ulm university universität ulm

International Graduate School in Molecular Medicine Ulm

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

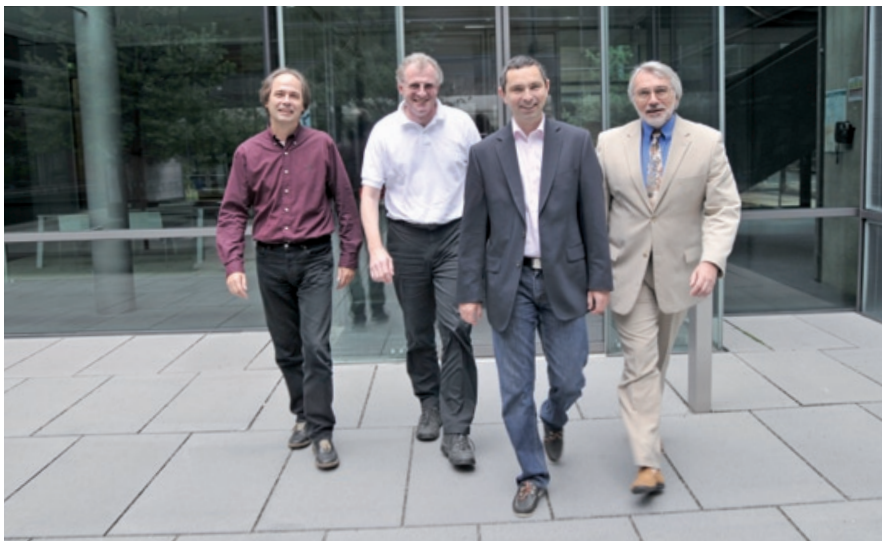
Biannual Report 2009

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

All started with seven PhD students receiving funds from the Medical Faculty of Ulm University to join the newly established *International PhD Programme in Molecular Medicine* – a three year training programme for doctoral students seeking to be awarded the international degree of *Doctor of Philosophy* (PhD), or the German degree of *Doctor rerum naturalium* (Dr. rer. nat.). In 2006 this PhD programme became the basis for establishing in Ulm an International Graduate School in Molecular Medicine with the mission to train doctoral students to the highest international standards. Rapid developments soon followed and then in 2007 our Graduate School, being one out of 39 graduate schools, was awarded funds from the Excellence Initiative of the German federal and state governments. Today in July 2009, more than 75 PhD students are being trained by the Graduate School and many of these receive grants from the Graduate School. It was at our International Spring Meeting in 2009 that the first ever graduation day was celebrated.

As its name suggests, the Graduate School's chief scientific topic is *Molecular Medicine*, that is, the identification and understanding of molecular and cellular mechanisms underlying diseases. Ulm University and its Medical Faculty both have a long and successful history in this area of research, specifically in the fields of Haematology/Oncology, Ageing and Apoptosis, Cardio Metabolic Diseases, Signal Transduction, Biomaterials/Musculoskeletal Research, Neurosciences and Infectious Diseases. To assist this research, the Medical Faculty obtained more than € 35 million in third party funding in 2008 from national and international research foundations. Within the last ten years, the Medical Faculty of Ulm University has roughly doubled its third party funding and gained an upper third ranking among German Medical Faculties. In 2009 the Medical Faculty is proud to house two Collaborative Research Centres (*Sonderforschungsbereiche*), four Clinical Research Units (*Klinische Forschergruppen*), a Transregio-Research Group (*Transregio-Forschergruppe*) and a Research Training Group (*Graduiertenkolleg*). All these are funded by the German Research Foundation (DFG). Several BMBF-networks (*Bundesministerium für Bildung und Forschung*/Federal Ministry of Education and Research) as well as EU-networks are located at the Medical Faculty. Interdisciplinary research networks in the field of Molecular Medicine obtain grants from the German Cancer Society, the High Q Foundation (USA) and the National Institutes of Health (NIH, USA). There are also additional initiatives to follow that will help this successful development progress further. A very important aspect of these research networks is to promote the training of young scientists and PhD students, and it is this very training that has become the principal task of the International Graduate School in Molecular Medicine Ulm.

In addition to the scientific training and training positions, the Graduate School offers several programmes to develop the careers of young scientists. These include mobility programmes for short and long term stays in laboratories abroad and training in key competence skills such as biosafety, good scientific practice, bioethics, patent law,



project management and career workshops. There are also workshops on scientific writing and presentation skills, to mention but a few, and various social assistance programmes. For instance, the Graduate School finances the day care of children for PhD students and offers temporary housing for students coming from abroad until they are able to find suitable permanent accommodation. Mentoring is a key aspect at the Graduate School and is catered for on several levels. For example, there is a Thesis Advisory Committee specifically for each PhD student that consists of two supervisors from Ulm and one international supervisor as well as mentoring for students conducted by senior PhD students themselves, Finally, there is the comprehensive M4M mentoring programme organised by the ZAWiW (*Zentrum für Allgemeine Wissenschaftliche Weiterbildung*/Centre for General Scientific Continuing Education).

What is our next step to be? Although we have achieved so much these past four years, there are still a number of things to do. We would like to mention two of our priorities. Firstly, we wish to expand our international cooperation with other scientific institutes to establish international PhD programs. In this respect we have already made a promising start with our present partners in Padua (Italy), Oulu (Finland), Chapel Hill (USA) and Wuhan (China). Secondly, we would also like to see the establishment of a Junior Faculty where young graduates could be helped to establish their own research groups.

We hope that you enjoy reading our brochure and would like to express our thanks to Larissa Dickhaut and Julia Kutzenberger who 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

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 analyse the molecular mechanisms of the origin of diseases with the long-term goal of developing innovative diagnostic and therapeutical 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 ageing, 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 will be of immense relevance for the future.

PhD training in Molecular Medicine at Ulm University

Modern concepts in Molecular Medicine utilize interdisciplinary approaches combining 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 now 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 programme entitled *International PhD Programme in Molecular Medicine*. The major aims of this programme 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 programme 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 *Doctor rerum naturalium*. Each PhD student has an interdisciplinary Thesis Advisory Committee (TAC) consisting of scientists from Ulm University and abroad who 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 programme, the students have 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 programme *Experimental Medicine*. In order to participate in this programme, students of human medicine have to interrupt their course of studies for nine month to work full time in a laboratory. During this period the students are supported by a fellowship of the Medical Faculty of € 500 per month. Besides their lab work, the doctoral students have to visit seminars, have to prepare literature reports and have to give progress reports. It is expected that with this structured programme for MD thesis work, the quality of the medical dissertations will increase significantly. In addition, medical students are excellently prepared for a PhD training.

Proven excellence

In 2006, the *Molecular Medicine* study programmes of Ulm University have been 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 5 years. The 'Excellence Initiative' was started in 2005 to grant competitive awards to the best performing German universities – a great success for our Graduate School, the Medical Faculty and Ulm University.

Recently, our Bachelor, Master and PhD programmes have been 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 programmes we offer.

International and Interdisciplinary:
Our TAC members are from:
Aachen/Germany
Bellinzona/Switzerland
Berlin/Germany
Bonn/Germany
Chapel Hill/USA
Copenhagen/Denmark
Dijon/France
Essen/Germany
Florence/Italy
Freiburg/Germany
Galway/Ireland
Geneva/Switzerland
Giessen/Germany
Göttingen/Germany
Gosselies/Belgium
Halle/Germany
Hamburg/Germany
Hannover/Germany
Heidelberg/Germany
Karlsruhe/Germany
Konstanz/Germany
Leuven/Belgium
Ljubljana/Slovenia
London/Great Britain
Lund/Sweden
Magdeburg/Germany
Mainz/Germany
Mannheim/Germany
Munich/Germany
Newcastle/Great Britain
Oulu/Finland
Padova/Italy
Pittsburgh/USA
Regensburg/Germany
Reutlingen/Germany
Rome/Italy
Rostock/Germany
Tübingen/Germany
Würzburg/Germany
Wuhan/China

Mentoring of PhD students

Scientific mentoring

Scientific excellence depends on excellently trained young researchers. The training of such 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 self-responsibility of PhD students
- improvement of employability through training in key competences.

Each doctoral student is supervised by a Thesis Advisory Committee (TAC) consisting of three members: the group leader of the laboratory where the thesis work is performed; a scientist from another institute of Ulm University; and an external reviewer either from industry or from a research institute. The external reviewer can be a national or an international scientist. Within each TAC, scientists from different disciplines are involved to ensure interdisciplinary training and mentoring in research. The TAC supervises PhD students in their daily laboratory work to help them with formal or technical problems and evaluates oral examinations as well as the written dissertation. This multiple supervision approach supports the independence of our PhD students as young researchers.

From the beginning of their PhD studies, doctoral students are organized and trained in smaller, thematically focussed **Research Training Groups** which concentrate on specific research areas in Molecular Medicine implemented at Ulm University and defined by the externally funded cooperative research networks like Collaborative Research Centres or Clinical Research Units. One of these Research Training Groups (GRK 1041: Molecular Diabetology and Endocrinology in Medicine) gets a special fund by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG).

The Graduate School's Research Training Groups (August 2009)

Research Training Group	Coordinators	Principal Investigators	Research Objectives
Signalling Networks in Development and Degeneration	Böckers, Gierschik	Böckers, Gierschik, Kestler, Knöchel, Kühl, Lehmann-Horn, Liss, Ludolph, Nienhaus, Scharffetter-Kochanek, Rudolph, Schöning, Wirth	Understanding the principles of cellular signal reception/detection, intracellular signal transduction networks, knowing the fundamental aspects of the regulation of embryonic and postembryonic development and survival by signal transduction and genetic regulatory networks as well as epigenetic influences; knowing the molecular determinants of neural development; elucidating the mechanisms of degenerative conditions and diseases such as ageing and neuro-degeneration.
Signalling Networks in the Hematopoetic System and Oncology	Fulda, Wirth	Debatin, Döhner, Fehling, Fulda, Huber-Lang, Kestler, Kirchhoff, Rodewald Walther, Wirth	Understanding the principles of hematopoesis and immune cell function, understanding the molecular mechanisms underlying malignant transformation including regulation of apoptosis
Signalling Networks in CardioMetabolic Disorders (Funded by the DFG: GRK 1041: Molecular Diabetology and Endocrinology in Medicine)	Böhm, Spindler	Böhm, Fehling, Fischer, Lehmann-Horn, Scharffetter-Kochanek, Spindler, Walther, Wirth	Understanding molecular principles of hormone action, understanding physiology and pathobiology of diabetes including autoimmunity, β-cell loss and vascular complication
Signalling Networks in Infectious Diseases	Mertens	NN	The research objectives and profile will be defined in 2010.

The graduates are actively integrated into the international scientific community: Each year the Graduate School organizes international meetings where students give presentations or talks and seek advice for their work from professional international scientists. We also hold scientific retreats where graduates have the opportunity to exchange ideas among themselves and with senior scientists in a relaxed atmosphere. Furthermore, our PhD students have the chance to attend meetings and conferences abroad with the financial support of a travel grant from the Graduate School.

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

Boehringer Ingelheim

Multilevel 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 their study life in general. It is the first point of contact for applicants and assists them from their first acceptance into the programme, and throughout the period of their PhD studies to their final graduation. It also advises on issues concerning visas, contracts, work permits, accommodation, health insurance, etc.

M4M – *Mentorship for Molecular Medicine PhD Students* is the name of a social mentoring programme that brings together doctoral students and mature persons living in Ulm (so-called senior consultants) for mutual exchange and support. The idea of the programme is to give our international students a positive impression of everyday German culture through such social activities as excursions and themed evenings. This personal contact and individual support offers them the chance to integrate into German society more easily.

Each year the graduates elect a student to represent their interests on the different boards and committees of the Graduate School and to act as their official contact on student issues.

Last but not least, we have several student tutors who give new students advice concerning the PhD programme from a student's perspective and who assist them to become more familiar with the university and its facilities (i.e. internet access, university library etc.).

Mentorship for
Molecular Medicine
PhD Students

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 making strong efforts to develop a doctoral training programme within an international context. A central element of our internationalization strategy is the previously mentioned Spring and Fall Meetings attended by speakers of international renown. A second important element is the promotion of international cooperation in the form of exchange programmes and international PhD programmes.

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

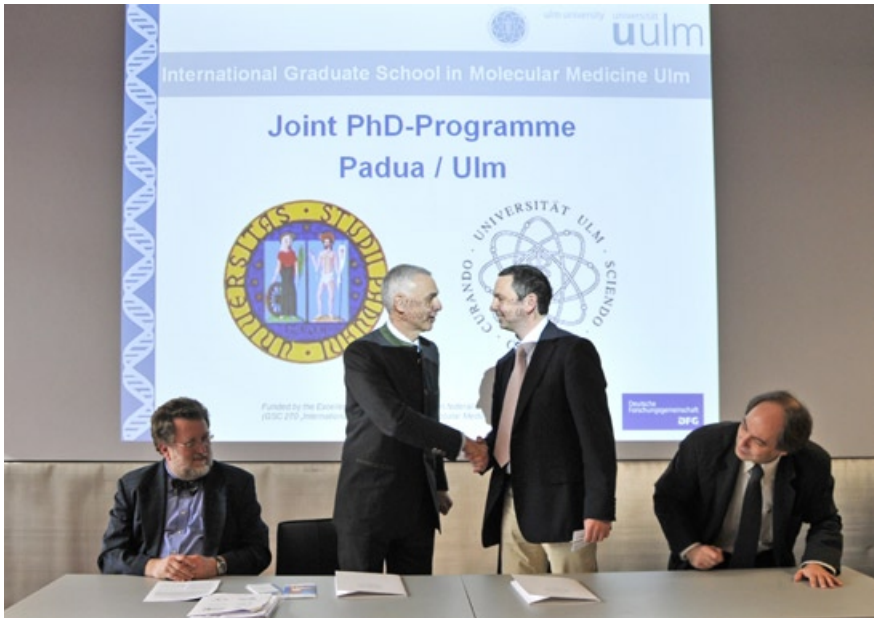
- Our most long-standing international relationship is that with the Biocenter Oulu, Finland. The Biocenter Oulu regularly invites students from the Graduate School to summer schools in Finland. Likewise, the Graduate School shares the insights of its research in Germany to Finnish graduates by inviting them to attend meetings and visit our laboratories. German and finnish students also have the possibility of participating in practical training courses at either institution.

- Each year we organize 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. In 2009, the Third Summer School on Signalling will be held at Houazhong University of Science and Technology/Tongji Medical College in Wuhan, China. A similar event took place in Timisoara, Romania in 2008 and Bejing, China in 2009.

BIOCENTER OULU

Huazhong University of Science & Technology

DEUTSCH-CHINESISCHES
Jahr der Wissenschaft und Bildung
2009/10



- A joint PhD programme with the University of Padua in Italy will be launched in the course of 2009. Doctoral students taking part in this programme will be supervised by Thesis Advisory Committees consisting of scientists from Ulm and Padua, and will spend a part of their studies at both universities.

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

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL

University of North Carolina at Chapel Hill

- The Graduate School is currently working on a new partnership with the University of North Carolina at Chapel Hill, USA. Some of the PhD students joining our programme in October 2009 will perform scientific cooperation projects between Ulm and Chapel Hill. These PhD students will spend a part of their studies at both universities.

Besides the activities of the Graduate School itself, scientists from Ulm University are involved in externally reviewed international collaborative research networks, for example, Marie Curie Research Training Networks or NIH-funded groups. In addition, extensive international contacts are regularly established with individual scientists whose works are published jointly. These contacts provide the Graduate School with the additional opportunity for doctoral student exchanges.

Additional Benefits for PhD Students

Our programme offers additional benefits for PhD students. The most frequently requested programmes include:

Mobility Programme

In order to enhance the integration of our PhD students into the international scientific community, the Graduate School offers a mobility programme awarding financial support to PhD students who wish to participate in meetings and practical training abroad. Students can obtain funding for short visits to international conferences or for long-term stays at foreign laboratories lasting up to several months.

Doctoral Student Award

To motivate doctoral students and to honour extraordinary achievements, the Doctoral Student Award is presented once a year on Graduation Day by the Graduate School. Awards are conferred for excellent 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. The award amounts to € 2,500 and is presented to the doctoral student in person. The student is free to use it for any purpose that helps to promote his/her career in the field of science.

Postdoc Fellowships

The Graduate School provides postdoctoral fellowships for a period of 3-6 months and these are intended 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 6 months. Soft skill courses also offer assistance in writing grant applications and have proved useful for those beginning a new postdoctoral career.

Child Care Programme

At present, up to 66 % 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 and doctoral students with children. For example, our child care programme provides financial support for child day care and practical help in finding the right day care centre. Re-entry fellowships are provided for doctoral students who may have had to interrupt their work due to maternity leave.

Alumni Network

The Graduate School is currently establishing an alumni network so that on our yearly alumni day, former students can be informed about the annual development of the Graduate School. These former students are invited to give talks about their careers and experiences, regarding, for example, the transition from studying at university to working in industry. Our alumni are also invited to attend science meetings and seminars organized by the Graduate School. These events bring former and current doctoral students together to promote an enthusiastic doctoral culture at the Graduate School.

What do our alumni think about the Graduate School?

Anton Lebedev, Clinic of Dermatology and Allergic Diseases

Former Student Speaker

How do you create an excellent Graduate school? Simple! Just invite the right people to the right place. As a recent alumnus, I can say that Ulm is the spot, the place to be to carry out research, to enjoy fruitful discussions and finally graduate with a PhD in your pocket. It's all about people who create a great atmosphere for learning and sharing their knowledge. And I am very proud of all my small contributions to the Graduate School's development over the years since 2005.
What now? Yes...I am very excited about joining an outstanding 'cancer' lab at the McGill University in Montreal.

Sandrine Sander, Institute of Physiological Chemistry

After finishing medical school, the PhD programme offered by the International Graduate School in Molecular Medicine Ulm gave me the possibility of becoming a basic research scientist. Through my training at the Institute of Physiological Chemistry and by attending numerous seminars, lectures, workshops etc., organized by the Graduate School, I was able to increase my knowledge in molecular biology and improve my scientific skills. Working within a multidisciplinary program was sometimes challenging but also very fascinating.
Having obtained my PhD, I now feel well prepared to pursue a career in academic science. I am still interested in the field of leukaemia and lymphoma research and have now the chance to join the Immune Disease Institute at Harvard Medical School as a postdoctoral fellow. Thus, the PhD programme in Molecular Medicine at the International Graduate School in Ulm offers a great opportunity for all enthusiastic students to achieve their goals.

Michael Retlich, Institute of Pharmacology and Toxicology

The International PhD Program in Molecular Medicine at Ulm University is timely and unique. I got hands-on research training in a collaborative and state-of-the-art scientific environment that was not just confined to my own group. My work included aspects of pharmacology, biochemistry, molecular and cell biology as well as biophysics. With generous funding from the German government, the programme includes retreats, international conferences, workshops and training courses. And there are also soft skill courses such as scientific writing, journal clubs and, of course, a community of other PhD students from all over the world. I can highly recommend this programme to anyone aiming for a PhD!

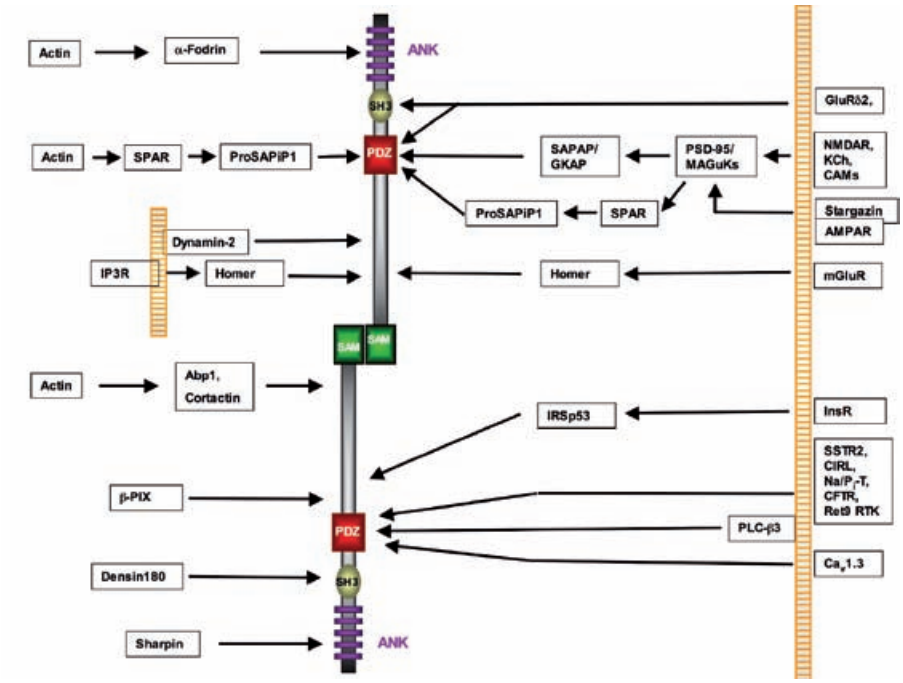
Institute of Anatomy and Cell Biology

Analysis of Synaptic Contacts: Molecular Composition and Cell Adhesion

The Team:
Head of the Institute: T. Böckers
Professor: N. Golenhofen
Group Leaders/Postdocs: B. Bartelt-Kirbach, A. Böckers, J. Bockmann, U. Fassnacht, S. Liebau, Ch. Pröpper, M. Schmeisser
PhD Students: A. Grabrucker, J. Heinrich, N. Kanwal, G. Kuh, M. Schön, T. Schmidt
Additional Members of Thesis Advisory Commitees: E. Gundelfinger (Magdeburg), A Ludolph (Ulm), U. Nienhaus (Ulm, Karlsruhe), W. Robberecht (Leuven)

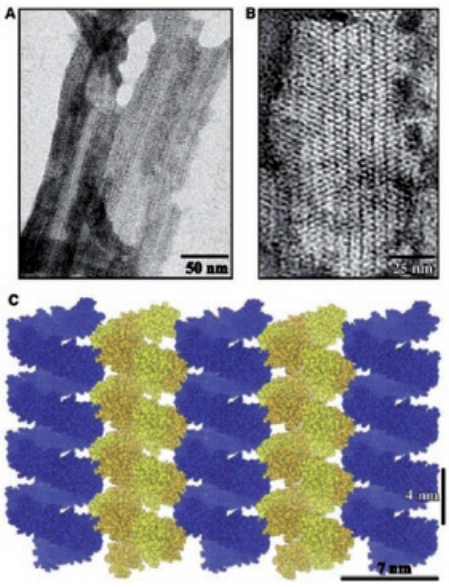
Glutamatergic synapses in the central nervous system are specific cellular junctions characterized by synaptic vesicles that are attached to the active zone of the presynapse and to an electron-dense web underneath the postsynaptic membrane known as the postsynaptic density (PSD). The pre- and postsynaptic membranes are interconnected by synaptic cell adhesion proteins (i.e. neurexin-neuroligin, cadherins) that are analysed in the laboratory (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. 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. Andreas Grabrucker's, Jutta Heinrich's and Noreen Kanwal's projects concentrate on the role of ProSAP/Shank molecules 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. In addition, we are working 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 tries to identify novel dynactin interacting proteins. A wide range of methods and models including Drosophila melanogaster and transgenic mice are employed.



ProSAP/Shank molecules are multidomain molecules that assemble via their SAM domain. They are core components of the postsynaptic density and cluster several PSD molecules directly or indirectly.

The ProSAP2 SAM domain forms a sheet of fibre-like structures attached together in a side-by-side antiparallel manner. This interaction is zinc dependent.



Selected Publications:

- *Proepper Ch, Johannsen S, Liebau St, Bockmann J, Vaida B, Kreutz MR, Gundelfinger ED, Boeckers TM (2007) Abi-1, a PSD and nuclear protein, is essential for regulated dendrite morphogenesis and synapse formation, EMBO J 7, 26, 1397-1409.*
- *Liebau St, Vaida B, Storch A, Boeckers TM (2007) Maturation of synaptic contacts in differentiating neural stem cells (NSCs), Stem Cells 25, 1720-1729.*
- *Durand CM, Betancur C, Boeckers TM, Bockmann J, Chaste P, Fauchereau F, Nygren G, Rastam M, Anckarsäter H, Sponheim E, Goubran-Botros H, Delorme R, Chabane N, Mouren-Simeoni MC, Bieth E, Rogé B, Héron D, Burglen L, Gillberg Ch, Leboyer M, Bourgeron Th (2007) Mutations of the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders, Nature Genetics 39, 25-27.*
- *Wendholt D, Spilker C, Schmitt A, Dolnik A, Smalla KH, Pröpper Ch, Bockmann J, Sobue K, Gundelfinger ED, Kreutz MR, Boeckers TM (2006) ProSAP interacting protein1 (ProSAPiP1), a novel postsynaptic density protein that links the spine associated Rap-Gap (SPAR) to the scaffolding protein ProSAP2/Shank3, J Biol Chem 12, 281, 13805-13816.*
- *Baron MK, Boeckers TM, Vaida B, Faham S, Gingery M, Sawaya M, Salyer D, Gundelfinger ED, Bowie JU (2006) An architectural framework that may lie at the core of the postsynaptic density. Science 311, 531-535.*
- *Boeckers TM, Liedtke Th, Dresbach Th, Bockmann J, Kreutz MR, Gundelfinger ED (2005) C-terminal synaptic targeting elements for postsynaptic density proteins ProSAP1/Shank2 and ProSAP2/Shank3, J Neurochem 92, 519-524.*

Institute of Applied Physiology

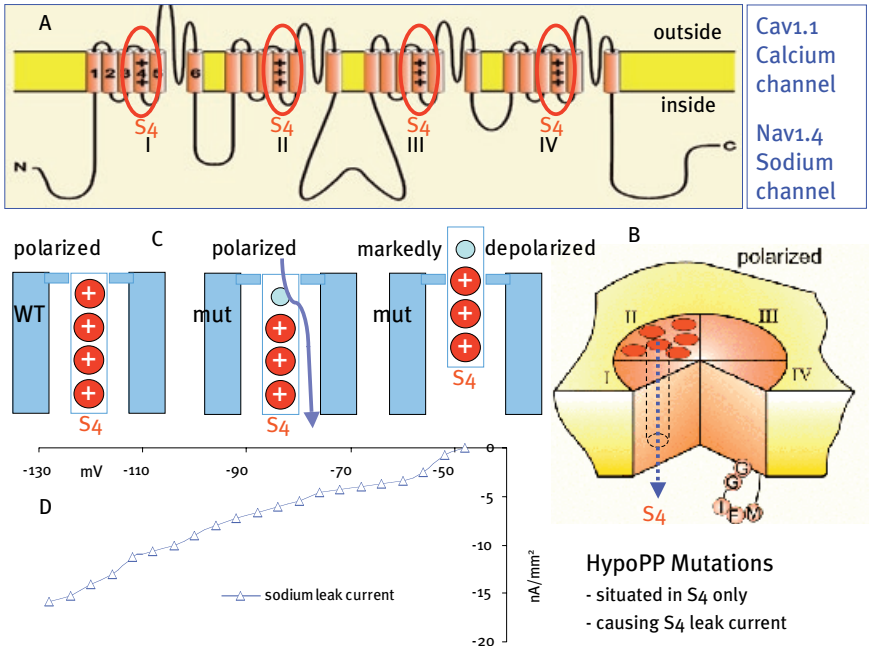
Translational Research on Channelopathies

Channelopathies are diseases caused by the dysfunction of ion channels expressed in many cell types, tissues, and organs, which thus explains the wide phenotypic diversity of their clinical manifestations. One of these, hypokalemic periodic paralysis (HypoPP), is clinically characterized by paroxysmal episodes of generalized weakness triggered by hypokalemia, and 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.

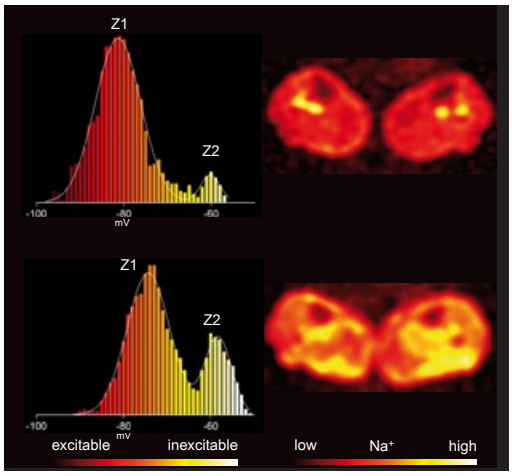
We have recently shown that patients harbouring such mutations have many myofibres with a depolarized membrane exhibiting physiological concentrations of extracellular potassium, and that most of the cells were depolarized at low levels of potassium concentration. This is in contrast to the Nernst equation which predicts membrane hyperpolarization at low potassium levels. The paradoxical depolarization of these cells is explained by a cation leak that leads to an intracellular sodium overload. These leaks reflect the flow of monovalent cations (sodium and protons) through mutation-induced crevices close to the channel voltage-sensor segments (so called S_4 segments) where the mutations are located.

The Team:
Head of the Institute: F. Lehmann-Horn
Group Leaders/Postdocs: Y. Da, X. Gao, M. Fauler, B. Holzherr, K. Jurkat-Rott, M.-A. Weber
PhD Students: C. Beyer, C. Fan, E. Nied, A. Paczulla, M. Wolf

A common diuretic drug, acetazolamide, was shown to normalize the intracellular sodium concentration of cells with mutant channels. However, the mode of action of this drug requires further study. Our results solve the paradox that small-leak mutations lead to paralytic attacks in cases of severe and potentially life-threatening



HypoPP mutations and S4 voltage sensor leak. (A) Scheme of the voltage-gated Cav1.1 calcium and Nav1.4 sodium channels containing 4 similar repeats I-IV; marked - S4 voltage sensors with residues that are replaced by HypoPP mutations. (B) Bird view scheme of a voltage-gated channel; marked: the six transmembrane segments of repeat II and particularly the S4 segment. (C) Hypothesized positions of a wildtype (WT) and mutant (mut) S4 voltage sensors relative to the channel backbone at polarized and markedly depolarized membrane potentials; in the polarized position the mutation causes a crevice that connects extracellular and intracellular spaces. (D) Sodium leak current of a mutant channel through the crevice.



Bimodal distribution of resting membrane potentials of myofibres (left) and ^{23}Na magnetic-resonance images of lower legs (right) of control (top) and a hypokalaemic periodic paralysis female (bottom). Her permanent muscle weakness is based on many depolarized=inexcitable myofibres caused by a membrane channel leak that leads to an intracellular Na^+ overload which is not compensated by Na-pump.

hypokalemia while larger leaks can cause permanent muscle weakness in cases of merely mild hypokalemia. Our results show that even a small membrane leak can markedly increase the relative frequency of depolarized (i.e paralyzed) cells despite the membrane potential of the polarized fibres being only slightly diminished. Similar leaks, such as those resulting from S4 mutations, can be caused by ionophores like gramicidin and amphotericin B as well as by mutations in other transporter proteins.

Selected Publications:

- *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, Fauler M, Lehmann-Horn F, Lerche H (2008) GLUT1 mutations are a cause of paroxysmal exertion-induced dyskinesias and induce haemolytic anaemia by a cation leak, J Clin Invest 118, 2157-68.*
- *Jurkat-Rott K, Lehmann-Horn F (2007) Do hyperpolarization-induced proton currents contribute to the pathogenesis of hypokalemic periodic paralysis, a voltage sensor channelopathy? J Gen Physiol. 130, 1-5.*
- *Jurkat-Rott K, Lehmann-Horn F (2005) Muscle channelopathies and critical points in functional and genetic studies, J Clin Invest. 115, 2000-9.*
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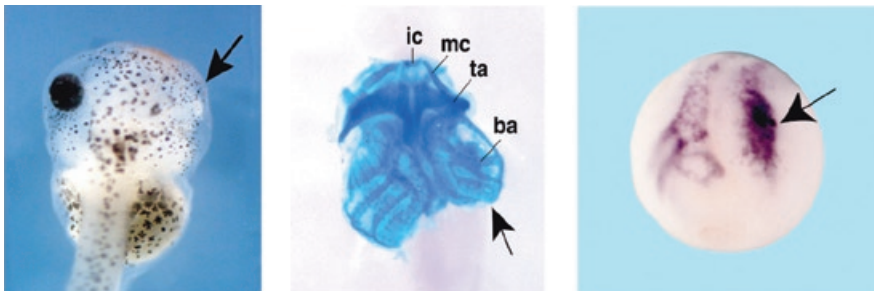
Institute of Biochemistry and Molecular Biology

Signalling Processes During Early Embryonic Development

Wnt proteins are glycoproteins that activate different intracellular signalling pathways which are interwoven to form a signalling network. The canonical Wnt pathway is characterized by the stabilization of cytoplasmic β-catenin whereas non-canonical Wnt pathways are independent of β-catenin. Wnt proteins have important functions during embryonic development and regeneration. Misregulation of Wnt signalling can lead to certain diseases including cancer. Our group characterizes intracellular Wnt signalling pathways and analyzes their role during embryogenesis in *Xenopus laevis, Drosophila melanogaster* and mice, which includes the use of murine embryonic stem cells.

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 certain Wnt signalling activities are required for vertebrate

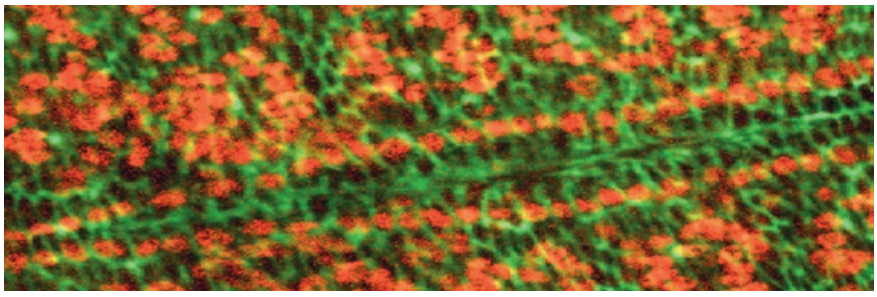
The Team:
Head of the Institute: M. Kühl
Group Leaders/Postdocs: K. Bundschu, S. Gessert, P. Pandur, I.O. Sirbu
PhD Students: V. Bugner, A. Erle, F. Herrmann, B. Kracher, T. Mann, Z. Mirzojan, T. P. Rao, S. Tao, A. Tecza, I. Tuduce
Additional Members of Thesis Advisory Committees: L. Bally-Cuif (GSF, München), E. Bellefroid (Gosselies), T. Böckers (Ulm), S. Britsch (Ulm), H.-J. Fehling (Ulm) T. Hollemann (Halle), H. Kestler (Ulm), E. Pera (Lund), V. Taylor (Freiburg), S. Vainio (Oulu), D. Wedlich (Karlsruhe)



Pescadillo is required for anterior neural development. The unilateral loss of pescadillo function leads to failure in eye development (left), defects in cartilage development (middle, ic: infrarostral cartilage, mc: Meckel's cariladge, ta: tectum anterius, ba: brabchial arches) and defects in neural crest cell migration (right). Neural crest cells are labelled by the marker gene FoxD3.

cardiac development. In *Xenopus*, we have characterized for the first time the transcription factor Islet-1. We are currently extending these analyses using *Drosophila melanogaster* as a model system (PhD project Tabea Mann). In this model, we are also analyzing the transcription factors of the Iroquois family (PhD project Zhasmine Mirzoyan). Furthermore, retinoic acid signalling and its cross talk with Wnt signalling seems to be an important factor during cardiac and neural development. Within this context, our analysis includes the function of novel non-canonical Wnt signalling components and potential target genes during murine cardiac development (PhD project Tata Rao).

During neural development non-canonical Wnt signalling pathways regulate the expression of selected targeted genes. One of these target genes is Pescadillo, which regulates eye development and neural crest cell migration. Within this context we are currently investigating the molecular mechanisms underlying Pescadillo function (PhD work Verena Bugner). Retinoic acid signalling and non-canonical Wnt signalling are also important for neural tube closure defects (PhD work Ioana Tuduce) that can lead to developmental neural malformations. Targets of non-canonical Wnt signalling are also investigated during pronephros development (PhD project Aleksandra Tecza).



A dorsal view of a Drosophila melanogaster embryo at stage 15/16 stained for Dmef2 (red) and Discs large (green). Dmef2 labels the two rows of myocardial cells of the dorsal vessel. In addition, Dmef2 labels the segmentally arranged somatic muscle cells.

The molecular design of the Wnt signalling network is finally analyzed by modelling Wnt signalling and 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 by the use of computer-based simulations that can either be verified or falsified by experimental means in cell based assays.

Selected Publications:

- *Gessert S, Maurus D, Brade T, Pandur P, Kühl M (2008) DM-GRASP/ALCAM/CD166 is required for cardiac morphogenesis and maintenance of cardiac identity in first heart field derived cells, Dev. Biol. 321, 150-161.*
- *Gessert S, Maurus D, Rössner A, Kühl M (2007) Pescadillo is required for Xenopus laevis eye and neural crest development, Dev. Biol. 310, 99-112.*
- *Brade T, Gessert S, Kühl M, Pandur P (2007) Islet-1 is required for cardiovascular development in Xenopus laevis, Dev. Biol. 311, 297-310.*
- *Maurus D, Heligon C, Bürger-Schwärzler A, Brändli A, Kühl M (2005) Noncanonical Wnt-4 signaling and EAF2 are required for eye development in Xenopus laevis, EMBO J. 24, 1181-1181.*
- *Pandur P, Läsche M, Eisenberg L, Kühl M (2002) Wnt-11 stimulation of a non-canonical Wnt-pathway is required for cardiogenesis, Nature 418, 636-641.*
- *Kühl M, Sheldahl L, Malbon CC, Moon RT (2000) Calmodulin-dependent kinase II is stimulated by Wnt and Frizzled homologs and promotes ventral cell fates in Xenopus, J. Biol. Chem. 275, 12701-12711.*

The Team:
Head of the Institute: G. U. Nienhaus*
Group Leaders/Postdocs: K. Clauss, C. Röcker, K. Tron

*Prof. Nienhaus left Ulm University in 2009 and now holds the chair at the Institute of Applied Physics of the University of Karlsruhe.

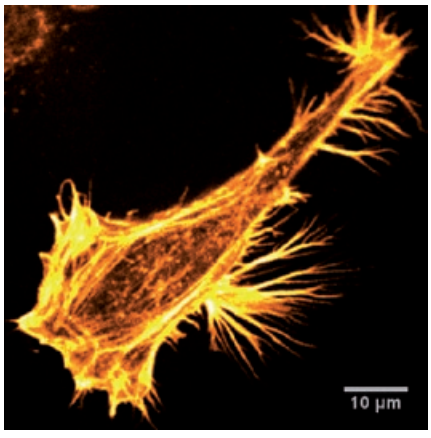
Institute of Biophysics

Advanced Optical Imaging of Biomolecular Function

The complex processes occurring within the living cell are governed by the structures, dynamics and interactions of a huge number of biological macromolecules. For many years, detailed insights into the molecular machinery of the cell could only be gained by in vitro biochemical and biophysical studies. With the advent of powerful microscopy techniques in recent years, the elucidation of biomolecular interactions within the environment of the living cell has taken centre stage.

Our institute is actively involved in the development of high-performance fluorescence imaging tools with extremely high spatial resolution (optical nanoscopy) and sensitivity (single-molecule detection). We have set up a variety of advanced microscopes based on total internal reflection fluorescence (TIRF), confocal, multi-photon, and 4Pi detection schemes. Subdiffraction imaging with single-molecule localization (PALM etc.) has also been established. A spinning-disk confocal microscope designed for imaging fast processes has been developed that is particularly well suited for studying biomolecular localization, transport or interaction within living cells.

Functional fluorescence imaging relies on the availability of strong fluorescent markers that can be specifically attached to the molecules of interest. To this end, novel fluorescent proteins are being developed and characterized with biochemical and biophysical techniques. In addition to this, nanoparticles are also synthesized, characterized and used as bright fluorophores. These techniques are utilized in a variety of biomedical applications with the emphasis on particle, vesicle, and protein transport within living cells.



Spinning-disk confocal image of the actin skeleton of a HeLa cell stained with rhodamine phalloidin.

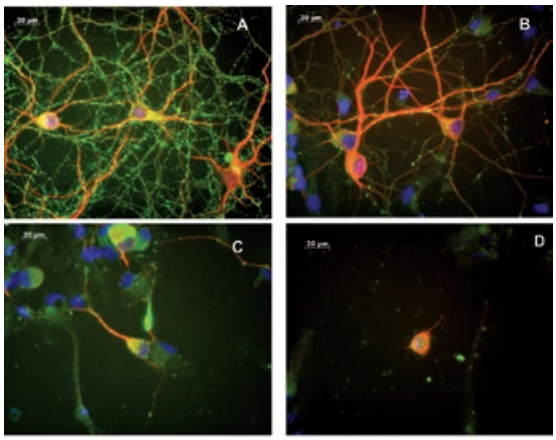
Selected Publications:

- *Ivanchenko S, Glaschick S, Röcker C, Oswald F, Wiedenmann J, Nienhaus GU (2007) Two-photon Excitation and Photoconversion of EosFP in Dual-color 4Pi Confocal Microscopy, Biophys. J. 92, 4451-4457.*
- *Nienhaus K, Nienhaus GU, Wiedenmann J, Nar H (2005) Structural Basis for Photo-Induced Protein Cleavage and Green-to-Red Conversion of Fluorescent Protein EosFP, Proc. Natl. Acad. Sci. USA 102, 9156-9159.*
- *Kuzmenkina EV., Heyes CD, Nienhaus GU (2005) Single Molecule FRET Study of Protein Dynamics under Denaturing Conditions, Proc. Natl. Acad. Sci. USA 102, 15471-15476.*
- *Wiedenmann J, Ivanchenko S, Oswald F, Schmitt F, Röcker C, Salih A, Spindler K-D, Nienhaus GU (2004) EosFP, a Fluorescent Marker Protein with UV-Inducible Green-to-Red Fluorescence Conversion, Proc. Natl. Acad. Sci. USA 101, 15905-15910.*
- *Wiedenmann J, Schenk A, Röcker C, Girod A, Spindler K-D, Nienhaus GU (2002) A Far-Red Fluorescent Protein with Fast Maturation and Reduced Oligomerization Tendency from Entacmaea quadricolor (Anthozoa, Actinaria), Proc. Natl. Acad. Sci. USA 99, 11646-11651.*
- *Ostermann A, Waschipky R, Parak FG, Nienhaus GU (2000) Ligand Binding and Conformational Motions in Myoglobin, Nature 404, 205-208.*

The Team:
Head of the Clinic: J. Fegert
Group Leaders/Postdocs: A. Ludolph, U. Schaz; **PhD Student:** P. Udvardi

Clinic of Child and Adolescent Psychiatry/Psychotherapy

Cell Biological Effects of Psychotropic Substances in Maturing Neuronal Systems



Hippocampal neuronal cell cultures, DIV 8, MAP2 as a neuron marker und Bassoon as a marker for synapses:
A. controls; B – D: cell cultures treated with fluoxetine for 72h. B. 10 µM; C. 20 µM; D. 50 µM

With increasing frequency, psychotropic medications are being prescribed to young children. Paediatric psychopharmacology can only be properly understood within the context of developmental neurobiology. In a joint venture between the Clinic of Child and Adolescent Psychiatry and the Institute of Anatomy and Cell Biology, we are conducting *in vitro* studies on neuronal cell cultures and *in vivo* studies on rodents (also in collaboration with the Department of Neurobiology, Ulm University) to assess the potential impact of psychotropic substances on cell development. Among the most frequently used substances are: methylphenidate, a psychostimulant and dopamine transporter inhibitor; atomoxetine, a selective norepinephrine transporter inhibitor, (both of these 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 transporter molecules, all three substances seem to have an impact on cell cycle and apoptotic processes. Our working group was able to detect neuroprotective effects of methylphenidate. Fluoxetine and atomoxetine exerted a dose-dependent effect on cell viability. Higher concentrations caused a reduction of neuronal arborisation and synaptic density. In collaboration with the Department of Anaesthesiology, we were able to show that atomoxetine inhibits the NMDA-receptor, a mechanism that influences apoptosis in the developing brain. We are currently investigating a possible age-dependency of the effects of these substances on the expression of various membrane proteins (PhD work Patrick Udvardi).

Selected Publications:

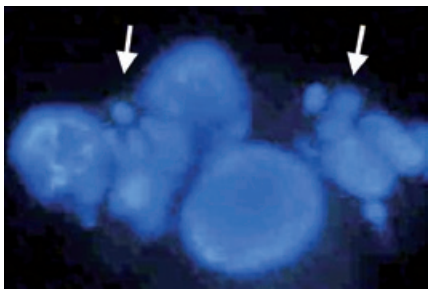
- *Ludolph AG, Kassubek J, Schmeck K, Glaser C, Wunderlich A, Buck AK, Reske SN, Fegert JM, Mottaghy FM (2008) Dopaminergic dysfunction in attention deficit hyperactivity disorder (ADHD), differences between pharmacologically treated and never treated young adults: A > 3,4-dihdroxy-6-[18F]fluorophenyl-L-alanine PET study, NeuroImage 41, 718-727.*
- *Ludolph AG, Böckers TM, Fegert JM, Schulze A, Schaz U (2007) Fluoxetine, paroxetine and atomoxetine show differential apoptotic and antiapoptotic effects in neuronal cells (abstract), Journal of Child and Adolescent Psychopharmacology 17, 883-884.*
- *Ludolph AG, Schaz U, Storch A, Liebau S, Fegert JM, Böckers TM (2006) No neurotoxic but neuroprotective effects of Methylphenidate in primary mesencephalic cultures, J Neural Transm 113, 1927-34.*

University Children's Hospital

Work Group 'Deregulation of Apoptosis in Human Diseases'

Head: Simone Fulda

The overall goal is to decipher apoptosis programmes in normal and malignant cells in order to transfer basic knowledge on apoptosis signalling into medical application, i.e. the development of new diagnostic and therapeutic tools for diseases, particularly in cancer and leukaemia.



Hallmarks of apoptosis: nuclear condensation, DNA fragmentation and formation of apoptotic bodies.

Apoptosis or programmed cell death is the cell's intrinsic death programme that plays an important role in various physiological and pathological situations and is highly conserved throughout evolution. Tissue homeostasis in the human body is maintained by a subtle balance between proliferation on the one hand and cell death on the other. As a consequence, too little apoptosis can contribute to tumour formation. In addition, defects in apoptosis programmes may confer resistance to cytotoxic therapies since the reaction of cancer cells to current treatment approaches is largely due to their ability to undergo cell death in response to cytotoxic stimuli. Thus, further insight into the regulation of apoptosis pathways in human cancers and in cancer therapy will provide a molecular basis for the design of new diagnostic and therapeutic strategies for the treatment of human cancers.

The Team:
Head of the Clinic: K.M. Debatin
Professors: C. Beltinger, S. Fulda, G. Lahr
Group Leader/Postdoc: G. Strauss
PhD Students: A. Bangert, A. Bender, N. Hartmann, C. Jennewein, S. Karl, I. Mader, K. Man, I. Naumann, S. Saxena, D. Stadel, T. Unterkircher, K. Vellanki, L. Wagner
Additional Members of Thesis Advisory Committees: P. Agostinis (Leuven), B. Baumann (Ulm), A. Bürkle (Konstanz), C. Classen (Rostock), C. Friesen (Ulm), I. Jeremias (Neuherberg), P. Lovat (Newcastle), O. Micheau (Dijon), T. Seufferlein (Halle), S. Stilgenbauer (Ulm), M. Wabitsch (Ulm), L. Wiesmüller (Ulm), R. Zwacka (Galway)

Objectives are:

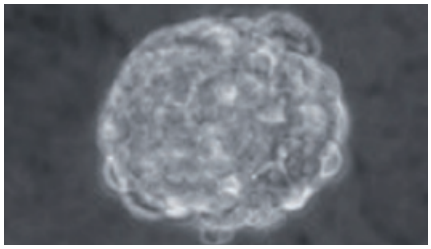
(i) To identify key apoptosis regulators in normal and malignant cells.

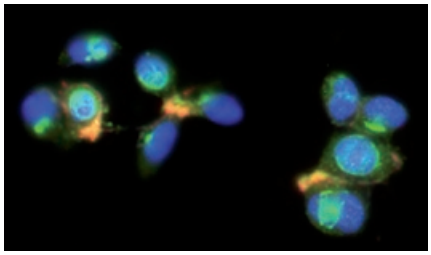
(ii) To evaluate apoptosis regulators as diagnostic tools for individualized treatment.

(iii) To develop new molecular therapeutics targeting deregulated apoptosis pathways for anti-tumour treatment. Solid tumours as well as leukaemias are studied using animal models of cancer, tumour cell lines and primary patient samples. The perspective is to implement functional assays into clinical monitoring of patients, treatment response and outcome within multicentre clinical trials in oncology as well as to develop novel experimental therapeutics.

Work Group 'Genesis and Targeted Therapy of Paediatric Neuroectodermal Tumours'

Head: Christian Beltinger





Tumour-initiating cells of Ewing Sarcoma: Growth as spheres, neuronal (green) and glial (orange) differentiation capacity.

Our aim is to delineate the cellular and molecular genesis of paediatric neuroectodermal tumours, in particular neuroblastoma, brain tumours and Ewing sarcoma, and to develop novel therapies targeting these and other entities. The perspective is to transfer the results into collaborative clinical trials to improve the stratification and therapy of children with such tumours.

Stem and progenitor cells are the potential cells of origin for embryonic paediatric tumours. Molecular circuits crucial for embryonic and adult stem cells support these cells. Dysregulation of the circuits contribute to the genesis and aggressiveness of the tumours and their stem or tumour-initiating cells, which may dictate the fate of the tumours. Eradicating tumour-initiating cells and their progeny by novel therapies targeting stemness-associated molecular circuits promises to improve the outcome of children with neuroectodermal and other tumours.

Objectives:

- To identity stem, progenitor and mature cells as the cells of origin for pediatric neuroectodermal tumours
- To identify the role of stemness-associated molecular circuits in these malignancies
- To identify the cancer stem cell of these cancers
- To evaluate the prognostic relevance of stemness-associated genes and cancer stem cells in these tumours, and to implement these findings into multi-centre paediatric oncology trials
- To develop novel molecular and cellular approaches to target stemness-associated circuits and cancer stem cells in these and other entities, and to implement them into multi-centre paediatric oncology trials

Selected Publications:

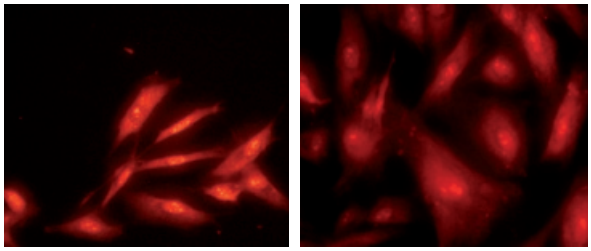
- *Fakler M, Loeder S, Vogler M, Schneider K, Jeremias I, Debatin KM, Fulda S (2009) Small molecule XIAP inhibitors cooperate with TRAIL to induce apoptosis in childhood acute leukemia cells and overcome Bcl-2-mediated resistance, Blood 113, 1710-22.*
- *Opel D, Westhoff MA, Bender A, Braun V, Debatin KM, Fulda S (2008) Phosphatidylinositol 3-kinase inhibition broadly sensitizes glioblastoma cells to death receptor- and drug-induced apoptosis, Cancer Res. 68, 6271-80.*
- *Ushmorov A, Hogarty MD, Liu X, Knauß H, Debatin KM, Beltinger C (2008) N-myc-augments death and attenuates protective effects of Bcl-2 in trophically stressed neuroblastoma cells, Oncogene 27, 3424-3434.*
- *Meyer LH, Karawajew L, Schrappe M, Ludwig WD, Debatin KM, Stahnke K (2006) Cytochrome c-related caspase-3 activation determines treatment response and relapse in childhood precursor B-cell ALL, Blood 107, 4524-31.*
- *Wei J, Blum S, Unger S, Lamparter M, Jarmy G, Geishauser A, Chan G, Fischer KD, Rattat D, Debatin KM, Beltinger C (2004) Embryonic endothelial progenitor cells armed with a suicide gene target hypoxic lung metastases after intravenous delivery, Cancer Cell 5, 477-488.*
- *Fulda S, Wick W, Weller M, Debatin KM (2002) Smac agonists sensitize for Apo2L/TRAIL- or anticancer drug-induced apoptosis and induce regression of malignant glioma in vivo, Nat Med 8, 808-815.*

Clinic of Dermatology and Allergic Diseases

Work Group 'Ageing – Mechanisms and Novel Preventive Strategies'

Head: Karin Scharffetter-Kochanek

Life expectancy has risen continuously in developed societies and yet the mystery of ageing has still not been resolved. As a consequence, the prevalence of infectious, autoimmune, endocrine, mental diseases and connective tissue degeneration such as osteoporosis, arthrosis, skin atrophy, impaired wound healing, and arteriosclerosis has sharply increased. To prevent this trend, we intend to identify ways to promote successful healthy ageing. The overall hypothesis we are testing is whether oxidative stress and/or DNA damage pathways of different evolutionary conserved gerontogenes are of general relevance to the intrinsic and extrinsic ageing of the immune system, the central nervous system and the connective tissue. Therefore we have generated a connective tissue specific SOD2-deficient mouse model. These mice reveal a



Enhanced ROS levels in old versus young fibroblasts.
Senescent human dermal fibroblasts spontaneously generate high levels of reactive oxygen species compared to young fibroblasts as detected in the intensity differences between Dihydroethidium ROS-dependent oxidation and a fluorescent product.

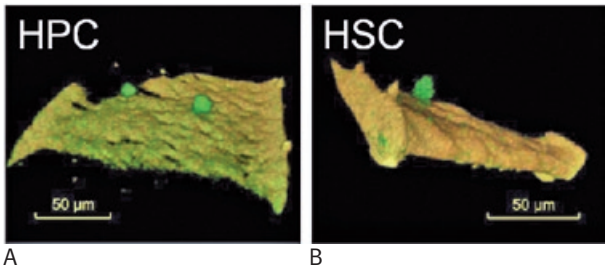
The Team:
Head of the Clinic:
K. Scharffetter-Kochanek
Professors: H. Geiger, J. M. Weiss
Labmanager: M. Wlaschek
Group Leaders/Postdocs: A. Basu, M. C. Florian, D. Frenzel, S. Iben, A. Lebedev, P. Maity, S. Mamidi, T. Peters, C. Pfeiffer, A. Sindrilaru, N. Treiber, V. Vas
PhD Students: F. Ferchiu, Y. Qi, A. Schlecht, Kamayani Singh, Karmveer Singh, B. Überle

complex ageing phenotype. Interestingly, the SOD2 gene has been identified as a major gerontogene in lower organisms while distinct polymorphisms in humans are related to longevity. We now intend to elucidate the underlying signalling pathways to develop novel targeting strategies. We are interested in determining whether changes in concentrations of superoxide anions or hydrogen peroxide may have an impact on signalling pathways involved in the organisation of the extracellular matrix, organ maintenance, metabolic homeostasis and the renewal capacities of haematopoietic stem cells (PhD project Karmveer Singh). While the DNA damage response pathway (DDR) resulting in cellular senescence will be addressed in more detail in dermal fibroblasts (PhD project Florentina Ferchiu), the information on DDR in mesenchymal stem cell ageing is virtually nonexistent. This information, however, would be highly valuable since mesenchymal stem cells contribute to regeneration, repair and tissue homeostasis (PhD project Yu Qi).

Work Group 'Haematopoiesis and Haematopoietic Stem Cells'

Head: Hartmut Geiger

Haematopoiesis is the process by which mature blood cells are formed from haematopoietic stem cells (HSCs). Abnormal haematopoiesis and stem cell regulation are associated with a wide spectrum of diseases ranging from anaemia to cancer. Research in our laboratory is mostly centred on stem cell ageing, leukaemia and DNA damage responses. In mice and humans there is a successive functional 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 haematopoiesis and to differentiate into red blood cells and lymphoid cells. The mechanisms of HSC ageing have remained largely unexplored.



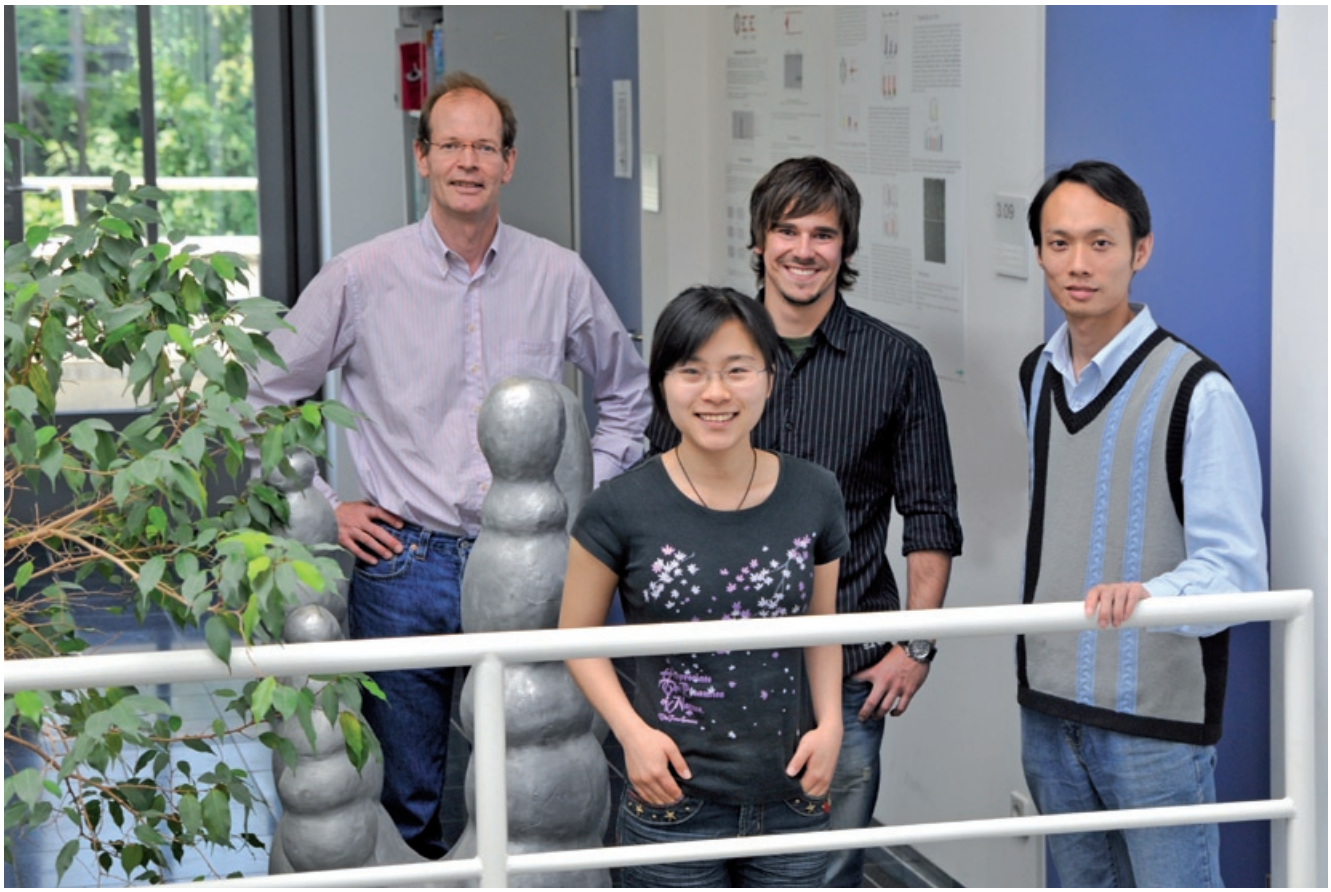
A B

CFSE-labeled HPCs (Lin-, Sca-1-, c-Kit+; L-S-K+) or HSCs (Lin-, Sca-1+, c-Kit+; L-S+K+) were transplanted in recipient animals. The tibia of recipient animals were analyzed between 16 to 40 hours post transplant by intravital time-lapse 2 photon microscopy to monitor CFSE-labelled green (A) L-S-K+ cells and (B) L-S+K+ cells close to the endosteal region (brown signal, autofluorescence) of the bone.

Our data supports the view that the elevated activity of Cdc42 found in haematopoietic cells in aged animals results in altered adhesion to stroma cells. This is further supported by data indicating that Cdc42 is central for regulating adhesion of HSCs to the niche. In collaboration with the laboratory of Prof. Dr. Gunzer in Magdeburg, we were recently able to demonstrate that aged stem cells are indeed more active inside the bone marrow niche in vivo, which most likely results in less stable stem cell stroma interactions. We can therefore assume that altered adhesion to the niche/stroma is at least one underlying cause for phenotypes associated with aged HSCs.

Selected Publications:

- *Lebedev A, Scharffetter-Kochanek K, Iben S (2009) A novel activity enhances promoter escape of RNA polymerase I, Biochem Biophys 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 Vav3-/- mice due to impaired β2-integrin dependent macrophage functions, Blood 113, 5266-5276.*
- *Lebedev A, Scharffetter-Kochanek K, Iben S (2008) Truncated Cockayne syndrome B protein represses elongation by RNA polymerase I, J Mol Biol. 382, 266-74.*
- *Wang H, Peters T, Sindrilaru A, Kess D, Oreshkova T, Yu X-Z, Seier AM, Schreiber H, Wlaschek M, Blakytny R, Röhrbein J, Schulz G, Weiss JM, Scharffetter-Kochanek K (2008) TGF-β-dependent suppressive function of regulatory T-cells requires CD18 wild-type levels in a psoriasis murine model, J Clin Invest. 118, 2629-2639.*
- *Yang L, Wang L, Geiger H, Cancelas JA, Mo J, Zheng Y (2007) Rho GTPase Cdc42 coordinates haematopoietic stem cell quiescence and niche interaction in the bone marrow, Proc Natl Acad Sci USA 104, 5091-5096.*
- *Geiger H, Van Zant G (2002) The ageing of lympho-haematopoietic stem cells, Nat Immunol. 3, 329-333.*



Division of Gene Therapy

Viral Vectors for Therapeutical Approaches

We are working on the development of new therapeutic procedures for diseases, for which there is currently no treatment. We use and develop techniques of viral and non-viral gene transfer to introduce genes into cells *in vitro* and *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. Our scientific focus is on the enhancement and further development of gene transfer vectors and to use them for selected inborn or acquired disorders and new vaccine strategies.

The Team:
Head of Division: S. Kochanek
Group Leaders/Postdocs:
S. Espenlaub, B. Huang, F. Kreppel, J. Laakkonen, T. Lukas
PhD Students: X. Dong, M. Kron, S. Zong
Additional Members of Thesis Advisory Committees: H. Bujard (Heidelberg), P. Clemens (Pittsburgh), A. Ludolph (Ulm), D. Pinschewer (Geneva), H. Reimann (Ulm), R. Schirmbeck (Ulm)

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 virology and molecular

biology point of view. Several projects in our laboratory thus relate either to the improvement of adenovirus vectors or to their use in different genetic and non-genetic diseases.

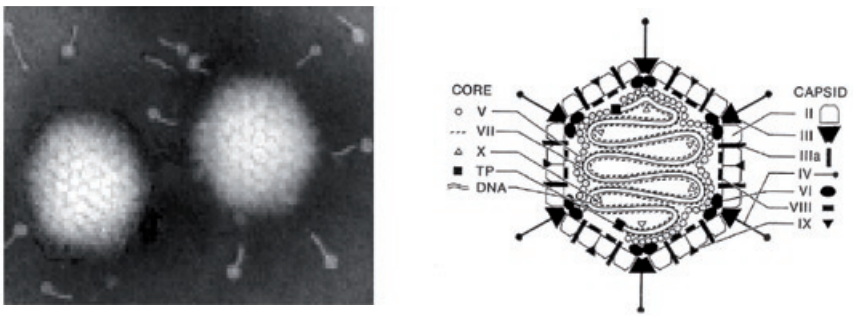
Vectors for Genetic Vaccination

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 responses, when the antigen is expressed following gene transfer, is completely understood. In the past we have seen that the immunogenicity of adenovirus vectors limits the multispecificity of T-cell responses against vector-encoded antigens. Such studies could lead to an improved vector design through an enhanced understanding of the basic principles of immune response induction.

Matthias Kron (PhD project), using adenovirus- and plasmid-based delivery systems, is investigating whether gene transfer-mediated expression of a recombinant antigen in non-immune tissue influences qualitative and quantitative profiles and kinetics of immune responses. Another project (PhD project Shan Zong) is directed at the generation of a genetic vaccine against malaria by also using an adenovirus vector.

Vectors for Functional Studies

Besides their use in 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



Adenovirus particles: EM and scheme.

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.

Selected publications:

- *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.*
- *Huang B, Schiefer J, Sass C, Landwehrmeyer GB, Kosinski CM, Kochanek S (2007) High-capacity adenoviral vector-mediated reduction of huntingtin aggregate load in vitro and in vivo, Hum Gene Ther 18, 303-11.*
- *Chuah MK, Schiedner G, Thorrez L, Brown B, Johnston M, Gillijns V, Hertel S, Van Rooijen N, Lillicrap D, Collen D, VandenDriessche T, Kochanek S (2003) Therapeutic factor VIII levels and negligible toxicity in mouse and dog models of haemophilia A following gene therapy with high-capacity adenoviral vectors, Blood 101, 1734-43.*
- *Semkova I, Kreppel F, Welsandt G, Luther T, Kozlowski J, Janicki H, Kochanek S, Schraermeyer U (2002) Autologous transplantation of genetically modified iris pigment epithelial cells: a promising concept for the treatment of age-related macular degeneration and other disorders of the eye, Proc Natl Acad Sci USA 99, 13090-5.*

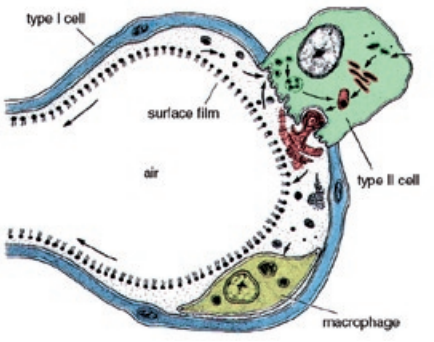
Institute of General Physiology

Work Group ‘Cellular 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 life cell imaging techniques.

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, signalling and trafficking, and at understanding basic pathogenic mechanisms of pulmonary disease.



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

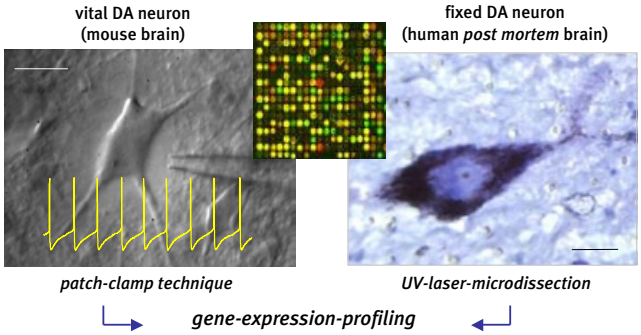
The Team:
Head of the Institute: P. Dietl
Professor: B. Liss
Postdocs: E. Dragicevic, E. Felder, P. Miklavc, O. Wittekindt
PhD Students: G. Fois, Y. Meifang, F. Schlaudraff, S. Usmani, X. Zheng

Work Group 'Molecular Neurophysiology'

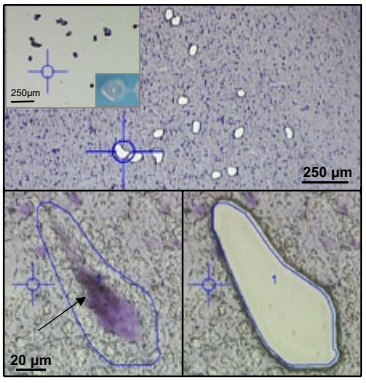
Head: Birgit Liss

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

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



Schematic overview for analyzing electrophysiological function and gene expression of individual dopaminergic (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

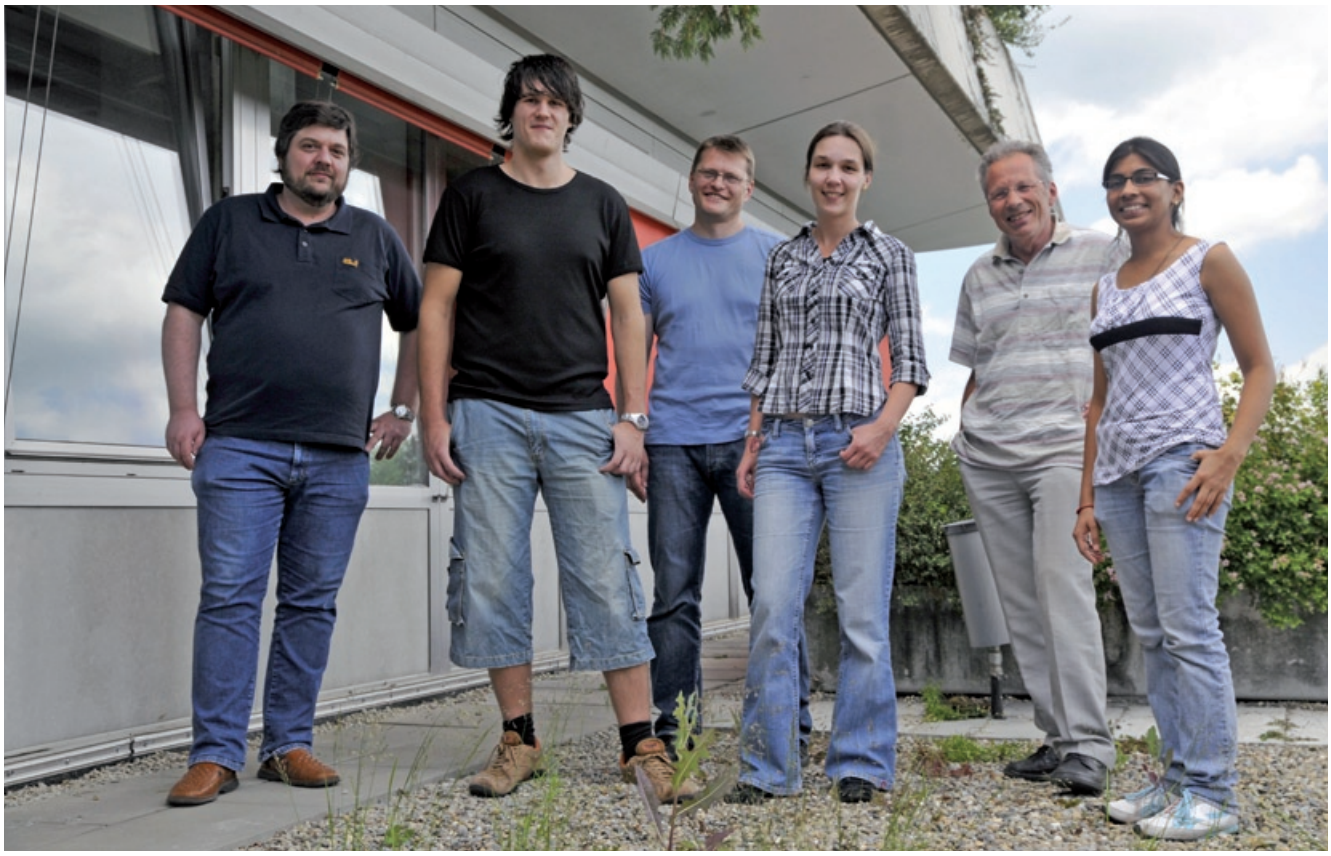


UV-LMD enables contact-free isolation of individual DA neurons from human *post mortem* brains for subsequent gene-expression analysis. Upper panel: 15 individual DA neurons were isolated via UV-LMD from a fixed human midbrain section. Insert: cap-control of collected cells. Lower panels: One individual neuromelanin-containing (arrow) DA neuron before (left) and after UV-LMD (right).

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, as their cell-specific activity directly defines neuronal activity in health and disease states.

Selected Publications:

- *Miklavc P, Albrecht S, Wittekindt OH, Schullian P, Haller T, Dietl P (2009) Existence of exocytotic hemifusion intermediates with a life time up to seconds in type II pneumocytes. Biochem.J, in press, doi:10.1042/BJ20091094.*
- *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. N.Y.Acad.Sci. 1152, 43-52.*
- *Liss B, Roeper J (2008) Indivdual dopamine midbrain neurons: Functional diversity and flexibility in health and disease. Brain Research Reviews 58, 314-321.*
- *Gründemann J, Schlaudraff F, Haeckel O, Liss B (2008) Elevated alpha-synuclein mRNA levels in individual UV-lasermicrodissected dopaminergic substantia nigra neurons in idiopathic Parkinson disease, Nucleic Acids Research 36, e38.*
- *Liss B, Haeckel O, Wildmann J, Miki T, Seino S, Roeper J (2005) K-ATP channels promote the differential degeneration of dopaminergic midbrain neurons, Nature Neuroscience 8, 1272-51.*



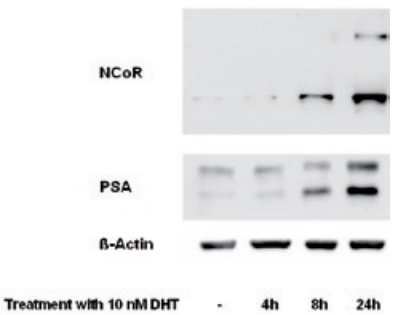
Institute of General Zoology and Endocrinology

Regulation of Androgen Receptor Corepressors

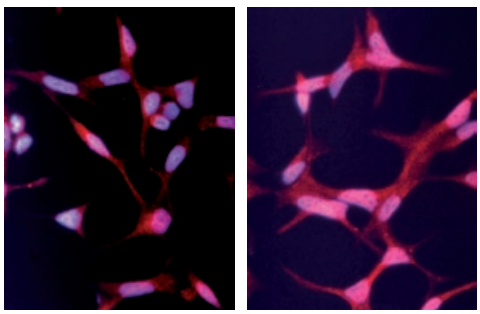
Prostate cancer (PCa) is the most common cancer diagnosed in elderly men in western countries. The development and progression of PCa is initially androgen-dependent but hormone refractory tumours frequently occur after hormone ablation therapy. This may result from the dysregulation of androgen receptor cofactors interacting with the receptor that regulates its transcriptional activity.

The Team:
Head of the Institute: K.-D. Spindler
Group Leaders/Postdocs: M. Cronauer, A. Hessenauer, R. B. Marienfeld*
PhD Students: G. Jain, M. Laschak

* Member of the Institute of Physiological Chemistry



Upregulation of NCoR-protein by androgen treatment (DHT) in LNCaP prostate cancer cells. PSA = prostate



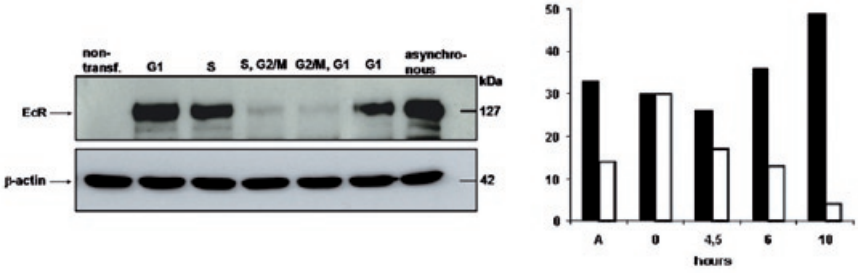
NCoR localization is not influenced by androgen treatment. Immunostaining of NCoR in DHT-treated (right) and untreated (left) LNCaP prostate cancer cells.

The interaction between nuclear receptors and cofactors effects posttranslational modifications most commonly by phosphorylation. Protein kinase CK2 is a serine/threonine kinase which is elevated in various tumours and is a prognostic marker for prostate carcinoma. The nuclear receptor corepressor (NCoR), which inhibits the transcriptional activity of the AR, contains several CK2 phosphorylation sites. We are interested in the phosphorylation of NCoR, its influence on the regulation of NCoR- and androgen receptor-function, and its relevance for prostate cancer progression.

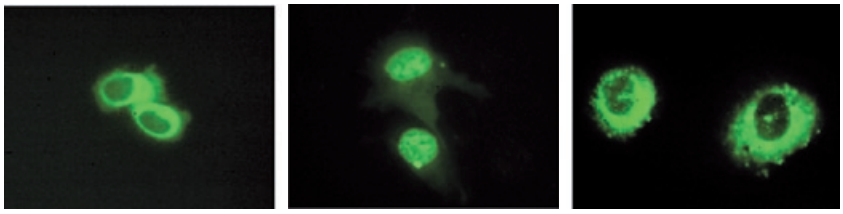
Regulation of Nuclear Receptor Activity by Modulation of the Receptor Concentration

Cooperation project with the Institute of Physiological Chemistry

Transcriptional activity of nuclear receptors is mainly determined by: receptor concentration; intracellular localization; interaction with ligand; proteins; and hormone response element. Our work will focus on posttranscriptional modifications of the human androgen receptor and the Drosophila ecdysteroid receptor (phosphorylation, ubiquitinylation, sumoylation) and their influence on receptor activity, stability and localization.



Cell cycle dependent changes in EcR concentration (A) and localization (B) in CHO cells.
Black bars = exclusively nuclear localization,
white bars = exclusively cytoplasmic localization;
A = asynchronous cells.



Short term inhibition of GSK-3β activity by SB216763 induces nuclear export of the AR.
Fluorescence microscopy of a GFP-tagged AR in PC3 cells:
(left) absence of androgens; (middle) presence of androgens; (right) pre-treatment with androgens and subsequent incubation with SB216763.

Selected Publications:

- *Schäfer B, Götz C, Dudek J, Hessenauer A, Matti U, Montenarh M (2009) KIF5C: a new binding partner for protein kinase CK2 with a preference for the CK2alpha' subunit, Cell Mol Life Sci. 66, 339-49.*
- *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.*
- *Rinnab L, Hessenauer A, Schmid E, Küfer R, Hautmann RE, Spindler K-D, Cronauer MV (2008) Rolle des Androgenrezeptors im hormonrefraktären Prostatakarzinom, Urologe A 47, 314-25.*
- *Marienfeld R, Palkowitsch L, Ghosh S (2006) Dimerization of the I kappa B kinase-binding domain of NEMO is required for tumour necrosis factor alpha-induced NF-kappaB activity, Mol Cell Biol 26, 9209-9219.*
- *Cronauer M, Schulz WA, Burchardt T, Anastasiadis AG, de la Taile A, Ackermann R, Burchardt M (2003) The androgen receptor in hormone-refractory prostate cancer: relevance of different mechanisms of androgen receptor signalling, Int J Oncol 23, 1095-1102.*
- *Hessenauer A, Montenarh M, Götz C (2003) Inhibition of CK2 activity provokes different responses in hormone-sensitive and hormone-refractory prostate cancer cells, International Journal of Oncology 22, 1263-70.*

Clinic of Gynaecology/Division of Gynaecological Oncology

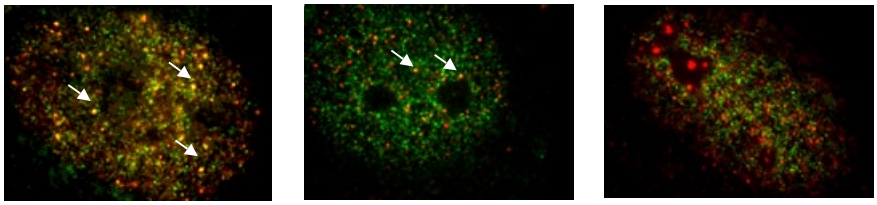
Tumour Prevention through High-Fidelity DNA Repair

The Team:
Head of the Clinic: R. Kreienberg
Head of Division: L. Wiesmüller
Group Leaders/Postdocs: M. Böhringer, S. A. Gatz, M. Uhl
PhD Students: S. Aydyn, C. Baumann, A. Dacke, M. Färber, M. Keimling, S. Siehler, M. Volcic
Additional Members of Thesis Advisory Committees: M. Filipic (Lubljana), S. Fulda (Ulm), U. Gerischer (Ulm), F. Grosse (Jena), K.-D. Spindler (Ulm)

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. Moreover, DSBs arise during the physiological processes of meiosis in germ cells and antibody diversification in the immune system. Efficient DSB repair is essential for the survival of a cell because unrepaired breaks can lead to chromosome fragmentation and active cell death i.e. apoptosis. Deregulated recombination events cause genomic instabilities that can be detected cytogenetically as translocations, gene amplifications and deletions. Chromosomal rearrangements due to error-prone DNA exchange processes accelerate the multistep process of tumorigenesis.

Our group characterizes tumour suppressor proteins with dual functions in checkpoint control and DNA repair. For these investigations we have developed and continuously optimize sensitive assay systems for the quantitative and qualitative analysis of all DSB repair mechanisms on the basis of viral cell lysis or fluorescence detection. We apply these tools on immortalized and primary cells from human

beings and genetically engineered mice. Our goal is to solve questions related to the specific mechanisms underlying tumorigenic genome rearrangements in order to understand the links between DNA repair and apoptosis, and to develop novel biomarkers for the identification of genotoxicities, chemopreventive effects and cancer risk.



p53pSer15 / Rad51 p53pSer15 / Rad54 p53pSer15 / Rad52

Nuclear p53 phosphorylated on serine 15 (p53pSer15, green) colocalizes with the initial homologous recombination enzyme Rad51 (red) and also to a lesser degree with the auxiliary factor Rad54 (red), but not with Rad52 (red) involved in Single-Strand Annealing.

Cells without functional p53, which is mutated in more than 50 % of tumours, accumulate chromosomal aberrations. Our studies revealed that p53 counteracts the exchange between divergent sequences during homologous recombination (HR), thereby suppressing mutagenic genome rearrangements between repetitive sequences within the genome. Importantly, this new tumour suppressor function of p53 is independent of its well-described activities in transcription, induction of cell cycle arrest and apoptosis. Further up within the hierarchy of DSB repair surveillance, the breast cancer susceptibility gene products, BRCA1 and BRCA2, channel DSB repair into the least error-prone pathway, namely HR, thereby indirectly suppressing mutagenic pathways such as Non-Homologous End Joining (NHEJ) and Single-Strand Annealing (SSA). Ongoing studies address the role of posttranslational modifications in the coordination of multiple tumour suppressor activities, the precise role of mismatch repair factors in the fidelity control of DSB repair, the molecular mechanisms, which destabilize chromosomal breakpoint cluster regions leading to chemotherapy-induced secondary leukaemias, and the precise functions of newly emerging breast cancer susceptibility genes such as ATM, Chk2, Nbs1, Rad50, and FancJ/Bach1/Brip1.

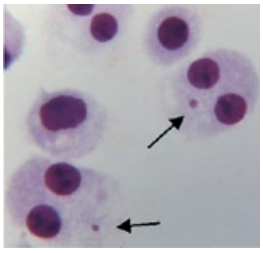
Selected Publications:

- *Keimling M, Kaur J, Bagadi SA, Kreienberg R, Wiesmüller L, Ralhan R (2008) A sensitive test for the detection of specific DSB repair defects in primary cells from breast cancer specimens, Int J Cancer 123, 730-736.*
- *Gatz SA, Keimling M, Baumann C, Dörk T, Debatin KM, Fulda S, Wiesmüller L (2008) Resveratrol inhibits double-strand break repair pathways in an ATM/ATR-p53 and -Nbs1 dependent manner in lymphoblastoid cell lines, Carcinogenesis 29, 519-527.*
- *Ralhan R, Kaur J, Kreienberg R, Wiesmüller L (2007) Links between DNA double strand break repair and breast cancer: accumulating evidence from both familial and non-familial cases, Cancer Lett. 248, 1-17.*
- *Gatz SA, Wiesmüller L (2006) p53 in recombination and repair, Cell Death Differ 13, 1003-1006.*
- *Restle A, Janz A, Wiesmüller L (2005) Differences in the association of p53 phosphorylated on serine 15 and key enzymes of homologous recombination, Oncogene 24, 4380-4387.*
- *Akyüz N, Boehden GS, Süsse S, Rimek A, Preuss U, Scheidtmann KH, Wiesmüller L (2002) DNA substrate dependence of the p53-mediated regulation of double-strand break repair, Mol Cell Biol 22, 6306-6317.*

The Team:
Head of the Institute: W. Vogel
Group Leader/Postdoc: C. Maier
PhD Students: M. Lüdeke, A. Rinckleb, H. Surowy
Additional Members of Thesis Advisory Committee: K. Spindler (Ulm), B. Wullich (Erlangen)

Institute of Human Genetics

Human Genetics in Patient Care and Research



Binucleated lymphocytes with a micronucleus stained with Giemsa Micronuclei arise during mitosis from acentric chromosome fragments. They represent unrepaired DNA-double strand breaks and can be used to quantitate DNA-repair capacity.

The Institute of Human Genetics at Ulm University has its structure in a number of workgroups that together cover the entire field of human genetics. The Institute's working fields include patients care with genetic counselling, cytogenetic and molecular diagnosis, and research in the following areas: functional characterization of disease-causing mutations and their detection; the identification of genetic variants conferring susceptibility in complex diseases; and functional characterization of DNA-repair and mutagenicity testing.

One of our research areas focusses on prostate and breast cancer susceptibility. In prostate cancer, familial clustering allows the linkage analysis of the largest German collection of families while collections of sporadic cases and controls can be used for association studies. These approaches using genetic epidemiology were recently refined by including functional criteria from the tumour. About 50% of prostate cancers harbour the oncogenic TMPRSS 2:ERG fusion, which we have shown to arise on the basis of a genetic predisposition and which can be used for a stratification in linkage and association. The genetic predisposition for fusion seems to consist of a reduced DNA repair capacity. Following linkage analysis in families with fusion positive prostate cancer, candidate genes from DNA-repair pathways were identified in the highlighted regions. Sequencing of these genes did not reveal any deleterious mutation but a considerable number of unclassified variants. Their relevance will be assessed by association studies and functional tests (PhD project M. Lüdeke).

Selected Publications:

- *Hofer MD, Küfer R, Maier C, Herkommer K, Perner S, Demichelis F, Paiss T, Vogel W, Rubin MA, Högel J (2009) Genome-wide linkage analysis of TMPRSS2-ERG fusion in familial prostate cancer, Cancer Res. 69, 640-646.*
- *Camp NJ, Cannon-Albright LA, Farnham JM, Baffoe-Bonnie AB, George A, Powell I, Bailey-Wilson JE, Carpten JD, Giles GG, Hopper JL, Severi G, English DR, Foulkes WD, Maehle L, Moller P, Eeles R, Easton D, Badzioch MD, Whittemore AS, Oakley-Girvan I, Hsieh CL, Dimitrov L, Xu J, Stanford JL, Johanneson B, Deutsch K, McIntosh L, Ostrander EA, Wiley KE, Isaacs SD, Walsh PC, Thibodeau SN, McDonnell SK, Hebbring S, Schaid DJ, Lange EM, Cooney KA, Tammela TL, Schleutker J, Paiss T, Maier C, Gronberg H, Wiklund F, Emanuelsson M, and Isaacs WB (2007) Compelling evidence for a prostate cancer gene at 22q12.3 by the International Consortium for Prostate Cancer Genetics, Hum. Mol. Genet. 16, 1271-1278.*
- *Vogel W, Surowy H (2007) Reduced DNA repair in BRCA1 mutation carriers undetectable before onset of breast cancer?, Br. J. Cancer 97, 1184-1186.*
- *Maier C, Vesovic Z, Bachmann N, Herkommer K, Braun AK, Surowy HM, Assum G, Paiss T, Vogel W (2006) Germline mutations of the MSR1 gene in prostate cancer families from Germany, Hum. Mutat. 7, 98-102.*
- *Varga D, Hoegel J, Maier C, Jainta S, Hoehne M, Patino-Garcia B, Michel I, Schwarz-Boeger U, Kiechle M, Kreienberg R, Vogel W (2006) On the difference of micronucleus frequencies in peripheral blood lymphocytes between breast cancer patients and controls, Mutagenesis 21, 313-320.*
- *Maier C, Herkommer K, Hoegel J, Vogel W, and Paiss T (2005) A genomewide linkage analysis for prostate cancer susceptibility genes in families from Germany, Eur. J. Hum. Genet. 13, 352-360.*

The Team:
Head of the Clinic: F. Gebhard
Professor: M. Huber-Lang
PhD Student: U. Amara
Additional Members of Thesis Advisory Committee: T. Böckers (Ulm), J. Köhl (Lübeck)

Clinic of Orthopaedic Trauma, Hand-, Plastic- and Reconstructive Surgery/Trauma Laboratory

Role of Serine Protease Systems after Severe Tissue Trauma

Severe tissue trauma is associated with an extensive activation of the coagulation and complement system. Both cascades mainly house serine proteases and are important ingredients of innate immune effectors, which sense and transmit incoming signals of danger, and pathogen-associated molecular patterns. Excessive activation and deregulation of the coagulation and complement system seem to trigger the systemic inflammatory response which often leads to cellular and organ dysfunction. Molecular mechanisms of the interaction between the coagulation and the complement cascade have often been proposed but are insufficiently understood. Therefore, our group focuses on the cross-talk between the coagulation and complement system (PhD Project Umme Amara). Findings from our group suggest that stress, trauma and sepsis are associated with extensive production of the powerful anaphylatoxin C5a, which may contribute to the disturbance of haemostasis and the cellular stress response. The generation of C3a and C5a especially can be induced by the coagulation system as determined by cleavage of the key proteases of the complement system, C3 and C5 respectively, through the coagulation factors FXa, FXIa, FIXa, plasmin and thrombin. We have defined more closely the postulated cross-talk and molecular mechanisms involved. The present data suggest a common serine protease system that includes both the coagulation and complement system as important players in the host's haemostatic and innate immune response in the early stages following trauma.

Selected Publications:

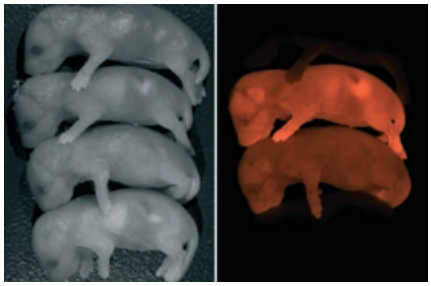
- *Umme A, Rittirsch D, Flierl M, Bruckner U, Klos A, Gebhard F, Lambris J, Huber-Lang M (2008) Interaction between the coagulation and complement system, Adv Exp Med and Biol, in press.*
- *Flierl MA, Perl M, Rittirsch D, Bartl C, Schreiber H, Fleig V, Schlaf G, Liener U, Brueckner UB, Gebhard F, Huber-Lang M (2008) The role of C5a in the innate immune response after experimental blunt chest trauma, Shock 29, 25-31.*
- *Flierl MA, Rittirsch D, Nadeau BA, Chen AJ, Sarma JV, Zetoune FS, McGuire SR, List RP, Day DE, Hoesel LM, Gao H, Van Rooijen N, Huber-Lang MS, Neubig RR, Ward PA (2007) Phagocyte-derived catecholamines enhance acute inflammatory injury, Nature 449, 721-25.*
- *Huber-Lang M, Sarma JV, Zetoune FS, Rittirsch D, Neff TA, McGuire SR, Lambris JD, Warner RL, Flierl MA, Hoesel LM, Gebhard F, Younger JG, Drouin SM, Wetsel RA, Ward PA (2006) Generation of C5a in the absence of C3: a new complement activation pathway, Nature Med 12, 682-87.*
- *Huber-Lang M, Sarma JV, Rittirsch D, Schreiber H, Weiss M, Flierl M, Younkin E, Schneider M, Suger-Wiedeck H, Gebhard F, McClintock SD, Neff T, Zetoune F, Bruckner U, Guo RF, Monk PN, Ward PA (2005) Changes in the novel orphan, C5a receptor (C5L2), during experimental sepsis and sepsis in humans, J Immunol 174, 1104-10.*
- *Huber-Lang M, Younkin EM, Sarma VJ, McGuire SR, Lu KT, Guo RF, Padgaonkar VA, Curnutte JT, Erickson R, Ward PA (2002) Complement-induced impairment of innate immunity during sepsis, J Immunol 169, 3223-31.*

The Team:
Head of the Institute: H. R. Rodewald
Head of Division: H.-J. Fehling
Group Leaders/Postdocs: N. T. Rao
PhD Student: A. Tasdogan

Institute of Immunology/Division of Molecular Immunology

Gene Knock-in Strategies to Visualize Developmental Fate Decisions

Gene targeting in embryonic stem (ES) cells is one of the key technical activities of the 'Molecular Immunology' group. We use this approach for sophisticated genetic manipulations such as the introduction of non-invasively detectable marker genes into developmentally interesting gene loci.



Expression of tandem-dimer red fluorescent protein (tdRFP) in mice. A litter of newborn pups from an inter-cross of heterozygous Rosa-tdRFP parents, in which one ROSA-tdRFP allele is constitutively activated. The newborns have the following genotype (from top to bottom): wild-type, homozygous ROSA-tdRFP, heterozygous ROSA-tdRFP and again wild-type.

We successfully targeted GFP into the *Brachyury* gene locus to allow direct visualization of developmental fate decisions into cells with mesodermal potential. We have subsequently generated double knock-in ES cell lines by targeting cDNAs encoding a tandem-dimer red fluorescent protein (tdRFP) or a modified human CD8 molecule into the pancreatic master regulator pdx-1 (PhD project of Nageswara Tata Rao). These double knock-in ES cells are being tested for their usefulness in optimizing cell culture conditions for the efficient generation of insulin-secreting pancreatic beta cells and their separation from teratocarcinoma-causing undifferentiated ES cells. For the second part of his project, Nageswara Tata Rao has introduced an IRES-YFP (internal ribosomal entry site-yellow fluorescent protein) expression cassette into the 3' end of the GATA-3 gene. Analysis of the corresponding knock-in mice has revealed intense and specific labelling of GATA-3 expressing cells, allowing their non-invasive isolation and characterization. Nagaswara Tata Rao completed his PhD *(Dr.biol. hum.)* in February 2009 and continues his work on GATA-3 knock-in mice as a post-doctoral scientist in my group. He also participates in a second project that involves the characterization of mouse mutants lacking the candidate tumour suppressor gene *Mixed-Lineage-Leukemia-5*.

Selected Publications:

- *Madan B, Madan V, Weber O, Tropel P, Blum C, Kieffer E, Viville S, Fehling H.J (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.*
- *Irion S, Luche H, Gadue P, Fehling HJ, Kennedy M, Keller G (2007) Identification and targeting of the ROSA26 locus in human embryonic stem cells, Nat Biotechnol 25,1477-1482.*
- *Luche H, Weber O, Rao TN, Blum C, Fehling HJ (2007) Faithful activation of an extra-bright red fluorescent protein in "knock-in" Cre-reporter mice ideally suited for lineage tracing studies, Eur J Immunol. 37, 43-53.*
- *Huber TL, Kouskoff V, Fehling HJ, Palis J, Keller G (2004) Haemangioblast commitment is initiated in the primitive streak of the mouse embryo, Nature 432, 625-630.*
- *Fehling HJ, Lacaud G, Kubo A, Kennedy M, Robertson S, Keller G, Kouskoff V (2003) Tracking mesoderm induction and its specification to the hemangioblast during embryonic stem cell differentiation, Development 130, 4217-27.*

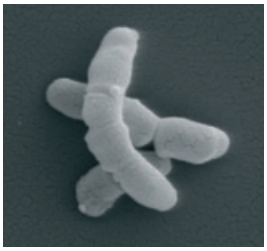
The Team:
Head of the Institute: P. Dürre
PhD Students: D. Meisohle, S. König, T. Rimpf

Institute of Microbiology and Biotechnology

Gene Structure-Function Relationship in Anaerobic Bacteria

Our research focuses on obligately anaerobic bacteria. Major projects include: cell differentiation (spore formation) in clostridia; regulation of acetone and butanol formation in *Clostridium acetobutylicum*; metabolic engineering of solvent-producing strains for industrial use (bulk chemicals and biofuel); construction and application of clostridial recombinant endospores for cancer treatment; and identification of acne-causing enzymes in *Propionibacterium acnes* for selective inhibition and hence disease therapy. We have extensive experience in the field of clostridial genetics, which includes developing techniques for transformation, electroporation, conjugation, transposon mutagenesis and mutant selection. Numerous genes have been cloned, sequenced, and analyzed. The genome of *P. acnes* has been sequenced. Metagenome banks are used as a source for novel enzymes (e.g. butanol dehydrogenases), and their analysis and improvement as a source for industrial application.

In the field of molecular medicine, two projects are pursued:
Clostridial endospores germinate only under hypoxic conditions, a situation found only in mammals and in proximity to tumours. Therefore, these survival forms are ideally suited for targeting solid cancer structures. If apathogenic clostridia are provided with genes that encode tumour-attacking proteins, the application of recombinant spores and their selective germination at the tumour allows multiplication and a specific therapy.

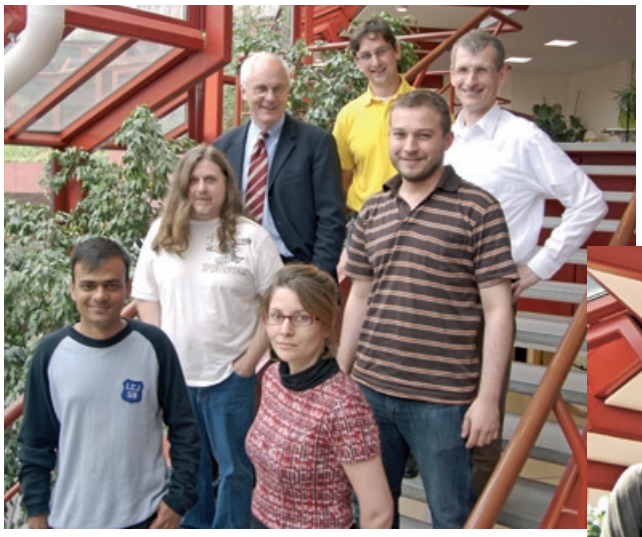


Propionibacterium acnes

P. acnes is the major cause of acne vulgaris, a skin disease affecting more than 85 % of all teenagers, of whom 10-30 % require medical treatment. Sequencing the genome of this organism has provided the tools for identifying pathogenic factors and then those agents that specifically inhibit them.

Selected publications:

- *Dürre P (2007) Biobutanol: an attractive biofuel, Biotechnol J 2, 1525-1534.*
- *Dürre P (2007) Clostridia: Encyclopedia of Life Sciences 2007, doi:10, 1002/9780470015902, a0020370.*
- *Theys J, Pennington O, Dubois L, Landuyt W, Anné J, Burke P, Anlezark G, Dürre P, Wouters BG, Minton NP, Lambin P (2006) Repeated systemic treatment cycles of Clostridium-directed enzyme prodrug therapy results in sustained anti-tumour effects in vivo, Br J Cancer 95, 1212-1219.*
- *Dürre P (2005) Handbook on Clostridia, CRC Press-Taylor and Francis Group, Boca Raton, USA.*
- *Brüggemann H, Henne A, Hoster F, Liesegang H, Wiezer A, Strittmatter A, Hujer S, Dürre P, Gottschalk G (2004) The complete genome sequence of Propionibacterium acnes, a commensal of human skin, Science 305, 671-673.*
- *Dürre P, Hollergschwandner C (2004) Initiation of endospore formation in Clostridium acetobutylicum, Anaerobe 10, 69-74.*

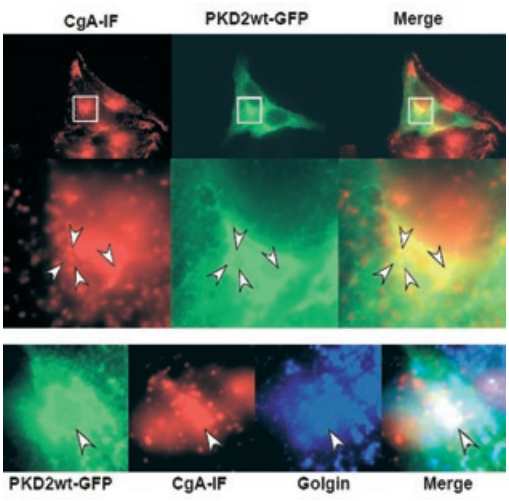


Clinic of Internal Medicine I

Laboratory of Gastrointestinal Growth Regulation

Heads: Thomas Seufferlein*, G. von Wichert

The main focus of our research activity is the compartment-specific visualization and biochemical characterization of intracellular signalling mechanisms that are relevant to the generation and propagation of gastrointestinal cancer, and in particular to pancreatic cancer and cancer stem cells. Within this context, we examine the role of the keratin cytoskeleton in migration and regulation of the viscoelastic properties of tumour cells. Finally, we investigate the mechanisms that drive regulated secretion in tumour and non-tumour models such as β-cells. Since it is a major signalling pathway regulating growth and secretion in GI tumour cells, we also examine the protein kinase D family. This family of serine threonine kinases comprises 3 members (PKD1,2,3) from which we were the first to clone and characterize the second isoform, PKD2. Data from our laboratory and others demonstrate that PKDs play a key role in growth regulation, migration and constitutive secretion in many cell types. In particular, these kinases regulate vesicle shedding from the trans Golgi network.



Colocalization of chromogranin A (CgA), PKD2 and golgin in human neuroendocrine tumour cells

The Team:
Head of the Clinic: G. Adler
Head of Laboratory of Gastrointestinal Growth Regulation: T. Seufferlein*
Postdocs: N. Azoitei
PhD Students: G.V. Pusapati
Additional Members of Thesis Advisory Committees: H. Kestler (Ulm), J. Van Lint (Leuven)
Head of Division of Endocrinology and Diabetes: B.O. Böhm
Postdocs: T. Burster, S. Merger, S. Rosinger, A. Spyrantis
PhD Students: U. Chinaka, D. Kuon, K. Pryss, N. Schäfer
Additional Members of Thesis Advisory Committees: P. Gierschik (Ulm), D. Leslie (London), P. Pozzilli (Rome)

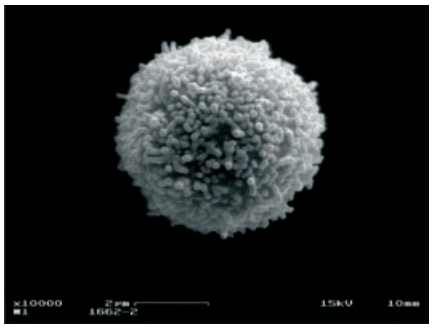
* Prof. Seufferlein left Ulm University in 2008. He is now the head of the Clinic of Internal Medicine I of the University of Halle.

Division of Endocrinology and Diabetes

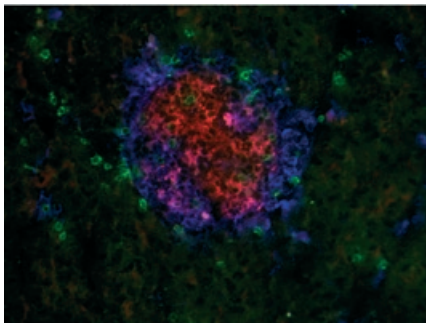
Head: Bernhard Böhm

Auto Reactive T-cells in Type 1 Diabetes

Type 1 diabetes is the result of a progressive T cell–mediated autoimmune 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 animal models.



Electron microscopy of a human insulin-reactive T cell clone.



RIP B7.1 tg mouse, 14 days after DNA vaccination with proinsulin. Pancreas (triple immunofluorescence staining) Red, insulin; green, CD4+ T cells; blue, CD8+ T cells.

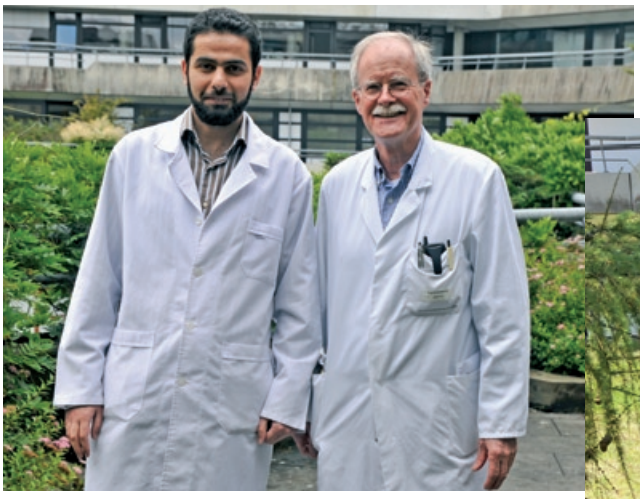
T cell-mediated loss of pancreatic ß-cells is the crucial event in the development of type 1 diabetes (T1D). We have been able to define a diabetes-associated phenotype of GAD65- and proinsulin-reactive T cells. The autoreactive T cells of patients could be distinguished from those of control subjects by their coexpression of CD25 and CD134. Spreading of the T cell repertoire was also seen. Autoantigen-reactive T cells in people with T1D recognize more peptides from various autoantigens compared to controls. Dual expression of CD25 and the costimulatory molecule CD134 on memory T cells provides a novel marker for T1D-associated T cell immunity in humans.

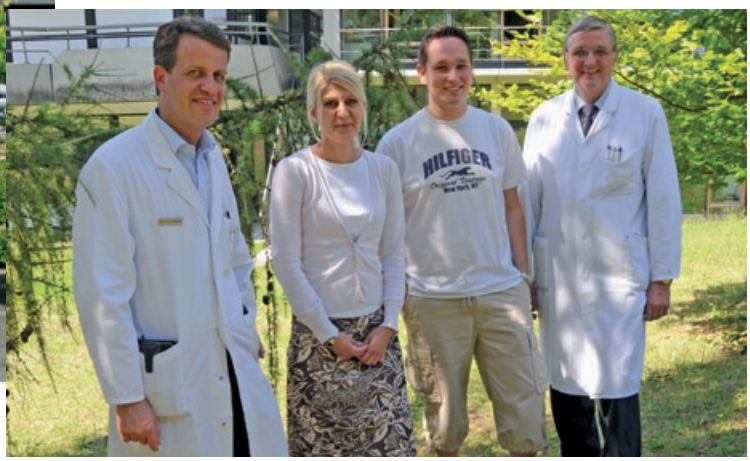
Insulin is a major autoantigen in T1D and has also been used to modify T cell autoimmunity in experimental models of T1D. We showed that insulin can trigger autoimmune diabetes. Preproinsulin (ppIns) DNA treatment diminished natural diabetes resistance in male non-obese diabetic (NOD) mice. We also found that diabetes development was critically dependent on CD8 T cells. In ongoing research antigen-processing and mitigation of autoreactive T cell responses are studied with altered peptide ligands.

Immune-mediated loss of pancreatic ß-cells is the crucial event in T1D development. During ongoing ß-cell inflammation, an imbalance between autoimmune destruction and insufficient regeneration of islet cells finally leads to hyperglycaemia. We have recently defined fundamental differences between human and rodent islet physiology and pathobiology by emphasizing species-specific reactivity of ß-cells. In ongoing studies we will evaluate the impact of bone-derived growth factors and nutrients on islet cell proliferation.

Selected publications:

- *Brun T, He KH, Lupi R, Boehm B, Wojtusciszyn A, Sauter N, Donath M, Marchetti P, Maedler K, Gauthier BR (2008) The diabetes-linked transcription factor Pax4 is expressed in human pancreatic islets and is activated by mitogens and GLP-1, Hum Mol Genet. 17, 478-89.*
- *Von Blume J, Knippschild U, Dequiedt F, Giamas G, Beck A, Auer A, Van Lint J, Adler G, Seufferlein T (2007) Phosphorylation at Ser244 by CK1 determines nuclear localization and substrate targeting of PKD2, EMBO Journal 26, 4619-33.*
- *Endl J, Rosinger S, Schwarz B, Friedrich SO, Rothe G, Karges W, Schlosser M, Eiermann T, Schendel DJ, Boehm BO (2006) Coexpression of CD25 and OX40 (CD134) receptors delineates autoreactive T-cells in type 1 diabetes, Diabetes 55, 50-60.*
- *Durinovic-Belló I, Rosinger S, Olson JA, Congia M, Ahmad RC, Rickert M, Hampl J, Kalbacher H, Drijfhout JW, Mellins ED, Al Dahouk S, Kamradt T, Maeurer MJ, Nhan C, Roep BO, Boehm BO, Polychronakos C, Nepom GT, Karges W, McDevitt HO, Sønderstrup G (2006) DRB1*0401-restricted human T cell clone specific for the major proinsulin73-90 epitope expresses a down-regulatory T helper 2 phenotype, Proc Natl Acad Sci USA 103, 11683-8.*
- *Yeaman C, Ayala MI, Wright JR, Bard F, Bossard C, Ang A, Maeda Y, Seufferlein T, Mellman I, Nelson WJ, Malhotra V (2004) Protein kinase D regulates basolateral membrane protein exit from trans-Golgi network, Nat Cell Biol 6, 106-112.*
- *Beil M, Micoulet A, Von Wichert G, Paschke S, Walther P, Omary MB, Van Veldhoven PP, Gern U, Wolff-Hieber E, Eggermann J, Waltenberger J, Adler G, Spatz J, Seufferlein T (2003) Sphingosylphosphorylcholine regulates keratin network architecture and visco-elastic properties of human cancer cells, Nat Cell Biol. 5, 803-811.*





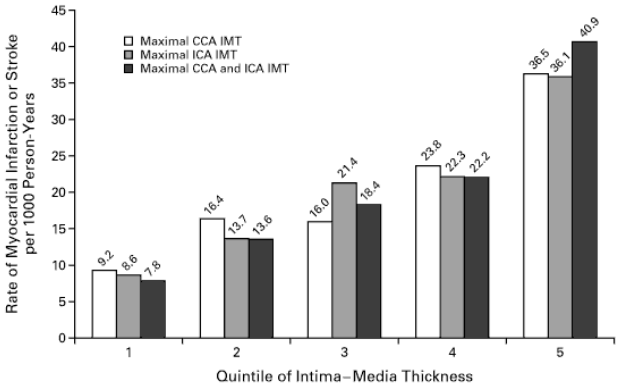
Clinic of Internal Medicine II

Work Group 'Molecular Epidemiology and Prevention of Cardiovascular Disease'

Head: Wolfgang Koenig

Atherosclerosis and its complications represent a complex disease. The evaluation of various intermediate, subclinical and laboratory parameters and phenotypes, which are both intimately related to atherosclerosis and plaque vulnerability, will further enhance our understanding of the pathophysiology and pathogenesis of this common disorder. It has recently been shown that increases in the thickness of the intima and media of the carotid artery, as measured non-invasively by high-resolution ultrasonography, are directly associated with an increased risk of myocardial infarction and stroke in older adults with no previous history of cardiovascular disease.

Our group is currently working on the genomics and functional analyses in subclinical phenotypes of cardiovascular diseases within the ATHEROGENOMICS project of the NGFN-Plus programme. The overall goal of this project is to assess a large array of gene variants using GWA approaches and to evaluate their associations with phenotypes of subclinical atherosclerosis such as carotid intima media thickness (IMT), as researched in the MONICA/KORA F_4 study and the Gutenberg-Heart-Study. Other such phenotypes are endothelial dysfunction (FMD) /peripheral arterial tonometry (EndoPAT), ankle brachial index (ABI) and microalbuminaria. The evaluation of a specific cardiovascular disease SNP chip (50K IBC chip) in a large prospective cohort represents another project within the NGFN-Plus consortium.



Unadjusted Incidence of Myocardial Infarction or Stroke According to Quintiles of Carotid-Artery Intima–Media Thickness.

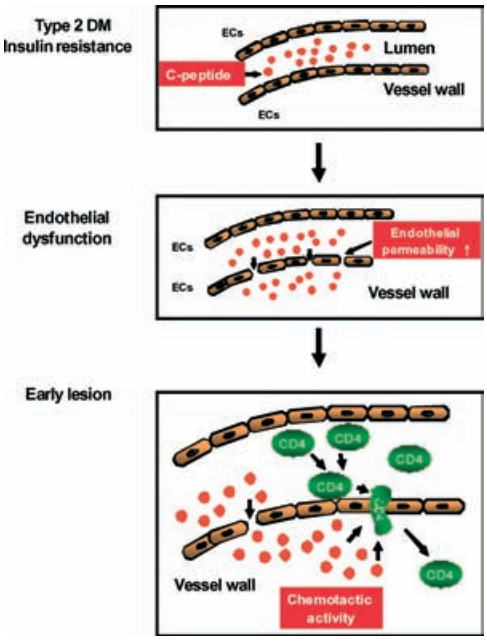
The Team:
Head of the Clinic: V. Hombach
Professors: W. Koenig, N. Marx
Group Leaders/Postdocs: M. Burgmaier, K. Heß, M. Karakas, D. Walcher
PhD Students: S. Dasdemir, P. Heinz, D. Vasic
Additional Members of Thesis Advisory Committees: B. O. Böhm (Ulm), C. Hengstenberg (Regensburg)

Work Group 'Diabetes and Atherosclerosis'

Head: Nicolaus Marx

Inflammatory processes in the vessel wall contribute to atherogenesis and lesion development. In addition, several lines of evidence indicate a connection between atherosclerosis, inflammation and diabetes. Various studies have found that elevated plasma levels of fibrinogen, a C-reactive protein, and interleukin-6 are associated with an increased risk of coronary heart disease. The multicentre Insulin Resistance Atherosclerosis Study (IRAS) showed a correlation between insulin resistance (IR) and plasma CRP-levels and it has been suggested that inflammation may represent the 'common soil' for arteriosclerosis and diabetes mellitus. Adipocytokines, such as resistin, TNF-a and adiponectin, released from visceral adipose tissue in patients with IR most likely contribute to this inflammatory state, which may also promote lesion development and thrombus formation.

In line with these findings, patients with diabetes exhibit endothelial dysfunction leading to endothelial activation and leukocyte recruitment into developing lesions. Such mechanisms are likely to promote lesion development in these high-risk patients. Inflammatory mediators released from the adipose tissue can directly activate endothelial cells and recent data suggest that the proinsulin cleavage product C-peptide may contribute to monocyte and T cell migration into the vessel wall during endothelial dysfunction thus hinting at a close link between insulin resistance and atherogenesis.. We are currently examining the role of C-peptide as a mediator of lesion development in diabetes in various animal models. In addition we investigate how activators of nuclear transcription factors (PPARs and LXRs) can modulate vascular disease and the activation of cells in the vessel wall.



Potential role of C-peptide in early atherogenesis in patients with insulin resistance and early type 2 diabetes mellitus. During endothelial dysfunction with increased endothelial permeability, C-peptide can deposit lymphocytes in the intima and, through its chemotactic activity on CD4+, facilitate the recruitment of these inflammatory cells into the vessel wall.

Selected Publications:

- *Glynn RJ, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Ridker PM (2009) A randomized trial of rosuvastatin in the prevention of venous thromboembolism, N Engl J Med. 360, 1851-61.*
- *Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Trial Study Group (2009) Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial, Lancet 373, 1175-82.*
- *Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Study Group (2008) Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein, N Engl J Med. 359, 2195-207.*
- *Walcher D, Heß K, Heinz P, Petscher K, Vasic D, Kintscher U, Clemenz M, Hartge M, Raps K, Hombach V, Marx N (2008) Telmisartan inhibits CD4-positive lymphocyte migration independent of the angiotensin type 1 receptor via PPARgamma, Hypertension 51, 259-26.*
- *Walcher D, Babiak C, Poletek P, Rosenkranz S, Bach H, Betz S, Durst R, Grüb M, Hombach V, Strong J, Marx N (2006) C-peptide induces smooth muscle cell proliferation - involvement of src-kinase, phosphatidylinositol 3-kinase and extracellular signal-regulated kinase 1/2, Circ Res 99, 1181-7.*
- *Marx N, Wöhrle J, Nusser T, Walcher D, Rinker A, Hombach V, Koenig W, Höher M (2005) Pioglitazone reduces neointima volume after coronary stent implantation: a randomized, placebo-controlled, double-blind trial in non-diabetic patients, Circulation 112, 2792-2798.*

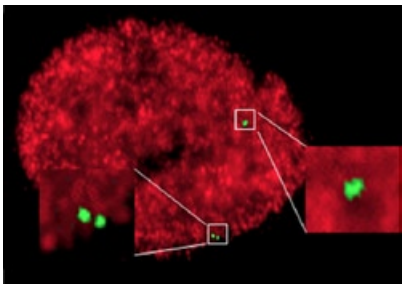
Clinic of Internal Medicine III

Identification and Characterization of Genetic Lesions and Development of Novel Therapies in Patients with Leukaemia and Lymphoma

The Team:
Head of the Clinic: H. Döhner
Professors: K. Döhner, S. Stilgenbauer
Group Leaders/Postdocs: L. Bullinger, A. Dolnik, I. Idler, D. Mertens, T. Zenz
PhD Students: D. Allegra, N. Bhattacharya, B. Jebaraj, S. Lück, J. Mohr, A. Philippen, A. Russ
Additional Members of Thesis Advisory Committees: J. Dürig (Essen), H.J. Fehling (Ulm), T. Fischer (Magdeburg), P. Lichter (Heidelberg), R. Renkawitz (Gießen), B. Schlegelberger (Hannover), T. Seufferlein (Halle), A. Silahtaroglu (Copenhagen), T. Wirth (Ulm)

The Department of Internal Medicine III has as its major research focus the pathomechanism of acute and chronic leukaemias and lymphomas. Students of the International PhD programme investigate: i) Genetic mechanisms leading to autonomous cell growth and clinical disease progression in Chronic Lymphocytic Leukaemia (CLL) and ii) genome- and transcriptome-wide characterization of Acute Myeloid Leukaemia (AML).

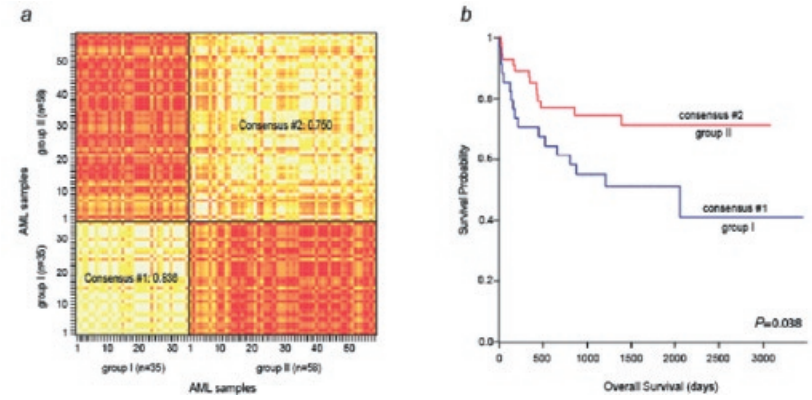
CLL is the most common leukaemia in the western world and is a disease with a highly variable clinical course (Dohner 2000). Patients can be prognostically stratified depending on genetic alterations. However, in vivo growth and expansion of CLL cells are also assumed to be dependent on external factors. This bivalent characteristic of CLL will be addressed by employing different strategies:
Loss of genomic material from a critical region in chromosomal band 13q14.3 is detected in more than 50% of cases thus making it the most common aberration in CLL. To date, no single tumour suppressor gene has been identified in this region but we have described an epigenetic regulatory mechanism in 13q14.3. In her PhD project, Angela Philippen will characterize in detail the epigenetic makeup of the critical region on



The two genetically identical copies are epigenetically different. This can be visualized by an asynchronous replication timing of the two copies of 13q14 i.e. one copy has already been replicated while the other is still non-replicated. This asynchrony is dependent on the chromatin packaging and results in monoallelic expression of the candidate tumour suppressor genes already in non-malignant cells. Therefore, deletion of the single active copy immediately results in complete loss of gene function because while the second copy is genetically intact, it is epigenetically silenced.

13q14.3 while 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 11q or 17p, are important prognostic factors and the aim of Julia Mohr is to identify and characterize the signalling pathways involved. To complement this approach, Nupur Bhattacharya quantitates and models signalling pathways involved in the interaction between CLL cells and their microenvironment. The findings of these projects will be useful for elucidating the underlying pathomechanism of CLL and for identifying the novel therapeutic options for this incurable disease.

Understanding the biology of the clinical heterogeneity of AML is a prerequisite for determining the reason why some patients respond to treatment better than others. Technological advances in genomics offer the opportunity to capture the molecular variation of AML and recently we were able to define novel clinically-relevant subgroups of AML with normal karyotype and novel core binding factor leukaemia (CBF) subclasses by means of gene expression profiling (GEP). These findings may soon translate into improved stratification of AML patients through the use of specific and individualized therapies.



GEP-based class discovery of clinically-relevant CBF leukemia subtypes.
(a) Colorimetric "heatmap" depicts consensus clustering of CBF samples stratified into two main subgroups by unsupervised hierarchical clustering analysis.
(b) Kaplan–Meier estimates of overall survival in the two CBF consensus clusters; the difference between cluster#1 and #2 was significant (P=0.038; log-rank test).

We are currently aiming to elucidate the biological basis of the two newly identified CBF leukaemia subgroups. To achieve this, we are focusing on differentially regulated pathways and genes; both leukaemic cell lines and primary patient material are employed in specific pathway intervention and RNAi studies (PhD project Sonja Lück). MicroRNAs (miRs) are often deregulated in human tumours and may contribute to tumour formation through the altering of mRNA profiles. Therefore, we recently profiled miR expression in a large cohort of AML cases and identified characteristic miR profiles for certain AML subgroups. By integrating this data with corresponding gene expression profiles, we found potential leukaemia-relevant miR targets and are currently investigating their functional role in AML (PhD project Annika Ruß).

Selected Publications:

- *Zenz T, Mohr J, Eldering E, Kater AP, Bühler A, Kienle D, Winkler D, Dürig J, van Oers MH, Mertens D, Döhner H, Stilgenbauer S (2009) miR-34a as part of the resistance network in chronic lymphocytic leukaemia, Blood 113, 3801-8.*
- *Roos, G, Krober A, Grabowski P, Kienle D, Buhler 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.*
- *Bullinger L, Rücker FG, Kurz S, Du J, Scholl C, Sander S, Corbacioglu A, Lottaz C, Krauter J, Fröhling S, Ganser A, Schlenk RF, Döhner K, Pollack JR, Döhner H (2007) Gene Expression Profiling Identifies Distinct Subclasses of Core Binding Factor Acute Myeloid Leukemia, Blood 110, 1291-300.*
- *Mertens D, Wolf S, Tschuch C, Mund C, Kienle D, Ohl S, Schroeter P, Lyko F, Döhner H, Stilgenbauer S, Lichter P (2006) Allelic silencing at the tumour-suppressor locus 13q14.3 suggests an epigenetic tumour-suppressor mechanism, Proc Natl Acad Sci USA 103, 7741-6.*
- *Bullinger L, Döhner K, Bair E, Fröhling S, Schlenk RF, Tibshirani R, Döhner H, Pollack JR (2004) Use of gene-expression profiling to identify prognostic subclasses in adult acute myeloid leukaemia, N Engl J Med 350, 1605-16.*
- *Döhner, H, Stilgenbauer S, Benner A, Leupolt E, Krober A, Bullinger L, Döhner K, Bentz M, Lichter P (2000) Genomic aberrations and survival in chronic lymphocytic leukemia, N Engl J Med 343, 1910-6.*

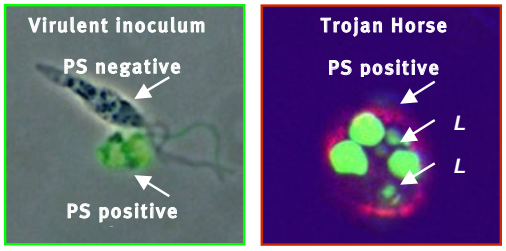
Institute of Microbiology and Hygiene

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, enable the intracellular survival of the 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.

The Team:
Head of the Institute: S. Stenger
Professor: B. Spellerberg
Group Leader/Postdoc:
G. van Zandbergen
PhD Students: H. Bruns, J. Dick, C. Florindo, J. B. Hagemann, A. Hofmann, D. Nickel, L. Pfleiderer, A. Sagar, C. Schropp, S. Swoboda

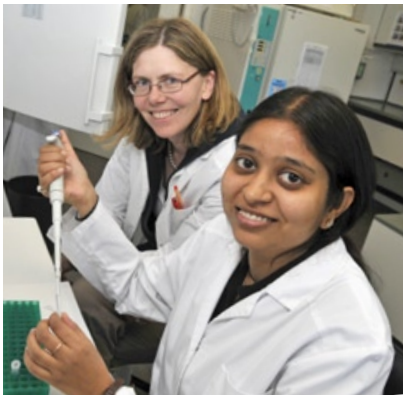


Left micrograph: Apoptotic Leishmania promastigotes (green) in the virulent inoculum enable disease development.

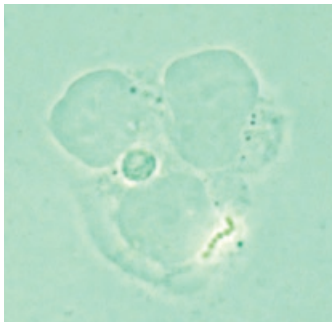
Right micrograph: Neutrophil granulocyte (PMN, red) serves as a Trojan Horse for leishmania entry into macrophages.

Work Group 'Molecular Mechanisms of Streptococci in Human Infections'

Head: Barbara Spellerberg



The work of our group focuses on molecular mechanisms of streptococci that are an important factor 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 harbours genes (lmb, scpB) involved in adhesion to host extracellular matrix structures and the evasion of host defenses. This mobile genetic element is of special importance for human infections since the genes carried by it are induced in the presence of human serum.



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.

In contrast to human strains, it is missing in many bovine isolates. At the graduate school, we pursue a project investigating the role of C-reactive protein (CRP) for streptococcal infections. While CRP has been detected and named for its ability to bind itself 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.

Selected publications:

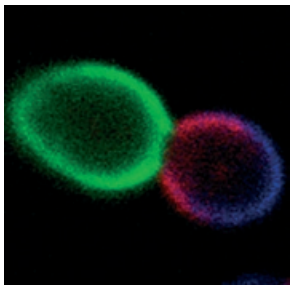
- *Eickel V, Kahl B, Reinisch B, Dübbers A, Küster P, Brandt C, Spellerberg B (2009) Emergence of respiratory Streptococcus agalactiae isolates in cystic fibrosis patients, PLoS ONE 4, e4650, Epub 2009 Feb 27.*
- *Bastian M, Braun T, Bruns H, Röllinghoff M, Stenger S (2008) Mycobacterial Lipopeptides Elicit CD4+ CTLs in Mycobacterium tuberculosis-Infected Humans, J Immunol. 180, 3436-46.*
- *Gottschalk B, Bröker G, Kuhn M, Aymanns S, Gleich-Theurer U, Spellerberg B (2006) Transport of Multidrug Resistance substrates by the Streptococcus agalactiae hemolysin transporter, Journal of Bacteriology 188, 5984-92.*
- *Liu PT, Stenger S, Li H, Wenzel L, Tan BH, Krutzik SR, Ochoa MT, Schauber J, Wu K, Meinken C, Kamen DL, Wagner M, Bals R, Steinmeyer A, Zügel U, Gallo RL, Eisenberg D, Hewison M, Hollis BW, Adams JS, Bloom BR, Modlin RL (2006) Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response, Science 312, 1874-5.*
- *Van Zandbergen G, Bollinger A, Wenzel A, Kamhawi S, Voll R, Klinger M, Müller A, Hölscher C, Herrmann M, Sacks D, Solbach W and Laskay T (2006) Apoptotic Leishmania promastigotes in the virulent inoculum enable disease development, Proc. Natl. Acad. Sci. USA 103, 13837-42.*
- *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.*

The Team:
Head of the Institute: N. Johnsson
Group Leaders/Postdocs: A. Dünkler, T. Gronemeyer, J. Müller
PhD Students: C. Tian, K. Labedzka, A. Rieke, C. Schneider, Y. Wu, M. Zapatka

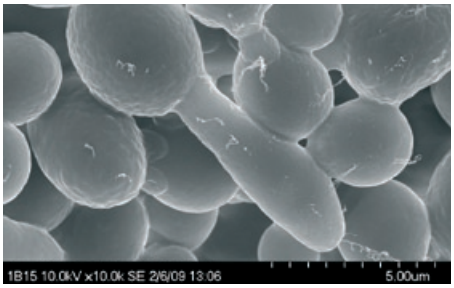
Institute of Molecular Genetics and Cell Biology

Cell Separation at the End of the Cell Cycle

The separation of mother and daughter cell at the end of each cell cycle requires the coordinated and precise activity of several processes. The cell must eventually constrict and then fuse the plasma membrane to create two distinct cytosols by synthesizing a special cell wall between mother and daughter cell. Finally, it must 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. Formins are a family of proteins that contribute to the reorganization of the actin cytoskeletton in eucaryotic cells during the cell cycle. The budding yeast *S. cerevisiae* possesses two formins, Bni1p and Bnr1p. Although the proteins are functionally redundant, they are organized into two different kinds of actin structures, the long actin cables (Bni1p) and the generation of actin filaments (initiated by Bnr1p). Septins are a second protein family important for cytokinesis that build a diffusion barrier at the bud neck to separate the bud specific proteins from proteins of the mother cell and, presumably, recruit the proteins of the cytokinesis apparatus to the bud neck. We recently discovered highly interesting interactions between the septins and Bnr1p but not Bni1p. Our aim is to decipher the functional importance of the interaction between Bnr1p and the septins, and septin-related proteins for the proper progession of cell separation.



Multicolour labelling with synthetic fluophores on the surface of S.cerevisiae



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

Selected Publications:

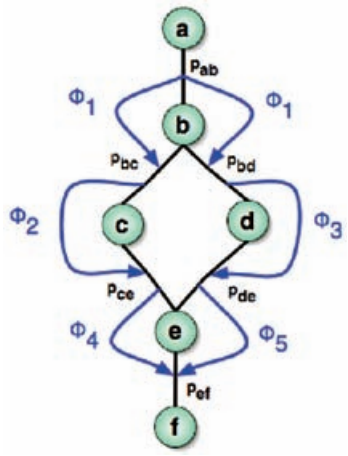
- *Müller J, Johnsson N (2008) Split-Ubiquitin and the Split-Protein Sensors: Chessman for the Endgame, Chembiochem. 9, 2029-2038.*
- *Johnsson N, Johnsson K (2007) Chemical tools for biomolecular imaging, ACS Chem Biol. 2, 31-8.*
- *Reichel C, Johnsson N (2005) The split-ubiquitin sensor: measuring interactions and conformational alterations of proteins in vivo, Methods Enzymol. 399, 757-76.*
- *Vivero-Pol L, George N, Krumm H, Johnsson K, Johnsson N (2005) Multicolor imaging of cell surface proteins, J Am Chem Soc. 127, 12770-1.*
- *Wang X, Johnsson N (2005) Protein kinase CK2 phosphorylates Sec63p to stimulate the assembly of the endoplasmic reticulum protein translocation apparatus, J Cell Sci. 118, 723-32.*
- *Johnsson N, George N, Johnsson K (2005) Protein chemistry on the surface of living cells, Chembiochem. 6, 47-52.*

The Team:
Head of the Clinic of Internal Medicine I: G. Adler
Head of the Institute of Neural Information Processing: G. Palm
Head of the Working Group: H. A. Kestler
PhD Students: A. Groß, M. Hopfensitz, J. Huth, J. Kraus, L. Lausser, C. Wawra,
Additional Members of Thesis Advisory Committees: P. Frasconi (Florenz), J. Hoheisel (Heidelberg), M. Kühl (Ulm)

Institute of Neural Information Processing/ Clinic for Internal Medicine I

Bioinformatics and Systems Biology

In the future biology will increasingly focus not only on single molecules but on biological systems. This 'systems' approach, which is based on the hypothesis that biology is basically an informational science, requires the generation and formalization of knowledge on different levels including the establishment of links between genes and cell status, and the characterization of co-regulated genes or associating gene changes to pathways or networks. The methods used for these investigations largely stem from the field of machine learning. We were recently able to find generalization error bounds that can be used for model selection and the classification of conjunctions of Boolean variables. We are currently investigating this topic further with the aid of boosting algorithms (PhD project Ludwig Lausser). Another project 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 modelling signal transduction and gene regulation with Boolean functions from data via reverse engineering (PhD work Alexander Groß). Other approaches being investigated are models based on differential equations, which consist of many parameters that cannot all be calculated based on data alone but also require the inclusion of more global knowledge (PhD project Christian Wawra). In this regard, we were able to extend a model of the Wnt/β-catenin pathway via time-delay differential equations and substantiate the model's principal behaviour by conducting an extended robustness analysis.



Rule-based random graph model for modelling qualitative interactions. Edge probabilities p_t are introduced that represent interaction probabilities (in its broadest sense) and then apply rules Φ that modify pt based on the current edge state of the graph (interaction present or not) and the current probability distribution.

Selected Publications:

- *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.*
- *Kestler HA, Kühl M (2008) From individual Wnt pathways towards a Wnt signalling network, Philos Trans R Soc Lond B Biol Sci.*
- *Wawra C, Kühl M, Kestler HA (2007) Extended analyses of the Wnt/beta-catenin pathway: Robustness and oscillatory behaviour, FEBS Lett 581/21, 4043–4048.*
- *Müller A, Holzmann KH, Kestler HA (2007) Visualization of genomic aberrations using Affymetrix SNP arrays, Bioinformatics 23, 496–7.*
- *Kestler HA, Lindner W, Müller A (2006) Learning and feature selection using the set covering machine with data-dependent rays on gene expression profiles, in Schwenker F, Marinai S (eds.), Artificial Neural Networks in Pattern Recognition, vol. LNAI 4087, 286–297. Heidelberg, Springer-Verlag, 2006.*
- *Kestler HA, Müller A, Gress TM, Buchholz M (2005) Generalized Venn Diagrams: A new method of visualizing complex genetic set relations, Bioinformatics 21, 1592–5.*

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

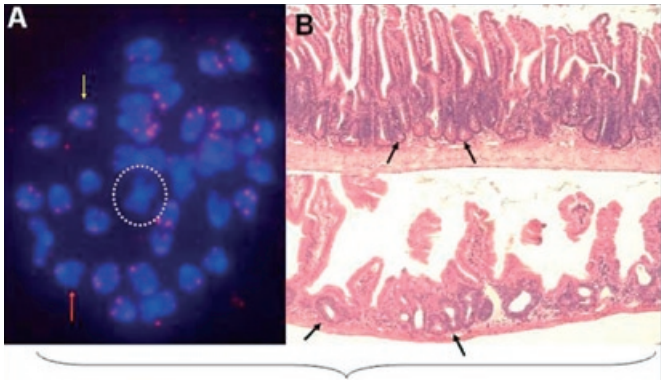
Stem Cell Ageing, Regeneration and Cancer

Telomere shortening limits the proliferative capacity of human fibroblast to 50-75 cell divisions by inducing senescence or apoptosis. There is growing evidence that telomere shortening has an impact on human ageing, diseases and cancer: (i) Telomere shortening occurs in almost all human tissues during human ageing; (ii) Telomere shortening is accelerated in chronic human disease; (iii) Telomere shortening and telomerase reactivation occur in the vast majority of human cancers; (iv) Telomerase mutations are associated with a shortened lifespan, organ failure and increased cancer risk in humans.

Using telomerase knockout mice as a model system, we were able to show that telomere-shortening impairs the maintenance of the organ system with high rates of cell turnover, which is associated with a shortened lifespan. Besides, we were able to demonstrate that telomere shortening limits stress responses and organ regeneration in response to injury, it induces chromosomal instability as well as it increases the rate of cancer initiation while suppressing the progression of tumours.

The Team:
Head of the Institute: K. L. Rudolph
Group Leaders/Postdocs: C. Günes, A. Lechel; **PhD Students:** P. Eshraghi, D. Hartmann, S.-F. Katz
Additional Members of Thesis Advisory Committees: C. Beltinger (Ulm), H.J. Fehling (Ulm), C. Klein (Regensburg), N. Malek (Hannover), G. v. Wichert (Ulm), L. Zender (Braunschweig)

We are currently analyzing the influence of ageing and telomere shortening on changes in cell-to-cell variation in the gene expression of stem cells and differentiated organ cells (PhD Project Sarah-Fee Katz). Furthermore, we are trying to identify target genes for telomerase activation in the crisis stage of hepatocarcinogenesis (PhD Project Daniel Hartmann). Regarding the role of p27, we are investigating its impact on maintaining stem cell function and organ homeostasis during ageing in the context of telomere dysfunction (PhD Project Parisa Eshraghi).



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

(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 is showing a p-p-arm fusion) and the induction of chromosomal instability.

(B)
Telomere shortening in vivo is associated with accelerated stem cell ageing. The photographs show the loss of intestinal stem cells in the basal crypts of the small intestine in ageing telomerase knockout mice. The arrows point to the basal crypts containing the stem and progenitor cells.

Selected Publications:

- *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) p53 deletion impairs clearance of chromosomal-instable stem cells in aging telomere-dysfunctional mice, Nat Genet, Epub ahead of print.*
- *Choudhury RA, Ju Z, Djojosubroto MW, Schienke A, Lechel A, Schaetzlein S, Jiang H, Stepczynska A, Wang C, Buer J, Lee HW, von Zglinicki T, Ganser A, Schirmacher P, Nakauchi H, Rudolph KL (2007) p21-deletion prolongs lifespan of telomere dysfunctional mice without accelerating cancer formation, Nat Genet 39, 99-105.*
- *Ju Z, Jiang H, Jaworski M, Rathinam C, Gompf A, Klein C, Trumpp A, Rudolph KL (2007) Telomere dysfunction induces environmental alterations limiting hematopoietic stem cell function and engraftment, Nat Med. 13, 742-7.*
- *Lechel A, Holstege H, Begus Y, Schienke A, Kamino K, Lehmann U, Kubicka S, Schirmacher P, Jonkers J, Rudolph KL (2007) Telomerase deletion limits progression of p53-mutant hepatocellular carcinoma with short telomeres in chronic liver disease, Gastroenterology 132, 1465-75.*
- *Schaetzlein S, Kodandaramireddy NR, Ju Z, Lechel A, Stepzynska A, Lilli DR, Clark AB, Rudolph C, Kuhnel F, Wei K, Schlegelberger B, Schirmacher P, Kunkel TA, Greenberg RA, Edelmann W, Rudolph KL (2007) Exo1 deletion impairs DNA damage signalling and prolongs lifespan of telomere dysfunctional mice, Cell 30, 863-77.*
- *Rudolph KL, Millard M, Bosenberg MW, DePinho RA (2001) Telomere dysfunction and evolution of intestinal carcinoma in mice and humans, Nat. Genet. 28, 155-9.*

Clinic of Neurology

Molecular Mechanisms in Neurodegenerative Diseases

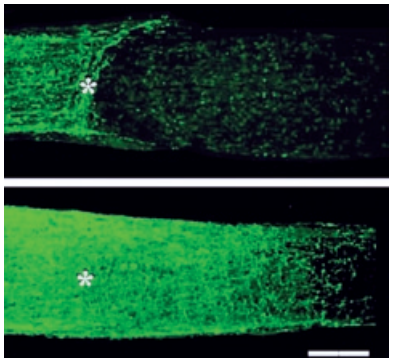
The Department of Neurology of Ulm University focuses its clinical and experimental work mainly on understanding the molecular mechanisms underlying such neurodegenerative diseases as Alzheimer´s, Parkinson´s and Huntington´s disease; amyotrophic lateral sclerosis/motor neuron disease (ALS/MND) and traumatic injuries of the CNS in conjunction with the development of novel strategies for CNS repair. Structurally, it consists of a number of large outpatient clinics each serving their respective patient populations in addition to a clinical trial centre, which specializes in the clinical studies of selected groups of patients. There is also a gene and biobank, an inpatient clinic for acutely neurologically ill patients, and an experimental section in which more than 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 signalling of the ß-amyloid precursor protein (APP) and associated proteins

The Team:
Head of the Clinic: A. Ludolph
Professors: C. von Arnim, D. Fischer
PhD Students: B. von Einem, A. Beyer, K. Braunstein, D. Lulé, A. Müller
Additional Members of Thesis Advisory Committees: T. Böckers (Ulm), E. Fisher (London), M.W. Riepe (Berlin), J. Walter (Bonn), J. May (Aachen), N. Birbaumer (Tübingen)

(including motor proteins), and their subcellular compartimentalization. The work focuses on aspects of trafficking in AD, employing novel molecular imaging techniques (FLIM, TIRF). The ultimate goal of these studies is the translation of the findings into clinical therapeutic approaches, which can be supported by imaging techniques in small animals and humans.

The group of Prof. Dr. Fischer concentrates on the development of novel strategies to protect central neurons from apoptosis and to stimulate their axonal regeneration after traumatic injuries of the CNS, stroke or other neurodegenerative diseases. To achieve this goal, the Fischer laboratory uses a broad spectrum of methods (molecular biology, biochemistry, histology, cell culture, tissue culture and neurosurgery) including in vitro and in vivo paradigms, to study the outcome of pharmacological and genetherapeutic intervention on neuroprotection and axonal regeneration in the CNS.



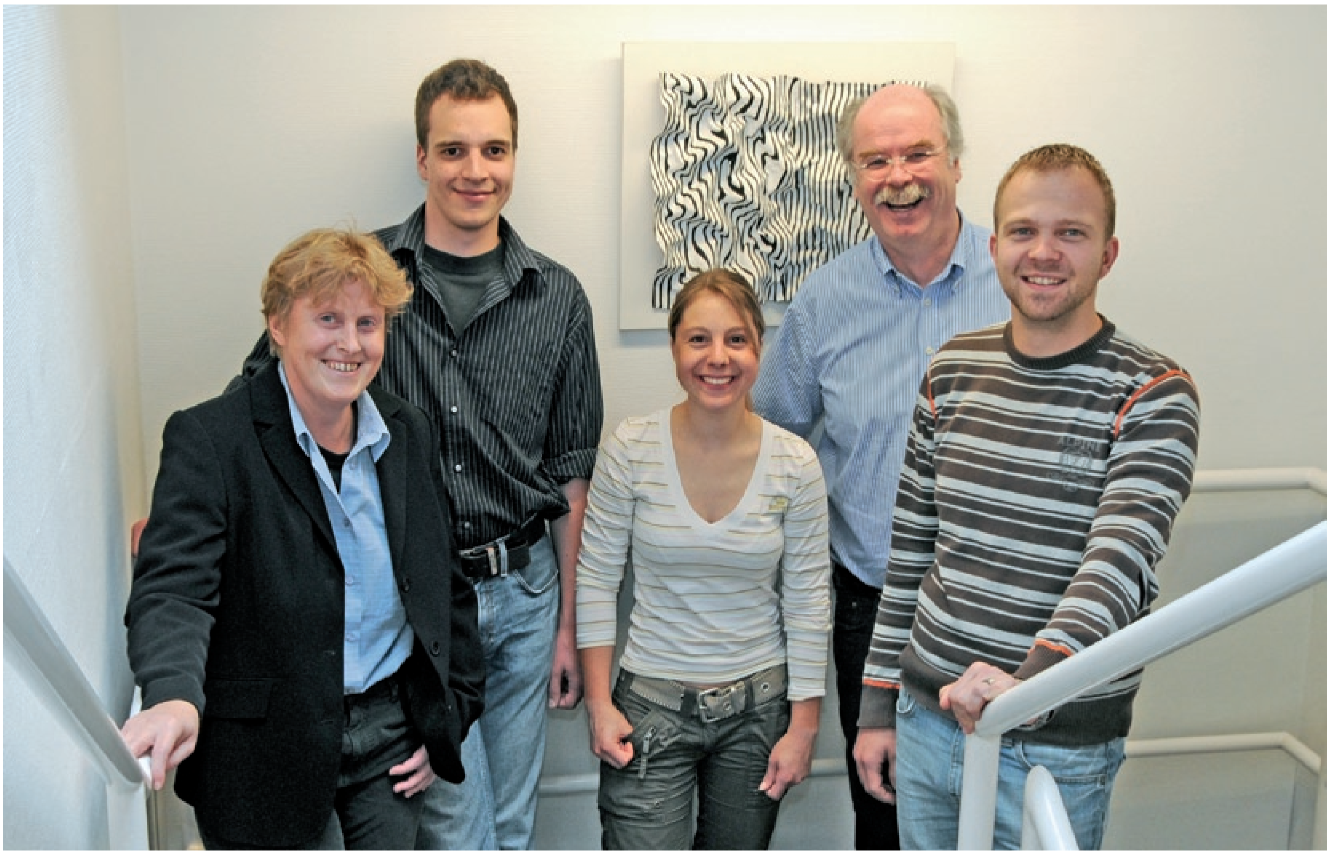
Axons (green) normally fail to regenerate into the damaged optic nerve, which is part of the central nervous system (upper panel). After treatments developed in the Fischer laboratory, axons can regenerate over considerable distances beyond the lesion site as indicated by the asterisk (lower panel).

Another focus is on the discovery and characterisation of new genes associated with successful regeneration in the CNS and their gene- therapeutic use to stimulate axonal growth. The final goal is to translate these experimental strategies into practical therapeutic approaches in the clinic.

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 centre 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.

Selected Publications:

- *Dupuis L, Fergani A, Braunstein KE, Eschbach J, Holl N, Rene F, Gonzalez De Aguilar JL, Zoerner B, Schwalenstocker B, Ludolph AC, Loeffler JP (2009) Mice with a mutation in the dynein heavy chain 1 gene display sensory neuropathy but lack motor neuron disease, Exp Neurol. 215, 146-152.*
- *Von Arnim CAF, von Einem B, Weber P, Wagner M, Schwanzar D, Spoelgen R, Strauss WLS, Schneckenburger H, (2008) Impact of Cholesterol Level upon APP and BACE Proximity and APP Cleavage, Biochem Biophys Res Commun, 370, 207-12.*
- *Bucher S*, Braunstein KE*, Niessen HG, Kaulisch T, Neumaier M, Boeckers TM, Stiller D, Ludolph AC (2007) Vacuolization correlates with spin-spin relaxation time in motor brainstem nuclei and behavioural tests in the transgenic G93A-SOD1 mouse model of ALS, Eur J Neurosci. 26, 1895-1901. * contributed equally*
- *Müller A, Hauk TG, Fischer D (2007) Astrocyte-derived CNTF switches mature RGCs to a egenerative state following inflammatory stimulation, Brain 130, 308-3320.*
- *Von Arnim CAF, Spoelgen R, Peltan ID, Deng M, Courchesne S, Koker M, Matsui T, Kowa H, Lichtenthaler SF, Irizarry MC, Hyman BT (2006) GGA1 acts as a spatial switch altering amyloid precursor protein trafficking and processing, J Neurosci 26, 9913-9922.*
- *Cao C, Lawrence DA, Li Y, Von Arnim CAF, Herz J, Su EJ, Makarova A, Hyman BT, Strickland DK, Zhang L (2006) Endocytic receptor LRP together with tPA and PAI-1 coordinates Mac-1-dependent macrophage migration, Embo J 25, 1860-1870.*



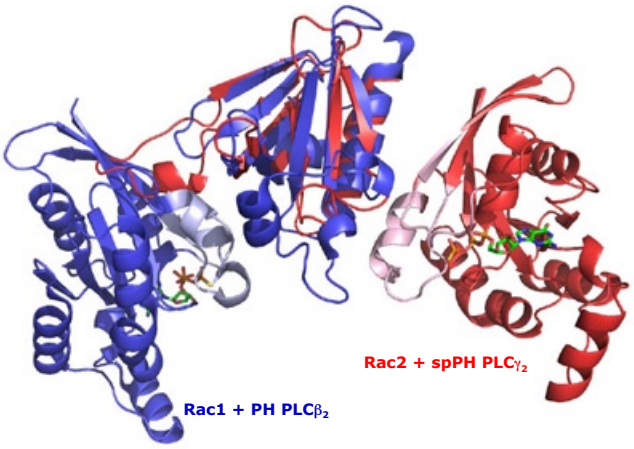
The Team:
Head of the Institute: P. Gierschik
Group Leaders/Postdocs: B. Möpps, C. Walliser
PhD Students: C. König, T. Langer, M. Pfreimer, Z. Rasonabe
Additional Members of Thesis Advisory Committees: T. Böckers (Ulm), T. Joos (Reutlingen), T. Mertens (Ulm), G.U. Nienhaus (Ulm), K.D. Spindler (Ulm), M. Thelen (Bellinzona), T. Wieland (Mannheim)

Institute of Pharmacology and Toxicology

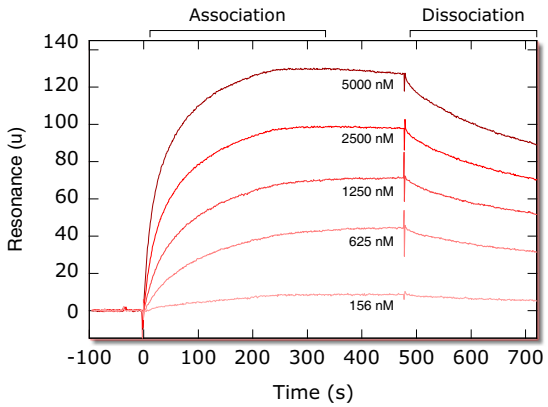
Signal Transduction Mediated by Heterotrimeric and Rho GTPases

GTPases 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 that include secretion, contraction, phagocytosis, and various sensory and neuronal cell functions. GTPases bind and hydrolyze GTP to GDP; they are timers of molecular events and act by turning these events on in their GTP-bound state and off upon GTP hydrolysis. Aside from their central role in cell biology and physiology, GTPases are of paramount clinical importance by contributing to the pathogenesis of human diseases and to the action of a major portion of the drugs currently used in clinical practice.

The project of Zinna Rasonabe examines the mechanisms by which phospholipase C-γ_2 (PLCγ_2) is activated by the Rho GTPase Rac2. This activation is likely to contribute to the physiological functions of PLCγ_2 and their pathological alterations in several cell types such as B cells, mast cells, macrophages and platelets. We have recently



The pleckstrin homology (PH) domains of phospholipase C-β_2 and -γ_2 are differentially engaged by activated Rac GTPases. The three-dimensional structures of the heterodimeric complexes between the N-terminal PH domain of PLCβ_2 and activated Rac1 and between the internal, split PH domain of PLCγ_2 and activated Rac2 are shown in blue and red, respectively. The structures of the two PH domains are superimposed. Two molecules of the poorly hydrolyzable guanine nucleotide GTP[S] rendering the Rac GTPases active are also shown. The switch I and switch II regions of the two Rac GTPases are depicted in light blue and light red. The figure was created with PyMOL (http://www.pymol.org).



Interaction between the isolated FERM domain of the tumor suppressor merlin-1 with Rho GTPase GDP dissociation inhibitor RhoGDIα determined by surface plasmon resonance (SPR) spectroscopy. The purified recombinant FERM domain (band four-point-one, ezrin, radixin, and moesin homology domain) of merlin-1 was immobilized to the SPR sensor chip and exposed to purified recombinant RhoGDIα at the indicated, increasing concentrations. Analysis of the results reveals that the two proteins interact with an equilibrium dissociation constant K_d of approximately 150 nM. Further, preliminary analysis of the binding data suggests, however, that the interaction may be more complex than a simple bimolecular interaction.

shown that activated Rac2 interacts with PLCγ_2 *via* the split pleckstrin homology (spPH) domain of PLCγ_2. In cooperation with the Institute of Biophysics at Ulm University, Zinna will use fluorescence spectrometry and quantitative fluorescence microscopy to examine the specificity and dynamics of the spPH$_N$-spPH$_C$-interaction and the regulatory role of activated Rac2 in shaping this interaction.

Mariana Pfreimer set out to investigate the mode of activation of Rho GTPases by chemokine receptors, which are the key regulators of a broad range of immune and inflammatory responses as well as cellular differentiation and organismal development. Recent evidence suggests that Rho GTPases, activated by chemokine receptors *via* certain G proteins and Rho guanine nucleotide exchange factors (RhoGEFs), are involved in both initiating and determining the patterns of these responses.

The main hypothesis addressed by Carolin König is that some chemokine receptors, e.g. the CC chemokine receptors CCR2a and CCR2b, are present on human adipocytes to regulate the functions of these cells during terminal differentiation and/or their interaction with monocytes/macrophages and other cell types in the adipose tissue. The latter interactions are thought to give rise to the chronic inflammatory response witnessed in the adipose tissue of obese individuals and its systemic sequelae, such as insulin resistance and atherosclerosis.

Torben Langer studies the interaction of the tumor suppressor merlin (moesin-, ezrin- and radixin-like protein) with proteins involved in regulating the dissociation of GDP from (and hence the binding of GTP to) Rho GTPases and designated RhoGDIs (GDP dissociation inhibitors). Inactivating mutations of the gene encoding merlin are the cause of human type II neurofibromatosis, a neurocutaneous syndrome defined by multiple benign tumours growing along nerves and/or under the skin. The project is driven by the hypothesis that merlin interferes with the activation of GDP-bound Rho GTPases from a heterodimeric complex with RhoGDIs.

Selected Publications:

- *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.*
- *Walliser C*, Retlich M*, Harris R, Everett KL, Josephs MB, Vatter P, Esposito D, Driscoll PC, Katan M, Gierschik P, Bunney TD (2008) Rac regulates its effector phospholipase C-γ_2 through interaction with a split PH domain, J Biol Chem 283, 30351-30362. (*shared first authorship)*
- *Moepps B, Tulone C, Kern C, Minisini R, Michels G, Vatter P, Wieland T, Gierschik P (2008) Constitutive serum response factor activation by the viral chemokine receptor homologue pUS28 is differentially regulated by Gαq/11 and Gα16, Cell Signal 20, 1528-1537.*
- *Bunney TD, Harris R, Gandarillas NL, Josephs MB, Roe SM, Sorli SC, Paterson HF, Rodrigues-Lima F, Esposito D, Ponting CP, Gierschik P, Pearl LH, Driscoll PC, Katan M (2006) Structural and mechanistic insights into Ras association domains of phospholipase C-ε, Mol Cell 21, 495-507.*
- *Piechulek T, Rehlen T, Walliser C, Vatter P, Moepps B, Gierschik P (2005) Isozyme-specific stimulation of phospholipase C-γ_2 by Rac GTPases. J Biol Chem 280, 38923-38931.*

The Team:
Head of the Institute: T. Simmet
Professor: J. Kirchheiner
Group Leaders/Postdocs: M. Hagn, B. Jahrsdörfer, Laumonnier, Y. K. Pitterle, A. Seeringer, T. Syrovets
PhD Students: A. L. Godoy, Y. He, E. Lebedeva, Q. Li, X. Li, O. Lunov, J. Martinez, S. Morad, S. Parmar
Additional Members of Thesis Advisory Committees: J. Brockmöller (Göttingen), T. Seufferlein (Halle)

Institute of Pharmacology of Natural Products and Clinical Pharmacology

Work Group 'Proinflammatory Activation of Immune Cells'

Head: Thomas Simmet

Monocytes and other antigen-presenting cells play a central role in the chronic phase of inflammation and are implicated in several human diseases such as atherosclerosis, arthritis, impaired wound healing and others. These pathological processes are generally accompanied by increased expression of proteolytic enzymes like thrombin

and plasmin. Plasminogen-deficient patients can suffer from recurrent respiratory infections, vulvovaginitis, impaired wound healing and other diseases. At the same time, the increased expression of fibrinolytic genes in atherosclerotic plagues may have a causal effect on the development of atherosclerosis.
We have found that the effects of plasmin are not solely restricted to their role in fibrinolysis but that plasmin is a potent proinflammatory activator of human monocytes and macrophages. In monocytes, plasmin, but not proteolytically inactive plasminogen, triggers a signal cascade that includes G proteins as well as the proteins, kinase C and G-kinase, leading to activation of JAK1. This is followed by phosphorylation of STAT1 and STAT3 transcription factors, the activation of MKK3/6-p38, which triggers additional phosphorylation of STAT1 and STAT3 on serines, and also of ATF2, a member of the AP-1 transcription factor family.
In addition, plasmin activates IKKβ inducing IκBα degradation with subsequent activation of NF-κB. Activation of the aforementioned transcription factors results in the induction of proinflammatory genes (chemokine monocyte chemoattractant protein-1, CD-40, tissue factor, and cytokines TNF-α and IL-1). These mediators are crucial for atherogenesis and other chronic inflammatory diseases.

These data, which form part of the PhD thesis of Qun Li, have helped to unravel the initial process of activation and have demonstrated that the plasmin-induced signalling mechanism leads to full-scale proinflammatory activation of macrophages and is an important factor in any kind of chronic inflammation.

Work Group ‚Clinical Pharmacology'

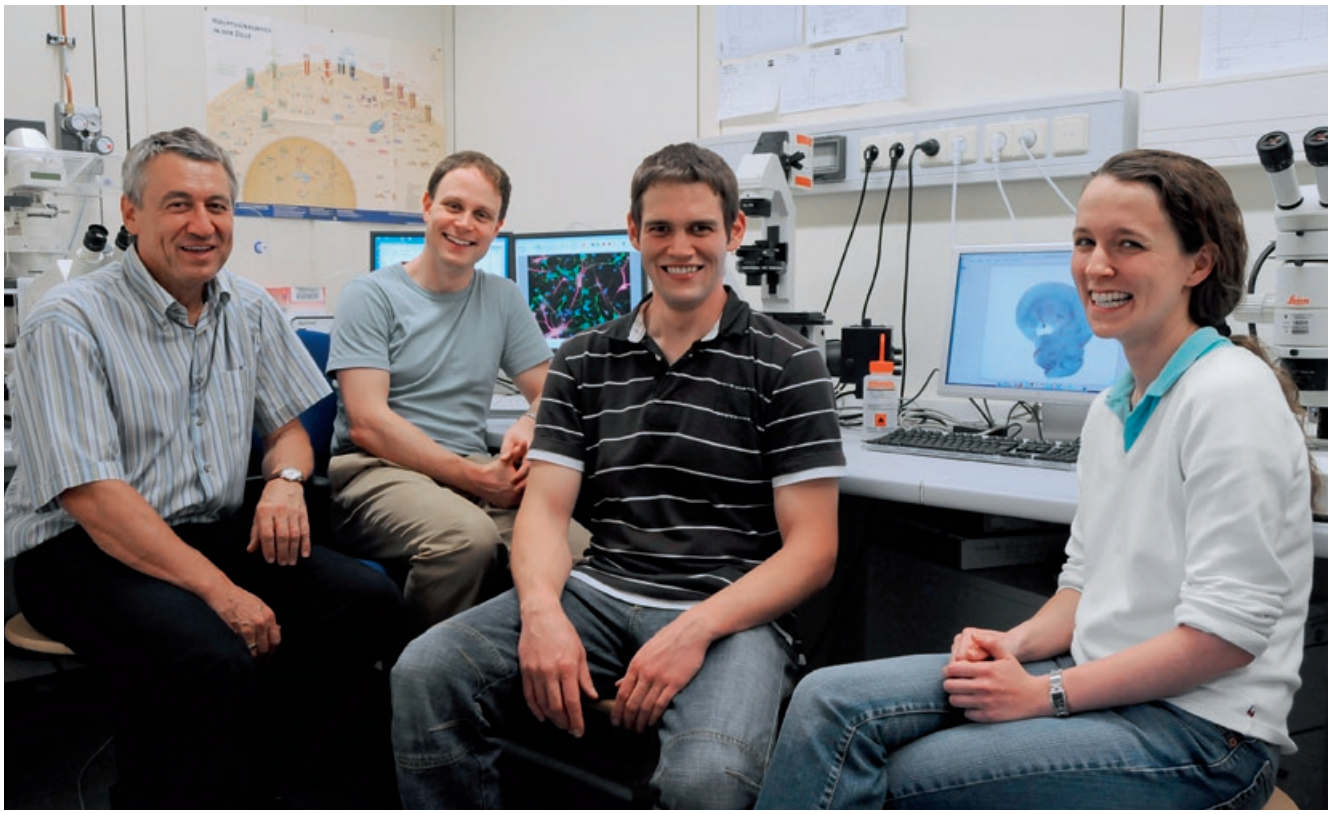
Head: Julia Kirchheiner

Pharmacogenetics for Patient-tailored Drug Treatment: Individual Mechanisms of Cytarabine Toxicity

Cytarabine (AraC) is a major component in the therapy of acute myeloid leukaemia (AML). The therapy with AraC shows good efficiencies but it is in many cases associated with high toxicity and severe side-effects. Bone marrow suppression especially and haematological toxicity, which both lead to poor haematologic reconstitution, neutropenia and thrombopenia, are frequent therapy- related problems. Furthermore, this particular therapy can cause mucositis, neurotoxicity and acute pulmonary syndrome. The bone marrow suppression and haematological toxicity often induce a deficient immune status associated with severe infections, which constitute the most frequent cause of morbidity and mortality after intensive chemotherapy for AML. It would therefore be valuable to have predictive markers for the individual probability and severity of AraC associated side effects.
The aim of the PhD project of Sumit Parmar 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, we are using human lymphocytes from 100 healthy volunteers in order to examine the inter-individual differences in AraC toxicity and correlate these findings with genetic factors.

Selected Publications:

- *Vormfelde et al., (2009) Relative Impact of Genotype and Enzyme Induction on the Metabolic Capacity of CYP2C9 in Healthy Volunteers, Clin Pharmacol Ther. [Epub ahead of print].*
- *Kirchheiner et al., (2008) Genetic variants in FKBP5 affecting response to antidepressant drug treatment, Pharmacogenomics 9, 841.*
- *Kirchheiner et al., (2008) Effects of the CYP2D6 gene duplication on the pharmacokinetics and harmacodynamics of tramadol, J Clin Psychopharmacol 28, 78.*
- *Kirchheiner et al., (2005) Pharmacogenetics based therapeutic recommendations – ready to go into clinical practice? Nature Reviews Drug Discovery 4, 639-48.*
- *Kirchheiner et al., (2004) Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response, Mol Psychiatry 9, 442.*



Institute of Physiological Chemistry

Molecular Pathways Regulating Differentiation and Disease

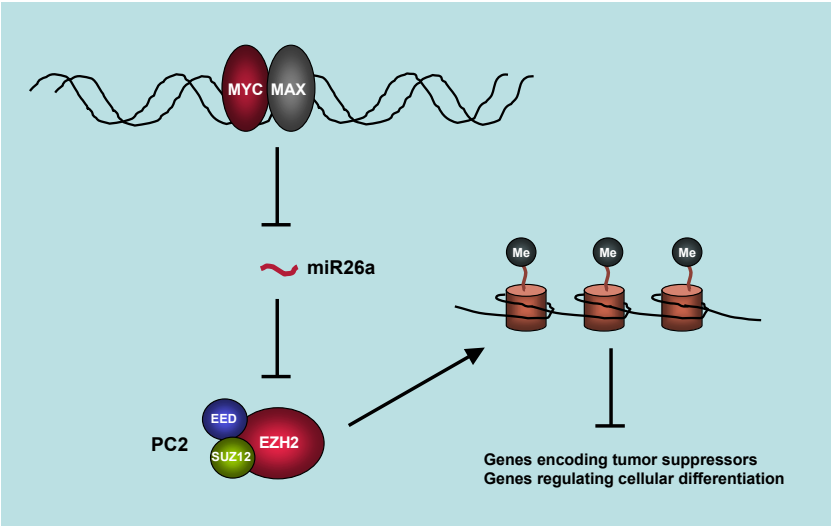
We use sophisticated conditional mouse genetics to investigate the functions of defined transcriptional regulators and key components of signalling pathways in normal differentiation processes as well as in animal disease models. In most cases, tetracycline-regulated gene expression systems are used in transgenic mice to activate or block a certain signalling pathway by using the corresponding alleles. This type of approach has provided a deep insight into both developmental as well as patho-physiological processes.

The family of NF-κB transcription factors is composed of five members, which form various homo- and heterodimers. 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 IκB-proteins. A multitude of stimuli induces the activity of a kinase complex 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 concrete proof. Using genetic activation or blocking of this signaling pathway, we have

The Team:
Head of the Institute: T. Wirth
Group Leaders/Postdocs: B. Baumann, C. Brunner, H.J. Maier, U. Schmidt-Straßburger, Y. Sunami, A. Ushmorov
PhD Students: N. Hipp, A. Maqbool, S. Sander, T. Schips
Additional Members of Thesis Advisory Committees: T. Böckers (Ulm), T. Braun (Bad Nauheim), D. Eick (München), K.-L. Rudolph (Ulm), E. Serfling (Würzburg), S. Stilgenbauer (Ulm), M. Wagner (Ulm), H. Wajant (Würzburg)

identified several key ways by 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 tumour 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). Cellular and tissue homeostasis is tightly regulated and, in addition to NF-κB, the FoxO proteins play an important role in these processes. 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.

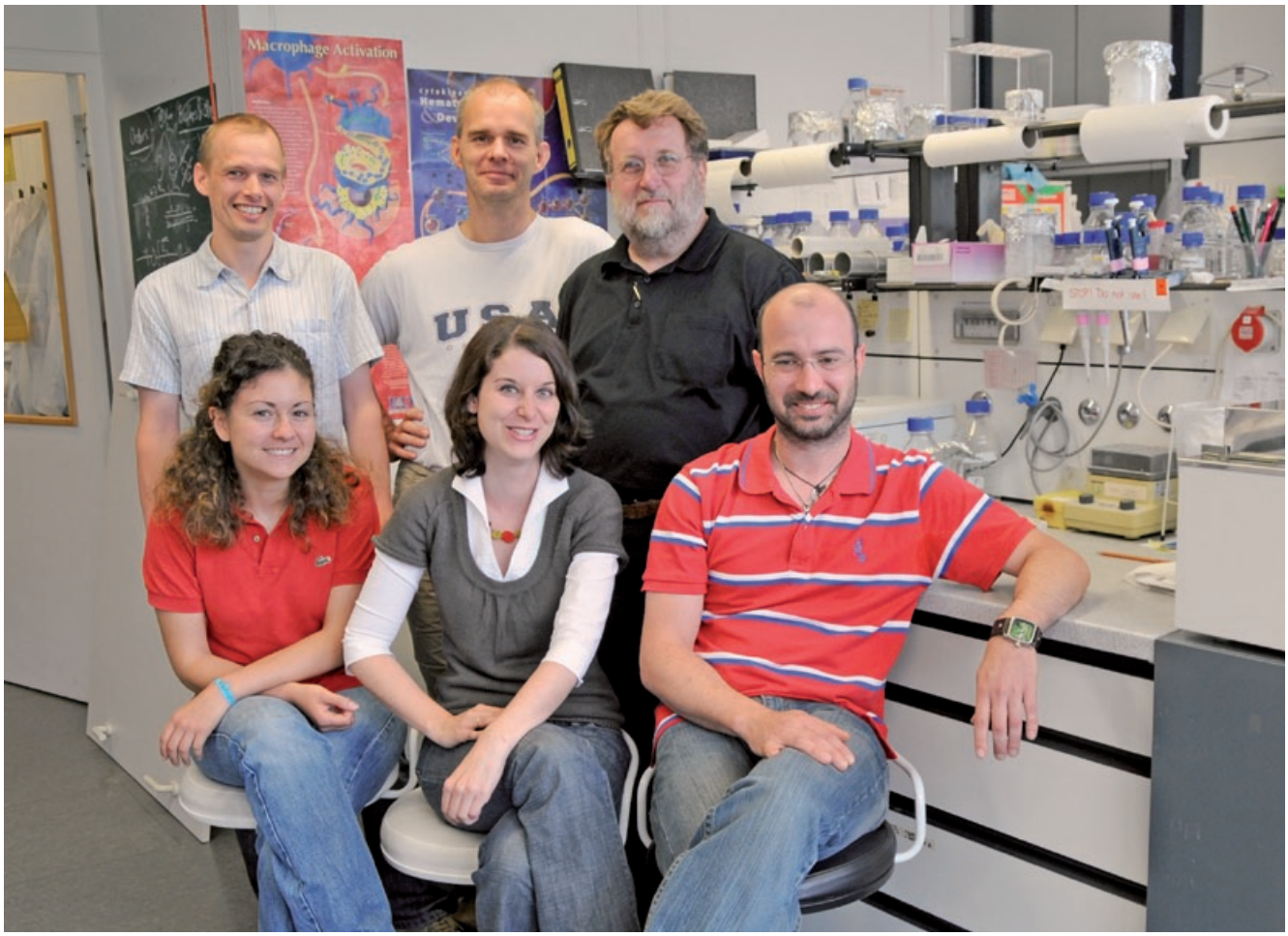
Basic mechanisms of tumorigenesis are also the focus of a set of experiments analyzing the molecular mechanisms involved in lymphomagenesis by the c-myc oncogene. In addition to commonly known protein encoding genes, Myc also regulates the expression pattern of miRNAs (micro RNAs). Recent work has identified this novel aspect of Myc-induced transformation and identified miRNAs as well as relevant miRNA targets. This was the PhD project of Dr. Sandrine Sander and the work is currently being continued in the PhD project of Nora Hipp. The interplay between the Myc-oncogene and the NF-κB system in lymphomas is also being investigated. 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 co-activators, which by themselves are critical regulators of lymphocyte differentiation and function.



We have discovered a novel function of the c-Myc oncogene, which contributes to its tumorigenic potential in lymphomas. Myc represses the expression of the miR26a micro RNA. This micro RNA normally inhibits the expression of the polycomb complex 2 (PC2) protein EZH2. EZH2 is a protein-methyl-transferase, which methylates histone H3 at lysine residue K27. Due to the repression of miR26a, there is excess activity of the PC2 complex with excess methylation of histones at specific target genes. As a consequence, such target genes, which encode tumor suppressors and genes required for cellular differentiation, are not expressed.

Selected Publications:

- *Sander S, Bullinger L, Klapproth K, Fiedler K, Kestler HA, Barth TF, Möller P, Stilgenbauer S, Pollack JR & Wirth T (2008) Myc stimulates EZH2 expression by repression of its negative regulator miR-26a, Blood 112, 4202-4212.*
- *Brunner C, Sindrilaru A, Girkontaite I, Fischer KD, Sunderkötter C & Wirth T (2007) BOB.1/OBF.1 controls the balance of TH1 and TH2 immune responses, EMBO J. 26, 3191-3202.*
- *Baumann B, Wagner M, Aleksic T, von Wichert G, Weber CK, Adler G & Wirth T (2007) Constitutive IKK2 activation in acinar cells is sufficient to induce pancreatitis in vivo, J. Clin. Invest. 117, 1501-1513.*
- *Ushmorov A, Leithauser F, Sakk O, Weinhausel A, Popov SW, Moller P & Wirth T (2006) Epigenetic processes play a major role in B-cell-specific gene silencing in classical Hodgkin lymphoma, Blood 107, 2493-2500.*
- *Herrmann O, Baumann B, de Lorenzi R, Muhammad S, Zhang W, Kleesiek J, Malfertheiner, M, Köhrmann M, Potrovit I, Maegele I, Beyer C, Burke JR, Hasan MT, Bujard H, Wirth T, Pasparakis M & Schwaninger M (2005) IKK mediates ischemia-induced neuronal death, Nat. Med. 11, 1322-1329.*
- *Huber MA, Azoitei N, Baumann B, Grünert S, Sommer A, Pehamberger H, Kraut N, Beug H & Wirth T (2004) NF-κB is essential for epithelial-mesenchymal transition and metastasis in a model of breast cancer progression, J. Clin. Invest 114, 569-581.*



Institute of Virology

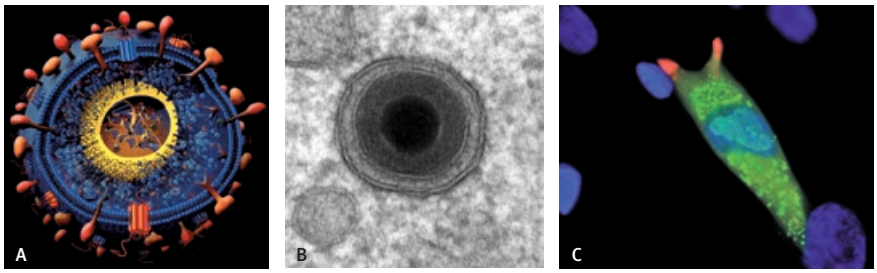
Work Group 'Morphogenesis, Pathogenesis and Therapy in Human Cytomegalovirus (HCMV) Infection'

Head: Thomas Mertens

The Team:
Head of the Institute: T. Mertens
Professors: F. Kirchhoff *, J. Münch,
Group Leaders/Postdocs: N. Arhel, G. Frascaroli, J. von Einem, B. Reinhardt, A. Schubert
PhD Students: J. Schmökel, A. Specht, K. Mohammad, C. Gnanadurai, M. Yolamanova, A. Shabir, K. Kim, S. Straschewski, A. Schreiber, M. Chevillotte
Additional Members of Thesis Advisory Committees: P. Gierschik (Ulm), M. J. Reddehase (Mainz)

* Frank Kirchhoff is now head of the Institute of Molecular Virology at Ulm University

Human Cytomegalovirus (HCMV), a member of the Herpes viruses, is a threatening pathogen for individuals with an immature or compromised immune system following primary infection or reactivation from latency. Our group characterizes HCMV genes and their gene products, and analyses the consequences of viral infection on the host cells as well as the interaction of viral and cellular proteins. We are analysing the impact of HCMV infection on the immune functions of monocytes and macrophages. In cooperation with the Central Unit of Electron Microscopy, we are investigating viral transport and egress mechanisms by focusing on the interactions of HCMV tegument proteins with cellular proteins. Another focus of our work concerns the pathomechanism of HCMV in vasculopathies. In cooperation with the Department of Pharmacology, we are investigating the molecular biology and function of the HCMV G-protein coupled with receptor homologues. The impact of antiviral therapy and viral



A) The Human Cytomegalovirus (HCMV) particle. The envelope (blue) is derived from the host cell membrane and contains several viral glycoproteins (red). The space between the envelope and the DNA-containing capsid (yellow) is filled with tegument proteins. Bar: 100 nm. B) Electron microscopic picture of a mature HCMV particle in a vesicle of an infected human fibroblast cell. Bar: 100 nm. C) Immunohistological localisation of the tegument protein pp150 (red) and pp65 (green) in HCMV UL48 deletion mutant infected fibroblast cells. Cell nuclei are counterstained with DAPI. Bar: 10 µm.

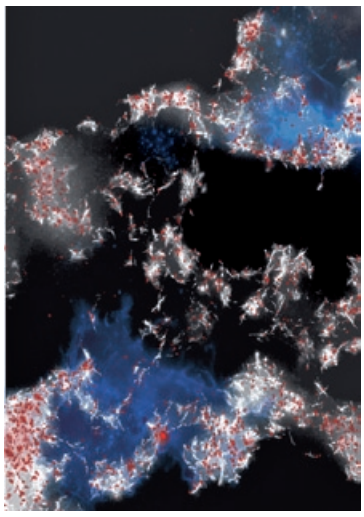
resistance is constantly increasing. We are analysing the two genes, UL97 and UL54, known to be responsible for HCMV antiviral resistance with regard to their biological function. We are also compiling a database for the correlation of resistant pheno- and genotypes in collaboration with the Department of Neuroinformatics.

Work Group 'Molecular Biology of HIV-1, AIDS Pathogenesis and Identification of Endogenous Factors affecting HIV-1 Transmission and Replication'

Head: Frank Kirchhoff *

HIV-1 infection damages the immune system. The development of AIDS is driven by the chronic hyperactivation of the immune system that is associated with increased T cell proliferation and death. Monkeys naturally infected with simian immunodeficiency viruses (SIV) do not show high levels of immune activation but maintain stable CD4+ T cell counts and remain healthy. One viral factor that modulates viral pathogenicity is the viral Nef protein. The HIV-1 Nef protein leads to increased T cell proliferation, activation, and activation-induced cell death (AICD). In strict contrast, SIV Nef alleles suppress the activation of infected CD4+ T cells by downmodulating CD3 from the cell surface. Our data suggest that this Nef function protects naturally SIV-infected monkeys against the loss of CD4+ T cells and high levels of immune activation, which are both hallmarks of AIDS. We are currently extending these analyses by characterizing various SIV´s derived from naturally infected primates.

The second major task in the laboratory is to identify endogenous peptides or proteins that affect HIV infection by screening human blood or semen derived from peptide libraries. Using this strategy we were able to identify a number of factors that either enhance or block HIV-1 infection. We are currently establishing assay systems to allow the identification of natural factors blocking HCV, HSV-2 or Influenza virus infection, and are also generating peptide libraries from human saliva, milk and vaginal fluid.



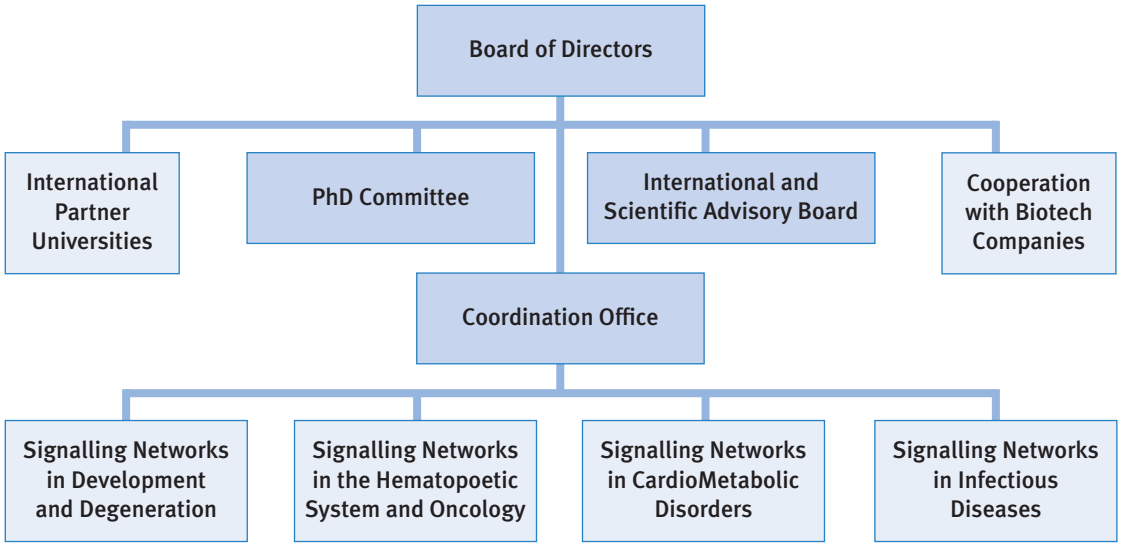
Confocal microscopy image showing how SEVI fibrils enhance HIV infection. SEVI fibrils (white) capture HIV virions (red) and virion-loaded fibrils efficiently bind target cells (blue) thereby enhancing virus infection.

Selected publications:

- *Münch J, Rücker E, Ständker L, Adermann K, Goffinet C, Schindler M, Wildum S, Chinnadurai R, Rajan D, Specht A, Giménez-Gallego G, Sánchez PC, Fowler DM, Koulov A, Kelly JW, Mothes W, Grivel JC, Margolis L, Keppler OT, Forssmann WG, Kirchhoff F (2007) Semen-derived amyloid fibrils drastically enhance HIV infection, Cell 131, 1059-71.*
- *Münch J, Ständker L, Adermann K, Schulz A, Schindler M, Chinnadurai R, Pöhlmann S, Chaipan C, Biet T, Peters T, Meyer B, Wilhelm D, Lu H, Jing W, Jiang S, Forssmann WG, Kirchhoff F (2007) Discovery and optimization of a natural HIV-1 entry inhibitor targeting the gp41 fusion peptide, Cell 129, 263-75.*
- *Frascaroli G, Varani S, Moepps B, Sinzger C, Landini MP, Mertens T (2006) Human cytomegalovirus subverts the functions of monocytes, impairing chemokine-mediated migration and leukocyte recruitment, J Virol. 80, 7578-89.*
- *Reinhardt B, Winkler M, Schaarschmidt P, Pretsch R, Zhou S, Vaida B, Schmid-Kotsas A, Michel D, Walther P, Bachem M, Mertens T (2006) Human cytomegalovirus-induced reduction of extracellular matrix proteins in vascular smooth muscle cell cultures: a pathomechanism in vasculopathies? J Gen Virol. 87, 2849-58.*
- *Schindler M, Münch J, Kutsch O, Li H, Santiago ML, Bibollet-Ruche F, Müller-Trutwin MC, Novembre FJ, Peeters M, Courgnaud V, Bailes E, Roques P, Sodora DL, Silvestri G, Sharp PM, Hahn BH, Kirchhoff F (2006) Nef-mediated suppression of T cell activation was lost in a lentiviral lineage that gave rise to HIV-1, Cell 125, 1055-67.*
- *Michel D, Mertens T (2004) The UL97 protein kinase of human cytomegalovirus and homologues in other herpesviruses: impact on virus and host, Biochim Biophys Acta 1697, 169-80.*

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 and a managing director. The Board of Directors is responsible for the scientific profile of the Graduate School, the interdisciplinary training, the regulation of programmes, the performance-based allocation of resources and public relations. While the chairman acts as the representative of the Graduate School towards the outside world, 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 programmes on offer etc.



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

External Members of the International and Scientific Advisory Board (September 2009):

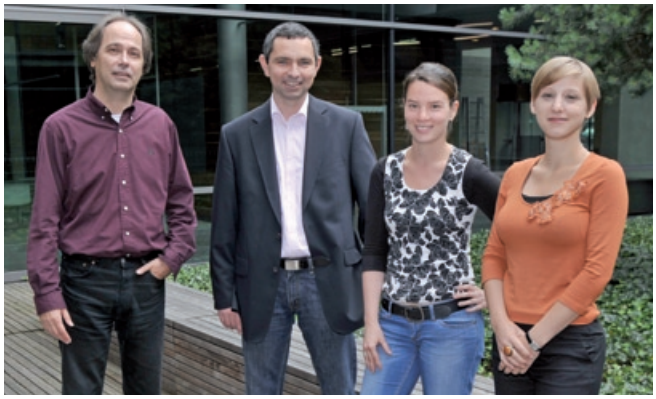
Academic Representatives	Industrial Representatives
Y. Kloog, Tel Aviv	H. Allgaier, Merckle Biotec
M. J. Lohse, Würzburg	U. Bücheler, Boehringer Ingelheim
P. Pozzilli, Rome	N. Rentschler, BioRegionUlm
S. Rich, Wake Forest	H. Wendt, Bayer

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 defence. It is responsible for the assessment of applications in order to maintain the high standards of research required by the programme. Furthermore, the PhD Committee supervises the school's compliance with the regulations of the programme and constantly improves them. It also conducts the intermediate as well as the final evaluation of students. The PhD Committee consists of 8 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. Moreover, highly proficient medical students are trained in clinical research by participating in the programme of **Experimental Medicine.**

Advice and support for applicants and PhD students are provided by the **Coordination Office** of the Graduate School. The office 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. It also 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

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 *Improve your Textbook Knowledge* for our first-year PhD students as well as a *Journal Club* and the biweekly seminar *Progress Report* which are compulsory for all PhD students. The lecture *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 our 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. In addition, 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, patent rights, scientific writing 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 two weeks. This practical training allows graduates to learn new and innovative techniques in Molecular Medicine.

A particular element of our study concept is the two intermediate examinations that our students must pass 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 of each year. While the first intermediate examination consists of a poster presentation before the Thesis Advisory Committee (TAC), the second intermediate examination also includes a scientific talk in addition to this. Only those students who successfully pass their intermediate examinations may proceed to their respective second or third year of study.

Study Plan International PhD Programme in Molecular Medicine Ulm										
Course	1st Year			2nd Year			3rd Year			CP
	Term 1	Term 2		Term 1	Term 2		Term 1	Term 2		
Lecture Series										3
Improve your textbook knowledge										2
Journal Club										6
Progress Report										3
2 Optional Courses (workshops, excursions,etc)										3
3 Practical courses										3
Doctoral thesis										
Disputation										
Sum Credit Points =										20

Explanation

- Lecture
- Year round
- Optional courses
- Practical courses
- Thesis
- Examination

How to apply

Do you find the study concept of our International PhD Programme attractive and wish to participate in it? The following information will advise you about our application and selection procedures as well as the financing of PhD positions etc.

Our PhD Selection Procedure

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

- 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. On 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 for which they have applied.

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

- The candidate's oral presentation and the personal interviews have been evaluated with an overall grade of 2,0 or 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 (www.uni-ulm.de/med/med-molmed/jobs.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 PhD position.

Application

If you wish to apply for our PhD Programme, please submit the following documents:

- Application form
- Photocopies of all academic transcripts (high school diploma, bachelor certificate, master certificate, mark sheets of ALL semesters, diploma supplements etc.)
- A curriculum vitae outlining your previous education and professional experience
- Documentation of publications related to your subject (if applicable)
- Certified documentation of professional experience related to your subject (if applicable)
- A photograph of yourself

Important remarks

- Applications are accepted by post or by email.
- Do not send original documents as applications will not be returned. Documents must be in word or pdf format.
- All submitted documents must be in English or German. If original documents are not in English or German, certified translations are required.
- Incomplete applications will automatically be rejected.
- Applicants who are invited to our PhD Selection Days can request financial support to cover their travel costs.
- The presentation at Ulm University is part of our selection procedure and cannot be replaced by telephone interviews.
- Please note that applicants who succeed in our PhD Selection Days can only be accepted for the PhD programme if they have been accepted for a PhD position by the Graduate School or by a supervisor from Ulm University.

Please send your completed application to the following address:
International Graduate School in Molecular Medicine Ulm
Meyerhofstraße N 27/2.011
89081 Ulm
Germany
email: phd.molmed@uni-ulm.de

How to finance a PhD position

Acceptance into our PhD Programme and securing a PhD position at Ulm University does 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.

Science City Ulm, May 2008

Ulm University and Science City

Founded in 1967, Ulm University is the youngest university in the state of Baden-Württemberg. At 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 centres 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 around 7,000 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, technology- and process-management, will be established in the near future. A new Bachelor course of study in psychology has recently been introduced.

The main university campus is located on a hill above the city of Ulm (*Eselsberg*) and houses a wide range of research and development centres as well as several hospitals that together comprise what is known as the Science City or *Wissenschaftsstadt*. The close 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 so called *Kunstpfad* (art trail) exhibits the artworks of internationally renowned and talented young artists distributed throughout the campus.

Press Office of Ulm University

Awarding of the Hertie Senior Professorship 2009 to Prof. Frank Lehmann-Horn by Prof. Annette Schavan, Federal Minister, Federal Ministry of Education and Research.

DFG/Querbach

Awarding of the Gottfried Wilhelm Leibniz Prize 2009 to Prof. Frank Kirchhoff (left) by Prof. Matthias Kleiner, President of the German Research Foundation (DFG, right).

DFG/Querbach

Awarding of the Gottfried Wilhelm Leibniz Prize 2009 to Prof. Karl Lenhard Rudolph (left) by Prof. Matthias Kleiner, President of the German Research Foundation (DFG, right).

Prof. Guido Adler, Vicepresident for Medicine of Ulm University (middle) with the two prize-winners of the German Cancer Award in 2005, Prof. Richard Hautmann (left) and Prof. Thomas Wirth (right).

About the City of Ulm

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

While Ulm is an ancient town, Neu-Ulm is relatively young. In Ulm, there are the charming Fisherman's and Tanners' Quarter with its old houses, alleyways and that air of medieval times. In Neu-Ulm, regularity in its architecture prevails since this was the only form considered to be stylish and elegant in the 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 centre 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 post-modern 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 modernisation of its city centre.

The twin city 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 theatre as well as several other smaller theatres. 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 from 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 34 percent between 1996 and 2005. At the same time, the unemployment rate has been reduced by more than 40 percent and a mere 4 per cent of Ulm's population are currently out of work. It is in this context that Ulm has recently been declared as Germany's *Wohlfühlregion Nr. 1* (Feel-good-region no. 1) in a survey by Deutsche Bank. 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 centre 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 & Figures

(August 2009)

PhD Students, International PhD Programme in Molecular Medicine

Total number of PhD students	**77**
Male	**32**
Female	**45**
International students	**30**
Parent students	**5**

Doctorates conferred (2008/2009), International PhD Programme in Molecular Medicine

Name	Title	Institute	Date of final Examination	Degree
Lebedev, Anton	Functional studies of Cockayne syndrome protein B in RNA polymerase I transcription	Clinic of Dermatology and Allergic Diseases	11/05/2009	PhD
Lulé, Dorothée	Evidence for extra-motor involvement in Amyotrophic lateral sclerosis (ALS)	Clinic of Neurology	01/30/2009	PhD
Retlich, Michael	Molecular Mechanisms of Phospholipase C-γ2 Activation by Rac GTPases	Institute of Pharmacology and Toxicology	04/17/2009	Dr. rer. nat.
Sander, Marie-Sandrine	Deregulated expression of microRNAs - a critical pathogenic mechanism in MYC-induced lymphoma	Institute of Physiological Chemistry	12/18/2008	Dr. rer. nat.
Wawra, Christian	Robustness Aspects of Signal Network Simulation	Institute of Neuroinformatics	05/08/2009	Dr. rer. nat.

PhD Students, Research Training Group GRK 1041

Total number of PhD students	16
Male	6
Female	10
International students	5
Parent students	2

Doctorates conferred (2004-2009), Research Training Group GRK 1041

Name	Title	Institute	Date of Examination	Degree
Aleksic, Milos	Signaling processes involved in C-peptide induced chemotaxis of CD4-positive lymphocytes	Clinic of Internal Medicine II	10/28/2005	Dr. biol. hum.
Azoitei, Anca	Characterization of hormone binding to the ecdysone receptor	Institute of General Zoology and Endocrinology	06/30/2008	Dr. rer. nat.
Betanska, Katarzyna	Intracellular localization of invertebrate nuclear receptors	Institute of General Zoology and Endocrinology	06/30/2007	Dr. rer. nat.
Heinrich, Christiane	Immunglobulin G-Isotypen der Autoantikörper gegen Glutamat-decarboxylase 65	Clinic of Internal Medicine I	10/23/2008	Dr. med.
Khuseyinova, Natalie	Emerging Role of Lipoprotein-associated Phospholipase A2 (Lp-PLA2) in Cardiometabolic Disorders	Clinic of Internal Medicine II	10/31/2008	Dr. med.
Rathmann, Silvia	Charakterisierung Präproinsulin-spezifischer CD8+ T-Zellen im humanen Typ 1 Diabetes mellitus	Clinic of Internal Medicine I	06/03/2005	Dr. biol. hum.
Spyrantis, Andreas	Induction of Type 1 Diabetes using Preproinsulin-based Vaccines in Experimental Autoimmune Diabetes (EAD)	Clinic of Internal Medicine I	07/20/2007	Dr. biol. hum.
Tata, Nageswara R.	Visualizing Pdx-1 expressing cells in vitro differentiating ES cell cultures	Institute for Immunology	06/30/2007	Dr. biol. hum.
Von Blume, Julia	Indentification of post-translational modifications regulating compartment specific substrate phosphorylation by Protein Kinase D2	Clinic of Internal Medicine I	12/08/2006	Dr. biol. hum.

Students of Programme “Experimental Medicine”

Total number of PhD students	**19**
Male	**9**
Female	**10**
International students	**0**
Parent students	**0**

Doctorates conferred (2006-2009), Programme “Experimental Medicine”

Name	Title	Institute	Date of final Examination	Degree
Jesse, Sarah	Charakterisierung einer neuen Isoform des humanen Transkriptionsfaktors Lef-1 in der Genese des Pankreaskarzinoms	Clinic of Internal Medicine I	05/30/2008	Dr. med.
Mangold, Stefanie	Apoptose von Alveolar Typ II Epithelzellen nach stumpfem Thoraxtrauma – Rolle der Alveolamakrophagen	Clinic of Trauma Surgery	07/16/2009	Dr. med.

Soft Skill Courses

Course name	Date	Organizer
Biosafety	04/15/2010 - 04/16/2010	Akademie für Wissenschaft, Wirtschaft und Technik
Project Management	11/27/2009 - 11/28/2009	GSC 270
Academic Presentation Skills – Improving performance at international conferences	09/28/2009 - 09/30/2009	International DAAD-Academy
Intercultural conflicts and mediation strategies	09/18/2009 - 09/20/2009	Evangelische Studentengemeinde Ulm
Bioethics	summer term 2007 summer term 2008 08/27/2009 - 08/31/2009	Master Programme Molecular Medicine
Good Scientific Practice	07/03/2008 - 07/04/2008 11/24/2008 - 04/28/2008 05/25/2009 - 05/29/2009 06/15/2009 - 05/19/2009	GSC 270
European Patent Law	06/27/2007 - 06/28/2009 07/30/2008 - 07/31/2008 04/24/2008 - 04/20/2009	Master Programme Molecular Medicine
In vivo Imaging Methods from Preclinical to Clinical Research	06/26/2009 - 06/27/2009	Master Programme Molecular Medicine
Career Workshop	04/24/2009 - 04/25/2009	GSC 270
German Course for beginners	winter term 2008/09 summer term 2009	GSC 270
German Course for advanced learners	summer term 2009	GSC 270

Excursions

Destination	Date	Organizer
Sanofi-Aventis, Berlin	06/25/2009 - 06/27/2009	GRK 1041
Boehringer Ingelheim, Biberach	09/24/2009	GSC 270
Boehringer Ingelheim, Biberach	05/14/2009	GSC 270
Rentschler Biotechnologie, Laupheim	01/16/2009	GSC 270
CANDOR Bioscience GmbH, Weißensberg	06/13/2008	GRK 1041
Ratiopharm GmbH, Ulm	06/21/2007	GRK 1041
Boehringer Ingelheim, Biberach	06/28/2006	GRK 1041
Altana Pharma, Konstanz	07/20/2005	GRK 1041

International Symposia

Meeting	Date	Organizer
Genetics of Diabetes Mellitus	10/14/2009	GRK 1041
Fall Meeting 2009	10/05/2009 -10/07/2009	GSC 270
Spring Meeting 2009	04/02/2009 - 04/04/2009	GSC 270
Fall Meeting 2008	10/16/2008 - 10/18/2008	GSC 270 & GRK 1041
Spring Meeting 2008	04/03/2008 - 04/05/2008	GSC 270
Fall Meeting 2007	10/11/2007 - 10/13/2007	GSC 270 & SFB 497
Steroid Hormones, Metabolism and Immune Function	12/12/2006 – 12/14/2006	GRK 1041
Founding Symposium GSC 270	10/26/2006 - 10/28/2006	GSC 270
Steroid Hormones, Metabolism and Immune Function	10/05/2006	GRK 1041
GRK Meeting of the Research Groups from Karlsruhe and Ulm	10/04/2006	GRK 1041
Hormones of marmots	10/20/2005	GRK 1041
Nuclear Receptors	10/06/2005	GRK 1041

Summer and Winter Schools

Topic	Date, Venue	Organizer
GRK Winter School 2009	12/15/2009 - 12/17/2009 Kühtai/Austria	GRK 1041
Third Tongji-Ulm Summer School in Molecular Medicine: Stem Cell Biology	07/27/2009 - 08/07/2009 Wuhan/China	GSC 270
20th International Summer School of Epidemiology	07/27/2009 - 07/31/2009 Günzburg/Germany	Inst. for Epidemiology, ICAS, GSC 270, UNC, Chapel Hill, USA
PENS Summer School - Metabolic Aspects of Chronic Brain Diseases	07/09/2009 - 07/15/2009 Günzburg/Germany	Clinic of Neurology Ulm University
Mouse Genetics	06/02/2009 - 06/06/2009 Oulu/Finland	Biocenter Oulu
Neurology	04/04/2009 - 04/18/2009 Peking/China	Clinic of Neurology, Ulm University, GSC 270
Second Tongji-Ulm Summer School in Molecular Medicine	07/21/2008 - 08/01/2008 Wuhan/China	GSC 270
Advances in Cell Death Research - from Basic Principles to New Therapeutic Concepts	07/16/2008 - 07/20/2008 Günzburg/Germany	Marie Curie Research Training Network
Summer School Timisoara	07/07/2008 - 07/20/2008 Timisoara/Romania	GSC 270
GRK Winter School 2007	12/12/2007 - 12/13/2007 Kühtai/Austria	GRK 1041
First Tongji-Ulm Summer School in Molecular Medicine: From Molecules to Therapies	08/13/2007 - 08/25/2007 Wuhan/China	GSC 270

Retreats

Topic	Date, Venue	Organizer
Genetics and Molecular Biology	09/25/2009 - 09/27/2009 Asheville/USA	University of North Carolina at Chapel Hill, USA
Signalling Networks in Oncology: molecules, mice and men	08/06/2009 - 08/08/2009 Allensbach-Hegne/Germany	GSC 270
G protein-coupled chemokine and Wnt receptors as regulators of mammalian development and cancer progression	06/21/2009 - 06/24/2009 Bigorio/Switzerland	GSC 270

Minisymposia/Workshops

Topic	Date	Organizer
Workshop at Bayer Schering Pharma	10/14/2009 - 10/16/2009	University Children's Hospital
Women Career Development	09/26/2009	University Children's Hospital
Seminars in Cell and Developmental Biology	05/20/2009	GSC 270
Biostatistics Workshop	02/17/2009	Experimental Anesthesiology
Signal transduction in development, degeneration and disease	09/17/2008	GSC 270
Fat cells	10/11/2007	GRK 1041
Molecular Diabetology and Endocrinology in Clinical Medicine	04/27/2007	GRK 1041
GRK Mini-Symposium, Heinrich-Fabri-Institute	04/21/2005	GRK 1041

Social Activities

Activity	Date
Get together	12/10/2009
Summer Party	08/05/2009
Visit of the Bundesfestung Ulm	08/04/2009
Jour fixe "Application procedure in Germany"	07/07/2009
Barbecue	07/02/2009
Excursion to "Nördlinger Ried"	06/20/2009
Visit of Ulm' s Fishermen's and Tanners' Quarter	06/02/2009
Jour fixe "Europe today"	05/05/2009
Movie "Slumdog Millionaire"	03/30/2009
Ski Excursion	03/15/2009
Jour fixe "Cinema"	03/03/2009
Jour fixe "Carnival"	02/10/2009
Welcome Evening	01/20/2009
Christmas Party	12/10/2008
Get together	07/27/2006
Get together	10/08/2004

Invited Speakers (2006-2009)

Topic	Speaker	Date	Organizer
The role of mitochondria in beta-cell stimulus-secretion coupling and the pathogenesis of type 2 diabetes	H. Mulder, Malmö/Sweden	11/19/2009	GRK 1041
Cytokines and beta-cell biology/pathology: from concept to clinical translation	T. Mandrup-Poulsen, Gentofte/Denmark	10/22/2009	GRK 1041
Moving targets – receptor diffusion and the mode of G protein activation	M. Freissmuth, Vienna/Austria	10/06/2009	GSC 270
Systems genetics of adult hippocampal neurogenesis	R. Overall, Dresden/Germany	10/06/2009	GSC 270
Identification of gene networks in hematopoietic stem cells	G. de Haan, Groningen/NL	10/06/2009	GSC 270
Forward genetics to identify genes regulating hematopoietic stem cells	G. Van Zant, Lexington/USA	10/06/2009	GSC 270
Gene therapy for Diabetes: moving forward to the clinic?	F. Bosch, Barcelona/Spain	10/06/2009	GSC 270
Recent development in gene therapy for hemophilia	T. VandenDriesschen, Leuven/NL	10/06/2009	GSC 270
Novel hyperactive transposases obtained by Darwinian evolution and selection for efficient stem cell gene delivery	T. Vanden Driesschen, Leuven/NL	10/06/2009	GSC 270
Gene therapy for chronic granulomatosis: ups and downs	M. Grez, Frankfurt/Germany	10/06/2009	GSC 270
GPCRs as metabolic sensors - physiology and pharmacology	S. Offermanns, Heidelberg/Germany	10/05/2009	GSC 270
Strategies for the differentiation of embryonic stem cells into the endoderm and pancreatic lineage	A. Wobus, Gatersleben/Germany	07/23/2009	GRK 1041
Not all in the genes: the origins of type 1 diabetes	D. Leslie, London/UK	07/16/2009	GRK 1041
Dual therapy improves stem cell recruitment, heart function, and survival after myocardial infarction	W.-M. Franz, Munich/Germany	07/16/2009	SFB 497
PTK7 signaling in neural crest migration	A. Borchers, Göttingen/Germany	07/08/2009	GSC 270
Induced and intrinsic clonal dominance in gene-modified hematopoiesis	C. Baum, Hannover/Germany	07/07/2009	SFB 497
Dynamics of Ras and Src Membrane Interactions in Live Cells and their Roles in Signaling	Y. Henis, Tel Aviv/Israel	07/06/2009	SFB 497
Identification, characterization and regulation of islet beta-cell (re)generation during normal development and autoimmune diabetes in mice	K. Pechhold, National Institute of Health/USA	06/08/2009	SFB 518
Is treatment of postmeal hyperglycaemia beneficial? How can we achieve postmeal glucose control?	H.-J. Wörle, Boehringer Ingelheim/Germany	06/04/2009	GRK 1041

Topic	Speaker	Date	Organizer
Gene regulation mechanisms by the transcriptional coactivator Mastermind-like 1	A. Wallberg, Stockholm/Sweden	06/04/2009	SFB 497
The diverse biological functions of START domain proteins in lipidmetabolism, signaling and cell transformation	M. Olayioye, Stuttgart/Germany	05/20/2009	GSC 270
Interaction of Wnt, Bmp and hedgehog signalling in limb musculoskeletal development and disease	S. Stricker, Berlin/Germany	05/20/2009	GSC 270
RunX1 and rhe origin of blood cells	C. Lancrin, Manchester/UK	05/20/2009	GSC 270
Molecular mechanisms of neuronal development in the dorsal spinal cord	C. Birchmeier-Kohler, Berlin/Germany	05/15/2009	SFB 497
Function of cytokines in lymphoid tissue development	D. Finke, Basel/Switzerland	05/14/2009	SFB 497
Molecular circuits controling (cardiac) muscle remodeling and regeneration	T. Braun, Bad Nauheim/Germany	05/07/2009	SFB 497 & SFB 518
Programming and selection of pluripotent stem cells towards distinct cardiovascular cell types	W.-M. Franz, Munich/Germany	05/06/2009	GSC 270
Kinase-dependent regulation of seven transmembrane proteins in vertebrate development	M. Philipp, Duke, North Carolina/ USA	04/30/2009	GSC 270
Borna Disease Virus - A tool to study mechanisms of selective neuronal degeneration in the hippocampus	B. Heimrich, Freiburg/Germany	04/27/2009	SFB 497
Molecular and cellular aspects of regulatory T cell generation and function	K. Kretschmer, Dresden/Germany	04/23/2009	SFB 497
Self-renewal versus differentiation in hematopoietic stem and progenitor cells	B. Giebel, Essen/Germany	04/16/2009	SFB 497
Senescence at the tumor/stroma interface	C. Schmitt, Berlin/Germany	04/04/2009	GSC 270
Leukemic stem cells in acute myeloid leukemia	C. Buske, Munich/Germany	04/04/2009	GSC 270
Pathogenesis of Hodgkin lymphoma	R. Küppers, Essen/Germany	04/04/2009	GSC 270
Cancer and metastasis: lessons from the embryo?	S. Piccolo, Padua/Italy	04/04/2009	GSC 270
Molecular strategies for the development of new antiviral drugs	G. Palù, Padua/Italy	04/03/2009	GSC 270
The bachelor of clinical science course of studies at University of Exeter	N. Toms, Plymouth/UK	04/03/2009	GSC 270
Modelling Downstream Effects of Signalling Pathway Deregulation	R. Spang, Regensburg/Germany	04/03/2009	GSC 270
Steps towards Spatial Multi-Level Modeling and Simulation in Computational Biology	A. Uhrmacher, Rostock/Germany	04/03/2009	GSC 270

Topic	Speaker	Date	Organizer
Tree based classification as Tool for Systems Biology	B. Lausen, Essex/UK	04/03/2009	GSC 270
Making it small: protein microarrays – arrays of applications	T. Joos, Reutlingen/Germany	04/03/2009	GSC 270
From loss of merlin to tumorigenesis	O. Hanemann, Plymouth/UK	04/03/2009	GSC 270
Developmental control of the cell cycle	B. Duronio, Chapel Hill/USA	04/03/2009	GSC 270
Cell-cell communication in the developing nervous system	E. Pera, Lund/Sweden	04/03/2009	GSC 270
Determination and differentiation during eye development	T. Hollemann, Halle/Germany	04/03/2009	GSC 270
Patterning of the early vertebrate heart	F. Conlon, Chapel Hill/USA	04/03/2009	GSC 270
Principles of CD8 T cell priming against cytomegalovirus	M. Reddehase, Mainz/Germany	04/02/2009	GSC 270
Leukemic Stem Cells in Acute Myeloid Leukemia	C. Buske, Munich/Germany	03/27/2009	Stem Cell & Tumor Stem Cell Club
In vitro characterization (2D and 3D) of osteoblasts and msc's from old sheep & establishment of a critical size defect in sheep for bone engineering application by using plate fixation	D. Hutmacher, Queensland/Australia	03/23/2009	Institute of Orthopaedic Research and Biomechanics
MAP-kinases downstream signaling in inflammation and beyond	A. Kotlyarov, Hannover/Germany	03/17/2009	SFB 518
Immunomodulation of T1D: GAD treatment and insulin secretion in recent-onset type1 diabetes	J. Ludvigsson, Linköping/Sweden	03/12/2009	GRK 1041
Mucin synthesis and regulated secretion in airway goblet cells	C. W. Davis, Chapel Hill/USA	03/02/2009	Institute of General Physiology
Danger sensing by complement: the curious case of an anaphylatoxin receptor	J. Köhl, Lübeck/Germany	02/16/2009	KFO-200 & GSC 270
Biosensors spy on biosensors: assembly and function of TRP channels	M. Schaefer, Leipzig/Germany	02/12/2009	GRK 1041
Funktionelle Genomanalysen beim Pankreaskarzinom	T. Gress, Gießen and Marburg/ Germany	01/29/2009	SFB 518
Thyroid Hormone Axis Beyond Textbooks: Novel Actors, Metabolites, Nutritive and Environmental Targets	J. Köhrle, Berlin/Germany	01/22/2009	GRK 1041
The Granulocyte Nuclear Envelope: Interactions with Heterochromatin and Cytoskeleton	D. & A. Olins, Maine/USA & Heidelberg/Germany	01/15/2009	SFB 518
Molecular and cellular aging – from mechanisms to clinical perspectives	R. G. Faragher, Brighton/UK	11/26/2008	KFO142
Molecular mechanisms for driving and braking T cell activation	D. Krappmann, Munich/Germany	11/20/2008	Institute of Physiological Chemistry
Wnt6 signalling and GATA transcription factors regulate heart muscle development in Xenopus	S. Hoppler, Aberdeen/UK	11/20/2008	Institute of Biochemistry and Molecular Biology

Topic	Speaker	Date	Organizer
DFG-Funding in the Life Sciences: Questions and Answers	F. Wissing, DFG/Germany	10/18/2008	GSC 270
The clinical manifestation of defective DNA repair in the hereditary cancer syndromes, Nijmegen Breakage Syndrome and Fanconi anaemia	M. Digweed, Berlin/Germany	10/18/2008	GSC 270
Identification of global chromatin modification patterns in leukemia by ChIP-Chip	C. Müller-Tidow, Münster/Germany	10/18/2008	GSC 270
Distinct gene expression profiles of acute myeloid/T-lymphoid leukemia with silenced CEBPA and mutations in NOTCH1	B. Wouters, Rotterdam/NL	10/18/2008	GSC 270
DFG's programmes supporting young researchers	A. Buckow DFG/Germany	10/17/2008	GSC 270
The role of the microenvironment in the pathogenesis of B cell chronic lymphocytic leukemia	M. Seiffert, Heidelberg/Germany	10/17/2008	GSC 270
PALB2, a recently identified gene associated with hereditary susceptibility to breast cancer	S. Solyom, Oulu/Finland	10/17/2008	GSC 270
Cellular model systems for neurodegenerative disease	M. Leist, Konstanz/Germany	10/17/2008	GSC 270
Integrative analysis for finding genes and networks involved in diabetes and other complex diseases	F. Pociot, Gentofte/Danmark & Lund/Sweden	10/17/2008	GSC 270
Increase in tissue endothelin-1 and ETA receptor levels in human aortic valve stenosis	T. Peltonen, Oulu/Finland	10/17/2008	GSC 270
The genetics of different forms of type 1 diabetes	P. Pozzilli Rome/Italy	10/17/2008	GSC 270
Assembling an organ: The kidney as a model system	S. Vainio Oulu/Finland	10/16/2008	GSC 270
Changing perspectives in diabetes: Declassifying diabetes	E. Gale, Bristol/UK	10/11/2008	SFB 518
Class II MHC: Biology and association with autoimmune disease	E. Mellins, Stanford/USA	10/11/2008	SFB 518
Genetic analysis of insulin action	E. Rother, Cologne/Germany	10/11/2008	SFB 518
Prime role for an insulin epitope in the development of type 1 diabetes	G. Eisenbarth, Aurora/USA	10/11/2008	SFB 518
Insulitis in type 2 diabetes: from concept to clinical translation	M. Donath, Zürich/Switzerland	10/11/2008	SFB 518
The CD4+ autoreactive T cell in T1D	G. Nepom, Seattle/USA	10/10/2008	SFB 518
Identification of a receptor for export of collagenVII from the endoplasmic reticulum	V. Malhotra, Barcelona/Spain	10/10/2008	SFB 518
Molecular Engineering of Cellular Environments: Cell Adhesion and Migration on Nano-Digital Surfaces	J. P. Spatz, Heidelberg/Germany	10/10/2008	SFB 518
Therapeutic potential of cancer Stem cell targeting	R. de Maria, Rome/Italy	10/10/2008	SFB 518

Topic	Speaker	Date	Organizer
Distinct Tumor Stem Cell Populations in Pancreatic Cancer – Implications for Tumor Biology	C. Heeschen, Munich/Germany	10/10/2008	SFB 518
Targeting IAPs TNFa and ubiquitin connections	D. Vucic, San Francisco/USA	10/10/2008	SFB 518
(X)IAP Inhibition and Apoptosis Induction: Explaining the Remarkable Synergy with Death Receptor Agonists	J. Gillard, Montreal/Canada	10/10/2008	SFB 518
Inducing Apoptosis with TRAIL Receptor Antibodies	R.C. Humphreys Rockville/USA	10/10/2008	SFB 518
From Caterpillars to Clinics: a rationally designed anti-cancer drug specifically kills tumour cells	J. Silke Victoria/Australia	10/09/2008	SFB 518
Defining the role of microRNAs Stem Cell self-renewal and differentiation	M. Castoldi Heidelberg/Germany	10/06/2008	Institute of Biochemistry and Molecular Biology
The emerging role of reversible protein oxidation in cellular signaling and regulation	T. Dick, Heidelberg/Germany	09/10/2008	SFB 497
The role of arginine methylation in transcriptional control	U.-M. Bauer, Marburg/Germany	08/14)2008	SFB 497
From molecules to modules: The opsin receptor at different levels of biological organisation	K.-P. Hofmann, Berlin/Germany	06/26/2008	SFB 497
Prognostic significance of islet autoantibodies in pre-Type 1 diabetes	P. Achenbach, Munich/Germany	06/19/2008	GRK 1041
Epigenetic networks and cellular reprogramming	R. Paro, Zürich/Switzerland	06/18/2008	SFB 497
The role of the homeobox gene Sax2 in brain development and homeostasis	R. Simon, New York/USA	06/12/2008	Institute of Molecular and Cellular Anatomy
Cyro-electron tomography of whole cells	M. Cyrklaff, Heidelberg/Germany	06/05/2008	SFB 518
From cells to functional tissues: A study of pancreatic islets and their blood vessels	E. Lammert, Düsseldorf & Dresden/ Germany	05/30/2008	GRK 1041
Genetic Control of Cell Behavior during Zebrafish Heart Morphogenesis	B. Jungblut, Bad Nauheim/Germany	05/15/2008	SFB 497
Wnt signalling in Drosophila: Insights into signal presentation and transduction	V. Katanaev, Konstanz/Germany	04/17/2008	SFB 497
Regulation of Golgi organization	F. Bard, Singapore	04/05/2008	GSC 270
Fundamental differences between human and rodent islet physiology: how can we trick human islets to proliferate	B. Gauthier, Geneva/Switzerland	04/05/2008	GSC 270
Molecular events controling cancer stem cell survival	G. Stassi, Palermo/Italy	04/05/2008	GSC 270
PTEN and hepatocellular carcinoma	D. Yang, Wuhan/China	04/04/2008	GSC 270

Topic	Speaker	Date	Organizer
Pdcd4, a colon cancer prognostic that is regulated by micro RNA 21	H. Allgayer, Mannheim/Germany	04/04/2008	GSC 270
Expression of mutant type XIII collagen in transgenic mice is associated with development of lymphomas	A. Tuomisto, Oulu/Finland	04/04/2008	GSC 270
Type XIII collagen on mouse skin carcinogenesis	J. Tahkola Oulu/Finland	04/04/2008	GSC 270
The effect of TRAIL on tumor cells	I. Jeremias, Munich/Germany	04/04/2008	GSC 270
Identification of a novel stem cell population that contributes to mammalian brain regeneration	V. Taylor, Freiburg/Germany	04/04/2008	GSC 270
Function of type XV collagen and Laminin 4 in peripheral nerve development	K. Rasi, Oulu/Finland	04/04/2008	GSC 270
Wnt-11 signalling in the control of heart development	I. Nagy Oulu/Finland	04/04/2008	GSC 270
Finding the pathway, mass cell migration directed by non-canonical Wnt-signalling	D. Wedlich, Karlsruhe/Germany	04/04/2008	GSC 270
Gene control in murine muscle and brain: essential functions of SRF	A. Nordheim, Tübingen/Germany	04/03/2008	GSC 270
Erythrocyte GLUT1 triggers dehydroascorbic uptake in mammals unable to synthesize vitamin C	N. Taylor, Montpellier/France	03/31/2008	Institute of Immunology
Role of the adipose tissue as an immunological organ	M. Schäffler, Regensburg/Germany	01/31/2008	GRK 1041
Early and late immunological checkpoints in the pathogenesis of autoimmune diabetes	C. M. Cilio, Lund/Sweden	01/09/2008	GRK 1041
CD8aa+ TcRab+ intraepithelial lymphocyte differentiation in the thymus	F. Lambolez, La Jolla/USA	12/20/2007	SBF 497
Fatty liver: a cause of viscera obesity?	D. Müller-Wieland, Hamburg/Germany	12/12/2007	GRK 1041
Targeting the Ubiquitin System	I. Dikic, Frankfurt/Germany	11/27/2007	SFB 497
Autoimmune diabetes in adults: recent findings on antibodies titre	M. Capizzi, Roma/Italy	11/22/2007	GRK 1041
Cellular poly (ADP-ribosyl)ation: a matter of life and death	A. Bürkle, Konstanz/Germany	11/15/2007	SFB 497
Prediction and Signal Classification using Reconstructed Phase Spaces	R. J. Povinelli, Marquette University/ USA	11/14/2007	SFB 518
The role of the nuclear receptor tailless in neurogenesis and brain tumor formation	G. Schütz, Heidelberg/Germany	10/18/2007	SFB 497
The role of Toll-like receptor stimulation in autoimmunity or tolerance	M. Ehlers, Berlin/Germany	10/16/2007	GRK 1041
Molecular mechanisms of assembly and plasticity of CNS synapses	E. D. Gundelfinger, Magdeburg/Germany	10/11/2007	SFB 497
Mutations in postsynaptic proteins link synapse formation to mental retardation	C. Sala, Milano/Italy	10/11/2007	SFB 497
Role of Shank associated protein in dendrite morphogenesis	L. Fagni, Montpellier/France	10/11/2007	SFB 497

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Possible targets for neuroprotectants against excitotoxicity - the postsynaptic density and beyond	M. Courtney, Kuopio/Finland	10/11/2007	SFB 497
Neuroligin function - From synaptogenesis to molecular mechanisms of autism	N. Brose, Göttingen/Germany	10/11/2007	SFB 497
Abnormal synaptogenesis and melatonin synthesis in autism spectrum disorders	T. Bourgeron Paris/France	10/11/2007	SFB 497
The role of serine kinases in lymphocytes	D. Cantrell, Dundee/UK	10/12/2007	SFB 497
Control of T cell activation and cytotoxic antitumor immunity by the E3 ligase Cbl-b	J. Penninger, Wien/Austria	10/12/2007	SFB 497
Calcium signalling in lymphocytes	A. Rao, Boston/USA	10/12/2007	SFB 497
Initiation and fine-tuning the calcium response of activated B cells	J. Wienands, Göttingen/Germany	10/12/2007	SFB 497
The plasticity of T cell responses to different antigen presenting cells	M. Gunzer, Braunschweig/Germany	10/12/2007	SFB 497
Spatiotemporal aspects of T cell activation in vitro and in vivo	M. Krummel, San Francisco/USA	10/12/2007	SFB 497
Wnt signaling directly represses hemocytespecific genes through a novel mechanism	K. Cadigan, Ann Arbor/USA	10/12/2007	SFB 497
Cross-talks between retinoic acid, Fgf and Shh signalling during early mouse caudal development	P. Dollé, Illkirch/France	10/12/2007	SFB 497
Cell fate decisions during sensory placode development	A. Streit, London/UK	10/12/2007	SFB 497
Natural and small molecule inducers of cardiogenesis	M. Mercola, La Jolla/USA	10/12/2007	SFB 497
Calcium signaling in zebrafish embryonic patterning and morphogenesis	D. C. Slusarski, Iowa City/USA	10/12/2007	SFB 497
The reversal of cell differentiation by nuclear transfer	J. Gurdon, Cambridge/UK	10/12/2007	SFB 497
Nanog; guardian of pluripotency, gateway to the germline	I. Chambers, Edinburgh/UK	10/13/2007	SFB 497
Epigenetic landscape in stem cells	HH Ng, Singapore	10/13/2007	SFB 497
Dissecting self-renewal and programmed cell death in pluripotent embryonic stem cells	T. P. Zwaka, Houston/USA	10/13/2007	SFB 497
From ES cells to neural stem cells to functional neurons	O. Brüstle, Bonn/Germany	10/13/2007	SFB 497
Lineage specific differentiation of embryonic stem cells	G. M. Keller, Toronto/Canada	10/13/2007	SFB 497
Transcriptional control of B cell immortalization by Epstein-Barr Virus nuclear antigens 2, 3A and 3C	B. Kempkes, Munich/Germany	09/20/2007	SFB 497
A human phenome-interactome network of protein complexes implicated in genetic disorders	F. Pociot, Gentofte/Denmark	09/13/2007	GRK 1041

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IKK/NF-kB signalling protects the liver and the gut from inflammation and cancer	M. Pasparakis, Köln/Germany	08/21/2007	SFB 497
The role of the non-receptor tyrosine kinase Syk for the control of the acute inflammatory response	B. Walzog, Munich/Germany	07/19/2007	SFB 497
Identification of novel Protein Kinase D targets	J. van Lint, Leuven/Belgien	07/16/2007	SFB 518
Advanced Glycation Endproducts (AGE) - Mediators of Tissue Ageing?	A. Simm, Halle-Wittenberg/ Germany	07/09/2007	KFO
Clinical use of human embryonic stem cells	T. Zwaka, Houston/USA	06/29/2007	SFB 451
Engineering myocardial tissue	T. Eschenhagen, Hamburg/Germany	06/29/2007	SFB 451
Stem cell therapy in stable and unstable angina	A. Zeiher, Frankfurt/Germany	06/29/2007	SFB 451
Cardiovascular molecular imaging	O. Schober, Münster/Germany	06/29/2007	SFB 451
Targeted contrast agents for imaging of atherosclerosis	Z. Fayad, New York/USA	06/29/2007	SFB 451
Principles of contrast agents in molecular imaging	S. Caruthers, St. Louis/USA	06/29/2007	SFB 451
Stem cell based repair of the myocardium	B. Fleischmann, Bonn/Germany	06/29/2007	SFB 451
Gene activity profiles in pre- and post-conditioning	M. Schaub, Zürich/Switzerland	06/29/2007	SFB 451
Connexin 43 and cardioprotection	G. Heusch, Essen/Germany	06/29/2007	SFB 451
The RAS as a target to modulate vascular disease	G. Nickenig, Bonn/Germany	06/29/2007	SFB 451
Antiatherogenic properties of nuclear receptors	B. Staels, Lille/France	06/29/2007	SFB 451
The role of chemokines in vascular inflammation	C. Weber, Aachen/Germany	06/29/2007	SFB 451
The role of Timp3 in diabetes and vascular inflammation	M. Federici, Rome/Italy	06/28/2007	SFB 451
Insulin resistance and vascular complications	S. del Prato, Pisa/Italy	06/28/2007	SFB 451
Epidemiology of diabetes, insulin resistance, and acute coronary syndromes	D. McGuire, Dallas/USA	06/28/2007	SFB 451
CRP promotes atherogenesis	I. Jialal, Sacramento/USA	06/28/2007	SFB 451
Animal models of CRP and atherosclerosis	J. Fan, Yamanashi/Japan	06/28/2007	SFB 451
Inflammation markers and cardiovascular risk	A. von Eckardstein, Zürich/Switzerland	06/28/2007	SFB 451
Senescence of endothelial cells	J. Händeler, Frankfurt/Germany	06/28/2007	SFB 451

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Physical activity and endothelial progenitor cells	U. Laufs, Homburg/Germany	06/28/2007	SFB 451
The role of ADMA	R. Böger, Hamburg/Germany	06/28/2007	SFB 451
Arrhythmias and Congenital Heart Disease in Drosophila	R. Bodmer, San Diego/USA	06/28/2007	SFB 497
Animal models for type 1 diabetes	B. Roep, Leiden/NL	06/14/2007	GRK 1041
Cylindromatosis in mice	R. Fässler, Martinsried/Germany	05/07/2007	SFB 497
Functional Genomics and Proteomics in Cancer Research	J. Hoheisel Heidelberg/Germany	04/24/2007	SFB 518
Receptor mechanisms in taste perception	W. Meyerhof, Potsdam/Germany	04/19/2007	SFB 497
New aspects in ALS	O. Hardiman, Dublin/Ireland	04/16/2007	Clinic of Neurology
Molecular analysis of the non-canonical NF-kappaB pathway	Y. Sunami, Berlin/Germany	04/16/2007	SFB 497
Do infectious diseases protect from the development of allergic?	K. Erb, Boehringer Ingelheim/ Germany	04/16/2007	Microbiological-Infectious Seminar
Regulation of Type 1 diabetes by NKT cells	A. Lehuen, Paris/France	04-05-2007	GRK 1041
Role of Poly(ADP-ribose) Polymerase1 in NF-kappaB-dependent Gene Expression	M. O. Hottiger, Zürich/Switzerland	03/22/2007	Children's Hospital
Molecular mechanisms of cellular senescene	F. d'Abba di Fagagna, Milan/Italy	03/19/2007	Institute of Dermatology and Allergology
Axon-glia interactions and the control of myelination	K.-A. Nave, Göttingen/Germany	03/14/2007	SFB 497
UV irradiation, caspase-1 and alternative protein secretion	H.-D. Beer, Zürich/Switzerland	03/13/2007	Institute of Dermatology and Allergology
Function of Myc target genes in growth and stress control of the nucleolus	D. Eick, Munich/Germany	02/15/2007	SFB 497
Adiponectin and mortality	W. März, Graz/Austria	02/08/2007	GRK 1041
Intestinal Antigen Acquisition and Processing	PH.-C. Reinecker, Boston/USA	01/24/2007	SFB 518
Seminar: Let there be light – bioluminescent reporter systems for in vitro and in vivo imaging of bacteria	C. Riedel, Cork/Ireland	01/15/2007	Institute of Microbiology and Biotechnology
Design of the Ludwigshafen Study – How to perform clinical studies	B. Winkelmann, Frankfurt/Germany	12/21/2006	GRK 1041
Study of transcriptionnals targets of Epstein-Barr virus (EBV) and apoptosis regulation by the pro-apoptotic receptor FAS (CD95) in EBV infected B cells: Role of LMP1	C. Le Clorennec, Limoges/France	12/18/2006	SFB 497

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Chlamydiae if they exist they are everywhere	A. Pospischil, Zürich/Switzerland	12/11/2006	Institute of Medical Microbiology and Hygiene
The changing face of autoimmune diabetes	D. Mauricio Barcelona/Spain	10/28/2006	GSC 270
Central mechanisms of tolerance	C. Bleul Freiburg/Germany	10/28/2006	GSC 270
In vivo imaging in drug discovery and development	D. Stiller, Boehringer Ingelheim, Biberach/Germany	10/28/2006	GSC 270
Analysis of signaling networks downstream of G-protein coupled receptors	M. Thelen, Bellinzona/Switzerland	10/27/2006	GSC 270
Bassoon, Piccolo and their voice in the ensemble of presynaptic proteins	E. D. Gundelfinger, Magdeburg/Germany	10/27/2006	GSC 270
The IKK complex is the central element in NF-kappaB activation by oxidative stress and DNA damage	J. Piette, Lüttich/Belgium	10/27/2006	GSC 270
Enhancing drug sensitivity in human cancer via death receptor-mediated apoptosis	S. De Jong, Groningen/NL	10/27/2006	GSC 270
Structural aspects of regulation of PLC isoforms	T. D. Bunney, London/UK	10/27/2006	GSC 270
Paradigm shifts in our understanding of estrogen signaling following the discovery of estrogen receptor beta	S-Å. Gustafsson, Stockholm/Sweden	10/27/2006	GSC 270
Molecular basis of cancer: The Wnt paradigm	J. Behrens, Erlangen/Germany	10/26/2006	GSC 270
Role of Sox proteins in glial cell differentation	M. Wegner, Erlangen/Germany	10/19/2006	SFB 497
Modeling and treating immune-mediated diseases in transgenic zebrafish	N. Trede, Salt Lake City/USA	10/02/2006	SFB 497
Sumoylation of the transcription factors C/EBPbeta and NFATc1 and the functional consequences for T cells	F. Berberich-Siebelt, Würzburg/Germany	09/14/2006	SFB 497
Cardio protection by embryonic endothelial progenitor cells: Paracrine effects	C. Kupatt, Munich/Germany	09/07/2006	SFB 451
NF-kappaB-dependent cell cycle regulation in pancreatic ductual adenocarcinoma cells	G. Schneider, Munich/Germany	08/24/2006	SFB 497
Osmo-protection of lungs against deformation injury	R. Hubmayr, Rochester/USA	08/04/2006	Institute of Applied and General Physiology
The surfactant film under thermal stress: Insights to a new paradigm for surfactant composition & function	S. Orgeig, Adelaide/Australia	08/01/2006	Institute of Applied and General Physiology
Dynamics of Ras and Src membrane interactions in live cells	Y. I. Henis, Tel Aviv/ Israel	07/28/2006	SFB 497
Turning blood into insulin-producing cells or, re-programming of human blood monocytes into surrogate beta-cells for the treatment of Type 1 diabetes	B. R. Gauthier Geneva/Switzerland	07/27/2006	GRK 1041

Topic	Speaker	Date	Organizer
Genetics of type 1 diabetes and monogenetic forms of atypical diabetes	C. Julier, Paris/France	07/20/2006	GRK 1041
Epigenetic shut-down of Oct-3/4	Y. Bergman, Jerusalem/Israel	07/20/2006	SFB 497
Regulation of glucose metabolism in Bacillus subtilis by protein-RNA interactions	J. Stülke, Göttingen/Germany	07/17/2006	Institute of Microbiology and Biotechnology
Culturing Hepatitis C Virus - slecting the right ingredients opens new perspectives	T. Pietschmann, Heidelberg/Germany	07/10/2006	Institute of Virology
Retinoic acid signalling during early mouse embryogenesis	I. O. Sirbu, San Diego/USA	06/30/2006	SFB 497
Diversity, plasticity, and mechanical role of titin in muscle	W. Linke, Münster/Germany	06/28/2006	Institute of General and Applied Physiology
Vascular Endothelial Growth Factor (VEGF) in Meningitis and Sepsis	M. van der Flier, Rotterdam/Belgium	06/26/2006	Institute of Medical Microbiology and Hygiene
Generation of insulin-producing cells from adult pancreatic stem cells	J. Seißler, Munich/Germany	06/22/2006	GRK 1041
Synaptic physiology: applications and perspectives	D. M. Kullmann, London/UK	06/19/2006	Clinic of Neurology
Chronic inflammation as a universal modifier of prion tropism: From tertiary follicles to granulomatous inflammation. From mouse to sheep	M. Heikenwälder, Zürich/Switzerland	06/12/2006	Institute of Immunology
The adaptor protein Nck, a new player in the regulation of the activity of the eukaryotic initiation factor eIF2	L. Larose, Montreal/Canada	06/08/2006	SFB 497 + SFB 451
Management of Hemolytic Disease of the Newborn: Past, Present, and Future	G.A. Denomme, Toronto/Canada	05/24/2006	Institute of Transfusion Medicine
Hematopoietic stem cell expansion ex vivo	K. Karjalainen, Basel/Switzerland	05/22/2006	Institute of Medical Microbiology and Hygiene
Gene regulatory networks in early neural development	S. Moody, Washington/USA	05/18/2006	SFB 497
Regulation of CNC and Maf transcription factors: knockouts, cytokines and stress	V. Blank, Montreal/Canada	05/18/2006	SFB 497
Clinical Utility of RHD Genotyping in 33,000 In- and Outpatients from Toronto	G. A. Denomme, Toronto/Canada	05/17/2006	Institute of Transfusion Medicine
Amphibians as model to study endocrine disruptors affecting reproduction and thyroid system	W. Kloas, Berlin/Germany	05/11/2006	GRK 1041
Mass blood group genotyping using microarray technology	G. A. Denomme, Toronto/Canada	05/10/2006	Institute of Transfusion Medicine
Degeneration of dopaminergic neurons - mouse models and mechanisms	B. Liss, Marburg/Germany	05/08/2006	Clinic of Neurology

Topic	Speaker	Date	Organizer
Early T-cell development	A. Krueger, Boston/USA	05/05/2006	SFB 497
The daily rhythms of genes, cells, and organs	U. Schibler, Geneva/Switzerland	04/20/2006	SFB 497
Molecular pathomechanism of acute and chronic testicular inflammation	A. Meinhardt, Giessen/Germany	04/06/2006	GRK 1041
Raf - Kinases and Treatment of Human Cancer	U. R. Rapp, Würzburg/Germany	03/16/2006	SFB 497
Elementary Properties of Exocytosis and Hormone Release	R. Zorec, Ljubliana/Slovenia	03/09/2006	Institute of Applied Physiology & Institute of General Physiology
Identifying activated vs. resting, helped vs. unhelped antigen-specific CD8 memory cells in healthy and HIV-infected individuals	P. V. Lehmann, Cleveland/USA	03/07/2006	GRK 1041
Recent advances in cardiac CT - Implications for research and clinical practice	U. Hoffmann, Boston/USA	02/23/2006	SFB 451
Understanding the switch from proliferative to terminally differentiated cardiomyocytes towards myocardial regeneration	M. Hesse, Calgary/Canada	02/20/2006	SFB 451
Electrostatic interactions in biological systems	R. Winkler, Jülich/Germany	02/07/2006	SFB 569
Diagnostic DNA microarrays for rapid identification of microbial pathogens and their antibiotic resistance	T. Bachmann, Stuttgart/Germany	02/06/2006	Institute of Medical Microbiology and Hygiene
Diabetes and Cardiovascular Disease: The Clock is Ticking	P. Grant, Leeds/UK	02/02/2006	SFB 451
Two Steps to Propagate Mesenchymal Stem Cells for Clinical Applications	D. Strunk, Graz/Austria	01/25/2006	Institute of Transfusion Medicine
Blood Monocytes Mimic Endothelial Progenitor Cells	E. Rohde, Graz/Austria	01/25/2006	Institute of Transfusion Medicine

Publications of Graduates

Aleksic, Milos:

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Jesse, Sarah:

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* equal contribution

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List of Abbreviations:

GSC 270	International Graduate School in Molecular Medicine Ulm
GRK 1041	Research Training Group 1041: Molecular Diabetology and Endocrinology in Medicine
KFO	Clinical Research Unit
SFB	Collaborative Research Centre

Publisher:
International Graduate School
in Molecular Medicine Ulm
Ulm University
Meyerhofstr. N 27/2.011
89081 Ulm · Germany
Phone +49 (0)731-50-36290
Fax +49 (0)731-50-36292
phd.molmed@uni-ulm.de
www.uni-ulm.de/mm

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Editors:
PD Dr. Dieter Brockmann
Prof. Dr. Michael Kühl
Larissa Dickhaut, M.A.

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artifox Communication Design Ulm
Gabriele Stautner, stautner@artifox.com
Proof reading:
artifox Pro-Client Edits
John McKeon, M.A., B.A. (Hons), mckeon@artifox.com
www.artifox.com

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International Graduate School
in Molecular Medicine Ulm
Ulm University
Meyerhofstr. N 27/2.011
89081 Ulm · Germany
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phd.molmed@uni-ulm.de
www.uni-ulm.de/mm