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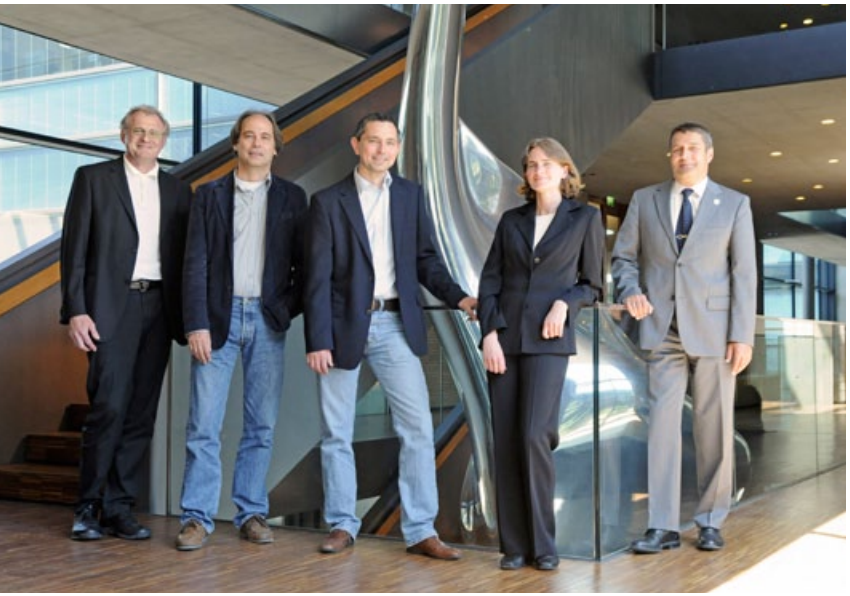
International Graduate School in Molecular Medicine Ulm | Biannual Report 2011

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



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

This is the second biannual report published by the International Graduate School in Molecular Medicine Ulm. Since the publication of our first report, our Graduate School has developed tremendously. The number of students we look after in our PhD program has increased to well above 100 and the structured program *Experimental Medicine*, which was set up by the Medical Faculty of Ulm University to improve the general framework and the quality of the theses of medical students, was fully integrated into the Graduate School. Currently, 35 students participate yearly in the program *Experimental Medicine*. These students are extremely successful as can be seen in their final grade, and the number and quality of papers they publish.

We have also substantially strengthened our international network. For instance, among our initiatives we have established double degrees with the University of Padua, Italy, in addition to several student exchange programs and common PhD projects with the BioCenter Oulu, Finland, the University of North Carolina at Chapel Hill, USA, and the Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China. A new cooperation agreement was signed with the OXION Initiative, Oxford University, UK, in 2011, which allows joint training activities in the field of ion channels and channelopathies. We are particularly proud of gaining Prof. Dr. Hiromitsu Nakauchi from Tokyo University, Japan, as a guest professor. Prof. Nakauchi is a well-known expert in the field of adult stem cell biology and his guest professorship will last up to five years. In addition to participating in the training activities, he has established a junior group at the Graduate School.

Current scientific developments at Ulm University have resulted in the profile of our Research Training Groups being sharply focused. For instance, aging and age-related diseases have become one of the major research areas adopted by several research networks such as the DFG-funded Clinical Research Unit: *KFO 142, Molecular and Cellular Mechanisms of Aging*, and the BMBF-funded network: *Gerontosys: Systems Biology of Aging* (SyStar). The application for the new DFG-funded Research Training Group: *Cellular and Molecular Mechanisms of Aging* (CEMMA) has successfully passed the first review step, while a promising initiative for a DFG-funded Collaborative Research Center dealing with age-related diseases has also been started. It has therefore been

necessary to include respective training activities into the Research Training Group: *Development and Degeneration*. Moreover, as a result of acquiring the Graduate College of Pharmaceutical Biotechnology, which is funded by the state of Baden-Württemberg, and the Carl-Zeiss-Foundation project: *Infection Biology of Human Macrophages*, a new Research Training Group entitled *Host-Microbe Interactions* was established in 2011.

Finally, the Board of Directors welcomes two new members: Prof. Dr. Peter Bäuerle, Vice-President of Science at Ulm University and Head of the Institute of Organic Chemistry II; and Prof. Dr. Tanja Weil, Head of the Institute of Organic Chemistry III. Prof. Bäuerle has replaced Prof. Dürre as the representative of the Presidium of Ulm University on the Board of Directors of the Graduate School. We would like to use this opportunity to thank Prof. Dürre for his enthusiastic support of the Graduate School over the years. Following the amendment of our administrative regulations, Prof. Weil was newly appointed as an additional member on the Board of Directors in order to strengthen the participation of the Faculty of Natural Sciences within the Graduate School.

What then will be the main tasks for the near future? 2011/2012 will clearly be dominated by our efforts to renew our external funding through the *Excellence Initiative of the German federal and state governments*. One particular focus will be on the establishment of training activities for postdocs and young group leaders. This will be of particular importance in preparing these young researchers for a university career.

We hope that you enjoy reading our brochure and would like to express our thanks to Bettina Braun and Julia Kutzenberger who both run our Coordination Office. Without their enthusiastic and engaged efforts, our Graduate School would not be the success it has become.
On behalf of the Board of Directors

Prof. Dr. Michael Kühl
Chairman

PD Dr. Dieter Brockmann
Managing Director

The Graduate School

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 multilevel 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 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 month to work full time in a laboratory. During this period students are supported by a fellowship of the Medical Faculty 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 excellently 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. This *Excellence Initiative* was initiated in 2005 to grant competitive awards to the best performing German universities and has subsequently proved to be a great success for our Graduate School, the Medical Faculty and Ulm University.

Recently, 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.

Promotion of Young Scientists

The Graduate School is committed to the promotion of young scientists and offers a variety of compatible programs in order to support and actively encourage young 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 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. 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. B. O. Böhm, Department of 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 the 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 conducting 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

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 28 stipends yearly (€ 500 per month over 10 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.

"Medical science is more than just being a "doctor". Thus, successful therapy strategies have to be based on profound research. The Study Programme Experimental Medicine allowed me to concentrate on my work. Through my experimental thesis I gained a deep insight into physiology as well as into medical research procedures. While I was finishing my thesis, I also passed my last exams. At the moment I'm in my final year of medical school learning practical medical skills. The theoretical, the experimental and the practical parts – all three will be important to fulfill my duties in my upcoming residency."
Susanne Albrecht studies human medicine at Ulm University and participated in the *Study Programme Experimental Medicine* from December 2007 till August 2008. In 2011 she received a doctoral award from the German Lung Foundation.

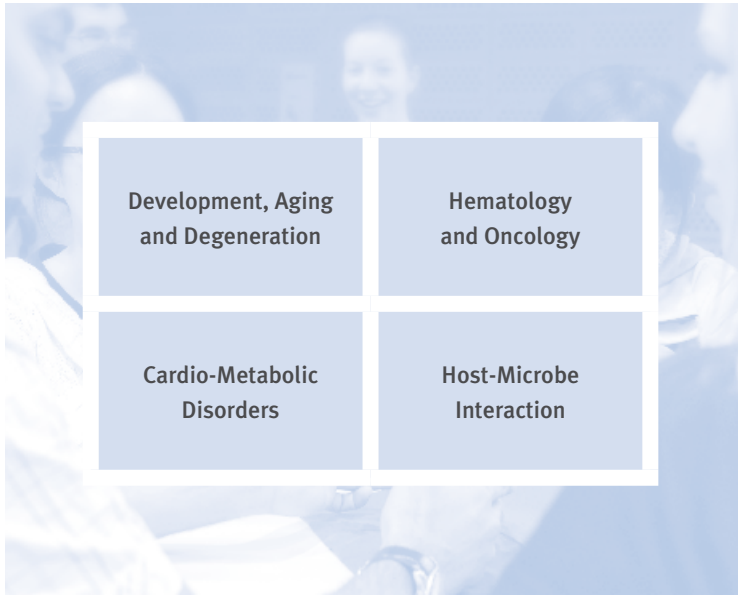
The Graduate School's Research Training Groups

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 Directors 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.

"It was a good opportunity for me to be a part of the Graduate School which had PhD students from diverse fields of biology. The best part that I liked was that it funded me to attend international conferences during which I could present my work and discuss my project with experts in the field. I enjoyed working at Ulm University and now I am a postdoc at the prestigious Stanford University, working on protein trafficking. I will do my best to contribute a significant piece of work to this field and I plan to take up a post in academics in the near future."
Ganesh Varma Pusapati is currently working as a postdoctoral research fellow at the Department of Biochemistry at Stanford University. He graduated in summer 2010.

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.

Careers

Our Alumni work in a variety of sectors. Below is a sample list of places where our former students are currently working:

- 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 and 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
- German Cancer Research Center (DKFZ), Heidelberg, Germany
- ETH Zurich, Institute of Pharmaceutical Sciences, Zurich, Switzerland
- Baltech AG, Hallbergmoos/Munich
- Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany
- Roche Deutschland Holding GmbH, Penzberg, Germany
- HiPP GmbH & Co. Vertrieb KG, Pfaffenhofen (Ilm)

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

"Looking back at my time at Ulm, I realize that both the excellent graduate training there and the diligent supervision, without taking away the freedom to develop projects in my own ways and along with the opportunity to travel to international conferences, were key to my future career. I hope that one day my work will contribute to the development of research strategies to normalize function in individuals with synaptopathies."

Andreas Grabrucker is currently working as a postdoctoral research fellow at the Department of Psychiatry and Behavioral Sciences at Stanford University. He graduated in fall 2009 with summa cum laude.

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 provides 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 precious time. This financing of technical assistants by the Graduate School is possible for a maximum period of one year.

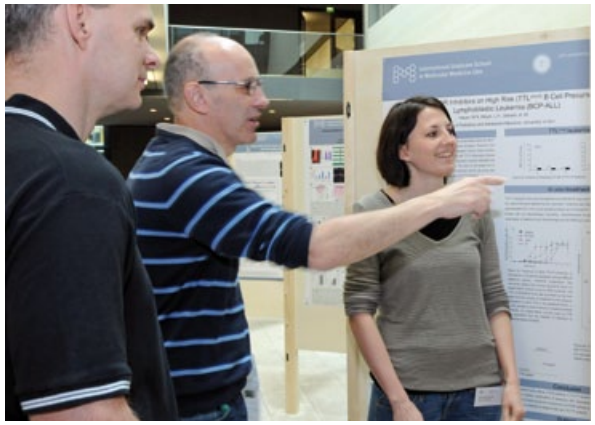
Female Mentoring

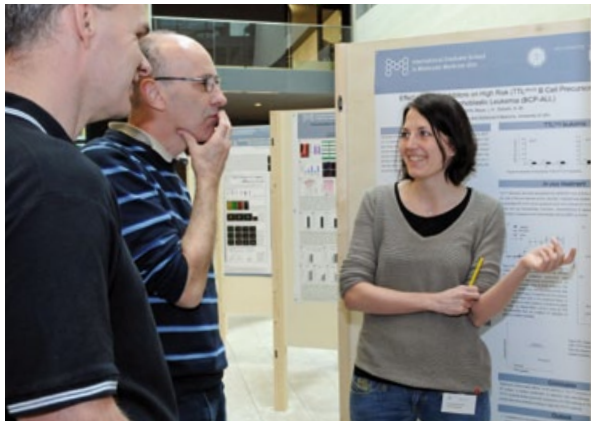
A Mentoring and Training program *(MuT)* enables our highly qualified female scientists to become acquainted with the ways and means of successfully tapping their career potential and exploring the opportunities available to them. It is there to support their personal development and assist in planning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

Scholarships

Many institutions offer a variety of 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 rate 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 young 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 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 young 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 even before their first acceptance 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 two 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 seniors 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 consultants 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 contacts between PhD students and senior consultants help to develop an atmosphere of confidence and familiarity.

Female Mentoring

The Graduate School supports the 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 supports their personal development and assists 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 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.

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, 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 3-6 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 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 foster a team spirit between doctoral students and supervisors.

"The interdisciplinary background of the program brought important new insights to my work and led to a collaboration with others that is still ongoing today, as well as opening doors to create various scientific networks. In addition, the training courses offered by the program equipped me well to further my scientific career. I think joining the International Graduate School in Molecular Medicine is a great opportunity for anyone aiming for a PhD and wishing to look beyond the end of their own nose!"
Meike Chevillotte has a postdoctoral position at the Rockefeller University in New York. She was Student Speaker of the *International PhD Programme in Molecular Medicine* Ulm and graduated in spring 2010 with summa cum laude. In 2009 she received the Doctoral Student Award of the Graduate School.

The Graduate School's International Networking

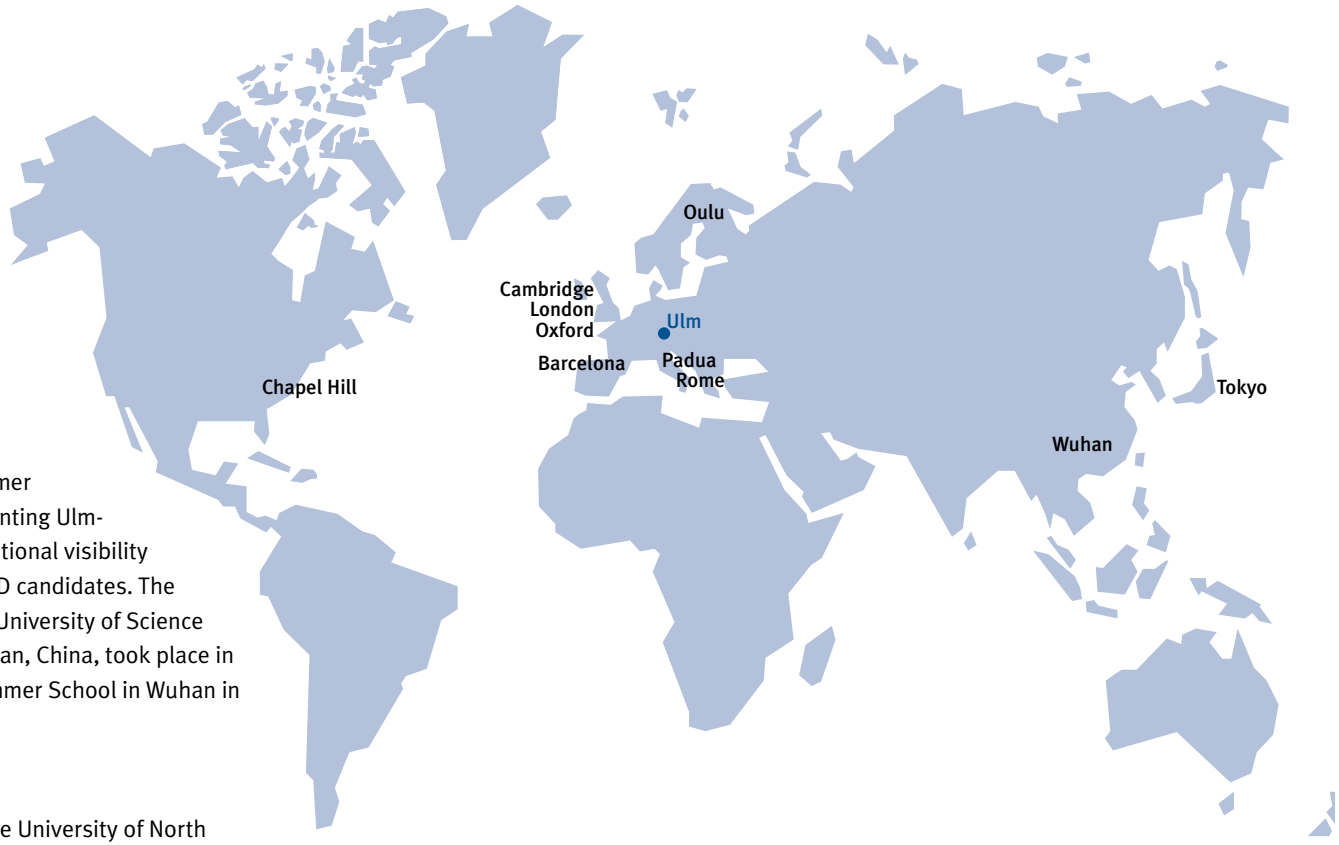
Scientific excellence not only depends on the outstanding performance of talented young researchers but also on the close cooperation with a worldwide network of renowned partner institutions. Consequently, the Graduate School is continually developing and maintaining scientific and research relations 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; the University of North Carolina at Chapel Hill, USA; the University of Padua in Italy; the Universities of Oxford, Cambridge, London and MRC Harwell; BioCenter Oulu, Finland; Bart's and Queen Mary's College in London; the Campus Bio-Medico University, Rome and the Universitat Autònoma de Barcelona.

Central elements of our internationalization strategy are the annual spring and fall meetings attended by speakers whose reputation is recognized internationally. A second important aspect is the promotion of international cooperation through various exchange programs and double degree agreements. In 2011, a new collaboration was initiated between the Graduate School and the OXION Ion Channels and Disease Initiative at the Universities of Oxford, Cambridge, London and MRC Harwell, with the aim of promoting joint training activities for PhD students. In 2010, the Graduate School was able to award Professor Hiromitsu Nakauchi, an internationally-renowned scientist in the field of stem cell research from the University of Tokyo, Japan, a visiting professorship. Furthermore, a joint PhD program with the University of Padua in Italy was also established.

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

Padua, Italy
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, Finland
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.

Wuhan, China
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 fifth Summer School in Wuhan in 2011 was Cancer: From Molecules to Disease.

Chapel Hill, USA
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, London and MRC Harwell, GB
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, London and MRC Harwell, began in 2011. Activities include joint lab courses and lab visits to learn novel techniques and to foster joint projects, as well as to allow students from both sides to participate in retreats and meetings.

A tri-national PhD program 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 11 institutes, 9 clinical-theoretical institutes and 14 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

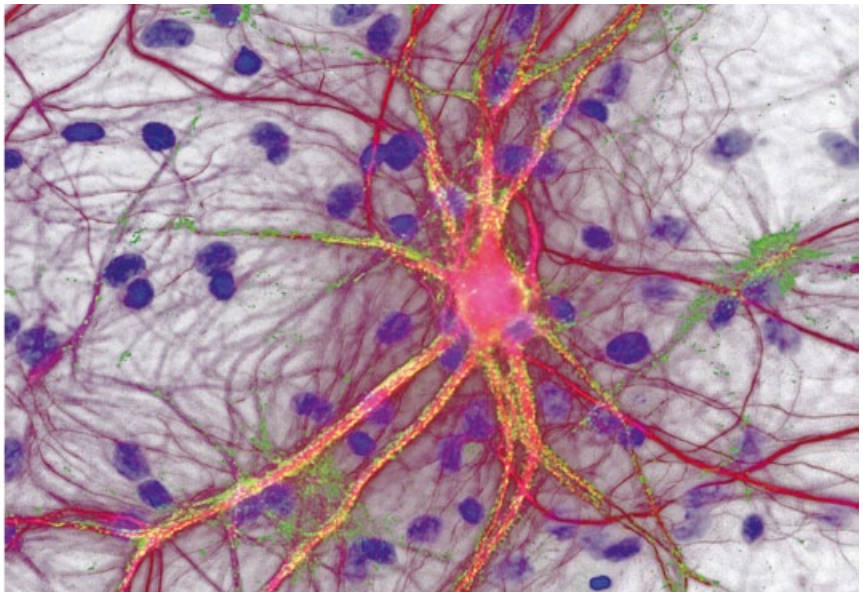
The Team:
Head of Institute: T. M. Böckers
Professor: N. Golenhofen
Group Leaders/Postdocs: B. Bartelt-Kirbach, A. Böckers, J. Bockmann, U. Fassnacht, St. Liebau, Ch. Pröpper, M. Schmeisser
PhD Students: J. Heinrich, A. Janssen, N. Kanwal, G. Kuh, L. Linta, T. Schmidt, P.T. Udvardi
Study Programme Experimental Medicine Student: M. Stockmann
Additional Members of Thesis Advisory Committees: H.J. Fehling (Ulm), E. Gundelfinger (Magdeburg), H.J. Kreienkamp (Hamburg), J. Kremerskothen (Münster), M. Kreutz (Magdeburg), A. Ludolph (Ulm), W. Robberecht (Leuven, B), A. Storch (Dresden)

Institute of Anatomy and Cell Biology

Proteins of Synaptic Contacts: Functional Characterization and Elucidation of their Possible Role in Neuropsychiatric Diseases

Head: Tobias Böckers

Glutamatergic synapses in the central nervous system are specific cellular junctions characterized by synaptic vesicles that are attached to the active zone of the presynapse and to an electron-dense web underneath the postsynaptic membrane known as the postsynaptic density (PSD). The pre- and postsynaptic membranes are interconnected by synaptic cell adhesion proteins (i.e. neurexin-neuroligin, cadherins) that are analyzed in the laboratory (PhD project Thomas Schmidt). 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.



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) and the synaptic protein synaptophysin (green) while the nuclei are labeled by DAPI (blue).
(Photo by Stefan Liebau)

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 and the PhD projects of Jutta Heinrich and Noreen Kanwal 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 (PhD project Michael Schmeisser). In addition, we are working on those drugs influencing synapse number and maturity (PhD project Patrick Udvardi) as well as on neuronal heat shock protein expression and dynactin mutations related to motorneuron degeneration (ALS). Within this context, Georges Kuh investigates the distribution of mutated dynactin fusion proteins in motor neurons and identifies novel dynactin interacting proteins. A wide range of methods and models, which includes Drosophila melanogaster and induced pluripotent stem cells (hiPS) as well as transgenic mice, are also employed.

Ulm University
Institute of Anatomy and Cell Biology
Prof. Dr. Tobias M. Böckers
Albert-Einstein-Allee 11
89081 Ulm, Germany
Tel. +49 (0)731 500 23220
Fax +49 (0)731 500 23217
tobias.boeckers@uni-ulm.de
www.uni-ulm.de/uni/fak/medizin/auz/

Selected Publications:

- *Grabrucker A, Garner C, Boeckers TM, Bondioli L, Ruozi B, Forni F, Vandelli M, Giovanni Tosi (2011) Development of novel Zn2+ loaded nanoparticles designed for cell-type targeted drug release in CNS neurons: in vitro evidences, Plos One, in press.*
- *Liebau S, Steinestel J, Linta L, Kleger A, Storch A, Schoen M, Steinestel K, Schmeißer MJ, Proepper C, Bockmann J, Boeckers TM (2011) An SK3 channel/ nWASP/Abi-1 complex is involved in early neurogenesis, Plos One, in press.*
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- *Schmeisser MJ, Grabrucker AM, Bockmann J, Boeckers TM (2009) Synaptic crosstalk between NMDA receptors and LAPSER1/β-catenin at excitatory synapses, J Biol Chem 284, 29146-57.*
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Institute of Molecular and Cellular Anatomy

Transcriptional Control of Neural Development

Head: Stefan Britsch

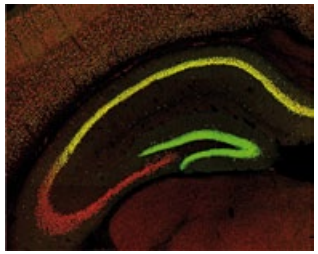
The ability of the mature nervous system to integrate, compute and distribute information results from developmental processes that create diversity, connectivity and the spatial organization of neurons. These processes are developmentally regulated by extrinsic and intrinsic mechanisms that act on presynaptic neurons with their navigating axons as well as on postsynaptic neurons with their differentiating dendrites. Both have to be precisely interconnected in order to establish functional neuronal circuits.

We are interested in the identification and functional characterization of transcriptional networks underlying the developmental control of these processes. Using whole transcriptome analyses, we have identified several novel candidate genes. To assess their developmental functions we employ gain- as well as loss-of-function techniques in mice. Recent work from our group demonstrated that two of our candidate genes, encoding the zinc finger transcription factors Bcl11a/CTIP1, and Bcl11b/CTIP2, are critical for the differentiation and wiring of neurons.

Transcriptional control of hippocampal neurogenesis

These studies focus on the function of Bcl11b during hippocampal development, adult neurogenesis as well as aging. The development of the hippocampus, a major brain structure involved in learning and memory, starts early in embryogenesis, continues postnatally and requires spatiotemporal expression of multiple factors. The dentate gyrus, the primary gateway for input information into the hippocampus, is one of only two brain regions with continuous neurogenesis in adult mammals. The differentiation and maturation process from progenitor cell to mature neuron requires several steps, including migration of newborn progenitor cells, correct positioning of immature neuronal cells and

The Team:
Head of Institute: S. Britsch
Professor: S. Schumacher
Group Leaders/Postdocs: K. Langer-Fischer, C. Schmidt, R. Simon, C. Wiegreffe
PhD Students: K. Franke, S. Glatz, S. Johannes, C. Steinhilber, S. Venkataramanappa
Study Programme Experimental Medicine Students: L. Baumann, E.-C. Nelles

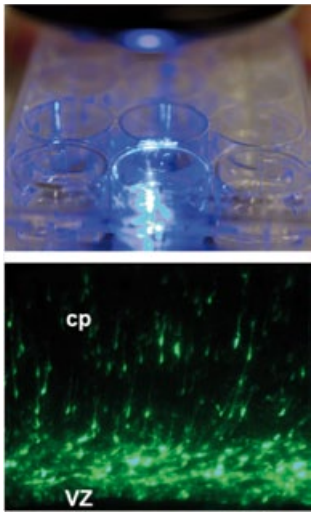


Cross section through the adult mouse hippocampus. Expression of the transcription factors Bcl11a/CTIP1 (red) and Bcl11b/CTIP2 (green) is visualized by the help of specific antibodies.

finally, synaptic integration of the mature neuron. We found that Bcl11b, as expressed in postmitotic cells, is required for postnatal development as well as adult neurogenesis of the dentate gyrus, (project Lisa Baumann). Our data reveal phase-specific functions of Bcl11b demonstrated by feedback control of the progenitor cell compartment as well as a cell- autonomous arrest of neuronal cell differentiation leading to impaired learning and memory behavior. Further studies will focus on elucidating the mechanism of Bcl11b regulation of neurogenesis and its role in neurodegenerative diseases as well as the aging process.

Bcl11a in neocortex development

In the neocortex, Bcl11a is expressed by postmitotic neurons during embryonic development and at postnatal stages. Analysis for forebrain-specific conditional mouse mutants suggests that Bcl11a is essential for neocortical development. Histological examination, immunofluorescence, BrdU birthdating, and cell cycle analysis are used to assess the phenotype in detail (project Eva-Cathrin Nelles). Using the in utero electroporation technique, we are able to selectively study the phenotype caused by overexpression or knockdown of Bcl11a and its transcriptional target genes in subsets of neocortical cells. With our studies we expect to improve our knowledge of transcriptional regulation of neocortical development.

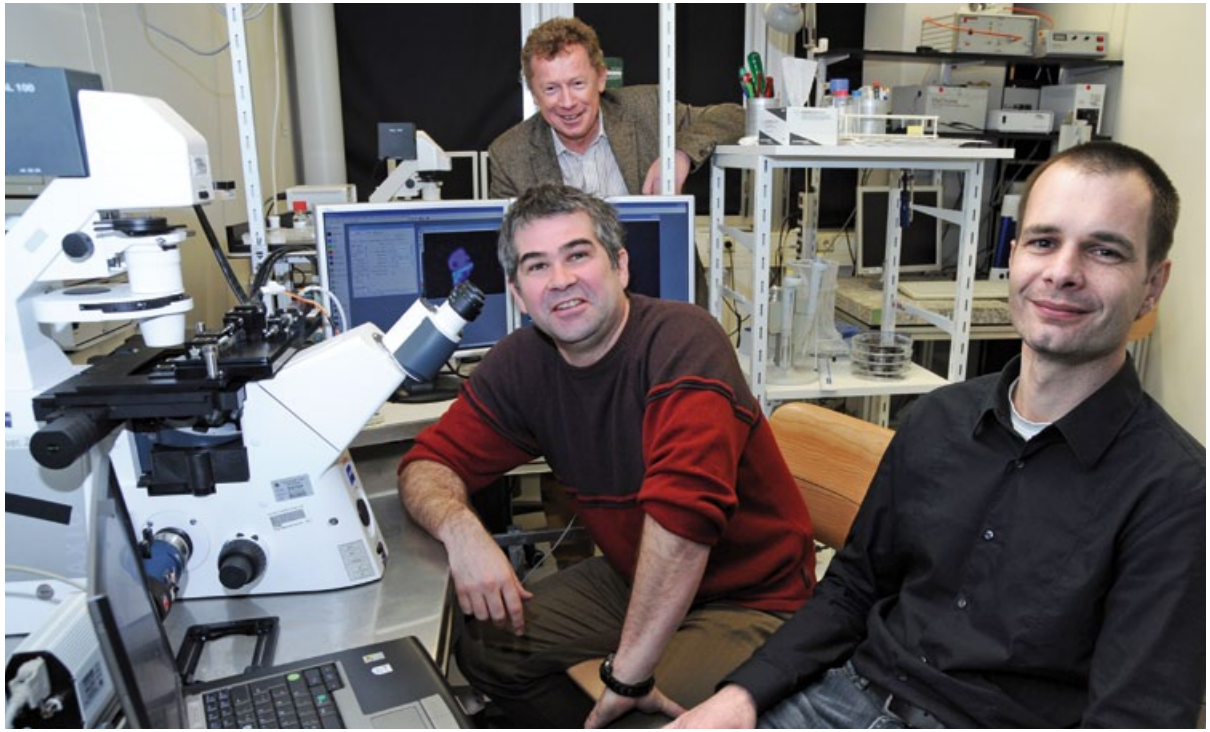


Floating-sections of mouse brains are screened for GFP fluorescence using a stereomicroscope (top). GFP+ neurons migrating away from the ventricular zone (vz) and entering the cortical plate (cp) (bottom).

Ulm University
Institute of Molecular and Cellular Anatomy
Prof. Dr. Stefan Britsch
Albert-Einstein-Allee 11
89081 Ulm, Germany
Tel. +49 (0)731 500 23101
Fax +49 (0)731 500 23102
stefan.britsch@uni-ulm.de
www.uni-ulm.de/med/med-anatomie.html

Selected Publications:

- *Simon R, Britsch S, Bergemann A (2011) Ablation of Sax2 gene expression prevents diet-induced obesity, FEBS Journal 278, 371-382.*
- *Schweickert A, Deißler K, Britsch S, Albrecht M, Ehmann H, Mauch V, Gaio U, Blum M (2008) Left-asymmetric expression of Galanin in the linear heart tube of the mouse embryo is independent of the Nodal coreceptor gene cryptic, Dev Dyn 237, 3557-3564.*



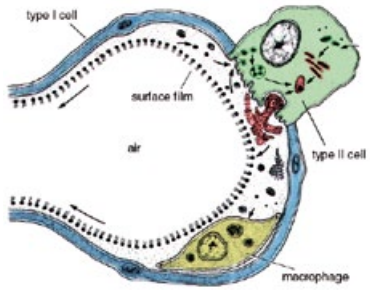
Institute of General Physiology

Cellular and Molecular Lung Physiology

Head: Paul Dietl

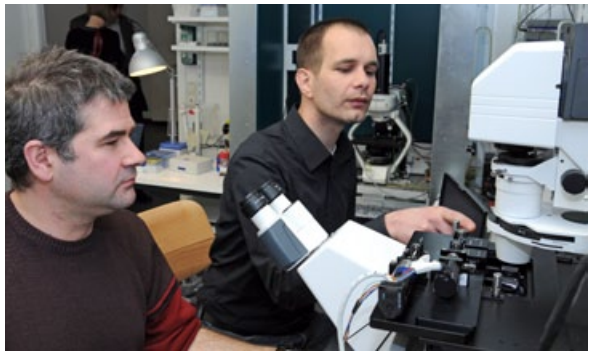
Surfactant, a lipid-rich and lipoprotein-like substance, is the secretory product of type II pneumocytes stored in vesicles called lamellar bodies (LBs). Surfactant secretion is essential for life and occurs through regulated exocytosis of LBs. In addition, LB exocytosis is unique in many respects (vesicle size and physico-chemical features of contents), and this makes it a good model for studying the exocytotic process using live cell imaging techniques.

The Team:
Head of Institute: P. Dietl
Group Leaders/Postdocs: M. Frick, E. Felder, P. Miklavc, O. Wittekindt
PhD Students: G. Fois, Y. Usmani



Schematic drawing of a pulmonary alveolus including a type II cell in the process of exocytosis.

We have recently developed several new microscopy techniques to study essential steps during this process. Using combinations of live cell imaging techniques (darkfield microscopy, fluorescence microscopy, LASER scanning microscopy, FRET, FRAP, etc.) with molecular tools (adenovirus vectors of fluorescence proteins, cell transfection etc.), our goal is to elucidate cellular and molecular mechanisms of hemifusion, fusion pore formation, fusion pore expansion and content release. These experiments aim at improving mechanistic insights into membrane merger, lipid and content mixing, signaling and trafficking, and at understanding basic pathogenic mechanisms of pulmonary disease.



Ulm University
Institute of General Physiology
Prof. Dr. Paul Dietl
Albert-Einstein-Allee 11
89081 Ulm, Germany
Tel. +49 (0)731 500 23231
Fax +49 (0)731 500 23242
paul.dietl@uni-ulm.de
www.uni-ulm.de/med/allgphys.html

Selected Publications:

- *Hecht E, Usmani SM, Albrecht S, Wittekindt OH, Dietl P, Mizaikoff B, Kranz C (2010) Atomic force microscopy of microvillous cell surface dynamics at fixed and living alveolar type II cells, Anal Bioanal Chem, in press.*
- *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, PLoS One 5, e10982.*
- *Albrecht S, Usmani SM, Dietl P, Wittekindt OH (2010) Plasma membrane trafficking in alveolar type II cells, Cell Physiol Biochem 25, 81-90.*
- *Miklavc P, Albrecht S, Wittekindt OH, Schullian P, Haller T, Dietl P (2009) Existence of exocytotic hemifusion intermediates with a lifetime up to seconds in type II pneumocytes, Biochem J 424, 7-14.*
- *Gerstmair A, Fois G, Innerbichler S, Dietl P, Felder E (2009) A device for simultaneous live cell imaging during uni-axial mechanical strain or compression, J Appl Physiol 107, 613-20.*
- *Miklavc P, Wittekindt OH, Felder E, Dietl P (2009) Ca2+-dependent actin coating of lamellar bodies after exocytotic fusion: a prerequisite for content release or kiss-and-run, Ann NY Acad Sci 1152, 43-52.*

Institute of Applied Physiology

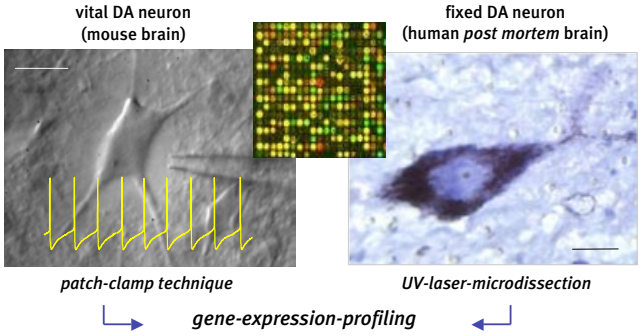
Work Group: “Molecular Neurophysiology”

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, such as in Parkinson’s disease, but also plays a crucial role in emotional and cognitive brain functions, and in related disorders such as schizophrenia, drug addiction and attention-deficit-hyperactivity disorders (ADHD).

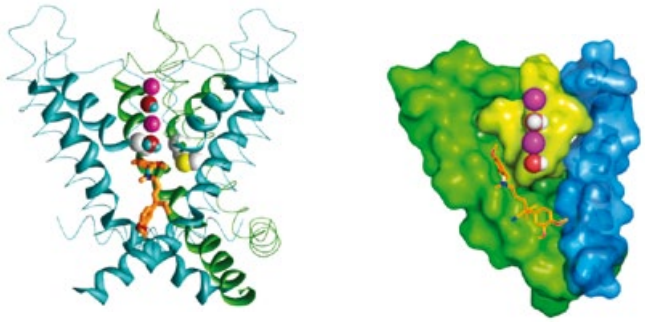
Our main research goal is to define functional and molecular mechanisms of different types of DA midbrain neurons with projections that define their distinct physiological roles and their selective transitions to disease states. By combining brain-slice in vitro electrophysiology and UV-laser microdissection 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, particularly in Parkinson’s disease.

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 post mortem 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.



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

The Team:
Head of Institute: B. Liss
Professor: S. Grissmer
Group Leaders/Postdocs:
E. Dragicevic, M. Fauler, W. Melzer, A. Rjasanow
PhD Students: J. Duda, M. Janbein, A. Nikouee, M. Orynbayev, C. Poetschke
Additional Members of Thesis Advisory Committees:
P. Dietl (Ulm), J. Roeper (Frankfurt)



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

Ulm University
Institute of Applied Physiology
Prof. Dr. Birgit Liss
Albert-Einstein-Allee 11, M25 + N27
89081 Ulm, Germany
Tel. +49 (0)731 500 36200 / 36214
Fax +49 (0)731 500 36202
birgit.liss@uni-ulm.de
www.uni-ulm.de/med/angewphys.html

Work Group: “Ion Channel Structure/Function”

Head: Stephan Grissmer

We are interested in the properties, modification and modulation of ion channels in cell membranes. Our aim is to clarify the physiological role of ion channels in cellular responses and in diseases. Recently, we 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 and peptide toxins, to identify the binding site of those blockers and, by means of 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:

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- *Liss B and Roeper J (2010) Ion channels and regulation of dopamine neuron activity. Book chapter in: The Dopamine Handbook; Oxford University Press, edited by A. Bjorklund, S. Dunnett, L. Iversen, S. Iversen, ISBN: 0195373030.*
- *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, 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, 4531-6.*
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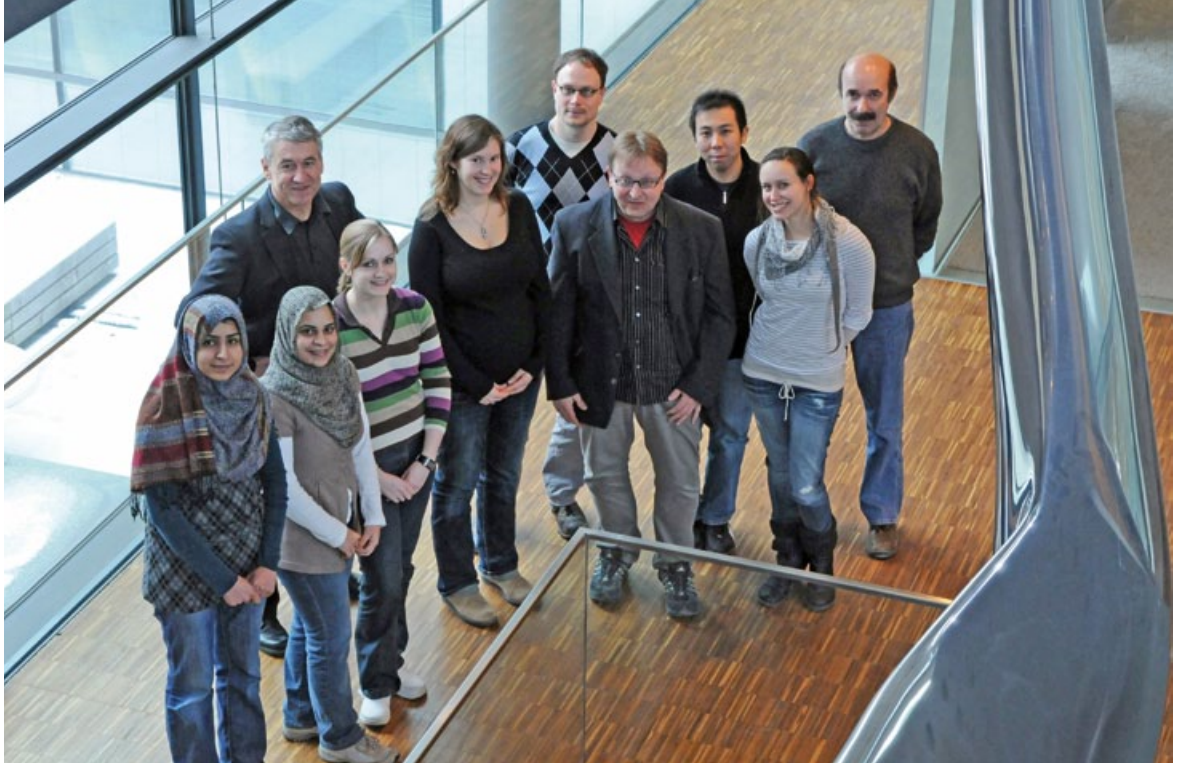
- *Lammel L, Hetzel A, Haeckel O, Jones I,Liss B,Roeper J (2008) Unique properties of mesoprefrontal neurons within a dual mesocorticolimbic dopamine system, Neuron 57, 760-73.*



Institute of Physiological Chemistry

Molecular Pathways Regulating Differentiation and Disease

Head: Thomas Wirth

We use sophisticated conditional mouse genetics to investigate the functions of defined transcriptional regulators and key components of signaling pathways in normal differentiation processes as well as in animal disease models. 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 patho-physiological processes.

One of the pathways we are specifically interested in is the IKK/NF-κB signaling pathway. NF-κB transcription factors are composed of homo- and heterodimers of five family members in mammals. The most common heterodimer is the p50/RelA heterodimer present in most cells, albeit in an inhibited and inactive form. Inhibition is brought about by a second class of proteins named the

The Team:
Head of Institute: T. Wirth
Professor: B. Knoell
Group Leaders/Postdocs: B. Baumann, C. Brunner, H.J. Maier, U. Schmidt-Straßburger, Y. Sunami, A. Ushmorov
PhD Students: S. Anastasiadou, S. Gul, N. Hipp, A. Magnutzki, A. Maqbool, T. Schips, M. Vogel
Study Programme Experimental Medicine Students: J. Faerbinger, K. Kloiber
Additional Members of Thesis Advisory Committees: T. Böckers (Ulm), T. Braun (Bad Nauheim), D. Eick (Munich), K.-L. Rudolph (Ulm), T. Luedde (Aachen), P. Strnad (Ulm), M. Wagner (Ulm), H. Wajant (Würzburg)

Ulm University
Institute of Physiological Chemistry
Prof. Dr. Thomas Wirth Albert-Einstein-Allee 11
89081 Ulm, Germany
Tel. +49 (0)731 500 23270
Fax +49 (0)731 500 22892
thomas.wirth@uni-ulm.de
www.uni-ulm.de/med/med-physchem.html

IκB-proteins. A multitude of stimuli induces the activity of a kinase complex (IKK) that phosphorylates the IκB-proteins, which are subsequently degraded. In this way, the NF-κB transcription factors are released and activated. Many aspects of development and disease have been associated with the NF-κB system but in the majority of cases, there is a lack of decisive proof. Using genetic activation or blocking of this signaling pathway, we have identified several key ways in which this system contributes to such acute diseases as stroke or acute pancreatitis, and have also unraveled its decisive role in epithelial mesenchymal transition, a process thought to be the key event in tumor metastasis. Our recent work focuses on the role of NF-κB for efficient neuronal differentiation, its contribution to various types of heart and liver disease, and the analysis of the NF-κB system for in vivo progression of pancreatic carcinoma. Within this context, we are analyzing the function of IKK2 in the formation and differentiation of chemical synapses and the consequences of changes in IKK2 activity on learning and memory processes (PhD project Ayesha Maqbool). Interestingly, we have recently demonstrated that NF-κB can function as a tumor suppressor in lymphomas transformed by the myc-oncogene. The PhD project of Nora Hipp investigates the interplay between the Myc-oncogene and NF-κB in additional tumor entities. Furthermore, since we have shown that Myc also regulates the expression pattern of a set of miRNAs (micro RNAs), we are now studying their contribution to tumor development/progression. Furthermore, our work on lymphomagenesis has identified epigenetic control mechanisms as crucial steps for specific types of B cell lymphoma. These epigenetic alterations affect the expression of transcription factors and transcriptional coactivators which by themselves are critical regulators of lymphocyte differentiation and function. These are topics of the MD project of J. Faerbinger.

Cellular and tissue homeostasis is also critically regulated by the FoxO proteins, transcription factors downstream of, for example, the insulin receptor signaling pathway. We have generated transgenic mice that allow conditional cell-type-specific modulation of FoxO3 activity. The role of FoxO3 in the heart is analyzed in the PhD project of Tobias Schips and its function in the liver is investigated in the PhD project of Sarah Gul. Katharina Kloiber is studying the effect of FoxO3 on neuronal development in her MD project.

Selected Publications:

- *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.*
- *Klapproth K, Sander S, Marinkovic D, Baumann B and Wirth T (2009) The IKK2/NF-κB-pathway suppresses Myc-induced lymphomagenesis, Blood 114, 2448-2458.*
- *Kokai E, Voss F, Fleischer F, Kempe S, Marinkovic D, Wolburg H, Leithäuser F, Schmidt V, Deutsch U and Wirth T (2009) Myc regulates embryonic vascular permeability and remodelling, Circ. Res. 104, 1151-1159.*
- *Sander S, Bullinger L, Klapproth K, Fiedler K, Kestler HA, Barth TF, Möller P, Stilgenbauer S, Pollack JR and Wirth T (2008) Myc stimulates EZH2 expression by repression of its negative regulator miR-26a, Blood 112, 4202-4212.*

Institute of Biochemistry and Molecular Biology

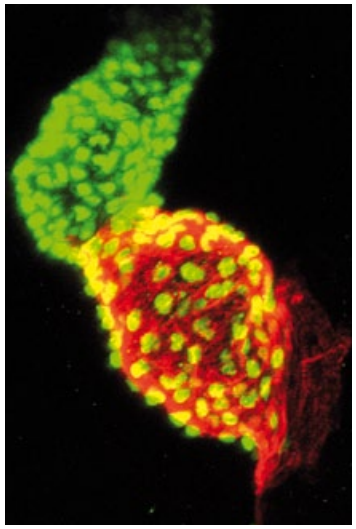
Signaling Processes During Early Embryonic Development

Head: Michael Kühl

The main research focus adopted at the Institute of Biochemistry and Molecular Biology lies in the field of organogenesis. For this purpose we use different model organisms that include *Xenopus laevis, Danio rerio, Drosophila melanogaster* and mice. In many projects we try to identify the role of Wnt signaling pathways for organogenesis.

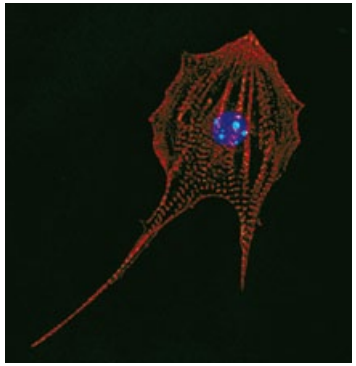
The Team:
Head of Institute: M. Kühl
Group Leaders/Postdocs: K. Bundschu, S. Kühl (née Gessert), P. Pandur, M. Philipp, I.O. Sirbu
PhD Students: V. Bugner, W. Cizelsky, F. Herrmann, B. Kracher, Z. Mirzojan, R.P. Tata, S. Tao, A. Tecza, I. Tuduce, G. Yanchun, K. Werner
Additional Members of Thesis Advisory Committees:
H. Aberle (Münster), L. Bally-Cuif (Paris, F), E. Bellefroid (Gosselies, B), T. Böckers (Ulm), S. Britsch (Ulm), F. Conlon (Chapel Hill, USA), H. J. Fehling (Ulm), T. Hollemann (Halle), S. Hoppler (Aberdeen, GB), H. Kestler (Ulm), E. Pera (Lund, S), V. Taylor (Edinburgh, GB), S. Vainio (Oulu, FIN), D. Wedlich (Karlsruhe)

The heart is the first functional organ during vertebrate development. Defects in the development of cardiac tissue 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 active in early heart development have been linked to congenital cardiovascular malformation. A detailed analysis of normal heart development at the molecular level will deepen our understanding of pathological changes in congenital heart diseases. Furthermore, 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. We have recently shown that Wnt signaling is required for vertebrate cardiac development and are currently analyzing this role in more detail (PhD projects of Guo Yanchun and Wiebke Cizelsky). In *Xenopus* and *Drosophila*, we have characterized for the first time the transcription factor Islet-1. In flies we are also investigating transcription factors of the Iroquois family (PhD project Zhasmine Mirzoyan) and are attempting to identify novel regulators of cardiac development (PhD project Kathrin Werner). Furthermore, retinoic acid signaling, and its



A two-chambered zebrafish heart at day 2 of development is shown. The atrium specific motor protein myh6 is stained in red. All nuclei of cardiomyocytes are stained in green.

cross talk with Wnt signaling, seems to be an important factor during cardiac and neural development. Within this context, our analysis includes the function of novel non-canonical Wnt signaling components and potential target genes during murine cardiac development (PhD project Tata Rao). During neural development non-canonical Wnt signaling pathways regulate the expression of selected targeted genes. Within this context, we are currently investigating the molecular mechanisms underlying the function of Peter Pan and IRS1 (PhD work Verena Bugner). Retinoic acid signaling and non-canonical Wnt signaling are also important for neural tube closure defects (PhD work Ioana Tuduce) that can lead to developmental neural malformations. Targets of non-canonical Wnt signaling are also investigated during pronephros development (PhD project Aleksandra Tecza). In cooperation with the group of Lenhard Rudolph, we analyze the function of Wnt during hematopoetic stem cell aging in mice (PhD project Si Tao). The molecular design of the Wnt signaling network is finally analyzed by modeling Wnt signaling together with the group of Hans Kestler. For this purpose we use quantitative models based on ordinary differential equations (PhD project Franziska Herrmann) and qualitative models (PhD project Barbara Kracher). In both cases, hypotheses will be generated through the use of computer-based simulations that can either be verified or falsified by experimental means in cell-based assays.



A cardiomyocyte generated by in vitro differentiation of murine embryonic stem cells. The contractile apparatus is stained with an antibody against α-actinin. The nucleus is counterstained in blue using DAPI.

Ulm University
Institute of Biochemistry and Molecular Biology
Prof. Dr. Michael Kühl
Albert-Einstein-Allee 11
89081 Ulm, Germany
Tel. +49 (0)731 500 23283
Fax +49 (0)731 500 23277
michael.kuehl@uni-ulm.de
www.uni-ulm.de/med/med-biomolbio.html

Selected Publications:

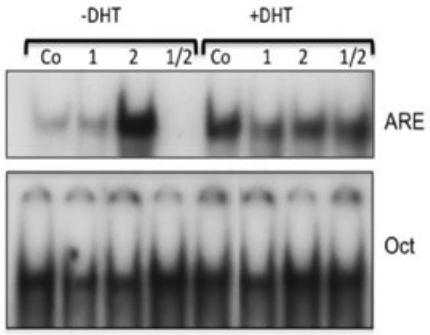
- *Tata RP, Tata NR, Kühl M, Sirbu IO (2011) Identification of a novel epigenetic regulatory region within the pluripotency associated microRNA cluster, EEmiRC, Nucleic Acids Res, 39, 3574-81.*
- *Bugner V, Tecza A, Gessert S, Kühl M (2011) Peter Pan functions independent of its role in ribosome biogenesis during early eye and craniofacial cartilage development in Xenopus laevis, Development, 138, 2369-78.*
- *Gessert S, Bugner V, Tecza A, Pinker M, Kühl M (2010) FMR1/FXR1 and the miRNA pathway are required for eye and neural crest development, Dev Biol 341, 222-35.*
- *Gessert S and Kühl M (2010) The multiple phases and faces of Wnt signaling during cardiac differentiation and development, Circ Res 107, 186-99.*
- *Mann T, Bodmer R, Pandur P (2009) The Drosophila homolog of vertebrate Islet1 is a key component in early cardiogenesis, Development 136, 317-26.*
- *Gessert S and Kühl M (2009) Comparative gene expression analysis and fate mapping studies suggest an early segregation of cardiogenic lineages in Xenopus laevis, Dev Biol 334, 395-408.*

Institute of General Zoology and Endocrinology

Modification of Androgen Receptor Activity by the NF-kappaB/IKK Signaling Pathway and Regulation of Androgen Receptor Signaling by Corepressors

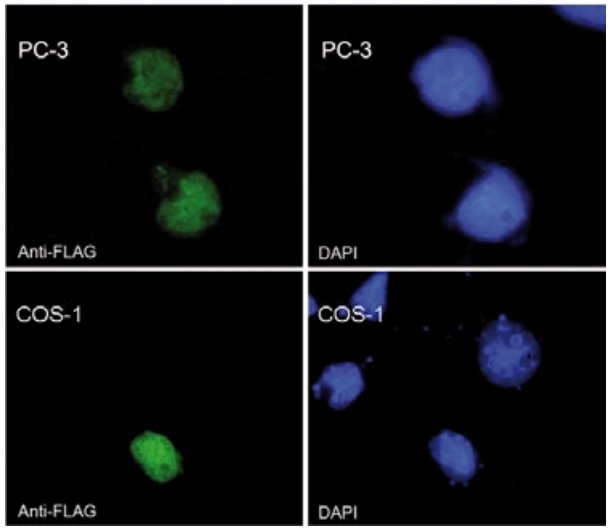
Former Head: Klaus-Dieter Spindler, Professor Emeritus

The androgen receptor (AR) and the NF-kappaB/IKK signaling pathway are two transcriptional systems shown to be important for the initiation and progression of prostate carcinoma (PCa). Furthermore, recently published studies imply a cross-talk between these two transcriptional systems. In order to define this cross-talk, we impaired the NF-kappaB/IKK system by using either pharmaceutical inhibitors or siRNAs specific for IKK and NF-kappaB proteins. Results from these studies imply that IKK inhibitors might be a useful tool for the therapy of PCa.



Effect of siRNA-mediated IKK knock-down in the prostate carcinoma cell line 22Rv1. Whole cell extracts from cells either left untreated or from cells stimulated with hormone were used for EMSA analysis for androgen receptor activity or Oct-binding. Knock-down of IKK2 has a positive effect, knock-down of IKK1 together with IKK2 impairs basal activity of androgen receptor.

The Team:
Former Head of Institute: K.-D. Spindler
Group Leaders/Postdocs: M. Cronauer, A. Hessenauer, R. B. Marienfeld*
*Institute of Pathology
PhD Students: G. Jain, M. Laschak
Additional Members of Thesis Advisory Committees:
G. Assum (Ulm), Z. Culig (Innsbruck, A), M. Montenarh (Homburg)



Staining of Flag-NCoR in PC-3 prostate cancer and COS-1 monkey kidney cells

Prostate cancer (PCa) is the most common cancer diagnosed in elderly men and the second leading cause of cancer-related death in the western world. The development and progression of PCa is initially androgen dependent but castration resistant tumours frequently occur after hormone ablation therapy. A reason for that is a dysregulation of androgen receptor (AR) cofactors. Cofactors are proteins that interact with nuclear receptors and either upregulate (coactivators) or downregulate (corepressors) the transcriptional activity of their target genes. These cofactors play a crucial role in tumour progression and development of castration resistant tumours. We investigated the corepressors NCoR (nuclear receptor corepressor) and SMRT (silencing mediator of retinoic acid and thyroid hormone receptor) in prostate and non-prostate cells using amongst others transactivation studies and mammalian two hybrid assays. The corepressors are localized exclusively in the nucleus, even in the absence of hormone (Fig. 2).

Ulm University
Institute of General Zoology and Endocrinology
Albert-Einstein-Allee 11
89081 Ulm
Fax +49 (0)731 50-22581
www.uni-ulm.de/nawi/nawi-bio1.html

Selected Publications:

- *Spindler KD, Laschak M, Cronauer MV (2011) Nitric oxide – a tool to block nuclear receptor activity, in: MK Bates: Nuclear Receptors, Nova Science Publishers, in press.*
- *Palkowitsch L, Marienfeld U, Brunner C, Eitelhuber A, Krappmann D, Marienfeld RB. (2011) The Ca2+-dependent phosphatase calcineurin controls the formation of the Carma1/Bcl10/Malt1 complex during T cell receptor induced NF-{kappa}B activation. J Biol Chem, 286(9), 7522-34.*
- *Schneider CC, Hessenauer A, Götz C, Montenarh M (2009) DMAT, an inhibitor of protein kinase CK2 induces reactive oxygen species and DNA double strand breaks, ONCOLOGY REPORTS 21, 1593-7.*
- *Leidner J, Palkowitsch L, Marienfeld U, Fischer D, Marienfeld R. (2008) Identification of lysine residues critical for the transcriptional activity and polyubiquitination of the NF-kappaB family member RelB. Biochem J, 416, 117-27.*
- *Palkowitsch L, Leidner J, Ghosh S, Marienfeld RB (2008) Phosphorylation of serine 68 in the IkappaB kinase (IKK)-binding domain of NEMO interferes with the structure of the IKK complex and tumor necrosis factor-alpha-induced NF-kappaB activity. J Biol Chem, 283, 76-86.*
- *Rinnab L, Hessenauer A, Schmid E, Küfer R, Hautmann RE, Spindler KD, Cronauer MV (2008) Rolle des Androgenrezeptors im hormonrefraktären Prostatakarzinom, Urologe A 47, 314-25.*

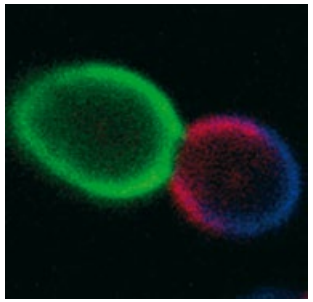
Institute of Molecular Genetics and Cell Biology

Cell Separation at the End of the Cell Cycle

Head: Nils Johnsson

The separation of mother from daughter cells at the end of each cell cycle requires the coordinated and precise activity of several processes. The cell must constrict and then fuse the plasma membrane to create two distinct cytosols and synthesize a special cell wall between mother and daughter cell to avoid cell lysis during this process. Finally, it must carefully break this wall to liberate both cells from each other. A comprehensive understanding of cell separation during cytokinesis requires not only a detailed knowledge of each of these processes but also a molecular understanding of how these different activities are coordinated in time and space.

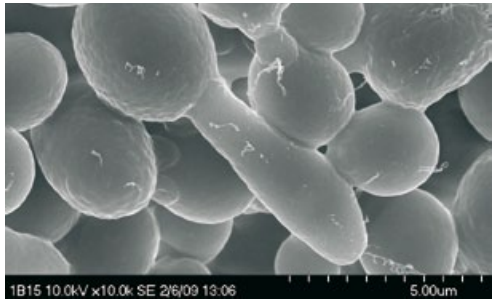
The Team:
Head of Institute: N. Johnsson
Group Leaders/Postdocs: A. Dünkler, T. Gronemeyer, J. Müller, D. Moreno
PhD Students: J. Neller, C. Renz, A. Rieke, L. Rieger, C. Schneider, C. Tian, Y. Wu, M. Zapatka
Additional Members of Thesis Advisory Committees: T. Böckers (Ulm), J. Dohmen (Cologne)



Multicolor labeling with synthetic fluophores on the surface of S.cerevisiae

Ulm University
Institute of Molecular Genetics and Cell Biology
Prof. Dr. Nils Johnsson
James-Franck-Ring N27
89081 Ulm, Germany
Tel. +49 (0)731 500 36301
Fax +49 (0)731 500 36302
nils.johnsson@uni-ulm.de
www.uni-ulm.de/nawi/nawi-molgen.html

We have recently identified a protein that is directly involved in the formation of the contractile acto-myosin ring structure (CAR) at the site of cell division. Cells lacking the corresponding gene fail to stabilize myosin at the position of the CAR. Mutations within this gene cause mislocalization of the protein and lead to the formation of myosin fibrils at the wrong places in the cytosol of the cell. To better understand the role of this protein in CAR assembly, we are currently trying to establish its influence on the formation of myosin fibrils in vitro.



Electron microscopy of S.cerevisiae lacking a kinase which is crucial for proper bud neck formation

Selected Publications:

- *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.*
- *Cailleteau L, Estrach S, Thyss R, Boyer L, Doye A, Domange B, Johnsson N, Rubinstein E, Boucheix C, Ebrahimian T, Silvestre JS, Lemichez E, Meneguzzi G, Mettouchi A (2010) Alpha2beta1 integrin controls association of Rac with the membrane and triggers quiescence of endothelial cells, J Cell Sci 123, 2491-501.*
- *Müller J, Johnsson N (2008) Split-Ubiquitin and the Split-Protein Sensors: Chessman for the Endgame, Chembiochem 9, 2029-2038.*

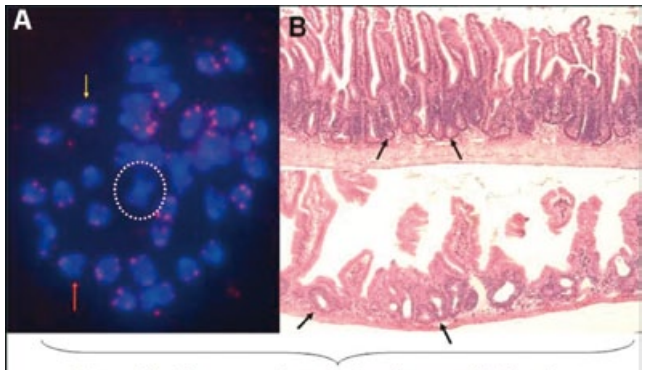
Institute of Molecular Medicine and Max-Planck-Research-Group on Stem Cell Aging

Stem Cell Aging, Regeneration and Cancer

Head: Karl Lenhard Rudolph

The Team:
Head of Institute: K. L. Rudolph
Group Leaders/Postdocs: C. Günes/Y. Morita/ A. Lechel, S. Tümpel, M. Burghalter, A. Illing, C. Falandry, M. Kumar, H.Q. Sun, Z. Ju, J. Feng, T. Sperka
PhD Students: A. Avila, A. Baig, P. Eshraghi, D. Hartmann, S.-F. Katz, K. Kleinhans, Y. Zhou
Additional Members of Thesis Advisory Committees: C. Beltinger (Ulm), C. Buske (Ulm), H.J. Fehling (Ulm), H.G. Forssmann (Hannover), H. Hermeking (Munich), F. Kirchhoff (Ulm), C. Klein (Regensburg), N. Malek (Hannover), D.A. Ramsden (Chapel Hill, USA), G. v. Wichert (Ulm), L. Zender (Braunschweig)

The main focus of our current research is on molecular mechanisms limiting the function of stem cells during aging and in response to stress (diseases/environmental factors). Stem cells are present in most adult mammalian tissues and organs, and contribute to their lifelong maintenance and repair. Evidence has emerged that the functional capacity of stem cells declines during organismal aging. Our working hypothesis indicates that age-/stress-related alterations in stem cell self renewal and function contribute to the impairment in organ homeostasis and regenerative capacities, with an increased risk in cancer formation.
For the analysis of stem cell aging, we use genetic mouse models focusing on hematopoietic and intestinal stem cells. In addition, we have started to analyze primary hematopoietic stem cells from adult humans. Our previous work has shown that both cell intrinsic pathways and cell extrinsic alteration in the environment (stem cell niche and systemic acting factors) can contribute to stem cell dysfunction during aging. Our research has revealed that mechanisms of stem cell aging (e.g. responses of stem cells to DNA damage) show significant differences in different tissue compartments also affecting cancer formation.
The main goals of our current research are:



(A)
Telomere shortening leads to loss of telomere capping function. The picture shows a metaphase from a bone marrow cell of telomerase knockout mice. Telomeres are marked in red. Normally, each chromosome end is capped by a telomere (yellow arrow). When telomeres become critically short, they lose their capping function (red arrow points to telomere-free ends). The cell recognizes telomere-free ends as DNA damage. Checkpoint responses (senescence/apoptosis) are induced. In addition, DNA-repair pathways are activated. This leads to chromosomal fusions (the circled chromosome pair shows a p-p-arm fusion) and the induction of chromosomal instability.
(B)
Telomere shortening in vivo is associated with accelerated stem cell aging. The photographs show the loss of intestinal stem cells in the basal crypts of the small intestine in aging telomerase knockout mice. The arrows point to the basal crypts containing the stem and progenitor cells.

Stem cell aging
– impaired self renewal & function
– chromosomal instability
– impaired organ maintenance
– increased cancer formation

1. To delineate the role of cell intrinsic pathways in controlling self renewal and the functional capacity and transformation of adult stem cells. We are currently analyzing the influence of DNA damage checkpoints, repair pathways and metabolic pathways at stem cell level.
2. To conduct interspecies (mouse/human) and inter-compartment comparisons (hematopoietic, intestine and muscle stem cells) to delineate molecular pathways affecting stem cell function (common pathways as well as tissue specific pathways). We aim to employ bioinformatics and systems biology approaches.
3. To determine cell-extrinsic alterations in the stem cell niche and the systemic environment that impact on stem cell function. This work will focus on mouse models of damage accumulation (telomere dysfunction, oxidative stress). In addition, we have started to screen human serum-derived peptide fractions to identify human serum peptides and proteins influencing hematopoietic stem cells (self renewal, quiescence).
4. To conduct functional genomics in vivo screens to identify new mechanisms involved in stem cell self renewal, stress resistance and transformation. For this purpose, we use lentiviral shRNA libraries to conduct in vivo screens on different stem cell compartments.

The ultimate goal of our research is to identify genetic and environmental factors that limit stem cell function and increase the risk of stem cell-derived cancers during life cycle. We aim to translate this knowledge to identify new compounds that can be used as regenerative or cancer preventive drugs. We have started compound screens to inhibit targets genes based on our previous work that has provided an in vivo proof of principle that specific genetic components limit stem cell function in the context of aging-associated alteration (e.g. p21 and Exo1 in response to telomere dysfunction).

Ulm University
Institute of Molecular Medicine
and Max-Planck-Research-Group on Stem Cell Aging
Prof. Dr. Karl Lenhard Rudolph
Albert-Einstein-Allee 11
89081 Ulm, Germany
Tel. +49 (0)731 500 36100
Fax +49 (0)731 500 36102
lenhard.rudolph@uni-ulm.de
www.uni-ulm.de/einrichtungen/instmolmed.html

Selected Publications:

- *Hartmann D, Srivastava U, Thaler M, Kleinhans KN, N' Kontchou G, Scheffold A, Bauer K, Kratzer RF, Kloos N, Katz SF, Song Z, Begus-Nahrmann Y, Kleger A, von Figura G, Strnad P, Lechel A, Günes C, Potthoff A, Deterding K, Wedemeyer H, Ju Z, Song G, Xiao F, Gillen S, Schrezenmeier H, Mertens T, Ziol M, Friess H, Blöcker H, Manns MP, Beaugrand M and Rudolph KL (2011) Telomerase gene mutations are associated with cirrhosis formation, Hepatology, in press.*
- *Nalapreddy K, Choudhury A, Gompf A, Ju Z, Ravipati S, Leucht T, Lechel A, Rudolph KL (2010) CHK2-independent induction of telomere dysfunction checkpoints in stem and progenitor cells, EMBO Reports 11, 619-25.*
- *Song Z, von Figura G, Lin Y, Kraus JM, Torrice C, Dillon P, Rudolph-Watabe M, Ju Z, Kestler HA, Sanoff H, Rudolph KL (2010) Lifestyle impacts on the aging associated expression of biomarkers of DNA damage and telomere dysfunction in human blood, Aging Cell 115, 1481-9.*
- *Song Z, Wang J, Guachalla LM, Terszowskif G, Ju Z, Rudolph KL (2010) Alterations of the systemic environment are the primary cause of impaired B- and T-lymphopoiesis in telomere dysfunctional mice, Blood 115, 1481-9.*
- *Begus-Nahrmann Y, Lechel A, Obenauf AC, Nalapareddy K, Peit E, Hoffmann E, Schlaudraff F, Liss B, Schirmacher P, Kestler H, Danenberg E, Barker N, Clevers H, Speicher MR, Rudolph KL (2009) p53deletion impairs clearance of chromosomal instable stem cells in aging telomere dysfunctional mice, Nature Genetics 41, 1138-43.*
- *Jiang H, Schiffer E, Song Z, Wang J, Zürbig P, Thedieck K, Moes S, Saal N, Bantel H, Jantos J, Brecht M, Jenö P, Hall MN, Hager K, Manns MP, Hecker H, Ganser A, Döhner K, Bartke A, Meissner C, Mischak H, Ju Z, Rudolph KL (2008) Proteins induced by telomere dysfunction and DNA damage represent biomarkers of human aging and disease, Proc Natl Acad Sci U S A 105, 11299-304.*

Institute of Neural Information Processing

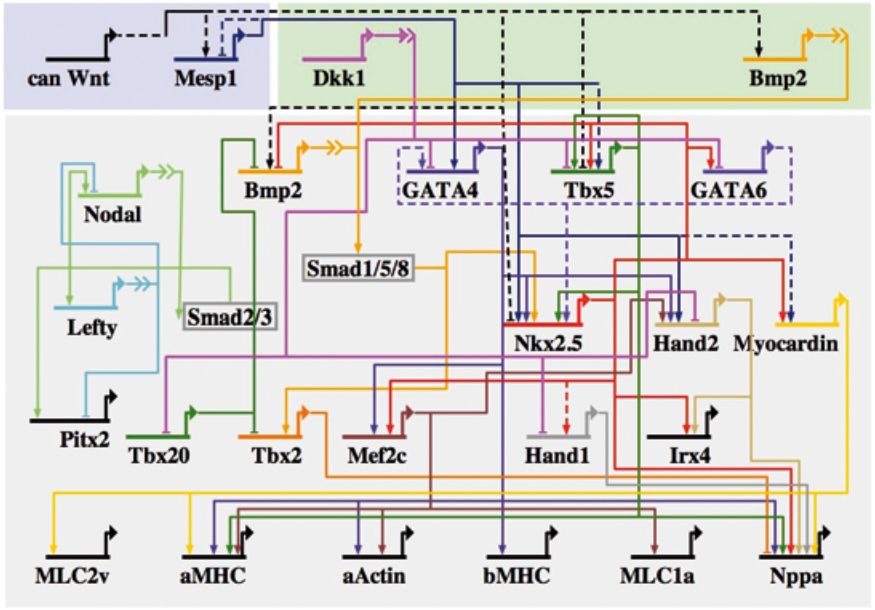
Work Group: “Bioinformatics and Systems Biology”

Head: Hans Armin Kestler

The Team:
Head of Institute: G. Palm
Head of the Working Group: H. A. Kestler
Group Leader/Postdoc: M. Maucher
PhD Students: A. Groß, M. Hopfensitz, J. Huth, J. Kraus, L. Lausser, M. Grieb, M. Müssel
Additional Members of Thesis Advisory Committees: M. Kühl (Ulm), P. Frasconi (Florence, I), J. Hoheisel (Heidelberg), M. M. Comin (Padua, I)

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 associated gene changes to pathways or networks. The methods used for these investigations largely stem from the field of machine learning. One type of model is a Boolean network that can 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. We are currently investigating this topic further with the aid of boosting algorithms (PhD project Ludwig Lausser). 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 (PhD project Martin Hopfensitz). This is also directly linked to modeling signal transduction and gene regulation with Boolean functions from data via reverse engineering or direct inclusion of expert knowledge on known dynamics (PhD works Christoph Müssel and Melanie Grieb). Other approaches being investigated are models based on differential equations or probabilistic rules, which usually require the inclusion of more global knowledge (PhD project Alexander Groß).



Boolean model of gene regulation in cardiomyocyte development: from the determination of cardiogenic mesoderm until activation of differentiation gene batteries. Links show regulatory interactions between gene products and target genes, and are represented as Boolean formulas.

Ulm University
Institute of Neural Information Processing
Research Group: Bioinformatics and Systems Biology
89081 Ulm, Germany
Tel. +49 (0)731 500 24248
Fax +49 (0)731 500 24156
hans.kestler@uni-ulm.de

Selected Publications:

- *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, 206-17. *equal contribution*
- *Huth J, Buchholz M, Kraus JM, Schmucker M, von Wichert G, Krndija D, Seufferlein T, Gress TM, Kestler HA (2010) Significantly improved precision of cell migration analysis in time-lapse video microscopy through use of a fully automated tracking system, BMC Cell Biol 11, 24.*
- *Song Z, von Figura G, Liu Y, Kraus JM, Torrice C, Dillon P, Rudolph-Watabe M, Ju Z, Kestler HA*, Sanoff H, Rudolph KL* (2010) Lifestyle impacts on the aging associated expression of biomarkers of DNA damage and telomere dysfunction in human blood, Aging Cell 9, 607–615. *corresponding authors.*
- *Chevillotte M, von Einem J, Meier BM, Lin FM, Kestler HA*, Mertens T* (2010) A new tool linking human cytomegalovirus drug resistance mutations to resistance phenotypes, Antiviral Res 85, 318–327. *corresponding authors.*
- *Kraus JM, Kestler HA (2010) A highly efficient multi-core algorithm for clustering extremely large datasets, BMC Bioinformatics 11, 169.*
- *Kestler HA, Müller A, Kraus JM, Buchholz M, Gress TM, Liu H, Kane DW, Zeeberg BR, Weinstein JN (2008) VennMaster: Area-proportional Euler diagrams for functional GO analysis of microarrays, BMC Bioinformatics 9, 67.*

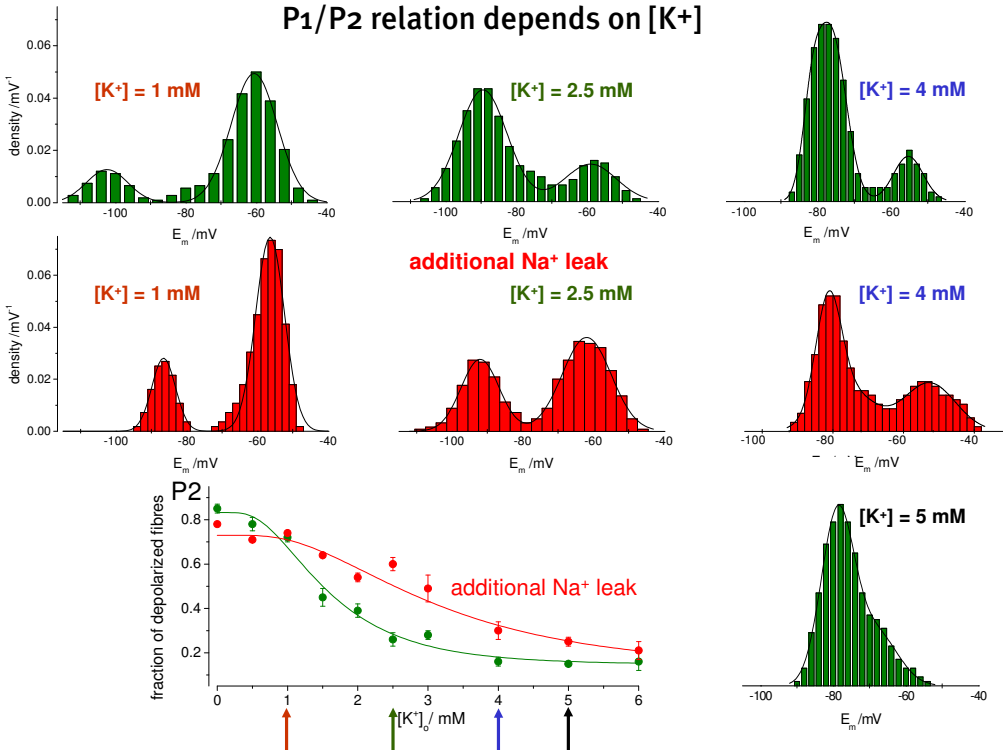
The Team:
Head of Institute: F. Lehmann-Horn,
Senior Research Professor of the Non-profit
Hertie-Foundation
Deputy Head of Institute:
K. Jurkat-Rott
Group Leaders/Postdocs: Z. Andronache,
B. Holzherr
PhD Students: C. Fan, L. Hollmann
Additional Members of Thesis Advisory Committees:
H. Brinkmeier (Karlsburg), Reinhardt Rüdel (Ulm)

Division of Neurophysiology

Translational Research on Channelopathies

Head: Frank Lehmann-Horn

Channelopathies are diseases caused by the dysfunction of ion channels as expressed in many cell types, tissues, and organs and this explains the wide phenotypic diversity of their clinical manifestations. One of them, hypokalemic periodic paralysis (HypoPP), is clinically characterized by paroxysmal episodes of generalized weakness triggered by hypokalemia and is caused by mutations in calcium and sodium channel genes expressed in skeletal muscle cells. The mutations replace positive arginines in the helical voltage sensors of these channels by uncharged residues and form an aberrant pore conducting Na^+ in addition to the central channel pore, i.e. HypoPP muscle fibers show an inward Na^+ leak current.



Bimodal distributions of resting membrane potentials of control and HypoPP model fibers. Note that the increase in the relative frequency of fibers in the P2 state with lowering extracellular K+ was more pronounced in HypoPP model than control fibers. This explains the sensitivity of HypoPP patients to low serum K+ and their muscle weakness. Below is shown a fit of the relative P2 frequencies dependent on external K+ for both control and HypoPP fibers (modified from Jurkat-Rott et al. 2009).

We have shown that the resting membrane potential of human muscle fibers is distributed around two electrically stable values. At physiological extracellular potassium concentration, most fibers are highly negative polarized (P1). However, the fraction of depolarized fibers (P2) is increased with lowering extracellular K^+. This paradoxical depolarization is contrary to the Goldman equation which predicts a membrane hyperpolarization at low-K. Due to the aberrant pore, HypoPP muscle preparations have revealed a pronounced paradoxical depolarization, intracellular sodium accumulation, an edema and muscle weakness.

Ulm University
Division of Neurophysiology
Prof. Dr. Dr. h.c. Frank Lehmann-Horn
Albert-Einstein Allee 11
89081 Ulm, Germany
Tel. +49 (0)731 500 23251
Fax +49 (0)731 500 23260
frank.lehmann-horn@uni-ulm.de
www.uni-ulm.de/med/medneurophysiology.html

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, Holzherr B, Fauler M, Lehmann-Horn F (2010) Sodium channelopathies of skeletal muscle result from gain or loss of function, Pflugers Arch, 460, 239–248.*
- *Ebert J, Fink S, Koitschev A, Walther P, Langer MG, Lehmann-Horn F (2010) Recovery of mechano-electrical transduction in rat cochlear hair bundles after postnatal destruction of the stereociliar cross-links, Proc Biol Sci 277, 2291-9.*
- *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.*
- *Weber YG, Storch A, Wuttke TV, (...) Lehmann-Horn F, Lerche H (2008) GLUT1 mutations are a cause of paroxysmal exertion-induced dyskinesias and induce hemolytic anemia by a cation leak, J Clin Invest 118, 2157-68.*
- *Wuttke TV, Penzien J, Fauler M, Seebohm G, Lehmann-Horn F, Lerche H, Jurkat-Rott K (2008) Neutralization of a negative charge in the S1-S2 region of the KV7.2 (KCNQ2) channel affects voltage-dependent activation in neonatal epilepsy, J Physiol 586, 545-55.*

Institute of Pathology

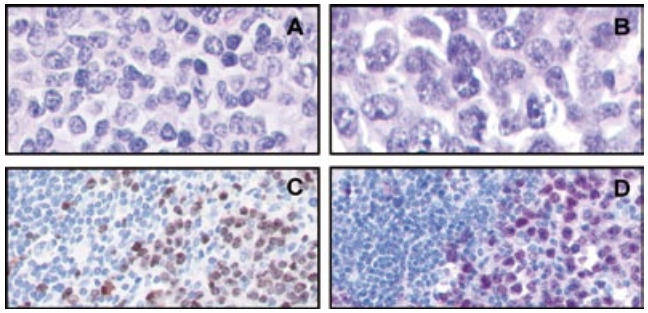
Gene Expression Profiling and SNP Analysis of B Cell Lymphoma of the Gastrointestinal Tract

Head: Peter Möller

As a national reference center for lymphoma diagnostics, the Institute of Pathology at Ulm University has been engaged for many years in the characterization of Hodgkin and non-Hodgkin lymphoma. Based on a large collection of fresh-frozen lymphoma tissue, the aim of the project is to analyze oncogenesis and the progression of extranodal marginal zone B cell lymphoma (MZBL) of the gastrointestinal (GI) tract by means of gene expression profiling and SNP analysis of microdissected lymphoma tissue.

MZBL, consisting of small cells, and aggressive diffuse large B cell lymphoma (DLBCL) of the GI tract are extranodal lymphomas with immunological, cytogenetic and clinical features that differ from nodal B cell lymphomas. It is well known that indolent MZBL and aggressive DLBCL can coexist in the GI tract. Within an inflammatory context caused by *Helicobacter pylori* infection, clonal evolution from the small to the large cell variant has been proven by means of molecular cytogenetics.

The Team:
Head of Institute: P. Möller
Professors: TFE Barth, R. Marienfeld
Group Leader/Postdoc: TFE Barth
PhD Students: L. Flossbach, K. Steinestel
Study Programme Experimental Medicine Student:
L. Schulte
Additional Members of Thesis Advisory Committees:
T. Wirth (Ulm), H. Kestler (Ulm), K. Holzmann (Ulm)

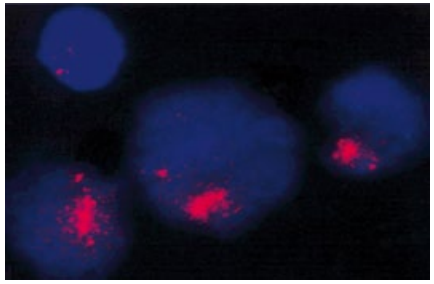


Composite lymphoma of an extranodal marginal B cell lymphoma of the stomach.
A: Hematoxylin-Eosin staining of the small cell component of a composite B cell lymphoma of the stomach. Cells have a lymphocytic appearance.
B: Hematoxylin-Eosin staining of the large cell component of the same lymphoma.
C: Immunostaining with the proliferation marker Ki-67. The large cell compartment shows a higher proliferation index than the small cell areas.
D: Immunostaining with an antibody specific for Bcl6. The small cell compartment is negative, while the large cell compartment shows strong expression of the Bcl6 protein.

Ulm University
Institute of Pathology
Prof. Dr. Peter Möller
Albert-Einstein-Allee 11
89081 Ulm, Germany
Tel. +49 (0)731 500 56320
Fax +49 (0)731 500 56384
peter.moeller@uni-ulm.de
www.uniklinik-ulm.de/struktur/institute/pathologie.html

Therefore, these tumors are referred to as “composite lymphoma” and represent a model of lymphoma progression. In a former study, we showed by transcriptional profiling that there is a close relationship between GI MALT lymphoma and their large cell variants. From these results, we concluded that DLBCL of the GI tract is a blastic, aggressive variant of MZBL.

We have identified that *c-REL* and *BCL6*, as candidate genes for lymphoma progression, can be activated by gene amplification or translocations. We have shown that an amplification of *c-REL* is frequently accompanied by a nuclear accumulation of *REL* protein in the nucleus of lymphoma cells. Our goal is to further characterize this finding of GI B cell lymphomas by using Affymetrix platforms for gene expression profiling and SNP analysis. Our aim is to identify specific markers associated with lymphoma progression from MZBL to DLBCL.



FISH with a probe for *c-REL* on a large B cell lymphoma of the stomach. The cloudy red signals reflect massive amplification on 2p16 that includes the *c-REL* gene.

Selected Publications:

- *Flossbach L, Antoneag E, Buck M, Siebert R, Mattfeldt T, Möller P; Barth TFE (2011) BCL6 gene rearrangement and protein expression are associated with large cell presentation of extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue, Int J Cancer 129, 70-7.*
- *Leeman JR, Weniger MA, Barth TF, Gilmore TD (2008) Deletion analysis and alternative splicing define a transactivation inhibitory domain in human oncoprotein REL, Oncogene 4, 6770-81.*

Institute of Virology

Work Group “Morphogenesis, Pathogenesis and Therapy in Human Cytomegalovirus (HCMV) Infection”

Head: Thomas Mertens

Human Cytomegalovirus (HCMV), a member of the Herpes virus family, is a highly significant 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 of a lifelong latent infection. Our group characterizes HCMV genes and their gene products with respect to viral morphogenesis, pathogenesis, antiviral therapy and resistance.

We therefore 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 and macrophages.

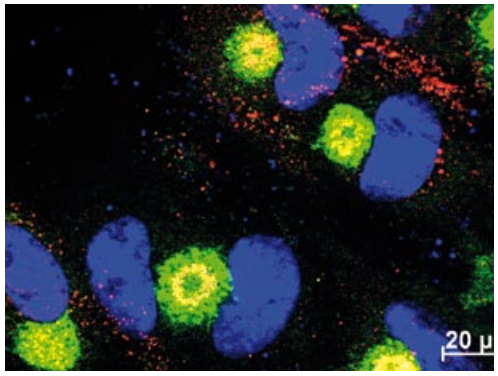
The Team:
Head of Institute: T. Mertens
Professors: C. Sinzger, D. Michel
Group Leaders/Postdocs: G. Frascaroli, B. Reinhardt, A. Schubert, J. von Einem
PhD Students: I. Brock, C. Bayer, I. Cappadona, I. Cobres, Z. Wu
Additional Members of Thesis Advisory Committees: W. Brune (Hamburg), G. Palù (Padua,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

Ulm University
Institute of Virology
Prof. Dr. Thomas Mertens
Albert-Einstein-Allee 11
89081 Ulm, Germany
Tel. +49 (0)731 500 65100
Fax +49 (0)731 500 65102
thomas.mertens@uni-ulm.de
www.uni-ulm.de/klinik/virologie/

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 concentrates on the pathomechanism of HCMV in vasculopathies. In cooperation with the Department of Pharmacology, we are investigating the molecular biology and function of the HCMV encoded G-protein-coupled receptor homologues.

The impact of antiviral therapy and viral resistance is constantly increasing. We are analyzing two genes, UL97 and UL54, known to be responsible for HCMV antiviral resistance with regard to their biological function.

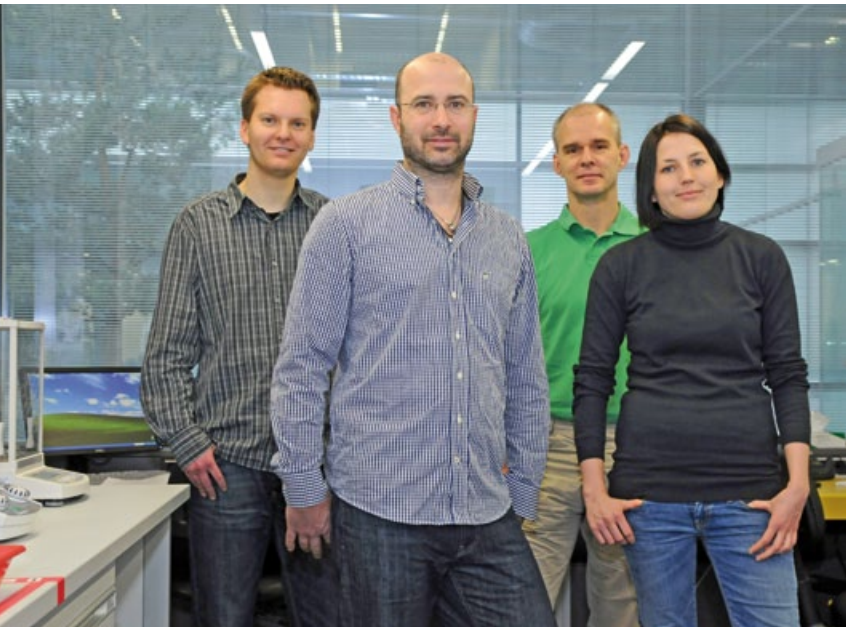
We are also compiling a database for the correlation of resistant pheno- and genotypes in collaboration with the Department of Neuroinformatics. This database is the first for HCMV and, having been made available on the internet, it is currently being used worldwide.



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

Selected Publications:

- *Schauflinger M, Fischer D, Schreiber A, Chevillotte M, Walther P, Mertens T, von Einem J (2011) The tegument protein UL71 of human cytomegalovirus is involved in late envelopment and affects multivesicular bodies, J Virol 85, 3821-32.*
- *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, 5004-11.*
- *Frascaroli G, Varani S, Blankenhorn N, Pretsch R, Bacher M, Leng L, Bucala R, Landini MP, Mertens T (2009) Human cytomegalovirus paralyzes macrophage motility through down-regulation of chemokine receptors, reorganization of the cytoskeleton, and release of macrophage migration inhibitory factor, J Immunol 182, 477-88.*
- *Chevillotte M, Landwehr S, Linta L, Frascaroli G, Lüske A, Buser C, Mertens T, von Einem J. Major (2009) tegument protein pp65 of human cytomegalovirus is required for the incorporation of pUL69 and pUL97 into the virus particle and for viral growth in macrophages, J Virol 83, 2480-90.*



The Team:
Head of Institute: F. Kirchhoff
Professor: J. Münch
Group Leaders/Postdocs: C. Goffinet, A. Specht, H. Yu, D. van der Merwe
PhD Students: F. Arnold, A. Gawanbacht, C. Gnanadurai, N. Götz, J. Heilmann, K. Mohammad, D. Palesch, D. Sauter, J. Schmökel, A. Shabir, C. Stürzel, M. Yolamanova, O. Zirafi
Additional Members of Thesis Advisory Committees:
P. Gierschik (Ulm), S. Pöhlmann (Hannover), R. Swanstrom (Chapel Hill, USA)

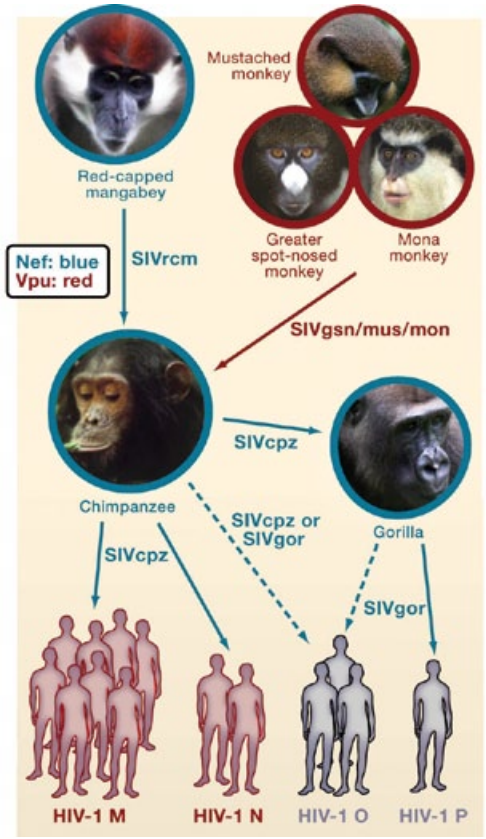
Institute of Molecular Virology

HIV-1 and AIDS

Head: Frank Kirchhoff

One of our major research interests is to clarify how “pathogenic” HIV-1 strains and “non-pathogenic” primate lentiviruses manipulate immune functions, and to elucidate why simian immunodeficiency viruses (SIVs) can persist efficiently in their simian hosts without causing disease. It is known that HIV-1, the causative agent of AIDS, increases the responsiveness of infected T cells to activation. We have shown that nef alleles from most primate lentiviruses exhibit a quite different phenotype and efficiently down-modulate TCR-CD3 to inhibit T cell activation and activation-induced cell death. This fundamental difference in Nef function might explain why high levels of immune hyper-activation are observed in progressing HIV-1 infection but absent in asymptomatic naturally SIV-infected monkeys. We have also examined 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 CD4 (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 CD4. This finding may explain why group M viruses are almost entirely responsible for the global HIV/AIDS pandemic.

Our second major focus is the isolation, characterization and optimization of novel inhibitors of HIV-1 and other viral pathogens. Therefore, 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- inhibitors. One of them, VIRIP, corresponds to the C-proximal region of a1-antitrypsin and blocks HIV-1 entry by a novel mechanism, i.e. direct binding to the gp41 fusion peptide. A cooperative first Phase 1/2 clinical study



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 blue 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.

has been completed and showed that mono-therapy with an optimized VIRIP variant reduces the viral loads by about 1.3 orders of magnitude without causing severe side effects. 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 virus titer by several orders of magnitude. We also showed that semen itself boosts HIV-1 infection. Thus, SEVI may play an important role in sexual transmission of HIV and represents a new target for its prevention. In our ongoing studies we have identified, among others, novel inhibitors and enhancers of HIV in breast milk and an as-yet unknown CXCR4 antagonist that blocks X4-tropic HIV-1 strains. We are also investigating the role of amyloids associated with neurological disorders for Neuro-AIDS.

Ulm University
Institute of Molecular Virology
Prof. Dr. Frank Kirchhoff
Meyerhofstraße 1
89081 Ulm, Germany
Tel. +49 (0)731 500 65150
Fax +49 (0)731 500 65153
frank.kirchhoff@uni-ulm.de
www.uniklinik-ulm.de/struktur/institute/molekulare-virologie.html

Selected Publications:

- *Sievers S, Karanicolas J, Chang H, Zhao A, Jiang L, Zirafi O, Stevens OT, Münch J, Baker D, Eisenberg D (2011) Structure-Based Design of Non-Natural Amino Acid Inhibitors of Amyloid Fibrillation, Nature, in press.*
- *Sauter D, Specht A, Kirchhoff F (2010) Tetherin: holding on and letting go, Cell 141, 392-8.*
- *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 mono-therapy in HIV-infected patients with a virus entry inhibitor against the gp41 fusion peptide, Sci Transl Med 2, 63re3.*
- *Kim KA, Yolamanova M, Zirafi O, Roan NR, Staendker L, Forssmann WG, Burgener A, Dejucq-Rainsford N, Hahn BH, Shaw GM, Greene WC, Kirchhoff F, Münch J (2010) Semen-mediated enhancement of HIV infection is donor-dependent and correlates with the levels of SEVI, Retrovirology 7, 55.*
- *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, 409-21.*
- *Arhel N, Lehmann M, Clauss K, Nienhaus GU, Piguet V, Kirchhoff F (2009) The inability to disrupt the immunological synapse between infected human T cells and APCs distinguishes HIV-1 from most other primate lentiviruses, J Clin Invest 119, 2965-75.*

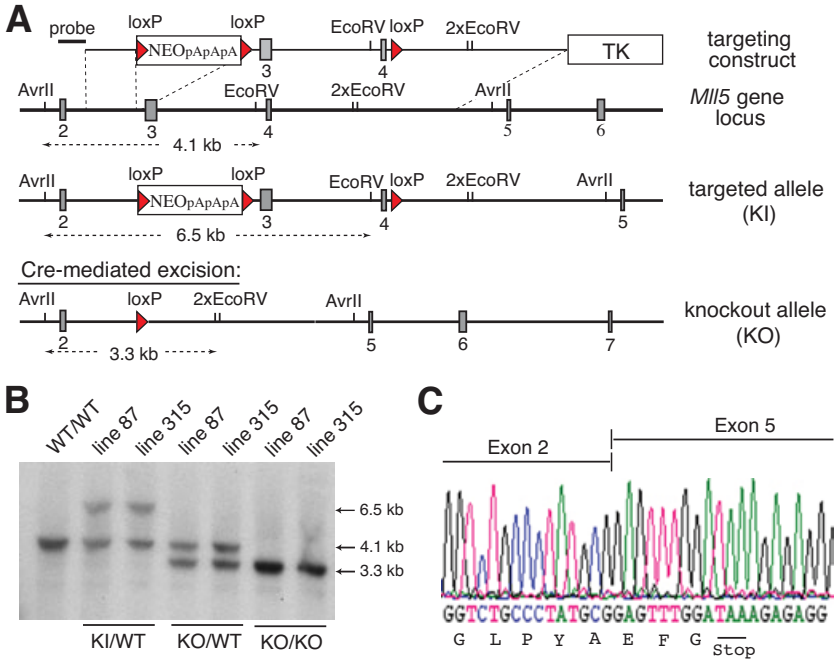
Institute of Immunology/Division of Molecular Immunology

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

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

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 in order to create mouse models of human diseases and also simply to assess unknown functions of novel genes. *Mixed-Lineage-Leukemia-5 (Mll5)* is the latest 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 gain an initial idea about the physiological role of *Mll5*, we have generated and characterized knockout mouse mutants. 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 is to obtain first insights into the molecular mechanisms underlying the described hematopoietic phenotypes. Towards this goal, Alpaslan is conducting several lines of investigation. For instance, he has established stable cell lines, including 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. Interestingly, these mutant cells also exhibit cell cycle defects and thus provide an easily accessible tool for molecular and biochemical studies into mechanisms of Mll5 function. To dissect the molecular pathways underlying the observed hematopoietic stem cell defects, it will be essential to identify relevant Mll5-regulated target genes. To this end, Alpaslan has set out to compare global gene expression patterns in long-term hematopoietic stem cell (LT-HSC) populations isolated prospectively from the pooled bone marrow of Mll5-deficient mice and littermate controls. Since these gene chip experiments are not



Generation of Mll5-deficient mice

A. Targeting strategy. Filled rectangles represent exons; red triangles, loxP sites. TK indicates the thymidine kinase gene; NEO, Neomycine resistance gene followed by 3 polyadenylation sites (pApApA); KI, knock-in; KO, knock-out.

B. Southern Blot of AvrII/EcoRV-digested genomic DNA isolated from mouse tail biopsies of the indicated lines and genotypes. The blot was hybridized with the external probe depicted in A.

C. Sequence analysis of Mll5 transcripts from knock-out mice confirming lack of exons 3 and 4 and the resultant shift in the reading frame, which leads to the appearance of an in-frame stop codon (TAA).

trivial due to the limited number of LT-HSCs per mouse, Alpaslan follows in parallel an "intelligent guess approach" by comparing expression levels of specific candidate target genes with quantitative real-time PCR, including, for instance, known or presumed regulators of HSC cycle control. Chromatin immunoprecipitation (ChIP) provides another systematic means to identify target genes of epigenetic regulators. As no ChIP-certified antibodies specific for Mll5 are available, Alpaslan has set out to attach "epitope-tags" to the carboxy-terminus of endogenous Mll5 via gene targeting in embryonic stem cells. The availability of epitop-tagged Mll5 knock-in mice and cell lines should significantly facilitate many functional 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 ChIP. The epitope-tagging experiments are done in collaboration with Prof. Dr. A.F. Stewart, Technical University Dresden.

Ulm University
Institute of Immunology
Prof. Dr. Hans Jörg Fehling
Albert-Einstein-Allee 11
89081 Ulm, Germany
Tel. +49 (0)731 500 65200
Fax +49 (0)731 500 65202
joerg.fehling@uni-ulm.de

Selected Publications:

- *Teupser D, Weber O, Rao NT, Sass K, Thiery J, Fehling HJ (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.*
- *Sawa S, Cherrier M, Lochner M, Satoh-Takayama N, Fehling HJ, Langa F, Di Santo JP, Eberl G (2010) Lineage relationship analysis of RORgammat + innate lymphoid cells, Science 330, 665-9.*
- *Irion S, Clark RL, Luche H, Kim I, Morrison SJ, Fehling HJ, Keller G (2010) Temporal specification of blood progenitors from mouse embryonic stem cells and induced pluripotent stem cells, Development 137,2829-39.*
- *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.*

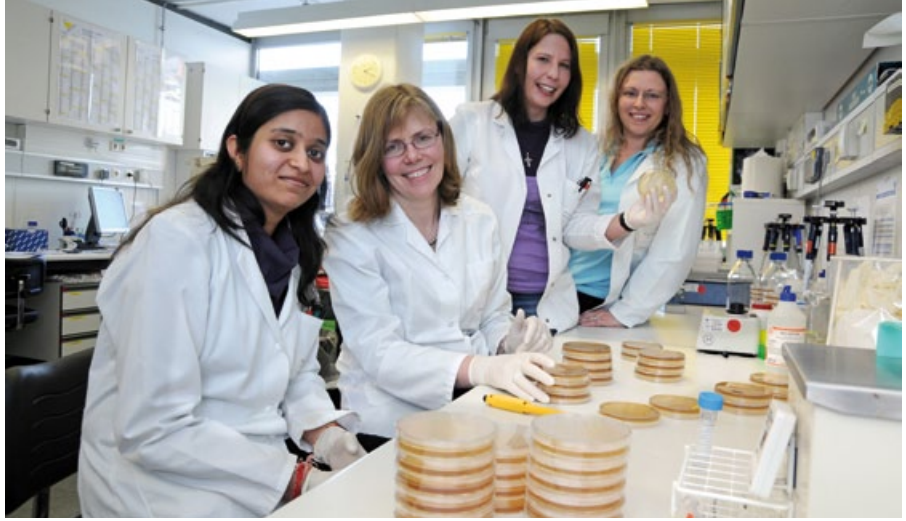
The Team:
Head of Institute: S. Stenger
Professor: B. Spellerberg
Group Leader/Postdoc: G. van Zandbergen
PhD Students: D. Asam, M. Busch, E. Blank, C. Florindo, D. Nickel, A. Sagar
Study Programme Experimental Medicine Student: J. Dick
Additional Members of Thesis Advisory Committees: H. Fehling (Ulm), E. Medina (Braunschweig)

Institute of Medical Microbiology and Hygiene

Microbial pathogens and the host
Work Group: “TvL-Lab; MyTB-Lab; Apoptosis-Lab. Apoptosis-Driven Infection”

Head: Steffen Stenger

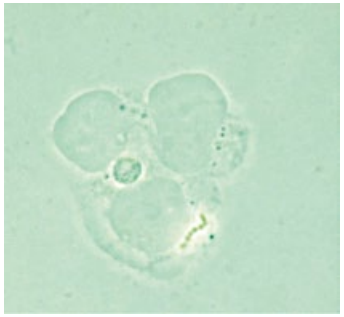
Professional phagocytes, such as polymorphonuclear neutrophil granulocytes (PMN) and macrophages (MF), kill pathogens as the first line of defense. These cells possess numerous effector mechanisms to eliminate a threat at first contact. However, several microorganisms, such as Leishmania and Mycobacteria, still manage to evade phagocytic killing and are able to survive and retain infectivity. Some pathogens have developed strategies to infect their preferred host phagocytes silently. The best example of an immune silencing phagocytosis process is the uptake of apoptotic cells. Immune responses are suppressed by the recognition of phosphatidylserine (PS) on the outer leaflet of their plasma membrane. Taking Leishmania major (L. major) as a prototypic intracellular pathogen, we have shown that these organisms can use the apoptotic “eat me” signal PS to enter PMN. PS-positive and apoptotic parasites, silently and in an altruistic way, and to enable the intracellular survival of viable parasites. Subsequently, these pathogens again use PS exposition, but now on infected PMN, and silently invade their definitive host cells, the macrophages. In the TvL lab (Death versus Life Lab, German: *Tod versus-Leben-Labor*), we focus on pathogenic evasion strategies based on the apoptotic system.



Ulm University
Institute of Medical Microbiology and Hygiene
Prof. Dr. Steffen Stenger
Albert-Einstein-Allee 11
89081 Ulm, Germany
Tel. +49 (0)731 500 65301
Fax +49 (0)731 500 65302
steffen.stenger@uniklinik-ulm.de
www.uniklinik-ulm.de/struktur/institute/medizinische-mikrobiologie-und-hygiene.html

Work Group: "Molecular Mechanisms of Streptococcal Pathogenicity"

Head: Barbara Spellerberg



A human monocytic cell line was infected with streptococci that were fluorescently labelled by the expression of green fluorescent protein. Streptococci can be seen in their typical morphology resembling beads on a chain.

The work of our group focuses on molecular mechanisms of streptococci that play an important role in human infections. Bacterial pathogenicity is a complex multifactorial interaction between microbial pathogens and their hosts, which are the natural habitat of human pathogens. Our laboratory is interested in the molecular details shaping the interaction between these partners. Within this context we were able to elucidate: the pyruvate oxidase of Streptococcus pneumoniae as an important determinant of pneumococcal virulence; the genetic background of Streptococcus agalactiae hemolysin production; and a composite transposon structure acquired by horizontal transfer between different hemolytic streptococci. It harbors genes (lmb, scpB) involved in adhesion to host extracellular matrix structures and interferes with the innate immunity responses towards microbial pathogens. At the Graduate School, we pursue two projects. The first investigates the role of C-reactive protein (CRP) for streptococcal infections. While CRP has been detected and named for its ability to bind to 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. The second project aims at elucidating the genetic background of Streptococcus anginosus ß-hemolysin production. While S. anginosus strains are often isolated from various abscesses, very little is known about the genes responsible for their pathogenicity.

Selected Publications:

- *Stenger S, van Zandbergen G (2011) Measuring the killing of intracellular pathogens: leishmania, Curr Protoc Immunol, Chapter 14, Unit14, 23.*
- *Aymanns S, Mauerer S, van Zandbergen G, Wolz C, Spellerberg B (2011) High level fluorescence labeling of gram-positive pathogens, PLoS One, accepted.*
- *Eickel V, Kahl B, Reinisch B, Dübbers A, Küster P, Brandt C, Spellerberg B (2009) Emergence of respiratory Streptococcus agalactiae isolates in cystic fibrosis patients, PLoS One 4, e4650.*
- *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.*
- *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.*
- *Bastian M, Braun T, Bruns H, Röllinghoff M, Stenger S (2008) Mycobacterial Lipopeptides Elicit CD4+ CTLs in Mycobacterium tuberculosis-Infected Humans, J Immunol 180, 3436-46.*

The Team:
Head of Institute: C. Kubisch
Professor: H. Kehrer-Sawatzki
PhD Students: J. Vogt, K. Bengesser, A. Roehl, T. Mußotter, S. Hampp, A. Zickler
Additional Members of Thesis Advisory Committees: H.J. Fehling (Ulm), L. Kluwe (Hamburg)

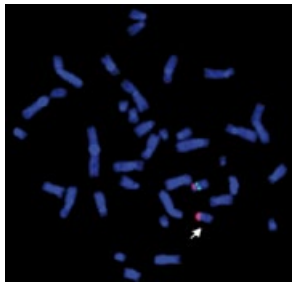
Institute of Human Genetics

Analyzing the Basis and Molecular Mechanisms of Human Hereditary Diseases

Head: Christian Kubisch

In addition to the clinical services in genetic counseling and in molecular as well as cytogenetic diagnostics, the Institute of Human Genetics focuses strongly on basic science. For example, independent working groups aim at disease gene identification in selected neurogenetic diseases by analyzing the mechanisms and consequences of genetic and genomic variability, and by studying mutagenesis.

The working group of Hildegard Kehrer-Sawatzki is working on the characterization of the molecular mechanisms underlying gross genome rearrangements associated with a number of human diseases. These mechanisms include nonallelic homologous recombination (NAHR), non-homologous end joining and microhomology-mediated replication-dependent recombination. Our work is primarily focused on the analysis of neurofibromatosis type-1 (NF1)-associated microdeletions which represent an excellent model system. *NF1* is a hereditary cancer predisposition syndrome that is characterized by tumors of the peripheral nerve sheaths. Large deletions encompassing the *NF1* gene and its flanking regions constitute the most frequently recurring copy number mutations causing *NF1*. Our work has contributed to the identification of four distinct types of large *NF1* deletion (type-1, type-2, type-3 and atypical) which differ with respect to the extent of the deleted region and the location of breakpoints. The most frequent type of *NF1* deletion is type-1 which encompasses 1.4 Mb; these deletions are caused by NAHR



FISH-analysis of human chromosomes indicating the lack of a green hybridization signal (white arrow) and thus a deletion on one chromosome 17.

occurring within two recombination hotspots, 2-3 kb in length, located within low-copy repeats flanking the *NF1* gene region. The vast majority of type-1 *NF1* deletions appear to be of meiotic origin. The second most frequent type of *NF1* deletion encompasses 1.2 Mb; the breakpoints of these type-2 deletions are located within the *SUZ12* gene and its pseudogene *SUZ12P*, located adjacent to the NF1-REPs. Our work indicated that the majority of these type-2 deletions are caused by mitotic NAHR.

Our studies of large *NF1* deletions have shown that both meiotic NAHR and mitotic NAHR occur non-randomly across the different *NF1*-flanking low copy repeats. The characteristic features of type-1 *NF1* deletions are largely consistent with the conclusion that certain NAHR hotspots operate exclusively during meiosis and not at all during mitosis. This suggests that there are fundamental mechanistic differences between meiotic NAHR and mitotic NAHR, particularly with regard to the determinants for recombination-inducing double strand DNA breaks. Large deletions in the *NF1* gene region have been found to be associated with an especially severe clinical phenotype. Thus, we observed significantly increased frequencies (relative to the general NF1 patient population) of plexiform neurofibromas (76%), subcutaneous neurofibromas (76%) and spinal neurofibromas (64%). The identification of deletion-predisposing genomic structural variants as well as disease-modifying genes is also a major research topic of the group. As in many other hereditary cancer syndromes, somatic mosaicism in *NF1* exerts a considerable influence on the clinical phenotype and the transmission risk of the disease. *NF1* also represents an excellent model system to study somatic mosaicism and this is currently being investigated by the group by employing a variety of different techniques and strategies that have been specially developed in order to improve mosaicism detection and mutational analysis.
(PhD project, Julia Voigt)

Ulm University
Institute of Human Genetics
Prof. Dr. Christian Kubisch
Albert-Einstein-Allee 11
89081 Ulm, Germany
Tel. +49 (0)731 500 65400
Fax +49 (0)731 500 65402
christian.kubisch@uni-ulm.de
www.uniklinik-ulm.de/humangenetik

Selected Publications:

- *Messiaen L, Vogt J, Bengesser K, Fu C, Mikhail F, Serra E, Garcia-Linares C, Cooper DN, Lazaro C, Kehrer-Sawatzki H (2011) Mosaic type-1 micro-deletions as a cause of both generalized and segmental neurofibromatosis type-1 (NF1), Hum Mutat 32, 213-219.*
- *Roehl AC, Vogt J, Mussotter T, Zickler AN, Spöti H, Högel J, Chuzhanova NA, Wimmer K, Kluwe L, Mautner VF, Cooper DN, Kehrer-Sawatzki H (2010) Intrachromosomalmitotic nonallelic homologous recombination is the major molecular mechanism underlying type-2 NF1 deletions, Hum Mutat 31, 1163-1173.*
- *Mautner VF, Kluwe L, Friedrich RE, Roehl AC, Bammert S, Högel J, Spöri H, Cooper DN, Kehrer-Sawatzki H (2010) Clinical characterisation of 29 neurofibromatosis type-1 patients with molecularly ascertained 1.4 Mb type-1 NF1 deletions, J Med Genet 47, 623-630.*
- *Chen JM, Cooper DN, Férec C, Kehrer-Sawatzki H, Patrinos GP (2010) Genomic rearrangements in inherited disease and cancer, Semin Cancer Biol 20, 222-233.*
- *Bengesser K, Cooper DN, Steinmann K, Kluwe L, Chuzhanova NA, Wimmer K, Tatagiba M, Tinschert S, Mautner VF, Kehrer-Sawatzki H (2010) A novel third type of recurrent NF1 microdeletion mediated by non-allelic homologous recombination between LRRC37B-containing low-copy repeats in 17q11.2, Hum Mutat 31, 742-751.*
- *Roehl AC, Cooper DN, Kluwe L, Helbrich A, Wimmer K, Högel J, Mautner VF, Kehrer-Sawatzki H (2010) Extended runs of homozygosity at 17q11.2: an association with type-2 NF1 deletions?, Hum Mutat 31, 325-334.*

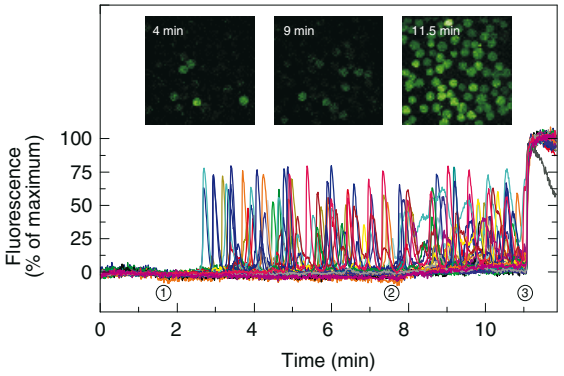
The Team:
Head of Institute: P. Gierschik
Professor: H. Barth
Group Leaders/Postdocs: B. Möpps, C. Walliser, J. Fahrer
PhD Students: Z. Rasonabe, A. Bühler, M. Pfreimer, C. König, T. Langer, L. Dmochewitz, M. Lillich
Study Programme Experimental Medicine Students: H. Christow, J. Rausch
Additional Members of Thesis Advisory Committees: G.U. Nienhaus (Karlsruhe), B. Nürnberg (Tübingen), R. Marienfeld (Ulm), R. Wetzker (Jena), T. Böckers (Ulm), T. Wieland (Mannheim), K.D. Spindler (Ulm), M. Thelen (Bellinzona, CH), T. Mertens (Ulm), T. Joos (Reutlingen), S. Kochanek (Ulm), M. Schwarz (Tübingen), C. Montecucco (Padua, I)

Institute of Pharmacology and Toxicology

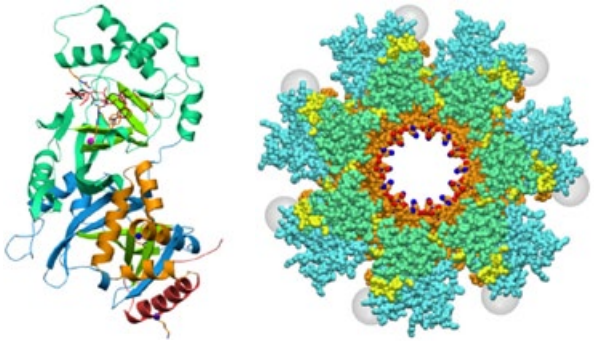
Signal Transduction Mediated by Heterotrimeric and Rho GTPases

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, 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. Five doctoral projects currently underway at the Institute are concerned with the structure/function relationships of GTPases. Zinna Rasonabe and Anja Bühler study the mechanisms of phospholipase C-γ_2 activation by the Rho GTPase Rac2. Mariana Pfreimer investigates the mode of Rho GTPase activation by chemokine receptors through heterotrimeric GTPases (G proteins) and the leukemia-associated **R**ho **g**uanine nucleotide exchange factor (RhoGEF) LARG. Carolin König explores 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. Torben Langer examines the interaction of the tumor suppressor merlin (**m**oesin-, **e**zrin-, and **r**adixin-**l**ike prote**in**) with proteins involved in regulating Rho GTPases.



B-cell-antigen-receptor-mediated increase of intracellular calcium ion concentration in genetically modified B cells. The colored traces correspond to the change in calcium concentration determined by confocal fluorescence microscopy in single chicken DT40 B cells. The genes encoding endogeneous phospholipase C-γ_2 had been inactivated by homologous recombination to allow for transgenic expression and functional characterization of chicken PLCγ_2 on a null background.
1) Addition of the B cell antigen receptor ligand anti-IgM in the absence of extracellular Ca^{2+}.
2) Addition of 1 mM extracellular Ca^{2+} in the continued presence of anti-IgM.
3) Addition of the Ca^{2+} ionophore ionomycin. The three insets show the fluoromicrographs obtained at the indicated times.



Three-dimensional structure of the binary *Clostridium botulinum* C2 toxin. Left, ribbon plot of the enzymatic component C2I. Right, model of the binding/translocation component C2IIa shown in an inflated-stick-mode. The expected docking site of the enzymatic component C2I is depicted in yellow. From Schleberger *et al.* (2006) J. Mol. Biol. 364, 705-715.

Drug Delivery Into Cells Exploiting Bacterial Exotoxins

Bacterial exotoxins are proteins that enter mammalian cells and enzymatically modify specific substrates in the cytosol, resulting in cell damage and symptoms of severe diseases such as diphtheria, anthrax or botulism. To enter cells, a binding/translocation domain mediates the transport of an enzyme domain into the cytosol. This unique mode of action makes exotoxins ideal Molecular Trojan Horses for targeted delivery of macromolecules into cells. We focus on genetic engineering and biotechnical production of tailor-made transporters based on clostridial toxins to deliver pharmacologically active molecules into the cytosol of monocytes/macrophages.

Lydia Dmochewitz develops recombinant fusion toxins that selectively induce apoptosis in monocytes/macrophages. The C3-toxin from *Clostridium botulinum* is taken up in those cells, but not in epithelial cells or fibroblasts. Thus, enzymatically inactive C3 is used to deliver enzymes into cells to induce apoptosis, but are not taken up on their own. The vision behind this approach is the therapeutic use of C3-fusion toxins in monocyte/macrophage-associated diseases. Maren Lillich constructs toxin-based transporters to deliver mammalian proteins (tumor suppressor protein, RNAse) into cells. The binding/transclocation moieties of clostridial toxins are coupled 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.

Ulm University
Institute of Pharmacology and Toxicology
Prof. Dr. Peter Gierschik
Albert-Einstein-Allee 11
89081 Ulm, Germany
Tel. +49 (0)731 500 65500
Fax +49 (0)731 500 65502
peter.gierschik@uni-ulm.de
www.uni-ulm.de/pharmtox

Selected Publications:

- *Everett KL, Buehler A, Bunney TD, Margineanu A, Baxendale RW, Vatter P, Retlich M, Walliser C, Manning HB, Neil MA, Dunsby C, French PM, Gierschik P, Katan M (2011) Membrane environment exerts an important influence on Rac-mediated activation of phospholipase C-γ_2, Mol Cell Biol 31, 1240-1251.*
- *Dmochewitz L*, Lillich M*, Kaiser E, Jennings LD, Lang AE, Buchner J, Fischer G, Aktories K, Collier RJ, Barth H (2011) Role of CypA and Hsp90 in membrane translocation mediated by anthrax protective antigen, Cell Microbiol 13, 359-373. (* shared first authorship)*
- *Fahrer J*, Kuban J*, Heine K*, Rupps G, Kaiser E, Felder E, Benz R, Barth H (2010) Selective and specific internalization of clostridial C3 ADP-ribosyltransferases into the cytosol of Macrophages, Cell Microbiol 12, 233-247. (*shared first authorship)*
- *Gutman O*, Walliser C*, Piechulek T, Gierschik P[§], Henis YI[§] (2010) Differential regulation of phospholipase C-β_2 activity and membrane interaction by $G\alpha_q$, $G\beta_1\gamma_2$, and Rac2, J Biol Chem 285, 3905-3915. (shared first* and last[§] authorships)*
- *Bunney TD, Opaleye O, Roe SM, Vatter P, Baxendale RW, Walliser C, Everett KL, Josephs MB, Christow C, Rodrigues-Lima F, Gierschik P, Pearl LH, Katan M (2009) Structural insights into formation of an active signaling complex between Rac and phospholipase C-γ_2, Mol Cell 34, 223-233.*
- *Kaiser E, Pust S, Kroll C, Barth H (2009) Inhibition of peptidyl prolyl cis/trans isomerases (PPIases) by Cyclosporin A and Tacrolimus (FK506) protects mammalian cells from intoxication with Clostridium botulinum C2 toxin by preventing toxin translocation into the cytosol, Cell Microbiol 11, 780-795.*

The Team:
Head of Institute: Th. Simmet
Professors: J. Stingl (formerly Kirchheiner), T. Syrovets
Group Leaders/Postdocs: B. Büchele, A. Seeringer, Y. Jin
PhD Students: M. Elgaafary, A. L. Godoy, O. Koshova, C. Loos, O. Lunov, S. Parmar, T. Paul, K. Stiebel, C. Schmidt
Additional Members of Thesis Advisory Committees: G.U. Nienhaus (Karlsruhe), V. Mailänder (Mainz), J. Brockmöller (Göttingen), T. Seufferlein (Halle), H. McLeod (Chapel Hill, USA)

Institute of Pharmacology of Natural Products and Clinical Pharmacology

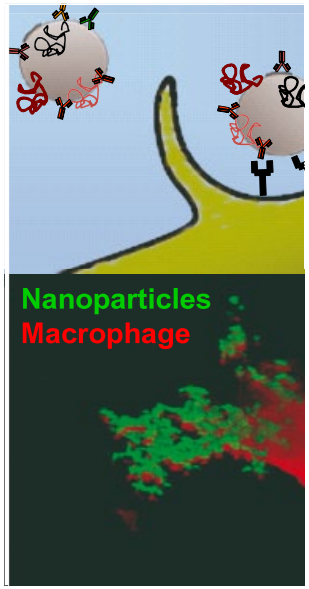
Work Group: "Molecular Pharmacology and Biophysics"

Head: Thomas Simmet

Modulation of Immune 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. Such nanosized particles could of course bias 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 investigated. The goals of our studies are: i) to learn in greater detail how distinct surface properties 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 therapeutic purposes. Various cell and molecular biological as well as biophysical methods, including advanced imaging, are used to address these questions.

This project is performed in collaboration with the Max-Planck-Institute for Polymer Chemistry (Prof. K. Landfester), Mainz, and the Institute of Applied Physics (Prof. G.U. Nienhaus), KIT, Karlsruhe.



Interaction between nanoparticles and macrophages

Ulm University
Institute of Pharmacology of Natural Products and Clinical Pharmacology
Helmholtzstraße 20
D-89081 Ulm, Germany
Tel. +49 (0)731 500 65600
Fax +49 (0)731 500 65602
www.uni-ulm.de/klinik/nhk/

Work Group: “Clinical Pharmacology”

Head: Julia Stingl (formerly Kirchheiner)

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

With reference to 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 inhibition 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:

- *Parmar S, Seeringer A, Denich, D, Gärtner F, Pitterle K, Syrovets T, Ohmle B, Stingl JC (2011) Variability in transport and biotransformation of cytarabine is associated with its toxicity in peripheral blood mononuclear cells, Pharmacogenomics, in press.*
- *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.*
- *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.*
- *Lunov O, Syrovets T, Röcker C, Tron K, Nienhaus GU, Rasche V, Mailänder V, Landfester K, Simmet Th (2010) Lysosomal degradation of the carboxydextran shell of coated superparamagnetic iron oxide nanoparticles and the fate of professional phagocytes, Biomaterials 31, 9015-22.*
- *Lunov O, Syrovets T, Büchele B, Jiang X, Röcker C, Tron K, Nienhaus GU, Walther P, Mailänder V, Landfester K, Simmet Th (2010) The effect of carboxydextran-coated iron oxide nanoparticles on c-Jun N-terminal kinase-mediated apoptosis in human macrophages, Biomaterials 31, 5063-71.*
- *Stingl JC, Parmar S, Huber-Wechselberger A, Kainz A, Renner W, Seeringer A, Brockmöller J, Langsenlehner U, Krippl P, Haschke-Becher E (2010) Impact of CYP2D6*4 genotype on progression free survival in tamoxifen breast cancer treatment, Curr Med Res Opin, 26, 2535-42.*

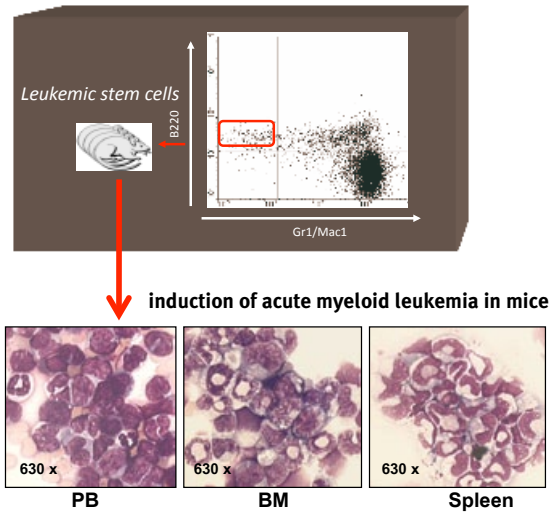
Institute of Experimental Cancer Research

Characterization of the Molecular Biology of Normal and Leukemic Hematopoiesis

Head: Christian Buske

It is widely 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 that cause malignant transformation of normal hematopoietic stem cells into leukemic stem cells using a wide panel of different murine models which mimic human leukemias. Using murine bone marrow transplantation assays and retroviral gene transfer, we could 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 such as the fusion gene *AML1-ETO* and the *FLT3 length mutation*. We also used murine leukemia models to profile leukemic stem cells and to identify differences between normal and leukemic stem cells and thus could show that in acute myeloid leukemia characterized by the fusion gene CALM-AF10, the leukemic stem cell differs from its normal counterpart by the expression of the lymphoid- associated

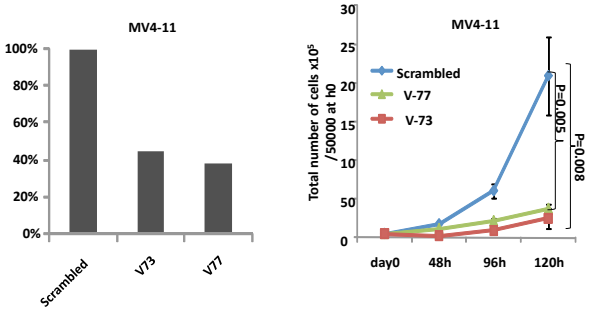
The Team:
Head of Institute: C. Buske
Professor: V.P.S. Rawat
Group Leaders/Postdocs: A. Muranyi, A. Rouhi, N. Vegi, M. Feuring-Buske, F. Kuchenbauer
PhD Students: S. Bamezai, D. Daria, K. Edmaier, J. Huang, S. Ihme, J. Klappacher, A. Rasalkar
Study Programme Experimental Medicine Student: A. Grünenberg
Additional Members of Thesis Advisory Committees: S. Fulda (Frankfurt), H. Glimm (Heidelberg)



We discovered that CALM-AF10 positive acute myeloid leukemia is propagated by a leukemic stem cell which expresses the lymphoid-associated antigen B220 but lacks expression of the myeloid antigens Gr1/Mac1. Highly purified B220$^+$/Gr1$^-$Mac1$^-$ cells are able to induce acute myeloid leukemia in transplanted mice *(Deshpande et al., Cancer Cell 2006)*.

Ulm University
Institute of Experimental Cancer Research
Prof. Dr. Christian Buske
Albert-Einstein-Allee 11
89081 Ulm, Germany
Tel. +49 (0)731 500 65801
Fax +49 (0)731 500 65802
christian.buske@uni-ulm.de
www.uniklinik-ulm.de/tumorforschung

antigen B220. The group currently focuses on the function of the TET protein family in normal and malignant hematopoiesis (VPS Rawat), the genetic and epigenetic characterization of leukemic stem cells (A. Rouhi), the role of non-coding RNAs in leukemogenesis (F. Kuchenbauer), the relevance of lymphoid antigen expression in acute myeloid leukemias (M. Feuring-Buske), and the biology of NPM1 mutated leukemias (A. Muranyi). For this purpose, the institute has access to state-of-the-art FACS technology as well as to next generation sequencing technology that have both been introduced to the University campus.



VENTX is a novel protein involved in human leukemogenesis: depletion of VENTX by shRNA constructs (V73 and V77) impairs proliferation of human AML cells lines in contrast to the control (scrambled) *(Rawat et al., PNAS 2010)*.

Selected Publications:

- *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, 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.*
- *Rawat VP, Thoene S, Naidu VM, Arseni N, Heilmeier B, Metzeler K, Petropoulos K, Deshpande A, Quintanilla-Martinez L, Bohlander SK, Spiekermann K, Hiddemann W, Feuring-Buske M, Buske C (2008) Overexpression of CDX2 perturbs HOX gene expression in murine progenitors depending on its N-terminal domain and is closely correlated with deregulated HOX gene expression in human acute myeloid leukemia, Blood 111, 309-19.*

The Team:
Head of Department: G. von Wichert (temporary)
Head of Division of Endocrinology and Diabetes: B. O. Böhm
Head of the Laboratory of Mucosal Immunology and Inflammatory Bowel Disease: J. H. Niess
Professor: R. Schirmbeck
Group Leaders/Postdocs: S. Merger, S. Rosinger, A. Spyrantis
PhD Students: U. Chinaka, Z. Fang, C. Manta, K. Radulovic, V. Rossini, N. Schäfer
Additional Members of Thesis Advisory Committees: P. Gierschik (Ulm), S. Kochanek (Ulm), D. Leslie (London, GB), P. Pozzilli (Rome, I), H.-C. Reinecker (Boston, USA)

Department of Internal Medicine I

Division of Endocrinology and Diabetes

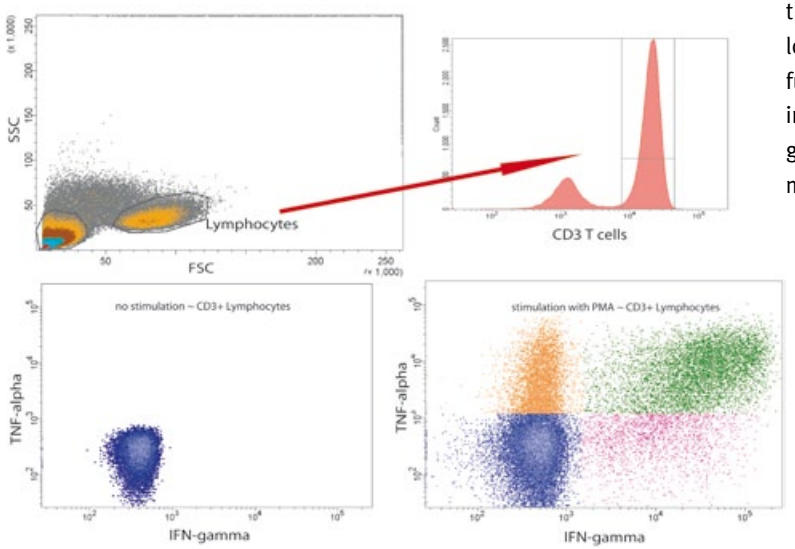
Head: Bernhard O. Böhm

Auto Reactive T-cells in Type 1 Diabetes

Type 1 diabetes is the result of a progressive immune-mediated destruction of insulin-producing ß-cells in the pancreatic islets of Langerhans. Type 1 diabetes is a model disease for studying the progression of autoimmunity. Preservation of ß-cell function is a central goal in type 1 diabetes (type 1 DM) immune intervention. Our group studies T cell responses in type 1 diabetes in humans and in various animal models. In clinical trials, we modulate ß-cell specific autoimmunity with the use of immunomodulatory drugs.

Genetic Basis of Diabetes Mellitus

By employing genome-wide association studies, we try to unravel the genetic basis of type 1 and type 2 diabetes. We recently identified novel signals for type 1 (adult-onset autoimmune diabetes) and type 2 diabetes in cohorts of European descent. The genetic loci identified in type 2 diabetes overlap those loci implicated in monogenic and multifactorial forms of diabetes. In addition, T2D-associated signals also show evidence of the enrichment of genes involved in cell cycle regulation. To understand in greater detail the impact of identified risk loci, we make use of extended functional studies of the ß-cell in humans and have also generated novel ko-mouse models.



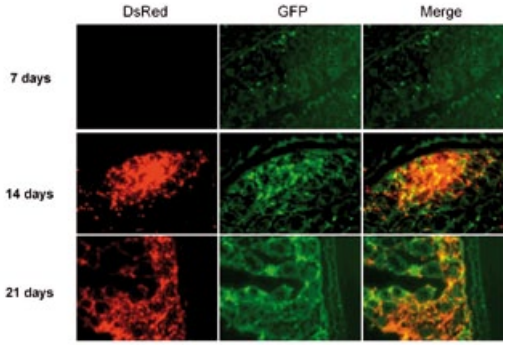
Functional analysis and profiling of PBMC: 6hr mitogen-stimulated PBMC are screened for TNF-alpha and IFN-gamma secretion using intracellular multicolour FACS staining. RNA profiling is applied performing Real-Time PCR array analysis.

Ulm University
Department of Internal Medicine I
Goetz von Wichert
Albert-Einstein-Allee 23
89081 Ulm, Germany
Tel. +49 (0)731 500 44501
Fax +49 (0)731 500 44502
almuth.stein@uniklinik-ulm.de
www.uniklinik-ulm.de/innere1

Laboratory of Mucosal Immunology and Inflammatory Bowel Disease

Head: Jan Hendrik Niess

The mucosal immune system is continuously exposed to challenges provided by the intestinal microflora. We are interested in studying mechanisms by means of which the mucosal immune system has adapted to challenges provided by the intestinal microflora. The focus of our research is the identification of host factors that are involved in maintaining mucosal homeostasis and in regulating intestinal inflammation, such as that found in Crohn´s disease and ulcerative colitis. Within this context, we investigate pathways by which the host recognizes constituents of the intestinal pathway. We have identified a major cell in the intestinal lamina propria involved by taking samples of the intestinal microflora and initiating innate and adaptive immune responses. Intestinal mononuclear phagocytes are reduced in the LP of germ-free animals. As a consequence, IL-17-producing Th17 cells are greatly reduced in germ-free animals. Finally, we have recently identified the activation antigen CD69 as a key regulator of mucosal immune responses. In particular, the activation antigen CD69 is involved in the development of oral tolerance, a key mechanism for preventing potentially harmful mucosal immune responses.



CX3CR1-GFP/RAG$^{-/-}$ animals were reconstituted with CD45RB(high) CD4 T cells from DsRed–transgenic mice, in which cells express the red fluorescent protein under the control of chicken *Actb* promoter. Colonic tissues were taken from transplanted CX3CR1-GFP/RAG$^{-/-}$ animals in the first, second or third week after reconstitution with CD4 T cells and then fixed and analyzed using fluorescent microscopy.

Selected Publications:

- *Burster T, Böhm BO (2010) Processing and presentation of (pro)-insulin in the MHC class II pathway: the generation of antigen-based immunomodulators in the context of type 1 diabetes mellitus, Diabetes Metab Res Rev 26, 227-38.*
- *Voight BF et al. (2010) Twelve type 2 diabetes susceptibility loci identified through large-scale association analysis, Nat Genet 42, 579-89.*
- *Rajasalu T, Brosi H, Schuster C, Spyrantis A, Böhm BO, Chen L, Reimann J, Schirmbeck R (2010) Deficiency in B7-H1 (PD-L1)/PD-1 coinhibition triggers pancreatic beta-cell destruction by insulin-specific, murine CD8 T-cells, Diabetes 59, 1966-73.*
- *Diegelmann J, Seiderer J, Niess JH, Haller D, Göke B, Reinecker HC and Brand S (2010) Expression and regulation of the chemokine CXCL16 in Crohn's disease and models of intestinal inflammation, Inflamm Bowel Dis 16, 1871-81.*
- *Preising J, Philippe D, Gleinser M, Wei H, Blum S, Eikmanns BJ, Niess JH and Riedel CU (2010) Selection of bifidobacteria for amelioration of murine colitis based on adhesion and anti-inflammatory capacity in vitro, Appl Environ Microbiol 76, 3048-51.*
- *Niess JH and Adler G (2010) The Enteric Flora Selectively Expand Gut Lamina Propria CX3CR1+ Dendritic Cells Supporting Inflammatory Immune Responses under normal and inflammatory conditions, J Immunol 15, 2026-37.*

Department of Internal Medicine II

Work Group: Molecular Pathogenesis of Myofibrillar Myopathies

Head: Wolfgang Rottbauer

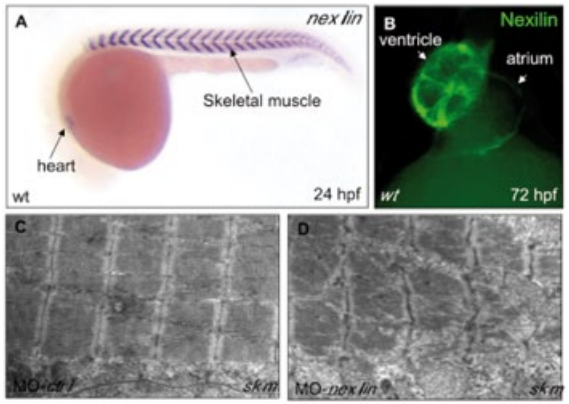
Myofibrillar myopathies (MFM) are progressive diseases of human heart and skeletal muscle with a severe impact on the quality of life and life expectancy of affected patients. They are histopathologically characterized by desmin-positive protein aggregates and myofibrillar degeneration. Although during the last decade some MFM disease genes, encoding sarcomeric and extra-sarcomeric proteins such as desmin, filamin C, plectin, VCP, ZASP, myotilin and αB-crystallin, could be identified, most genetic causes are still unknown due to the lack of families suitable for classical linkage analyses. Furthermore, the precise mechanisms and signaling events that translate MFM-causing mutations into the myopathic phenotype are not well understood even though they are of immense clinical importance for the development of specific therapies.

The Team:
Head of Department: W. Rottbauer
Group Leader/Postdoc: S. Just
PhD Student: J. Bührdel

Adult zebrafish (left), zebrafish embryo (right). For the profound dissection of novel genetic causes and pathways involved in the pathogenesis of myopathies, genetic animal models, such as the zebrafish *(Danio rerio)*, have proven extremely helpful. One of the most important advantages of the zebrafish model is the fast development and transparency of the zebrafish embryo that allows easy and direct in vivo analysis of heart and skeletal muscle development, structure and function using light microscopy. Most important is the fact that zebrafish embryos with cardiac misfunction are still able to develop to early larval stages since the lack of blood circulation can be compensated by absorbing oxygen through the skin.

Ulm University
Department of Internal Medicine II
Prof. Dr. Wolfgang Rottbauer
Albert-Einstein-Allee 23
89081 Ulm, Germany
Tel. +49 (0)731 500 45001
Fax +49 (0)731 500 45005
wolfgang.rottbauer@uniklinik-ulm.de
www.uniklinik-ulm.de/struktur/kliniken/innere-medizin/klinik-fuer-innere-medizin-ii.html

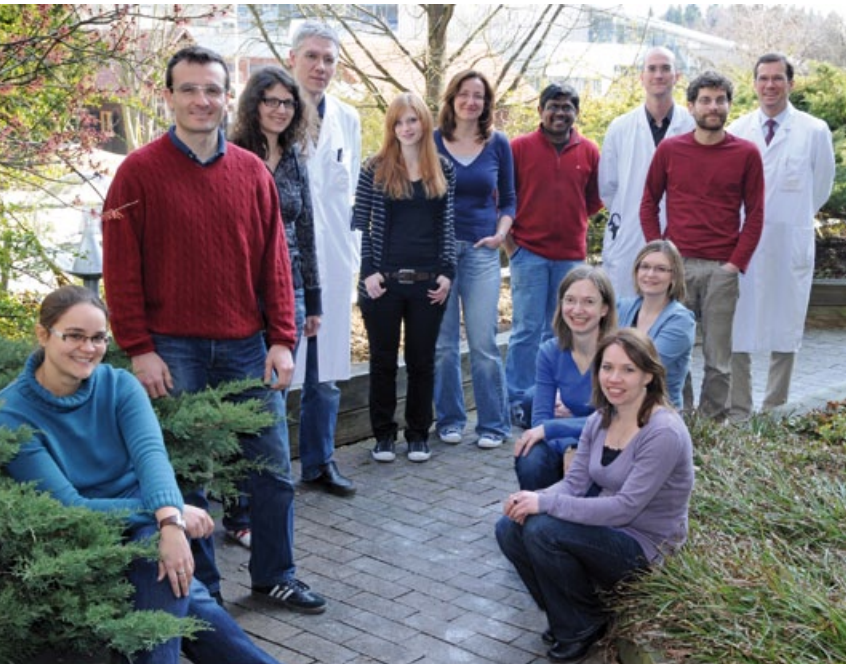
During the last decade, we successfully used forward and reverse genetic strategies in the zebrafish model to dissect novel molecular causes and mechanisms of heart and skeletal muscle myopathies. In an attempt to develop novel targeted treatment strategies for human MFMs, our research aims to elucidate further the genetic basis and the precise molecular mechanisms that translate known MFM mutations into the myopathic phenotype by using forward and reverse genetic approaches in zebrafish.



Nexilin is expressed in the heart (A, B) and skeletal muscle (A) during zebrafish development. Loss of Nexilin function leads to severe cardiac and skeletal muscle myopathy. Transmission electron microscopy analysis of skeletal muscle (skm) ultrastructure from stimulated Nexilin-deficient *(MO-nexilin)* (D) and Control *(MO-ctrl)* (C) zebrafish embryos. Sarcomeric Z-disks appear irregular and detached in Nexilin-deficient embryos.

Selected Publications:

- *Meder B, Just S, Vogel B, Rudloff J, Gartner L, Dahme T, Huttner I, Zankl A, Katus HA, Rottbauer W (2010) Junb-cbfbeta signaling is essential to maintain sarcomeric z-disc structure and when defective leads to heart failure, J Cell Sci 123, 2613-2620.*
- *Hassel D, Dahme T, Erdmann J, Meder B, Huge A, Stoll M, Just S, Hess A, Ehlermann P, Weichenhan D, Grimmler M, Liptau H, Hetzer R, Regitz-Zagrosek V, Fischer C, Nurnberg P, Schunkert H, Katus HA, Rottbauer W (2009) Nexilin mutations destabilize cardiac z-disks and lead to dilated cardiomyopathy, Nat Med 15, 1281-1288.*
- *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.*



Department of Internal Medicine III

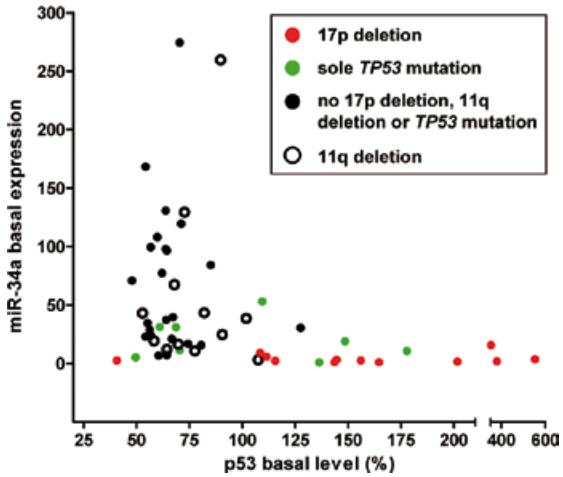
Identification and Characterization of Genetic Lesions and Development of Novel Therapies in Patients with Hematopoietic and Epithelial Malignancies

Head: Hartmut Döhner

The major research fields of the Department of Internal Medicine III are the pathomechanisms of acute and chronic leukemias, lymphoproliferative disorders, and epithelial malignancies. Students of the *International PhD Programme in Molecular Medicine* work in the areas of: (1) genetic and posttranscriptional mechanisms leading to autonomous cell growth and clinical disease progression in chronic lymphocytic leukemia (CLL); (2) genome and transcriptome-wide characterization of acute myeloid leukemia (AML); (3) comprehensive functional genetic and proteomic studies in AML and epithelial cancers.

CLL is the most common leukemia in the western world but the underlying pathomechanism remains unclear. Loss of genomic material from a critical region in chromosomal band 13q4.3 is detected in more than 50% of cases, thus making it the most common aberration in CLL. To date, no single tumor suppressor gene has been identified in this region but we have described an epigenetic regulatory mechanism in 13q14.3. In his PhD project, Danilo Allegra characterizes the non-coding RNA genes localized in this region. Billy Jebaraj is focusing on the pathogenetic link between telomere attrition and CLL. Additional genomic alterations, such as loss of chromosome 11q or 17p, are important prognostic factors, and Julia Mohr has identified and characterized the signaling pathways involved. The findings of these projects will be useful for elucidating the pathomechanism of CLL and for identifying novel therapeutic options for this incurable disease.

The Team:
Head of Department: H. Döhner
Professors: K. Döhner, S. Stilgenbauer
Group Leaders: L. Bullinger, S. Fröhling, D. Mertens, C. Scholl
Postdocs: A. Dolnik, A. Philippen, N. Azoitei
PhD Students: D. Allegra, M. Dedic, K. Faber, B. Jebaraj, B. Koch, S. Lück, J. Mohr, A. Ruß
Study Programme Experimental Medicine Students:
K. Lang, R. Wiehe, S. Grasedieck
Additional Members of Thesis Advisory Committees:
J. Dürig (Essen), H.J. Fehling (Ulm), T. Fischer (Magdeburg), S. Fulda (Frankfurt), T. Kindler (Mainz), B. Schlegelberger (Hannover), T. Seufferlein (Halle), A. Silahtaroglu (Copenhagen, DK), K. Spiekermann (Munich), T. Wirth (Ulm)



FACS-based quantification of TP53 protein and qPCR analysis of miR-34a in 55 CLL samples with different genomic aberrations show different patient subgroups (Mohr, Blood 2010).

In time, technological advances in genomics will provide the opportunity to capture the molecular variation of AML. By means of gene expression profiling (GEP), SNP microarray analysis and DNA methylation profiling, we are currently aiming to elucidate the biological basis of AML. In two newly identified core-binding factor leukemia subgroups, differentially regulated pathways, such as apoptotic signaling with the use of, for example, IAP (inhibitor of apoptosis protein) inhibitors, will be targeted (PhD project Sonja Lück). Similarly, by profiling microRNAs in a large cohort of AML cases and by integrating this data with corresponding GEP information, we found potential leukemia-relevant miR target genes of functional relevance (PhD project Annika Ruß).

Several projects in 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, with a particular focus on alterations that can be exploited to design better therapeutic strategies. Katrin Faber is using functional genomic screens and transcriptional profiling to search for genetic vulnerabilities in specific subtypes of AML. Britta Koch is applying various 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.

Ulm University
Department of Internal Medicine III
Prof. Dr. Hartmut Döhner
Albert-Einstein-Allee 23
89081 Ulm, Germany
Tel. +49 (0)731 500 45501
Fax +49 (0)731 500 45505
sekr-dir.innere3@uniklinik-ulm.de
www.uniklinik-ulm.de/onkologie

Selected Publications:

- *Zenz T, Mertens D, Küppers R, Döhner H, Stilgenbauer S (2010) From pathogenesis to treatment of chronic lymphocytic leukaemia, Nat Rev Cancer 10, 37-50.*
- *Scholl C, Fröhling S, Dunn IF, Schinzel AC, Barbie DA, Kim SY, Silver SJ, Tamayo P, Wadlow RC, Ramaswamy S, Döhner K, Bullinger L, Sandy P, Böhm JS, Root DE, Jacks T, Hahn WC, Gilliland DG (2009) Synthetic lethal interaction between oncogenic KRAS dependency and STK33 suppression in human cancer cells, Cell 137, 821-34.*
- *Roos, G, Kröber A, Grabowski P, Kienle D, Bühler A, Döhner H, Rosenquist R, Stilgenbauer S (2008) Short telomeres are associated with genetic complexity, high-risk genomic aberrations, and short survival in chronic lymphocytic leukemia, Blood 111, 2246-52.*

The Team:
Head of Institute: H. Schrezenmeier
Head of Department: K. Schwarz
Group Leaders/Postdocs: S. Kempe, 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)

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 and suffer from recurrent and 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), thymic T cell egress (CORO1A-defect), antigen receptor structure (TRAC-defect) and DNA repair (V[D]J recombination and NHEJ factors) (Fig. 1).

Very recently, we elucidated the molecular defect and part of the molecular pathophysiology of the most severe SCID entity: Reticular Dysgenesis, an aleukoytosis with sensorineural deafness. Deficiencies in the nuclear-encoded mitochochondrial enzyme adenylate kinase 2 (AK2) affect leukocyte progenitor survival by increasing apoptotic propensity of the cells.

Although many genetic defects in SCID patients have now been detected, about 30% of SCID variants still lack a genetic diagnosis.

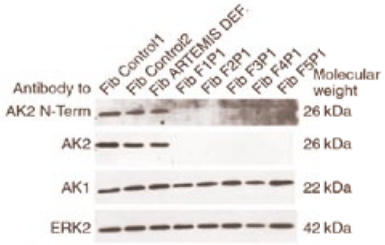


Fig. 1: Protein analyses in individuals (F1P1-F5P1) with reticular dysgenesis. Immunoblot of lysates from fibroblasts of affected individuals. Antisera directed against the N-terminal 100amino acids (AK2 N-Term), or complete AK2 and AK1 were used for detection. ERK2 staining served as loading control. Fibroblasts of two healthy and an ARTEMIS-deficient subject were used for control.

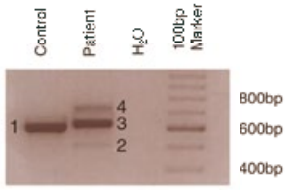


Fig. 2: RT-PCR of Artemis depicting expression of different Artemis splice variants in fibroblasts of a DCLRE1C mutant patient with symptoms of inflammatory bowel disease. "1" depicts wt Artemis cDNA (Ex 5-11), whereas in the band number "2" a deletion of an exon , in band number "3" an insertion of 12 and 18 bp and in band number "4" an insertion of 120 and 122 bp was indentified by sequencing.

In collaboration with the bone marrow transplantation unit of the Clinic for Pediatric- and Adolescent Medicine (University Medical Center Ulm), novel SCID cases are constantly being identified by our group on the basis of clinical and immunological data.

The focus of our group is to analyse 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/exomesequencing 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.

Ulm University
Institute of Transfusion Medicine
Prof. Dr. Hubert Schrezenmeier
Helmholtzstraße 10
89081 Ulm, Germany
Tel. +49 (0)731 500 150 550
Fax +49 (0)731 500 150 500
h.schrezenmeier@blutspende.de

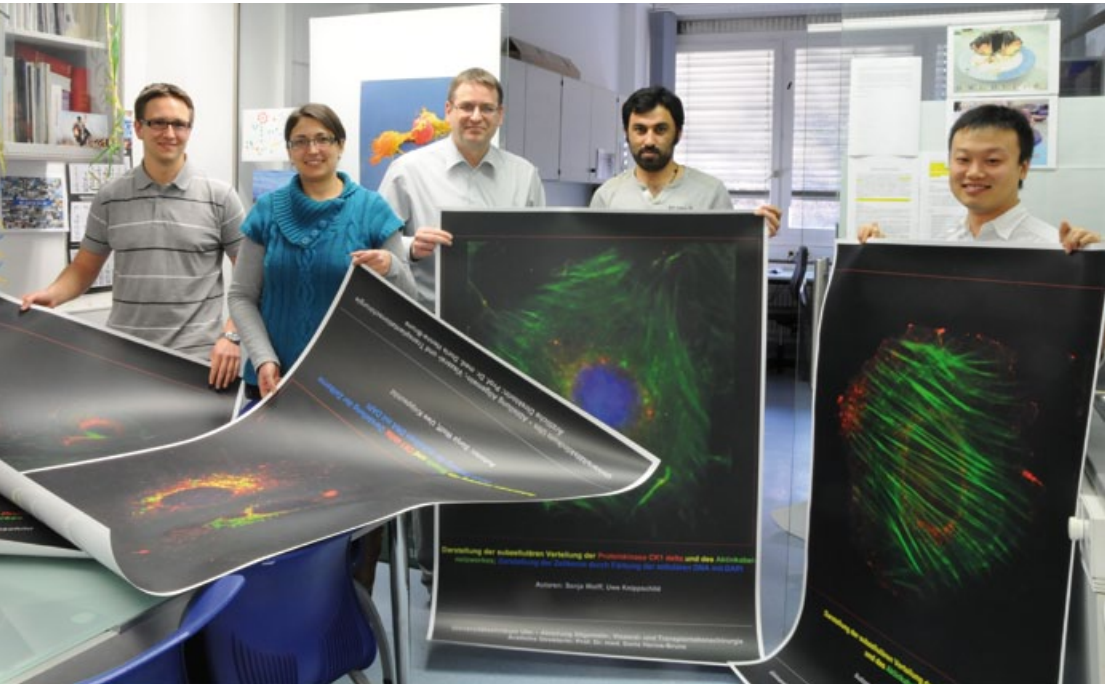
Selected Publications:

- *Maul-Pavicic A, Chiang SC, Rensing-Ehl A, Jessen B, Fauriat C, Wood SM, Sjöqvist S, Hufnagel M, Schulze I, Bass T, Schamel WW, Fuchs S, Pircher H, McCarl CA, Mikoshiba K, Schwarz K, Feske S, Bryceson YT, Ehl S (2011) ORAI1-mediated calcium influx is required for human cytotoxic lymphocyte degranulation and target cell lysis, Proc Natl Acad Sci U S A 108, 3324-3329.*
- *Pannicke U, Hönig M, Schulze I, Rohr J, Heinz G, Braun S, Janz I, Rump E-M, Seidel MG, Matthes-Martin S, Soerensen J, Greil J, Stachel D K, 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 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 Clinic Immunol 230, 314-320. *Equal contribution*
- *Radecke, S, Radecke, F, Cathomen, T Schwarz (2010) Zinc-finger nuclease-induced gene repair with oligodeoxynucleotides: Wanted and unwanted target locus modifications, Mol Therapy 18, 743-753.*
- *Pannicke U, Hönig M, Hess I, Holzmann KH, Friesen C, Rump EM, Barth TF, Rojewski MT, Schulz A, Böhm 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, Niehues T (2008) A novel type of combined immunodeficiency caused by hypomorphic RAG mutations, N Engl J Med 358, 2030-2038.*

Department of General, Visceral and Transplantation Surgery

Identification of CK1δ C-terminal Targeting Kinases and Characterization of Their Role in Regulating the Activity of CK1δ

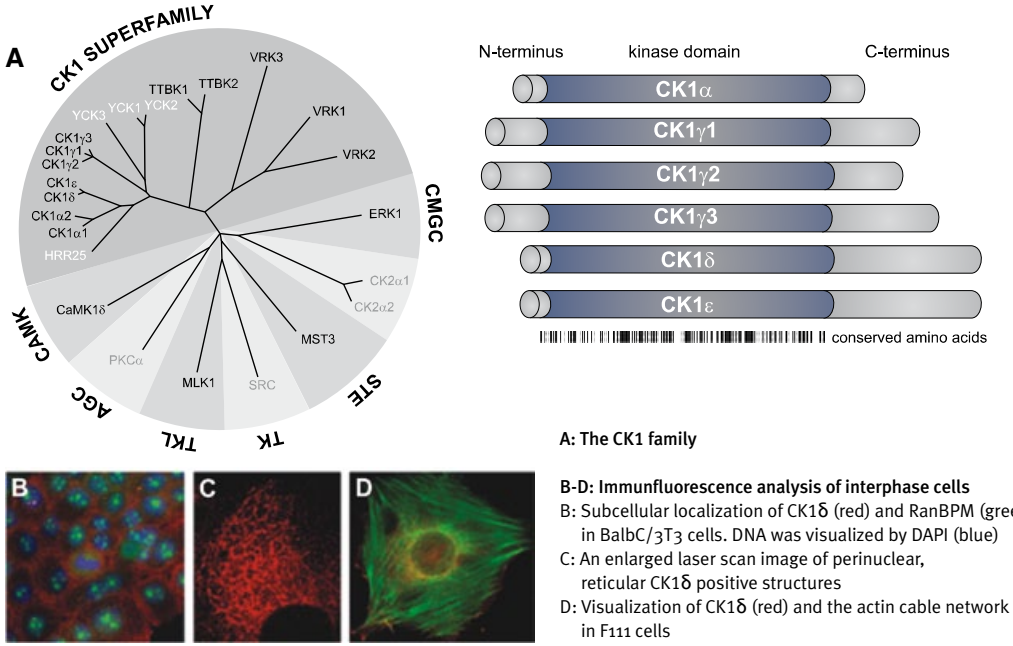
Head: Doris Henne-Bruns



The Team:
Head of Department: D. Henne-Bruns
Professor: U. Knippschild
Group Leader/Postdoc: H. Hirner
PhD Students: J. Bischof, K. Ullah
Additional Members of Thesis Advisory Committees:
M. Huber-Lang (Ulm), L. Pinna (Padua, I)

Research in the Department of General, Visceral and Transplantation Surgery is mainly concentrated on malignant diseases by focusing 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 receive detailed information regarding their functions and regulation mechanisms. 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 diverse cellular processes, including membrane trafficking, circadian rhythms, cell cycle progression, chromosome segregation, apoptosis and cellular differentiation. Mutations and deregulation of CK1 expression and activity have been linked to various diseases, including such neurodegenerative disorders as Alzheimer's and Parkinson's diseases, sleeping disorders, as well as proliferative diseases such as cancer. Therefore, interest in the identification of mechanisms involved in the regulation of CK1 activity and in developing CK1 specific inhibitors has enormously increased.



A: The CK1 family

B-D: Immunfluorescence analysis of interphase cells
B: Subcellular localization of CK1δ (red) and RanBPM (green) in BalbC/3T3 cells. DNA was visualized by DAPI (blue)
C: An enlarged laser scan image of perinuclear, reticular CK1δ positive structures
D: Visualization of CK1δ (red) and the actin cable network in F111 cells

CK1 activity has been shown to be tightly regulated on different levels. Extracellular stimuli, subcellular localization, interaction with various cellular proteins as well as proteolytic cleavage of their C-terminal regulatory domain and reversible phosphorylation play important roles in modulating the activity of CK1 isoforms. On the protein level, autophosphorylation and site-specific phosphorylation by cellular kinases have been reported to modulate the activity of CK1δ. Previously, we provided evidence that phosphorylation of CK1δ at serine 370 by PKA influences CK1δ dependent processes. Therefore, the PhD student Joachim Bischof is now concentrating on the identification of additional CK1δ C-terminal targeting kinases, the identification of their phosphorylation sites on the CK1δ molecule and on the characterization of their impact in modulating CK1δ specific functions in tissue culture and animal models.

Ulm University
Department of General, Visceral and Transplantation Surgery
Prof. Dr. Doris Henne-Bruns
Steinhövelstraße 9
89075 Ulm, Germany
Tel. +49 (0)731 500 53500
Fax +49 (0)731 500 53503
doris.henne-bruns@uniklinik-ulm.de
www.allgemeinchirurgie.uni-ulm.de

Selected Publications:

- *Bischof J, Müller A, Fänder M, Knippschild U*, Fischer D* (2011) Neurite outgrowth of mature retinal ganglion cells and PC12 cells requires activity of CK1δ and CK1ε, PLoS One, in press. *shared senior authorship and corresponding authors*
- *Udelnow A, Kreyes A, Landfester K, Walther P, Klapperstueck T, Wohlrab J, Henne-Bruns D, Knippschild U*, Peter Würl P* (2011) Omeprazole Inhibits Proliferation and Modulates Autophagy in Pancreatic Cancer Cells, PLoS One 6, e20143. *shared senior authorship*
- *Wacker SA, Alvarado C, von Wichert G, Knippschild U, Wiedenmann J, Clauss K, Nienhaus GU, Hameister H, Baumann B, Borggrefe T, Knochel W, and Oswald F (2011) RITA, a novel modulator of Notch signalling, acts via nuclear export of RBP-J, EMBO J 30, 43-56.*
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- *Peifer C, Abadleh M, Bischof J, Hauser D, Schattel V, Hirner H, Knippschild U and Laufer S (2009) 3,4-Diaryl-isoxazoles and -imidazoles as potent dual inhibitors of p38alpha mitogen activated protein kinase and casein kinase 1delta, J Med Chem 52, 7618-7630.*
- *Brockschmidt C, Hirner H, Huber N, Eismann T, Hillenbrand A, Giamas G, Radunsky B, Ammerpohl O, Bohm B, Henne-Bruns D, Kalthoff H, Leithauser F, Trauzold A and Knippschild U (2008) Anti-apoptotic and growth-stimulatory functions of CK1 delta and epsilon in ductal adenocarcinoma of the pancreas are inhibited by IC261 in vitro and in vivo, Gut 57, 799-806.*

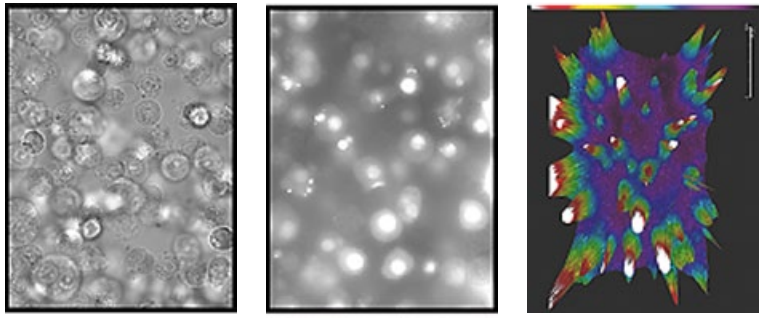
Department of Orthopedic Trauma, Hand, Plastic and Reconstruction Surgery

Therapeutic Potential of Fas-induced Apoptotic and Inflammatory Signal Transduction in the Pathogenesis of Trauma-induced Septic Acute Lung Injury (ALI)

Head: Florian Gebhard

The Team:
Head of Department: F. Gebhard
Professors: M. Huber-Lang, M. Perl
Study Programme Experimental Medicine Student:
M. Messer

Hypoxemia, diffuse bilateral infiltrates of the lung often accompanied by pulmonary edema, reduction of lung compliance and a decrease in the functional residual capacity of the lungs are key features of Acute Lung Injury (ALI). The incidence of ALI has been reported to be around 80 per 100,000 people per year and is highest during sepsis. ALI is associated with a fatality rate of around 40%. However, up till now no real pathophysiological-driven therapeutic intervention has yet become available.



Cells transfected with a Cy-5-labeled Fas-anti-apoptotic siRNA.

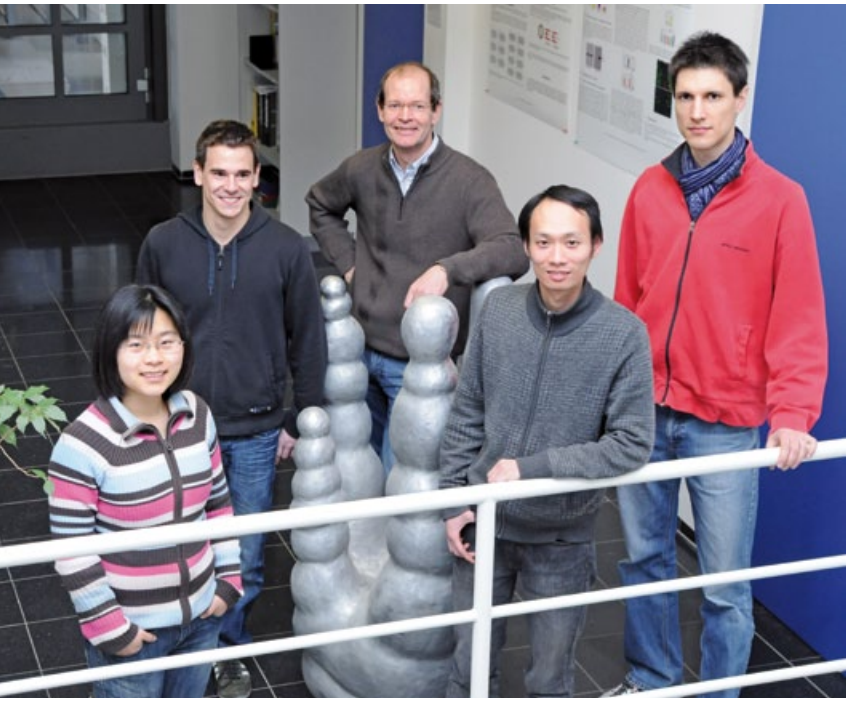
Ulm University
Department of Orthopedic Trauma, Hand, Plastic and Reconstruction Surgery
Prof. Dr. Florian Gebhard
Steinhövelstraße 9
89075 Ulm, Germany
Tel. +49 (0)731 500 4500
Fax +49 (0)731 500 4502
unfall.chirurgie@uniklinik-ulm.de
www.uniklinik-ulm.de/unfallchirurgie

During ALI, apoptotic cell death of the lung epithelium occurs and correlates with the clinical outcome of these patients. Furthermore, Fas-associated apoptotic cell death has been shown experimentally and clinically to contribute to this epithelial cell injury as seen during septic ALI. Our research group has further indicated that the silencing of different key molecules of the Fas-associated proapoptotic machinery in lung epithelial cells using a small interfering RNA-based interventional therapeutic approach beneficially affects the survival of the pulmonary epithelium and may even reduce the degree of lung damage during septic ALI. In this regard, it is currently the focus of our research group, as included in the theses of M. Messer, S. Weber, B. Bruns and T. Hönle, to advance this knowledge by testing the pathophysiological relevance of novel apoptotic key molecules and evaluating the feasibility of this approach in different types of ALI as in cases of response to direct lung trauma.

The research project is financed by an Emmy Noether-Grant from the Deutsche Forschungsgemeinschaft (DFG-PE 908/2).

Selected Publications:

- *Perl M, Lomas-Neira J, Venet F, Chung CS, Ayala A (2011) Pathogenesis of indirect (secondary) acute lung injury, Expert Rev Respir Med 5, 115-26.*
- *Perl M*, Liener UC*, Huber-Lang MS, Seitz DH, Brückner UB, Gebhard F, Knöferl MW (2011) Is the function of alveolar macrophages altered following blunt chest trauma?, Langenbecks Arch Surg 396, 251-9. *Both Authors contributed equally*
- *Perl M, Chung CS, Perl U, Thakkar R, Lomas-Neira J, Ayala A (2010) Therapeutic accessibility of caspase-mediated cell death as a key pathomechanism in indirect acute lung injury, Crit Care Med 38, 1179-86.*
- *Perl M, Chung CS, Lomas-Neira J, Ayala A (2008) Epithelial Apoptosis and Neutrophil Recruitment in Acute Lung Injury – A Unifying Hypothesis? What we have learned from small interfering RNAs, Mol Med 14, 465-75.*
- *Perl M*, Seitz DH*, Mangold S, Neddermann A, Braumüller S, Zhou S, Bachem MG, Huber-Lang MS, Knöferl MW (2008) Pulmonary Contusion Induces Alveolar Type II Epithelial Cell Apoptosis: Role of Alveolar Macrophages and Neutrophils, Shock 30, 537-44. *Both Authors contributed equally*



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 and diverse problems need to be solved before a safe and successful therapy can be possible. This is achieved only through the close cooperation of various scientific and medical disciplines. One of our main scientific interests is focused on the development of gene transfer vector technology by means of genetic and chemical engineering and the use of improved vectors for selected inborn or acquired disorders in addition to new vaccine strategies in preclinical models.

Viruses as a Delivery Vehicle for Genes

Since viruses frequently coevolve 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 to specific cells. 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 nongenetic diseases.

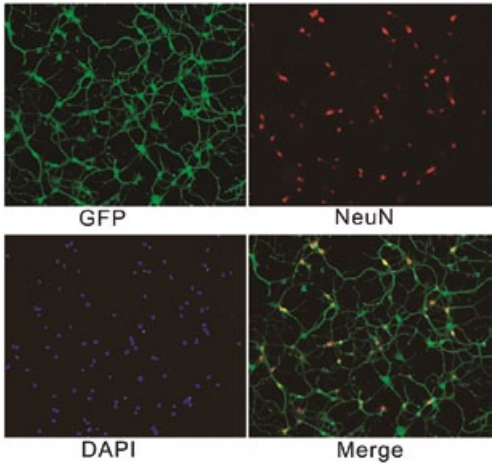
Overcoming barriers in gene therapy

So far, in vivo gene therapy has not been successful and the main reason for this has been the lack of gene transfer efficiency due to interaction of vectors with barriers in the body. Jan-Michael Prill (PhD project) uses chemical modification of adenovirus vectors with inert polymers to address and overcome those barriers with the aim of achieving targeted gene delivery to specific tissues.

Vectors for Genetic Vaccination

Genetic vaccination shows considerable promise as a solution for overcoming the limitations of classic vaccines. However, neither the mechanisms of induction nor the persistence of adaptive immune

The Team:
Head of Department: S. Kochanek
Group Leader: F. Kreppel
Postdocs: S. Espenlaub, B. Huang, J. Laakkonen, T. Lukas, A. Denzel
PhD Students: M. Kron, X. Dong, S. Zong, J.-M. Prill
Additional Members of Thesis Advisory Committees: H. Bujard (Heidelberg), P. Clemens (Pittsburgh, USA), A. Ludolph (Ulm), D. Pinschewer (Geneva, CH), H. Reimann (Ulm), R. Schirmbeck (Ulm), P. Ng (Houston, USA), K. Ulbrich (Prague, CZ), M. Ogris (Munich)



Very efficient transduction of primary neuronal cells with a high-capacity adenovirus vector expressing EGFP (Xiaomin Dong).

responses are completely understood when the antigen is expressed following gene transfer. In the past, we have seen that the immunogenicity of adenovirus vectors limits the multispecificity of T-cell responses against vector-encoded antigens and we are working on this mechanism. Such studies will likely open avenues for an improved vector design through an enhanced understanding of the basic principles of immune response induction.

Matthias Kron (PhD project) uses adenovirus- and plasmid-based delivery systems to investigate to what degree gene transfer-mediated expression of recombinant antigens in non-immune tissues influences qualitative and quantitative profiles and kinetics of immune responses. In another project, Shan Zong (PhD project) is generating a genetic vaccine against malaria based on different adenovirus vector types and evaluates vector activities in preclinical models.

Vectors for Functional Studies

Besides their use in gene therapy and vaccination, adenovirus vectors are very efficient tools for functional studies. We have a strong interest in the development of therapeutic strategies for Huntington's Disease, a severe neurodegenerative disorder caused by the expansion of a trinucleotide repetition in the huntingtin gene. In previous studies, we have shown that we can use adenovirus-mediated huntingtin gene transfer to model parts of the disease in vitro and in vivo and to block the expression of huntingtin. Xiaomin Dong (PhD project) is generating adenovirus vectors expressing fusions between huntingtin and a fluorescence protein as a tool for following the fate of huntingtin within cells through the use of cell biology methods. He has already developed a new in vitro model that quite closely mimics certain aspects of Huntington's disease.

Department of Gene Therapy
Ulm University
Prof. Dr. Stefan Kochanek
Helmholtzstraße 8/1
89081 Ulm, Germany
Tel. +49 (0)731 500 46103
Fax +49 (0)731 500 46102
stefan.kochanek@uni-ulm.de
www.uni-ulm.de/gentherapie

Selected Publications:

- *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 detargeting or targeting with potential evasion from Kupffer cells, Mol Ther 19, 83-92.*
- *Stephen SL, Montini E, Sivanandam VG, Al-Dhalimy M, Kestler HA, Finegold M, Grompe M, Kochanek S (2010) Chromosomal integration of adenoviral vector DNA in vivo, J Virol 84, 9987-94.*
- *Schirmbeck R, Reimann J, Kochanek S, Kreppel F (2008) The immunogenicity of adenovirus vectors limits the multispecificity of CD8 T-cell responses to vector-encoded transgenic antigens, Mol Ther 16, 1609-16.*
- *Huang B, Schiefer J, Sass C, Kosinski CM, Kochanek S (2008) Inducing huntingtin inclusion formation in primary neuronal cell culture and in vivo by high-capacity adenoviral vectors expressing truncated and full-length huntingtin with polyglutamine expansion, J Gene Med 10, 269-79.*
- *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.*
- *Espenlaub S, Wortmann A, Engler T, Corjon S, Kochanek S, Kreppel F (2008) Reductive amination as a strategy to reduce adenovirus vector promiscuity by chemical capsid modification with large polysaccharides, J Gene Med 10, 1303-14.*

Department of Anesthesiology

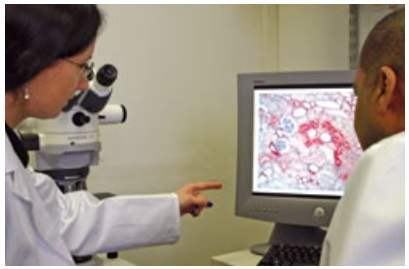
Carbamylated Erythropoietin-FC Fusion Protein During Porcine Aortic Balloon Occlusion-induced Kidney Ischemia/Reperfusion Injury

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 (I/R). 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 defence 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, A. Gauss, R. Meierhenrich, J. Vogt, M. Weiss
Study Programme Experimental Medicine Student: Š. Matějková

Aortic cross-clamping during surgery for abdominal aortic aneurysm repair is a typical clinical example of I/R injury, the most vulnerable organs being the kidneys. Recombinant human erythropoietin (rhEPO) was demonstrated to protect against I/R injury but has several undesired side effects that are attributed to the activation of a homodimeric receptor complex (EPO-R/EPO-R). The organ-protective properties are referred to the activation of an alternative receptor complex consisting of the EPO-R and the common β receptor, and the stimulation of this EPO-R/βcR alone is devoid of the undesired side effects. Carbamylated Epo derivatives (cEPO) only bind to the EPO-R/βcR and thus may be an alternative to rhEPO. 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 kidney dysfunction. Therefore, our group focuses on the clinical potential of a newly developed carbamylated EPO-FC fusion protein in a porcine model of thoracic aortic balloon occlusion-induced I/R injury. In order to mimic the clinical scenario we use animals with familial hypercholesterinemia that, due to a special diet, develop the typical symptoms of a “metabolic syndrome” that causes ubiquitous vascular sclerosis 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 even high doses of cEPO derivatives is much less pronounced under conditions of pre-existing kidney disease and is most likely due to the minor effect on tissue inflammation and apoptosis.

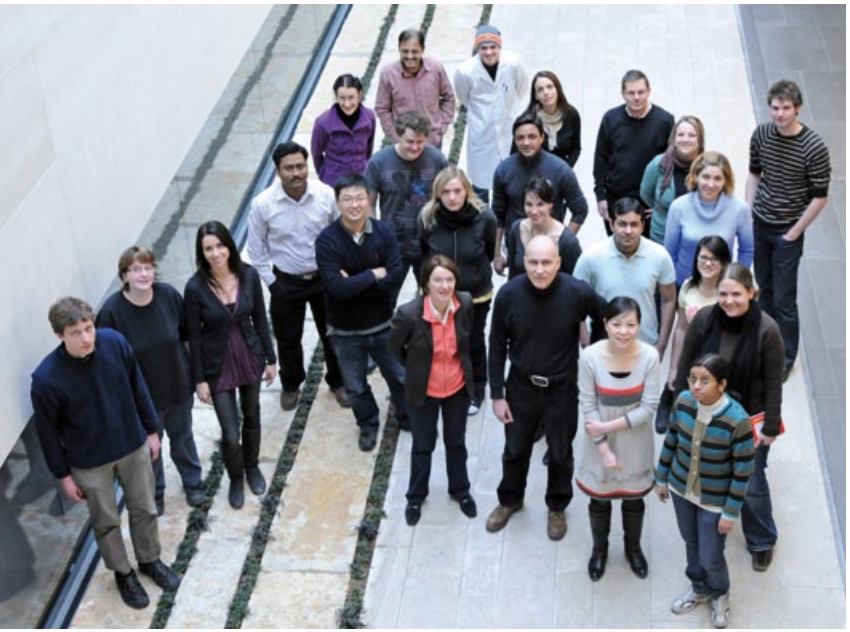


Student analyzing an immune histochemistry staining of the kidney for the neutrophil gelatinase-associated lipocalin.

Ulm University
Department of Anesthesiology
Prof. Dr. Dr. h.c. Michael Georgieff
Steinhövelstraße 9
89075 Ulm, Germany
Tel. +49 (0)731 500 60001
Fax +49 (0)731 500 60002
michael.georgieff@uni-ulm.de
www.uniklinik-ulm.de/struktur/kliniken/anaesthesiologie.html

Selected Publications:

- *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.*
- *Baumgart K, Wagner F, Gröger M, Weber S, Barth E, Vot JA, Wachter U, Huber-Lang M, Knöferl MW, Albuszies G, Georgieff M, Asfar P, Szabó C, Calzia E, Radermacher P, Simkova S (2010) Cardiac and metabolic effects of hypothermia and inhaled H2S in anesthetized and ventilated mice, Crit Care Med 38, 588-95.*
- *Gröger M, Öter S, Simkova V, Bolten M, Koch A, Warninghoff V, Georgieff M, Muth CM, Speit G, Radermacher P (2009) DNA damage after long-term repetitive hyperbaric oxygen exposure, J Appl Physiol 106, 311-5.*
- *Simon F, Giudici R, Scheuerle A, Gröger M, Asfar P, Vogt JA, Wachter U, Ploner F, Georgieff M, Möller P, Laporte R, Radermacher P, Calzia E, Hauser B (2009) Comparison of cardiac, hepatic and renal effects of arginine vasopressin and noradrenaline during porcine fecal peritonitis: a randomized, controlled trial, Crit Care 13, R113.*
- *Barth E, Bassi G, Maybauer DM, Simon F, Gröger M, Öter S, Speit G, Nguyen CD, Hasel C, Möller P, Wachter U, Vogt JA, Matejovic M, Radermacher P, Calzia E (2008) Effects of ventilation with 100% oxygen during early hyperdynamic porcine fecal peritonitis, Crit Care Med 36, 495-503.*



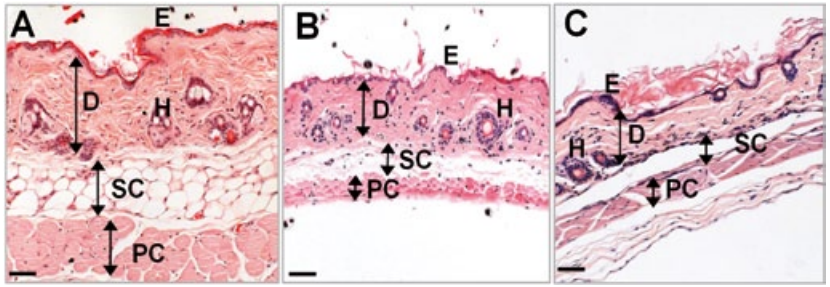
The Team:
Head of Department: K. Scharffetter-Kochanek
Professors: H. Geiger, J. M. Weiss
Labmanager: M. Wlaschek
Group Leaders/Postdocs: A. Basu, L. Borkner, M. C. Florian, D. Frenzel, S. Iben, D. Jiang, P. Maity, T. Peters, A. Sindrilaru, N. Treiber, S. Vanderbeken, V. Vas
PhD Students: R. Assfalg, J. de Vries, F. Ferchiu, O. G. Gonzalez, N. Guidi, S. Koch, S. Köllner, Y. Qi, A. Schlecht, Kamayani Singh, Karmveer Singh, B. Überle
Additional Members of Thesis Advisory Committees:
M. Berneburg (Tübingen), C. Niessen (Cologne), R. Nischt (Cologne), K.L. Rudolph (Ulm), A. Wells (Pittsburgh, USA), T. Wirth (Ulm), L. Wiesmüller (Ulm), G. Van Zant (Lexington, USA)

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 immune system, the central nervous system and the connective tissue. We have generated a connective tissue specific SOD2 deficient mouse with a complex aging phenotype. We are interested in determining whether changes in concentrations of free radicals may have an impact on signaling pathways involved in the organization of the extracellular matrix, organ maintenance, metabolic homeostasis and renewal capacities of hematopoietic stem cells (Karmveer Singh). The DNA damage response pathway (DDR) resulting in cellular senescence is addressed in dermal fibroblasts (Florentina Ferchiu). The nucleolus is studied as stress sensor of DDR and related signaling pathways (Robin Assfalg) that possibly also affect ribosomal biogenesis (Sylvia Koch). Information on DDR in mesenchymal stem cell (MSC) aging is virtually nonexistent. This information would be highly valuable since MSC contribute to regeneration, repair and tissue homeostasis (Yu Qi). Molecular and cellular mechanisms of wound repair by MSC in mouse models of impaired regeneration will be analyzed (Andrea Schlecht).



A. Histology of young skin, B. Histology of skin under oxidative stress due to deficiency of manganese superoxide dismutase, C. Histology of intrinsically aged skin. Note the severe atrophy of the epidermis, the dermis and the subcutaneous fat tissue in skin under oxidative stress and intrinsically aged skin.

E – epidermis, D – dermis, H – hair follicle, SC – subcutaneous fat tissue, PC – Panniculus carnosus muscle

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.

Ulm University
Department of Dermatology and Allergic Diseases
Prof. Dr. Karin Scharffetter-Kochanek
Maienweg 12
89075 Ulm, Germany
Tel. +49 (0)731 500 57500
Fax +49 (0)731 500 57502
karin.scharffetter-kochanek@uniklinik-ulm.de
www.uniklinik-ulm.de/struktur/kliniken/dermatologie-und-allergologie.html

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.*
- *Florian MC, Geiger H (2010) Polarity in stem cells, disease, and aging, Stem Cells 28, 1623-9.*
- *Ryan MA, NattamaiKJ, Xing E, Schleimer, Daria D, Sengupta A, Köhler A, Liu W, Gunzer M, Jansen M, Ratner N, Le Cras TD, Waterstrat A, Van Zant G, Cancelas JA, Zheng Y, Geiger H (2010) Pharmacological inhibition of EGFR signaling enhances G-CSF induced hematopoietic stem cell mobilization, Nat Med 16, 1141-6.*
- *Lebedev A, Scharffetter-Kochanek K, Iben S (2009) A novel activity enhances promoter escape of RNA polymerase I., BiochemBiophys Res Commun 380, 695-8.*
- *Sindrilaru A, Peters T, Veleva-Oreshkova T, Wang H, Schymeinsky J, Mannella F, Wlaschek M, Sunderkötter C, Walzog B, Bustelo XR, Fischer KD, Scharffetter-Kochanek K (2009) Wound healing defect of Vav$^{3-/-}$ mice due to impaired β_2-integrin dependent macrophage functions, Blood 113, 5266-5276.*

The Team:
Head of Department: R. Kreienberg
Head of Division: L. Wiesmüller
Group Leaders/Postdocs: B. Gole, D. Salles, M. Uhl, S. Gatz
PhD Students: M. Volcic, I.C. Ireno
Additional Members of Thesis Advisory Committees: M. Filipic (Lubljana, SLO), S. Fulda (Frankfurt), G. Speit (Ulm), H. Pospiech (Oulu, FIN)

Department of Gynecology and Obstetrics/ Division of Gynecological Oncology

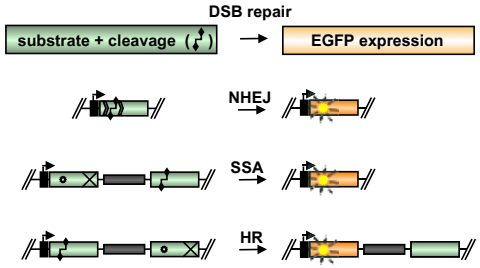
Regulation of DNA Repair by Tumor Suppressor Proteins and Longevity Factors

Head: Lisa Wiesmüller

Chromosomal double-strand breaks (DSBs) are the most detrimental type of DNA damage. DSBs can originate from external sources such as ionizing radiation and chemotherapeutic treatment or from free radicals generated by the organism itself. Efficient DSB repair is essential for the survival of a cell. However, deregulated or error-prone repair causes genomic instabilities that accelerate the multistep process of tumorigenesis. The purpose of our research is to understand the molecular details of genome stabilizing and DNA damage response mechanisms and their deregulation in chromosome instability syndromes, cancer and during aging. We have developed assay systems for the quantitative and qualitative analysis of DSB repair in immortalized and primary cells from different organs including hematopoietic stem cells. Our fluorescence-based assay system comprises a series of different substrates, designed for the qualitative and quantitative analysis of all DSB repair pathways (non-homologous end-joining: NHEJ, single-strand annealing: SSA, homologous recombination: HR). The power of pathway-specific testing to detect even subtle and genetically determined DSB repair deficiencies was documented by testing lymphoblastoid cells derived from a series of *Ataxia telangiectasia*, Nijmegen breakage syndrome and Fanconi anemia patients with various mutations as well as from a collection of breast cancer patients with heterozygous mutations in *BRCA1, BRCA2* or *CHEK2*. Together with our clinical partners, we now focus on investigations of primary cells from blood samples, skin and tumor material to detect DSB repair defects based on the newly discovered repair patterns associated with predisposing mutations. Additionally, we utilized fluorescence-based DSB repair testing in combination with genomic PCR and quantitative analysis of nuclear structures indicative for DNA lesions, repair intermediates and/or repair enzyme complexes to elucidate the particular mechanisms underlying

genetic destabilization in hematopoietic malignancies involving deregulation of tyrosine kinase signaling, such as upon mutation of Janus kinase 2 or expression of BCR-ABL, or of constitutive NF-κB activation. Our goal is to solve questions related to the specific mechanisms underlying tumorigenic genome rearrangements and to develop novel biomarkers for the identification of cancer risk and therapeutic responsiveness.

Evidence from genetic, mouse model, cell biological, and biochemical studies in existing literature revealed striking links between replicative senescence, telomere maintenance, aging, and DSB repair. There are large differences between DNA repair in rodents and humans and this is why we purposefully focus on man. Interestingly, it has also been demonstrated that the DNA break sensor Poly [ADP-ribose] polymerase 1 (PARP1), which has become an extremely promising target for therapies selectively eliminating HR-defective tumor cells, mediates regulation of telomere length. We have characterized the role of and functional interactions between different aging-related proteins in DSB repair such as SIRT1, WRN and PARP1. The challenge will now be to understand the details of how DSB is regulated during the aging process in differentiated versus stem cells and to identify candidate genes, which underlie these changes.



Structure of DSB repair substrates and products. Targeted cleavage of the substrate by the endonuclease I-*Sce*I triggers repair via the mechanisms NHEJ, SSA or HR. Successful repair can be monitored by wild-type enhanced GFP (EGFP) production.

mutated pathway	DSB repair mechanism		
	NHEJ	SSA	HR
BRCA1	↑↑	↑	
BRCA2		↑	↓↓
NBN	↓	↓↓	↓
p53	↑	↑	↑

Upon inactivation of a pathway involving one of the breast cancer susceptibility genes *BRCA1*, *BRCA2*, *NBN* or *p53*, specific changes are detectable in distinct DSB repair mechanisms. Arrow upwards/downwards: stimulation/repression of the respective pathway.

Ulm University
Department of Gynecology and Obstetrics
Division of Gynecological Oncology
Prof. Dr. Lisa Wiesmüller
Prittwitzstraße 43
89070 Ulm, Germany
Tel. +49 (0)731 500 58800
Fax +49 (0)731 500 58504
lisa.wiesmueller@uni-ulm.de
www.uni-ulm.de/klinik/ufk/cms/html/forschung_gyn-onko.htm

Selected Publications:

- *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.*
- *Uhl M, Csernok A, Aydin S, Kreienberg R, Wiesmüller L, Gatz S (2010) Role of SIRT1 in homologous recombination, DNA Repair 9, 383-393.*
- *Keimling M, Wiesmüller L (2009) DNA double-strand break repair activities in mammary epithelial cells – influence of endogenous p53 variants, Carcinogenesis 30, 1260-1268.*
- *Plo I, Nakatake M, Malivert M, Villartay JP, Ciraudier S, Villeval JL, Wiesmüller L, Vainchenker W (2008) JAK2 stimulates homologous recombination and genetic instability: potential implication in the malignancy of myeloproliferative disorders, Blood 112, 1402-1412.*

Department of Neurology

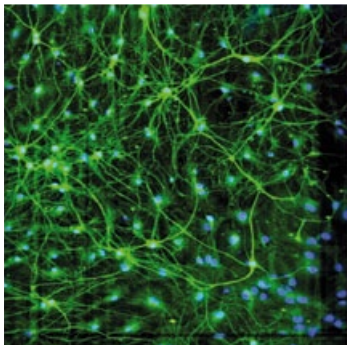
Molecular Mechanisms in Neurodegenerative Diseases

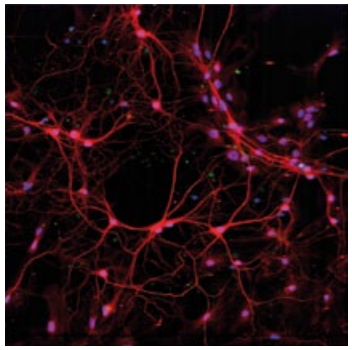
Head: Albert C. Ludolph

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, the department consists of a number of large outpatient clinics, each serving their respective patient populations, in addition to a clinical trial center, which specializes in 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 50 scientists work in 10 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 ß-amyloid precursor protein (APP) and associated proteins (including motor proteins), and their subcellular compartimentalization. The work focuses on aspects of trafficking in AD and employs novel molecular

The Team:
Head of Department: A.C. Ludolph
Professors: C. von Arnim, M. Otto, H. Braak
Group Leaders/Postdocs: C. Schnack, A. Witting
PhD Students: A. Hellrung, M. Leibinger, T. Hering
Study Programme Experimental Medicine Students:
S. Kirschmer, L. Campanelli, W. Ruf, H. Tritschler, M. Büchsel
Additional Members of Thesis Advisory Committees:
P. Gierschik (Ulm), N. Weidner (Heidelberg)





In green primary hippocampal neurons are stained with the neuronal marker beta-tubulin III and in red microtubule associated protein 2 is stained to visualize dendrites. Nuclei are stained in blue with DAPI. Images were taken with IN Cell Analyzer 3000, which allows high throughput screening with microscopic approach.

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 may open new avenues of therapeutic intervention 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. Although interventions for treatment are classically limited to pharmacological approaches, nutritional and physiopsychological approaches to treatment are also the subject of intensive investigation. In the near future Prof. Dr. Danzer will join the department as junior professor. She works on oligomer (alpha-synuclein) 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.

Ulm University
Department of Neurology
Prof. Dr. Albert C. Ludolph
Oberer Eselsberg 45
89081 Ulm, Germany
Tel. +49 (0)731 177 1201
Fax +49 (0)731 177 1202
albert.ludolph@rku.de
www.uniklinik-ulm.de/struktur/kliniken/neurologie.html

Selected Publications:

- *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 C.A.F. (2010) Genetic variants in presenilin genes and correlation to cerebrospinal β- amyloid 42 concentrations and diagnosis of Alzheimer's disease, Neurobiol Aging, in press.*
- *Beyer AS, 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, in press.*
- *von Einem B, Rehn F, Schwanzar D, Beyer AS, Weber P, Wagner M, Schneckenburger H, von Arnim CAF (2010) Competition of the low density lipoprotein receptor related protein (LRP) with Amyloid precursor protein (APP) for beta-secretase, Exp Neurol 225, 85-93.*
- *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.*
- *Róna-Vörös K, Weydt P (2010) The Role of PGC-1alpha in the Pathogenesis of Neurodegenerative Disorders, Curr Drug Targets 11, 1262-9, in review.*
- *Weydt P, Soyal SM, Gellera C, Didonato S, Weidinger C, Oberkofler H, Landwehrmeyer GB, Patsch W (2009) The gene coding for PGC-1alpha modifies age at onset in Huntington's Disease, Mol Neurodegener 4, 3.*

The Team:
Head of Department: K.-M. Debatin
Professors: C. Beltinger, G. Lahr, M. Wabitsch
Group Leaders/Postdocs: D. Fabricius, S. Fischer, P. Fischer-Posovszky, L.H. Meyer, G. Strauss, A. Westhoff
PhD Students: A. Bangert, A. Bender, C. Dorneburg, S. Enzenmüller, J. Frontzek, N. Hartmann, N. Hasan, C. Jennewein, S. Karl, V. Klinkosch, S. Löder, I. Mader, I. Naumann, S. Saxena, D. Stadel, T. Unterkircher, K. Vellanki, L. Wagner
Study Programme Experimental Medicine Students:
L. Breckerbohm, M. Herrmann, B. Mandel, B. Nussbaum, S. Ostrowska, V. Panitz, J. Philipp, F. Seyfried, J. Stursberg
Additional Members of Thesis Advisory Committees:
P. Agostinis (Leuven, B), B. Baumann (Ulm), A. Bürkle (Konstanz), C. Classen (Rostock), C. Friesen (Ulm), I. Jeremias (Neuherberg), P. Lovat (Newcastle, GB), O. Micheau (Dijon, F), T. Seufferlein (Halle), S. Stilgenbauer (Ulm), L. Wiesmüller (Ulm), R. Zwacka (Galway, IRL), G. te Kronnie (Padua, I)

Department of Pediatrics and Adolescent Medicine

Apoptosis and Cancer Therapy

Head: Klaus-Michael Debatin

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, thus reducing side effects and without the loss of potency, while concurrently enhancing tumor-specificity. Many of these approaches are currently evaluated in vivo or are already being transferred to a clinical setting.

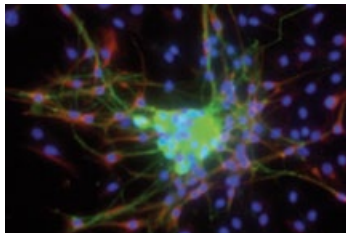
Objectives:
- To elucidate molecular mechanisms of cancer-associated therapy resistance
- To identify molecular markers for targeted therapy that will allow for individualized therapy approaches
- To develop novel therapeutic strategies to overcome therapy resistance
- To analyze the effect of new therapeutic approaches on additional aspects of tumor behavior.

Leukemia

Head: Lüder Hinrich Meyer, Klaus-Michael Debatin

Our group works in close cooperation with the Laboratory of Pediatric Oncohematology at our partner university in Padua, Italy, as part of the Graduate School's joint PhD Program. Our main interest is to identify mechanisms responsible for the development of resistance and relapse in pediatric acute Lymphoblastic Leukemia (ALL), the most frequent malignancy in children.

Objectives:
- Characterization of relapse and resistance in a NOD/SCID/huALL xenograft model
- Identification of molecular mechanisms
- Evaluation of the prognostic relevance of identified resistance features
- Development and evaluation of newly targeted treatment strategies based on these findings.



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

Pathogenesis and Experimental Therapy of Pediatric Tumors

Head: 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 plays an important role. Within this framework, Shobit Saxena analyzes the formation of neuroblastoma from sympatoadrenergic progenitors, the assumed cells-of-origin of neuroblastoma. Carmen Dorneburg preclinically characterizes the molecular mechanisms and the therapeutic efficacy of g-secretase-inhibitors. The preliminary results of both projects promise progress in the understanding and therapy of neuroblastoma.

Immunoregulation and GVHD

Head: 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 themselves and induce 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 proliferation and how pathogens can use these pathways to evade the immune response. The second main focus of our work is the development of new treatment strategies for GVHD by interfering with death receptor pathways or by using myeloid-derived suppressor cells.

Ulm University
Department of Pediatrics and Adolescent Medicine
Prof. Dr. Klaus-Michael Debatin
Eythstraße 24
89075 Ulm, Germany
Tel. +49 (0)731 500 57001
Fax +49 (0)731 500 57002
bianca.welz@uniklinik-ulm.de
www.uniklinik-ulm.de/?id=7717

Selected Publications:

- *Meyer LH, Eckhoff SM, Queudeville M, Kraus JM, Giordan M, Stursberg J, Zangrando A, Vendramini E, Möricke 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 ALL Is Identified by Time to Leukemia in NOD/SCID Mice and Is Characterized by a Gene Signature Involving Survival Pathways, Cancer Cell 19, 206-17.*
- *Hartmann N, Leithäuser F, Albers C, Duyster J, Möller P, Debatin KM, 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, 848-55.*
- *Stadel D, Mohr A, Ref C, MacFarlane M, Zhou S, Humphreys R, Bachem M, Cohen G, Möller P, Zwacka RM, Debatin KM, Fulda S (2010) TRAIL-induced apoptosis is preferentially mediated via TRAIL receptor 1 in pancreatic carcinoma cells and profoundly enhanced by XIAP inhibitors, Clin Cancer Res 16, 5734-49.*
- *Wahl J, Bogytjureva L, Boukamp P, Rojewski M, van Valen F, Fiedler J, Hipp N, Debatin KM, Beltinger C (2010) Ewing's sarcoma cells with CD57-associated increase of tumorigenicity and with neural crest-like differentiation capacity, Int J Cancer 127, 1295-307.*
- *Loeder S, Zenz T, Schnaiter A, Mertens D, Winkler D, Döhner H, Debatin KM, Stilgenbauer S, Fulda S (2009) A novel paradigm to trigger apoptosis in chronic lymphocytic leukemia, Cancer Res 69, 8977-86.*
- *Strauss G, Lindquist JA, Arhel N, Felder E, Karl S, Haas TL, Fulda S, Walczak H, Kirchhoff F, Debatin KM (2009) CD95 co-stimulation blocks activation of naive T cells by inhibiting T cell receptor signaling, J Exp Med 206, 1379-93.*

The Team:
Head of Department: M. Schrader
Professor: A. Schrader
Group Leaders/Postdocs: M. Cronauer, C. Maier
PhD Students: M. Lüdeke, S. Schütz, A. Rinckleb, W. Streicher
Additional Members of Thesis Advisory Committees: K. Spindler (Ulm), B. Wullich (Erlangen)

Department of Urology

Research in Urology

Head: Mark Schrader

The Department of Urology has recently merged two long-established prostate cancer study groups – Molecular Endocrinology and the Familial Prostate Cancer Project – to form one newly created research laboratory. This affiliation in the vicinity of the Clinic will enrich traditional projects by incorporating novel scopes of translational research.

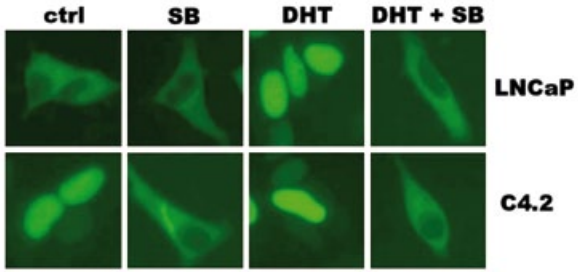
Molecular Endocrinology

Androgen receptor (AR) signaling plays a pivotal role in the development and growth of the prostate. The initial androgen-dependency of prostatic epithelial cells is the reason why most prostate cancer cells respond to androgen ablation therapy. However, during hormone ablation, the majority of prostate cancer cells progress to a state of the disease, known as Castration-Resistant Prostate Cancer (CPRC), where they can activate the AR under subphysiological levels of circulating androgens.

In order to generate genomic signals, the AR must be transported into the nucleus. The main focus of the Molecular Endocrinology Group consists of the analysis of factors involved in the nucleo-cytoplasmic shuttling of the AR. Identification and drug targeting of these factors may yield new strategies to diminish AR-signaling, especially in advanced CPRC.

Genetic Susceptibility of Prostate Cancer

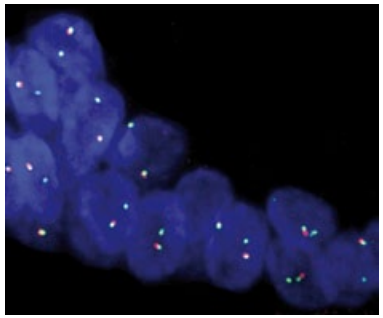
Familial clustering of prostate cancer has long been recognized and the heritable component of this malignancy is expected to be stronger than for any other common cancer. Nevertheless, dissection of the responsible germline risk factors has proven difficult since it appears that a series of genes is involved where each one is hidden in a condition known as “complex inheritance”. In this context, two strategies seem promising for facilitating disease gene identification. The first entails collecting data from as many families as possible in order to strengthen the statistical power for capturing particular genes in approaches to genetic epidemiology. The second strategy aims at defining distinct subgroups of cancer, where the predisposing factors are hopefully more homogeneous.



Inhibition of GSK-3β by the maleimide SB216763 induces nuclear export of the AR in hormone-dependent LNCaP and castration-resistant C4.2 prostate cancer cells: (treatment: ctrl = untreated controls, SB = SB216763; DHT = dihydrotestosterone; DHT + SB = dihydrotestosterone + SB216763, detection by fluorescence microscopy of the AR).

Ulm University
Department of Urology
Prof. Dr. Mark Schrader
Prittwitzstraße 43
89075 Ulm, Germany
Tel. +49 (0)731 500 58000
Fax +49 (0)731 500 58002
mark.schrader@uniklinik-ulm.de
www.uniklinik-ulm.de/urologie

The "Familial Prostate Cancer Project" established by the Institute of Human Genetics and the Department of Urology at Ulm University has been engaged in both strategies: (1) For the generation of profound sample sizes, the unique German study cohort has been incorporated into large international prostate cancer consortia to conduct whole genome studies that include linkage, association and sequencing approaches. (2) Reducing heterogeneity by sample splitting is a special research focus pursued locally. For this purpose, the previously identified oncogene fusion *TMPRSS2-ERG* was introduced as a surrogate marker for a homogeneous pathomechanism to define a potentially distinct entity of prostate cancer. Within the PhD study of Manuel Lüdeke, candidate gene sequencing and association studies have revealed promising germline variants that appear to be substantially enriched in fusion positive prostate cancer cases. For the purpose of functional validation, an in vitro *TMPRSS2-ERG* induction assay has now been utilized to measure effects on fusion formation by knocking out the two candidate genes *POLI* (polymerase iota) and *ESCO1* (establishment of cohesion-1).



Genetic epidemiology on defined phenotype: *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 indicates an intact chromosome 21. Absence or separation of a red signal indicates deletion of the intergenic region, suggesting the fusion of *TMPRSS2* to *ERG*.

Selected Publications:

- *Christensen GB et al. (2010) Genome-wide linkage analysis of 1,233 prostate cancer pedigrees from the International Consortium for Prostate Cancer Genetics using novel sumLINK and sumLOD analyses, Prostate 70, 735-744.*
- *Schütz SV, Cronauer MV SV, Rinnab L (2010) Inhibition of glycogen synthase kinase-3β promotes nuclear export of the androgen receptor through a Crm1-dependent mechanism in prostate cancer cell lines, J Cell Biochem 109, 1192-1200.*
- *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.*
- *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.*
- *Eeles RA, and the PRACTICAL Consortium (2009) Identification of seven new prostate cancer susceptibility loci through a genome-wide association study, Nat Genet 41, 1116-1121.*
- *Rinnab L, Schütz SV, Jeannine Diesch J, Schmid E, Küfer R, Hautmann RE, Spindler KD, Cronauer MV (2008) Inhibiton of Glycogen-Synthase Kinase-3 (GSK) in Androgen Responsive Prostate Cancer Cell Lines - Are GSK-Inhibitors Therapeutically Useful? Neoplasia 10, 624-634.*

Department of Child and Adolescent Psychiatry/Psychotherapy

Head: Jörg M. Fegert

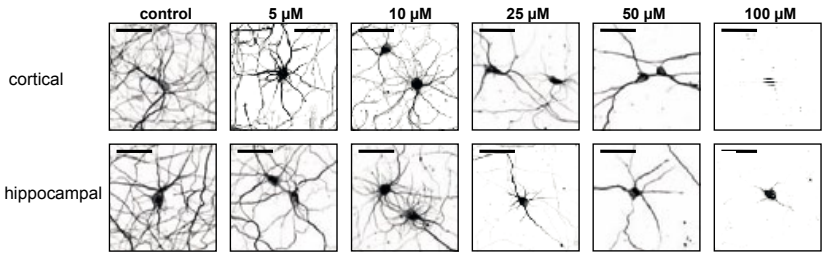
Cooperation Project: “Age-dependent Cell Biological Effects of Psychotropic Substances in Maturing Neuronal Systems”

Cooperation Partners: Andrea G. Ludolph, Department of Child and Adolescent Psychiatry/Psychotherapy and T. M. Böckers, Institute of Anatomy and Cell Biology

In recent years it has been extensively debated if the prevalence of psychiatric disorders in childhood and adolescence is increasing. In contrast, the increased frequency of prescribing psychotropic medications to minors cannot be doubted. Most psychotropic substances are used “off-label”, meaning there is a huge lack of knowledge about the cell biological effects of 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
Heads of the Working Group:
A. G. Ludolph, T. M. Böckers
PhD Student: P. T. Udvardi
Additional Member of Thesis Advisory Committee:
A. Storch (Dresden)

In a joint venture between the Department 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 the 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 on the expression of PSD scaffolding proteins since the NMDA-receptor is embedded in a much larger complex of proteins associated with the post-synaptic density (PSD).

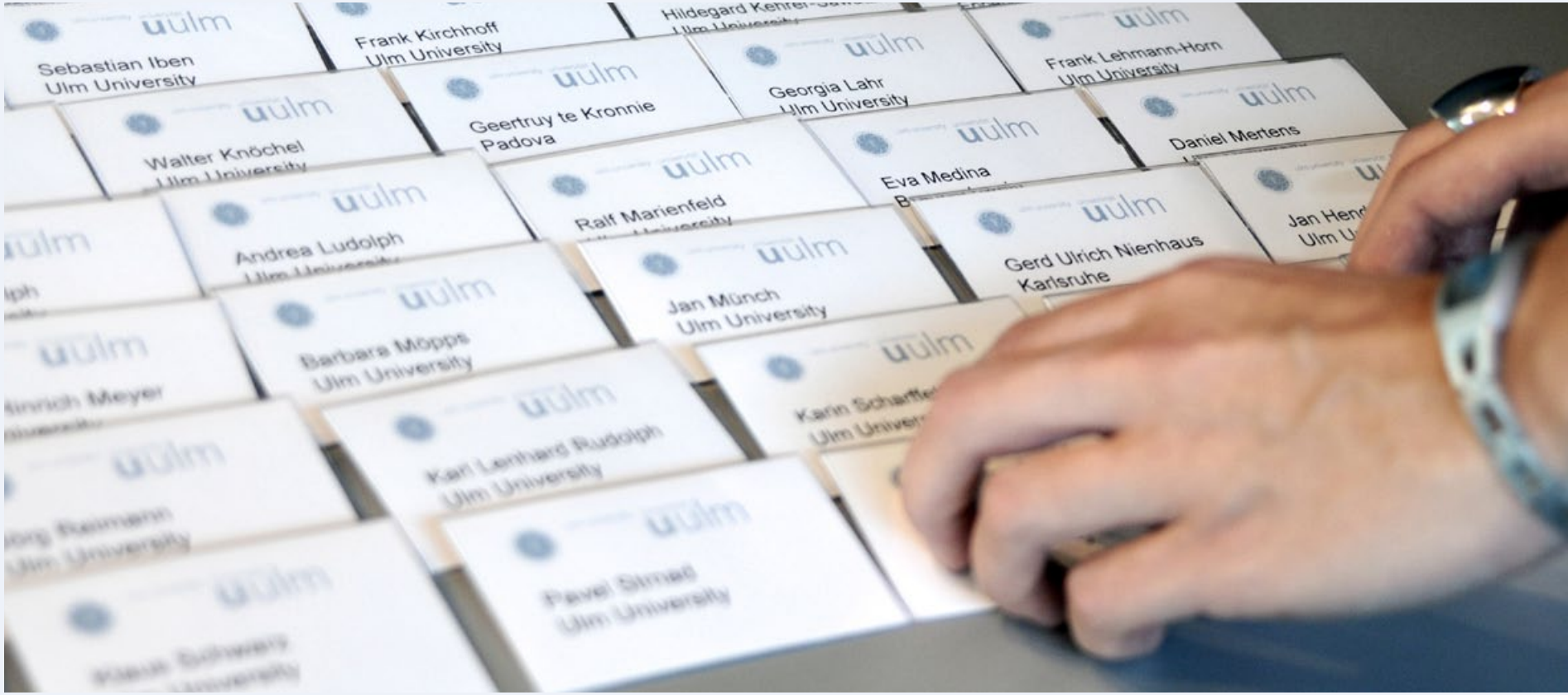


Effect of atomoxetine on cortical and hippocampal neurons. The neuronal cells were treated on DIV 5 for 72 h with the indicated concentrations of atomoxetine. The neurons were immunolabeled with antibodies against MAP2 (microtubular-associated protein 2). Bar = 20 µm. Loss of sprouting emerged in cortical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

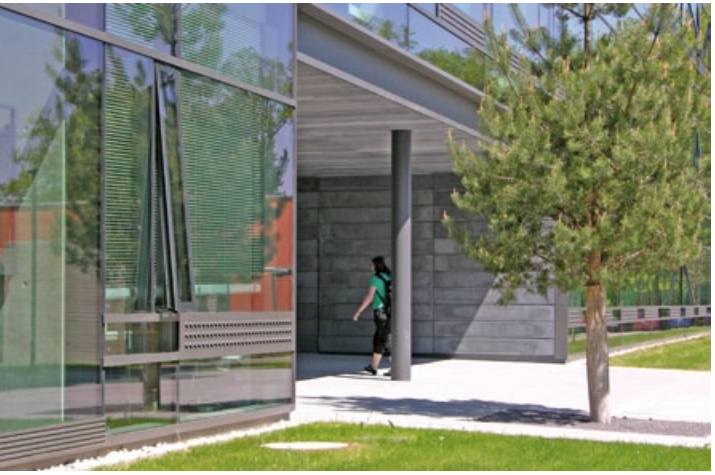
Ulm University
Department of Child and Adolescent Psychiatry/
Psychotherapy
Prof. Dr. Jörg M. Fegert
Steinhövelstraße 5
89075 Ulm, Germany
Tel. +49 (0)731 500 61600
Fax +49 (0)731 500 61602
joerg.fegert@uniklinik-ulm.de
www.uni-ulm.de/klinik/kjp/

Selected Publications:

- *Schaz U, Föhr KJ, Liebau S, Fulda S, Koelch M, Fegert JM, Boeckers TM, Ludolph AG (2011)Dose-dependent modulation of apoptotic processes by fluoxetine in maturing neuronal cells: an in vitro study, World J Biol Psychiatry 12,89-98.*
- *Ludolph AG, Udvardi PT, Schaz U, Henes C, Adolph O, Weigt HU, Fegert JM,Boeckers TM, Föhr KJ (2010) Atomoxetine acts as an NMDA receptor blocker in clinically relevant concentrations, Br J Pharmacol 160, 283-91.*
- *Allroggen M, Udvardi PT, Plener PL, Koelch M, Fegert JM, Ludolph AG (2010)Langzeiteffekte von Psychostimulanzien – welche Auswirkungen sind uns aus präklinischen und klinischen Studien bekannt? Psychopharmakotherapie 17, 125-131.*
- *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.*



Organization of the Graduate School



Who we are - Organization of the Graduate School

The International Graduate School in Molecular Medicine Ulm is an interdisciplinary central 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 program. 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 program 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.

External Members of the International and Scientific Advisory Board

Academic Representatives	Industrial Representatives
Y. Kloog, Tel Aviv	U. Bücheler, Boehringer Ingelheim
M. J. Lohse, Würzburg	N. Rentschler, BioRegionUlm
S. Moody, Washington D.C.	H. Wendt, Bayer
G. Nienhaus, Karlsruhe	
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 25 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: Development, Aging and Degeneration; Hematology and Oncology; Cardio-Metabolic Disorders; and Host-Microbe Interaction.

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

The **Coordination Office** is responsible for the administration and organization of the Graduate School. It is the principal contact point for all students, supervisors and applicants, and gives advice and support concerning Graduate School policies and procedures, as well as answering questions concerning academic issues. The office also preselects applications and coordinates the selection procedure. It organizes curricular and extracurricular activities as well as meetings and examinations, and is responsible for the Graduate School's public relations. In addition, it coordinates the smooth interaction and cooperation between the large number of people and institutions involved in the Graduate School.

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.

In addition to curricular seminars and lectures, we offer PhD students a large 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. 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.

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 Seminar „Good Scientific Practice”	2	
1.5	Others (minisymposia, excursions, workshops etc.); optional participation in 2 activities à 8 hrs	1	
	Sum 1st year	7	
	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 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 must be acquired 5 more credit points.

For the successful completion of the PhD programme, after the 3rd year the PhD student must have acquired 180 credit points (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 program 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 better 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 program on condition that:

- The candidate's oral presentation and the personal interviews have been evaluated with an overall grade of 2.0 or better 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 program, 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 program 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 program 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 approximately €1,200 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. 145 km/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 19th 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 large 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% between 1998 and 2007. At the same time, the unemployment rate has been reduced by more than 40% and a mere 3.6 % 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 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.

Facts and Figures

Facts and Figures

(May 2011)

PhD Students, *International PhD Programme in Molecular Medicine*

Total number of PhD students	115
Male	37
Female	78
International students	42
Parental students	4

PhD Students, Research Training Group GRK 1041

Total number of PhD students	11
Male	5
Female	6
International students	7
Parental students	1

Students of Programme “Experimental Medicine”

Total number of PhD students	37
Male	3
Female	8
International students	0
Parental students	1

Doctorates conferred (2009-2011), *International PhD Programme in Molecular Medicine*

Name	Topic	Institute	Date of final examination	Degree
Amara, Umme	Interactions of the Complement and Coagulation Cascades	Department of Orthopedic Trauma, Hand, Plastic and Reconstruction Surgery	09/28/2009	PhD
Bender, Ariane	Role of phosphoinositide-3-kinase (PI3K)/Akt signaling in chemotherapy-induced apoptosis regulation of neuroblastoma	Department of Pediatrics and Adolescent Medicine	12/21/2010	Dr. rer. nat.
Beyer, Anja-Silke	Interaction between amyloid-b (A4) precursor protein (APP) and engulfment adaptor PTB domain containing 1 (GULP1) and its physiological impact on APP metabolism	Department of Neurology	12/07/2010	Dr. rer. nat.
Bhattacharya, Nupur	Microenvironmental signaling in chronic lymphotic leukemia	Department of Internal Medicine III	11/04/2010	PhD
Chevillotte, Meike	Novel approaches for optimisation of human cytomegalovirus antiviral therapy based on viral resistance profiles	Institute of Virology	04/20/2010	PhD
Einem, Björn	Modulation of amyloid precursor protein (APP) and β-site of APP cleaving enzyme 1 (BACE1) intracellular transport and its influence on APP processing in Alzheimer´s disease	Department of Neurology	12/02/2010	Dr. rer. nat.
Karl, Sabine Konstanze	Identification of a novel role of Nuclear Factor kappaB in the regulation of the DNA damage response and apoptosis in glioblastoma	Department of Pediatrics and Adolescent Medicine	04/01/2010	Dr. rer. nat.
Löder, Isabella Sandra	Combining small molecule XIAP inhibitors and death receptor ligands as promising approach to overcome apoptosis resistance in acute and chronic lymphocytic leukemia	Department of Pediatrics and Adolescent Medicine	12/17/2010	Dr. rer. nat.
Mader, Isabelle	Identification of a novel proapoptotic function of resveratrol: Sensitization of fat cells to TRAIL-induced apoptosis in a SIRT1-independent manner	Department of Pediatrics and Adolescent Medicine	06/15/2010	Dr. rer. nat.
Mohr, Julia	The p53 Network in Chronic Lymphocytic Leukemia	Department of Internal Medicine III	05/15/2011	Dr. rer. nat.
Müller, Adrienne	Molecular mechanisms underlying the switch of mature retinal ganglion cells to a regenerative state after inflammatory stimulation	Department of Neurology	10/09/2009	Dr. rer. nat.
Philippen, Angela	Genetic and Epigenetic Lesions in Chronic Lymphocytic Leukemia (CLL): The impact of aberrations in single genes, complex loci and whole genomes on the pathomechanism of CLL	Department of Internal Medicine III	02/11/2011	Dr. rer. nat.
Purushothama Rao, Tata	Transcriptional regulation of a pluripotency association miRNA cluster, EEmiRC: an epigenetic mystique	Institute of Biochemistry and Molecular Biology	03/21/2011	PhD
Pusapati, Venkata Ganesh Varma	Protein kinase D2-regulated protein transport at the trans-Golgi network requires its targeting to this compartment by ADP-ribosylation factor 1	Department of Internal Medicine I	06/17/2010	PhD
Vellanki, Sri HariKrishna	Small molecule XIAP inhibitors enhance γ-irradiation-induced apoptosis in glioblastoma	Department of Pediatrics and Adolescent Medicine	12/14/2009	PhD

Workshops	Date	Organizer
Project Management for Research Projects – Basic level	11/25/2011 - 11/26/2011	GSC 270
Extramural Funding – The road from idea to getting funded!	10/28/2011 - 10/29/2011	GSC 270
European Patent Law	08/09/2011 - 08/10/2011	GSC 270
Career Planning	07/08/2011	GSC 270
Team work & leadership competencies in academia and beyond	06/17/2011	GSC 270
Networking for academics – Creating perspectives through contacts	05/27/2011	GSC 270
German course – German for Beginners	every Monday, start: 05/16/2011	GSC 270
Good Scientific Practice	05/9/2011 05/11/2011 05/13/2011	GSC 270
Sicherheit in der Gentechnik	05/05/2011 - 05/06/2011	GSC 270
In vivo Imaging Methods from Preclinical to Clinical Research	04/15/2011 - 04/16/2011	GSC 270
Bioethics	04/12/2011 04/26/2011 - 04/29/2011	GSC 270
Research Managment training workshop for young researchers, Brussels	03/31/2011 - 04/01/2011	GSC 270
Good Laboratory Practice	03/25/2011 - 03/26/2011	GSC 270
Communication & presentation in the academic context	03/17/2011 - 03/18/2011 09/22/2011 - 09/23/2011	GSC 270
Academic Writing	02/25/2011	GSC 270
Project Management for Research Projects – Advanced Level	01/21/2011 - 01/22/2011	GSC 270
Project Management for Research Projects – Basic Level	11/26/2010 - 11/27/2010	GSC 270
Intercultural Training	11/13/2010	GSC 270
Grant Acquisition	11/05/2010 - 11/06/2010	GSC 270
German course – German for Beginners	every Monday, start: 10/25/2010	GSC 270
Communication & presentation in the academic context	09/17/2010	GSC 270
In vivo imaging methods	04/23/2010 - 04/24/2010	GSC 270
Sicherheit in der Gentechnik	04/15/2010 - 04/16/2010	GSC 270
Team work & leadership competencies in academia and beyond	06/18/2010	GSC 270

Workshops	Date	Organizer
Project management for Research Projects – Advanced Level	01/22/2010 - 01/23/2010	GSC 270
Project Management for Research Projects – Basic Level	11/27/2010 - 11/28/209	GSC 270
Project Management in Biotechnological Industries	11/13/2009	GSC 270
Detection of Antigen-Specific T Cells using Multiparameter Flow Cytometry	individually arranged	GRK 1041
Analysis of Proteases by using Biochemical Methods	individually arranged	GRK 1041
Functional analysis of the androgen receptor (AR) signalling	individually arranged	GRK 1041
Analysis of androgen receptor protein complexes in prostate carcinoma cell lines	individually arranged	GRK 1041

Excursions	Date	Organizer
Boehringer Ingelheim Pharma GmbH& Co.KG	05/04/2011	GSC 270
Rentschler Biotechnologie GmbH	02/16/2011	GSC 270
Roche Diagnostics GmbH	01/28/2011	GRK 1041
Carl Zeiss AG	12/08/2010	GSC 270
Boehringer Ingelheim Pharma GmbH& Co.KG	05/05/2010	GSC 270
Rentschler Biotechnologie GmbH	01/21/2010	GSC 270
Boehringer Ingelheim Pharma GmbH& Co.KG	11/24/2009	GSC 270

Symposia	Date	Organizer
Fall Meeting 2011	10/06/2011 - 10/08/2011	GSC 270
Tag der Molekularen Medizin	04/16/2011	Students
Spring Meeting 2011	04/07/2011 - 04/09/2011	GSC 270
4th International Symposium “Signalling Pathways in Stem Cell Biology”	10/14/2010 - 10/16/2010	SFB 497
Fall Meeting 2010	10/07/2010 - 10/09/2010	GSC 270
International DFG-Meeting: “Functional compartmentalization of PIP2 signaling”, Günzburg	09/09/2010 - 09/11/2010	P. Gierschik
Statistical Computing 2010 42nd Meeting of the Working groups “Statistical Computing” and “Klassifikation und Datenanalyse in den Biowissenschaften”, Günzburg	06/20/2010 - 06/23/2010	H. Kestler
Chinese Science Colloquium	05/03/2010	UU
Spring Meeting 2010	04/25/2010 - 04/27/2010	GSC 270
Tag der Molekularen Medizin	04/16/2010	Students
Minisymposium: Pulmonology together with Boehringer Ingelheim Pharma GmbH& Co.KG	03/09/2010	P. Dietl
Minisymposium: Neurosciences together with Boehringer Ingelheim Pharma GmbH& Co.KG	02/15/2010 - 02/16/2010	T. Böckers

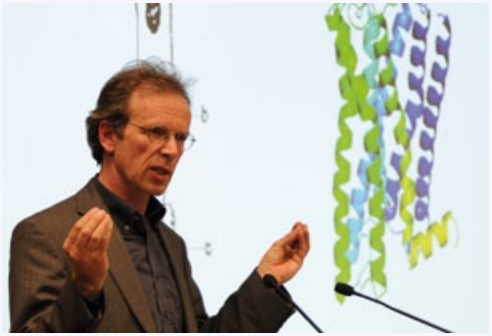
Summer and Winter Schools	Date	Organizer
Bregenz Summer School in Endocrinology 2011	07/24/2011 - 07/28/2011	GRK 1041, 1208, KFO 218
5th Tongji-Ulm Summer School in Molecular Medicine: Cancer: From Molecules to Disease Wuhan/China	07/25/2011 - 05/08/2011	GSC 270
GRK Winter School 2010, Kühtai	12/14/2010 - 12/16/2010	GRK 1041
4th Tongji-Ulm Summer School in Molecular Medicine: Infectious Diseases Wuhan/China	07/26/2010 - 08/06/2010	GSC 270
21st International Summer School of Epidemiology; together with UNC, Ulm/Germany	07/26/2010 - 07/30/2010	GSC 270
Bregenz Summer School in Endocrinology 2010	07/18/2010 - 07/22/2010	GRK 1041

Retreats	Date	Organizer
Molecular Biology and Genetics Myrtle Beach/USA	09/16/2011 - 09/18/2011	UNC Chapel Hill
Faces of Neuroscience Development, Plasticity& Disease Loch Lomond/Scotland	09/05/2011 - 09/09/2011	T. Böckers
Cellular and Molecular Mechanisms of Ageing, Günzburg/Germany	09/15/2011 - 09/16/2011	H. Geiger
Protein structure and function and kinases as drug targets Athens/Greece	09/22/2010 - 09/26/2010	U. Knippschild
Molecular Biology and Genetics, together with UNC Chapel Hill Myrtle Beach/USA	09/17/2010 - 09/19/2010	UNC Chapel Hill
Signaling pathways in development and regeneration Reisensburg Günzburg/Germany	06/08/2010 - 06/11/2010	M. Kühl
Meeting GRK 1041 and internal retreat GRK 1208 Berlin Reisensburg Günzburg/Germany	04/12/2010 - 04/14/2010	GRK 1041

Social Activities	Date
Summer Party	07/13/2011
M4M: Excursion to the Swabian Jura	04/16/2011
M4M: Excursion to Riezlern, Kleinwalsertal	03/13/2011
M4M: Excursion to Lake Constance	03/12/2011
Basketball Match: Students vs Supervisors	02/24/2011
M4M: Excursion to Mercedes-Benz Museum	02/12/2011
M4M: Visit of the "Narrensprung" Carnival	02/06/2011
M4M: Chinese Spring Festival	01/29/2011
M4M: Excursion to Oberstdorf	01/22/2011
M4M: Thematical evening: Regional game tradition "Mutscheln"	01/21/2011
M4M: Observatory/planetarium Laupheim	01/05/2011
Christmas Party	12/15/2010
M4M: Guided city tour Ulm	09/15/2010
Oktoberfest, Munich	09/29/2010
M4M: Guided tour Botanic Garden	08/04/2010
M4M: Traditional/cultural regional events and "public viewing" of the semi finale FIFA world cup	07/07/2010
Summer Party	06/30/2010
M4M: Excursion to Switzerland: Rheinfall and Zurich	06/19/2010
M4M: Excrsion to Lake Constance	06/12/2010
M4M: Guided City tour for Newcomers	05/19/2010
M4M: Soirée Européenne	03/12/2010
M4M: Excursion to Munich, Deutsches Museum	03/06/2010
M4M: Games Germans play	03/03/2010
M4M: Chinese New Year	02/13/2010

Social Activities	Date
M4M: 2010 welcome evening	02/03/2010
Christmas Party	12/16/2009
M4M: Excursion to Esslingen	12/12/2009
M4M: Pakistani Evening	11/22/2009
M4M: Excursion: Centrotherm photovoltaics AG, Blaubeuren	11/04/2009
M4M: The German language	11/03/2009
M4M: Climate change and climate protection	10/14/2009

Invited Speakers (2009-2011)



Topic	Speaker	Date	Organizer
Molecular and cellular functions of the Dek oncogene	Susanne Wells Cincinatti/USA	05/26/2011	SFB 497
Generation of functional organs from ES/iPS cells	Hiromitsu Nakauchi Tokyo/Japan	05/23/2011	GSC 270
Analysing structured data – symbolic and probabilistic approaches	Luc De Raed Leuven/Belgium	05/23/2011	GSC 270
Bone Marrow Niche Signaling that regulates Hematopoietic Stem Cell Hibernation	Hiromitsu Nakauchi Tokyo/Japan	05/18/2011	GSC 270
Intestinal microbiota at the cross-road between inflammation and metabolism	Dirk Haller Munich/Germany	04/28/2011	GRK 1041
Spying on drugs and metabolites in living cells	Kai Johnsson Lausanne/Switzerland	04/09/2011	GSC 270
Regulation of collagen prolyl 4-hydroxylase II in chondrocytes by the hypoxia response pathway	Ellinoora Aro Oulu/Finland	04/09/2011	GSC 270
Super-resolution Fluorescence Microscopy with Novel Fluorescent Protein Markers	Ulrich Nienhaus Karlsruhe/Germany	04/09/2011	GSC 270
Aspects of human B cell lymphoma pathogenesis	Ralf Küppers Essen/Germany	04/08/2011	GSC 270
Small and Long non-coding RNAs in Cancer	Sven Diederichs Heidelberg/Germany	04/08/2011	GSC 270
Generation of the LODAVIN and IDTR mice to study murine kidney development	Subramanian Muruga Oulu/Finland	04/08/2011	GSC 270
From Synapse to Nucleus and Back Again – Communication Over Distance Within Neurons	Michael Kreutz Magdeburg/Germany	04/08/2011	GSC 270
Receptor-mediated signaling	Martin Lohse Würzburg/Germany	04/07/2011	GSC 270
The after party: Wound recrudescence after failure to stop healing	Alan Wells Pittsburgh/USA	04/07/2011	SFB 497
Characterization of autoreactive T cells in autoimmune diabetes	Corrado Cillio Malmö/Sweden	02/10/2011	GRK 1041
Entschlüsselung des Neandertaler-Genoms	Johannes Krause Tübingen/Germany	12/02/2010	GRK 1041
Tales of Wnt signaling and regeneration: Cellular and molecular mechanisms of bone regeneration in the zebrafish fin	Gilbert Weidinger Dresden/Germany	11/30/2010	SFB 497

Topic	Speaker	Date	Organizer
Pancreas development and regeneration	Heiko Lickert Munich/Germany	11/25/2010	GRK 1041
Surviving sepsis: Lessons from mice	Hartmut Weiler Milwaukee/USA	11/22/2010	SFB 497
Epigenetic Aspects from stem cell research and reproductive medicine	Ulrich Zechner Mainz/Germany	11/18/2010	SFB 497
Polyclonal T cell activation for cancer therapy by bispecific antibodies	Patrick A. Baeuerle München/Germany	11/04/2010	SFB 497
Cell transformation by human adenovirus	Thomas Dobner Hamburg/Germany	10/21/2010	SFB 497
Of vectors, viruses and cancer	Christof von Kalle Heidelberg/Germany	10/16/2010	SFB 497
Pharmacological mobilization of progenitor cells	Sara M. Rankin London/UK	10/16/2010	SFB 497
Ex vivo expansion of hematopoietic stem cells – new possibilities	Connie J. Eaves Vancouver/Canada	10/16/2010	SFB 497
Tracking stem cells at the single cell level: New tools for old questions	Timm Schröder Munich/Germany	10/16/2010	SFB 497
Targeting the Rho GTPase Cdc42 for hematopoietic stem cell mobilization and engraftment	Yi Zheng Cincinnati/USA	10/16/2010	SFB 497
Development and migration of primordial germ cells in zebrafish	Erez Raz Münster/Germany	10/16/2010	SFB 497
TGF-b induces hematopoietic stem cell hibernation as a BM niche signal	Hiromitsu Nakauchi Tokyo/Japan	10/15/2010	SFB 497
Genome stability mechanisms in C. elegans germline stem cells	Björn Schumacher Cologne/Germany	10/15/2010	SFB 497
Lgr5 gastrointestinal stem cells in self-renewal and cancer	Nick Barker Utrecht/Netherlands	10/15/2010	SFB 497
Control of intestinal stem cell proliferation in aging Drosophila	Heinrich Jasper Rochester/USA	10/15/2010	SFB 497
Identification and analysis of stem cells in cardiac and skeletal muscle	Thomas Braun Bad Nauheim/Germany	10/15/2010	SFB 497
Benign and malignant cross-talk in the stem cell niche	Dorothy A. Sipkins Chicago/USA	10/15/2010	SFB 497

Topic	Speaker	Date	Organizer
Stem cell regulation via dynamic interactions of the nervous and immune systems with the microenvironment	Tsvee Lapidot Rehovot/Israel	10/15/2010	SFB 497
Neural regulation of stem cell microenvironment	Paul S. Frenette New York/USA	10/15/2010	SFB 497
Dynamic niches: Implications of stem cell trafficking for stem cell function	Amy Wagers Boston/USA	10/15/2010	SFB 497
Stem cells, systemic factors, and the control of oogenesis by diet in Drosophila	Daniela Drummond-Barbosa Baltimore/USA	10/15/2010	SFB 497
The role of E-cadherin in pluripotency and reprogramming	Daniel Besser Berlin/Germany	10/14/2010	SFB 497
Transposon-reprogrammed induced pluripotent stem cells are powerful exploratory tools	Andras Nagy Toronto/Canada	10/14/2010	SFB 497
X-chromosome reactivation during transcription factor induced reprogramming	Jason Tchieu Los Angeles/USA	10/14/2010	SFB 497
Gene targeting in human pluripotent cells using zinc-finger nucleases	Dirk Hockemeyer Boston/USA	10/14/2010	SFB 497
Modeling human neural development and disease in pluripotent stem cells	Stuart Chambers New York/USA	10/14/2010	SFB 497
Induction of pluripotency in adult stem cells	Hans R. Schöler Münster/Germany	10/14/2010	SFB 497
Transcriptional control of myeloid cell diversification	Frank Rosenbauer Berlin/Germany	10/09/2010	GSC 270
Endostatin and arresten, basement membrane components with various roles in tumor growth	Mari Aikio Oulu/Finland	10/09/2010	GSC 270
Inflammatory signaling pathways in models of liver disease	Tom Lüdde Aachen/Germany	10/09/2010	GSC 270
DNA damage response in skin stem cells	Cédric Blanpain Bruxelles/Belgium	10/08/2010	GSC 270
Harnessing the zebrafish to elucidate mechanisms governing spatiotemporal gene expression	Gray Camp Chapel Hill/USA	10/08/2010	GSC 270
Genome-wide measurement of transcription factor binding dynamics by competition-ChIP	Colin Lickwar Chapel Hill/USA	10/08/2010	GSC 270
DNA damage induced silencing of gene transcription	Roger Greenberg Philadelphi/USA	10/08/2010	GSC 270

Topic	Speaker	Date	Organizer
Introduction to the German Mouse Clinic	Helmut Fuchs Munich/Germany	10/08/2010	GSC 270
Genetic associations with plasma adiponectin level in Filipino young adults	Damien Croteau-Chonka Chapel Hill/USA	10/08/2010	GSC 270
Molecular approaches to the treatment of muscle atrophy	Paula Clemens Pittsburgh/USA	10/08/2010	GSC 270
Stem cells and their future therapeutic potentials	Hiromitsu Nakauchi Tokyo/Japan	10/07/2010	GSC 270
Nephronectin: A new regulator of heart patterning	Felix B. Engel Bad Nauheim/Germany	09/23/2010	SFB 497
Quality Control for Assembly of HLA Class II Peptide Receptors-Polymorphism Induced Dysfunction of HLA-DQ Peptide Receptors	Norbert Koch Bonn/Germany	06/17/2010	GRK 1041
Phagocytes – A new endocrine organ	Michael Flierl Denver/USA	05/21/2010	ZMFU
Molekulare Therapie von Knorpelschäden	Henning Madry Homburg, Saar/Germany	05/18/2010	ZMFU
DNA damage in aging and longevity	Bjoern Schuhmacher Cologne/Germany	05/14/2010	SFB 497
Maintaining an immature neural state: A tricky tale of transcription	Sally A. Moody Washington D.C./USA	04/19/2010	SFB 497
Targeting the self-renewal programms of normal and leukemic stem cells	R. Keith Humphries Vancouver/Canada	03/27/2010	GSC 270
Cancer stem cells in pancreatic cancer: researchers´s view and clinical impact	Christiane Bruns Munich/Germany	03/27/2010	GSC 270
Developmental signaling under the control of G protein-coupled receptor kinases	Melanie Philipp Duke/USA	03/26/2010	GSC 270
Hypoxia-inducible factor (HIF)-1a stabilization in normoxic, hypoxic and reoxygenated mouse embryonic fibroblasts lacking HIF prolyl 4-hydroxylase 3	Anu Laitala Oulu/Finland	03/26/2010	GSC 270
Drosophila motoraxons recognize and follow Sidestep-labelled substrates	Hermann Aberle Münster/Germany	03/26/2010	GSC 270
microRNAs in development and disease	Scott Hammond Chapel Hill/USA	03/26/2010	GSC 270

Topic	Speaker	Date	Organizer
Features of Pluripotency in Xenopus	Ralph Rupp Munich/Germany	03/25/2010	GSC 270
Pinosomes and podosomes: Protease biology links two dendritic cell “organelles”	Colin Watts Dundee/UK	03/18/2010	SFB 518
The link between motor proteins and striatal pathology	Krisztina Vörös	03/18/2010	IZKF
Two isoforms of human RNA polymerase III with specific functions in cell growth, differentiation and transformation	Martin Teichmann Bordeaux/France	03/11/2010	SFB 497
Identifying diabetes-relevant autoreactive T cells	Ezio Bonifacio Dresden/Germany	03/04/2010	GRK 1041
A cross talk between the transcription factors Pdx1 and TFAM explains mitochondrial dysfunction in an islet beta cell model of MODY4	Benoit Gauthier Geneva/Switzerland	02/25/2010	GRK 1041
Human Immunosenescence and Infection	Graham Pawelec Tübingen/Germany	02/22/2010	KFO 142
How do cells sense mechanical forces? – Exploration of mechanotransduction in cells and it´s implications for cancer biology	Yasuhiro Sawada Singapore	01/14/2010	SFB 518
Hepatocyte-Specific NEMO Deletion: An Animal Model To Study Liver Disease Progression	Christian Trautwein Aachen/Germany	12/10/2009	SFB 518
The role of medullary thymic epithelial cells in central tolerance: Self-antigen factories or autonomous tolerogenic APCs	Ludger Klein Munich/Germany	12/10/2009	GRK 1041
Foxp3+ regulatory T(reg) cells in autoimmune diabetes	Markus Feuerer Heidelberg/Germany	12/08/2009	SFB 518
The Endocannabinoidsystem in Adipose Tissue	Isabel Wagner Lübeck/Germany	12/03/2009	GRK 1041
Investigating hematopoietic stem cells and neutrophils in the bone marrow in vivo	Matthias Gunzer Magdeburg/Germany	11/18/2009	SFB 497

Publications of PhD students 2009-2011

(until May 2011)

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Bender A, Opel D, Naumann I, Kappler R, Friedman L, von Schweinitz D, Debatin KM, Fulda S (2011) PI3K inhibitors prime neuroblastoma cells for chemotherapy by shifting the balance towards pro-apoptotic Bcl-2 proteins and enhanced mitochondrial apoptosis. Oncogene 30:494-503

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Kleger A, Loebnitz C, Pusapati GV, Armacki M, Müller M, Tümpel S, Illing A, Hartmann D, Brunner C, Liebau S, Rudolph KL, Adler G, Seufferlein T (2011). Protein kinase d2 is an essential regulator of murine myoblast differentiation. PLoS One 6:e14599

Liebau S, Steinestel J, Linta L, Kleger A, Storch A, Schoen M, Steinestel K, Proepper C, Bockmann J, Schmeisser MJ, Boeckers TM (2011) An SK3 channel/nWASP/Abi-1 complex is involved in early neurogenesis. PLoS One 6:e18148

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Ulm University
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89081 Ulm · Germany
Tel. +49 (0)731-50-36293
Fax +49 (0)731-50-36292
gs.molmed@uni-ulm.de
www.uni-ulm.de/mm

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Editors
PD Dr. Dieter Brockmann
Prof. Dr. Michael Kühl
Julia Kutzenberger, M.A.

Design, organization
Gabriele Stautner, Artifox Communication Design Ulm
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John McKeon, Artifox Communication Design Ulm

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International Graduate School
in Molecular Medicine Ulm
Ulm University
Meyerhofstr. N 27/2.011
89081 Ulm · Germany
Tel. +49 (0)731-50-36293
Fax +49 (0)731-50-36292
gs.molmed@uni-ulm.de
www.uni-ulm.de/mm