2012	KFO 167
Stem cells, niches and lineage commitment during early mouse development	Sebastian Arnold Freiburg/Germany	05/10/2012	GRK 1041
Novel roles for Hfe and Hepcidin in metabolism	Maja Vujic Heidelberg/Germany	04/17/2012	GRK 1041
Neural regulation of hematopoietic stem cell hibernation	Hiromitsu Nakauchi Tokyo/Japan	04/10/2012	GSC 270
Is Chronic Bronchitis an Acquired Form of CF?	Robert Tarran North Carolina/USA	04/02/2012	GSC 270
Fidelity of double strand break repair	Dale A. Ramsden Chapel Hill/USA	03/30/2012	GSC 270
Using the HIV Surface Protein to Navigate Viral Transmission and Pathogenesis	Ron Swanstrom Chapel Hill/USA	03/30/2012	GSC 270
Identification and characterization of semen-derived amyloids that enhance HIV infection	Nadia Roan San Francisco/USA	03/30/2012	GSC 270
The role of telomeres in initiation and progression of human skin cancer	Petra Boukamp Heidelberg/Germany	03/30/2012	GSC 270
Development of a microfluidic device for tagless analysis of cell surface proteins directing lung metastasis	S.H. Vellanki Newark/USA	03/30/2012	GSC 270
Towards Genetics of Aging: The short-lived killifish Nothobranchius furzeri as a new model for age research	Christoph Englert Jena/Germany	03/29/2012	GSC 270

Topic	Speaker	Date	Organizer
Talk on Stem Cells	Axel Behrens London/UK	03/05/2012	GSC 270
Talk on genetic cell modification to enhance hematopoietic regeneration	Christopher Baum Hannover/Germany	02/23/2012	GSC 270
Talk on lung cancer: an attempt(s) to increase the treatment sensitivity	Boris Zhivotovsky Stockholm/Sweden	02/01/2012	KFO 167
Stem Cell Aging in Drosophila	Henry Jasper California/USA	12/13/2011	GSC 270
Aging of hematopoietic stem cells	Gerald de Haan Groningen/Netherlands	12/01/2011	GRK 1041
Peroxisome proliferator-activated receptor γ coactivator 1alpha (PGC-1alpha)	Christian Handschin Basel/Switzerland	12/01/2011	GRK 1041
Seminar: Multiple roles of retinoic acid signaling in zebrafish fin regeneration	Gerrit Begemann Konstanz/Germany	10/19+20/2011	SFB 497
Lateral organization of membranes studied by fluorescence microscopy	Luis A. Bagatolli Odense/Denmark	10/19/2011	Department of General Physiology
Self-Regulating Systems in Stem Cell Biology	Hans Sieburg California/USA	10/19/2011	GSC 270
Wnt signalling and Wnt inhibitors in heart development	Stefan Hoppler Aberdeen/UK	10/07/2011	GSC 270
Castor and cell fate decisions in the mammalian heart	Kerry Dorr Chapel Hill/USA	10/07/2011	GSC 270
The role of SOX2 in optic cup patterning	Whitney Heavner Chapel Hill/USA	10/07/2011	GSC 270
Structural studies of GABA-A receptors	Paul Miller Oxford/UK	10/07/2011	GSC 270
Impaired synaptic function in an Alzheimer's disease mode	Olivia Shipton Oxford/UK	10/07/2011	GSC 270
The root-associated microbiota as an extended phenotype	Derek Lundberg Chapel Hill/USA	10/06/2011	GSC 270
Deriving biochemical functions from protein structure	Klaus Scheffzek Innsbruck/Austria	10/06/2011	GSC 270

Topic	Speaker	Date	Organizer
Tracking conformational changes by X-ray crystallography exemplified by H-Ras p21	Axel Scheidig Kiel/Germany	10/06/2011	GSC 270
Mechanism of activation and inactivation of Gq/phospholipase C-beta signaling nodes	Ken Harden Chapel Hill/USA	10/06/2011	GSC 270
Ras-like GTP binding proteins and diseases	Alfred Wittinghofer Dortmund/Germany	10/06/2011	GSC 270
Adipocyte-DerivedFactors: Physiological Roleand Clinical Relevance	Philipp E. Scherer Dallas-Texas/USA	10/05/2011	GSC 270
Stem cell theories and models – Computational studies on stem cell aging, niche effects and leukemia	Ingo Röder Dresden/USA	09/29/2011	GSC 270
Seminar: Oncogenic signaling in the PI3K pathway	Peter K. Vogt California San Diego/USA	09/08/2011	SFB 497
Seminar: Preserving genomic integrity in somatic and mouse embryonic stem cells	Peter J. Stambrook Cinncinati/USA	09/01/2011	SFB 497
Mammalian Sirtuins: Linking transcription to metabolism and cell proliferation	Renate Voit Heidelberg/Germany	07/21/2011	SFB 497
The roles of cd137 in hematopoiesis and tumorigenesis	Herbert Schwarz Singapore	07/18/2011	SFB 497
p53-activated Sestrins link genotoxic stress to autophagy and metabolism	Andrei Budanov California San Diego/USA	06/30/2011	SFB 497
BaG family – Novel transcriptional regulators of cell fate decisions in the immune system	Kai Hildner Erlangen-Nuernberg/ Germany	06/21/2011	GSC 270
The Brain and Fat: Dissecting Systemic Control of Metabolism and Aging in the NAD World	Shin-ichiro Imai Missouri/USA	06/15/2011	KFO 142
Vpu prevents natural killer cell destruction of HIV-infected cells	Edward Barker Chicago/USA	06/01/2011	GSC 270
Intestinal microbiota at the crossroad between inflammation and metabolism	Dirk Haller Munich/Germany	04/28/2011	GRK 1041

Publications of PhD students 2011-2013

(until May 31, 2013)

2013

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Hartmann N, Messmann JJ, Leithäuser F, Weiswange M, Kluge M, Fricke H, Debatin KM, Strauss G (2013): Recombinant CD95-Fc (APG101) prevents graft-versus-host disease in mice without disabling antitumor cytotoxicity and T-cell functions. Blood. 121:556-65.

Hermann M, Maier F, Masroor A, Hirth S, Pfitzner AJ, Pfitzner UM (2013): The Arabidopsis NIMIN proteins affect NPR1 differentially. Front Plant Sci.12, 4:88.

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