



Departments and Institutes

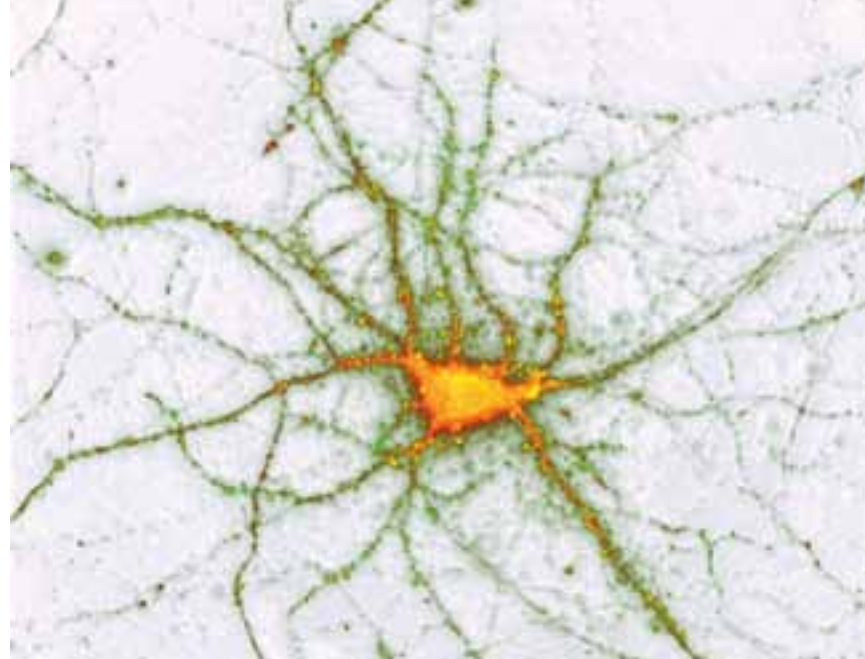
Ulm University Medicine is comprised of ten preclinical institutes, nine clinical-theoretical institutes and 34 medical institutes and departments.

Some of these have been combined to create Medical Centers.

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Hippocampal neuron in culture immunostained for a dendritic marker (red) and a synaptic molecule (Abi-1) in green.

Institute of Anatomy and Cell Biology

Head of Institute: Prof. Dr. Tobias M. Böckers

Keywords: Cell adhesion | heat shock proteins | neurogenesis | stem cells | synapses

The Institute of Anatomy and Cell Biology is concerned with research in the area of neuroscience and teaches human anatomy (macroscopy, histology and embryology) to students studying medicine and dentistry within the preclinical parts of their medical training. The *prosektur* is also part of the institute. It has in all 30 employees among whom are two professors (Prof. Tobias Böckers and Prof. Nikola Golenhofen), postdocs, seven PhD students and six medical students.

Our research topics concentrate on synaptic contacts within the central nervous system. Glutamatergic synapses in the central nervous system are specific cellular junctions that are characterized by synaptic vesicles attached to the active zone of the presynapse and 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-neurologin, cadherins) that are analyzed in the lab. 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 that suggest that several mental disorders have their molecular defect at the synapse/PSD level. The generation of induced pluripotent cells (iPS cells) from patients that can be differentiated into neurons of different kinds will help in understanding the pathophysiology of neuropsychiatric disorders.

The research group of Prof. Golenhofen investigates the role of several cell adhesion molecules within synaptic contact zones during development and plastic changes. Moreover, the group elucidates the physiological function of heat shock proteins in neurons, with respect to de- and regeneration, as well as in different neurological disease models.

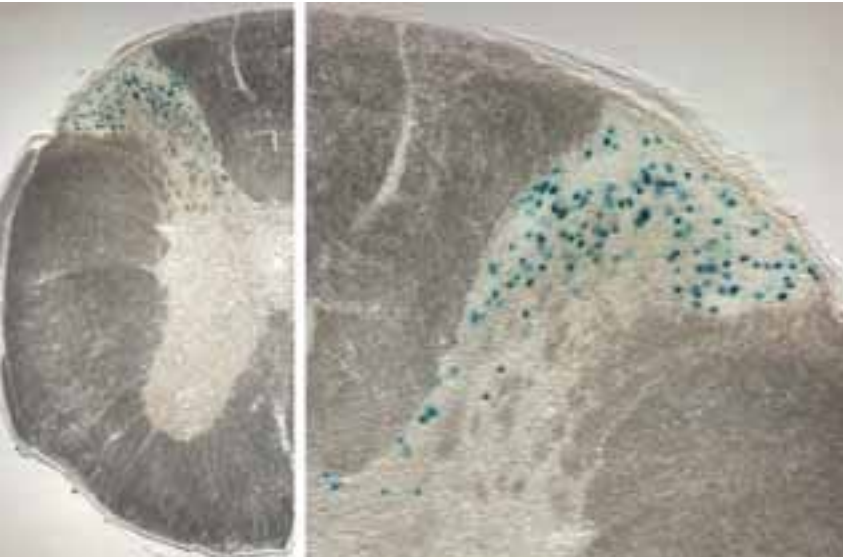


Teaching anatomy in the newly built *Theatrum anatomicum* neighboring the dissection room.

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Selected Publications:

- Schmeisser MJ, Grabrucker AM, Bockmann J, Boeckers TM (2009): Synaptic crosstalk between NMDA receptors and LAPSER1/ β -catenin at excitatory synapses. *J Biol Chem*, 284: 29146-29157.
- Grabrucker AM, Vaida B, Bockmann J, Boeckers TM (2009): Efficient targeting of proteins to postsynaptic densities of excitatory synapses using a novel pSDTarget vector system. *J Neurosci Methods* 181: 227-234.
- Liebau S, Proepper C, Schoen M, Schmidt Th, Bockmann J, Boeckers TM (2009): ProSAPiP2, a novel postsynaptic density protein that interacts with ProSAP2/Shank3. *BBRC*, 385: 460-465.
- Johannsen S, Duning K, Pavenstädt H-J, Kremerskothen J, Boeckers TM (2008): Temporal-spatial expression and novel biochemical properties of the memory-related protein KIBRA. *Neuroscience*, 155: 1165-1173.
- Spilker Ch, Samorano P, Boeckers TM, Kreutz MR, Gundelfinger ED (2008): SPAR2, a novel SPAR-related protein with GAP activity for Rap1 and Rap2. *J Neurochem*, 104: 187-201.
- Dieterich D, Karpova A, Mikhaylova M, Zdobnova I, König I, Landwehr M, Kreutz M, Smalla K-H, Richter K, Landgraf P, Reissner C, Boeckers TM, Zuschratter W, Spilker C, Seidenbecher C, Garner CC, Gundelfinger ED, Kreutz MR (2008): Caldendrin-Jacob: a protein liaison that couples NMDA receptor signalling to the nucleus. *PLoS Biology* 6(2) e34.



Cross sections through the mouse spinal cord at low (left panel) and higher (right panel) magnification. Dorsal spinal neurons expressing Gbx1 are visualized by insertion of a genetic reporter (IRES-nls-lacZ) into the genomic locus of Gbx1 (blue signals).

Institute of Molecular and Cellular Anatomy

Head of Institute: Prof. Dr. Stefan Britsch

Keywords: Dendrites | mouse genetics | microRNA | spinal cord | spines

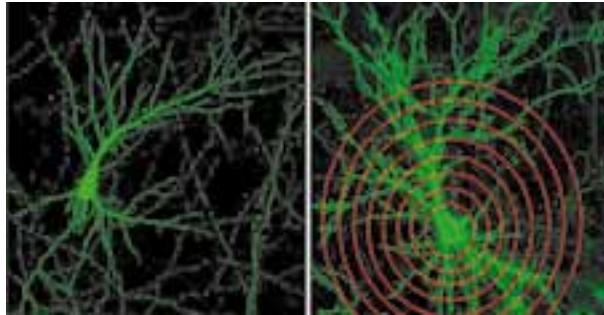
The ability of the mature nervous system to integrate, compute, and distribute information results from developmental processes that create diversity, connectivity, and the spatial organization of neurons. Our group is interested in the identification and functional characterization of genes involved in the molecular control of these processes.

Research Group: Transcriptional Control of Dorsal Spinal Cord Development

Head: Prof. Dr. Stefan Britsch

The dorsal spinal cord processes information from nociceptive, mechanosensory and proprioceptive primary sensory neurons and relays it to higher brain centers. The cellular basis of these functions resides in a large number of interneurons that are located within distinct layers of the dorsal spinal cord. The molecular characteristics of these interneurons, as well as the mechanisms underlying their development are incompletely defined. We identified novel candidate genes that are enriched in the dorsal spinal cord. Among these are the homeodomain transcription factor Gbx1 and two C₂H₂ zinc finger transcription factors, Bcl11a and Bcl11b. We showed that Gbx1 identifies a previously uncharacterized population of late-born, Lbx1⁺, Lhx1/5⁺, Pax2⁺ dorsal spinal neurons, which undergo GABAergic differentiation. The generation of loss-of-function mutations in mice allows us to determine the fate of Gbx1 mutant neurons during development. Gbx1 mutant mice are viable, however, display severe neurological defects indicating a critical role of Gbx1 in dorsal spinal development.

Bcl11a and b are closely related zincfinger transcription factors, which are expressed in the embryonic brain, spinal cord and peripheral nervous system. To analyze their functions during nervous system development, we have generated CNS-specific conditional mouse mutants for the Bcl11a and b genes (in collaboration with N. Copeland, Singapore). Conditional mutant animals die after birth indicating that both genes serve critical functions during nervous system development. Recent work from our group demonstrated that Bcl11a plays a key role in neuronal differentiation and the formation of functional neuronal circuits in the central nervous system.



Primary hippocampal neurons in culture overexpressing EGFP (left panel) or CALEB/NGC (right panel). The dendritic tree of the neuron overexpressing CALEB/NGC is much more complex due to enhanced dendritic branching (red concentric circles are drawn for Sholl analysis of dendritic tree complexity).

Research Group: Molecular Mechanisms of Neuronal Connectivity

Head: Prof. Dr. Stefan Schumacher

The development of dendritic arbors is essential for neuronal information processing but the underlying mechanisms remain largely unclear. We are interested in proteins that regulate the elaboration of dendritic trees, the differentiation of dendritic spines and the formation of synapses. The elucidation of these processes is important for understanding how neuronal networks are established during development. Furthermore, a better understanding of the molecules which govern neuronal connectivity will help to better manage repair processes after lesion of the central nervous system. One of the proteins we are currently focusing on is CALEB/NGC, a neuronal member of the EGF family of differentiation factors. We found that CALEB/NGC is important for regulating dendritic tree complexity.

MicroRNAs are small, naturally occurring antisense RNA molecules that inhibit translation of target mRNAs. Over 80 microRNA genes are expressed in the mammalian brain. Our focus is on the functions of microRNAs in regulating the expression of target genes that are important for establishing neuronal connectivity.

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Selected Publications:

- Podygajlo G, Wiegrefe C, Scaal M, Bicker G (2010): Integration of human model neurons (NT2) into embryonic chick nervous system. *Dev Dyn*, 239: 496-504.
- Smorodchenko A, Rupprecht A, Sarilova I, Ninnemann O, Bräuer AU, Franke K, Schumacher S, Tschritz S, Nitsch R, Schuelke M, Pohl EE (2009): Comparative analysis of uncoupling protein 4 distribution in various tissues under physiological conditions and during development. *Biochim Biophys Acta*, 1788: 2309-2319.
- Wolfram U, Schmitz B, Heuer F, Reinehr M, Wilke H-J (2009): Vertebral trabecular main direction can be determined from clinical CT datasets using the gradient structure tensor and not the inertia tensor-A case study. *J Biomech*, 42: 1390-1396.
- Wiegrefe C, Christ B, Huang R, Scaal M (2009): Remodeling of aortic smooth muscle during avian embryonic development. *Dev Dyn*, 238: 624-631.
- Schweickert A, Deißler K, Britsch S, Albrecht M, Ehmann H, Mauch V, Gaio U, Blum M (2008): Left-asymmetric expression of Galanin in the linear heart tube of the mouse embryo is independent of the Nodal coreceptor gene cryptic. *Dev Dyn*, 237: 3557-3564.
- Brandt N, Franke K, Buck F, Harder S, Hassel B, Nitsch R, Schumacher S (2008): B56beta, a regulatory subunit of protein phosphatase 2A, interacts with CALEB/NGC and inhibits CALEB/NGC-mediated dendritic branching. *FASEB J*, 22: 2521-2533.



Computer-controlled cell stretch device mounted on the stage of an inverted microscope. Lung cells are grown on the silastic membrane on top of the objective.



Institute of General Physiology

Head of Institute: Prof. Dr. Paul Dietl

Keywords: Dopamine | exocytosis | ion channels | lung | Parkinson's disease

Research Group: Cellular Lung Physiology

Head: Prof. Dr. Paul Dietl

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

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

Research Group: Molecular Neurophysiology

Head: Prof. Dr. Birgit Liss

Our research is focused on the dopamine midbrain system. This system – and the activity of dopamine releasing midbrain neurons – is not only involved in motor control and movement disorders, such as Parkinson's disease, but also plays a crucial role for emotional and cognitive brain functions and related disorders, such as schizophrenia, drug addiction, or attention-deficit-hyperactivity-disorders (ADHD). Our main research goal is to define molecular mechanisms which define the distinct functions of different types of dopamine midbrain neurons in healthy and diseased states. By combining brain-slice in vitro electrophysiology and UV laser microdissection with quantitative RNA and DNA analysis at the single cell level, we aim to define the signaling pathways that control dopamine neuron activity as well as the selective activation of disease pathways, in particular in Parkinson's disease. To address these issues, we analyze individual dopamine midbrain neurons from respective disease mouse-models as well as from *post mortem* human brains and compare them to respective controls. We focus on analyzing the cell-specific roles of ion channels and receptors since their cell-specific activity directly defines neuronal activity in healthy and diseased states.

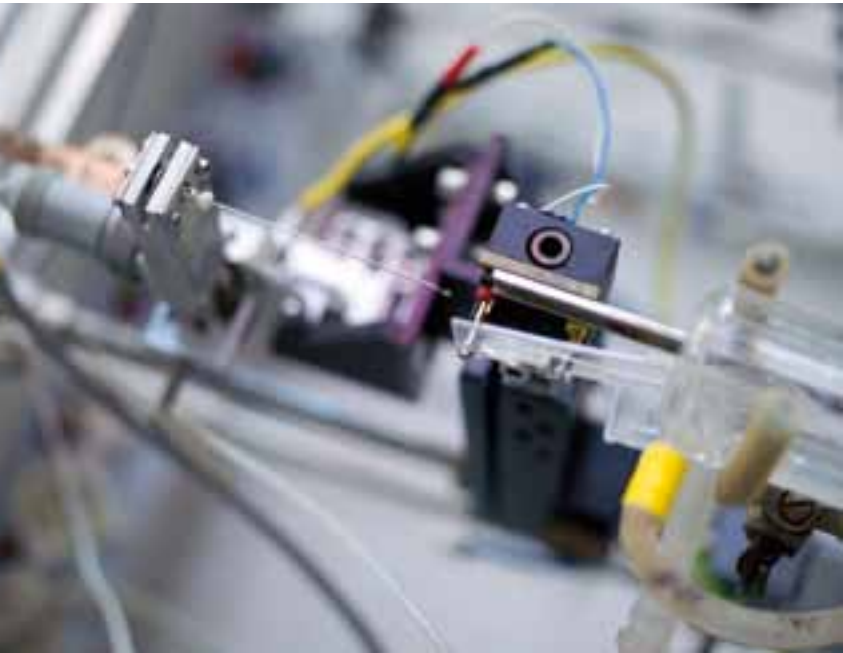


Contact-free UV laser microdissection of individual dopamine neurons.

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Selected Publications:

- Dietl P, Liss B, Felder E, Miklavc P, Wirtz H (2010): Lamellar Body Exocytosis by Cell Stretch or Purinergic Stimulation: Possible Physiological Roles, Messengers and Mechanisms. *Cell Physiol Biochem*, 25: 1-12.
- Miklavc P, Albrecht S, Wittekindt OH, Schullian P, Haller T, Dietl P (2009): Existence of exocytotic hemifusion intermediates with a lifetime of up to seconds in type II pneumocytes. *Biochem J*, 424: 7-14.
- Gerstmair A, Fois G, Innerbichler S, Dietl P, Felder E (2009): A device for simultaneous live cell imaging during uni-axial mechanical strain or compression. *J Appl Physiol*, 107: 613-620.
- Lammel L, Hetzel A, Haeckel O, Jones I, Liss B, Roeper J (2008): Unique properties of mesoprefrontal neurons within a dual mesocorticolimbic dopamine system. *Neuron*, 57: 760-773.
- Liss B, Roeper J (2008): Individual 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-laser-microdissected dopaminergic substantia nigra neurons in idiopathic Parkinson's disease. *Nucleic Acids Research*, 6: e38.



Setup for muscle strength recording.

Institute of Applied Physiology

Head of Institute: Prof. Dr. Dr. h.c. Frank Lehmann-Horn

Keywords: Channelopathies | ion channels | nervous system | skeletal muscle | translational research

Our Institute employs 22 members, 55% of whom are women. Native languages differ from German by 30%.

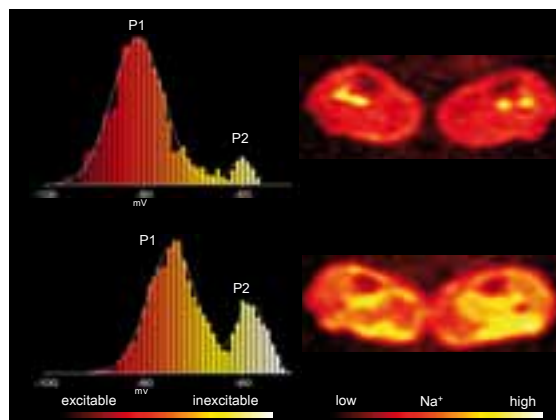
We are studying ion channels, i.e. integral proteins in the cell membrane. Their essential property is a pore that acts as a selectively conducting pathway for certain ions between the intra- and extracellular spaces. The pore is opened and closed by gates that are activated and inactivated by ligands, transmitters or voltage changes. The channels provide the basis for the regulation of electrical cell excitability (nervous system, skeletal and cardiac muscle), of hormone and enzyme secretion and of signal transduction that mediates muscle excitation-contraction coupling and voltage control of intracellular Ca release from storage cisternae.

We are studying various aspects of ion channels, e.g. their coding genes, the splicing of the RNA, the function of the channel proteins, and their modulation by exo- and endogenous ligands and toxins. Our main effort is to identify the pathogenesis of diseases that are caused by pathologically altered channel proteins known as channelopathies, such as myotonias, periodic paralyses, epilepsies, ataxias, migraine or neuropathic pain. For the study of the function of normal or mutant channels, we use the patch clamp technique which allows us to determine voltage dependence and kinetics of the gating of channel ensembles or single channel proteins. For the study of structure-function relationships in the nanoscale range, we combine patch clamping and fluorescence or atomic force microscopy.

A scientific highlight was our observation that the resting membrane potential of muscle fibers can switch between two values, one highly polarized according to Nernst for potassium (P1, excitable) and the other about -60 mV (P2, paralyzed), and that even a small membrane leak can markedly increase the relative P2 frequency and cause permanent weakness although P1 is only slightly reduced. The membrane leak can be caused by a channel voltage sensor mutation, such as in the model disease hypokalemic periodic paralysis, or by ionophores, such as gramicidin or amphotericin, or probably also by ischemia.

Recent academic highlights were: the election of Frank Lehmann-Horn as Endowed Research Senior Professor 2008 of Neurosciences of the Hertie-Foundation and as member of the Heidelberg Academy of Sciences in 2009; the election of Holger Lerche as Head of Department of Neurology and Epileptology in Tübingen in 2009; the Eva Luise Köhler Research Prize on Rare Diseases awarded to Karin Jurkat-Rott in 2010; and the 2nd Felix-Jerusalem Prize given to Zoita Andronache.

In addition to our scientific work and teaching responsibilities, we perform special diagnostic muscle and molecular genetic tests and take care of many patients with rare diseases, particularly channelopathies. We inform and advise patients, family doctors and neurologists about appropriate diagnosis and off-label therapy. Frank Lehmann-Horn is currently Chairman of the Neuromuscular Centre Ulm. In recognition of our patient care, he was awarded the Art of Listening Award by the Genetic Alliance, Washington DC, in 2009.



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

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Selected Publications:

- Ebert J, Fink S, Koitschev A, Walther P, Langer MG, Lehmann-Horn F (2010): Recovery of mechano-electrical transduction in rat cochlear hair bundles after postnatal destruction of the stereociliar cross-links. *Proceedings of the Royal Society B*, [in press].
- 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 U S A*, 106: 4036-4041.
- Andronache Z, Hamilton SL, Dirksen RT, Melzer W (2009): A retrograde signal from RyR1 alters DHP receptor inactivation and limits window Ca^{2+} release in muscle fibers of Y522S RyR1 knock-in mice. *Proc Natl Acad Sci U S A*, 106: 4531-4536.
- Tuluc P, Molenda N, Schlick B, Obermair GJ, Flucher BE, Jurkat-Rott K (2009): A $\text{CaV}1.1$ Ca^{2+} channel splice variant with high conductance and voltage-sensitivity alters EC coupling in developing skeletal muscle. *Biophys J*, 96: 35-44.
- Weber YG, Storch A, Wuttke TV, Brockmann K, Kempfle J, Maljevic S, Margari L, Kamm C, Schneider SA, Huber SM, Pekrun A, Roebeling R, Seebohm G, Koka S, Lang C, Kraft E, Blazevic D, Salvo-Vargas A, Fauler M, Mottaghy FM, Münchau A, Edwards MJ, Presicci A, Margari F, Gasser T, Lang F, Bhatia KP, Lehmann-Horn F, Lerche H (2008): *GLUT1* mutations are a cause of paroxysmal exertion-induced dyskinesias and induce hemolytic anemia by a cation leak. *J Clin Invest*, 118: 2157-2168.
- Küppers E, Gleiser C, Brito V, Wachter B, Pauly T, Hirt B, Grissmer S (2008): *AQP4* expression in striatal primary cultures is regulated by dopamine - implications for proliferation of astrocytes. *Eur J Neurosci*, 28: 2173-2182.



Dr. Harald J. Maier characterizes a mouse model for dilated cardiomyopathy (DCM).

Institute of Physiological Chemistry

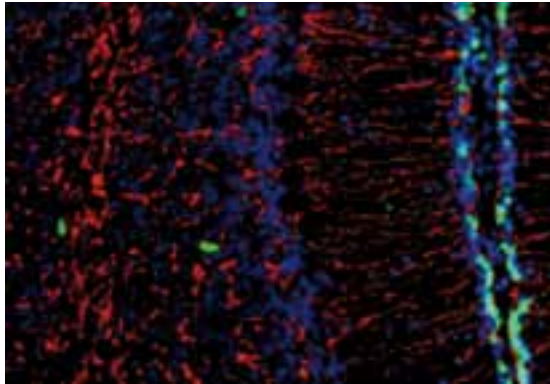
Head of Institute: Prof. Dr. Thomas Wirth

Keywords: Burkitt's lymphoma | Hodgkin lymphoma | inflammation | Myc | NF- κ B

The Institute of Physiological Chemistry is located in the new research building of the university. It has about 40 members who receive most of their funding from third-parties. In addition to the group of Professor Wirth, an associate professorship (currently vacant because the previous holder, Prof. Fischer, accepted a full professorship in Magdeburg) and a junior professorship (Prof. Dr. Ralf Marienfeld) are responsible for research and the teaching of students of medicine, dental medicine, molecular medicine, biochemistry and biology.

Research activities focus on several aspects of the involvement of signaling networks in differentiation and disease. We have a long-standing interest in the analysis of gene regulation in lymphopoiesis and lymphoid tumors, and have also developed sophisticated genetic tools to study the role of NF- κ B transcription factors in physiological and patho-physiological processes.

Our work on lymphopoiesis originated from our interest in transcriptional regulation of the immunoglobulin genes, which was an aspect of our research that was started approximately 25 years ago. We have substantially contributed to the elucidation of the molecular players that regulate



The role of NF- κ B for brain development and disease.

immunoglobulin gene transcription and have determined that transcription factors constitutively present in B-lymphocytes also show inducible functions in T-lymphopoiesis. Recent results from this line of research have unraveled a decisive role of this gene regulatory system in T-helper cell differentiation. We also discovered that this gene regulatory network is inactivated in classical Hodgkin lymphoma, a tumor arising from B-lymphocytes that has however lost almost all of its B-cell specific signatures. In recent studies, we have been able to determine that epigenetic mechanisms are largely responsible for the extinction of these B-cell specific genetic programs. In order to gain more insight into the basic mechanisms of B-cell lymphomagenesis, we have developed a conditional mouse model of B-cell lymphoma development driven by the *Myc*-oncogene. Due to the regulated oncogene expression, all mice develop lymphoid tumors, which can nonetheless be ablated by oncogene inactivation. Using this model system, we have recently been able to identify that repression of specific micro-RNAs essentially contributes to lymphomagenesis and, furthermore, have identified the unanticipated role of NF- κ B as a tumor suppressor for *Myc*-induced lymphomagenesis.

The IKK/ NF- κ B system is believed to be involved in a multitude of differentiation and disease processes. In order to generate definitive genetic evidence and the contribution of this system to some of these events, we have developed mouse models allowing conditional activation or repression of this pathway in a cell-type and developmental-stage-specific manner. These strategies allow us to determine initiating or modulating roles of NF- κ B. We were able to document that NF- κ B activation by itself is responsible for inducing severe acute inflammatory processes in the mouse (pancreatitis) and that it modulates/aggravates the outcome of acute lesion models as shown by our investigation into the role of NF- κ B in strokes. More recent experiments identified crucial roles of NF- κ B activation in liver fibrosis and cardiomyopathies. We have also unraveled critical roles for NF- κ B in neuronal differentiation and one of the research groups at the Institute studies the molecular and biochemical pathways activating NF- κ B in T cells.

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Selected Publications:

- Guan H, Xie L, Leithäuser F, Flossbach L, Möller P, Wirth T, Ushmorov A (2010): *KLF4 is a tumor suppressor in B-cell non-Hodgkin lymphoma and in classical Hodgkin lymphoma*. *Blood*, [in press].
- Maier HJ, Schmidt-Strassburger U, Huber MA, Wiedemann E, Beug H, Wirth T (2010): *NF- κ B promotes epithelial mesenchymal transition, migration and invasion of pancreatic carcinoma cells*. *Cancer Lett*, [in press].
- Klapproth K, Sander S, Marinkovic D, Baumann B, Wirth T (2009): *The IKK2/NF- κ B-pathway suppresses Myc-induced lymphomagenesis*. *Blood*, 114: 2448-2458.
- Kokai E, Voss F, Fleischer F, Kempe S, Marinkovic D, Wolburg H, Leithäuser F, Schmidt V, Deutsch U, Wirth T (2009): *Myc regulates embryonic vascular permeability and remodelling*. *Circ Res*, 104: 1151-1159.
- Sander S, Bullinger L, Klapproth K, Fiedler K, Kestler HA, Barth TFE, 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.
- Ushmorov A, Leithäuser F, Ritz O, Barth TF, Möller P, Wirth T (2008): *ABF-1 is frequently silenced by promoter methylation in follicular lymphoma, diffuse large B-cell lymphoma and Burkitt's lymphoma*. *Leukemia*, 22: 1942-1944.



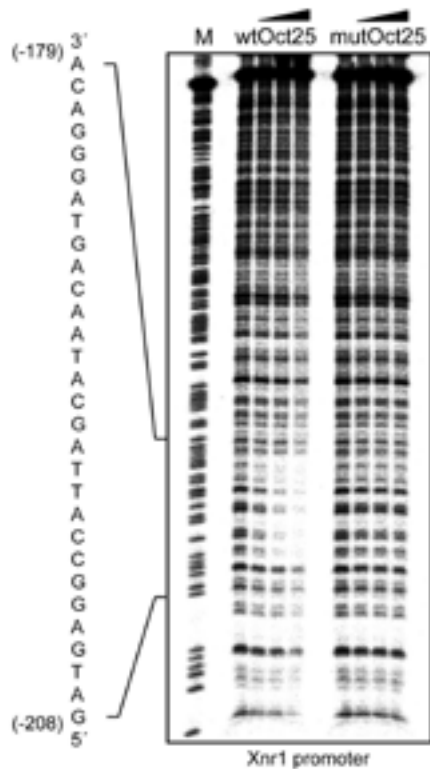
Institute of Biochemistry

Head of Institute: Prof. Dr. Dr. Walter Knöchel

Keywords: Amphibia (*Xenopus laevis*) | differentiation and pluripotency factors | embryogenesis | Fox transcription factors | gene regulation

The main tasks of the Institute involve teaching and basic research. Together with the Institute of Physiological Chemistry and the Institute of Molecular Biology and Biochemistry, about 500 students of medicine, dental medicine, molecular medicine and biochemistry are trained each year in the theory and practice of basic biochemistry. Scientific topics of the Institute are the analysis of growth factors and transcription factors in vertebrate embryogenesis as well as the analysis of pluripotency factors and their role in the transition from pluripotency to differentiation. The Institute also participates in the Collaborative Research Center 497 (projects A1 and D1).

A fundamental step in vertebrate embryogenesis is the loss of pluripotency and the formation of the three germ layers known as ectoderm, mesoderm and endoderm. This decisive event is subsequently followed by the differentiation of tissues and organs. By using amphibia as a model system, we characterize at the molecular level those genes which participate in the formation of mesoderm. Induction of this germ layer proceeds in the equatorial zone of the embryo by signals, which are emitted from the vegetal half. We investigate growth factors of the TGF- β superfamily being expressed in the embryo for their mesoderm-inducing capacity and their signaling cascades. Phenotypic effects achieved by overexpression (gain of function) or depletion (loss of function) of pluripotency and differentiation factors are studied on a molecular basis using various marker genes. Ectopic expression of pluripotency factors combined with promoter studies of target genes led to the identification of regulatory mechanisms governing the transition from pluripotency to differentiation. It was shown that members of the POU-V subfamily are essential inhibitors of differentiation in that they interfere with the inducing cascades. The temporal and spatial patterns of POU-V factors thereby control the timing and localization of early differentiation events within the embryo.



Footprint analysis of a pluripotency factor (Oct25) on a target gene. Left side: wild type protein. Right side: mutated protein lacking DNA binding activity.

Differential expression of genes is achieved by the activation of specific transcription factors. By regulating the activity of their target genes or whole gene cascades, they are thus essential keys for tissue differentiation. Many of these transcription factors contain evolutionary conserved DNA binding modules, which allow them to be assigned to defined multigene families. We have focused our interest on certain members of the Fox family containing the fork head/HNF-3 or winged helix motif. FoxO proteins play important roles in lifespan regulation as well as in insulin-like signaling. The activity and subcellular localization of these proteins are regulated by post-translational interconversion. Recently performed knockdown studies revealed specific defects in organogenesis, such as in eye and heart formation. Genetic dysregulations underlying these defects are currently being investigated.

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Selected Publications:

- Cao Y, Oswald F, Wacker SA, Bundschu K, Knöchel W (2010): Reversal of *Xenopus Oct25* function by disruption of the POU domain structure. *J. Biol Chem*, 285: 8408-8421.
- Schuff M, Siegel D, Bardine N, Oswald F, Donow C, Knöchel W (2010): FoxO genes are dispensable during gastrulation but required for late embryogenesis in *Xenopus laevis*. *Dev Biol*, 337: 259-273.
- Siegel D, Schuff M, Oswald F, Cao Y, Knöchel W (2009): Functional dissection of XDppa2/4 structural domains in *Xenopus* development. *Mech Dev*, 126: 974-989.
- Woltering JM, Vonk FJ, Müller H, Bardine N, Tudu IL, de Bakker MA, Knöchel W, Sirbu IO, Durston AJ, Richardson MK (2009): Axial patterning in snakes and caecilians: Evidence for an alternative interpretation of the Hox code. *Dev Biol*, 332: 82-89.
- Bardine N, Donow C, Korte B, Durston AJ, Knöchel W, Wacker S (2009): Two Hoxc6 transcripts are differentially expressed and regulate primary neurogenesis in *Xenopus laevis*. *Dev Dyn*, 238: 755-765.
- Cao Y, Siegel D, Oswald F, Knöchel W (2008): Oct25 represses transcription of nodal/activin target genes by interaction with signal transducers during *Xenopus* gastrulation. *J Biol Chem*, 283: 34168-34177.



Genes can be functionally studied during development by microinjection experiments in *Xenopus laevis*.



Institute of Biochemistry and Molecular Biology

Head of Institute: Prof. Dr. Michael Kühl

Keywords: Developmental biology | regenerative medicine | stem cell biology

Within the Institute we currently have 24 employees, 12 of whom are PhD students. 87.5 % of employees are female and 29 % have come from abroad.

The major focus of our research is the analysis of signaling processes during early embryonic development. Wnt proteins, for example, are glycoproteins that activate different intracellular signaling pathways that are interwoven to form a signaling network. The canonical Wnt pathway is characterized through 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 signaling can lead to certain diseases including cancer. Our group characterizes intracellular Wnt signaling pathways and analyzes their role during embryogenesis in different model systems. 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 still-births and spontaneous abortions. Defects in regulatory molecules that act early in 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 a new perspective in the long term therapy of heart diseases and reinforces the necessity to understand the process of normal cardiac development. We have recently shown that certain Wnt signaling activities are required for vertebrate 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. In this model, we are also analyzing transcription factors of the Iroquois family. Furthermore, retinoic acid signaling and its cross talk with Wnt signaling seems to be important during cardiac and neural development. In this context, we are analyzing the function of novel non-canonical Wnt signaling components and potential target genes during murine cardiac development. During neural development non-canonical Wnt signaling pathways regulate the expression of selected targeted genes. One of these target genes is *Pescadillo* which regulates eye development and neural crest cell migration. In this context we are currently investigating the molecular mechanisms underlying *Pescadillo* function. Retinoic acid signaling and non-canonical Wnt signaling are also important for neural tube closure defects that can lead to developmental neural malformations. Targets of non-canonical Wnt signalling are also investigated during pronephros development. The molecular design of the Wnt signaling network is finally analyzed by modeling Wnt signaling.



Mutants of *Drosophila melanogaster* can be used to analyze gene function.

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Selected Publications:

- Gessert S, Bugner V, Tecza A, Pinker M, Kühl M (2010): *FMR1/FXR1 and the miRNA pathway are required for eye and neural crest development*. *Dev Biol*, [in press].
- Gessert S, Kühl M (2009): *Comparative gene expression analysis and fate mapping studies suggest an early segregation of cardiogenic lineages in Xenopus laevis*. *Dev Biol*, 334: 395-408.
- Zhao X, Sirbu IO, Mic FA, Molotkov A, Kumar S, Duester G (2009): *Retinoic acid promotes limb induction through effects on body axis extension but is unnecessary for limb patterning*. *Curr Biol*, 19: 1050-1057.
- Mann T, Bodmer R, Pandur P (2009): *The Drosophila homolog of vertebrate Islet1 is a key component in early cardiogenesis*. *Development*, 136: 317-326.
- Gessert S, Maurus D, Brade T, Walther P, 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.
- Sirbu IO, Zhao X, Duester G (2008): *Retinoic acid controls heart anterior-posterior patterning by downregulating *Isl1* through the *Fgf8* pathway*. *Dev Dyn*, 237: 1627-1635.



The faculty at work.

Institute of the History, Philosophy and Ethics of Medicine

Head of Institute: Prof. Dr. Heiner Fangerau

Keywords: Clinical ethics | history of medicine | medical ethics | philosophy of medicine

Our Institute is dedicated to research and education covering a wide spectrum of medical theory and practice: that includes the history and ethics of medicine in addition to medical theory and the philosophy of science. These topics are vital for medical practitioners and the researchers of tomorrow. Furthermore, the Institute coordinates and conducts a counseling service to tackle ethical questions in the fields of medicine and health care at the University Hospital.

The Institute connects the history of medicine and the life sciences to modern dilemmas concerning philosophy and medical ethics. By exploring the social and cultural dimensions of medicine, it helps to bridge the gap between biomedical research, clinical practice and social issues as reflected in the humanities and social sciences. With a faculty covering various scientific backgrounds – medicine and the life sciences, cultural and historical anthropology, philosophy, political studies, history and history of science – the Institute practices a truly transdisciplinary approach.

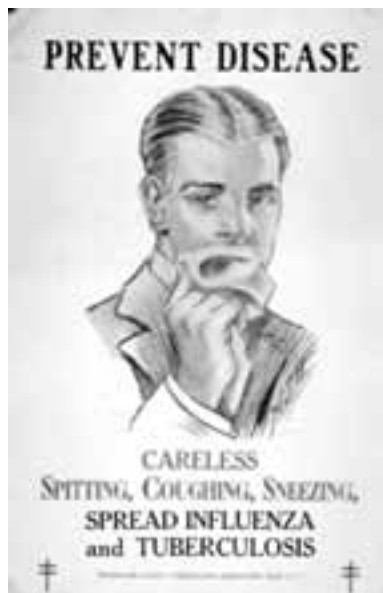
At the Institute medical students and students of molecular medicine are taught the historical, philosophical and ethical backgrounds of their field to enable them to cope adequately with the challenges of their later everyday professional life. Furthermore, the Institute presents on-the-job training for physicians, nurses and other hospital staff.

Research at the Institute includes a great variety of methods and topics, such as international comparative studies in the history of medicine and biology, the origins of biomedicine, and the philosophy of science and medicine, while placing a special focus on medical ethics. Current projects include the shaping of medicine as a life science since the year 1900, the transfer of medical knowledge and scientific networks, classification and evolution in medical diagnostics and medical imaging, the ethics of stem cell research, and the development of clinical ethics from an intercultural perspective.

The Institute also coordinates the University's Center of Medicine and Society. In the field of biomedical sciences, responsible future-oriented research will only happen by means of dialog with contemporary society and by considering the basic historical, theoretical and ethical principles of medical research and action. In this respect, the center intends to offer an interdisciplinary and multiperspective approach. To achieve this, Ulm University with its record of intense research provides the perfect setting and conditions. The Center of Medicine and Society is able to act as a showcase for biomedicine and the humanities dealing with medical issues. It serves as a platform for the life sciences to reflect upon their actions. The Institute offers its expertise in the arts and humanities as well as the social sciences to act as an interpreter and promoter of interdisciplinary medical research.

The Institute established a Reference Library which houses a constantly expanding collection of specialized books and research literature. In addition, current journals on the history, philosophy and ethics of medicine are also available. The entire collection is listed in the online catalog of the University Library. Moreover, there is an index of newspaper articles concerning numerous scientific issues on the history, philosophy and ethics of medicine.

Public health poster from Spanish flu era, ca. 1918, Poster by Rensselaer County (New York) Tuberculosis Association. The figure shows a classical example of material that requires analysis from a cultural perspective. The understanding of current scientific discourses and public fears about the pandemics of today and tomorrow demand an analytical approach and the background of the history of medical knowledge and medical ethics.



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Selected Publications:

- Fangerau H (2010): *Spinning the Scientific Web: Jacques Loeb (1859-1924) und sein Programm einer internationalen biomedizinischen Grundlagenforschung*, Akademie Verlag, Berlin.
- Fangerau H (2009): *Genetics and the Value of Life: Historical Dimensions*. *Med Stud*, 1: 105-112.
- Fangerau H (2009): *From Mephistopheles to Iesajah: Jacques Loeb, Science and Modernism*. *Soc Stud Sci*, 39: 229-256.
- Fangerau H (2009): *Research ethics, publication ethics and the dialectics of scientists trying not to behave badly: a comment on the advantages and limitations of Twin Assessment of Clinical Trials (TACT)*. *J Public Health*, 17: 433-434.
- Polianski I, Schwartz (2009): *Die Spur des Sputnik. Kulturhistorische Expeditionen ins kosmische Zeitalter*, Campus, Frankfurt am Main.
- Polianski I (2008): *Das Unbehagen der Natur: Sowjetische Populärwissenschaft als semiotische Lektüre*. In: Matthias Schwartz, Wladimir Veliminski, Torben Philipp (Ed.), *Laien, Lektüren, Laboratorien: Künste und Wissenschaften in Russland 1860-1960*, Frankfurt am Main, S. 71-113.

Institute of Epidemiology

Head of Institute: Prof. Richard Peter Ph.D. (Provisional Head)

Keywords: Asthma and allergies in children | physical activity among the elderly | social epidemiology | work stress and health

The Institute of Epidemiology currently employs two professors, 11 scientists of different backgrounds (physicians/epidemiologists, psychologists, social scientists), and 13 non-scientific staff (medical documentalists, secretaries). The proportion of female employees amounts to 46% and the proportion of employees from abroad is 4%. In 2009, we had five doctoral students working at our institute.

In 2009, 14 studies, funded by the EU, the Federal Ministry for Education and Research (BMBF), the Federal Ministry for Work and Social Affairs and the German Science Foundation (DFG), have been conducted by the Institute of Epidemiology. Several studies were started in 2008/2009. Many of these studies are the result of international collaboration. The research topics and some of the highlights of our research are as follows:

Social Epidemiology, Medical Sociology, Work Stress

The lidA- Study (*leben in der Arbeit*) is one of the highlights. lidA is a planned nationwide study extending over a period of 12 years to observe the effects of work stress, work ability and health among the older workforce in Germany. Data sampling will start next year in two age groups with the aim of including more than 6,000 employed men and women. The expected impact of this study on both politics and science will be high since, due to demographic changes, the German work force is predicted to grow older more quickly than workforces in other countries.

Asthma and Allergies in Children and Adolescents

The GABRIEL and PASTURE studies investigate the gene-environment interactions as they occur in different EU countries and have shed light on some of the differences between children growing up on farms and those living in cities.





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Physical Activity and Health

Physical activity is an important condition for health among all ages. Regular activity is associated with better physical and psychological functioning, less chronic disease and a better quality of life. In recent studies, physical activity has been measured with the help of standardized questionnaires and has thus become susceptible to over reporting.

Our ActiFE Study (Activity and Function in the Elderly in Ulm) is the only investigation worldwide applying an objective measurement of activity with the help of accelerometers in a large population-based sample (N=1500) of older men and women. From ActiFE we expect to gain new insights into the association between physical activity and medication, falls, chronic disease, physical and psychological functioning, and cellular aging processes. A follow-up of the ActiFE population is planned within the next two years. Furthermore, the ActiFE-study serves as a platform for clinical research. Collaborating partners at the Medical Faculty include Neurology, Psychiatry, Pulmology, Rehabilitation and Sports Medicine, and Pharmacology among others.

The URMEL-ICE Study investigated the effects of an activity focused intervention program in children with the aim of reducing obesity and improving cardiovascular functioning. The URMEL-ICE was a collaborative investigation involving several departments of the Medical Faculty of Ulm University.

Selected Publications:

- Rapp K, Cameron ID, Kurrle S, Klenk J, Klein A, Heinrich S, König HH, Becker C (2010): Excess mortality after pelvic fractures in institutionalized older people. *Osteoporosis Int*, January 8 [epub ahead of print].
- Nagel G, Wabitsch M, Galm C, Berg S, Brandstetter S, Fritz M, Klenk J, Peter R, Prokopchuk D, Steiner R, Stroth S, Wartha O, Weiland SK, Steinacker J (2009): Determinants of obesity in the Ulm Research on Metabolism, Exercise and Lifestyle in Children (URMEL-ICE). *Eur J Pediatr*, June 28 [epub ahead of print].
- Fahlen G, Goine H, Edlund C, Arrelöv B, Knutsson A, Peter R (2009): Effort-reward imbalance, „locked in“, and long-term sick leave. *Int Arch Occup Environ Health*, 82: 191-197.
- de Jonge J, van der Linden S, Schaufeli W, Peter R, Siegrist J (2008): Factorial invariance and stability of the effort-reward imbalance scales: a longitudinal analysis of two samples with different time lags. *Int J Behav Med*, 15: 62-72.
- Gehring U, Strikwold M, Schram-Bijkerk D, Weinmayr G, Genuneit J, Nagel G, Wickens K, Siebers R, Crane J, Doekes G, Di Domenicantonio R, Nilsson L, Priftanj A, Sandin A, Strachan D, van Hage M, von Mutius E, Brunekreef B, and the ISAAC Phase II study Group (2008): Asthma and allergic symptoms in relation to house and dust endotoxin. Phase two of the international study on Asthma and Allergies in Childhood (ISAAC II). *Clin Exp Allergy*, Sept 3 [epub ahead of print].
- Nagel G, Peter R, Braig S, Hermann S, Rohrmann S, Linseisen J (2008): The impact of education on risk factors and occurrence of multimorbidity in the EPIC-Heidelberg cohort. *BMC Public Health*, 8: 384.



Discussion of statistical methodology

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Institute of Biometrics

Head of Institute: Prof. Dr. Rainer Muche (Provisional Head)

Keywords: Biometry | clinical trials | data management | statistical consultancy | statistical methodology

The Institute is part of the Medical Faculty of Ulm University. Five scientists in mathematics and statistics as well as 15 medical documentalists are currently employed.

The principal tasks are the teaching of biomathematics and biometric methodical consultancy. Teaching is intended for students of human and molecular medicine, mathematical biometry, informatics and biology, and those of the School for Medical Documentation. Courses are offered in statistical software such as SAS and R. Statistical consultancy is provided for medical researchers and doctoral students, and includes study planning, sample size estimation, statistical analysis, biometrical reporting, and the visualization and compiling of expertise for ethical committees, study protocols or animal experiments. The institute is involved in the implementation, data management, realization and analysis of several multicenter randomized clinical trials.

The main scientific focus is on methodological research in “imputation of missing values”, “mixed and hierarchical models”, and “predictive models”. The institute operates in cooperation with several external pharmaceutical companies and research institutes. The interim director is engaged in biometrical associations e.g. as chair of the Certificate Commission for Medical Documentalists.

Selected Publications:

- Franz AR, Pohlandt F, Bode H, Mihatsch WA, Sander S, Kron M, Steinmacher J (2009): Intrauterine, early neonatal, and postdischarge growth and neurodevelopmental outcome at 5.4 years in extremely preterm infants after intensive neonatal nutritional support. *Pediatrics*, 123: 101-109.
- Feuerlein S, Kreuzer G, Schmidt SA, Muche R, Juchems MS, Aschoff AJ, Brambs HJ, Pauls S (2009): The cisterna chyli: prevalence, characteristics and predisposing factors. *Eur Radiol*, 19: 73-78.
- Denzer C, Thiere D, Muche R, Koenig W, Mayer H, Kratzer W, Wabitsch M (2009): Gender-specific prevalences of fatty liver in obese children and adolescents: roles of body fat distribution, sex steroids, and insulin resistance. *J Clin Endocr Metab*, 94: 3872-3881.
- Wieshammer S, Dreyhaupt J, Basler B, Marsovszky E (2009): NT-proBNP for pulmonologists: not only a rule-out test for systolic heart failure but also a global marker of heart disease. *Respiration*, 77: 370-380.
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- Sauer G, Schneiderhahn-Marra N, Kazmaier C, Hutzel K, Koretz K, Muche R, Kreienberg R, Joos T, Deissler H (2008): Prediction of nodal involvement in breast cancer based on multiparametric protein analyses from preoperative core needle biopsies of the primary lesion. *Clin Cancer Res*, 14: 3345-3353.



Data management in clinical trials



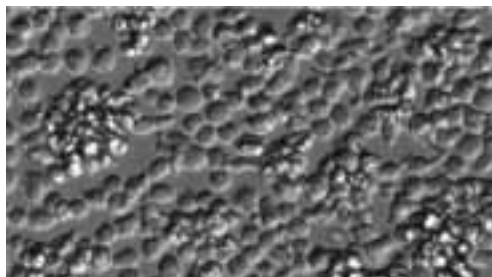
Statistical consultancy

Institute of Forensic Medicine

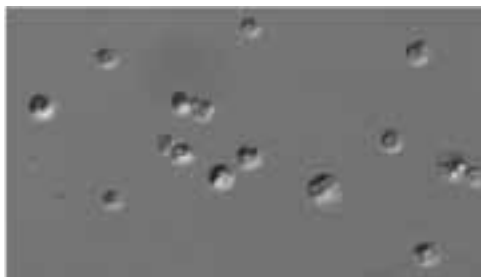
Head of Institute: Prof. Dr. Erich Miltner

Keywords: Apoptosis | cancer | DNA-methylation | medical law | methadone

The Institute of Forensic Medicine has 35 employees and concentrates on three fields of work to perform all routine services: forensic medicine; forensic toxicology; and forensic genetics. Distinctive features include: the performance of CT-scans with scanner adjacent before routine autopsies; services in the DNA laboratory for DNA profiling of single skin scales after microscopical selection; heteroplasmy evaluation in mitochondrial DNA control region using pyrosequencing; and analysis of DNA-methylation in different human tumor tissues. Additionally, we conduct scientific work in medical law. In the molecular research laboratory, we focus on oncology in such areas as apoptosis, DNA-damage and cell cycle signaling of anticancer drugs, radiation and opioids, and the development of new strategies for cancer treatment. We have discovered that methadone, which is commonly used to break addictions to opioid drugs, has the surprising power to kill leukemia cells and solid tumors, including those in the treatment of resistant forms of cancer. This finding provides the basis for developing new strategies to establish methadone as an additional therapeutic anticancer drug and also for further investigations to combine methadone with chemotherapy or radiation to overcome chemo- and radioresistance in cancer in order to improve therapeutic success.



Conventional chemotherapeutic drugs failed to kill chemo-resistant leukemia cells.

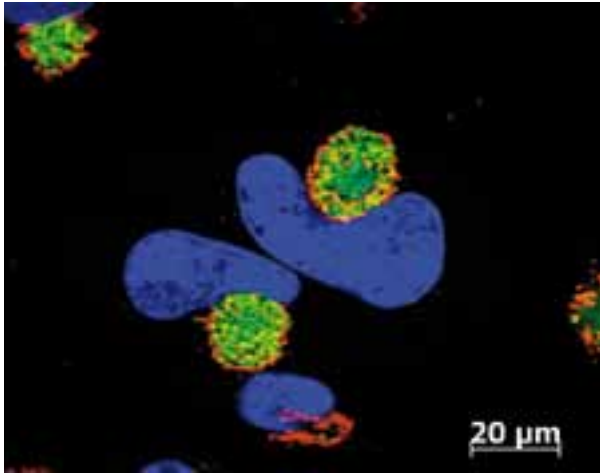


Methadone inhibits proliferation and breaks chemoresistance in leukemia cells.

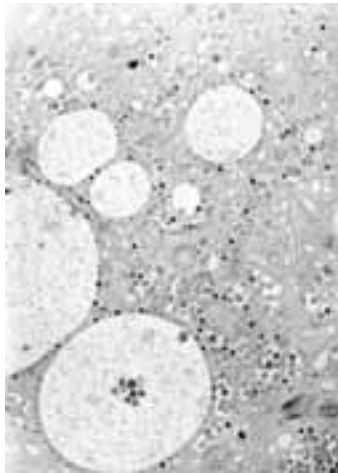
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Selected Publications:

- Anjum GM, Du W, Klein R, Amara U, Huber-Lang M, Schneider EM, Wiegand P (2010): Pyrosequencing-based strategy for a successful SNP detection in two hypervariable regions: HV-I/HV-II of the human mitochondrial displacement loop. *Electrophoresis*, 31: 309-314.
- Wiegand P, Heibold C, Klein R, Immel U, Stiller D, Klintschar M (2010): Transfer of biological stains from different surfaces. *Int J Legal Med*, [in press].
- Ratzel R, Lippert HD (2010): Kommentar zur Musterberufsordnung der Deutschen Ärzte (MBOÄ 1997), 5. Auflage, 2010, Springer-Verlag, Heidelberg.
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- Friesen C, Roscher M, Alt A, Miltner E (2008): Methadone, commonly used as maintenance medication for outpatient treatment of opioid dependence, kills leukemia cells and overcomes chemoresistance. *Cancer Res*, 68: 6059-6064.
- Friesen C, Uhl M, Pannicke U, Schwarz K, Miltner E, Debatin KM (2008): DNA-Ligase IV and DNA-PK play a critical role in deficient caspases activation in apoptosis-resistant cancer cells using doxorubicin. *Mol Biol Cell*, 19: 3283-3289.



Localization of cytomegaloviruses (green) and a cellular protein (red) near the cell nucleus (blue).



Individual viruses can only be visualized by electron microscopy. Multiple cytomegalovirus particles are adjacent to and budding into cellular vesicles.

Institute of Virology

Head of Institute: Prof. Dr. Thomas Mertens

Keywords: Cytomegalovirus | diagnostic | Pathogenesis-Morphogenesis | resistance | therapy

The Institute performs the virological diagnostic for Ulm University Hospital as well as for some external clients. For the most part, these are highly specialized laboratory services based on specifically established and validated methods. One main focus is on the monitoring of immunosuppressed patients, especially bone marrow transplant recipients in pediatric and adult medicine. This monitoring is decisive for the outcome of highly specialized therapies since these patients are often prone to life-threatening exogenous and reactivated viral infections. Another focus is on the diagnosis of respiratory infections and of virus infections during pregnancy.

Research is focused on Human Cytomegalovirus (HCMV), a member of the Herpes virus family. Teaching is provided for students studying Human Medicine, Molecular Medicine, Dentistry, Biology and Informatics as well as for graduate students in Molecular Medicine at the International Graduate School in Molecular Medicine Ulm.

In addition to two permanent professorships, the Institute consists of six assistants and twelve medical technicians, most of whom work in the diagnostic section.

For many years, close cooperation has been established with the universities of Padua and Bologna and thus there are always a number of Italian PhD students and postdocs working at the Institute. As regards research on CMV, various groups study such topics as the mechanisms of HCMV-resistance against existing antiviral substances. This work resulted in essential findings concerning CMV-coded proteins and has been published in high-ranking journals. Methods and procedures have since been established and towards the end of 2009 a data base was released to enable interested parties to conduct research via the internet in order to correlate mutations in CMV genomes that confer resistance to corresponding resistance phenotypes. During the last few months, we have noted that this website has been used extensively.

The Director of the Institute is head of a network of the Robert Koch-Institute that focuses on infections during pregnancy and immune suppression. At present, the network is planning a study on the clinical evaluation of CMV-resistance testing of patients at risk in collaboration with laboratories in Belgium, Italy, Great Britain, France and Israel. The Institute is a national reference laboratory for human CMV.

Another research group is working on the function of viral tegument proteins for the morphogenesis of CMV. This research is funded through a central program (*Schwerpunktprogramm*) of the German Research Foundation. This project will not only result in some understanding of the biology of this very complex virus but will also enable the identification of new targets for antiviral intervention. One research project focuses on the effects of CMV-Infection on monocytes and macrophages. A special aspect of this work is the observation that these cells are central cells of the immune response and are thus not only infected but are clearly also used as sites of latent CMV infection. In this context, results have shown that differentially polarized macrophages vary significantly as regards HCMV-infection.

In the field of CMV-research, the modulation of cellular genes by viral gene expression is also examined. This aspect reveals the special importance of research into human diseases that are not primarily classified as infectious diseases, e.g. atherosclerosis. Results may show that after infection, cells relevant to atherosclerosis develop into a phenotype that supports atherosclerosis. In the field of clinical virology, close cooperation with various other clinical departments and institutes focuses on research into different viral infections.

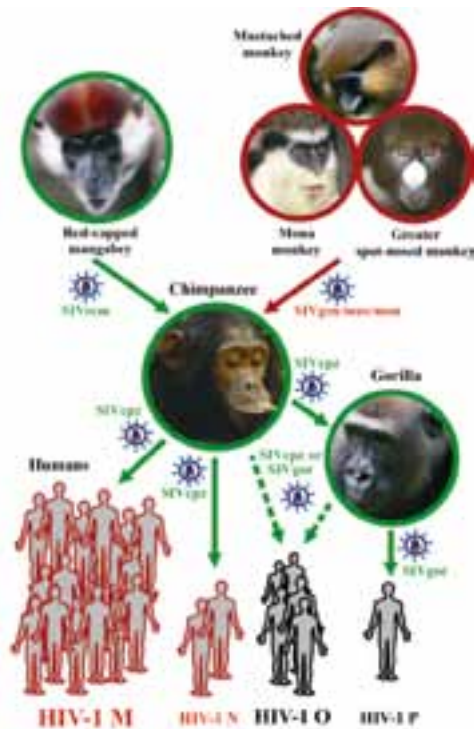


International research
Dr. Jens von Einem with two PhD
students (Martina Caduco, Padua
(left), Daniela Fischer (right)).

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Selected Publications:

- Straschewski S, Warmer M, Frascaroli G, Hohenberg H, Mertens T, Winkler M (2010): Human cytomegaloviruses expressing yellow fluorescent fusion proteins-characterization and use in antiviral screening. *PLoS One*, 11: e9174.
- Chevillotte M, von Einem J, Meier BM, Lin FM, Kestler HA, Mertens T (2010): A new tool linking human cytomegalovirus drug resistance mutations to resistance phenotypes. *Antiviral Res*, 85: 318-327.
- Chevillotte M, Schubert A, Mertens T, von Einem J (2009): Fluorescence-based assay for phenotypic characterization of human cytomegalovirus polymerase mutations regarding drug susceptibility and viral replicative fitness. *Antimicrob Agents Chemother*, 53: 3752-3761.
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- Frascaroli G, Varani S, Blankenhorn N, Pretsch R, Bacher M, Leng L, Bucala R, Landini MP, Mertens T (2009): Human cytomegalovirus paralyzes macrophage motility through down-regulation of chemokine receptors, reorganization of the cytoskeleton, and release of macrophage migration inhibitory factor. *J Immunol*, 182: 477-488.



Evolution of HIV-1. SIVcpz represents a recombinant of the precursors of viruses nowadays found in Red-capped mangabeys and Cercopithecus monkeys (i.e. Greater spot-nosed, mustached and mona monkeys: GSN, MUS, MON, respectively) and was subsequently transmitted to humans and gorillas. Nef-mediated tetherin antagonism is indicated by green and Vpu-mediated tetherin antagonism by red lines or contours, respectively. As indicated by the dashed line it is unknown whether HIV-1 group O strains originated from chimpanzees or gorillas. Photos of nonhuman primates are courtesy of M.L. Wilson, Cecile Neel and Martine Peeters. Adapted from Sauter et al., Cell 2010.

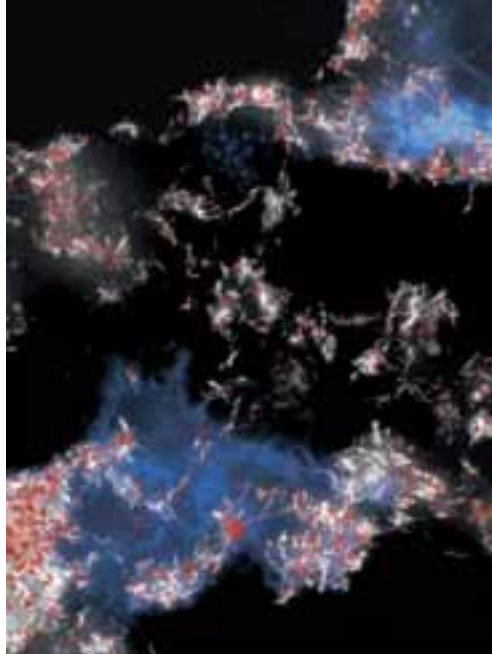
Institute of Molecular Virology

Head of Institute: Prof. Dr. Frank Kirchhoff

Keywords: Accessory viral proteins | AIDS | HIV | immune evasion | SIV

The Institute of Molecular Virology was established in Spring 2009 and currently has 24 members (15 of them women) that include three scientists, six research technicians, eight PhD students, two diploma students and two part-time secretaries. Six employees come from abroad, i.e. India, China, Korea and South Africa.

The major research topic is HIV-1, the major causative agent of AIDS, which has afflicted about 60 million people and caused more than 20 million deaths. One goal is to clarify why simian immunodeficiency viruses (SIVs) replicate efficiently in their simian hosts without causing disease. It is known that HIV-1 increases the responsiveness of infected T cells to activation. Recently, we showed that nef alleles from most SIVs exhibit a different phenotype and efficiently down-modulate TCR-CD3 to inhibit T cell activation and activation-induced cell death. This fundamental difference in Nef function might explain why high levels of immune activation are observed in progressing HIV-1 infection but are absent in asymptomatic naturally SIV-infected monkeys. We also examined why only one of four zoonotic transmissions of SIVs found in chimpanzees or gorillas to humans is responsible for the AIDS pandemic. Our results showed that only pandemic HIV-1 M strains evolved a fully functional Vpu that counteracts tetherin (a cellular factor that blocks virus release) and degrades CD4 (the primary receptor of HIV) to promote the release of fully infectious viral particles. This may explain why group M viruses are almost entirely responsible for the global HIV/AIDS pandemic.



SEVI binds to HIV-1 virions and mediates their attachment to target cells. Cells are depicted in blue, SEVI fibrils in white and virions in red. Almost all viral particles are associated with fibrils. Kindly provided by Dr. Walther Mothes (New Haven, USA).

Another major focus is the isolation, characterization and optimization of novel inhibitors of HIV-1 and other viral pathogens. In cooperation with Prof. Wolf-Georg Forssmann (Hannover), we screened complex peptide-protein libraries from natural sources, such as hemofiltrate, semen, spleen, saliva, and breast milk, for natural compounds affecting HIV-1 infection. These studies have led to the discovery of several HIV-1 inhibitors. One of them, VIRIP, blocks HIV-1 entry by a novel mechanism, i.e. direct binding to the gp41 fusion peptide. A Phase 1/2 clinical study has just been completed and has shown that mono-therapy with an optimized VIRIP variant reduces the viral loads without causing severe side effects. We also used this approach to identify endogenous factors involved in sexual transmission of HIV-1 and found that fragments of the abundant semen marker prostatic acidic phosphatase (PAP) form amyloid fibrils, termed Semen-derived Enhancer of Virus Infection (SEVI), that capture HIV virions and enhance their infectious virus titer by several orders of magnitude. Thus, SEVI may play an important role in sexual transmission of HIV and represents a new target for its prevention. In our ongoing studies, we identified, among others, novel inhibitors and enhancers of HIV in breast milk, as well as an as-yet unknown CXCR4 antagonist that blocks X4-tropic HIV-1 strains, and found evidence that human blood contains several compounds capable of reactivating latent HIV-1 proviruses.

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Selected Publications:

- Sauter D, Specht A, Kirchhoff F (2010): Tetherin: Sticking together and letting go. *Cell*, [in press].
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- Arhel N, Lehmann M, Clauss K, Nienhaus GU, Piguet V, Kirchhoff F (2009): The inability to disrupt the immunological synapse between infected human T cells and APCs distinguishes HIV-1 from most other primate lentiviruses. *J. Clin Invest*, 119: 2965-2975.
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Harvesting mouse bone marrow cells for a multi-colour FACS (Fluorescence Activated Cell Sorting) experiment.

Institute of Immunology

Head of Institute: Prof. Dr. Hans-Reimer Rodewald (Provisional Head)

Keywords: Fate mapping | Hematopoiesis | Mast cells | Mixed-Lineage-Leukemia | Thymus

The Institute of Immunology currently employs two professors, three post-docs, three graduate students, three technical assistants, two master students and one secretary. The Institute hosts research groups headed by Hans-Reimer Rodewald and by Hans Jörg Fehling.

Research Group: Developmental Immunology and Hematopoiesis

Head: Prof. Dr. Hans-Reimer Rodewald

The Rodewald lab has a long-standing interest in the characterization of hematopoietic stem and progenitor cells. The role of cytokines and their receptors in lymphocyte development has been a second focus of the lab that has uncovered the crucial functions of the receptor tyrosine kinase c-Kit in fetal and adult hematopoiesis by using stem cell mutants. The lab developed a strategy to target mutations in the thymus epithelium and identified a second thymus in mice. Members of this group study the development and function of mast cell proteases, mast cell heparin synthesis and the regulation of mast cell numbers in skin inflammation. A further research highlight was the development of a “universal” stem cell recipient mouse that accepts not only histocompatible but also histoincompatible donor stem cells without prior irradiation of the host.

Research Group: Molecular Immunology

Head: Prof. Dr. Hans Jörg Fehling

The generation and analysis of genetically modified mouse mutants is the prime technical focus of the Molecular Immunology Group headed by Hans Jörg Fehling. Members of the laboratory have generated conditional knock-out mice to assess *in vivo* roles of *Dppa4* (Developmental-Pluripotency-Associated-4) and *Mll5* (Mixed-Lineage-Leukemia-5), two genes with proposed roles in stem cell function. Contrary to predictions, *Dppa4* was shown to be completely dispensable in stem cells but essential for mouse embryogenesis. Targeted inactivation of *Mll5* revealed a critical role in hematopoietic stem cell function. As loss of *Mll5* in humans is associated with myeloid malignancies, our conditional *Mll5*-mouse mutants may provide a valuable animal model for investigating mechanisms of leukemogenesis. The Molecular Immunology Group also pursues projects with the goal of directly visualizing developmental fate decisions of hematopoietic cells. To this end, members of the group have generated several sophisticated “knock-in” mouse strains, including a very popular red fluorescent Cre-reporter mouse, which is currently being used in more than 150 laboratories worldwide.

Over the past ten years, both research groups at the Institute have jointly made considerable efforts to establish a technically and scientifically ambitious research environment, ranging from the construction of complex targeting vectors to the functional analysis of mouse mutants newly generated in the Institute. Several of these mouse mutants were aimed at quantitatively deciphering physiological pathways in hematopoiesis *in vivo*. These experiments have recently led to new insights into the regulation of developmental choices of T cell progenitors by *Notch1* and into the fundamental dichotomy of the hematopoietic tree into distinct lymphoid and myeloid branches, each of which arises from separate progenitors



Analysis of complex data from a multi-colour FACS (Fluorescence Activated Cell Sorting) experiment with mouse hematopoietic cells.

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Selected Publications:

- Schlenner S, Madan V, Busch K, Tietz A, Läuble C, Costa C, Blum C, Fehling HJ, Rodewald HR (2010): Fate mapping reveals separate origins of T cells and myeloid lineages in the thymus. *Immunity*, 32: 426-436.
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Institute of Medical Microbiology and Hospital Hygiene

Head of Institute: Prof. Dr. Steffen Stenger

Keywords: Apoptosis in infectious | disease infection immunology | infection epidemiology | intracellular pathogens | microbial pathogenesis

The Institute of Medical Microbiology and Hospital Hygiene is responsible for the diagnosis of microbial infections in a broad spectrum of clinical samples. Each year about 60,000 materials are investigated for the presence of bacteria, fungi and parasites. In addition to its activities as a clinical diagnostic laboratory, the hospital hygiene section (headed by Prof. Dr. Heike von Baum) is responsible for the hygiene management of the university clinic.

Teaching activities include lectures and practical courses for students of the Medical School, the Dental School and bachelor and master students of Molecular Medicine. Traditional lectures are supplemented by more interactive teaching in problem-oriented learning (POL) courses and e-learning programs.

The scientific activity of the institute is covered by five independent research groups specializing in various aspects of infectious diseases that entails basic science as well as more clinically-oriented research.

Research Group: Infection Epidemiology

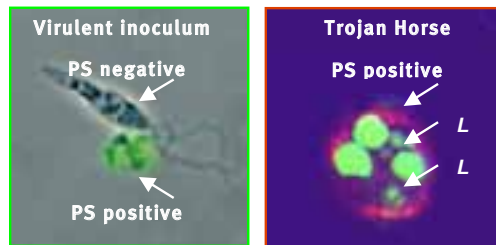
Head: Prof. Dr. Heike von Baum

This group is focusing on infection epidemiology of methicillin resistant *S. aureus* strains (MRSA), pathogens in drinking water and community acquired pneumonia.

Research Group: Chlamydia

Head: Prof. Dr. Andreas Essig

The research activities are centered on the intracellular pathogens *Chlamydia pneumoniae*, *Chlamydia trachomatis* and *Chlamydia abortus*. Current projects of the group are aimed at the identification of antigenic surface structures of chlamydia that could serve as diagnostic markers in serological investigations.



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.

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Research Group: Streptococcal Research

Head: Prof. Dr. Barbara Spellerberg

This group is interested in the molecular mechanisms of invasive streptococci. Research topics include horizontal gene transfer mechanisms and the identification of streptococcal virulence determinants.

Research Group: MyTB Laboratory

Head: Prof. Dr. Steffen Stenger

This group focuses on the immunological mechanisms directed against mycobacteria. The major goal of the group is the analysis of innate and adaptive effector pathways of the human immune system.

Research Group: TvL Laboratory

Head: PD Dr. Ger van Zandbergen

The TvL laboratory is interested in the phagocytic mechanisms leading to the elimination of a broad range of microbial pathogens. The main focus lies on the strategy of microbial pathogens to use host cells as trojan horses for gaining access to specific host compartments.

Scientific highlights of our institute during the last year included the elucidation of a big legionella outbreak in Ulm caused by a legionella-infected cooling tower at the beginning of 2010. In 2009, the research from our institute was published in the Journal of Clinical Investigation and characterized the molecular mechanism of how anti-TNF immunotherapy reduces CD8+ T cell-mediated antimicrobial activity against *Mycobacterium tuberculosis* in humans. Further research characterized the way *Chlamydia pneumoniae* hides inside apoptotic neutrophils to silently infect and propagate in macrophages, and also the host specific induction of a major streptococcal virulence factor upon exposure to human serum.

Selected Publications:

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Institute of Human Genetics

Head of Institute: Prof. Dr. Walther Vogel

Keywords: Cancer genetics | DNA repair | Genetic epidemiology | genotype/phenotype analysis

The institute is located in two places: research and teaching are generally conducted in the main building of the University while patient care and diagnostics take place in the city center. The institute comprises about 50 employees, 73% of whom are female. Twelve PhD students are supported by state grants and industrial funds.

Genetic counseling is offered and delivered in the *Sektion Genetische Beratung* (Head: N.N.), which is maintained by three genetic counselors and one technician. Together with the adjacent diagnostic labs, this setting offers the opportunity to specialize either in Human Genetics and/or Medical Genetics. Genetic counselors are also involved in the teaching of medical students to provide a hands-on environment in Medical Genetics.

The research profile of the institute focuses mainly on genetics of neoplasias. The genetics of familial prostate cancer are studied within an international framework comprising geneticists, epidemiologists and urologists. Genome-wide genetic linkage and association studies have been performed to identify putative candidate gene regions of familial prostate cancer. The data can be analyzed in-house by a genetic epidemiologist. Functional studies of candidate genes are another tool for studying genes with dysregulation in tumor tissue. DNA damage and repair is another

field of interest being investigated by a group focusing on genotoxic effects of environmental and industrial substances. Fibromatous tumors of the skin, typical of Neurofibromatosis type I, are subject to additional genetic analyses. Genotype/phenotype correlations and attempts for an oligonucleotide-driven gene therapy are the main topics of this research project. The characterization of large deletions in the *NF1* gene and similar copy number variations in the genome of humans and other primates are another field of research. Molecular genetics of rare monogenetic disorders is a further focal point at the institute. Within a European network of genetic counselors, pediatricians and geneticists, genotype/phenotype correlations will be established for the Branchio-Oculo-Facial Syndrome. The genetics of mammalian sex determination and associated disorders are studied in an animal model in collaboration with a Dutch group. Not all projects rely solely on basic genetic techniques but include novel technologies, such as arrays, robotics, and chip technologies, which are supplemented by fundamental epidemiological and statistical evaluation of the data.

The institute employs several specialists for the diagnostics of selected genetic disorders. We therefore obtain diagnostic samples not only from the local area but also from European-wide healthcare professionals. The main focus lies on the genetics of neuromuscular disorders and several forms of mental retardation syndromes. We also offer diagnostic testing for familial breast cancer, colorectal cancer and neurofibromatosis. This gives us the opportunity to transfer our knowledge and experience to the classroom where students are taught during the clinical phase of their studies.



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Selected Publications:

- Roehl AC, Cooper DN, Kluwe L, Helbrich A, Wimmer K, Hogel J, Mautner VF, Kehrer-Sawatzki H (2010): Extended runs of homozygosity at 17q11.2: an association with type-2 *NF1* deletions? *Hum Mutat*, 31: 325-334.
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- Cooper DN, Kehrer-Sawatzki H (2008): *Handbook of Human Molecular Evolution*. John Wiley & Sons, Hoboken, NJ.



Institute of Pharmacology and Toxicology

Head of Institute: Prof. Dr. Peter Gierschik

Keywords: Bacterial protein toxins | chemokine receptors | GTP-binding proteins | Rho GTPases | Signal transduction

The primary and long-term mission of the institute is to advance the field of Molecular and Cellular Pharmacology and Toxicology in research, teaching and application. Our research efforts are directed both at addressing fundamental scientific questions by conducting basic research and at translating basic research findings into sustainable health care improvements by cooperating with the pharmaceutical industry. Our research focus is centered on exploring the transfer of extracellular information of both abstract and concrete essence across the cell membrane. According to the broad and deep impact of pharmacology and toxicology in medicine and the life sciences, the scope of our teaching activities is wide and multidisciplinary, and ranges from medicine, dentistry and molecular medicine to biology, biochemistry, chemistry and pharmaceutical biotechnology. Teaching is conducted both at under- and postgraduate level and in collaboration with the pharmaceutical industry, on such topics as national and international (EU) principles of new drug development, registration, and post-marketing risk assessment.

Several research groups are concerned with the role of signal-transducing GTP-binding proteins (both heterotrimeric G proteins and small GTPases of the Ras superfamily) as well as their cell surface receptors, intracellular regulatory proteins and effectors in cellular signal transduction. Among the G-protein-coupled-receptors (GPCRs), we are particularly interested in chemokine receptors, which play pivotal and indispensable roles in health and disease by controlling multiple aspects of many cell and tissue functions, most notably, those of the immune, hematopoietic and nervous systems. For example, chemokines and their receptors steer the directed migration of leukocytes and tumor cells to sites of inflammation and metastasis and thus contribute to the development, maintenance and progression of both inflammatory and neoplastic diseases. Among the small GTPases and intracellular effector proteins, the focus is on Rho GTPases and inositol-phospholipid-specific phospholipases C (PLCs), respectively. For example, we were the first to show that certain



PLCs are activated by several Rho GTPases of the Rac/Cdc42 subfamily. In collaboration with other research groups, the laboratory has determined the three-dimensional structure and characterized the functional properties of the heterodimeric complexes between certain Rac GTPases with their regulatory and effector proteins.

The institute's research group devoted to toxicological research and health concerns is headed by Prof. Holger Barth and uses biochemical, molecular pharmacological and cell biological methods to characterize the molecular mechanisms of action of bacterial protein toxins, particularly those of the genera *Clostridia* and *Salmonella*. We are specifically interested in the transfer of these toxins across the cell membrane and their refolding into active biomolecules inside the cell. Our results recently showed that certain intracellular folding enzymes, termed chaperones and peptidyl-prolyl cis/trans isomerases, are required for these processes. It is expected that these findings will not only contribute broadly to our understanding of the impact of these toxins as virulence factors, but will also provide new avenues for the drug therapy of bacterial infections. One important translational corollary of this work is the use of certain structural elements of the toxins to introduce foreign, e.g. therapeutic, proteins into human cells as „Trojan Horses“. These are currently being developed by the group as recombinant fusion proteins and are expected to become promising new tools in future pharmacological research and development.

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Selected Publications:

- Theveneau E, Marchant L, Gull M, Moepps B, Parsons M, Eickholt B, Mayor R (2010): Contacts dependent cell polarity is essential for chemotaxis during collective migration. *Dev Cell*, [in press].
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- 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 α 2 through interaction with a split pleckstrin homology domain. *J Biol Chem*, 283: 30351-30362.



Institute of Pharmacology of Natural Products and Clinical Pharmacology

Head of Institute: Prof. Dr. Thomas Simmet

Keywords: Immunopharmacology | natural products chemistry | natural products pharmacology | pharmacogenomics | signal transduction

The Institute is located at Science Park I of Ulm University. Our Institute has 24 employees: 67% are female; 12.5% of the employees are from abroad; and 5 graduate students are currently attending our PhD program. We teach clinical and basic pharmacology to medical students and to students of basic sciences. The Institute maintains a strong research profile with state of the art equipment designed for demanding research projects, which are often conducted in collaboration with other research groups on the campus as well as from abroad.

As the result of a concept unique to Ulm that combines Clinical Pharmacology with Pharmacology of Natural Products, the Institute is subdivided into five research groups: natural products chemistry; natural products pharmacology; biochemical and immunopharmacology; and pharmacogenomics. With regards to Pharmacology of Natural Products, our research interests include the isolation as well as the chemical and pharmacological characterization of natural compounds with the goal of identifying lead compounds for the therapeutic modulation of distinct signal transduction mechanisms in inflammation and cancer. In this respect, we possess significant expertise in the molecular characterizing of small molecule-protein interactions by means of surface plasmon resonance analysis. Highly sensitive analytical methods readily developed in our chemistry labs allow us to analyze pharmacokinetics in minute amounts of plasma, e.g. in the circulation of chicken embryos.

Molecular pharmacological and biochemical studies are aimed at the elucidation of proteolytic signal transduction mechanisms in cells engaged in chronic inflammatory processes, which are the most frequent reasons for patients seeking medical advice and treatment.

The group working on Tumor and B Cell Immunology investigates immunopharmacological questions in the area of B cell immunology. One focus is to identify novel immunopharmacological agents with the potential to regulate activation and apoptosis of normal and malignant B cells. The identification of CpG oligonucleotides as potent inducers of apoptosis and immunogenicity in malignant B cells from patients with B chronic lymphocytic leukaemia (B-CLL) formed the basis for a clinical phase I/II trial. Further projects address the general question of how B cell function and differentiation can be therapeutically manipulated.

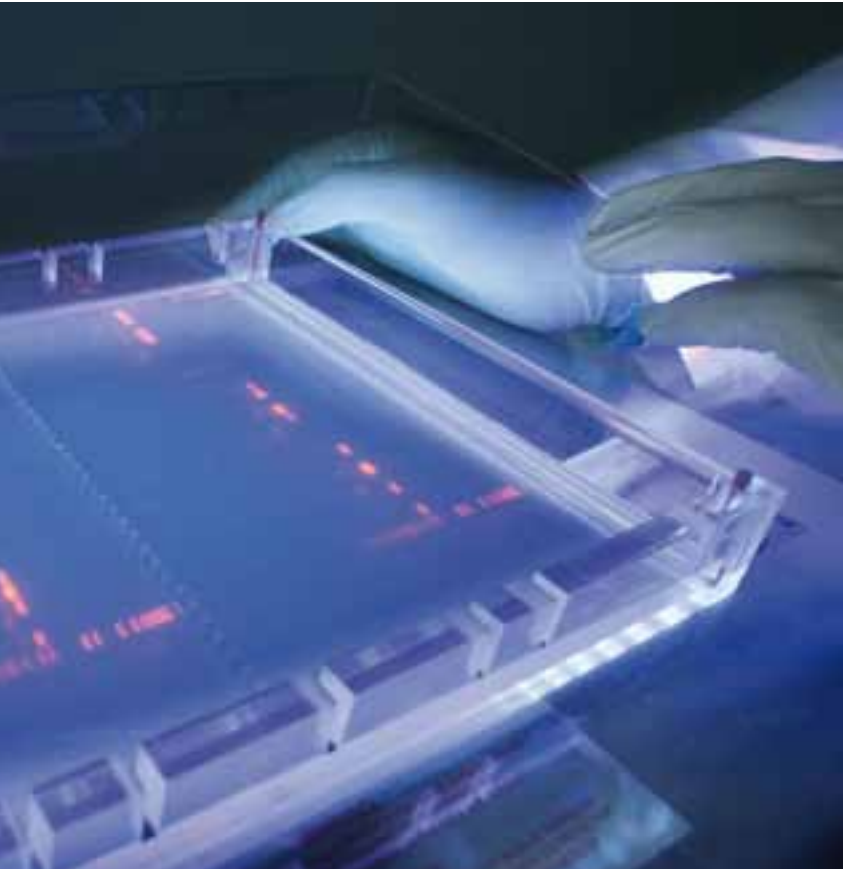
The Clinical Pharmacology section of the Institute (Prof. Dr. Julia Kirchheiner) has its main area of research in pharmacogenetics and pharmacogenomics. Here, we perform studies on genetic variants which can affect the drug efficacy in clinical studies and in molecular experiments. In addition, we advise clinicians on specific questions concerning genetically based changes in pharmacokinetics. On account of our expertise, we run the core-facility *Animal Models in Cancer Research* by offering advice to other departments and providing them with mostly xenotransplantation models (nude mice, chick chorioallantoic membranes). However, this unit is also available for external contract research and we thus offer a pharmacological information service for clinicians, general practitioners and the public.



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Selected Publications:

- Jahrsdörfer B, Vollmer A, Blackwell SE, Maier J, Sontheimer K, Beyer T, Mandel B, Lunov O, Tron K, Nienhaus GU, Simmet T, Debatin KM, Weiner GJ, Fabricius D (2010): Granzyme B produced by human plasmacytoid dendritic cells suppresses T cell expansion. *Blood*, 115: 1156-1165.
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Institute of Experimental Cancer Research

Head of Institute: Prof. Dr. Christian Buske

Keywords: Leukemia | stem cell biology | tumor biology | tumor stem cells

The institute focuses mainly on research and the teaching of students enrolled in medicine, molecular medicine or biology. The institute currently employs an international team of 18 members with six postdoctoral fellows, six PhD students as well as six technicians who are involved in high quality research in the field of stem cell and tumor cell biology.

As a clinical institute of the Comprehensive Cancer Center Ulm (CCCU), our central goal is to advance translational research in tumor biology and to act as a bridge between research institutes of the University and the clinical departments of the University Medical Center Ulm. The institute aims to transfer research findings from experimental models to a clinical setting and to use these new insights for the development of novel therapeutic strategies. At the same time, the institute aims to translate those findings from the clinic into valid experimental models, thereby opening up the possibility of analyzing the functional mechanisms of tumor growth in detail. The focus of our research lies in the mechanisms of tumorigenesis and in particular the use of acute leukemias as a model disease of cancer.

Functional Analysis of Genetic Alterations in Acute Leukemia

We try to understand the mechanisms through which leukemia-specific genetic aberrations convert normal hematopoietic cells to leukemic cells. To analyze this, leukemia-specific alterations are expressed in normal human or murine blood cells. The behavior of these genetically modified blood cells is then investigated in vitro or in vivo. The institute is particularly interested in leukemias induced by the AML1-ETO fusion gene, the NPM1 mutation or leukemogenic HOX genes, which are all aberrations found in patients with acute myeloid leukemia.



Importance of Non-Encoding RNA for Normal and Malignant Hematopoiesis

A further focus of our institute is to dissect the function of non-encoding RNA molecules (RNA that do not encode proteins) in normal and malignant hematopoiesis. Using different in vivo models, our group aims at identifying crucial differences in the expression of non-encoding RNAs between healthy and leukemic stem cells and to clarify which microRNA acts as an oncogene and which one acts as a tumor suppressor gene. Another major objective of our work is to develop strategies to use microRNAs as potential therapeutics.

Identification of Tumor Stem Cells

Another major focus of the institute lies in the characterization of leukemic stem cells and to define differences between healthy and leukemic stem cells. This would allow the development of therapeutic approaches which selectively kill leukemic stem cells. In line with this, the group was able to show in a murine model that leukemic stem cells of acute myeloid leukemia express surface proteins that are not found on normal blood stem cells. Currently, we are examining whether leukemic stem cells also differ from normal blood stem cells in patients with acute myeloid leukemia regarding their surface profile.

Characterization of Stem Cell Regulating Factors

The understanding of normal blood hematopoiesis is the basis for our understanding of malignantly transformed hematopoiesis. Hence, several projects deal with the question of determining which factors are crucial for the function of normal blood stem cells. Those factors being investigated in particular are the so-called homeobox genes, which play a crucial role in normal hematopoiesis and, if malfunctioning, can initiate leukemogenesis.

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Selected Publications:

- Metzeler KH, Dufour A, Benthous T, Hummel M, Sauerland M-C, Heinecke A, Berdel WE, Büchner T, Wörmann B, Mansmann U, Braess J, Spiekermann K, Hiddemann W, Buske C*, Bohlander SK* (2009): *ERG expression is an independent prognostic factor and allows refined risk stratification in cytogenetically normal acute myeloid leukemia: A comprehensive analysis of ERG, MN1 and BAALC transcript levels using oligonucleotide microarrays.* *JCO*, 27: 5031-5038 (*both authors contributed equally).
- Thoene S, Rawat VPS, Heilmeier B, Hoster E, Metzeler KH, Herold T, Hiddemann W, Gökbuget N, Hoelzer D, Bohlander SK, Feuring-Buske M, Buske C (2009): *The homeobox gene CDX2 is aberrantly expressed and associated with an inferior prognosis in patients with acute lymphoblastic leukemia.* *Leukemia*, 23: 649-655.
- Metzeler KH, Hummel M, Bloomfield CD, Spiekermann K, Braess J, Sauerland M-C, Heinecke A, Radmacher M, Marcucci G, Whitman SP, Maharry K, Paschka P, Larson RA, Berdel WE, Büchner T, Wörmann B, Mansmann U, Hiddemann W, Bohlander SK*, Buske C* (2008): *An 86 probe set gene expression signature predicts survival in cytogenetically normal acute myeloid leukemia.* *Blood*, 112: 4193-4201 (*both authors contributed equally).
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- Rawat VP, Thoene S, Naidu VM, Arseni N, Heilmeier B, Metzeler K, Petropoulos K, Deshpande A, Quintanilla-Martinez L, Bohlander SK, Spiekermann K, Hiddemann W, Feuring-Buske M, Buske C (2008): *Overexpression of CDX2 perturbs HOX gene expression in murine progenitors depending on its N-terminal domain and is closely correlated with deregulated HOX gene expression in human acute myeloid leukemia.* *Blood*, 111: 309-319.
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Extraction device to remove bile stones.

Department of Internal Medicine I

Head of Department: Prof. Dr. Guido Adler

Keywords: Gastroenterology | gastrointestinal cancer | hepatology | inflammatory bowel disease | pancreas

The Department of Internal Medicine I combines the fields of gastroenterology, metabolism, dietetics, endocrinology and nephrology. The Department of Gastroenterology focuses on the treatment of patients with diseases of the digestive system. We aim to diagnose and to provide care for patients with a wide range of gastroenterological conditions including cancers of the digestive tract, inflammatory bowel disease, liver diseases, nutritional problems and many others. The department has about 160 employees consisting of more than 50 medical doctors and scientists, 110 nurses, and technical staff. The head of the department is Prof. Dr. G. Adler. The department provides four wards with 94 inpatient beds and runs the emergency room for the center for Internal Medicine, an oncological outpatient clinic, and outpatient clinics for endoscopy, sonography, hepatology and endocrinology. In 2009, more than 4,400 patients were treated on our wards and more than 11,000 patients were seen in the outpatient clinics.

The Department of Internal Medicine I consists of two divisions:

- Endocrinology (Prof. Dr. B.O. Boehm), where the focus is on outpatient and inpatient care for patients with endocrine diseases as well as for those with diabetes and diabetes-associated complications;
- Nephrology (Prof. Dr. F. Keller), where the focus is on the treatment of patients with acute and chronic renal diseases. In addition, patients before and after kidney transplants are treated.

The Department of Internal Medicine I focuses heavily on translational and clinical research in gastroenterology and oncology in addition to endocrinology, and engages in frequent interaction and collaboration with research groups around the world. The Department of Internal Medicine I

also runs a collaborative research center (SFB 518, see page 14) where many interdisciplinary groups address the etiology and treatment of pancreatic diseases including diabetes. There are also research groups that work on cancer-development, metastasis, immunology, cell biology, hepatology and many other topics.

Our treatment concept is in line with the latest national and international standards. The department offers the whole spectrum of current examination methods in endoscopy and sonography as well as a full array of diagnostic tests to detect digestive diseases and liver problems. The department has a Clinical Trial Unit (CTU) with a team of highly trained medical doctors and study nurses. More than 40 clinical trials of phase I-II (early development of novel and promising agents) and of phase III-IV (randomized treatment trials) are currently active. A large proportion of patients are treated within such controlled clinical trials in order to ensure innovative patient care of the highest quality.

Our department is part of the Comprehensive Cancer Center Ulm (CCCU) founded in 2006. All patients with gastrointestinal tumors are assessed by an interdisciplinary team of experts from various fields including pathology, radio diagnostics, nuclear medicine, radiation therapy and gastroenterology/oncology. We operate a multidisciplinary approach to patient management and liaise closely with doctors from surrounding community hospitals and private gastroenterologists/ oncologists.

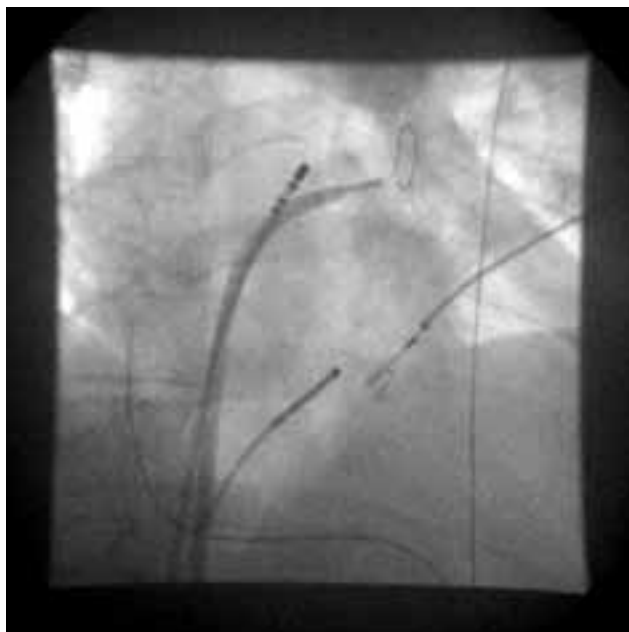


Abdominal sonography.

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Selected Publications:

- Krndija, D, Schmid H, Eismann JL, Lothar U, Adler G, Oswald F, Seufferlein T, von Wichert G (2010): Substrate stiffness and the receptor-type tyrosine-protein phosphatase alpha regulate spreading of colon cancer cells through cytoskeletal contractility. *Oncogene*, [epub ahead of print].
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Fluoroscopy during catheter ablation of atrial fibrillation. Different catheters are seen, which are placed in the coronary sinus and in the left atrium. The ring-shaped LASSO catheter is placed at the ostium of the left upper pulmonary vein for signal evaluation of ablation success.

Department of Internal Medicine II

Head of Department: Prof. Dr. Wolfgang Rottbauer

Keywords: Basic vascular and myocardial research | innovative cardiovascular imaging | interventional cardiovascular medicine

The department comprises the division of Cardiology, Angiology, Intensive Care Medicine, and two subdivisions: Pulmonology (Head Dr. Schumann); and Sports and Rehabilitation Medicine (Head Prof. Dr. Steinacker). It represents these areas in inpatient and outpatient care, clinical and basic research, and in teaching and medical education (82 regular ward beds, five beds for monitoring sleep disorders, 52 telemetry options and 12 ICU beds). There are currently 46 full-time physicians, three physicists, 20 technical assistants and health data administrators in the clinical routine, and 12 technical assistants and study nurses part-time or full-time in research. The number of PhD students currently trained in the different scientific research groups at present is eight.

The Cardiology and Angiology division offers the whole spectrum of modern non-invasive and invasive diagnostic and interventional procedures. In the three cath labs, besides routine and emergency percutaneous interventions on coronary arteries, peripheral arteries including renal and carotid arteries, complex interventional procedures, such as revascularisation of chronic total occlusions, percutaneous aortic valve replacement and mitral repair, as well as occlusion of patent foramen ovale or atrial/ventricular septal defects, are routinely provided. The electrophysiology group implants approximately 300 pace-makers and ICD a year including CRT. In the electrophysiology suite, about 250 radiofrequency ablations of supraventricular and ventricular tachycardias are annually performed. The department houses two cardiac MRI scanners (1.5 Tesla and one 3.0 Tesla) and performs 3,000 scans per year. In the Pulmonology subdivision, all modern diagnostic and interventional techniques as well as innovative therapeutic strategies have been implemented for the treatment of lung diseases,



MitraClip system for percutaneous mitral repair. The figure shows the clip to join the opposing leaflets at the location of the mitral regurgitation origin.

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especially lung cancer and malignant pleuramesothelioma. The Sports and Rehabilitation Medicine subdivision offers outpatient clinics for a variety of sports disciplines and supervises many athletes and national teams by providing ambulatory cardiac rehabilitation, in particular post-myocardial infarction and post-cardiovascular surgery.

The department pursues many projects in clinical and basic research with its main focus on vascular and myocardial pathologies. Our basic vascular research concentrates in particular on atherogenesis and the etiology of pulmonary hypertension, and for this purpose, several mouse models, such as LDL-receptor knock-out mice and apoE-deficient mice, are available. Myocardial research focuses on myocardial inflammation, in particular in the context of myocarditis and dilative cardiomyopathy, and also on the genetic etiology and pathophysiology of myocardial diseases. To address questions in these fields, studies in animal models, such as mice and zebrafish, in addition to large scale population-based approaches, such as genome-wide association studies, are performed. Moreover, on a population level, the genomics of myocardial infarction and particularly inflammatory processes are investigated. Clinical research is coordinated by a clinical trial unit that allows recruitment and monitoring of large patient cohorts according to standards that allow FDA or EMEA approval. Our preventive cardiology program focuses on the identification and evaluation of new biomarkers for cardiometabolic diseases. In addition, a large experimental cardiovascular imaging group concentrates on the assessment of the role of MRI for the diagnosis of cardiovascular diseases and in particular the risk stratification for atherosclerotic diseases.

Selected Publications:

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- Glynn RJ, Danielson E, Fonseca FAH, Genest J, Gotto AM Jr, Kastelein JJP, 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. *NEJM*, 360: 1851-1861.
- Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM Jr, Kastelein JJP, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ (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: 1175-1182.
- Hassel D, Dahme T, Erdmann J, Meder B, Hüge A, Stoll M, Just S, Hess A, Ehlermann P, Weichenhan D, Grimminger M, Liptau H, Hetzer R, Regitz-Zagrosek V, Fischer C, Nürnberg P, Schunkert H, Katus HA, Rottbauer W (2009). Nexilin Mutations Destabilize Cardiac Z-disks and Lead to Dilated Cardiomyopathy. *Nat Med*, 15: 1281-1288.
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The Department of Internal Medicine III combines cutting-edge basic scientific and translational research with comprehensive patient care and innovative treatment approaches.

Department of Internal Medicine III

Head of Department: Prof. Dr. Hartmut Döhner

Keywords: Biology | leukemial lymphoma | therapy | tumor

The Department of Internal Medicine III is one of the largest of its kind in Germany with over 250 employees engaged in patient care and research, 108 inpatient beds and spacious outpatient facilities.

The department focuses on the diagnosis and treatment of patients with benign and malignant disorders of the hemato-lymphopoietic system (e.g. anemias, acute and chronic leukemias, myelodysplastic syndromes, myeloproliferative diseases, Hodgkin-/non-Hodgkin lymphomas, multiple myeloma, aplastic anemia) and of patients with various solid tumors (e.g. lung cancer, renal cell carcinoma, breast-cancer, glioblastoma, sarcomas, germ cell tumors). The spectrum of activities comprises all modern diagnostic and therapeutic approaches such as conventional chemotherapies, innovative treatments with monoclonal antibodies, biologicals, molecular-targeted approaches with novel compounds, vaccination strategies and bone marrow/peripheral stem cell transplantation. The transplant unit has operated for more than 35 years and is among the most experienced in the world. Another focus of the department is on the treatment of patients with hemophilia and thrombophilia (Division of Hemostaseology), and of patients with autoimmune/rheumatological diseases. The Division of Infectious Diseases and Clinical Immunology focuses on the treatment of patients with infectious diseases, in particular HIV/AIDS, tuberculosis and tropical diseases or echinococcosis. It provides vaccinations and consultation for travelers to foreign countries. It is both a partner and leader of the Comprehensive Infectious Disease Center (CIDC).

Research activities center on the identification and characterization of molecular pathogenesis, and on the development of novel therapies in patients with leukemia and lymphoma as well as other oncological diseases. A wide spectrum of clinical trials is active and thus continuously offers access to innovative treatments in oncology for our patients to ensure the highest quality of patient care.

Medical doctors and scientists from our department are nationally and internationally renowned for their research work. This was attested in 2009 by the publication of over 80 articles in various international scientific journals, more than 5 million Euro in external research funding awarded to the department, and by its participation in the development of international guidelines (see refs.).

The Laboratory for Cytogenetic and Molecular Genetic Diagnostics is a central reference laboratory for genetic analyses within a number of multicenter clinical trial groups for the German-Austrian AML Study Group (AMLSG), the German CLL Study Group (GCLLSG) and the German Multiple Myeloma Study Group (DSMM), as well as for international pharmaceutical industry-sponsored trials.

To promote clinical research, the department hosts a Clinical Trial Unit (CTU) with a team of highly trained medical doctors and oncology study nurses. More than 70 clinical trials of phase I-II (early development of novel and promising anti-cancer agents) and of phase III-IV (randomized treatment trials) are currently active. A large proportion of patients are treated within clinical trials to promote innovation and ensure the highest quality of patient care. The department is an active partner of the Comprehensive Cancer Center Ulm (CCCU).



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Selected Publications:

- Döhner H, Estey EH, Amadori S, Appelbaum FR, Büchner T, Burnett AK, Dombret H, Fenaux P, Grimwade D, Larson RA, Lo-Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ, Sanz M, Sierra J, Tallman MS, Löwenberg B, Bloomfield CD (2010): *Diagnosis and management of acute myeloid leukemia in adults: Recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood, 115: 453-474.*
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- Stilgenbauer S, Zenz T, Winkler D, Bühler A, Schlenk RF, Groner S, Busch R, Hensel M, Dührsen U, Finke J, Dreger P, Jäger U, Lengfelder E, Hohloch K, Söling U, Schlag R, Kneba M, Hallek M, Döhner H (2009): *Subcutaneous Alemtuzumab in Fludarabine-Refractory Chronic Lymphocytic Leukemia: Clinical Results and Prognostic Marker Analyses from the CLL2H Study of the GCLLSG. J Clin Oncol, 27: 3994-4001.*
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- Schlenk RF*, Döhner K*, Krauter J, Fröhling S, Corbacioglu A, Bullinger L, Haddank M, Späth D, Morgan M, Benner A, Schlegelberger B, Heil G, Ganser A, Döhner H (2008): *Mutations and treatment outcome in cytogenetically normal acute myeloid leukemia. N Engl J Med, 358: 1909-1918.*



Processing of somatic cell therapy products in a GMP-grade clean room at the Institute of Transfusion Medicine Ulm.

Institute of Transfusion Medicine

Head of Institute: Prof. Dr. Hubert Schrezenmeier

Keywords: Hemapoietic stem cells | mesenchymal stromal cells | molecular diagnostics | transfusion

The institute is supported by the German Red Cross Blood Donor Service of Baden-Wuerttemberg – Hestia and acts in close collaboration with the Institute of Clinical Transfusion Medicine and Immunogenetics Ulm (IKT Ulm) as a joint venture of the German Red Cross Blood Donor Service of Baden-Wuerttemberg – Hestia and the University Medical Center Ulm.

Research activities focus on the two fields:

- Molecular diagnostics in immunogenetics, blood group genotyping, and defects of hematopoiesis and the immune system,
- development of large-scale GMP grade selection, manipulation, and expansion of stem cell preparations and somatic therapy with cellular products.

In the Department Molecular Diagnostics and Experimental Transplantation, disease-causing mutations and pathophysiology for severe inborn errors of hematopoiesis and the immune system have been successfully elucidated and this has become the basis for developing diagnostic tools.

In the Department Immunology, methods for sequenced-based typing of HLA-A, -B, -C and HLA-DRB1 as well as a CE-certified kit for efficient high throughput HLA-typing have been developed. The impact of Null-alleles and non-HLA-gene polymorphisms (e.g. cytokine genes, NOD/CAD, receptors of natural killer cells) on outcome after allogeneic stem cell transplantation is analyzed.

In the Department Blood Group Serology and Immunohematology, the genetic basis of the RhD-negative and weak-D phenotype, as well as many variants in the Rhesus blood group system, have been elucidated. In a European consortium, the group contributed to the development of the first blood group genotyping chip.



Robotic work station for high throughput HLA typing using a CE-marked kit developed by the Institute of Transfusion Medicine Ulm for sequence-based HLA-typing.

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Activities in the Department Stem Cells and Cellular Therapy include the collection of peripheral blood stem cells, selection of CD34-positive hematopoietic progenitor cells, lymphocyte depletion of stem cell preparations as well as preparations for adoptive immunotherapy (donor lymphocytes, opsonized lymphocytes, dendritic cells). A main area of research is the functional characterization and ex vivo expansion of mesenchymal stroma cells (MSC). A large-scale GMP-grade protocol for efficient ex vivo expansion of MSC up to $> 1 \times 10^8$ cells within a one-step culture of 12 to 15 days has been developed with a new platelet-derived growth factor preparation as a major component. Our GMP clean room is one production site among European Networks funded by the 7th Framework Program of the European Commission. The project CASCADE studies the regenerative potential of MSC for wound healing and is performed in close cooperation with the Department of Dermatology and Allergology. In the REBORNE project, MSC are explored for their potential in bone healing in close cooperation with the Department of Trauma Surgery Research and Biomechanics, the Department of Orthopedic Trauma, Hand, Plastic and Reconstructive Surgery, and the Department of Internal Medicine II. In collaboration with the Max-Planck-Institute for Polymer Research in Mainz, MSC are loaded with nanoparticles, which are used as a delivery system for bioactive substances and for labeling of the cells in order to allow non-invasive in vivo tracking of the cells by magnetic resonance imaging (in cooperation with the Department of Internal Medicine II).

Another project studies the oxydative impact of eosinophilic granulocytes on biological activity of damage-associated molecular patterns (DAMPs), which are typically associated with necrotic tissue of tumor cells, and investigates the impact of DAMPs on components of the tumor environment e.g. maturation of dendritic cells, and the migration and proliferation of MSC.

The IKT Ulm delivers the whole range of blood products, blood group typing, immunohematology and transplantation immunology lab methods for the University Medical Center Ulm and many other hospitals in Baden-Wuerttemberg.

Selected Publications:

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- Mailänder V, Lorenz M, Musyanovych A, Holzappel V, Fuchs K, Wiesneth M, Walther P, Landfester K, Schrezenmeier H (2008): Carboxylated superparamagnetic iron oxide particles labelled cells intercellularly without transfection agents. *Mol Imaging Biol*, 10: 138-146.



In vitro kinase assays. To characterize the kinetic parameters of cellular kinases ^{32}P gamma-ATP is used in in vitro phosphorylation reactions of different substrats.

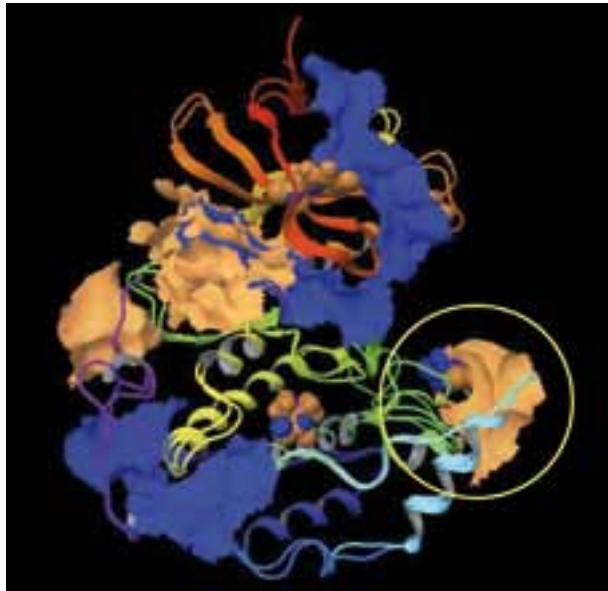
Department of General, Visceral, and Transplantation Surgery

Head of Department: Prof. Dr. Doris Henne-Bruns

Keywords: Colorectal Cancer | Gastrointestinal Stroma Tumors | Molecular Biology | Pancreatic Cancer | Surgical Oncology

The Department of General, Visceral, and Transplantation Surgery employs 35 physicians and 115 employees in nursing services for 76 patient beds placed on two regular wards, a special ward for children, and a surgical intensive care unit. Our focus is on surgical oncology and all standard procedures of general visceral and endocrine surgery are performed. Special fields of expertise are bariatric surgery and kidney transplantation. The department also includes a section in pediatric surgery headed by Dr. med. C. Leriche.

Research is mainly concentrated on malignant diseases by focusing on basic and translational research projects. At present, several PhD students and postdocs work in the laboratory as well as medical students from EU countries, China and Pakistan, who are completing their MD thesis. The central role of our research is to characterize the alterations in signal transduction pathways, the identification of new target molecules and prognostic factors, especially for pancreatic, colorectal and gastrointestinal stroma tumors. Individual projects are: the characterization of the importance of growth factors and growth factor receptors for the pathogenesis of pancreatic cancer (M. Kornmann, MD); the validation of members of the CK1 family as new target molecules for the development of inhibitors for new treatment concepts of malignancies (U. Knippschild, PhD); the identification of prognostic factors for various GI-malignancies (A. Formentini, MD); gastrointestinal stroma tumors (K. Kramer, MD); and the characterization of the importance of obesity (adipositas)



Three-dimensional model of the kinase domain of CK1 delta highlighting several surface areas.

in the development of malignancies (A. Wolf, M.D.). In a new and fascinating project, S. Paschke, MD, is investigating biophysical properties of tumor cells. Biological behavior, such as the migratory potential of cells (Boyden-Chamber-Assay), is compared with physical properties in the Optical-Stretcher. Regularly used laboratory space is available at the Department of General, Visceral, and Transplantation Surgery at Safranberg Hospital. A variety of cell culture, molecular biological methods, and animal models (Xenotransplantation and transgene models) have been established even for gene experiments of safety level 2. Another special feature of the department is the availability of a large tissue bank that includes tumor, normal and fat tissues as well as the clinical data of patients. Many of these projects are currently being funded by the *Deutsche Forschungsgemeinschaft* (SFB 518 project B18, M. Kornmann) and the *Deutsche Krebshilfe* (CK1 delta project, U. Knippschild). More detailed information about the research activities of the groups can be found under www.allgemeinchirurgie.uni-ulm.de/index.php?id=379. In addition to this basic and translational research, our department currently participates in clinical multicenter trials concerning colon and rectal cancer. A phase-II trial of advanced colorectal cancer that includes more than 160 patients was recently completed and is being coordinated by the study center located in our department.

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Selected Publications:

- Chen G, Tian X, Liu Z, Zhou S, Schmidt B, Henne-Bruns D, Bachem M, Kornmann M (2010): Inhibition of endogenous SPARC enhances pancreatic cancer cell growth: modulation by FGFR1-III isoform expression. *Br J Cancer*, 102 (4): 188-195.
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- Kornmann M, Henne-Bruns D, Porzolt F (2008): Neoadjuvant treatment of rectal carcinoma: assessment of health care services by physicians and lay persons. *J Clin Oncol*, 26: 4866-4868.



A highly motivated and well-experienced team of doctors attends to the patients.

Department of Thoracic and Vascular Surgery

Head of Department: Prof. Dr. Karl-Heinz Orend

Keywords: Aortic surgery | apoptosis | ischemia reperfusion | lung cancer | traumatic aortic rupture

The Department is regarded as one of the most exceptional clinics in Germany. It is renowned throughout Europe for its distinguished university education relating to vascular diseases or illnesses of the breast space that has, uniquely, been separated from heart surgery. Not only are all surgical lung illnesses and tumors of the breast space operated on daily in two operating theaters but also all illnesses of the blood vessels, both arteries as well as veins. The spectrum of maximum care ranges from complete surgery on lung tumors through to endovascular operations on varicose veins. The department comprises an outpatient clinic, wards with a total of 55 beds, and an intensive care unit containing five beds. A highly motivated and well-experienced team of 15 doctors attends to the patients.

The advantage of our department lies in the narrow interface between scientific research and clinical practice. Our patients benefit from the latest scientific knowledge and the very best in modern technology. The closely-knitted cooperation with our partners in the Departments of Radiology, Angiology, Oncology and Pneumology allows us to offer a personal program of treatment suited to the needs of each individual patient. Our aim is to provide the most current and effective therapy for our patients around-the-clock.

The core competence of thoracic surgery lies in the therapy of cancer disease of the thorax. The national and international reputation of our department in the treatment of bronchial carcinomas, tumor of the mediastinum, and lung metastases is renowned. We have vast experience in conventional operations as well as minimum-invasive technologies that includes laser surgery. In cooperation with the Comprehensive Cancer Center Ulm (CCCU), we provide a stratified treatment concept and deal in particular with such questions as combining surgery with chemo- and/or radiation therapy (multimodal therapy or neo-adjuvant treatment; immediate operation or pre-treatment first?) so that the risks for the patient decrease and the quality of life and the chances

of a cure can be discussed. Our main focus in vascular surgery is on the treatment of aneurysms, claudication, stenosis of carotids, varicose veins, chronic wounds, ulcer cruris and diabetic foot syndrome. In addition to conventional bypass operations, we have gained long-standing expertise in interventional catheter technologies and endovascular therapy, or a combination of both technologies in what are known as hybrid operations, as well as operations on pre-treated patients. Our research and extensive experience in endovascular procedures (stent and stentgrafts) contribute to current therapy standards worldwide.

As an integral component of the department, our research laboratories benefit from their close proximity to the clinic. Essential therapy standards and basic research have been directed on a regular basis from Ulm. Research competence in endovascular therapy and vascular diseases are focused. Standard therapy after traumatic rupture is strongly influenced by the scientific work of the Ulm group and has saved many lives worldwide. Our scientists have acquired a great deal of competence in the research of ischemia/reperfusion injury and the fight of the SIRS in aortic surgery in addition to such subjects as ageing and apoptosis research following vascular-surgical interventions. The collection of tissue patterns from tumors of the breast space allows us to gain a better understanding of this disease and to make improvements to increase the potential for healing.

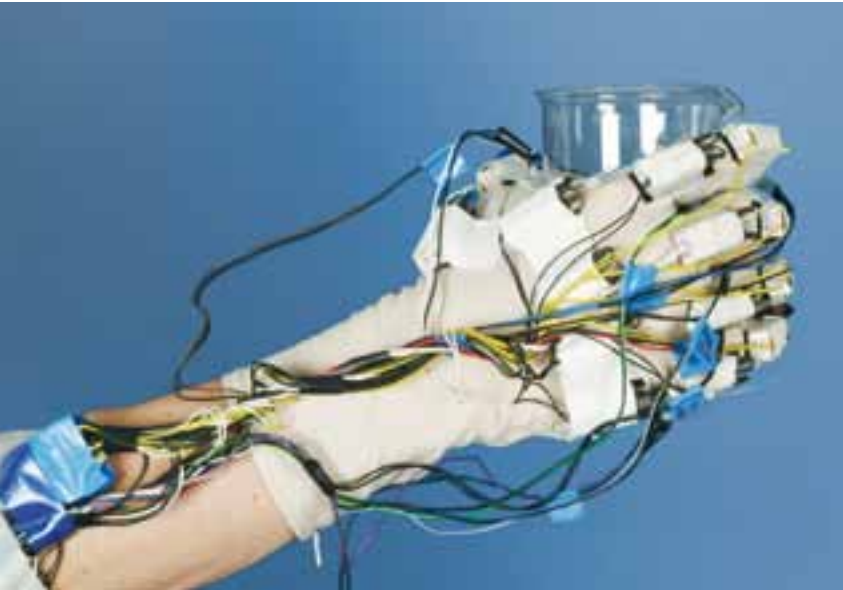


From benchmark to bed: essential therapy standards and basic research go hand in hand in our department.

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Selected Publications:

- Muehling BM, Bischoff G, Schelzig H, Sunder-Plassmann L, Orend KH (2010): Hybrid procedures for complex thoracoabdominal aortic aneurysms: early results and secondary interventions. *Vasc Endovascular Surg*, 44: 110-115.
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- Muehling BM, Halter G, Lang G, Schelzig H, Steffen P, Wagner F, Meierhenrich R, Sunder-Plassmann L, Orend KH (2008): Prospective randomized controlled trial to evaluate "fast-track" elective open infrarenal aneurysm repair. *Langenbecks Arch Surg*, 393: 281-287.
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Evaluation of motion patterns by a newly developed sensor glove.

Department of Orthopedic Trauma, Hand, Plastic and Reconstruction Surgery

Head of Department: Prof. Dr. Florian Gebhard

Keywords: Computer assisted surgery | hand surgery | inflammatory response | joint replacement | Trauma surgery

The Department of Orthopedic Trauma is the second oldest of its type in Germany. The department performs an average of 6,500 surgical procedures per annum and treats some 35,000 outpatients. The department is run by the Medical Director (Chair of Trauma Surgery), eight senior consultants (two specialized in hand surgery), and 24 doctors (three female, 18 registrars and interns). The Trauma Lab is supervised by a head technician and run by a further six female technicians. The department also incorporates the Division of Hand- and Plastic Surgery (PD Dr. Mentzel). The research focus of this division concentrates on the analysis of the functional movement of the hand. In order to evaluate motion patterns, a sensor glove has recently been developed in cooperation with the Department of Robotics and Computational Biology at the Technical University Berlin. With this new glove the analysis of the dynamic interaction of the finger joints can be examined. This model may improve handling of a myoelectric prosthesis of the hand or help evaluate the severity of injuries and ongoing rehabilitation.

The Trauma Lab is part of the Clinical Research Unit 200 that focuses on the inflammatory response and coagulation disorders of patients with multiple injuries. In a lab setting a rodent model has been developed to simulate multiple injuries consisting of a simultaneous head injury, chest injury, femur fracture and soft tissue injury. The aim is to elucidate the sequelae of the combination of injuries and identify the major factors of outcome. Further topics are the influence of multiple injuries on fracture healing and soft tissue recovery. An Emmy Noether group (Mario Perl) has been integrated into the Trauma Lab to focus on apoptosis in trauma. Within the European REBORNE project on stem cells and artificial bone substitutes, the department is part of a multicenter clinical evaluation of stem cell-loaded bone allograft in delayed fracture healing. The spine group led by Prof. Kramer deals with

the problem of chronic pain syndromes following spinal injuries. In association with the Fraunhofer Institute Darmstadt, a new diagnostic tool has been developed by using the technique of positioning fine-wire electrodes in predefined neck muscles. The dynamic EMG activity during head movements can differentiate substantially between patients and healthy subjects. With the help of virtual reality, it is now possible to control and monitor the head movement of patients and to apply specific training forces to the cervical spine. This worldwide unique device enables a physiological sensor-motoric training of the neck muscles and is superior to conventional resistance training. The spine group takes part in the development of spine implants in osteoporotic bone (Prof. Schultheiss). The multicenter study ORCHID (“Open Reduction and Fixation versus Closed Reduction in Distal Radius Fractures in the Elderly”) is now being conducted.

The department covers every type of fracture care, i.e. long bone and articular Fx, by using the latest implant technologies. As a Level I trauma center, the department is part of the German Trauma Network (DGU) and has been given a rating with the highest level of trauma care. Spinal surgery is performed using 3D computer guidance, a new technology that has been clinically evaluated in recent years in the department. Special expertise allows treatment of bone and soft tissue tumors (on average 200 cases per annum). To achieve the best individual therapy for rare

tumors, each case is discussed at the CCCU which generally recommends multimodality-based treatment. A further specialty is the analysis of leg deformities and correction that includes computer guidance. Posttraumatic or degenerative joint destruction is treated by replacement of the joint where knee joint replacement computer guidance is also used.

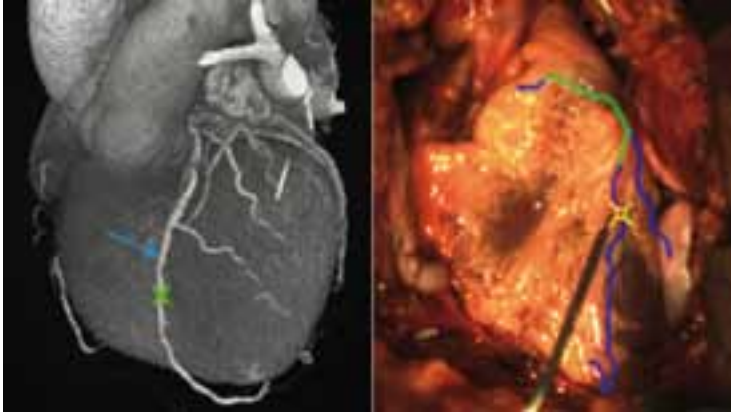


Force-Feedback-System for sensor-motoric neck muscle training after spine injury.

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Selected Publications:

- Kraus M, Gebhard F (2010): Can Computer-assisted Surgery Reduce the Effective Dose for Spinal Fusion and Sacroiliac Screw Insertion? *CORR*, [Epub ahead of print].
- Krischak GD, Krasteva A, Schneider F, Gulkin D, Gebhard F, Kramer M (2009): Physiotherapy after volar plating of wrist fractures is effective using a home exercise program. *Arch Phys Med Rehabil*, 90: 537-544.
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- Gebhard F, Huber-Lang M (2008): Polytrauma – pathophysiology and management principles. *Langenbecks Arch Surg*, 393: 825-831.



Cardiopointer: The registration method is capable of matching the relevant parts of a preoperatively extracted map of the coronaries with intraoperatively recorded optical tracking data. It can be used as a basis for a surgical navigation system to localize the optimal anastomotic site during CABG.

Department of Cardiac Surgery

Head of Department: Prof. Dr. Andreas Hannekum

Keywords: Atherogenesis | Cardio Pointer | LaMedica | percutaneous AVR

The Department of Cardiac Surgery at the University Medical Center Ulm is a specialist center for heart treatment with a nationwide reputation for excellence. A team of seven cardiac surgeons, 10 residents and more than 75 nurses and non-medical staff work closely with colleagues in cardiology, radiology and vascular surgery to deliver care that is safe, effective and compassionate. More than 700 operations, with or without a heart-lung machine, are performed annually and includes the entire spectrum in the treatment of acquired heart defects. Procedures range from valve reconstruction/replacement, coronary artery revascularization, surgical repair of the thoracic aorta, artificial heart, and novel minimally invasive procedures.

Our dedication to innovation has been encouraged by two major BMBF funded projects. LaMedica was the first multimedia-driven teaching platform that has now become a standard feature of the medical education at our institution. LaMedica is regarded as one of the pioneers of many e-learning programs. This funding subsequently offered the development of the Cardio-Pointer navigation system, an innovative method of image-guided navigation for multivessel coronary artery bypass grafting. For the first time it is now possible to locate precisely and in real-time specific coronary target regions with the assistance of a preoperative CT scan. This technology enables the explicit identification of the region of interest during surgery.

In order to provide medical care at the highest level, cutting-edge research is necessary. Therefore, we established our institutional laboratory where a group of scientists is working on myocardial regeneration, ischemia/reperfusion injury as well as new aspects in atherogenesis.

Recently, we investigated the onset and progression of coronary artery disease subject to specific mediators in the adipose tissue. Here, adiponectin, a protein with known anti-inflammatory and insulin sensitizing properties primarily secreted by mature adipocytes, may play a key role in the development of coronary artery disease. Its anti-atherogenic properties may represent a novel prospective therapeutic option in the treatment and prevention of cardiovascular diseases.

Another clinical and scientific focus is on the development and improvement of minimally invasive procedures such as percutaneous aortic valve replacement (AVR), which is being investigated as a new treatment for selected patients with severe symptomatic aortic stenosis (narrowing of the aortic valve opening). In collaboration with cardiologists and radiologists, our institution was the first center in the state of Baden-Württemberg to implant an aortic valve percutaneously. Our future projects will focus on less invasive strategies in cardiac surgery and we will introduce a novel minimized heart-lung machine where fundamental components are reduced to minimal elements. Preliminary studies confirmed these minimized systems to provide not only a less invasive solution to meet the requirements during cardiac surgery but also a more organ-preserving alternative to the standard heart-lung machine. The future trend in medicine as well as in cardiac surgery is to provide less intense and invasive therapeutic options with non-restrictive safety standards and improved outcome. We are trying to meet this challenge by improving the established standards while being open to new innovative techniques in order to further clinical and basic scientific research.



CoreValve: The Medtronic CoreValve® System permits the replacement of failing aortic heart valves using a beating-heart percutaneous interventional procedure. At the moment, this procedure is reserved for selected patients that do not qualify for conventional surgery.

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Selected Publications:

- Skrabal CA, Czaja J, Honz K, Emini R, Hannekum A, Friedl R (2010): Adiponectin – its potential to predict and prevent coronary artery disease. *Thorac Cardiovasc Surg*, [in press].
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Department of Cardiac Anesthesia

Head of Department: PD Dr. Helmut Reinelt (Provisional Head)

Keywords: Application of knowledge | Cardiac Anesthesia | teaching

Up to eight physicians of the Department of Cardiac Anesthesia are specialized in the perioperative treatment of cardiac surgery patients. We attach great importance to training in all the skills needed for competent and safe patient care.

Since the very beginning when our division was founded in 1997, we have highlighted the importance of teaching in clinical scenarios as well as in a preclinical setting. For our clinical students and as part of the framework of the faculty's elective course program, we offer the course Cardiac Anesthesia which is divided into two major parts: In the theoretical part we teach the basic knowledge needed within the context of cardiac anesthesia while in the practical part students gain first-hand experience by directly and concretely applying their newly acquired knowledge. During the complete duration of the course, we pay particular attention to the demands of acquiring a broad knowledge and those skills that will be useful not solely in the subject of cardiac anesthesia itself, which would be far too specific for the majority of our students, but also in many other important disciplines and contexts such as working in interdisciplinary Intensive Care Units, monitoring a patient's hemodynamic situation, interpreting the core values of invasive and non-invasive hemodynamic measurement, treating hemodynamic instabilities, handling cardiac emergencies or being in charge of patients suffering from cardiac disease.



During the preclinical stage, our seminar, Introduction into Clinical Medicine, bridges the gap between the basic sciences and their clinical application especially in the subjects of anatomy and physiology. The latter has become a subject of great importance in anesthesiology in general and in cardiac anesthesia in particular. This seminar includes such themes as Applied Physiology: Potassium and Heart Rhythm, Applied Physiology: Circulation and Gas Exchange in Extracorporeal Circulation and Applied Anatomy: Heart Chambers and Valves in the Surgical and the Echocardiographic View. The feedback of preclinical students participating in this module has been enormously positive and has shown that students very much appreciate the combination of preclinical knowledge and its clinical application.

On a voluntary basis, preclinical students have the additional opportunity to participate in our program Structured OR Hospitation where they must prepare obligatory pre-course assignments in a number of pre-selected subjects and afterwards accompany one of our cardiac anesthetists during his work in the OR to learn the practical application of the basic sciences in our daily work.

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Selected Publications:

- Rau T, Thumser-Dauth K, Liebhardt H, Böckers A, Muche R, Gulich M, Barth H, Kornmann M, Fegert J, Öchsner W (2010): Erarbeitung von Empfehlungen zu universitären Prüfungen an der Medizinischen Fakultät Ulm. *GMS Z Med Ausbild.* 27(1): Doc07, DOI: 10.3205/zma000644, URN: urn:nbn:de:0183-zma0006444.
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The BrainSuite allows intraoperative high quality imaging in brain tumor surgery for resection control and preservation of neurological function. Other conditions in which patients may benefit from this cutting edge technology are currently being explored scientifically.

Department of Neurosurgery

Head of Department: Prof. Dr. Christian Rainer Wirtz

Keywords: Intraoperative Imaging | Neurooncology | Peripheral Nerve Surgery | Traumatic Brain Injury | Vascular Surgery

The Department of Neurosurgery at Ulm University is headed by Professor Wirtz and is now one of the largest neurosurgical units in Germany. Twelve neurosurgeons and 13 residents provide outpatient care to more than 9,000 patients from around the world and perform more than 3,500 neurosurgical procedures each year. The team that includes eight women and five members from abroad is proud to cooperate with colleagues in other disciplines to offer expertise in treating a wide range of neurological and neurosurgical conditions. They are aided by outstanding and highly-skilled support staff. Our team of neurosurgeons provides thorough examinations, diagnoses and treatments for brain, nerve, and spinal cord diseases and disorders in children and adults. Each patient is treated individually since physical, psychological and cultural differences may affect treatment choices.

The Department of Neurological Surgery at Ulm University has two locations, namely, Ulm (State of Baden-Württemberg) and Günzburg (Federal State of Bavaria) with a total of 99 beds that includes intensive and intermediate care as well as normal ward units for adults and children.

Our facilities include cutting-edge equipment, i.e. modern surgical microscopes (including 5-ALA fluoromicroscopy and intraoperative infrared angiography), image-guided brain and spine navigation tools as well as monitoring techniques. Furthermore, we offer the most advanced neurosurgical theater in Europe, the BrainSuite©, which combines state-of-the-art neuronavigation and intraoperative magnetic resonance technology (Magnetom Espree® 1.5 Tesla) for the benefit of patients with a variety of conditions.

Our physicians are leaders in their field and contribute to advancements in brain, spine, endovascular and operative neurovascular surgery, neurotraumatology, pediatric neurosurgery and peripheral nerve care. Our goal is to provide optimal care to patients with neurological disorders and to enhance it through the continuous incorporation of advancing scientific knowledge. Our research efforts in neurovascular surgery, neuronavigation and tumor biology aim to break new scientific grounds that are relevant to neurosurgical practice.

Focused on brain surgery, peripheral nerve surgery, cerebrovascular concepts as well as neurotraumatology, our resident teaching programs are designed to promote a profound understanding of neurological surgery and to inspire patient care by fostering technical and surgical skills and by encouraging scientific inquiry.

The daily neurosurgical routine includes the training of medical students with an emphasis on practical bedside teaching. Training is offered either as a standard part of a student's curriculum or by individual appointment. We encourage students interested in the neurological and neurosurgical field to complete their dissertation in our department.

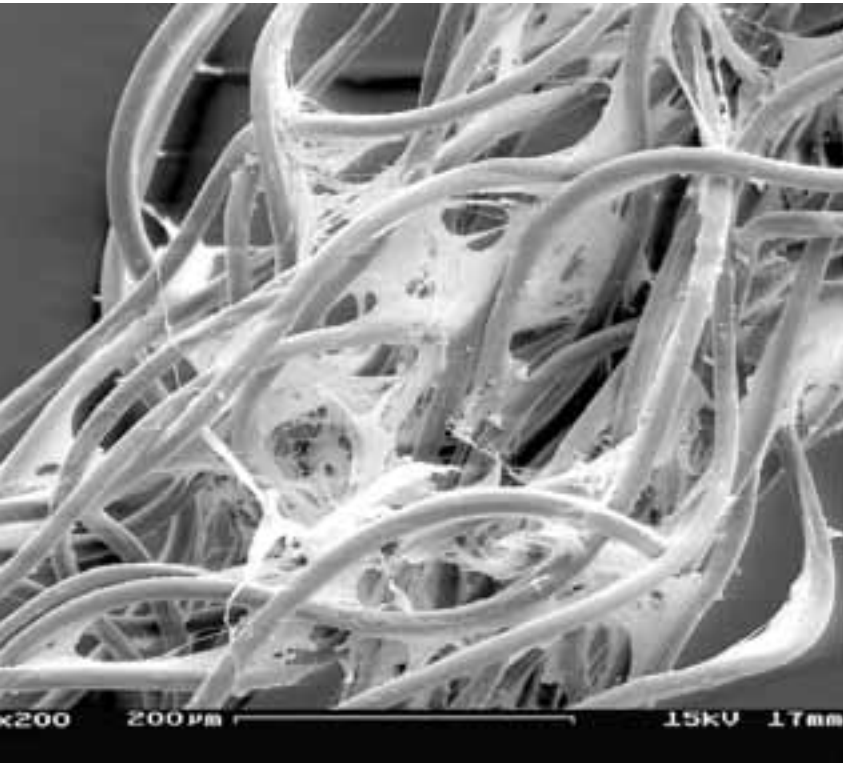


Modern neurosurgical procedures require high precision. Therefore many operations are performed with the aid of high-end operating microscopes also connected to other sources of information and guidance-like navigation.

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Selected Publications:

- Kapapa T, König K, Pfister U, Sasse M, Woischneck D, Heissler H, Rickels E (2010): Head trauma in children, part 1: admission, diagnostics, and findings. *J Child Neurol*, 25: 146-156.
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Mesenchymal stem cells cultivated on a scaffold made of polymer fibers.

Institute of Orthopedic Research and Biomechanics

Head of Institute: Prof. Dr. Anita Ignatius

Keywords: Bone regeneration | biomaterials | fracture healing | joint biomechanics | spine biomechanics

The Institute of Orthopedic Research and Biomechanics performs basic and translational research on the pathophysiology and treatment of musculoskeletal disorders. An interdisciplinary research team of 40 engineers, biologists, molecular biologists, physicians and veterinarians work closely together (10 postdocs, 17 PhD students, 13 technicians, two employees from abroad, 60% female).

The scientific work focuses on five main fields: fracture healing and bone regeneration; biomaterials and tissue engineering; cell biology; and joint as well as spine biomechanics.

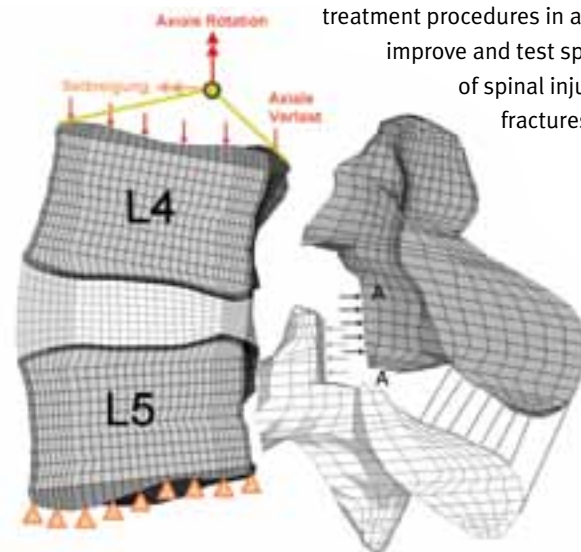
In the field of bone healing, the major goals are to increase the knowledge of the complex regeneration process itself and to improve the treatment of bone fractures. As bone regeneration significantly depends on mechanical factors, we are interested in the underlying mechanisms. Furthermore, we are interested in delayed healing associated with osteoporosis or inflammatory processes. We are currently a part of two DFG-funded research groups (FOR793, KFO200) dealing with the subjects of “Mechanisms in Fracture Healing and Bone Regeneration in Osteoporosis” and “Inflammatory Response after Musculoskeletal Trauma”.

There is an increasing demand for biomaterials to treat or replace injured or diseased tissues. In the biomaterial research group we investigate bone, ligament and intervertebral disc replacement materials with a focus on degradable materials since they increase the chances of a complete recovery. Several of our projects deal with the development of “smart”, structurally or biologically functionalized materials that allow specific control of cell function.

The aim of the cell biology group is to investigate the mechanisms of mechanotransduction in cells of the musculoskeletal system since regeneration and remodeling are strictly influenced by mechanical load. The involved pathways are of great interest as they can be possible targets for therapeutic intervention in regenerative therapies. Furthermore, we also investigate the interaction of cells with biomaterials. In EU-funded projects, we focus on the investigation of cellular changes in intervertebral disc degeneration and regeneration strategies.

The focus of the joint biomechanics research group is related to clinically relevant issues of the large joints. Cruciate ligament and meniscus surgery as well as total joint arthroplasty are of special interest. Biomechanical in vitro tests, finite-element-modeling, and in vivo functionality testing of implants are part of the scope of our research group.

The spine research team applies state-of-the-art in vitro and in vivo methods as well as finite-element models for basic research regarding spine biomechanics to gain a better understanding of loading and motions of the spine. The goal is to develop methods of diagnosis and evaluate treatment procedures in addition to regenerative strategies to improve and test spinal implants for the surgical treatment of spinal injuries, disc degeneration, osteoporotic fractures and deformities.



Finite element model of the L4/L5 spinal segment with applied forces and moments.

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Selected Publications:

- Tautzenberger A, Lorenz S, Kreja L, Zeller A, Musyanovych A, Schrezenmeier H, Landfester K, Mailänder V, Ignatius A (2010): Effect of functionalised fluorescence-labelled nanoparticles on mesenchymal stem cell differentiation. *Biomaterials*, 31: 2064-2071.
- Claes L, Veerer A, Göckelmann M, Simon U, Ignatius A (2009): A novel model to study metaphyseal bone healing under defined biomechanical conditions. *Arch Orthop Trauma Surg*, 129: 923-928.
- Neidlinger-Wilke C, Liedert A, Würtz K, Buser Z, Rinkler C, Kafer W, Ignatius A, Claes L, Roberts S, Johnson WE (2009): Mechanical stimulation alters pleiotrophin and aggrecan expression by human intervertebral disc cells and influences their capacity to stimulate endothelial migration. *Spine*, 34: 663-669.
- Liedert A, Kassem M, Claes L, Ignatius A (2009): Mechanosensitive promoter region in the human HB-GAM gene. *Biochem Biophys Res Commun*, 18: 289-293.
- Wilke HJ, Drumm J, Haussler K, Mack C, Steudel WI, Kettler A (2008): Biomechanical effect of different lumbar interspinous implants on flexibility and intradiscal pressure. *Eur Spine J*, 17: 1049-1056.
- Wilke HJ, Heuer F, Schmidt H (2009): Prospective design delineation and subsequent in vitro evaluation of a new posterior dynamic stabilization system. *Spine*, 34: 255-261.



Virology meets chemistry ...

Department of Gene Therapy

Head of Department: Prof. Dr. Stefan Kochanek

Keywords: Adenovirus | gene therapy | genetic vaccination | Huntington's disease

The Department of Gene Therapy was founded in 2003. Currently there are about 15 employees (60% female), who have studied various subjects including Biochemistry, Biology, Chemistry, Bioengineering, Molecular Medicine, Cell Biology, Virology and Medicine. Presently, there are four PhD students working in the laboratory, two from China and two from Germany.

The mission of the Department of Gene Therapy is to conduct high quality research and provide excellent teaching in the areas of gene transfer technology, somatic gene therapy and genetic vaccination.

One of the research topics is the development of improved technologies that allows the introduction of nucleic acids into somatic cells with improved efficiency, specificity and safety. We use viral and non-viral vectors to achieve these aims.

To achieve this aim, we develop adenoviral vectors that are modified in different ways at their surface. They may carry specific ligands on their capsid, either genetically introduced or chemically attached, that allow an improved targeting of cells carrying the corresponding receptor. In addition, the vector particles may carry polymer coats on their surface with the aim to reduce unspecific interactions with cells and proteins and to improve pharmacokinetics upon in vivo administration.

We also develop viral and non-viral vectors for genetic vaccination against infectious diseases. In our research we use either model antigens or relevant therapeutic vaccines, one of which is directed against malaria. One genetic vaccine project directed by Dr. Florian Kreppel has recently been awarded a prestigious grant by the BMBF within the *Gründungsoffensive Biotechnologie* (GO-BIO).

In a third research area we use adenovirus vectors to learn more about the pathogenesis of specific neurodegenerative diseases, in particular Huntington's disease, by performing experiments both in vitro and in vivo and by using adenovirus vectors to express full-length huntingtin with or without mutation.

Another research area deals with the use of "oncolytic" adenoviruses: here we are trying to develop vectors that can specifically destroy pancreatic and prostate cancer cells. We are also developing enhanced in vitro and in vivo models as the basis for vector improvement.

Finally, we are investigating the blood-brain-barrier (BBB) since we are interested in identifying improved strategies to deliver gene transfer vectors through the endothelial cell layer of the BBB.



... to develop potent tools for safe and efficient delivery of nucleic acids.

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Selected Publications:

- Flatz L, Hegazy AN, Berghaler A, Verschoor A, Claus C, Fernandez M, Gattinoni L, Johnson S, Kreppel F, Kochanek S, Broek M, Radbruch A, Lévy F, Lambert PH, Siegrist CA, Restifo NP, Löhning M, Ochsenbein AF, Nabel GJ, Pinschewer DD (2010): Development of replication-defective lymphocytic choriomeningitis virus vectors for the induction of potent CD8(+) T cell immunity. *Nat Med*, 16: 339-345.
- Espenlaub S, Wortmann A, Engler T, Corjon S, Kochanek S, Kreppel F (2008): Reductive amination as a strategy to reduce adenovirus vector promiscuity by chemical capsid modification with large polysaccharides. *J Gene Med*, 10: 1303-1314.
- Stephen SL, Sivanandam VG, Kochanek S (2008): Homologous and heterologous recombination between adenovirus vector DNA and chromosomal DNA. *oJ Gene Med*, 10: 1176-1189.
- 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: 1609-1616.
- 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: 269-279.
- 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.



Students practicing endotracheal intubation during induction of anesthesia using the patient simulator.

Department of Anesthesiology

Head of Department: Prof. Dr. Dr. h.c. Michael Georgieff

Keywords: Biomarker profiling | breath tests | investigational animal intensive care unit | oxidative stress | stable, non-radioactive isotope

The Department of Anesthesiology employs a staff of 92 MDs (31 % female) and is in charge of the perioperative care of all surgical disciplines. In addition to the main clinical department responsible for patients from the Departments of Orthopedic, Trauma and Plastic Surgery, Vascular and Thoracic Surgery and Visceral Surgery, it comprises four clinical divisions: the Division of Special Anesthesiology (Head: Dr. med. Wolfram Schütz) responsible for the clinical care of ear, nose and throat, gynecology and obstetrics, ophthalmology and urology patients; the Division of Emergency Medicine (Head: Dr. med. Dr. rer. nat. Burkhard Dirks) in charge of all emergency cases in the city of Ulm and surrounding districts; the Division of Operative Intensive Care (Head: Prof. Dr. med. Heidemarie Suger-Wiedeck) responsible for all surgical disciplines; and the Division of Pain Therapy (Head: Dr. med. Peter Steffen) which takes care of all perioperative pain management and chronic pain patients. Approximately 33,500 patients are treated each year. The department organizes the Medical School teaching in emergency medicine, anesthesia and perioperative care, disaster medicine, diving and hyperbaric medicine as well as participating in numerous other courses in medicine and molecular medicine. In addition, it is responsible for the training of “standardized patients” by using actors for patient-simulator training, and thus has the largest teaching activity of all the clinical departments of the Medical Faculty. All student examinations are organized as *Objective Structured Clinical Evaluations* (OSCE).

The department comprises two research divisions:

1. Division of Experimental Anesthesiology

(Head: Prof. Dr. rer. nat. Elisabeth Marion Schneider). The main scientific topics are single nucleotide polymorphisms, biomarker profiling, and the role of the nuclear transcription factor- κ B in patients with sepsis and hemophagocytic diseases. Ion channel effects of anesthetics are evaluated using patch-clamp techniques.

2. Division of Pathophysiology and Process Development in Anesthesia

(Head: Prof. Dr. med. Dr. h.c. Peter Radermacher). The main scientific topics are: the preclinical evaluation of innovative treatments of circulatory shock of various etiologies; the quantification of whole body and organ-specific metabolic pathways using stable and non-radioactive labeled isotopes in blood and breath tests; the determination of the activity of the complexes of the mitochondrial respiratory chain under various conditions; and the assessment of oxidative DNA damage using single cell gel electrophoresis (comet assay). For this purpose, unique porcine and murine “investigational intensive care units” have been established to allow for clinically relevant experimental models. Finally, human applied physiology research is dedicated to apnea diving and the hyperbaric environment.

Further main clinical scientific topics of the Department of Anesthesiology are the molecular genetics of Malignant Hyperthermia, the echocardiography assessment of left ventricular diastolic function in high-risk patients, and the economics and organization of critical care.

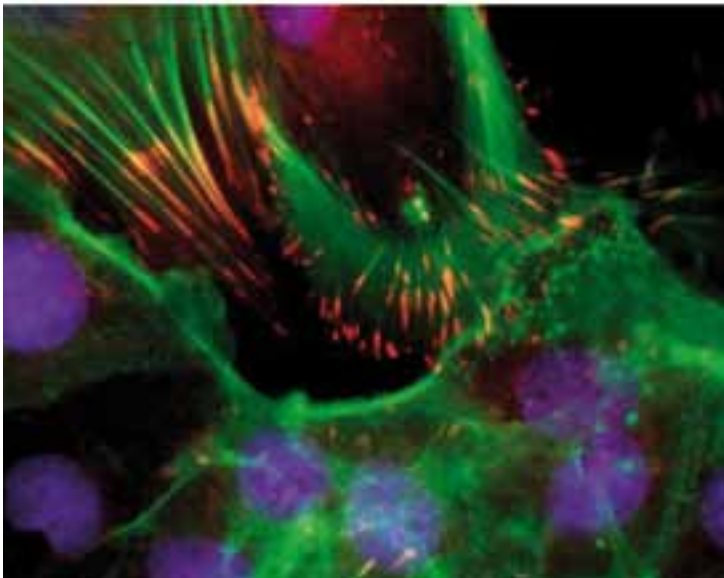
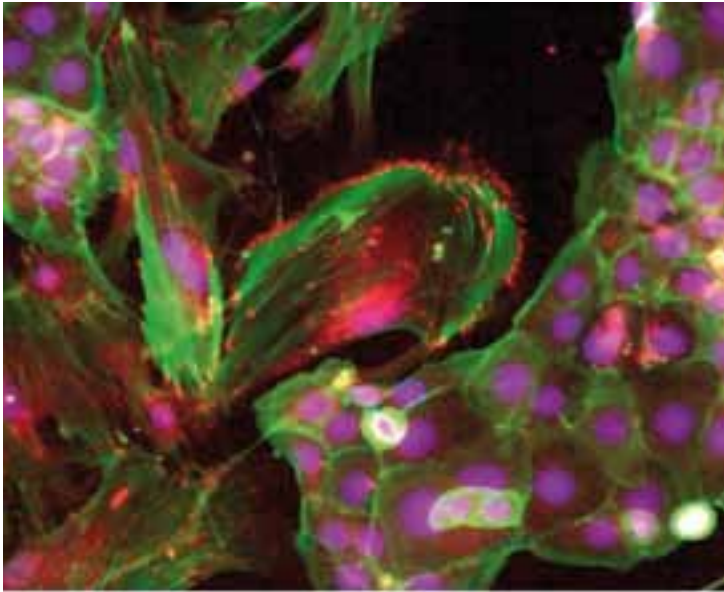


Addition of substrate during high resolution respirometry determination of the activity and the coupling status of the mitochondrial respiratory chain.

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anaesthesiologie.html

Selected Publications:

- Baumgart K, Wagner F, Gröger M, Weber S, Barth E, Vogt JA, Wachter U, Huber-Lang M, Knöfel MW, Albuszies G, Georgieff M, Asfar P, Szabó C, Calzia E, Radermacher P, Simkova V (2010): Cardiac and metabolic effects of hypothermia and inhaled hydrogen sulfide in anesthetized and ventilated mice. *Crit Care Med*, 38: 588-595.
- Hauser B, Barth E, Bassi G, Simon F, Gröger M, Öter S, Speit G, Ploner F, Möller P, Wachter U, Vogt JA, Matejovic M, Calzia E, Georgieff M, Radermacher P, Maybauer DM (2009): Hemodynamic, metabolic, and organ function effects of pure oxygen ventilation during established fecal peritonitis-induced septic shock. *Crit Care Med*, 37: 2465-2469.
- Vogt JA, Wachter U, Mehring J, Radermacher P, Georgieff M, Fischer H, Hölscher U, Moede M, Fabinski W (2009): Adaptation of the NDIR technology to $^{13}\text{CO}_2$ breath tests under increased inspiratory O_2 concentrations. *J Appl Physiol*, 107: 302-307.
- Gröger M, Öter S, Simkova V, Bolten M, Koch A, Warninghoff V, Georgieff M, Muth CM, Speit G, Radermacher P (2009): DNA damage after long-term repetitive hyperbaric oxygen exposure. *J Appl Physiol*, 106: 311-315.
- Woehrle T, Du W, Götz A, Hsu HY, Joos TO, Weiss M, Bauer U, Brückner UB, Marion Schneider E (2008): Pathogen specific cytokine release reveals an effect of TLR2 Arg753Gln during *Candida* sepsis in humans. *Cytokine*, 41: 322-329.



Department of Clinical Chemistry

Head of Department: Prof. Dr. Dr. Dr. h.c. Max G. Bachem

Keywords: Fibrogenesis | inflammation | laboratory medicine | molecular testing | pancreas diseases

The Department of Clinical Chemistry is a comprehensive central laboratory measuring over 300 clinical parameters. In 2009 we performed more than 3 million analyses for the purposes of patient care and clinical research. This facility also provides laboratory analyses for basic research using protocol-driven SOPs. The high quality of our department is testified by its accreditation granted in 2007.

The basic research of the Department of Clinical Chemistry is focused on diseases of the pancreas (fibrogenesis, cell-cell-interactions in pancreas carcinomas, acinar cell injury).

Pancreatic stellate cells move in culture toward pancreas carcinoma cells.

Triple immune fluorescence.

Blue – bisbenzimidide,

green – actin,

red – vinculin.

Laboratory Components

- Automated Spectrophotometry to quantitate the large number of chemical constituents in blood and urine simultaneously
- Hematology: automated and manual blood counts
- Coagulation testing and testing for thrombophilia
- Therapeutic drug monitoring and toxicology
- Immunoassays for hormones, cytokines, inflammatory mediators and tumor markers
- Electrophoresis (immunofixation electrophoresis and isoelectric focusing)
- Serological analyses for virus infections
- Multiplex protein quantitation (Luminex technology)
- Detection of autoantibodies by immunoassay and indirect immunofluorescence
- HPLC to measure drugs, hormones and vitamins.

The basic research of the department can be found in a SFB 518 project with the title *On the role of EMMPRIN and its interaction with pancreatic stellate cells in fibrogenesis and tumor desmoplasia.*



Discussion of the result of a Western blot.

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Selected Publications:

- Chen G, Tian X, Liu Z, Zhou S, Schmidt B, Henne-Bruns D, Bachem M, Kornmann M (2010): Inhibition of endogenous SPARC enhances pancreatic cancer cell growth: modulation by FGFR1-III isoform expression. *Br J Cancer*, 102: 188-195.
- Siech M, Zhou Z, Zhou S, Bair B, Alt A, Hamm S, Gross H, Mayer J, Beger HG, Tian X, Kornmann M, Bachem MG (2009): Stimulation of stellate cells by injured acinar cells: a model of acute pancreatitis induced by alcohol and fat (VLDL). *Am J Physiol Gastrointest Liver Physiol*, 297: G1163-1171.
- Geismann C, Morscheck M, Koch D, Bergmann F, Ungefroren H, Arlt A, Tsao MS, Bachem MG, Altevogt P, Sipos B, Fölsch UR, Schäfer H, Mierkötter SS (2009): Up-regulation of L1CAM in pancreatic duct cells is transforming growth factor beta1- and slug-dependent: role in malignant transformation of pancreatic cancer. *Cancer Res*, 69: 4517-4526.
- Li L, Bachem MG, Zhou S, Sun Z, Chen J, Siech M, Bimmler D, Graf R (2008): Pancreatitis-associated protein inhibits human pancreatic stellate cell MMP-1 and -2, TIMP-1 and -2 secretion and RECK expression. *Pancreatology*, 9: 99-110.
- Zhou S, Bachem MG, Seufferlein T, Li Y, Gross HJ, Schmelz A (2008): Low intensity pulsed ultrasound accelerates macrophage phagocytosis by a pathway that requires actin polymerization, Rho, and Src/MAPKs activity. *Cell Signal*, 20: 695-704.
- Bachem MG, Zhou S, Buck K, Schneiderhan W, Siech M (2008): Pancreatic stellate cells-role in pancreas cancer. *Langenbecks Arch Surg*, 393: 891-900.



Histologic techniques help to understand the pathogenesis of malignant melanoma and other skin diseases.

Department of Dermatology and Allergology

Head of Department: Prof. Dr. Karin Scharffetter-Kochanek

Keywords: Aging | allergy | autoimmunity | dermatology | stem cells wound healing

Dermatology has undergone an impressive development over the past fifteen years from descriptive morphology to understanding pathomechanisms and to systemic and targeted therapies. Advances in research and modern patient care in dermatology have paralleled the emphasis placed on contemporary technology and its results, and continue to provide a balanced approach to the understanding of physiology and pathology of the skin. A strong program aimed at education, research and patient service has been established with particular focus on: inflammatory skin diseases, including allergic, atopic and autoimmune diseases, and wound disorders; skin malignancies with melanoma, non-melanoma skin cancers and cutaneous lymphomas; skin aging and regenerative medicine; and infectious skin disorders. The Department of Dermatology employs more than 70 employees that include faculty and senior staff, residents, nurses, and technical and administrative personnel. The department offers fully accredited postgraduate training with Board Certification and opportunities to specialize further in histopathology, dermatosurgery, laser medicine and academic dermatology. The research facility is mainly supported through third party funding and engages 30 individuals (scientists, technicians, and PhD and MD students) from all over the world. The state-of-the-art equipped research laboratories offer easy access to the diverse core facilities that are located in the new Life Science Building of Ulm University. This is an ideal location since it allows intense interdisciplinary interaction. Our goals are to explore the mechanisms of skin biology and to gain new insights into aging, inflammatory diseases and wound healing with strong translational potential. We are committed to performing our work by offering high standards of education and training for our students. This goal is supported by the association of

PhD students with the International Graduate School in Molecular Medicine Ulm, which is funded by the Excellence Initiative. The Department of Dermatology and Allergic Diseases is funded by the German Research Association (DFG), the EU and the federal government (BMBF) with several collaborative research projects, among them the Clinical Research Group (KFO142): *Molecular and cellular aging – from mechanisms to clinical perspectives* (Spokesperson: Prof. Scharffetter-Kochanek, Scientific Leader: Prof. Geiger, see page 16). Major research topics include: molecular mechanisms of skin aging and aging-related diseases (K. Scharffetter-Kochanek and M. Wlaschek); immunosenescence of dendritic cells (J. M. Weiss) and immunosenescence of adaptive immunity (T. Peters); Polymerase I transcription in aging (S. Iben); aging of the hematopoietic stem cells and its niche (H. Geiger); polygenic base of allergic contact dermatitis/psoriasis (J. M. Weiss, K. Scharffetter-Kochanek); UVA in skin carcinogenesis (M. Wlaschek and K. Scharffetter-Kochanek); the role of innate immune cells in skin cancer (A. Sindrilaru); and molecular mechanisms of impaired wound healing (K. Scharffetter-Kochanek, A. Sindrilaru). Recent alumni include Dr. Anton Lebedev (now postdoc at the McGill University, Montreal, Canada) and Dr. Honglin Wang (now associate professor at Jiao Tong University, Shanghai, China).

Our clinic has been certified and accredited as a Center of Excellence for Allergic Diseases (Global Allergy and Asthma European Network) and of Skin Tumors (*Hauttumorzentrum*) as part of the Comprehensive Cancer Center Ulm with the goal of enhancing the interdisciplinary quality of patient care and research.



Skin cell cultures are irradiated with specific spectra of sun to simulate sun damage and sun-induced tumor progression.

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Selected Publications:

- Seier AM, Renkl AC, Schulz G, Uebele T, Sindrilaru A, Iben S, Liaw L, Kon S, Uede T, Weiss JM (2010): Antigen-specific induction of osteopontin contributes to the chronification of allergic contact dermatitis. *Am J Pathol*, 176: 246-258.
- Kohler A, Schmithorst V, Filippi MD, Ryan MA, Daria D, Gunzer M, Geiger H (2009): Altered cellular dynamics and endosteal location of aged early hematopoietic progenitor cells revealed by time-lapse intravital imaging in long bones. *Blood*, 114: 290-298.
- 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 β 2-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: 266-274.
- Briganti S, Wlaschek M, Hinrichs C, Bellei B, Flori E, Treiber N, Iben S, Picardo M, Scharffetter-Kochanek K (2008): Small molecular antioxidants effectively protect from PUVA-induced oxidative stress responses underlying fibroblast senescence and photoaging. *Free Radic Biol Med*, 45: 636-644.
- Wang H, Peters T, Sindrilaru A, Kess D, Oreshkova T, Yu X-Z, Seier AM, Schreiber H, Wlaschek M, Blakytyn 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.



Reproductive Medicine: one of the Art is the ICSI (intra cytoplasmic sperm injection) in which the sperm is injected directly into the oocyte.

Department of Gynecology and Obstetrics

Head of Department: Professor Dr. Rolf Kreienberg

Keywords: Angiogenesis | breast cancer risk | BRENDA | cryobanking | molecular staging | prediction of therapeutic responsiveness

The Department of Gynecology and Obstetrics is one of the leading gynecological departments in Germany with the status of a level 1 Obstetrics Center. It includes a certified breast and gynecological cancer center according to the standards of the *Deutsche Krebsgesellschaft* and the EUSOMA. Since 2008 the department has been an official training center for the European Board of Obstetrics and Gynecology (EBCOG). Research activities are centered on the following topics:

Applied Breast Cancer Research

Prof. Dr. Rolf Kreienberg

The German health services research project BRENDA 1 (Quality of Breast Cancer Care under Evidence-Based Guidelines) funded by the BMBF has shown that adjuvant therapy adhering to the recommendations of the national S3-guideline leads to a significantly better outcome concerning OAS and RFS (unicentric and multicentric, 16 network hospitals, 2003–05). Thus, BRENDA 1 results show that an optimized individual therapy following guideline recommendations should be mandatory for all patients with breast cancer.

Breast Cancer Risk

Prof. Dr. Lisa Wiesmüller

Within the CIMBA and other consortia, we identify susceptibility genes and risk modifiers in familial breast and ovarian cancer and define their frequencies and associated risks. In addition, gene-environment interactions relevant to sporadic breast cancer are analyzed (Helmut Deissler, Shan Wang-Gorke). Today, ten breast cancer susceptibility genes are known that are related to DNA double-strand break (DSB) repair. We have developed a fast and sensitive method for the analysis of specific DSB repair activities which mimic the phenotype of breast cancer predisposing mutant alleles (European Patent EP1399576). In BRENDA 1, we applied the method on blood samples and mammary tissues and detected a highly significant increase in these mutagenic repair activities in breast cancer patients and high-risk family members. This suggests that detection of specific DSB repair activities may be useful for extending the limits of genotypic characterization of high-risk susceptibility genes.



Lisa Wiesmüller (Division of Gynecological Oncology) developed a new method for breast cancer risk assessment and prediction of therapeutic responsiveness, and thus received the Innovation Award of the BioRegions in Germany in 2009.

Breast Cancer Staging

PD Dr. Helmut Deissler

Molecular sub-classification of malignancies for a more reliable assessment of patient prognosis may help decision-making between therapeutic options. Promising approaches include a breast biopsy-based quantification of proteins with bead-based multiplexed sandwich immunoassays. We have demonstrated that defined sets of derived protein concentrations are useful for predicting important clinical issues with high accuracy.

Angiogenesis

Prof. Dr. Christine Wulff

Dysregulation of angiogenesis and permeability leads to pathologies, such as neoangiogenesis during tumorigenesis or hyperpermeability with induction of edema, and ascites or pleural effusion. The corpus luteum is an outstanding experimental system because angiogenesis and permeability regulation only occur here in regular cycles in adults. We have established an in vitro corpus luteum model, in which molecular regulatory processes of endothelial junctions and hormonal control are studied, and adjusted it to investigate translated ovarian and breast cancer.

Reproductive Medicine

Dr. Vladimir Isachenko

Successful use of cryopreservation of reproductive cells in Assisted Reproductive Technologies (ART) is limited by decreased viability of these cells after storage in liquid nitrogen. Our first aim with ovarian tissue cryobanking is therapy contra Premature Ovarian Failure (POF) after aggressive anticancer treatment. Research activities focus on the development of new methods for the preservation of spermatozoa, oocytes, ovarian tissue and adult stem cells.

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Selected Publications:

- Hancke K, Denking MD, König J, Kurzeder C, Wöckel A, Herr D, Blettner M, Kreienberg R (2009): Standard treatment of female breast cancer patients decreases substantially for women aged 70 and older: a German clinical cohort study. *Ann Oncol*, Oct 13.
- Keimling M, Wiesmüller L (2009): DNA double-strand break repair activities in mammary epithelial cells - influence of endogenous p53 variants. *Carcinogenesis*, 30: 1260-1268.
- Sauer, G., Schneiderhan-Marra, N., Kazmaier, C., Hutzl, K., Koretz, K., Muche, R., Kreienberg, R., Joos, T. und Deissler, H (2008) Prediction of nodal involvement in breast cancer based on multiparametric protein analyses from preoperative core needle biopsies of the primary lesion *Clin. Cancer Res*, 14: 3345-3353.
- Rodewald M, Herr D, Duncan WC, Fraser HM, Konrad R, Hack G, Kreienberg K, Wulff C. (2009): Molecular mechanisms of ovarian hyperstimulation syndrome: paracrine reduction of endothelial claudin 5 by hCG in vitro is associated with increased endothelial permeability. *Hum Reprod*, 24: 1191-1199.
- Song H, Ramus SJ, Tyrer J, Bolton KL, Gentry-Maharaj A, Wozniak E, Anton-Culver H, Chang-Claude J, Cramer DW, DiCiccio R, Dörk T, Goode EL, Goodman MT, Schildkraut JM, Sellers T, Baglietto L, Beckmann MW, Beesley J, Blaakaer J, Carney ME, Chanock S, Chen Z, Cunningham JM, Dicks E, Doherty JA, Dürst M, Ekici AB, Fenstermacher D, Fridley BL, Giles G, Gore ME, De Vivo I, Hillemanns P, Hogdall C, Hogdall E, Iversen ES, Jacobs IJ, Jakubowska A, Li D, Lissowska J, Lubinski J, Lurie G, McGuire V, McLaughlin J, Medrek K, Moorman PG, Moysich K, Narod S, Phelan C, Pye C, Risch H, Runnebaum IB, Severi G, Southey M, Stram DO, Thiel FC, Terry KL, Tsai YY, Tworoger SS, Van Den Berg DJ, Vierkant RA, Wang-Gohrke S, Webb PM, Wilkens LR, Wu AH, Yang H, Brewster W, Ziogas A; Australian Cancer (Ovarian) Study; Australian Ovarian Cancer Study Group; Ovarian Cancer Association Consortium, Houlston R, Tomlinson I, Whittemore AS, Rossing MA, Ponder BA, Pearce CL, Ness RB, Menon U, Kjaer SK, Gronwald J, Garcia-Closas M, Fasching PA, Easton DF, Chenevix-Trench G, Berchuck A, Pharoah PD, Gayther SA (2009): A genome-wide association study identifies a new ovarian cancer susceptibility locus on 9p22.2. *Nat Genet*, 41: 996-1000.
- Isachenko V, Lapidus I, Isachenko E, Krivokharchenko A, Kreienberg R, Wriedh M, M. Bader, J.M. Weiss (2009): Vitrification and conventional freezing of human ovarian tissue: morphological, endocrinological and molecular biological evaluation. *Reproduction*, 138: 319-327.



Inpatient and outpatient clinic are closely connected and provide a continuous patient support by specialists for different neurological disorders.

Department of Neurology

Head of Department: Prof. Dr. Albert C. Ludolph

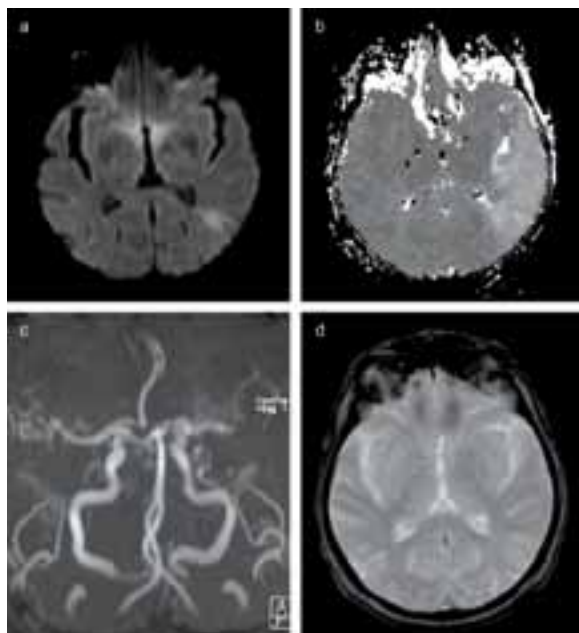
Keywords: Biomarker Assessment | Center for Clinical Studies | Databanking | Motor Neuron Diseases | Neurodegenerative Diseases

The clinics of the Department of Neurology comprise an inpatient clinic (RKU) and an outpatient clinic which together form various specialist consultation centers for different neurological disorders. The inpatient clinic combines both acute and rehabilitation facilities that include a 16-patient stroke unit/intermediate care unit in addition to an intensive care unit with 24/7 availability for the full spectrum of all modern stroke therapies. Furthermore, the acute inpatient services cover specialized concepts in focused topics (e.g. palliative care) and make use of advanced diagnostic procedures that include 24/7 availability of MRI, the department's own CSF laboratory with the full offer of CSF diagnostics, and its own histological laboratory for muscle biopsies so that a broad spectrum of clinical research can be performed on the basis of applications from these specialist clinical laboratories. The specialized outpatient clinics are organized as subunits covering neurological disorders that include motor neuron/neuromuscular disorders, movement disorders, such as Parkinsonian syndromes and Huntington's disease, inflammatory CNS diseases, dementias, epilepsy, pain and neurooncology. Beyond serving as a specialized teaching and training center for new doctors of the department and medical students, the outpatient services are the basis for the Center for Clinical Studies which is composed of these subunits and includes a gene bank for immortalized samples, a tissue bank, a CSF-/plasma bank and a large database for phenotype documentation. The Center is fully financed from external sources and is an important partner in national and international networks.

Experimental Neurology covers a broad spectrum of basic neurological research and is organized into one division (Section Neurophysiology, Prof. Kassubek) and various working group subunits. Major scientific subunits are: the group for Clinical Neuroanatomy (Prof. Braak) that works on the neuropathological assessment of neurodegenerative diseases; the group for Neuronal Degeneration and Axonal Regeneration (Prof. Fischer); and the groups for Cell Biology and in vivo Models of ALS/

MND (Prof. Ludolph), for Striatal degenerations (Prof. Landwehrmeyer) and for Neuroinflammation (Dr. Witting). Further topics of research are Alzheimer's disease (Prof. von Arnim), Frontal Dementias and CSF-based proteomics/biomarker assessment (Prof. Otto), and CSF diagnostics (Prof. Tumani/PD Brettschneider). The section for Neurophysiology focuses on neurophysiological assessment of oculomotor and vestibular functions together with functional neuroimaging. In addition, there are research topics with close clinical links such as Experimental Neuropsychology (Dr. Lulé/PD Uttner) and Neuroimaging/MRI (Profs. Kassubek/Riecker/Grodd). All these research groups participate in the Academic Neuroscience Center Ulm (NCU) and act in close cooperation with NCU members, in particular, the Department of Anatomy and Cell Biology, in addition to a multitude of external network partners, e.g. CNS Research Boehringer-Ingelheim, and many international academic neuroscience centers.

With regards to teaching, there is an intensive teaching concept for medical students, which includes various clinical courses and assessments via objective clinical evaluation and a structured teaching program for the Practical Year.



Magnetic resonance imaging (MRI) with 24/7 availability is one of the major diagnostic instruments for the stroke unit with respect to thrombolysis therapy.

As an example, stroke imaging in one patient with right-sided hemiparesis is shown with an acute left-hemispheric ischemic stroke (middle cerebral artery) in diffusion-weighted imaging (a), the diffusion-perfusion mismatch in perfusion-weighted imaging (b), the rarefaction of the left-sided middle cerebral artery in MR TOF angiography (c) without any demarcation of the damage in T2w MRI (d).

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Selected Publications:

- Ludolph AC, Bendotti C, Blauggund E, Chio A, Greensmith L, Loeffler JP, Mead R, Niessen HG, Petri S, Pradat PF, Robberecht W, Ruegg M, Schwalenstöcker B, Stiller D, van den Berg L, Vieira F, von Horsten S (2010): Guidelines for preclinical animal research in ALS/MND: A consensus meeting. *Amyotroph Lateral Scler*, 11: 38-45.
- Fernández-Santiago R, Hoenig S, Lichtner P, Sperfeld AD, Sharma M, Berg D, Weichenrieder O, Illig T, Eger K, Meyer T, Anneser J, Münch C, Zierz S, Gasser T, Ludolph A (2009): Identification of novel Angiogenin (ANG) gene missense variants in German patients with amyotrophic lateral sclerosis. *J Neurol*, 256: 1337-1342.
- Bensimon G, Ludolph A, Agid Y, Vidailhet M, Payan C, Leigh PN (2009): Riluzole treatment, survival and diagnostic criteria in Parkinson plus disorders: the NNIPPS study. *Brain*, 132: 156-171.
- 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.
- Ludolph AC (2009): Neuromuscular diseases: new hopes for alleviation and elimination. *Lancet Neurol*, 8: 16-17.
- Süßmuth SD, Brettschneider J, Ludolph AC, Tumani H (2008): Biochemical markers in CSF of ALS patients. *Curr Med Chem*, 15: 1788-1801.



Department of Ophthalmology

Head of Department: Prof. Dr. Gerhard K. Lang

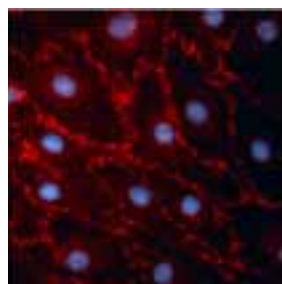
Keywords: Age-related macular degeneration and diabetic retinopathy | ophthalmic surgery | ophthalmology

The Department of Ophthalmology covers the entire spectrum of surgical and medical ophthalmology. With a team of 24 physicians, we treated 3,026 inpatients and 20,836 outpatients in 2009. Last year six fellows from other countries and 20 students worked in our department. Ophthalmic surgery in the department mainly focuses on cataract, refractive, glaucoma and lid surgery as well as vitreoretinal surgery. In the area of non-surgical ophthalmology, the section for medical retina focuses on retinal vascular diseases and age-related macular degeneration and provides diagnostic procedures and treatment. Retinal laser surgery, photodynamic therapy as well as intravitreal injections are also performed. In the area of the medical retina, clinical and basic research focus on age-related macular degeneration and diabetic retinopathy (Heads: Prof. Dr. Gabriele E. Lang; Dr. Heidrun Deißler).

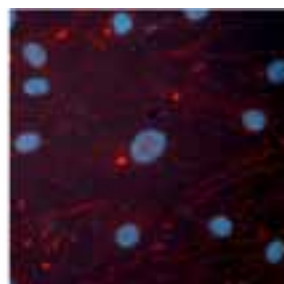
A daily morning conference as well as noontime case presentations in the clinic and daily rounds on the inpatient floors in addition to a weekly advanced training conference all contribute to a consistent and high level of education.

As a university hospital we consider it our duty to improve and expand our achievements by employing the latest research data and technology in diagnostics and treatment. Since the establishment of the Department of Ophthalmology, the entire team of doctors has continuously sought to provide optimal treatment for our patients. Our team also guarantees the best possible care of inpatients and outpatients.

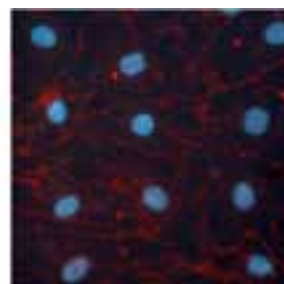
VEGF-inhibitors for the Treatment of Diabetic Macular Edema
Microvascular Endothelial Cells of the Retina



Normal



Plus growth factors (similar for DME)



Plus growth factors and inhibitors

Our efforts are regularly monitored by external questionnaires (PICKER-study 2004 and 2007) to evaluate patient satisfaction. An external questionnaire on health insurance schemes published in 2009 confirmed the achievement of our goals.

In the area of general satisfaction, results of treatment, and nursing care as well as information and communication, our department scored 4-7 % above average among all participating departments. The successful certification of patient care, teaching and research according to ISO 2001 was confirmed in 2009 in an external audit.

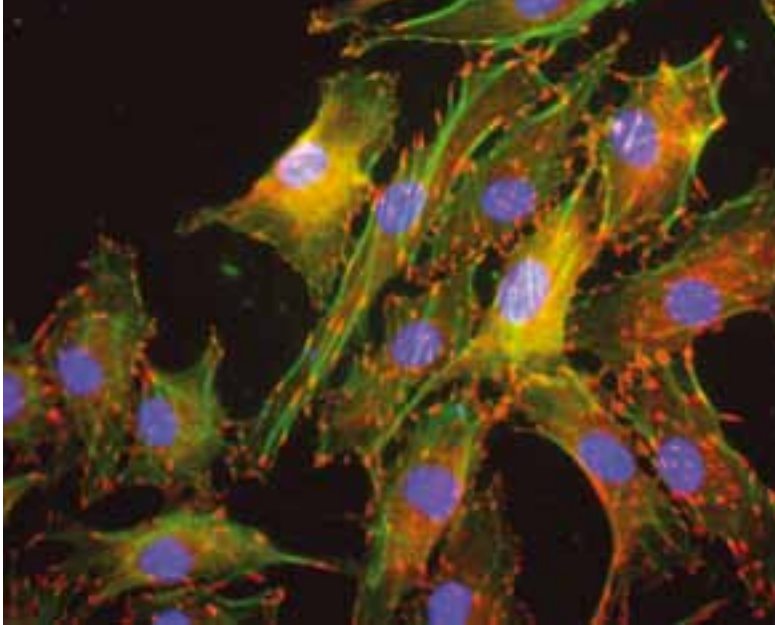
The residency program has a certification in line with the European Board of Ophthalmology regulations.

Our most important aim is the optimum care of our patients according to the highest standards and within a pleasant atmosphere. The results have so far been extremely satisfying and it is our intention to continue in this vein.

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Selected Publications:

- Kürzinger GR, Stender B, Lang GK, Lang GE (2010): Photodynamic Therapy with Verteporfin in Occult Choroidal Neovascularization in Age-Related Macular Degeneration. *Klin Monatsbl Augenheilkd*, [Epub ahead of print].
- Deissler HL, Deissler H, Lang GE (2010): Inhibition of protein kinase C is not sufficient to prevent or reverse effects of VEGF 165 on claudin-1 and permeability in microvascular retinal endothelial cells. *Invest Ophthalmol Vis Sci*, 51: 535-542.
- Deissler H, Deissler H, Lang S, Lang GE (2008): VEGF-induced effects on proliferation, migration and tight junctions are restored by ranibizumab (Lucentis) in microvascular retinal endothelial cells. *Br J Ophthalmol*, 92: 839-843.
- Deissler HL, Lang GE (2008): Effect of VEGF 165 and the VEGF aptamer pegaptanib on the protein composition of tight junctions in microvascular endothelial cells of the retina. *Klin Monatsbl Augenheilkd*, 225: 863-867.
- Cucera A, Lang GK, Buchwald HJ (2008): Intra- and interindividual comparison of corneal refraction measured by IOL-Master vs. corneal topography. *Klin Monatsbl Augenheilkd*, 225: 957-962.
- Lang GK (2008): *Augenheilkunde*. Thieme Verlag, Stuttgart, New York 4.th german edition, translated in 7 languages.



Multicolor fluorescence imaging (cytoskeleton and focal adhesions) of chondrocytes grown on a biomaterial.

Department of Orthopedics

Head of Department: Prof. Dr. Heiko Reichel

Keywords: Adult Reconstruction and Joint Replacement | Molecular Orthopedics | Orthopedic Oncology | Pediatric Surgery | Spine Surgery | Sports Medicine

The Department of Orthopedic Surgery at the RKU is one of the largest orthopedic university institutions in Germany and covers all aspects of musculoskeletal diseases, including in- and outpatient surgical and non-operative care, as well as orthotics and prosthetics. More than 3,500 surgical procedures are performed annually and about 12,000 patients are seen in our Outpatient Department. The wards, with a total of over 150 beds, include a special unit for spinal cord injury and a day clinic for a multidisciplinary musculoskeletal pain program. Before surgery, conservative treatment options are always taken into account. If the conservative approach fails to restore an acceptable level of function and to decrease pain, up-to-date procedures are performed. We guide patients through the various stages of their disease by diagnosis, treatment and rehabilitation.

Different sub-specialities focus on total joint replacements of hip, knee and shoulder joints as well as elbow and ankle joints, joint reconstruction, spine surgery, pediatric orthopedics, sports medicine, orthopedic oncology and orthopedic rheumatology. On referral, septic and revision surgery is another option. In some cases, fractures of the extremities and the spine are also treated. Modern trends lead to smaller incisions (minimal-invasive surgery), to computer-aided implantation

of joint replacements (navigation) and to bone-preserving implants. The best treatment of the individual is guaranteed by the selection of the most appropriate procedure and the optimized implant.

Research activities focus on biomechanical aspects (development and testing of joint and spinal implants) and molecular biological and biochemical techniques in bone and soft-tissues. Several dissertations and “Habilitationen” have been conducted at our Institute. The teaching of our students and residents together with an international instructional course in Spine Surgery are additional academic activities.

Important cooperation is maintained with the Department of Traumatology (Head: Prof. Dr. F. Gebhard), the Geriatric Clinic (Head: Prof. Dr. Th. Nikolaus), the CCCU (Comprehensive Cancer Center Ulm), and the Institute of Orthopedic Research and Biomechanics (Head: Prof. Dr. Anita Ignatius).

The Orthopedic Department incorporates the division for Biochemistry of Joint and Connective Tissue Diseases (Head: Prof. Dr. Rolf Brenner). This division concentrates on clinically-oriented basic research within the musculoskeletal system and coordinates the experimental research of the department. The interdisciplinary working group (covering medicine, biology, biochemistry and chemistry) consists of 14 employees (including five PhD students). Our research focuses on the pathophysiology and therapy of cartilage diseases (e.g. cartilage trauma and osteoarthritis), the role of mesenchymal stem cells in skeletal disease and tissue regeneration as well as cell-biomaterial interactions (e.g. surface functionalization of implants and nanotechnology). Research projects are currently funded by the DFG, the BMBF and the Center for Musculoskeletal Research Ulm. Furthermore, we are a partner of the center of excellence in medical technology (Medical Valley Nürnberg).



Navigation system for the implantation of orthopedic implants (e.g. total knee replacement).

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Selected Publications:

- Dornacher D, Cakir B, Reichel H, Nelitz M (2010): Early radiological outcome of ultrasound monitoring in infants with developmental dysplasia of the hips. *J Pediatr Orthop B*, 19: 27-31.
- Groll J, Fiedler J, Bruellhoff K, Moeller M, Brenner RE (2009): Novel surface coatings modulating eukaryotic cell adhesion and preventing implant infection. *Int J Artif Organs*, 32: 655-662.
- Cakir B, Schmidt R, Mattes T, Fraitzl CR, Reichel H, Käfer W (2009): Index level mobility after total lumbar disc replacement. Is it beneficial or detrimental? *Spine*, 34: 917-923.
- Joos H, Albrecht W, Laufer S, Reichel H, Brenner RE (2008): IL-1beta regulates FHL2 and other cytoskeleton-related genes in human chondrocytes. *Mol Med*, 14: 150-159.
- Habisch HJ, Fiedler J, Ludolph AC, Storch A, Brenner RE (2008): Altered migration and adhesion potential of pro-neurally converted human bone marrow stromal cells. *Cytotherapy*, 10: 824-833.
- Käfer W, Clessienne CB, Däxle M, Kocak T, Reichel H, Cakir B (2008): Posterior component impingement after lumbar total disc replacement: a radiographic analysis of 66 ProDisc-L prostheses in 56 patients. *Spine*, 33: 2444-2449.



Endoscopic sinus surgery being performed in one of the department's own four operation theaters.

Department of Otorhinolaryngology

Head of Department: Prof. Dr. Gerhard Rettinger

Keywords: Nasal Air Conditioning | plastic and reconstructive surgery | regenerative medicine | rhinosurgery | tissue engineering

The department employs 27 medical doctors. Furthermore, technical, nursing and scientific personnel account for more than 100 people. Guest doctors from various countries abroad frequently join the department as a result of its internationally well-established expertise in rhinosurgery, and facial plastic and reconstructive surgery. This is attested by operation courses specializing in these subjects that take place every year in March.

Along with the activities in rhinosurgery and facial reconstructive surgery, computer-assisted surgery is another field of expertise applied to anterior skull base and sinus surgery in difficult and revision cases. Middle ear surgery, including cochlear implantation, is also a specialist area.

The section of Phoniatrics and Pediatric Audiology is headed by Prof. Dr. Sibylle Brosch. Hearing tests in children, including the screening of newborns, brain stem audiometry, standardized speech audiometry and evaluations of intelligence, are performed on a regular basis. Speech development tests and those of central hearing are another area of expertise as well as the assessment of swallowing and speech.

One of the main research areas is intranasal air conditioning and the numerical simulation of intranasal air flow in computer models. The department developed and established a special "rhinological climate laboratory". Very few climate laboratories of this kind exist worldwide. Computer simulations in realistic nose models have allowed completely new insights into airflow behavior and nasal air conditioning. The effects of diseases of the nose and paranasal sinuses and nasal surgery on nasal air conditioning and airflow are investigated in this laboratory. Nasal diseases and also nasal surgery can negatively affect air conditioning and airflow. To prevent this in the future, researchers are hoping to control results of operations of the nose through the use of computer simulations.



Medical students in the skills lab learning how to change a tracheal cannula.

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In 2008 the research group *Tissue Engineering and Regenerative Medicine* was established. Projects deal predominantly with cartilage tissue engineering for reconstructive head and neck surgery and regeneration of salivary gland tissue.

Cartilage tissue engineering projects are funded by the European Union within the 6th framework program. The department is a partner of the Network of Excellence EXPERTISSUES where a variety of biomaterials are investigated for application in rhinosurgery. As part of the 7th framework program, a new project called EAREG was approved at the end of 2009 to devise novel strategies for auricular reconstruction.

Regeneration of salivary gland tissue is a major concern in patients suffering from severe dryness of mouth (xerostomia). The German-Israeli-Foundation funds a project on novel therapeutic strategies based on stem cells.

These research activities yield more than 40 peer reviewed publications each year.

As part of our teaching program, a one week medical student course has been introduced that includes a morning lecture with live surgery and practical training throughout the entire hospital in the afternoon. In addition, a multidisciplinary skills lab is provided to teach good practical skills. The department has already twice received the “Excellence in teaching”-award from the University.

Selected Publications:

- Rinker T, Alku P, Brosch S, Kiefer M (2010): Discrimination of native and non-native vowel contrasts in bilingual Turkish-German and monolingual German children: Insight from the Mismatch Negativity ERP component. *Brain Lang*, [in press].
- Lindemann J, Tsakiridou E, Keck T, Leickner R, Wiesmiller KM (2009): Nasal air conditioning in relation to acoustic rhinometry values. *Am J Rhinol Allergy*, 23: 575-577.
- Gorjup E, Danner S, Rotter N, Habermann J, Brassat U, Brummendorf TH, Wien S, Meyerhans A, Wollenberg B, Kruse C, von Briesen H (2009): Glandular tissue from human pancreas and salivary gland yields similar stem cell populations. *Eur J Cell Biol*, 88: 409-421.
- Skodacek D, Brandau S, Deutsche T, Lang S, Rotter N (2008): Growth factors and scaffold composition influence properties of tissue engineered human septal cartilage implants in a murine model. *Int J Immunopathol Pharmacol*, 21: 807-816.
- Rotter N, Oder J, Schlenke P, Lindner U, Böhrsen F, Kramer J, Rohwedel J, Huss R, Brandau S, Wollenberg B, Lang S (2008): Isolation and characterization of adult stem cells from human salivary glands. *Stem Cells Dev*, 17: 509-518.
- Kappe T, Papp J, Rozsasi A, Leickner R, Rettinger G, Keck T (2008): Nasal conditioning after endonasal surgery in chronic rhinosinusitis with nasal polyps. *Am J Rhinol*, 22: 89-94.



Department of Pediatrics and Adolescent Medicine

Head of Department: Prof. Dr. Klaus-Michael Debatin

Keywords: Cardiology | endocrinology | hematology/oncology | neonatology | neurology

As of 2010, the department has a capacity of 110 beds and just over 400 employees (87% female). On the basis of an up-to-date thorough knowledge in general pediatrics and in specialized areas, our overall goal is to attain optimal results using state-of-the-art medical care including innovative diagnosis and therapy in the treatment of children and adolescents. In addition to general pediatrics, including sub-specialties such as metabolic diseases, pulmonology, allergy and mucoviscidosis (Prof. Dr. M. Leichsenring), gastroenterology (Dr. C. Posovszky), nephrology (Dr. O. Beringer), our internationally recognized expertise is in pediatric hematology/oncology (Prof. Dr. D. Steinbach, PD Dr. H. Cario) with stem cell transplantation and immunology (PD Dr. A. Schulz, Dr. M. Hönig) as well as in the sections for pediatric endocrinology and diabetology (Prof. Dr. M. Wabitsch), and neonatology with pediatric intensive care (Prof. Dr. H. Hummler). Sections for pediatric cardiology (Dr. C. Galm), and pediatric neurology and social-pediatrics (Prof. Dr. H. Bode) add to this specialized range. This broad spectrum is complemented by the section for pediatric surgery of the Department of General Surgery of the university hospital.

Research in hematology/oncology is dedicated to understanding the role of cell death and cell death signaling in diseases, and possible mechanisms to modify cell death signaling for cancer therapy. Our lab was involved in the early discovery of one of the key apoptosis signaling pathways (CD95/APO/Fas) and this was followed by one of the first descriptions of the role of cell death signaling in cancer therapy in the journal *Nature Medicine* in 1996. Since then, we have addressed several issues of apoptosis regulators and apoptosis signaling as prognostic factors and therapeutic targets. By using xenotransplant models of primary leukemias in the NOD-SCID mouse, we are in the process of analyzing aspects of leukemia stem cell function and apoptosis sensitivity of leukemia initiating cells as well as parameters for treatment response and outcome in patients.

In the area of immunodeficiency and stem cell transplantation, our groups have characterized a number of novel immunodeficiencies and our clinic has always been at the forefront of novel developments in stem cell transplantation. Since one of the first ever bone marrow transplants in children in Europe was performed in the sixties at our institution, novel therapies such as haploidentical stem cell transplantations for treatment of leukemia, cell-based immunotherapy approaches and, most recently, radio immunotherapy-based conditioning for reduced toxicity have been developed.

The section specializing in pediatric endocrinology and diabetes focuses on childhood obesity and studies on the biology of adipocytes. Basic research projects involve the characterization of recently discovered obesity genes within the national genome network (NGFN). Our research group was the first to establish a human preadipocyte cell line (SGBS) which is now widely used for the study of adipogenesis and fat cell metabolism.

The research of the section for neonatology and pediatric intensive care is dedicated to clinical studies related to primary care of neonates and preterm infants. Our center participates in a number of multicenter randomized trials, including the coordination of a European multicenter study on the use of inhalative NO treatment, and has initiated a study on permissive hypercapnia in very immature preterm infants.

To provide the best possible care for families, we also provide as much outpatient treatment as possible. For this purpose, we have established a large daycare clinic especially for leukemia patients, tumor patients and patients with immuno-deficiencies in addition to patients for pre- and post stem cell-transplantation. For the parents of our inpatients, we provide a large number of apartments in our parent houses directly adjacent to the hospital (Hartmut-Blauw House, Maria-Hermann House). Special services include playrooms with trained childcare specialists, art therapy, visits of clinic clowns, special therapy services for children with neurodevelopmental deficits and



a consultation service comprising specialized doctors, nurses, social workers, psychologists, physiotherapists and diabetes specialists. We also provide in-house interpreters for Arab and Russian patients.



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Selected Publications:

- Strauss G, Lindquist JA, Arhel N, Felder E, Karl S, Haas T, Fulda S, Walczak H, Kirchhoff F, Debatin KM (2009): CD95 co-stimulation blocks activation of naive T cells by inhibiting T cell receptor signaling. *J Exp Med*, 206: 1379-1393.
- 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: 1710-1722.
- Gruhn B, Taub JW, Ge Y, Beck JF, Zell R, Häfer R, Hermann FH, Debatin KM, Steinbach D (2008): Prenatal origin of childhood acute lymphoblastic leukemia, association with birth weight and hyperdiploidy. *Leukemia*, 22: 1692-1697.
- Vogler M, Walczak H, Stadel D, Genze F, Haas T, Jovanovic M, Gschwend J, Simmet T, Debatin K-M, Fulda S (2008): Targeting XIAP bypasses Bcl-2-mediated resistance to TRAIL and cooperates with TRAIL to suppress pancreatic cancer growth in vitro and in vivo. *Cancer Res*, 68: 7956-7965.
- Meyer LH, Queueville M, Eckhoff SM, Creutzig U, Reinhardt D, Karawajew L, Ludwig W-D, Stahnke K, Debatin K-M (2008): Intact apoptosis signaling in myeloid leukaemia cells determines treatment outcome in childhood AML. *Blood*, 111: 2899-2903.
- Schuetz C, Huck K, Gudowius S, Megahed M, Feyen O, Hubner B, Schneider DT, Manfras B, Pannicke U, Willemze R, Knüchel R, Göbel U, Schulz A, Borkhardt A, Friedrich W, Schwarz K, Niehues T (2008): An immunodeficiency disease with RAG mutations and granulomas. *N Engl J Med*, 358: 2030-2038.



Minimal invasive transurethral surgery.

Department of Urology

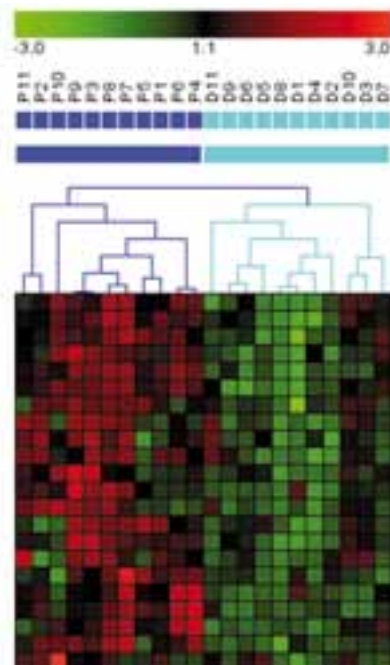
Head of Department: Prof. Dr. Mark Schrader

Keywords: Minimal invasive surgery | neobladder | prostate cancer | systemic therapy | urooncology

The Department of Urology is one of the largest urological centers in Germany that offers the whole spectrum of modern diagnostics and therapy in both adult and pediatric urology. Fifteen physicians (seven specialists and eight residents), 10 surgical nurses, 56 carers and general nurses, as well as eight administrative secretaries arrange an optimal daily academic and clinical routine.

Our commitment is to quality and value by providing facilities for advanced surgical procedures with friendly and professional care. Our department has 55 beds with all rooms offering the privacy and comfort of en-suite facilities, satellite TV and telephone. The hospital has four theaters (ORs), one minor procedures theater, a six-bed intensive care unit and a seven-bed high dependency unit. These facilities, combined with the latest technology and on-site support services, enable us to perform a wide range of procedures from routine investigations to complex surgery. This specialist expertise is supported by caring and professional medical staff that together with dedicated nursing teams and resident medical officers on duty 24 hours a day provide care within a friendly and comfortable environment.

The Department of Urology directed by Prof. M. Schrader, is particularly specialized in the treatment of urological malignancies. It is this clinic that conceived and developed the ileum neobladder, which has today become the most accepted form of continent urinary diversion worldwide for patients with invasive bladder cancer. Moreover, the Department of Urology and its members possess the skills and expertise for the treatment of localized and metastatic prostate, renal and testicular cancer. Several of our surgeons are specifically specialized in conventional and laparoscopic nerve sparing as well as radical prostatectomy. All therapeutic procedures are based on interdisciplinary tumor board decisions.



Result of a DNA-Microarray Analysis.

As a matter of course, we also offer up-to-date reconstructive, endoscopic and female urology surgery as well as special consultation hours for andrology and pediatric urology. Moreover, we possess an ultra-modern extracorporeal shock-wave lithotripter to locate urinary stones by applying ultrasound as well as X-ray technology.

The Department of Urology in Ulm is also active in clinical (phase I-IV) trials as well as basic research. We have a fully equipped laboratory for experimental/molecular urology that is operated by an experienced biologist who is a postdoctoral fellow in molecular biology, a PhD student in endocrinology, and two technicians. Our main focus is on the discovery of potentially clinically-relevant alterations in tumor biology and tumor cell signaling. This research area with its clear translational background is currently being established in close collaboration with the clinic.

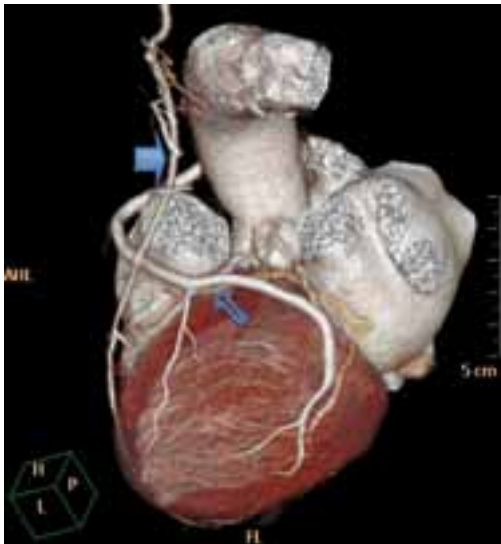
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Selected Publications:

- Jentzmik F, Stephan C, Miller K, Schrader M, Erbersdobler A, Kristiansen G, Lein M, Jung K (2010): Sarcosine in Urine after Digital Rectal Examination Fails as a Marker in Prostate Cancer Detection and Identification of Aggressive Tumours. *Eur Urol*, [Epub ahead of print].
- Jentzmik F, Schostak M, Stephan C, Baumunk D, Lingnau A, Weikert S, Lein M, Miller K, Schrader M (2009): Extraperitoneal radical cystectomy with extraperitonealization of the ileal neobladder: a comparison to the transperitoneal technique. *World J Urol*, [Epub ahead of print].
- Schrader M, Weissbach L, Hartmann M, Krege S, Albers P, Miller K, Heidenreich A (2009): Burden or Relief: Do Second-Opinion Centers Influence the Quality of Care Delivered to Patients with Testicular Germ Cell Cancer? *Eur Urol*, [Epub ahead of print].
- Schrader M, Hartmann M, Krege S, Heidenreich A, Miller K, Weissbach L (2009): Testicular germ cell cancer: interdependence between guidelines and a second-opinion system. *Urologe A*, 48:393-398.
- Schrader AJ, Rauer-Bruening S, Olbert PJ, Hegele A, Rustemeier J, Timmesfeld N, Varga Z, Hofmann R. (2009) Incidence and long-term prognosis of papillary renal cell carcinoma. *J Cancer Res Clin Oncol*, 135: 799-805.
- Jeron A, Pfoertner S, Bruder D, Geffers R, Hammerer P, Hofmann R, Buer J, Schrader AJ (2009): Frequency and gene expression profile of regulatory T cells in renal cell carcinoma. *Tumour Biol*, 30: 160-170.



Virtual anatomy display of the thorax for a patient with an acute pulmonary embolism (arrow). Volume rendering images were digitally generated on a workstation after 256 section CT scanning.



Volume rendering display of a heart with bypass grafts. The patient had an open arterial graft (closed arrow) to the anterior left coronary and open venous graft (open arrow) to the lateral left coronary artery two years ago.

Department of Diagnostic and Interventional Radiology

Head of Department: Prof. Dr. Hans-Jürgen Brambs

Keywords: CT coronary angiography | Diagnostic and Interventional Radiology

The department employs more than 40 physicians supported by almost 60 radiology technicians. The female to male ratio has increased considerably over the last few years and now more than 70% of the department's employees are female. The staff is internationally oriented and a multitude of nations are represented. The wide range of fields in radiology is organized into clinical subdivisions. The division of Neuroradiology (headed by Prof. B. Schmitz) was founded only a few years ago and has rapidly grown to encompass the fields of both diagnostic and interventional neuroradiology. The subdivision of Cardiovascular Radiology (headed by Prof. M. Hoffmann) is closely associated with the Cardiac Surgery and Cardiology divisions to perform diagnostic CT angiography and cardiac MRI procedures. This collaboration between the cardiac facilities has recently been expanded to perform transcatheter aortic valvular interventions in cross-divisional teams. The subdivision of Musculo-skeletal Radiology (headed by Dr. U. Schütz) has recently performed some important research projects. The subdivisions of Pediatric and Gastroenterologic Radiology (headed by Prof. H. J. Brambs and PD M. Juchems) are able to utilize brand new forms of technology for both diagnostic and interventional procedures.

The department is equipped with cutting edge technology. Diagnostic imaging is performed using six CT machines (16 to 256 section CT) and four MRI scanners (two 3T machines). Imaging is performed in a fully digital surrounding with both digital radiography and fully digital post-processing (PACS driven image distribution and speech recognition for report generation).

Two dedicated angiography units with digital bi-planar detectors operate in close association with neurosurgical and surgical facilities to provide a very wide range of interventional procedures. This includes high end neuro-radiological procedures under the auspices of our newly founded division of Neuroradiology. The range of interventional procedures is supplemented with an active program for percutaneous and transapical aortic valve replacements in close collaboration with the divisions of Cardiac Surgery and Cardiology. A wide range of hepatic, vascular and biopsy interventions is routinely performed at the two surgical hospital sites.

The clinical research activities of the department cover the entire field of radiology. CT coronary angiography has been established for clinical application during the last five years. The trans-European ultra-marathon of 2009 was tracked using an MRI scanner on a mobile truck to document the musculoskeletal changes under ultra-high stress levels. The interventional treatment of acute stroke patients has considerably improved through the use of temporary and permanent intracranial stent placements. The interventional treatment of intracerebral aneurysms has been expanded to include flow diversion in addition to surgical clipping and coiling procedures. Radiofrequency ablation has been modified with various electrode configurations.

Basic research topics are currently being explored in collaboration with Prof. Volker Rasche (Department of Internal Medicine II) and cover both spectral CT applications (in association with the Philips Research Laboratory in Hamburg) and the evaluation of various advanced MRI applications (e.g. RF multi-transmit techniques and 3T spectroscopy).

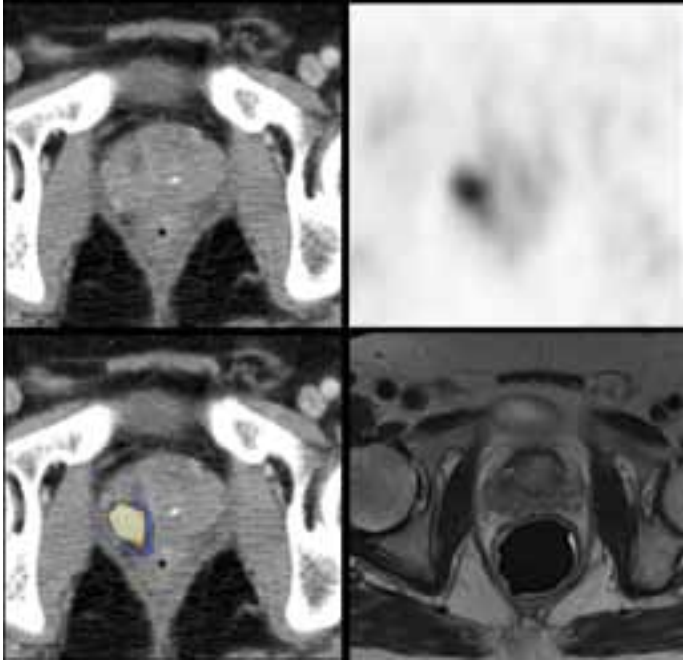


Intracranial interventional procedure performed with a large 60" LCD viewing display. Both interventional accuracy and radiation dose exposure are reduced due to the large area display unit.

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Selected Publications:

- Feuerlein S, Stolz J, Muche R, Hetzel M, Klass O, Brambs HJ, Pauls S (2010): Cisterna chyli in patients with malignancy- Influence of cardiovascular disease on the prevalence of the cisterna. *Eur J Radiol*, 34: 172-8.
- Feuerlein S, Pauls S, Juchems MS, Stuber T, Hoffmann MH, Brambs HJ, Ernst AS (2009): Pitfalls in abdominal diffusion-weighted imaging: how predictive is restricted water diffusion for malignancy. *AJR Am J Roentgenol*, 193:1070-6.
- Juchems MS, Ernst A, Johnson P, Virmani S, Brambs HJ, Aschoff AJ (2009): Electronic colon-cleansing for CT colonography: diagnostic performance. *Abdom Imagin*; 34:359-64.
- Klass O, Jeltsch M, Feuerlein S, Brunner H, Nagel HD, Walker MJ, Brambs HJ, Hoffmann MH (2009): Prospectively gated axial CT coronary angiography: preliminary experiences with a novel low-dose technique. *Eur Radiol*, 19:829-36.
- Klass O, Mutlu S, Hohl K, Feuerlein S, Jeltsch M, Brambs HJ, Hoffmann MH (2009): Multidetector computed tomography coronary angiography: sublingual nitroglycerine improves image quality significantly because of peripheral coronary vasodilatation. *J Comput Assist Tomogr*, 33:199-203.
- Feuerlein S, Kreuzer G, Schmidt SA, Muche R, Juchems MS, Aschoff AJ, Brambs HJ, Pauls S (2009): The cisterna chyli: prevalence, characteristics and predisposing factors. *Eur Radiol*, 19:73-8.



Cancer of the Prostate; C-11-Choline PET/CT and T2w MRI (right lower corner):
Depiction of a previously unknown primary tumor in the right lobe.

Department of Nuclear Medicine

Head of Department: Prof. Dr. Sven Norbert Reske

Keywords: PET/CT | pharmacokinetic modelling | prostate cancer | radioimmunotherapy | thyroid cancer

The Department of Nuclear Medicine provides the whole spectrum of diagnostic and therapeutic methods needed for a “tertiary referral center” setting. Among the 47 employees, 57% are female; one is resident and three are PhD students from abroad. There are currently 10 PhD/MD students who are members of the team.

The research focus of the Nuclear Medicine Clinic is the development of PET- and PET/CT- based molecular imaging techniques and targeted internal radiotherapy. The available infrastructure includes a molecular and cell biology working group, a radiochemistry section, a dosimetry and a tracer kinetic modeling group, a fully equipped PET center including an 8/16.5 MeV cyclotron, radiochemistry and pharmaceutical laboratories, and 1 PET/CT scanner. A “small animal PET scanner” is also available at the institute.

Expertise is practiced in the clinic in the fields of tumor metabolism, PET and PET/CT imaging, radiotracer development, with a special emphasis on radiolabeled nucleosides for measuring proliferation in vivo, and the development of strategies for targeted radiotherapy with monoclonal antibodies. State-of-the-art medical physics expertise is provided in dosimetry, PET and PET/CT imaging, tracer kinetic analysis and pharmacokinetic modeling.



SPECT/CT-Imaging:
Combining the function (SPECT) and anatomy (CT) allows correct and efficient diagnosis in one step or an individualized quantitative dosimetry before therapeutic applications.

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Current projects focus on the development of probes for measuring tumor proliferation (DFG RE 741/11-1), dosimetry (DFG GL 236/7-1, -2) and radioimmunotherapy with ^{90}Y labeled anti-CD66 or anti-CD45 monoclonal antibodies for dose escalation of conditioning prior to stem cell transplantation in high-risk leukemia (supported by the German *Jose Carreras Foundation* and *Deutsche Krebshilfe*). We are a partner in the integrated project *Novel Molecular Diagnostic Tools for the Prevention and Diagnosis of Pancreatic Cancer (MolDiag-Paca)* (6th framework program) which aims to develop and evaluate molecular imaging techniques in animal models for the early diagnosis of pancreatic ductal adenocarcinoma and its precursor lesions.

The management of thyroid diseases, with a particular focus on cancer therapy, represents a main field of interest in patient care. Another internationally respected highlight is the C-11-Choline-PET/CT-based multimodality prostate cancer imaging that allows real-time staging in this patient group. Studies on individualized dosimetry to calculate tailored therapy activities for various radionuclides (dose escalation) has resulted in optimized care for the conditioning of patients by using monoclonal antibodies in the preparation of stem cell transplantation in high-risk leukemia.

Selected Publications:

- Kletting P, Kull T, Bunjes D, Mahren B, Luster M, Reske SN, Glatting G (2010): Radioimmunotherapy with anti-CD66 antibody: Improving the biodistribution using a physiologically based pharmacokinetic model. *J Nucl Med*, 51: 484-491.
- Luster M, Karges W, Zeich K, Pauls S, Verburg FA, Dralle H, Glatting G, Buck AK, Solbach C, Neumaier B, Reske SN, Mottaghy FM (2010): Clinical value of 18-fluorine-fluorodihydroxyphenylalanine positron emission tomography/computed tomography (18F-DOPA PET/CT) for detecting pheochromocytoma. *Eur J Nucl Med Mol Imaging*, 37: 484-493.
- Zlatopolskiy BD, Morgenroth A, Kunkel FH-G, Urusova EA, Dinger C, Kull T, Lepping C, Reske SN (2009): Synthesis and Biologic Study of IV-14, a New Ribonucleoside Radiotracer for Tumor Visualization. *J Nucl Med*, 50: 1895-1903.
- Buck AK, Bommer M, Juweid ME, Glatting G, Stilgenbauer S, Mottaghy FM, Schulz M, Kull T, Bunjes D, Möller P, Döhner H, Reske SN (2008): First Demonstration of Leukemia Imaging with the Proliferation Marker 18F-Fluorodeoxythymidine. *J Nucl Med*, 49: 1756-1762.
- Morgenroth A, Deisenhofer S, Glatting G, Kunkel FH-G, Dinger C, Zlatopolskiy B, Vogg AT, Kull T, Reske SN (2008): Preferential Tumor Targeting and Selective Tumor Cell Cytotoxicity of 5-[^{131}I / ^{125}I]iodo-4'-thio-2'-Deoxyuridine. *Clin Cancer Res*, 14: 7311-7319.
- Reske SN, Blumstein NM, Glatting G (2008): [^{11}C]choline PET/CT imaging in occult local relapse of prostate cancer after radical prostatectomy. *Eur J Nucl Med Mol Imaging*, 35: 9-17.



Staff from the department demonstrate the tools for high precision patient positioning which is essential in modern treatment techniques such as rapid arc.

Department of Radiotherapy and Radiooncology

Head of Department: Prof. Dr. Thomas Wiegel

Keywords: Chemotherapy | prostate cancer | radiotherapy | resistance | tumour risk

The department has a staff of 60 employees specialized in the fields of medicine, physics, biology, informatics, radiation technique and nursing as well as administrative staff. Basic and clinical research concentrates on the areas detailed below.

Cellular Resistance to Cancer Treatment

With regards to the importance of combined or sequential radio-chemotherapy as a strategy in modern cancer treatment, cell biological studies in the mutual influence of chemoresistance and radioresistance are being conducted by using cell culture models of lung, prostate, and colorectal carcinoma. Cell survival (the gold standard of dose response relationships), gene expression and functionality of molecular pumps (RT-PCR, flow cytometric dye efflux determinations), cell alert signaling (microscopic immuno-cytometry) and DNA-damage repair (flow and image cytometry) are the major biological objectives in these studies.

Second Cancer Risk

Databank information from the years 1981-2007 covers over 12,000 one-year-survivors among our patients (with more than 60,000 person years of follow up) and is used for an analysis of the risk of second cancer after radiotherapy. Combining this information with retrospective in-field and out-of-field dose reconstruction, case to case and case-control studies are performed as a contribution to an EU funded international research project, ALLEGRO (2009-2011), on early and late normal tissue complications from established and upcoming radiotherapy modalities.

Improving the Quality of Prostate Cancer Treatment

Prostate cancer is the most common cancer in adult men. When assessing different therapy options, decision-making is largely influenced by aspects affecting quality of life. To reinforce decisions based on objective criteria, detailed analyses of stage-of-disease dependent treatment outcome are mandatory. By means of our data and expertise we are able to contribute to the most recent updates in treatment guidelines for prostate cancer.

Rapid Arc

A new radiation technique known as rapid arc is being incorporated into our array of linear accelerators. Rapid arc is a treatment modality whereby, during irradiation, the head of the therapy device moves around the longitudinal patient axis while it continuously adjusts the aperture of a multileaf collimator to the tumor contour which changes with the steadily shifting angle. This strategy aims to minimize the exposure of normal tissue to radiation.

Extending Our Range

A sister clinic is under construction in the city of Ehingen and will open in 2010. This facility will be run under the medical guidance of our department with the aim of improving the immediacy of treatment options and reducing traveling needs for outpatients living in the remoter outskirts of Ulm.

Involvement in Clinical Studies:

Glioblastoma multiforme: CENTRIC; Apogenix APG 101.

PNET/Medulloblastoma and ependymom in young patients: HIT-2000.

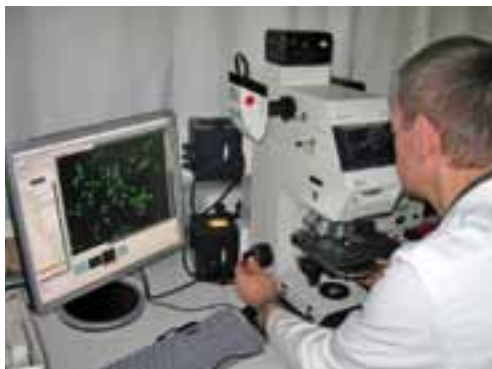
Prostate cancer: FE 200486 CS30; HAROW; ZEUS.

Rectum carcinoma: CAO/ARO/AIO-04

Squamos cell carcinoma of the head and neck: ACCRA-HN; DÖSAK pN1.

Hodgkin's lymphoma: PVAG-14; HD 18.

Non-small-cell lung cancer: PROCLAIM.



Defense strategies in tumor cells comprise molecular alert signaling. In a microscope these signals can be visualized by immunofluorescence.

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Selected Publications:

- Böhmer D, Wenz F, Martin T, Sedlmayr F, Hinkelbein W, Wiegel T (2010): Radiation therapy for prostate cancer in the new S3 guideline. Part 1: localized and locally advanced prostate cancer. *Urologe A*, 49: 211-215.
- Welte B, Suhr P, Bottke D, Bartkowiak D, Dörr W, Trott KR, Wiegel T (2010): Second malignancies in high-dose areas of previous tumor radiotherapy. *Strahlenther Onkol*, 186: 174-179.
- Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, Störkel S, Willich N, Semjonow A, Souchon R, Stöckle M, Rübe C, Weissbach L, Althaus P, Rebmann U, Kälble T, Feldmann HJ, Wirth M, Hinke A, Hinkelbein W, Miller K (2009): Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol*, 27: 2924-2930.
- Wiegel T, Lohm G, Bottke D, Höcht S, Miller K, Siegmann A, Schostak M, Neumann K, Hinkelbein W (2009): Achieving an undetectable PSA after radiotherapy for biochemical progression after radical prostatectomy is an independent predictor of biochemical outcome--results of a retrospective study. *Int J Radiat Oncol Biol Phys*, 73:1009-1016.
- Bartkowiak D, Stempfhuber M, Wiegel T, Bottke D (2009): Radiation- and chemoinduced multidrug resistance in colon carcinoma cells. *Strahlenther Onkol*, 185: 815-820.
- Bottke D, Wiegel T (2008): Postoperative adjuvant radiotherapy - standard of care? *Front Radiat Ther Oncol*, 41: 32-88.



Recording evoked potentials from the human brain.

Department of Psychiatry and Psychotherapy I

Head of Department: Prof. Dr. Wolfgang P. Kaschka

Keywords: Affective disorders | mechanisms of antidepressant action | neurobiology | social psychiatry | suicide research

The South Wuerttemberg Center for Psychiatry in Ravensburg provides comprehensive clinical psychiatric care services for a population of approximately 450,000 people. In total, around 600 inpatient beds are available for patients admitted by seven specialist psychiatric departments (Depression, Psychosomatic and Psychotherapy, Geriatric, General-Social, Addiction, Child and Youth, and Forensic). In an average year, approximately 4,000 inpatients pass through the Center. The academic staff includes 39 physicians and 21 psychologists. The percentage of female employees is slightly more than 50%.

The hospital provides specialized wards for patients with affective disorders and personality disorders. There is an outpatient clinic with special services for patients with affective disorders (lithium clinic), dementias (memory clinic) and drug or alcohol dependence. An integrated system of quality management is employed (KTQ, Cooperation for Transparency and Quality in the Health Care System).

Clinical and basic research is organized around two main topics. The first has a broad biological theme with a particular focus on electrophysiological, pharmacogenetic and neurobiological approaches to understanding the etiology of major depression. The second topic is social psychiatry and focuses on reducing violence and coercive interventions in psychiatry.

Electrophysiological techniques are being employed to characterize differences in habituation patterns between those patients identified as at particular risk for suicide and those that are not. Particular variations found in components (P₃₀₀) of patient encephalograms and in electrodermal activity (EDA) taken during auditory discrimination tests are subjected to further analysis and intergroup comparison (suicide attempters vs controls). The combination of clinical observation with electrophysiological profiling should provide additional insights into the risk factors associated with suicidal ideation and suicide attempts.

Pharmacogenetic approaches are being employed (in cooperation with Prof. Dr. Julia Kirchheiner, Institute of Naturopathic Medicine and Clinical Pharmacology) to study the relationship between inpatient response to antidepressant medication and their cytochrome P₄₅₀ drug metabolizing enzyme genotypes. It is hoped that this research will eventually provide the basis for more informed and effective initial antidepressant treatment strategies.

In the neurobiology laboratory, a simple animal (gastropod) model is being employed to investigate the relationship between stress-induced changes in behavior (“learned helplessness model”) and observed changes in neural plasticity and neuroendocrine function. Fluorescence imaging of neuronal recruitment is being used to map specific neurochemical and molecular changes in neural plasticity found after operant conditioning experiments. Neuroendocrine changes associated with operant conditioning experiments are characterized using a combination of cell extract assays and

a reverse transcriptase polymerase chain reaction. The aim of this research is to develop a better understanding of the “communication” that takes place between the CNS and the neuroendocrine system in response to stress, and why this varies between individuals.



Computer-assisted motion tracking equipment being used to record the behavior of *Planorbis* sp. snails during behavior suppression (operant conditioning) experiments.

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Selected Publications:

- Schwab M, Kaschka WP, Spina E (2010): *Pharmacogenomics in Psychiatry*. Karger, Basle.
- Jandl M, Kaschka WP (2010): *Treatment of Therapy-Resistant Auditory Verbal Hallucinations in Schizophrenia Patients by Repetitive Transcranial Magnetic Stimulation (rTMS)*. In: Elkis H, Meltzer H (eds.) *Therapy-Resistant Schizophrenia. Advances in Biological Psychiatry*, Vol. 26, pp. 177-194. Karger, Basle.
- Jandl M, Steyer J, Kaschka WP (2010): *Suicide risk markers in major depressive disorder: A study of electrodermal activity and event related potentials*. *J Affect Dis*, 123: 138-149.
- Kaschka WP, Kretzschmar R, Jandl M (2009): *Psychopharmaka kompakt*. Schattauer, Stuttgart.
- Künzel HE, Ackl N, Hatzinger M, Held K, Holsboer-Trachsler E, Ising M, Kaschka W, Kasper S, Konstantinidis A, Sonntag A, Uhr M, Yassouridis A, Holsboer F, Steiger A (2009): *Outcome in delusional depression comparing trimipramine monotherapy with a combination of amitriptyline and haloperidol - a double blind multicenter trial*. *J Psychiatr Res*, 43: 702-710.
- Steinert T, Eisele F, Goeser U, Tschöke S, Uhlmann S, Schmid P (2008): *Successful interventions on an organisational level to reduce violence and coercive interventions in in-patients with adjustment disorders and personality disorders*. *Clin Pract Epidemiol Ment Health*, 4: 27-31.



Department of Psychiatry and Psychotherapy II

Head of Department: Prof. Dr. Thomas Becker

Keywords: Gender-specific aspects | health economics | mental health care | meta-analysis | randomised controlled trials

The Department of Psychiatry and Psychotherapy II at *Bezirkskrankenhaus Günzburg* offers mental health care consisting of inpatient services, day care, an outpatient clinic and home treatment for 671,000 inhabitants of a catchment area in rural Bavaria.

The department has four research groups:

Mental Health Services Research Unit (PD Dr. Reinhold Kilian);
Psychoimmunology (Prof. Dr. Karl Bechter);
Psychopathology and Psychopharmacology (PD Dr. Markus Jäger);
and the Section Geriatric Psychiatry (Prof. Dr. Matthias Riepe).

In the following are listed some of the highlights of the department's numerous research projects:

- *Systematic Review of Meta-Analyses on the Efficacy of SSRI and SNRI in the Treatment of Major Depression.* To examine the quality of meta-analyses of serotonin reuptake inhibitors treatment of depression and to shed light on the influence of methodological aspects on the results of these meta-analyses.
- *Family Planning of Young Women with Severe Mental Illness between Individual Responsibility and Social Stigmatization.* To ascertain subjective attitudes of motherhood and family planning in women with mental disorders in order to identify needs for professional treatment and to help create and offer effective support strategies.



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with the Department of Psychiatry
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- *The Development of a Method for the Measurement of Empowerment in the Psychiatric Treatment of People with Severe Mental Disorders*. To develop a suitable, standardized questionnaire to assess empowerment in the process of psychiatric treatment for patients with affective (ICD-10 F30-F39) and schizophrenic (ICD-10 F20-F29) illnesses.
- *Clinical Decision-making and Outcome in Routine Care for People with Severe Mental Illness (CEDAR)*. To investigate the effect of clinical decision-making on crucial dimensions of clinical outcome (symptom level, quality of life and needs) by means of a multinational prospective study.
- *Child and Adolescent Mental Health in an Enlarged Europe: Development of Effective Policies and Practices (CAMHEE)*. To develop a European network in order to analyze national mental health policies in the field of child and adolescent mental health and, consequently, to provide the EU with policy and action recommendations
- *European Network for Promoting the Health of Residents in Psychiatric and Social Care Institutions (HELPS)*. To build a European network of experts and an information system to improve the physical health of residents of psychiatric social and health-care institutions.
- *Effectiveness and Cost-Effectiveness of “Needs-Oriented Discharge Planning and Monitoring for High Utilizers of Psychiatric Services” (NODPAM)*. To test, via a randomized controlled multicenter trial, the efficacy of an intervention aimed at smoothing the transition from inpatient to outpatient mental health care after hospital discharge.
- *Admission*. To document and compare practice of involuntary psychiatric admissions in rural areas of Bavaria, Baden-Wuerttemberg and Mecklenburg-Western Pomerania.

Selected Publications:

- Puschner B, Schöfer D, Knaup C, Becker T (2009): *Outcome management in in-patient psychiatric care*. *Acta Psychiatr Scand*, 120: 308-319.
- Knaup C, Kösters M, Schöfer D, Becker T, Puschner B (2009): *Effect of feedback of treatment outcome in specialist mental healthcare: meta-analysis*. *Br J Psychiatry*, 195: 15-22.
- Steffen S, Kösters M, Becker T, Puschner B (2009): *Discharge planning in mental health care: A systematic review of the recent literature*. *Acta Psychiatr Scand*, 120: 1-9.
- Kösters M, Becker T, Kilian R, Fegert JM, Weinmann S (2009): *Limits of Meta-Analysis: methylphenidate in the treatment of adult attention-deficit hyperactivity disorder*. *J Psychopharmacol*, 23: 733-744.
- Catty J, Lissouba P, White S, Becker T, Drake RE, Fioritti A, Knapp M, Lauber C, Rössler W, Tomov T, van Busschbach J, Wiersma D, Burns T (2008): *Predictors of employment and IPS effectiveness for people with severe mental illness: results of an international six-centre RCT*. *Br J Psychiatry*, 192: 224-231.
- Weinmann S, Hoerger S, Erath M, Kilian R, Gaebel W, Becker T (2008): *Implementation of a schizophrenia practice guideline – Clinical Results*. *J Clin Psychiatry*, 69: 1299-1306.



Transcranial magnetic stimulation. A coil is placed on the subject's skull to apply a strong electromagnetic field pulse. This pulse depolarizes cortical neurons in a region close to the coil. As a consequence of the neuronal activity, the muscles in the right hand will twitch since the coil is placed over the left motor cortex. This muscle twitch will be recorded by means of surface electrodes on the hand. Other coil positions include prefrontal, temporal or occipital areas in order to interact with higher cognitive functions, or even to achieve therapeutic effects.

Department of Psychiatry and Psychotherapy III

Head of Department: Prof. Dr. Dr. phil. Manfred Spitzer

Keywords: Cognitive neuroscience | event-related potentials | functional imaging | transcranial magnetic stimulation | translational research in education

The Department of Psychiatry and Psychotherapy III employs 19 physicians (nine female) and 13 non-medical scientists (six female). The department combines outpatient and inpatient state-of-the-art care of patients with psychiatric disorders (three wards with 54 beds, a day hospital and outpatient clinic). A special focus is placed on psychiatric acute care since the department is responsible for mental emergencies in the city of Ulm and surrounding districts that have a population of approximately 220,000 people.

The department's scientific focus is on systems neuroscience aspects of mental disorders. Cognitive neuroscience methods are used to understand high-level cognitive functions in normal subjects, and the development and maintenance of psychiatric disorders. Most of the research takes place in two divisions and one laboratory. Since 2004 research on memory and learning, and in particular on the transfer of neuroscience findings into educational practice, is conducted at a dedicated research center that is part of our department and known as the Transfer Center for Neuroscience and Learning (ZNL).

The division for Functional Imaging and Neuropsychology (Prof. Dr. phil. Georg Grön) includes a high-field magnetic resonance scanner dedicated for research. State-of-the-art brain imaging under different functional challenges is used to investigate and explore human brain functions under circumscribed experimental conditions. The focus is on mental functions (e.g. memory, reward processing, motivational and emotional processes) and dysfunctions that correlate with psychiatric disorders. Employing appropriate study designs, commonalities and differences between normal and impaired brain functioning are investigated.



A female subject is being prepared for an experimental session in the section's research-dedicated high-field magnetic resonance (MR) scanner operating at the field strength of 3.0 Tesla. She is already wearing an MR-compatible headset for communication and auditive stimulation. The researcher is mounting MR-compatible video goggles over her eyes.

Later, after the subject has been placed in the MR-tunnel (behind the subject's head), a memory task will be presented through the goggles and headset. The task is the cognitive challenge during which functional magnetic resonance images are acquired at high spatial resolution.

In the division for Cognitive Electrophysiology (PD Dr. phil. Markus Kiefer), the scientific focus is on language, higher conceptual representation and attention. A state-of-the art 64 channel electroencephalographic recording system permits the study of brain electrical activity at high temporal resolution.

In the laboratory for Transcranial Magnetic Stimulation (PD Dr. med. Thomas Kammer), the physiological background of this non-invasive brain stimulation technique is explored. In addition, using a system for spatial neuronavigation, pre-specified cortical regions are stimulated in order to study their role in higher cognitive functions. In clinical trials, the therapeutic potency of the TMS technique in several psychiatric disorders is investigated.

In the Transfer Center for Neuroscience and Learning (ZNL), a multidisciplinary team of teachers, psychologists and educational scientists integrates recent neuroscience findings into practical applications in the field of education in children and adults. The general aim is to use the well-established medical model of translational research in the field of education.

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Selected Publications:

- Fladung AK, Grön G, Grammer K, Herrnberger B, Schilly E, Grasteit S, Wolf RC, Walter H, von Wietersheim J (2010): A neural signature of anorexia nervosa in the ventral striatal reward system. *Am J Psychiatry*, 167: 206-212.
- Adolph O, Köster S, Georgieff M, Bäder S, Föhr KJ, Kammer T, Herrnberger B, Grön G (2010): Xenon-induced changes in CNS sensitization to pain. *Neuroimage*, 49: 720-730.
- Plichta MM, Vasic N, Wolf RC, Lesch KP, Brummer D, Jacob C, Fallgatter AJ, Grön G (2010): Neural hypo-responsiveness and hyper-responsiveness during immediate and delayed reward processing in adult attention-deficit/hyperactivity disorder. *Biol Psychiatry*, 65: 7-14.
- Abler B, Hahlbrock R, Unrath A, Grön G, Kassubek J (2009): At-risk for pathological gambling: imaging neural reward processing under chronic dopamine agonists. *Brain*, 132: 2396-2402.
- Kiefer M, Sim EJ, Herrnberger B, Grothe J, Hoenig K (2008): The sound of concepts: four markers for a link between auditory and conceptual brain systems. *J Neurosci*, 28: 12224-12230.
- Spitzer M, Fischbacher U, Herrnberger B, Grön G, Fehr E (2008): The neural signature of social norm compliance. *Neuron*, 56:185-196.

Department of Child and Adolescent Psychiatry and Psychotherapy

Head of Department: Prof. Dr. Jörg M. Fegert

Keywords: Clinical studies | evidence based treatments | home-treatment | infant psychiatry | psychotherapy research

The department provides inpatient and outpatient care as well as day treatment and mother-child treatment for children and adolescents with psychiatric disorders and psychosocial problems. The department provides two wards for adolescents with a total of 19 beds, one ward for children with 12 beds, a day-care unit for 13 patients and two apartments for mother-child or parent-child treatment in cases where parents and children suffer from psychiatric disorders, especially attachment disorders, which need to be treated simultaneously (Managing Medical Deputy Director PD Dr. Michael Kölch).

The department has three divisions:

The outpatient clinic for psychosocial care (PD Dr. Andrea Ludolph) with about 800 first visitations per year offers a differentiated network of home treatment for children placed in institutional care in our region.

There is in addition a newly developed section for psychotherapy research combined with a training institute in child and adolescent behavior therapy, and an outpatient psychotherapy clinic (AZVT, Prof. Dr. Lutz Goldbeck).

The third division is a research section in the interdisciplinary field of infant psychiatry and psychosocial care for young families with and without adaptation and attachment problems (PD Dr. Ute Ziegenhain). The scientific working group is supported by a methodological subdivision with a focus on the development of instruments, quality assessment and sequential analysis of data (Prof. Dr. Ferdinand Keller).

The scientific topics dealt with range from biological fundamental questions within the context of child psychiatric disorders and psychopharmacological treatment of children to many applied and translational projects in networking child protection and psychosocial interventions as well as to specific expertise in the ethical planning and conducting of clinical trials in children and adolescents.



Patient information book for primary school children based on the results of research projects on age appropriate information and participation funded by the Volkswagen Foundation.

The department is the coordinating center for a government-funded multicenter medication trial on St. John's wort as an antidepressant (PD Dr. Michael Kölch) and coordinates the German therapeutic drug monitoring network (Prof. Dr. Claudia Mehler-Wex). An infrastructure for clinical studies has been established in the department together with the competence-network of child and adolescent psychiatry and psychotherapy in Baden-Württemberg in cooperation with the universities of Heidelberg and Ulm, and the Central Institute of Mental Health, Mannheim.

PD Dr. Andrea Ludolph was honored in 2009 for outstanding research in the field of ADHD with the Kramer-Pollnow-Award for her work on the cellular mechanisms of psychopharmacological effects as found mainly in stimulants in collaboration with the Department of Anatomy of Ulm University (Prof. Dr. Tobias Böckers) and for her imaging studies on ADHD and Tourette's Syndrome (fMRI, MRI and PAD). PD Dr. Ute Ziegenhain was member of the national child and youth report commission and was one of the co-authors of the 13th Child and Youth Report on the intersection of medicine and psychosocial circumstances.

As a consequence of former and ongoing research projects, several specialized outpatient clinics have been developed: a foster care unit; a tic and Tourette's unit; and a trauma unit. The first worldwide online journal in child and adolescent psychiatry and child mental health, CAPMH (www.capmh.com), is run by Prof. Fegert as the editor-in-chief and Prof. Dr. Goldbeck as the associate editor together with Dr. Ben Vitiello from the NIMH as deputy editor and Dr. Tan from Oxford as associate editor. The editorial office is located in Ulm and the work of CAPMH is supported by a grant from the DFG. The department has developed several areas of expertise on behalf of the German Federal Ministry for Family Affairs, Senior Citizens, Women and Youth (BMFSFJ) within the context of child protection and childhood trauma.



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Selected Publications:

- Seitz DCM, Besier T, Debatin KM, Debling D, Dieluweit U, Hinz A, Kaatsch P, Goldbeck L (2010): Posttraumatic stress, depression, and anxiety among adult long term survivors of cancer in adolescence. *Eur J Cancer*, [in press].
- Besier T, Fegert JM, Goldbeck L (2009): Evaluation of Psychiatric Liaison-Services for Adolescents in Residential Group Homes. *Eur Psychiatry*, 24: 483-489.
- Koelch M, Prestel A, Singer H, Keller F, Fegert JM, Schlack R, Hoelling H, Knopf H (2009): Psychotropic Medication in Children and Adolescents in Germany: Prevalence, Indications and Psychopathological Patterns. *J Child Adolesc Psychopharmacol*, 19: 765-770.
- Plener PL, Libal G, Keller F, Fegert JM, Mühlenkamp JJ (2009): An international comparison of adolescent non-suicidal self-injury (NSSI) and suicide attempts: Germany and the USA. *Psychol Med*, 39: 1549-1558.
- Schulze UM, Calame S, Keller F, Mehler-Wex C (2009): Trait anxiety in children and adolescents with anorexia nervosa. *Eat Weight Disord*, 14: e163-168.
- 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 18 F]fluorophenyl-L-alanine PET study“. *NeuroImage*, 41: 718-727.



Department of Psychosomatic Medicine and Psychotherapy

Head of Department: Prof. Dr. Harald Gündel

Keywords: Emotion regulation | human-computer interaction | neuropsychology | psychosomatic medicine | psychotherapy

The department has approximately 53 staff members, half of whom are female, and PhD students from China and Italy.

In terms of specialized research units, the department has two divisions, namely, Medical Psychology (Prof. Dr. Harald C. Traue) and Forensic Psychotherapy (Prof. Dr. Friedemann Pfäfflin). The latter division will be closed by September 30, 2010 and will be replaced by the newly independent Department of Forensic Psychiatry and Psychotherapy at the BKH Günzburg. As part of the Psychosomatic Department, a new division will be established focusing on basic neurobiological research in Psychosomatic Medicine.

After a long tradition of very effective psychotherapy process research, the main topics of research will now focus on the development and evaluation of psychotherapeutic interventions within the hospital, the interface of work and personal health, and basic neurobiological research. Current research includes preventive studies within the workplace setting, studies in outpatient treatment of anorexia nervosa, psychosomatic disorders of migrants, the effects of psychotherapy on brain-function, further studies focusing on emotion regulation and on physiological processes while being stressed, and finally on transcultural psychosomatics. The significance of emotional behavior in terms of interpersonal contact and human computer interaction (HCI) is the focus of close

cooperation within the SFB/TR 62 “Companion technologies” (funded by the German Research Foundation) in which the division of Medical Psychology is involved by focusing on emotion recognition, emotion computing and usability, emotion regulation, emotion processing in various diseases, and method development.

Experimental methods for psychobiological emotion research are developed through fundamental research that includes psychometric tools (questionnaires), computer-based tests and experimental processes to measure eye movement (EEG, EMG, HR, GSR) and behavioral data. Some of the areas of application are the analysis of human computer interaction (HCI), interpersonal communication and the study of the etiological significance of emotional dysregulations in certain disorders (e.g. anxiety, depression and neurological dysfunctions).

The clinic offers in- and outpatient treatment as well as a day clinic for patients with the full spectrum of psychosomatic diseases that includes psychosomatic consultation and liaison services for patients of other university departments with the emphasis on psychooncology, chronic pain and psychosomatic co-morbidity in chronic somatic diseases. Furthermore, specific treatment programs for patients with transgenderism, and for violent and/or sex offenders have also been developed (Prof. F. Pfäfflin).



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Selected Publications:

- Traue HC, Johler R, Gavrilovic JJ (2010): *Migration, Integration, and Health: The Danube Region*. Pabst Science Publishers, Lengerich.
- Fladung AK, Grön G, Grammer K, Herrnberger B, Schilly E, Grastelt S, Wolf RC, Walter H, von Wietersheim J (2010): *A neural signature of anorexia nervosa in the ventral striatal reward system*. *Am J Psychiatry*, 167: 206-212.
- Cohen-Kettenis P, Pfäfflin F (2010): *The DSM diagnostic criteria for Gender Identity Disorder in adolescents and adults*. *Arch Sex Beh*, DOI 10.1007/s10508-009-9562-y [Online first].
- Pedrosa Gil F, Ridout N, Kessler H, Neuffer M, Schoechlin C, Traue HC, Nickel M (2009): *Facial emotion recognition and alexithymia in adults with somatoform disorders*. *Depress Anxiety*, 26: 26-33.
- Buchheim A, Heinrichs M, George C, Pokorny D, Koops E, Henningsen P, O' Connor MF, Gündel H (2009): *Oxytocin enhances the experience of attachment security*. *Psychoneuroendocrinology*, 34: 1417-22.
- Valet M, Gündel H, Sprenger T, Sorg C, Mühlau M, Zimmer C, Henningsen P, Tölle TR (2009): *Patients with pain disorder show gray-matter loss in pain-processing structures: a voxel-based morphometric study*. *Psychosom Med*, 71: 49-56.



Student dentists working on a patient in the student clinic of the Department of Conservative Dentistry and Periodontology.

Department of Conservative Dentistry and Periodontology

Head of Department: Prof. Dr. Bernd Haller

Keywords: Endodontics | esthetic dentistry | minimal invasive | periodontology | restorative dentistry

The Department of Conservative Dentistry and Periodontology encompasses the disciplines of preventive and operative dentistry, endodontics, periodontology and pediatric dentistry. Our global mission is to preserve natural teeth. In restorative treatment, we are specialized in bonded tooth-colored restorations using resin composites and ceramics with the main emphasis on esthetics and minimal invasive procedures. Clinical care in endodontics covers vital pulp therapies, root canal (re-)treatments, internal bleaching and endodontic emergencies using endo microscopes and endo motors for preparation of curved root canal with NiTi rotary instruments. Patient care in periodontology covers treatment of chronic and aggressive periodontitis by scaling/root planning, surgical procedures and full-mouth disinfection. Advanced microbiological diagnostics is provided by our laboratory of oral microbiology.

Research activities are focused on in-vitro and clinical testing of adhesive restorative biomaterials and on advanced antimicrobial strategies and regenerative procedures in periodontology.

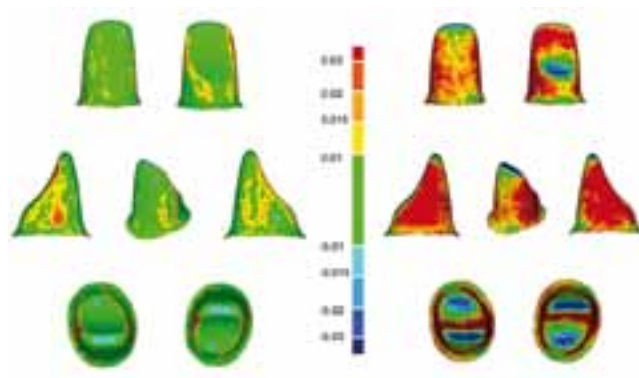
Team (full-time equivalency): academic staff, 10; dental assistants, 10.5; dental/medical technicians, 4.5; administrative staff, 2.25.

Dental treatment units:
23 (nine resident clinic, 14 student clinic).

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Selected Publications

- Rathke A, Haj-Omer D, Muche R, Haller B (2009): Effectiveness of bonding fiber posts to root canals and composite core build-ups. *Eur J Oral Sci*, 117: 604-610.
- Haller B (2009): Direkte Seitenzahnrestauration mit Komposit. *Thieme Zahnmedizin up2date*, 3: 579 – 602.
- Rathke A, Tymina Y, Haller B (2008): Effect of different surface treatments on the composite-composite repair bond strength. *Clin Oral Investig*, 13: 317-323.
- Haller B, Blunck U (2008): Schmelz- und Dentinhaftung. In: Kappert HF, Eichner K (Hrsg.): *Zahnärztliche Werkstoffe und ihre Verarbeitung. Band 2 Werkstoffe unter klinischen Aspekten*. 6. Aufl., S. 139-182. Georg Thieme Verlag KG, Stuttgart.
- Vymetal J, Slabý I, Spahr A, Vondrásek J, Lyngstadaas SP (2008): Bioinformatic analysis and molecular modelling of human ameloblastin suggest a two-domain intrinsically unstructured calcium-binding protein. *Eur J Oral Sci*, 116: 124-134.
- Ernst CP, Galler P, Willershausen B, Haller B (2008): Marginal integrity of class V restorations: SEM versus dye penetration. *Dent Mater*, 24: 319-327.



3D-analysis of different digitizing systems for dental CAD/CAM (computer-aided design/computer-aided manufacturing) systems.

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Department of Prosthetic Dentistry

Head of Department: Prof. Dr. Ralph Luthardt

Keywords: Applied material sciences | clinical trials | computer-aided dentistry and implantology |

3D-simulation

The Department of Prosthetic Dentistry administers comprehensive patient-oriented treatment after tooth loss. The primary goal is to preserve the remaining teeth and restore a healthy masticatory system. Our mission is to guarantee innovative and state-of-the-art care through the continuous ongoing education of the entire team. A total of 42 employees (67% female) are in charge of patient treatment, education and research: 12 dentists; 12 dental assistants; three trainees; five technicians; three technical assistants; seven research assistants; and one external researcher. Thirteen internal and external PhD students are also being supervised and we can host two guest dentists every year. Computer-aided manufacturing of dental restorations, 3D-planning based on cone beam CT for optimal implant positioning, minimal invasive implant surgery in addition to our synoptic patient centered treatment concept are the most innovative in prosthodontic care.

Our research topics are:

- clinical trials in soft-tissue management, dental implants and treatment strategies,
- cross-linking clinical trials, in vitro and computer simulations (SimTOM, www.simtom.eu),
- dental material testing of advanced ceramic implants, restorations and veneering,
- 3D-analysis of digital workflows (from conventional and digital impressions to computer-aided manufactured restorations).

Selected Publications:

- Luthardt RG, Marre B, Heinecke A, Gerss J, Aggstaller H, Busche E, Dressler P, Gitt I, Hannak W, Hartmann S, Heydecke G, Jahn F, Kern M, Mundt T, Pospiech P, Stark H, Wostmann B, Walter MH (2010): *The randomized shortened dental arch study (RaSDA): design and protocol. Trials, 11: [Epub ahead of print].*
- Walter MH, Weber A, Marré B, Gitt I, Gerß J, Hannak W, Hartmann S, Heydecke G, Huppertz J, Jahn F, Ludwig A, Mundt T, Kern M, Klein V, Pospiech P, Stumbaum M, Wolfart S, Wöstmann B, Busche E, Böning K, Luthardt RG (2010): *The randomized shortened dental arch study: tooth loss. J Dent Res, 89: [in print].*
- Luthardt RG, Walter MH, Quaas S, Koch R, Rudolph H (2010): *Comparison of the three-dimensional correctness of impression techniques in a randomized controlled trial. Quint Int, 41: [in print].*
- Haim M, Luthardt RG, Rudolph H, Koch R, Walter MH, Quaas S (2009): *Randomized controlled clinical study on the accuracy of two-stage putty-and-wash impression materials. Int J Prosthodont, 22: 296-302.*
- Watzke R, Frankenberger R, Naumann M (2009): *Probability of interface imperfections within SEM cross-sections of adhesively luted GFP. Dent Mater, 25: 1256-1263.*
- Luthardt RG, Walter MH, Weber A, Koch R, Rudolph H (2008): *Clinical parameters influencing the accuracy of 1- and 2-stage impressions: a randomized controlled trial. Int J Prosthodont, 21: 322-327.*



Extensive bone destruction in a maxillary molar (x-ray).



The same tooth after partial periodontal regeneration and new ossification after treatment with enamel matrix proteins

Department of Oral and Maxillofacial Surgery

Head of Department: Prof. Stephan Haase, M.D., M.D.M.

Keywords: Cleftpalate

The Department of Maxillo-Facial-Surgery within the Department of Odontology of Ulm University is a polyclinic equipped to provide maximum care. The work is undertaken by three maxillo-facial surgeons as well as three oral surgeons that are still in part-time education. Two of these oral surgeons are female. The Institute of Radiology, furnished with all the X-ray devices relevant for this specialty, has been integrated into the department. In particular, a new digital volume tomography was supplied in 2009.

As part of the dental curriculum, the following events are held:

1. Course operation I and II.
2. Main lecture in oral maxillo-facial surgery.
3. Lecture in dental medical science.
4. Lecture and course in radiology.

As part of a common research project of the departments for Dentistry, the department takes part in oral maxillo-facial surgery especially in the field of Periimplantitis.

With regards to maximum care, the whole spectrum of oral maxillo-facial surgery as well as oral surgery is provided.

The main focus is on the treatment of patients with cleft lip and palate performed in collaboration with the departments of Otorhinolaryngology, Phoniatrics and Pedaudiology, Gynecology, and Pediatrics. Another main focus lies in the application of dental implants employing all methods of augmentation.

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Selected Publications:

- Reiter R, Haase S, Brosch S (2010): *Submucous Cleft Palate – an Often Late Diagnosed Malformation. Laryngo-Rhino-Otol*, 89: 29-33.
- Reiter R, Haase S, Brosch S (2009): *Repaired Cleft Palate and Ventilation Tubes and their Associations with Cholesteatoma in Children and Adults. Cleft Palate-Craniofacial Journal*, 46: 598-602.



Surface electromyography in the face using multi-electrode arrays. This method allows the determination of basic anatomic and neurophysiologic parameters (e.g. muscle fiber directions and motor endplate locations) on the level of the smallest functional unit of human musculature, i.e. the single motor unit. Such information is of fundamental interest and is useful for optimizing functional diagnosis and therapeutic strategies.

Department of Dentofacial Orthopedics and Orthodontics

Head of Department: Prof. Dr. Bernd Lapatki

Keywords: Biomechanics | facial muscles | malocclusion | tooth movement | smart bracket

The department is an integral part of the Center of Dentistry and has approximately 25 employees that include orthodontists, postgraduate students, and scientists. The duties of the department are research and the education of dental students in orthodontics and patient care.

The main scientific topics belong to the fields of orthodontic biomechanics and neurophysiology of the orofacial system. A scientific

highlight is the development of smart brackets with an integrated sensor system for 3D force-moment measurements during orthodontic therapy. This project has been initiated in collaboration with the Institute of Microsystems Engineering of the University of Freiburg, Germany. Quantitative knowledge of the 3D force-moment systems applied for therapeutic tooth movement is of the utmost importance with regard to the predictability of tooth movement and the reduction of traumatic side-effects such as dental root resorption. We have been able to realize true-scale smart brackets which are currently applied for investigating force-moment systems applied to the individual teeth during simulated treatment situations. Telemetric components for data and energy transmission are currently being integrated to enable the future clinical application of smart bracket technology.

Patient care in our clinic covers the correction of dental malocclusion in children and adults. In collaboration with other departments, we also treat patients with significant dental disproportions, requiring both orthodontics and orthognathic surgery, and patients with cleft lip and palate. Furthermore, we are specialized in the diagnosis and treatment of the dental problems of wind instrumentalists.



Three-bracket-model with a true-scale smart bracket in the center. The smart bracket includes an adhesively attached slot for orthodontic wire insertion and a micro-electronic sensor chip (with cable supply) for monitoring the forces and moments applied to the individual tooth.

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Selected Publications:

- Lapatki BG, Oostenveld R, van Dijk JP, Jonas IE, Zwarts MJ, Stegeman DF (2010): Optimal placement of bipolar surface EMG electrodes in the face based on single motor unit analysis. *Psychophysiol*, 47: 299-314.
- Boryor A, Hohmann A, Geiger M, Wolfram U, Sander C, Sander FG (2009): A downloadable meshed human canine tooth model with PDL and bone for finite element simulations. *Dent Mater*, 25: e57-e62.
- Hohmann A, Wolfram U, Geiger M, Boryor A, Kober C, Sander C, Sander FG (2009): Correspondences of hydrostatic pressure in periodontal ligament with regions of root resorption: A clinical and a finite element study of the same human teeth. *Comput. Methods Programs Biomed*, 93: 155-161.
- Boryor A, Geiger M, Hohmann A, Wunderlich A, Sander C, Sander FG (2008): Stress distribution and displacement analysis during an intermaxillary disjunction – A three-dimensional FEM study of a human skull. *J Biomech*, 41: 376-382.
- Natali AN, Carniel EL, Pavan PG, Sander FG, Dorow C, Geiger M (2008): A Visco-Hyperelastic-Damage Constitutive Model for the Analysis of the Biomechanical Response of the Periodontal Ligament. *J Biomech Eng*, 130: 031004-1 – 031004-8.