

Philipps



Universität
Marburg

Research Report of the Medical Faculty 2015

Reference Period 2013 - 2014



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List of Abbreviations/Glossary

BMBF	Federal Ministry of Education and Research – Bundesministerium für Bildung und Forschung
BMFZ	Biomedical Research Centre – Biomedizinisches Forschungszentrum
CCC	Comprehensive Cancer Center
DFG	German Research Foundation / Deutsche Forschungsgemeinschaft
FOR	Research Unit / Forschergruppe
GRK	Research Training Group / Graduiertenkolleg
IMT	Institute for Molecular Biology and Tumor Research
JIF	Journal Impact Factor
KFO	Clinical Research Unit / Klinische Forschergruppe
KKS	Coordination Centre for Clinical Studies
LOEWE	State Offensive for the Development of Scientific-Economic Excellence / Landes-Offensive zur Entwicklung Wissenschaftlich-ökonomischer Exzellenz
LOF	Performance-related allocation of research and office space
LOM	Performance-related Funding / Leistungsorientierte Mittelvergabe
SFB	Collaborative Research Centre / Sonderforschungsbereich
TR	Transregional Collaborate Research Centre / Transregio
UKGM	University Hospital Giessen and Marburg Universitätsklinikum Gießen und Marburg
ZTI	Centre for Tumor and Immunobiology/ Zentrum für Tumor- und Immunbiologie

General Aspects

Main Fields of Research

According to the criteria of the German Research Council (DFG) at the School of Medicine of the Philipps University Marburg the following preferred research clusters are established:

- Cellular Compartmentation and Disease Relevance
- Clinical Immunology and Infection Biology
- Oncology and Tumor Biology
- Neuroscience

Associated infrastructural components already existent are the Biomedical Research Centre (BMFZ), the Institute for Molecular Biology and Tumor Research (IMT), the Center for Tumorbiology and Immunology (ZTI) the Comprehensive Cancer Center Marburg (CCC), the Carreras Leukaemia Centre and the Allergy Centre Hesse.

Research Cluster „Cellular Compartmentation and its Relevance for Disease“

The location of intracellular compartments and smaller entities such as protein complexes, nucleic acids, metals and lipids within a cell is prerequisite for the complexity and regulation of the biological functions performed by this particular cell. Failure to accurately localize cellular biomolecules is frequently associated with disease. In order to generate, maintain and modulate biogenesis, composition and location of various intracellular compartments, eukaryotic cells have developed sophisticated machineries to ensure transport of metals, metabolites, lipids, proteins, and nucleic acids across membranes and to support membrane trafficking within the cell. Work in the Research Cluster „Cellular Compartmentation and its Relevance for Disease“ (Figure) is dedicated to the elucidation of the molecular mechanisms underlying various membrane transport and compartmentalization processes in eukaryotic cells using yeast, pathogenic fungi, human cell culture, and mice as model systems. Participating groups of Philipps University and the Max-Planck-Institute for Terrestrial Microbiology analyze the mechanistic basis of the generation and maintenance of the intracellular compartmentation by using state-of-the-art

technology including proteomics, genomics, live-cell and super-resolution imaging methods. The groups also exploit pathologically altered cells to analyze and compare the changes in the intracellular compartments in order to define and distinguish normal and pathologically altered processes at the molecular level. A unifying goal of the research groups in this area is the identification and characterization of the molecular machineries participating in the biogenesis, maintenance and dynamic alteration of the various compartments of a eukaryotic cell. Further, the groups try to unravel the mechanisms underlying the intracellular transport of proteins, nucleic acids, lipids, metabolites, and metals.

Another central focus is on the impact of (highly pathogenic) viruses, intracellular parasites, and fungal pathogens on intracellular compartmentalization, and on the importance of compartment-specific tropism for pathogen reproduction and host cell toxicity. The common goal of these projects is the elucidation of how these pathogens alter and exploit cellular compartments to ensure their own survival. The thorough mechanistic investigation of the molecular basis of intracellular compartmentation is a prerequisite for the understanding of the disease-relevant phenotypes and the long-term development of therapeutic regimes.

The research cluster has been funded by several coordinated programs of DFG. This includes a Collaborative Research Center (SFB 593), a Graduate Research Training Group (GRK 1216), and a Research Unit (FOR 1086). All these coordinate funding programs have terminated in 2015. Efforts are currently on the way to acquire new funding opportunities within coordinated programs. These efforts are undertaken with partners from the University of Giessen.

We entertain intensive contacts with the Research Clusters of **Tumor Biology** and **Immune and Infection Biology**, since it has become evident that the problem of correct (sub-)cellular location also applies to these areas (Figure). Vice versa, the regulatory and signaling mechanisms studied within these two Clusters are of increasing interest for our area in order to understand how the cell maintains its overall homeostasis. As a consequence of these mutual interests in the two clusters, the participating research groups jointly address the regulation of the

intracellular localization of proteins, RNA and lipids in healthy cells and after tumorigenic and infectious alterations. The signaling pathways leading to alterations in cellular compartmentation in response to changing physiological conditions or external challenges are also studied jointly.

Our Research Cluster maintains fruitful contacts to and collaborations with the faculties of Biology, Chemistry and Pharmacy, as well as the Max-Planck-Institute of Terrestrial Microbiology (Figure). Finally, we participate in the activities of the LOEWE Center of Synthetic Microbiology.

Examples for research projects in this area:

- Analysis of the mechanisms of the intracellular vesicle transport and the molecular basis of cell polarization of, e.g., polarized epithelial cells
- Investigation of the role of mitochondria, cytosol and nucleus in the biogenesis of iron-sulfur proteins and the relevance for neurodegenerative, metabolic, and hematological diseases
- Analysis of the mechanisms of the intracellular transport, subcellular localization, membrane microcompartmentation of ion channels and lipids in the activation of signal-transducing processes (e.g., in caveolae)
- Investigation of various aspects of nucleo-cytoplasmic transport and protein und (micro)RNA transport across biological membranes

Study of transport processes between host cells and the malaria pathogen *Plasmodium falciparum* and its relevance for the lifecycle of the pathogen

- Investigation of the changes in intracellular compartmentation during the plant cell infection by pathogenic fungi
- Analysis of mechanisms how highly pathogenic viruses (Influenza, Marburg, Ebola, Lassa, Dengue etc.) exploit and alter the intracellular compartments (mainly the nucleus and secretory apparatus) for the own proliferation

Diseases include

- Disorders of transport processes with relevance for tumor development
- Ion channel diseases
- Sugar transport diseases
- Neurological disorders associated with the erroneous trafficking of macromolecules involved in intracellular transport
- Hypertension
- Various iron storage diseases, myopathies and anemias, and diverse neurological diseases (Lowe-, Bartter- und Anderson-Syndrome, Friedreich Ataxia) with a primary defect in the intracellular compartmentation
- Mitochondrial fatal encephalopathies and myopathies with multiple metabolic disorders
- Plant infections by pathogenic fungi (smut)
- Various viral diseases such as influenza and hemorrhagic fever

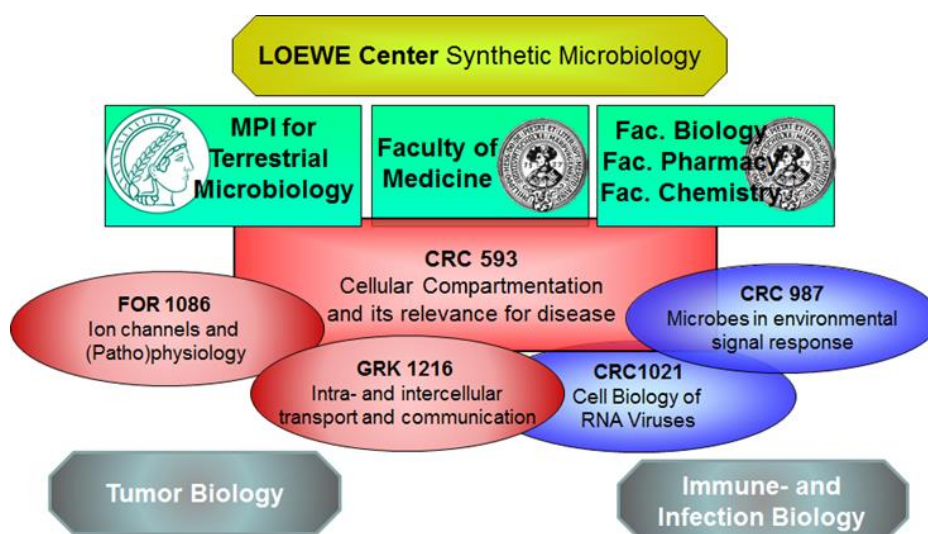


Fig. 1: Structure of the research cluster “Cellular Compartmentation and its Relevance for Disease” and its integration into the Marburg research landscape. Activities in red have been terminated in 2015

Research Cluster “Clinical Immunology and Infection Biology”

The research focus area “**Clinical Immunology and Infection Biology**” is mainly concerned on the one hand with the immunopathogenesis of chronic inflammatory processes, among which rare autoimmune diseases and allergies on the other hand with the pathogenesis of viruses that cause severe disease.

Starting point to investigate chronic inflammatory diseases was the awareness of a strong increase of these disease entities, particularly since the end of the Second World War and most of all in the industrialised regions of the world. The phenomenal increase in these illnesses cannot be explained solely by a genetic predisposition for the manifestation of the phenotype (gene-gene-interactions). The identification of protective or disease-promoting environmental influences from life style and diet have led to the so-called hygiene hypothesis, in whose further development there was crucial impact by research groups from Marburg. In the Transregional Collaborate Research Centre SFB/TR 22 ‘Allergic immune responses of the lung’ (Speaker Prof. Renz) epidemiological evidence from international prospective cohorts provides the basis for generating hypothesis. On the one hand the focus is on immunological regulation processes and signal paths of the innate and acquired immune system. On the other hand failing signalling paths of resident cells of the lungs and the respiratory passages such as epithelia, fibroblasts and smooth muscle cells are investigated. Overall the consortium follows a translational research approach aiming to develop new concepts for prevention and to identify new therapeutic targets, which will be clinically evaluated later in the project. This research field is broadly established in the School of Medicine involving the Departments of Pneumology, Dermatology and Pediatrics as well as the Institutes of Immunology, Medical Microbiology and Clinical Chemistry. In 2009 the LOEWE-Centre UGMLC – Universities Giessen and Marburg Lung Centre – was granted in collaboration with the Max-Planck-Institute for Heart and Lung Research at Bad Nauheim, in which the joint activities to explore infectious, inflammatory-allergic and vascular pulmonary diseases were brought together. In the recently established German centre for lung illnesses

(DZL) UGMLC is one of six national research centres for health. DZL has already taken up his research activities end of 2011. A main focus of the Marburg group within the DZL is the chronic inflammatory lung illnesses asthma and COPD.

Marburg University has a long tradition in working with highly pathogenic viruses which goes back to the isolation and characterization of Marburg virus in 1967. Since then the focus of the Institute of Virology is to understand the biology and pathogenesis of agents like Ebola, Lassa, Nipah and influenza virus. The construction of facilities allowing to work safely with these viruses was of crucial importance. Since 2008 the Philipps-University operates a modern Biosafety level 4 (BSL-4) laboratory where highly pathogenic viruses can be investigated, without harming the scientists and the environment. Most of the highly pathogenic viruses are zoonotic and transmission from the animal host to humans causes severe illness. Understanding the viral and host factors that contribute to the severity of the disease course is important for developing novel antiviral strategies and effective vaccines. These investigations are funded by the collaborative research center SFB 593 (Speaker Prof. Lill, <http://www.uni-marburg.de/sfb593>) and SFB 1021 (Speaker Prof. Becker, <http://www.uni-marburg.de/sfb1021>), the German Center for Infection Research (<http://www.dzif.de/>) as well as many grants from the European Union. The collaborative nature of these investigations becomes obvious by the fact that within the funded networks infection disease specialists work closely together with immunologists, cell biologists, clinical chemists, pharmaceutical chemists and biochemists from the faculty of medicine at the Philipps-University and other departments of the university.

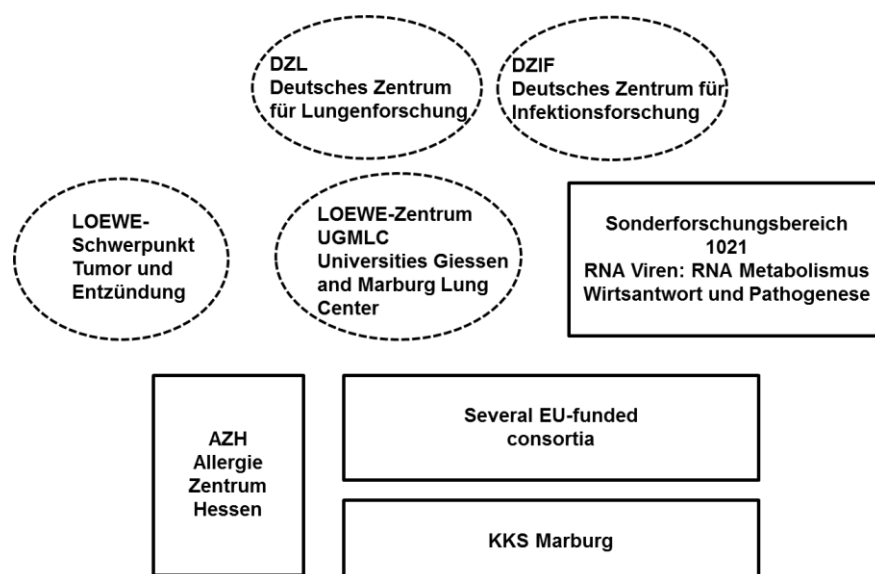


Fig. 2 "Organisation of the research cluster "Clinical Immunology and Infection Biology"

Research Cluster "Oncology and Tumor Biology"

In the research focus "Oncology and Tumor Biology" one of the main questions is, how oncogenic signaling, genetics and epigenetics interact to generate a cancer phenotype characterized by deregulation of proliferation control, invasive and metastatic growth, reprogramming of energy metabolism, and drug resistance. Current funding programmes are the Transregional Collaborative Research Centre SFB/TRR17 'Ras-dependent pathways in human cancer' (Speakers: Prof. Eilers, Würzburg and Prof. A. Neubauer, Marburg) and the Clinical Research Unit KFO 210 'Genetics of drug resistance in cancer' (Speaker: Prof. A. Neubauer; Head: Prof. A. Burchert) as well as the Transregional Collaborative Research Centre SFB/TRR81 'Chromatin changes in differentiation and malignancies' (Speaker: Prof. Brehm, Marburg). In this research center, dynamic alterations of the chromatin structure (epigenetics) in development and cancer are at the forefront of research. Interactions between tumor cells and host cells in the microenvironment of the tumor, which significantly affect tumor growth and progression, are the focus of the LOEWE research cluster 'Tumor & Inflammation' (Speaker: Prof. Müller). Research on tumor-host interactions will be fueled by the new

research building 'Center for Tumor and Immune Biology' that is funded by the BMBF and the State of Hessen.

Apart from this basic and translational research focus, the area of clinical oncology was continually and successfully developed. The central organizational platform of clinical oncology is the Anneliese Pohl Krebszentrum Marburg, Comprehensive Cancer Center (CCC). A new building for patient care and patient-oriented clinical research was erected by means of the Carreras Leukemia Foundation (Carreras Leukämie Centrum, Speaker Prof. A. Neubauer). The Carreras Leukämie Centrum contains a 'Clinical Trial Unit', in which experimental phase I/II studies concerning new signal modulators are carried out in cooperation with the Marburg Coordination Centre for Clinical Studies (KKS).

In addition, several accreditations have again been successfully implemented in 2013-2014, for instance a new "Onkologisches Zentrum" of the Deutsche Krebsgesellschaft, that hosts several organ specific tumor centers (oncomap.de). In Nov 2014, the international stem cell and leukemia accreditation JACIE was successfully implemented.

These accreditations underscore one important focus on clinical oncology at the university hospital Marburg. In keeping with this, oncology will be supplemented in research and clinic by a Particle Therapy Centre. For research tasks a professorship (all coordinated by Prof. T. Gress) and the national case data base 'Hereditary Pancreatic Carcinoma' ('FaPaCa', Coordinator: Prof. D. Bartsch) the investigation of the molecular and genetic mechanisms of cancerogenesis in the pancreas of

each for radiation biology and radiation physics will be established. Additional translational projects in the major research area tumor biology are concerned e.g. with the pancreatic carcinoma the EU-FP7 network "EPC-TM-NET", "CAM-PaC", BioPaC paramount interest and will serve as a basis for the development of new molecular target-oriented, diagnostic and therapeutic methods.

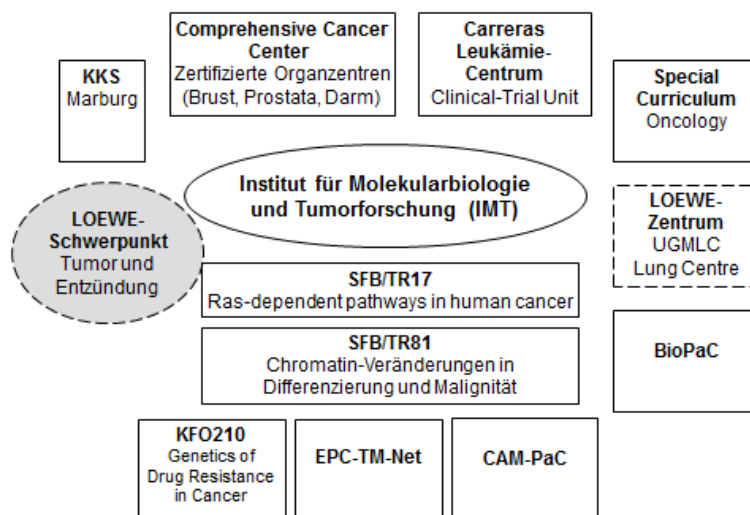


Fig. 3 Structure of the research cluster "Oncology and Tumorbiology"

Research Cluster "Neuro Science"

The scientific foci of the research cluster "**Psycho-Neurosciences**" are the aetiology of psychiatric and neurological disorders as well as the improvement of therapeutic interventions.

There is a sharp increase in mental and neurological disorders worldwide within the last decades. Mental disorders are currently the most cost intensive non-infectious diseases worldwide. Thus there is a pressing need to improve our etiological knowledge and therapeutic interventions. These topics are being investigated in several research consortia. The FOR 2107 "Neurobiology of Affective Disorders" (Speaker: Prof. Kircher, www.FOR2107.de) focuses on gene x environment interactions on brain development and the neurobiological course of illness in humans and rodent models. The SFB/TRR 135 "Cardinal mechanisms of perception" (Speaker: Prof. Gegenfurtner, <http://www.allpsych.uni->

www.sfb.de) deals with basic mechanism of human sensory perception and is complementary to the IRTG1091 "The brain in action" (Speaker: Prof. Bremmer, <http://www.irtg-brainact.de>). Genetic and epigenetic risk factors of neuro-psychiatric diseases are being investigated in the EU-projects "MicroRNA function in homeostatic plasticity in the mammalian brain" (EU, ERC-Grant "NEUROMIR"; coordinator: Prof. Schratt) and MicroRNAs in epilepsy (EpimiRNA; coordinator: Prof. Rosenow). More clinically focussed are the BMBF funded consortia "ASDnet" (Speaker: Prof. Kamp-Becker), "PROTECT-AD" (anxiety disorders, sub-project coordinators: Profs. Straube/Kircher), "BipoLife" (bipolar disorder, sub-project coordinators Profs. Jansen/Kircher), and "ESCALife" (ADHD, sub-project coordinator: Prof. Becker) were genetic and environmental causes on outbreak and course of illness, early detection and psychotherapeutic as well as neurobiological

therapies are being investigated. A Hertie Senior Research Professorship has been awarded to Prof. Oertel so that he continues to work on neurodegenerative diseases.

Important infrastructural facilities are the rodent animal housings in the ZTI, the Biochemical-Pharmacological Centre, the animal behaviour laboratory in the Faculty of Psychology, and the primate facility. Two MR scanners have been co-funded by the DFG and the University (DFG INST 160/456-1). A 3 Tesla MRI scanner with personnel

and IT is used for human research and a 7.0 T for animal MRI.

These neuroscience activities at the University are being coordinated in the forthcoming "Centre for Neuroscience". There are two newly established interdisciplinary master courses "Cognitive and Integrative Systems Neurosciences (MSc)" and "Molecular and Cellular Neuroscience (MSc)". All neuroscience teaching is supported by the Graduate Center for Life and Natural Sciences in its Section Experimental, Clinical and Cognitive Neuroscience (MARA).

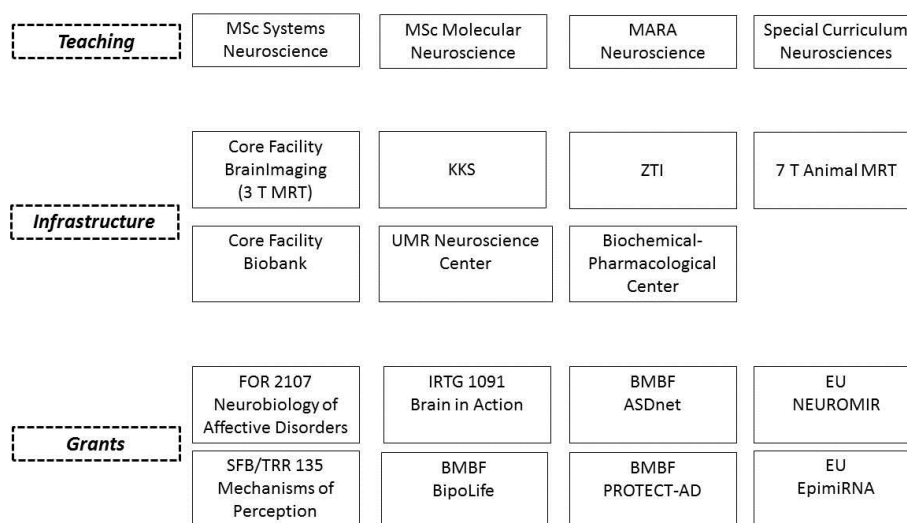


Fig. 4 Structure of the Research Cluster Psycho-Neurosciences

Coordination Centre for Clinical Studies (KKS)

Since the establishment of coordinating centres for clinical trials (KKS) by BMBF there is one of these centres at the department of medicine in Marburg. KKS Marburg started in 2000. Focus of the work of KKS is to increase the quality of clinical trials and the acceptance of clinical research in the academic environment and to implement the principles of "Good Clinical Practice" in everyday clinical practice. In 2005, all funded KKS in Germany have formed a consortium (KKS Network). The network offers a wide range of scientific services on a regional and national basis to scientists in universities, hospitals and industry. Beyond the actual tasks in clinical

research (trial planning, conducting and evaluation including publication of the trial results) KKS Marburg has taken over the following functions:

- Operating as sponsor for all investigator initiated trials with the principal investigator in Marburg
- Handling of all contracts dealing with patient oriented research at the Philipps University Marburg.
- Chair of the KKS network
- Chair of the Networkworking group 'data management' of the KKS Network
- Chair of the Networkworking group 'Monitoring' of the KKS Network

- Deputy Chair of the Networkworking group 'IT-systems' of the KKS Network
- Member of the European consortium ECRIN (European Clinical Research Infrastructures Network and Biotherapy)
- Deputy chair of the working group 'management of clinical trials' of the TMF e.V. (Technologie und Methodenplattform für die vernetzte medizinische Forschung)

The majority of supported clinical trials are investigator initiated trials. These trials are partly funded by the BMBF/DFG programm 'Clinical trials'. KKS supports the investigators at the submission / call for proposals, conduct the trials and publishes the results in cooperation with the investigators.

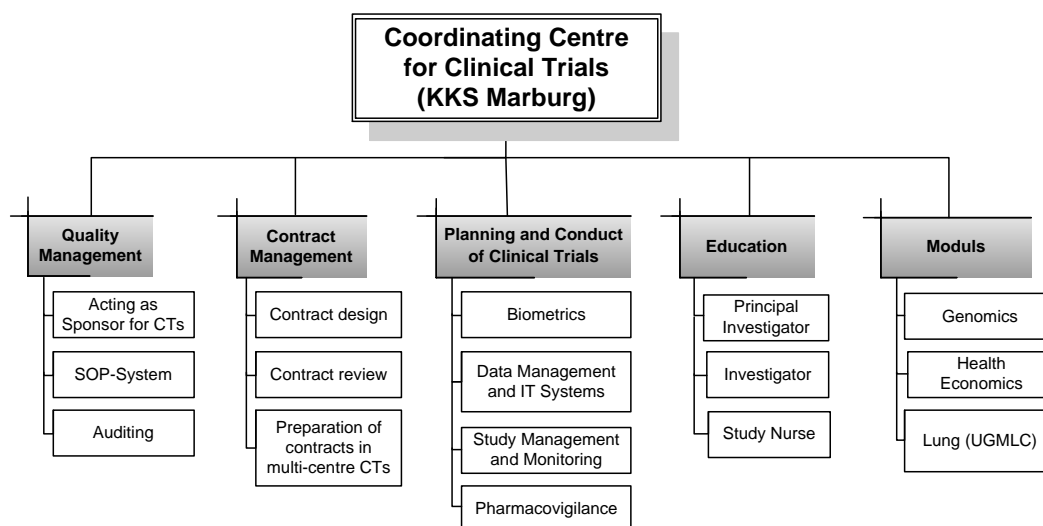


Fig. 5 Organisation chart of KKS Marburg

Technology-Transfer by TransMIT

The translational research approach, particularly of the clinically oriented research focus areas, leads to the generation of new knowledge and new technologies, whose innovative character has been recognised and whose intellectual authorship needs to be protected. For this purpose the TransMIT Society for Technology Transfer serves as the potential transfer facility for the middle Hessian universities and universities for applied science. TransMIT was awarded the first rank in the evaluation of all university-based transfer institutes in Germany (see also www.TransMIT.de). A number of university professors and lecturers from Marburg are involved in the TransMIT GmbH via TransMIT centres. The TransMIT GmbH is associated with the Hessian Intellectual Property Offensive (HIPO) alliance. Arising from this transfer of innovation the company 'sterna biologicals' has been founded,

which aims to use transcription factors as innovative targets for the treatment of chronic inflammations through the application of modern DNAzym-technology (2nd place in the nationwide start-up competition „Science4Life“ 2007).

Research Funding

An overview of total research funding of the School of Medicine from 2004 to 2014 is given in Table 1 and Fig. 6. This illustrates that the school has acquired considerable funding by being awarded three Collaborative Research Centres by the German Research Council. Overall third-party funding of the school in the last years amounts to around one third of the received state funding. During the last two years this percentage has considerably increased.

Performance-Related Internal Funding

There is no direct ex-post parameter-controlled and performance-related funding among the Medical Schools in the federal state of Hesse.

Performance-related funding has been introduced at the School of Medicine at Marburg University following the recommendations of the German Research Council (DFG) from July 2004 on 'Performance-Related Funding' (LOM) at Medical Schools. Thereby the same rules apply for all preclinical institutes, clinical-theoretical institutes and clinical departments. In the underlying assessment publication performance and acquired research funding are taken into account in equal proportions, extending over the past three years respectively. Thereby research funding granted after an external review process is taken into account in full. Research funding granted without an external review process, e.g. funding from industry, is taken into account with only 30 percent. Total expenditure of research funding per year is used for the calculation. Publication performance is quantified by the Journal Impact Factor (JIF) of the respective journal of all published original papers. Thereby first- and last authorship rate with one third of the JIF each, the remaining third of the JIF is divided between all middle authors.

The amount of funding of an institute received in the annual LOM corresponds to its overall contribution in terms of publication performance and acquired funding in relation to all other evaluated institutes. Currently the different sizes of institutes are not considered in the assessment and do not enter into the calculation.

From the year 2010 the school aims to introduce performance-related funding for teaching based on teaching assessments. Beyond this, in accordance with recommendations of the German Research Council, the school will enter into the concept of performance-related funding for the promotion of young researchers and into a performance-related allocation of research and office space (LOF). In the context of the LOF each institute will at first receive a parameter-based basic provision of research space (laboratory space). On a strictly temporary basis this basic provision of institutes will be supplemented by the dean's office taking into account proven research activities (e.g. third-party funded personnel). The remaining research and office space will be allocated on a flexible basis by the dean's office for currently funded research projects.

Year	DFG	DFG/SFB	FRG	EU	State	Sponsors	Foundation	Non-public Funding	Behring Röntgen Foundation	Funding by UKGM	Total Funding
2004	4.032.335 €	1.630.162 €	3.644.248 €	1.442.817 €	58.464 €	124.088 €	2.556.641 €	4.383.886 €			17.872.642 €
2005	3.437.788 €	2.433.628 €	2.234.492 €	937.891 €	187.710 €	169.522 €	2.022.637 €	4.906.584 €			16.330.253 €
2006	3.371.680 €	2.801.772 €	2.498.489 €	2.688.742 €	53 €	78.717 €	1.713.270 €	3.726.259 €			16.878.982 €
2007	3.558.746 €	4.109.933 €	2.621.109 €	1.685.985 €	11.789 €	175.683 €	1.511.093 €	5.151.000 €		490.963 €	19.316.300 €
2008	3.042.045 €	6.079.496 €	2.339.280 €	1.455.641 €	215.079 €	451.192 €	1.387.533 €	5.944.309 €	133.269 €	809.573 €	21.857.417 €
2009	3.094.743 €	4.902.592 €	2.380.916 €	1.251.064 €	224.920 €	404.231 €	1.834.115 €	5.181.587 €	484.088 €	654.282 €	20.412.537 €
2010	3.471.788 €	5.460.609 €	3.080.677 €	605.496 €	231.253 €	304.433 €	1.789.218 €	4.826.912 €	878.766 €	869.794 €	21.518.945 €
2011	3.665.755 €	6.282.114 €	3.470.365 €	1.466.384 €	170.246 €	243.214 €	1.450.148 €	4.946.463 €	1.204.043 €	1.131.638 €	24.030.371 €
2012	4.195.624 €	5.911.137 €	5.181.860 €	1.269.939 €	263.910 €	2.290.054 €	1.540.889 €	4.651.717 €	913.381 €	1.282.965 €	27.501.475 €
2013	3.493.985 €	6.209.817 €	4.784.043 €	1.822.795 €	276.241 €	388.782 €	1.750.293 €	4.642.531 €	1.129.849 €	988.635 €	25.486.972 €
2014	3.307.062 €	5.256.919 €	3.417.940 €	2.230.347 €	267.212 €	742.442 €	1.886.264 €	4.231.120 €	886.285 €	1.032.654 €	23.258.245 €

Table 1 Development of research funding from 2004 to 2014 in different funding categories

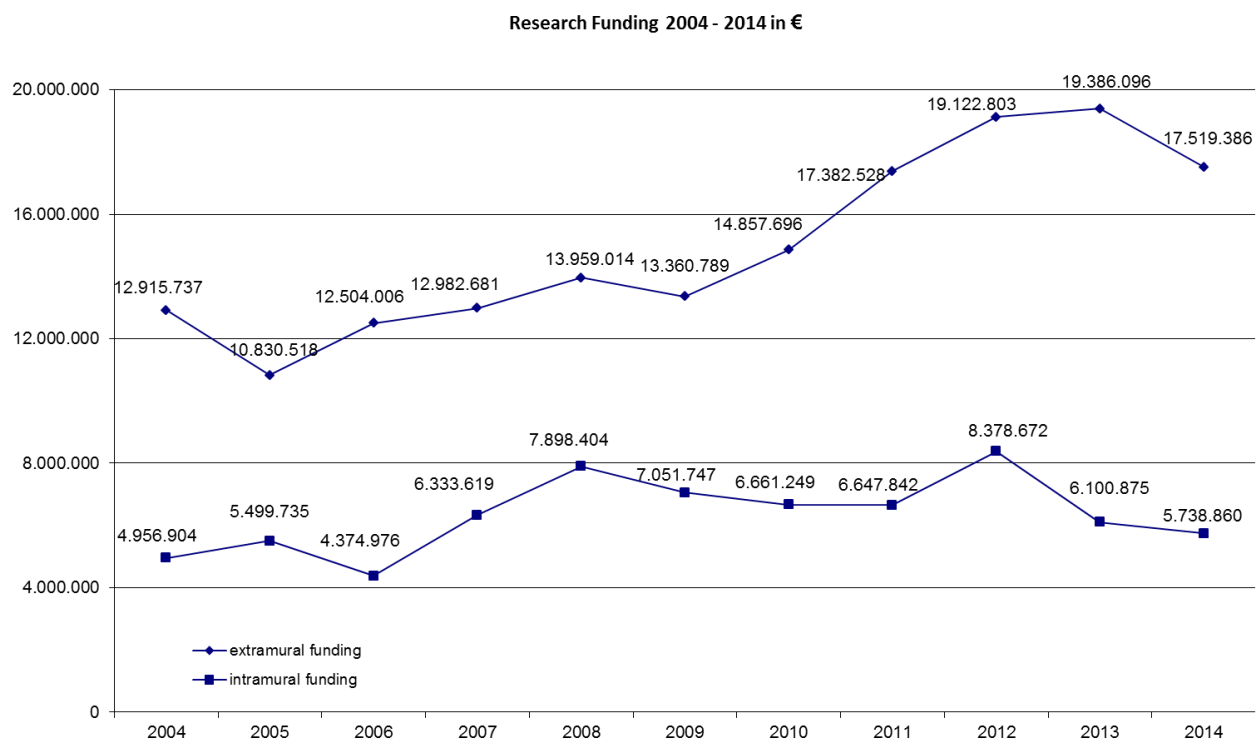


Fig. 6 Development of total research funding from 2004 to 2014

Institute of Anatomy and Cell Biology

Research Group Professor R. Kinscherf

Main fields of research

- Arteriosclerosis: Novel biomarkers in the blood
- Development and progression of Arteriosclerosis
- Role of GDF-15 in Arteriosclerosis
- Signal transduction of oxLDL
- Transfer of anti-angiogenic genes in Morris hepatoma: Molecular Mechanisms
- Signal transduction in tumor cachexia
- Molecular mechanisms of the anti-inflammatory, anti-proliferative and pro-apoptotic effects of phytopharmaka
- The plasma membrane Ca^{2+} -ATPase 2 (PMCA2) in breast cancer

Research projects

Title Hepatic factors of tumor cachexia: Metabolom-Analyses, ^{31}P -MR-Spectroscopy, as well as gene expression in perivenous and periportal hepatocytes and in Kupffer cells

Principal investigator(s) R. Kinscherf, W. Hildebrandt, G. A. Bonaterra, M. Schäfer, V. Fendrich, A. Kießling

Summary More than 50% of all tumor patients experience tumor cachexia (sarkopenia), which inversely influences quality of life and mortality. Early alterations of liver metabolism during sarcopenia – especially the negative nitrogen balance – are not clear. The aim of the study is to investigate the role of the liver during sarcopenia using an animal model, as well as human biopsies.

Funded by UKGM – University Medical Centre Giessen/Marburg

Funding period 2011-2013

Title Obstructive sleep apnoea syndrome (OSAS): Microcirculatory and metabolic changes of skeletal muscles

Principal investigator(s) W. Hildebrandt, R. Schulz, U. Koehler, N. Weissmann

Summary Hypoxia/Reoxygenation stress during obstructive sleep apnoea syndrome (OSAS) is suggested to be the reason for endothelial dysfunction and insulin resistance, which may result in loss of efficiency of heart and skeletal muscle. The aim of the study is to investigate molecular mechanisms of a reduced function of skeletal muscle during OSAS using an animal model, as well as human biopsies.

Funded by von Behring-Röntgen-Foundation

Funding period 2011-2013

Title Die Bedeutung parakrin freigesetzter Zytokine adulter kardialer Progenitorzellen für das Remodelling des insuffizienten Herzens

Principal investigator(s) Maxeiner, Wenzel, M Bette, Weigand, R Kinscherf, Böningand Schlüter

Summary Das beantragte Projekt hat zum Ziel, ein besseres Verständnis über die kardiale Wirkung parakriner Substanzen, die von CPCs freigesetzt werden, zu ermöglichen. Als Arbeitshypothese wird postuliert, dass die mögliche kardioprotektive Wirkung solcher Substanzen durch eine gezielte Interaktion verbessert werden kann und dass diese Wirkung auf das chronisch druckbelastete Herz abgestimmt werden muss.

Funded by von Behring-Röntgen-Foundation

Funding period 2012 – 2014

Title *In vitro* investigations of the possible protective effects of krill oil against lipopolysaccharide (LPS) treatment of human monocytes

Principal investigator R. Kinscherf

Summary The aim of the *in vitro* investigation is to determine the possible beneficial effects of krill oil (KO) in neutralizing lipopolysaccharide (LPS) or LPS binding.

Funded by B. Braun Melsungen AG (via TransMIT GmbH)

Funding period 2013 – 2014

Title Cytoprotective effects and impact on neuronal plasticity of STW 3-VI (St. John's wort) *in vitro*

Principal investigator R. Kinscherf

Summary The aim of our *in vitro* investigations is to determine the cytoprotective effects and impact on neuronal plasticity of STW 3-VI (St. John's wort) against cytotoxic substances.

Funded by Steigerwald GmbH (via TransMIT GmbH)

Funding period 2014 – 2016

Title *In vitro* cytoprotective effects of omega-3 fatty acids against cytotoxic drugs on human hepatocellular carcinoma cells, human kidney proximal tubule, murine intraglomerular mesangial or human lung adenocarcinoma cells.

Principal investigator R. Kinscherf

Summary The aim of our *in vitro* investigations is to determine the cytoprotective effects of omega-3 fatty acids against cytotoxic drugs on human hepatocellular carcinoma cells, human kidney proximal tubule, murine intraglomerular mesangial or human lung adenocarcinoma cells.

Funded by B.Braun Melsungen AG (via TransMIT GmbH)

Funding period 2014 – 2015

Most important publications

Mey L, Hörmann M, Schleicher N, Reuter P, Dönges S, **Kinscherf R**, Gassmann M, Gerriets T, Al-Fakhri N (2013) Neuropilin-1 modulates vascular endothelial growth factor-induced poly(ADP-ribose)-polymerase leading to reduced cerebrovascular apoptosis. *Neurobiol Dis* 59:111-25

Schwarz A, Wennemuth G, Post H, Brandenburger T, Aumüller G, Wilhelm B (2013). Vesicular transfer of membrane components to bovine epididymal spermatozoa. *Cell Tissue Res* 353(3):549-61

Bonaterre GA, Kelber O, Weiser D, **Kinscherf R** (2013) Mechanisms of the anti-proliferative and anti-inflammatory effects of the herbal fixed combination STW 5 (Iberogast®) on colon adenocarcinoma (HT29) cells in vitro. *Phytomedicine* 20:8-9

Schober A, Parlato R, Huber K, **Kinscherf R**, Hartleben B, Huber TB, Schütz G, Unsicker K (2013) Cell loss and autophagy in the extra-adrenal chromaffin organ of Zucker rats are regulated by glucocorticoid signalling. *J Neuroendocrinol* 25 (1): 34-47

Rossmann A, Mandic R, Heinis J, Hoeffken H, Kuessner O, **Kinscherf R**, Weihe E, Bette M (2014) Intraperitoneal oxidative stress in rabbits with papillomavirus-associated head and neck cancer induces tumoricidal immune response that is adoptively transferable. *Clin Cancer Res* 20(16):4289-301

Kunz P, Fellenberg J, Moskovszky L, Sápi Z, Krenacs T, Poeschl J, Lehner B, Szendrői M, Ewerbeck V, **Kinscherf R**, Fritzsche B (2014) Osteosarcoma microenvironment: whole-side imaging and optimized antigen detection overcome major limitations in immunohistochemical quantification. *PLoS One* 9(3):e90727

Farhat A, Malecki E, **Bonaterre GA**, Röthlein D, Wolf M, Schmitt J, Rosemeyer H, **Kinscherf R** (2014) Cytostatic/Cytotoxic effects of 5-fluorouridine nucleolipids on colon, hepatocellular and renal carcinoma cells: in vitro identification of a potential cytotoxic multi-anticancer drug. *Chem Biodivers* 11(3):469-82

Stern-Straeter J, **Bonaterre GA**, Juritz S, Birk R, Goessler UR, Bieback K, Bugert P, Schultz J, Hörmann K, **Kinscherf R***, Faber A* (2014) Evaluation of the effects of different culture media on the myogenic differentiation potential of adipose tissue- or bone marrow human mesenchymal stem cells. *Int J Mol Med* 33(1):160-70(* both are senior authors)

Research Group Professor E. Weihe

PD Dr. Michael Bette; Dr. Mirjam Bertoune; PD Dr. Burkhard Schütz; Dr. Martin K.-H. Schäfer; PD Dr. Reiner Westermann

Main fields of research

- Chemical coding of neurotransmission and neuroendocrine secretion
- Molecular and cellular mechanisms of preclinical and clinical pain
- Inflammation
- Neuroinfection (rabies, HIV/SIV encephalitis)
- Neuroimmune interactions and neurodegeneration (amyotrophic lateral sclerosis; Parkinson's disease)
- Neuropeptide signaling and pathophysiology; biological effects of ozone in cancer research
- Specialities: Core facility for molecular histology and laser microdissection (Schäfer/Weihe); cell-specific gene expression profiling; transgenic mouse models relevant for research on infection, inflammation, pain, cancer, diabetes and neurodegeneration

Research projects

Title VMAT2 as a target for imaging of beta-cell mass

Principal investigator(s) E. Weihe and M. Schäfer

Summary The main aim of the project was to evaluate species-specific expression patterns of the vesicular monoamine transporter 2 (VMAT2) in primate, pig and rodent pancreatic beta-cells, nerves and mast cells and to generate a new transgenic mouse model for beta-cell imaging with tetrabenazine based VMAT2 radioligands.

Funded by EU (FP7/2007-2013)

Funding period 2008-2013

Title Influence of the gene deficiency for calcitonin-gene related peptide alpha and pituitary adenylate cyclase activating peptide on the in vivo rabies virus infection

Principal investigator(s) M. Bertoune

Summary Aim of the project is to elucidate mechanisms for the biological effect of CGRP and PACAP during infection with rabies virus in the mouse model.

Funded by UKGM – University Medical Centre Giessen/Marburg

Funding period 2012-2013

Title Characterization of an astrocyte population susceptible for rabies virus

Principal investigator(s) M. Bertoune

Summary Aim of the project is to identify the molecular prerequisites that make a regionally defined population of fibrillary astrocytes in the

murine brain vulnerable to a mutated rabies virus vaccine strain.

Funded by Kempkes Foundation

Funding period 2012-2013

Title Involvement of peptidergic signaling pathways in ALS pathogenesis in human patients

Principal investigator(s) C. Ringer

Summary The disruption of the signaling pathways of PACAP and CGRP by genetic depletion resulted in a decelerated disease progression in the SOD1 mouse model of ALS. This study investigates if the two neuropeptides also influence ALS disease progression in humans.

Funded by Kempkes Foundation

Funding period 2012-2013

Title Mechanisms responsible for the selective vulnerability of CGRP expressing motoneurons in amyotrophic lateral sclerosis

Principal investigator(s) C. Ringer

Summary This study is based on the observation, that motoneurons expressing the neuropeptide CGRP selectively degenerate, whereas motoneurons without CGRP expression seemed to be resistant in the SOD1 mouse model of ALS. The aim is to clarify the underlying mechanisms of neuronal vulnerability and resistance, respectively, to ALS pathology.

Funded by German Society for Muscle diseases

Funding period 2012-2013

Title Regulation of the cholinergic gene locus in keratinocytes

Principal investigator(s) B. Schütz and E. Weihe

Summary The cholinergic gene locus (CGL) encodes two genes for proper cholinergic neuron function, i.e. choline acetyltransferase (ChAT) needed for the production of acetylcholine (ACh), and the vesicular acetylcholine transporter (VACHT) for regulated import of ACh into synaptic vesicles. We hypothesize that the transcriptional regulation of the CGL in the production and sequestration of keratinocyte ACh essentially differs from that found in neurons. In our project we thus aim to elucidate the regional, skin layer- and cell-specific activity of the CGL under physiological and pathophysiological situations (e.g. Inflammation, barrier function disturbances) in humans and rodent (mouse, rat) model systems, and the possibility of CGL regulation by exogenously applied substances using state of the art technologies (e.g. laser capture microdissection, qRT-PCR, in situ hybridization, transcriptome profiling).

Funded by LOEWE-Research Focus Giessen, Marburg, Frankfurt, "Non-neuronal cholinergic Systems", Project B3

Funding period 2012-2014

Title Impact of paracrine released cytokines for the remodeling of the insufficient heart

Principal investigator(s) R.Maxeiner, Wentzel and M. Bette

Summary Aim of this project is to proof the hypothesis that human cadial progenitor cells (CPC) exhibit it's therapeutic potential on remodeling and regeneration of the heart by the release of several cytokines. Main factors, identified by its potential to positively influence cardiac muscle contraction *in vitro*, are GDF-15, IL-6, IL-8, TIMP-1, and MCP-1. The impact of these factors on remodeling of the heart and on hypertension should be characterized in an *in vivo* rat model.

Funded by Von-Behring-Röntgen Foundation

Fundingperiod 2012-2014

Title German Lung Center (Deutsches Lungenzentrum, DLZ)

Principal investigator(s) E. Weihe

Summary The aim is to decipher the neuroimmune anatomy and role of neuropeptide and classical transmitter signaling in inflammatory and allergic airway diseases by using neuropeptide and neuropeptide receptor gene deficient mouse models (gene deficiencies for PACAP, PAC1, CGRP, RAMP1) and experimental stress conditions.

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2012-2015

Most important publications

Ringer C, Büning LS, Schäfer MK, Eiden LE, **Weihe E**, **Schütz B** (2013) PACAP signaling exerts opposing effects on neuroprotection and neuroinflammation during disease progression in the SOD1(G93A) mouse model of amyotrophic lateral sclerosis. *Neurobiol Dis* 54C:32-42

Schäfer MK, Hartwig NR, Kalmbach N, Kliez M, Anlauf M, Eiden LE, **Weihe E** (2013) Species-specific vesicular monoamine transporter 2 (VMAT2) expression in mammalian pancreatic beta cells: implications for optimising radioligand-based human beta cell mass (BCM) imaging in animal models. *Diabetologia* 56: 1047-1056

Makarova G, **Bette M**, Schmidt A, Jacob R, Cai C, Rodepeter F, Betz T, Sitterberg J, Bakowsky U, Moll R, Neff A, Sesterhenn A, Teymoortash A, Ocker M, Werner JA, Mandic R (2013) Epidermal growth factor-induced modulation of cytokeratin expression levels influences the morphological phenotype of head and neck squamous cell carcinoma cells. *Cell Tissue Res* 351:59-72

Krieg A, Mersch S, Boeck I, Dizdar L, **Weihe E**, Hilal Z, Krausch M, Möhlendick B, Topp SA, Piekorz RP,

Huckenbeck W, Stoecklein NH, Anlauf M, Knoefel WT (2014) New model for gastroenteropancreatic large-cell neuroendocrine carcinoma: establishment of two clinically relevant cell lines. *PLoS One* 9(2):e88713

Deckmann K, Filipowski K, Krasteva-Christ G, Fronius M, Althaus M, Rafiq A, Papadakis T, Renno L, Jurastow I, Wessels L, Wolff M, Schütz B, **Weihe E**, Chubanov V, Gudermann T, Klein J, Bschleipfer T, Kummer W (2014) Bitter triggers acetylcholine release from polymodal urethral chemosensory cells and bladder reflexes. *Proc Natl Acad Sci U S A* 111(22):8287-92

Rossmann A, Mandic R, Heinis J, Hoeffken H, Kuessner O, Kinscherf R, **Weihe E**, **Bette M** (2014) Intraperitoneal oxidative stress in rabbits with papillomavirus-associated head and neck cancer induces tumoricidal immuneresponse that is adoptively transferable. *Clin Cancer Res* 20(16):4289-301

Panneck AR, Rafiq A, Schütz B, Soultanova A, Deckmann K, Chubanov V, Gudermann T, **Weihe E**, Krasteva-Christ G, Grau V, Del Rey A, Kummer W (2014) Cholinergic epithelial cell with chemosensory traits in murine thymic medulla. *Cell Tissue Res* 358(3):737-48

Schütz B, **Schäfer MK**, Gördes M, Eiden LE, Weihe E (2014) Satb2-Independent Acquisition of the Cholinergic Sudomotor Phenotype in Rodents. *Cell Mol Neurobiol* 2014 Sep 20 [Epub ahead of print]

Research group Professor Y. Cetin

Main fields of research

It is well-known that heat-stable enterotoxins produced by *Escherichia coli* cause severe diarrhea that is a problem in various developing countries. These toxins activate a guanylatecyclase C-receptor localized in the mucous membrane of the gastrointestinal tract. Since the discovery of guanylin, an endogenous peptide isolated from the intestine and highly homologous to the short toxin peptides, it became obvious that this peptide is the true ligand of the guanylatecyclase C-receptor. To study the functional role of guanylin with regard to regulation of electrolyte/water secretion in the intestine, the working group analyzed various cellular signaling and effector proteins involved in guanylin action. Using molecular biology, immunochemical and immunohistochemical techniques, the expression of guanylin, guanylin-receptor guanylatecyclase C (GC-C), cystic fibrosis transmembrane conductance regulator (CFTR-) protein, cGMP-dependent Protein kinase GII (cGKII), and at least an anion exchanger type 2 (AE-2) was studied. Moreover, these proteins were detected at

the translational level and localized at the cellular level by specific antibodies to distinct cell types and functional membrane domains in the gastrointestinal tract.

Research projects

Title Expression and cellular localization of guanylin and uroguanylin and their functional coupling proteins in the rat kidney

Principal investigator(s) K. Schwabe & Y. Cetin

Summary This work demonstrates the expression and cellular localization of two related peptides guanylin and uroguanylin, their receptor guanylatecyclase C, as well as to the downstream signaling and effector proteins, i.e. protein kinase GII (Prkg2), CFTR, and the solute carrier family 4, anion exchanger, member 2 (Slc4a2) in the kidney of the rat. Guanylin, uroguanylin as well as Gucy2c, Prkg2, and CFTR are restricted to the epithelial cells of the tubules system in the renal cortex and in the inner stripes of the outer medulla (ISOM). Whereas Slc4a2 displayed an opposed distribution pattern; strong immunoreactivities in the tubule system of the cortex and in the inner medulla and no localization in the ISOM. We assume that guanylin/uroguanylin are synthesized in the tubules system of the kidney and were lumenally secreted into the urine, which activates the downstream signaling cascade as already described for the intestine.

Research group Professor B. Steiniger

Main fields of research

1. Cell kinetics of the monocyte-macrophage system in rats
2. Phenotype of lymphocytes, dendritic cells, endothelia and stromal cells in human primary and secondary lymphatic organs
3. Three-dimensional reconstruction of microvessels by means of serial sections
4. Cell composition of the human dental pulp and bone marrow

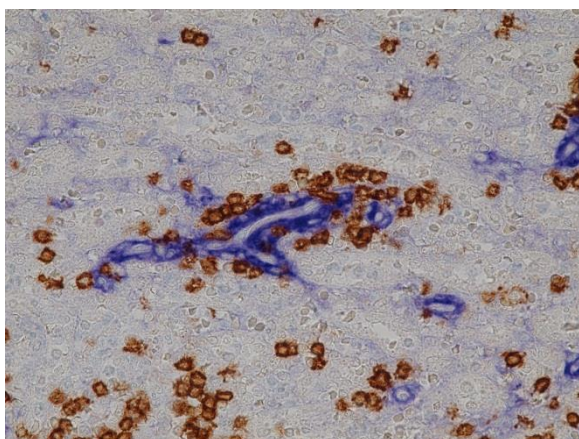
Research projects

Title Analysis of capillary sheaths and three-dimensional reconstruction of microvessels in human spleens

Principal investigator B. Steiniger

Summary The human splenic microvasculature is composed of arterioles, capillaries, venous sinuses and venules. Certain splenic capillaries are covered by so-called capillary sheaths of unknown cellular composition. We demonstrate that capillary sheaths consist of endothelial cells, pericytes, specialized stromal sheath cells, macrophages and B-lymphocytes. Capillary sheaths and periaarteriolar regions belong to the splenic B-lymphocyte

compartment scaffolded by phenotypically distinct stromal cells.



CD271⁺ stromal cells (blue) and CD20⁺ B-lymphocytes (brown) forming a human splenic capillary sheath

Title Stromal cells of T- and B-cell regions in human spleens

Principal investigator B. Steiniger

Summary We define the phenotype of a so far unknown third stromal cell type of the human splenic white pulp which exists in addition to fibroblastic reticulum cells of T-lymphocyte zones and follicular dendritic cells of B-lymphocyte follicles. This third cell type is located at the surface of the white pulp, especially at the surface of follicles, and expresses the mucosal cell adhesion molecule MAdCAM-1.

Title Microscopic anatomy of the human bone marrow

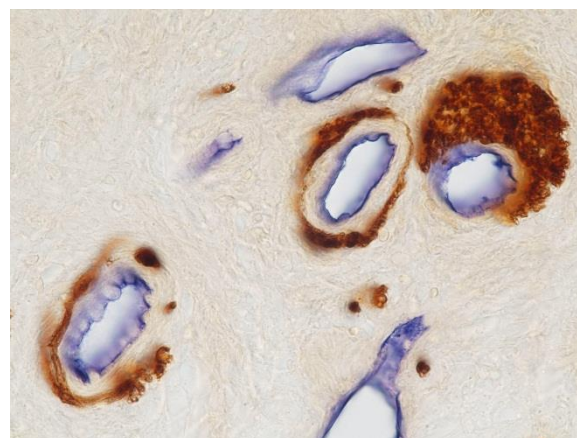
Principal investigator(s) B. Steiniger, V. Stachniss and V. Wilhelmi

Summary In cooperation with the clinics of orthopaedics and of orofacial surgery a special procedure for embedding large undecalcified bone marrow specimens (femoral head, iliac crest) in a special methacrylate was established. Using this method, undecalcified serial bone sections may be cut with a conventional microtome, stained by immunohistological procedures and reconstructed in three dimensions.

Title Microanatomy of the human dental pulp

Principal investigator(s) B. Steiniger & V. Stachniss

Summary The arrangement of nerves and arterioles in the dental pulp of human molars was reconstructed from serial ground sections. The majority of dental pulp arterioles were found embedded in myelinated nerve fibre bundles.



S100⁺ Schwann cells and CD34⁺ endothelial cells in arteriole/nerve associations of a human molar dental pulp. 25 µm-thick undecalcified ground tooth section

Most important publications

Steiniger BS, Bubel S, Böckler W, Lampp K, Seiler A, Jablonski B, Guthe M, **Stachniss V** (2013) Immunostaining of pulpal nerve fibre bundle/arteriole associations in ground serial sections of whole human teeth embedded in Technovit® 9100. *Cells Tissues Organs* 198:57-65

Steiniger BS, Seiler A, Lampp K, **Wilhelmi V**, **Stachniss V** (2014) B lymphocyte compartments in the human splenic red pulp: capillary sheaths and periaarteriolar regions. *Histochem Cell Biol* 141: 507-518

Steiniger BS, **Wilhelmi V**, Seiler A, Lampp K, **Stachniss V** (2014) Heterogeneity of stromal cells in the human splenic white pulp. Fibroblastic reticulum cells, follicular dendritic cells and a third superficial stromal cell type. *Immunology* 143:462-477

General information about the institute

Research funding 255.365,91 €

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Director: Professor Dr. Eberhard Weihe

Institute of Molecular Biology and Tumorbiology

Research Group Professor R. Müller

and the associated research group of Dr. Matthias Lauth

Main fields of research

Rolf Müller' research projects are focused on signaling networks and transcriptional regulation in human ovarian cancer in the context of therapy resistance, the tumor microenvironment and tumor metabolism (cooperation with Drs. Silke Reinartz and Uwe Wagner, Clinic for Gynecology). In addition, the group works on mechanisms of transcriptional regulation by the nuclear receptor PPAR β/δ , in particular its role in macrophage polarization, its interaction with cytokine signaling pathways and the evaluation of the therapeutic potential of newly developed inhibitory ligands.

Matthias Lauth's work is centered on the regulation and role of the Hedgehog signaling pathways in tumor cells and their crosstalk with the tumor stroma.

Research projects

Title Chromatin regulation by the nuclear receptor PPAR β/δ

Principal investigator(s) R. Müller

Summary The ligand-regulated nuclear receptor peroxisome proliferator-activated receptor β/δ (PPAR β/δ) can both activate and repress transcription, but the regulation, mechanistic principles and biological consequences of these functions are only partly understood. By using a combination of chromatin immunoprecipitation (ChIP) sequencing and transcriptional profiling we have defined distinct types of transcriptional responses of target genes to PPAR β/δ ligands or PPAR β/δ depletion. Elucidation of the molecular basis of these distinct target gene responses is the goal of this project.

Funded by DFG – German Research Foundation
Funded period 2011 – 2015

Title Design, synthesis, and molecular characterisation of selective inverse agonists and antagonists of PPAR β/δ

Principal investigator(s) T. Adhikary & W. Diederich, Institute of Pharmaceutical Chemistry

Summary We developed highly specific inverse agonists and antagonists of the nuclear receptor PPAR β/δ . The binding mode and induced conformational changes of the receptor are elucidated by X-ray crystallography, and specificity and bioavailability of the compounds are optimized. The inverse agonists block the upregulation of transcription of PPAR β/δ target genes by other

transcription factors in a dominant manner via an unknown mechanism; this is being investigated with biochemical and genetic means. In vitro data derived from primary human stromal cell cultures shows that these novel ligands are promising candidates for clinical use in targeted approaches against neoplastic and metabolic pathophysiological states.

Funded by DFG – German Research Foundation
Funding period 2013 – 2016

Title Suppression of oncogenic signaling and inhibition of cancer cell invasion by inhibition of PPAR β/δ

Principal investigator(s) R. Müller, D. Brandt & R. Grosse, Pharmacological Institute

Summary Besides its established functions in intermediary metabolism and developmental processes, the nuclear receptor PPAR β/δ plays a less defined role in tumorigenesis. We identified a function for PPAR β/δ in cancer cell invasion. We found that inhibitory ligands for PPAR β/δ strongly diminish the serum- and TGF β -induced invasion of MDA-MB-231 human breast cancer cells into a three-dimensional matrigel matrix. ChIP-Seq and transcriptome analyses identified which identified the gene encoding angiopoietin-like 4 (*ANGPTL4*) as the major transcriptional PPAR β/δ target in these cells. We could also show that repression of *ANGPTL4* transcription by inverse PPAR β/δ agonists is functionally linked to the inhibition of cancer cell invasion into a three-dimensional matrix. These findings indicate that a PPAR β/δ – *ANGPTL4* pathway is involved in the regulation of tumor cell invasion and that its pharmacological manipulation by inverse PPAR β/δ agonists is feasible.

Funded by DFG, SFB TRR17 – German Research Foundation, Transregional Collaborative Research Centre 17
Funded period 2004 – 2013

Title Regulation of IL-1 β signaling by cytoplasmic PPAR β/δ

Principal investigator R. Müller

Summary In cooperation with M. Kracht's group (Gießen) we discovered an unexpected cytoplasmic function of PPAR β/δ . We found that silencing of PPAR β/δ expression interfered with the expression of a large subset of interleukin-1 β (IL-1 β)-induced target genes in HeLa cells, which was preceded by an inhibition of the IL-1 β -induced phosphorylation of TAK1 and its downstream effectors, including the NF κ B α inhibitor I κ B α (NFKBIA) and the NF κ B α subunit p65 (RELA). PPAR β/δ enhances the interaction between TAK1 and the small heat-shock

protein HSP27, a known positive modulator of TAK1-mediated IL-1 β signaling. Our observations suggest that PPAR β/δ plays a role in the assembly of a cytoplasmic multi-protein complex containing TAK1, TAB1, HSP27 and PPAR β/δ , and thereby participates in the NF κ B response to IL-1 β .

Funded by DFG – German Research Foundation

Funding period 2011 – 2015

Title Phenotype and clinical relevance of ascites-associated macrophages in human ovarian carcinoma

Principal investigator(s) S. Müller-Brüsselbach & S. Reinartz, Clinic for Gynecology

Summary Ovarian cancer is typically accompanied by the occurrence of malignant ascites containing large number of macrophages. It has been suggested that these tumor-associated macrophages (TAMs) are skewed to alternative polarization (M2) and thereby play an essential role in therapy resistance and immune suppression. We have investigated the nature, regulation and clinical correlations of TAM polarization in serous ovarian cancer. Although surface expression of the M2-marker CD163 on TAMs was inversely associated with relapse-free survival (RFS), global gene expression profiles revealed a mixed-polarization phenotype unrelated to the M1/M2 classification. CD163 surface expression also correlated with the ascites levels of IL-6 and IL-10, both cytokines induced CD163 expression, and their ascites levels showed a clear inverse association with RFS. These findings define a subgroup of patients with high CD163 expression, high IL-6 and/or IL-10 levels and poor clinical outcome.

Funded by Sander Foundation and UKGM – University Hospital Giessen and Marburg

Funding period 2012 – 2014

Title Function and therapeutic potential of PPAR β/δ in tumor-associated macrophages in human ovarian carcinoma

Principal investigator(s) S. Müller-Brüsselbach, T. Adhikary & S. Reinartz, Clinic for Gynecology

Summary To elucidate its function of PPAR β/δ in tumor-associated macrophages (TAMs) we determined the PPAR β/δ -regulated transcriptome and cistrome for TAMs from ovarian carcinoma patients. Comparison with monocyte-derived macrophages showed that the vast majority of direct PPAR β/δ target genes are upregulated in TAMs and largely refractory to synthetic agonists, but repressible by inverse agonists. These include cell type-selective genes associated with immune regulation and tumor progression. Lipidomic analysis of malignancy-associated ascites revealed that this deregulation is caused by high concentrations of polyunsaturated fatty acids acting as potent

PPAR β/δ agonists. These observations suggest that the deregulation of PPAR β/δ target genes by ligands of the tumor microenvironment contributes to the pro-tumorigenic polarization of ovarian carcinoma TAMs. This conclusion is supported by the association of high *ANGPTL4* expression with a shorter relapse-free survival in serous ovarian carcinoma.

Funded by Sander Foundation

Funding period 2012 – 2014

Title Regulation of Hedgehog signaling by the DYRK1B kinase

Principal investigator(s) M. Lauth

Summary The aim of this project has been to investigate how the tumor-associated DYRK1B kinase affects mammalian Hedgehog signaling. The group could show that Dyrk1b functions as a negative regulator of the pathway. Furthermore, a molecular framework and a pathophysiological function for this interaction could be established.

Funded by DFG – German Research Foundation

Funding period 2010 – 2013

Title Evaluation of DYRK1A kinase as a therapeutic target in pancreatic carcinoma

Principal investigator M. Lauth

Summary Previous work suggests an oncogenic role of the DYRK1A kinase in Hedgehog-driven malignancies. In the present project, our group investigates the molecular mechanisms of the Hedgehog-DYRK1A relationship and the impact of this crosstalk on the pathway activity in normal and in cancer cells.

Funded by Deutsche Krebshilfe

Funding period 2011 – 2015

Title Inhibition of Notch and/or Hedgehog signaling pathways in the therapy of fibrosis

Principal investigator M. Lauth

Summary Both, Hedgehog and Notch signaling are involved in the development of several fibrotic conditions, but their functional interaction remains poorly understood. In collaboration with the group of Dr. Borggrefe (Institute of Biochemistry, Uni Gießen) we are investigating the mechanisms of Hedgehog-Notch crosstalk in order to understand the cellular interactions between these two pathways.

Funded by UKGM – University Hospital Giessen and Marburg

Funding period 2013 – 2015

Title GLI transcription factors: A suitable target structure in the future therapy of pancreatic cancer?

Principal investigator M. Lauth

Summary The Hedgehog pathway and its final effectors, the GLI proteins, have been implicated in

the etiology of pancreatic cancer. However, the relevance of Hedgehog/GLI in tumor cells versus the stroma is not clear. In this project, we have elucidated novel and unexpected tumor-halting functions of GLI1 in pancreatic cancer cells, raising questions about the utility of a Hedgehog/GLI directed therapy in this type of cancer. In line with our data, in vivo results from mouse models and patient data have led to the abortion of clinical trials using Hedgehog inhibitors in pancreatic cancer.

Funded by UKGM – University Hospital Giessen and Marburg

Funding period 2012 – 2014

Title Evaluating novel target structures in the therapy of lung fibrosis

Principal investigator M. Lauth

Summary Hedgehog signaling is involved in the development of lung fibrosis, but its role is not well defined. In collaboration with the group of Dr. Wygrecka (Institute of Biochemistry, Uni Gießen) we are investigating the Hedgehog pathway in lung fibrosis and test novel targeting approaches to combat this disease.

Funded by von Behring Röntgen Foundation

Funding period 2014 – 2016

Title Novel ciliary regulatory circuits in Hedgehog-dependent tumor entities

Principal investigator M. Lauth

Summary The primary cilium is crucial for proper Hedgehog signaling. However, the Hedgehog-induced molecular mechanisms within primary cilia are currently not well resolved. In this project, we characterize novel ciliary candidate molecules which we have previously identified and test their relevance in Hedgehog-driven cancer, such as medulloblastoma.

Funded by DFG – German Research Foundation

Funding period 2013 – 2016

Title Therapy of medulloblastoma (Research award)

Principal investigator M. Lauth

Summary Medulloblastoma is the most frequent malignant brain tumor in children and a large fraction of this cancer grows in a Hedgehog-dependent manner. Current selective therapies target the Hedgehog pathway component Smoothened, leading to good clinical responses but also to the development of drug-resistant clones, necessitating the need to identify additional drug targets. In this project, we have identified HDAC6 as an overexpressed gene in medulloblastoma and characterized this protein a novel drug target in the oncogenic Hedgehog signaling pathway.

Funded by Stiftung Tumorforschung Kopf-Hals, Römerwaldklinik

Funding period since 2014

Most important publications

AG Müller

Stockert J, Wolf A, Kaddatz K, Schnitzer E, Finkernagel F, Meissner W, **Müller-Brüsselbach S**, Kracht M, **Müller R** (2013) Regulation of TAK1/TAB1-mediated IL-1 β signalling by cytoplasmic PPAR β / δ . *PLoS ONE* 8(4):e63011

Adhikary T, Brandt DT, Kaddatz K, Stockert J, Finkernagel F, Naruhn S, Meissner W, Obert J, Lieber S, Scharfe M, Jarek M, Toth PM, Scheer F, Diederich WE, Reinartz S, Grosse R, **Müller-Brüsselbach S**, **Müller R** (2013) Inverse PPAR β / δ agonists suppress oncogenic signaling to the *ANGPTL4* gene and inhibit cancer cell invasion. *Oncogene* 32:5241-5252

Adhikary T, **Müller R** (2013) In vivo studies of PPAR-chromatin interactions: chromatin immune-precipitation for single-locus and genome-wide analyses. *Meth Mol Biol* 952: 175-185

Reinartz S, Schumann T, Finkernagel F, Wortmann A, Jansen JM, Meissner W, Krause M, Schwörer A-M, Wagner U, **Müller-Brüsselbach S**, **Müller R** (2014) Mixed-polarization phenotype of ascites-associated macrophages in human ovarian carcinoma: correlation of CD163 expression, cytokine levels and early relapse. *Int J Cancer* 134: 32-42

AG Lauth

Tariki M, Wiczorek SA, Schneider P, Bänfer S, Veitinger S, Jacob R, Fendrich V, **Lauth M** (2013) RIO kinase 3 acts as a SUFU-dependent positive regulator of Hedgehog signaling. *Cell Signal* 25(12):2668-75

Tariki M, Dhanyamraju PK, Fendrich V, Borggrete T, Feldmann G, **Lauth M** (2014) The Yes-associated protein controls the cell density regulation of Hedgehog signaling. *Oncogenesis* 3:e112

Knoop RF, Sparn M, Waldmann J, Plassmeier L, Bartsch DK, **Lauth M**, Hudemann C, Fendrich V. (2014) Chronic Pancreatitis and Systemic Inflammatory Response Syndrome Prevent Impact of Chemotherapy with Gemcitabine in a Genetically Engineered Mouse Model of Pancreatic Cancer. *Neoplasia* 16(6):463-70

Dhanyamraju PK, Holz PS, Finkernagel F, Fendrich V, **Lauth M** (2014) Histone deacetylase 6 represents a novel drug target in the oncogenic Hedgehog signaling pathway. *Molecular Cancer Therapeutics*; in press

Research Group Professor A. Brehm

Main fields of research

Chromatin structure plays an important role in regulating the activity of eukaryotic genomes in both healthy and diseased cells. We investigate enzymes and protein factors that establish, modulate and maintain chromatin structures to regulate gene expression by using biochemical and genomic approaches.

Research projects

Title ATP-dependent chromatin remodeling complexes in *Drosophila*, TR81 Project A1

Principal investigator(s) A. Brehm

Summary We have unraveled molecular mechanisms that recruit the ATP-dependent Chromatin remodeler dMi-2 to stress-induced genes. This work has uncovered an unexpected role of Poly-ADP-Ribose and RNA in guiding dMi-2 to heat shock genes.

Funded by DFG, SFB TRR81 – German Research Foundation, Transregional Collaborative Research Centre 81: Chromatin changes in differentiation and malignancies

Funded period 2010 – 2014

Title Recruitment mechanisms of the chromatin remodeler dMi-2/CHD4, TR81 Project A1

Principal investigator(s) A. Brehm

Summary We are using a comprehensive approach to identify different molecular mechanisms used to target dMi-2 to chromatin.

Funded by DFG, SFB TRR81 – German Research Foundation, Transregional Collaborative Research Centre 81: Chromatin changes in differentiation and malignancies

Funded period 2014 – 2018

Title Mechanism of chromatin regulation by the LINT complex

Principal investigator(s) A. Brehm

Summary We have characterised composition and function of LINT, a chromatin repressor that contains the *Drosophila* tumour suppressor L(3)mbt and the corepressor CoREST.

Funded by DFG – German Science Foundation, Research Grant 2102/6-1

Funded period 2009 - 2013

Title Functional characterisation of LINT and other CoREST-containing complexes

Principal investigator(s) A. Brehm

Summary We are using systematic approaches to identify and characterise dCoREST-containing protein complexes that regulate chromatin structure and gene activity.

Funded by DFG – German Science Foundation, Research Grant 2102/6-2

Funded period 2013 – 2016

Title IRTG 1384 Project

Principal investigator(s) A. Brehm

Summary We have analysed the functional and physical interactions between the chromatin remodeler dMi-2 and the nuclear hormone receptor EcR.

Funded by DFG, International Research Training Group/IRTG 1384: Enzymes and multienzyme complexes acting on nucleic acids

Funded period 2011 – 2015

Most important publications

Meier K, Brehm A (2014) Chromatin regulation: How complex does it get? *Epigenetics* 9(11): 1485-95

Bergs JW, Neuendorff N, van der Heijden G, Wassenaar E, Rexin P, Elsässer HP, Moll R, Baarends WM, Brehm A (2014) Differential expression and sex chromosome association of CHD3/4 and CHD5 during spermatogenesis. *PLoS One* 9(5):e98203

Research Group Professor G. Suske

Main fields of research

We study physiological and mechanistic aspects of members the Sp family of transcription factors, which are key transcriptional regulators of various developmental and cellular processes. Particularly, we focus on posttranslational modifications and on chromatin-based mechanisms that determine specificity of individual Sp family members.

Research projects

Title Molecular mechanisms of transcriptional control by Sp2

Principal investigator(s) G. Suske

Summary In this project we focus on the transcription factor Sp2, which is the least characterized Sp family member. By the combination of biochemical, molecular biology and cell biology techniques we aim to obtain mechanistic clues towards understanding the mode of action of Sp2.

Funded by DFG – German Research Foundation, Research Grant SU 102/8-1

Funding period 2012 – 2015

Title Mechanisms of SUMO-dependent gene silencing

Principal investigator(s) G. Suske

Summary SUMO modification of many transcription factors including Sp3 is linked to transcriptional

repression. Our previous investigations revealed that SUMO modification of transcription factors can act as a molecular beacon for the recruitment of chromatin-modifying machineries that impose epigenetic silencing on target genes. Following the mechanistic clues provided by these findings we analyze further the role of SUMOylation in gene silencing.

Funded by DFG, German Research Foundation, Transregional Collaborative Research Centre 81: Chromatin changes in differentiation and malignancies

Funding period 2010 – 2014

Title Recruitment and mechanisms of action of the L3MBTL2-containing non-canonical PRC1 complex

Principal investigator(s) G. Suske

Summary The polycomb group protein Lethal(3) Malignant Brain Tumor-Like 2 (L3MBTL2) is a subunit of the non-canonical PRC1.6 complex. Genome-wide analysis of L3MBTL2 occupancy in chromatin revealed that L3MBTL2 is predominantly bound to proximal promoter regions. We aim to analyse the mode of recruitment to chromatin, and to decipher the repression mechanisms mediated by L3MBTL2 and the entire PRC1.6 complex.

Funded by DFG, German Research Foundation, Transregional Collaborative Research Centre 81: Chromatin changes in differentiation and malignancies

Funding period 2014 – 2018

Title Integrated Research Training Group on Epigenetics and Chromatin

Principal investigator(s) G. Suske

Summary Within the TRR81, the Integrated Research Training Group provides a platform for high-level structured training on epigenetics and chromatin accompanied by a career development programme. The daily research activities of the PhD students are complemented by lectures, seminars, courses, workshops and retreats including Dutch-German meetings and exchanges. Particular emphasis is placed on fostering the independence of the PhD students.

Funded by DFG, German Research Foundation, Transregional Collaborative Research Centre 81: Chromatin changes in differentiation and malignancies

Funding period: 2010 – 2014 and 2014 - 2018

Most important publications

Diezko R, **Suske G** (2013) Ligand binding reduces SUMOylation of the peroxisome proliferator-activated receptor γ (PPAR γ) activation function 1 (AF1) domain. *PLoS ONE* 8: e66947

Stielow C, Stielow B, Finkernagel F, Scharfe M, Jarek M, **Suske G** (2014) SUMOylation of the polycomb group protein L3MBTL2 facilitates repression of its target genes. *Nucleic Acids Res* 42:3044-3058

Research Group Professor U. M. Bauer

Main fields of research

Protein arginine methyltransferases (PRMTs) play an important role in the regulation of chromatin structure and chromatin-dependent processes. In mammals, the enzymes constitute a family of 9 members (PRMT1-9), which share a conserved catalytic domain and perform mono- and dimethylation of arginine residues in proteins. A subgroup of PRMTs methylates histones as well as non-histone chromatin proteins. Like other chromatin-modifying enzymes, they function as transcriptional coregulators, contribute either to activation or repression of gene expression and thereby control important cellular processes, such as proliferation, differentiation and apoptosis. We wish to elucidate the molecular function of PRMTs in the regulation gene expression.

Research projects

Title Functional analysis of the histone arginine methyltransferase PRMT6, TR81 Project A3

Principal investigator(s) U. - M. Bauer

Summary In our previous work we identified PRMT6 as the major mammalian methyltransferase for histone H3 R2. We established that the enzyme counteract H3 K4 trimethylation and thereby transcriptional activation. Important questions, such as how PRMT6 is recruited to chromatin, which are the genome-wide target genes of PRMT6, is PRMT6 part of a multi-subunit corepressor complex, and what are the biological functions of PRMT6, are still unsolved, which we would like to unravel in this project.

Funded by DFG, SFB TRR81 – German Science Foundation, Transregional Collaborative Research Centre 81, Chromatin changes in differentiation and malignancies

Funding period 2010 – 2014

Title Transcriptional control by protein arginine methylation

Principal investigator(s) U. - M. Bauer

Summary We are characterizing the functional interaction between the chromatin remodeller CDH3/4CHD4 and PRMT4.

Funded by DFG – German Research Foundation, Research Grant BA 2292/1-3

Funding period 2013 – 2016

35043 Marburg

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Director: Professor Dr. Rolf Müller

Title Epigenetics of the nuclear oncoprotein Ski in AML

Principal investigator(s) U. - M. Bauer, A. Neubauer, S. Stiewe

Summary We are characterizing the function of the corepressor Ski in acute myeloid leukemia.

Funded by DFG – German Research Foundation, Research Grant SPP1463

Funded period 2012 – 2015

Title Deciphering the role of protein arginine methyltransferases (PRMTs) in lung development and lung cancer.

Principal investigator(s) U. - M. Bauer, T. Braun (MPI, Bad Nauheim)

Summary We are characterizing the function of PRMT5 in lung development and cancer.

Funded by LOEWE priority research program “Lung Center”, Grant

Funded period 2013 – 2015

Title Genome-wide mapping of histone modifications in the establishment of disease phenotype pulmonary arterial hypertension

Principal investigator(s) U. - M. Bauer, S. Pullamsetti (MPI, Bad Nauheim)

Summary We are characterizing the function of HDAC1, 2 and 8 in idiopathic pulmonary arterial hypertension.

Funded by LOEWE priority research program “Lung Center”, Grant

Funded period 2013 – 2015

Most important publications

Streubel G, Bouchard C, Berberich H, Zeller MS, Teichmann S, Adamkiewicz J, Müller R, Klempnauer K-H, **Bauer UM** (2013) PRMT4 Is a Novel Coactivator of c-Myb-Dependent Transcription in Haematopoietic Cell Lines. *PLoS Genet* 9, e1003343

General information about the institute

Research funding 3.174.022,55 €

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35032 Marburg

and

Center for Tumor Biology and Immunology (ZTI)

Hans-Meerwein-Str. 3

Institute of Physiological Chemistry

Research Group Professor G. Schratt

Main fields of research

Our laboratory is interested in the molecular mechanism of synapse development and plasticity in mammalian neurons, with a special focus on the role of microRNA-dependent control of local mRNA translation in the synpto-dendritic compartment. We are studying the function of microRNAs in Hebbian and homeostatic forms of synaptic plasticity and its implications for memory formation, using both primary cell culture and animal models. Moreover, we are investigating the role of aberrant microRNA function in neurological diseases characterized by synaptic dysfunction, including cognitive impairments, epilepsy and depression. Finally, we are interested in the mechanisms that control miRNA function at synapses, focusing on activity-dependent miRNA transport and processing.

Research projects

Title microRNA function in homeostatic plasticity in the mammalian brain

Principal investigator(s) G. Schratt

Summary The aim of this project is to investigate the role of the miR379-410 cluster in homeostatic forms of plasticity in the developing mammalian brain. Using primary neurons, we demonstrated an important contribution of the miR379-410 cluster to synaptic downscaling (Fiore et al., 2014). We will use genetic mouse models to study the effects of miR379-410 loss-of-function in experience-dependent development of the mouse visual cortex and Di George Syndrome mice, a model for schizophrenia.

Funded by European Research Council (EU FP7, Starting Grant)

Funded period 2010 – 2015

Title Molecular mechanisms underlying dendritic transport and processing of neuronal microRNAs

Principal investigator(s) G. Schratt

Summary The aim of this project is to characterize the molecular mechanisms that are responsible for the regulated trafficking of microRNA precursors to dendrites and for the activity-dependent processing near synapses of hippocampal neurons. We are also investigating the relevance of these mechanisms for synaptic plasticity. A study describing an RNA-binding protein that is important for the transport of the synaptic miR-134 has already been published (Bicker et al., 2013)

Funded by DFG, SFB 593 – German Research Foundation, Collaborative Research Centre 593

Funded period 2011 - 2014

Title The function of microRNA-dependent regulation of Ube3a in mammalian synapse development

Principal investigator(s) G. Schratt, R. Fiore

Summary The aim of this project is to study the regulation by microRNAs of a neuronal ubiquitin ligase (Ube3a) which is mutated in Angelman Syndrome, a neurodevelopmental disorder characterized by mental retardation and autism. In particular, we are investigating the regulation of the miR379-410 cluster by a specific Ube3a transcript isoform by a ceRNA mechanism.

Funded by UKGM – University Medical Centre Giessen / Marburg

Funded period 2012 - 2014

Title microRNAs in the pathogenesis, treatment and prevention of epilepsy “EpimiRNA”

Principal investigator(s) G. Schratt

Summary The aim of this project is to identify novel miRNAs involved in the development of epilepsy and to characterize their mode of action, focusing on the regulation of synapse structure and function. Moreover, a screening platform will be established to identify natural compounds with anti-epileptogenic activity targeting microRNAs.

Funded by European Union (EU FP7, HEALTH)

Funded period 2013 – 2018

Title microRNAs as regulators of neuroplasticity in affective disorders

Principal investigator(s) G. Schratt

Summary The aim of this project is to identify microRNAs involved in the regulation of neuronal homeostasis with relevance for affective disorders, including bipolar disorder and major depression. Parallel small RNA sequencing studies in humans and rats are performed to delineate common deregulated miRNAs in depressed human subjects and rat models of affective disorders.

Funded by DFG, FOR2107 – German Research Foundation, Researcher Group 2107

Funded period 2014 – 2017

Most important publications

Bicker S, Khudayberdiev S, Weiss K, Zocher K, Baumeister S, **Schratt G** (2013) The DEAD-box helicase DHX36 mediates dendritic transport of the neuronal precursor-microRNA-134. *Genes Dev*

27:991-996

Khudayberdiev S, Zampa F, Rajman M, **Schratt G** (2013) A comprehensive characterization of the nuclear microRNA repertoire of post-mitotic neurons. *Front Mol Neurosci* 6:43

Forstner AJ, Degenhardt F, **Schratt G**, Nöthen MN (2013) MicroRNAs as the cause of schizophrenia in 22q11.2 deletion carriers, and possible implications for idiopathic disease: a mini-review. *Front Mol Neurosci* 6:47

Fiore R, Rajman M, Schwale C, Bicker S, Antoniou A, Bruehl C, Draguhn A, **Schratt G** (2014) miR-134-dependent regulation of Pumilio2 is necessary for homeostatic synaptic depression. *EMBO J* 33:2231-46

Aksoy-Aksel A, Zampa F, **Schratt G** (2014) microRNAs and synaptic plasticity – a mutual relationship. *Phil Trans R Soc Lond B* 369:1652

Bicker S, Lackinger M, Weiss K, **Schratt G**. (2014) microRNA-132, -134, and -138: A microRNA troika rules in neuronal dendrites. *Cell Mol Life Sci* 71:3987-4005

Schratt G (2014) Neurobiology: A molecular knife to dice depression. *Nature* 516:7529

Research Group Professor M. Rust

Main fields of research

Neuronal actin dynamics is crucial for a number of processes that are essential for brain development and functionality and that ultimately control behavior, e. g. neuronal migration and differentiation, synaptogenesis, neurotransmitter release, or synaptic plasticity. However, only little is known about the actin-binding proteins and upstream regulatory mechanisms that control actin dynamics in neurons. By exploiting gene-targeted mice, we aim to identify novel regulators of neuronal actin dynamics and to comprehensively characterize their function in the brain.

Research projects

Title Functional role of the actin-binding proteins CAP1 and CAP2 in the mammalian brain

Principal investigator(s) M. Rust

Summary Recent studies revealed a role for the actin-binding proteins CAP1 and CAP2 in actin dynamics of non-neuronal cells. We found a broad expression for both proteins in the developing and mature mouse brain. By exploiting gene-targeted mice, we aim to characterize the function of CAP1 and CAP2 in the mouse brain, focusing on neuronal

migration and differentiation, synaptic physiology, and behavior.

Funded by UKGM – University Medical Centre Giessen / Marburg

Funded period 2014 – 2015

Most important publications

Wolf M, Zimmermann AM, Görlich A, Gurniak CB, Sassoè-Pognetto M, Friauf E, Witke W, **Rust MB** (2014) ADF/cofilin controls synaptic actin dynamics and regulates synaptic vesicle mobilization and exocytosis. *Cereb Cortex*, 2014 Apr 25 (Epub ahead of print)

Zimmermann AM, Jene T, Wolf M, Görlich A, Gurniak CB, Sassoè-Pognetto M, Witke W, Friauf E, **Rust MB** (2014) ADHD-like phenotype in a mouse model with impaired synaptic actin dynamics. *Biol Psychiatry*, 2014 Mar 21 (Epub ahead of print)

Kullmann JA, Wickertsheim I, Minnerup L, Costell M, Friauf E, **Rust MB** (2014) Profilin1 activity in cerebellar granule neurons is required for radial migration *in vivo*. *Cell Adh Migr*, 2014 Dec 12 (Epub ahead of print)

Pirone A, Kurt S, Zuccotti A, Rüttiger L, Pilz P, Brown D, Franz C, Schweizer M, **Rust MB**, Rübsamen R, Friauf E, Knipper M, Engel J (2014) $\alpha_2\delta_3$ is essential for normal structure and function of auditory nerve synapses and is a novel candidate for auditory processing disorders. *J Neurosci* 34(2): 434-445.

Önel SF, **Rust MB**, Jacob R, Renkawitz-Pohl R (2014) Tethering membrane fusion: Common and different players in myoblasts and at the synapse. *J Neurogenet*, 28(3-4): 302-315

General information about the institute

Research funding 1.194.466,31 €

Contact Details:

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Director: Professor Dr. Gerhard Schratt

Institute of Physiology and Pathophysiology

Research Group Professor J. Daut

Main fields of research

1. Intracellular traffic of potassium channels. We are studying the sorting signals which direct potassium channels to specific intracellular compartments. The channels include two-pore-domain potassium channels (K2P-channels), inward rectifier channels (Kir channels).
2. Regulation of single-channel conductance and kinetics of K2P-channels. We are studying the mechanisms by which biophysical properties of potassium channels are regulated.
3. Potassium channels in cardiac muscle cells. We are studying the role of the two-pore-domain potassium channels (K2P) TASK-1 and TREK-1 in cardiac muscle cells and we investigate the mechanisms by which G-protein-coupled receptors modulate these ion channels.

Research projects

Title Intracellular traffic of potassium channels

Principal investigator(s) J. Daut

Summary We are studying the mechanisms underlying the intracellular traffic of potassium channels (TASK-1, TASK-3, TREK-1, THIK-2, Kir2.1, Kir2.2). We investigate the following transport steps detail: (1) The export from the ER. (2) The transport between ER and the cis-Golgi complex. (3) The transport from the Golgi complex to the surface membrane. (4) Endocytosis into the early endosome.

Funded by DFG, SFB 593, PA4, – German Research Foundation, Collaborative Research Centre 593

Funding period 2010 – 2014

Title The function and signal transduction of TASK-1 and TREK-1 channels in the cardiovascular system

Principal investigator(s) J. Daut

Summary We are studying the contribution of the potassium channels TASK-1 and TREK-1 to the whole-cell currents and to the action potential in cardiomyocytes using electrophysiological and cell biological methods.

Funded by DFG, FOR 1086 Project 7 – German Research Foundation, Research Unit Programme 1086

Funding period 2010-2014

Most important publications

Anders C, Higuchi Y, Koschinsky K, Bartel M, Schumacher B, Thiel P, Nitta H, Preisig-Müller R, Schlichthörl G, Renigunta V, Ohkanda J, **Daut J**, Kato

N, Ottmann C (2013) A semisynthetic fusicoccane stabilizes a protein-protein interaction and enhances the expression of k(+) channels at the cell surface. *Chem Biol* (4):583-93.

Schickel J, Lindner M, Hetzel A, Wemhöner K, Renigunta V, Schlichthörl G, Decher N, Oliver D, **Daut J** (2013) Inhibition of the potassium channel TASK-1 in rat cardiac muscle by endothelin-1 is mediated by phospholipase C. *Cardiovasc Res* 97(1):97-105

Renigunta V, Fischer T, Zuzarte M, Kling S, Zou X, Siebert K, Limberg MM, Rinné S, Decher N, Schlichthörl G, **Daut J** (2014) Cooperative endocytosis of the endosomal SNARE protein syntaxin-8 and the potassium channel TASK-1. *Mol Biol Cell* ;25(12): 1877-91

Renigunta V, Zou X, Kling S, Schlichthörl G, **Daut J** (2014) Breaking the silence: functional expression of the two-pore-domain potassium channel THIK-2. *Pflugers Arch Eur J Physiol* 466(9):1735-45

Rinné S, Renigunta V, Schlichthörl G, Zuzarte M, Bittner S, Meuth SG, Decher N, **Daut J**, Preisig-Müller R (2014) A splice variant of the two-pore domain potassium channel TREK-1 with only one pore domain reduces the surface expression of full-length TREK-1 channels. *Pflugers Arch Eur J Physiol* 466(8):1559-70

Kilisch M, Lytovchenko O, Schwappach B, Renigunta V, **Daut J** The role of protein-protein interactions in the intracellular traffic of the potassium channels TASK-1 and TASK-3. *Pflugers Arch Eur J Physiology (in press)*

Bodnár M, Schlichthörl G, **Daut J** The potassium current carried by TREK-1 channels in rat cardiac ventricular muscle. *Pflugers Arch Eur J Physiology (in press)*

Research Group Professor N. Decher

Main fields of research

Our group focuses on several aspects of ion channel research. We study the molecular pharmacology and the structure and function of different channels. In addition, to these experiments in heterologous expression systems, we study ion channels in native tissue including Patch Clamp experiments of native cardiomyocytes and brain slices. Another focus is the functional study of ion channel mutations causing human arrhythmias. These studies analyze the disease causing mechanism of inherited arrhythmias.

Our recent novel field of research analyzes how RNA editing alters the function and pharmacology of ion channels.

Research projects

Title TASK channels in the heart and their extracellular pore structure

Principal investigator(s) N. Decher

Summary In this project we analyzed native TASK-1 channels in the sino-atrial node, using the TASK-1 knock-out mouse, HL-1 cells and novel TASK blockers. In addition, we have analyzed the extracellular pore structure of the cardiac K_{2P} channel TASK-1. The third focus of the project was on the characterization of novel K_{2P} channel mutations causing inherited forms of arrhythmias.

Funded by DFG – German Research Foundation

Funding period 2012 – 2015

Title The role of ‘side pockets’ for the inhibition of Kv channels by polyunsaturated fatty acids and potassium channel blockers

Principal investigator(s) N. Decher

Summary Voltage-gated potassium channels (Kv channels) are novel drug targets for pharmaceuticals currently under development against many diseases. Our studies are supposed to provide a major contribution to the understanding of the molecular pharmacology of Kv1 channels and set the stage for the rational ‘drug design’ and the development of drugs, acting via the newly discovered ‘side pockets’ of the channels.

Funded by DFG – German Research Foundation

Funding period 2014 – 2017

Title Mutations in the Popeye domain containing protein 2 gene (Popdc2) as a cause of congenital AV-block

Principal investigator(s) S. Rinné

Summary Popeye domain containing (Popdc) proteins interact with the ion channel TREK-1, a member of the two-pore-domain potassium (K_{2P}) channel family, playing a role in setting the resting membrane potential. Mice deficient for Popdc2 developed a stress-induced sinus bradycardia. In our study we analyze a heterozygous *Popdc2* mutation in a patient with severe atrioventricular block and reveal the disease-causing mechanism.

Funded by UKGM – University Medical Centre Giessen / Marburg

Funding period 2014 – 2015

Most important publications

Marzian S, Stansfeld PJ, Rapedius M, **Rinné S**, Nematian-Ardestani E, Abbruzzese JL, Steinmeyer K, Sansom MSP, Sanguinetti MC, Baukrowitz T, **Decher N** (2013) Side pockets provide the basis for a new mechanism of Kv channel-specific inhibition. *Nat Chem Biol* 9: 507-513

Limberg M, Zumhagen S, **Netter MF**, Coffey AJ, Grace A, Rogers J, Böckelmann D, **Rinné S**, Stallmeyer B, [§]**Decher N**, [§]Schulze-Bahr E (2013) Non dominant-negative *KCNJ2* gene mutations leading to Andersen-Tawil syndrome with an isolated cardiac phenotype. *Basic Res Cardiol* 108: 353. [§]Shared senior authors

Dolga A, **Netter MF**, Perocchi F, Doti N, Meissner L, Tobaben S, Grohm J, Zischka H, Plesnila N, **Decher N**, Culmsee C (2013) Mitochondrial small conductance SK2 channels prevent glutamate-induced oxytosis and mitochondrial dysfunction. *J Biol Chem* 88: 10792-10804

Schickel J, Lindner M, Hetzel A, **Wemhöner K**, Renigunta V, Schlichthörl G, **Decher N**, Oliver D, Daut J (2013) Inhibition of the potassium channel TASK-1 in rat cardiac muscle by endothelin-1 is mediated by phospholipase C. *Cardiovasc Res* 97: 97-105

Streit AK, **Matschke LA**, Dolga AM, **Rinné S**, **Decher N** (2014). RNA Editing in the Central Cavity as a Mechanism to Regulate Surface Expression of the Voltage-Gated Potassium Channel Kv1.1. *J Biol Chem* 289: 26762-26771

Friedrich C, **Rinné S**, Zumhagen S, **Kiper AK**, **Silbernagel N**, **Netter MF**, Stallmeyer B, Schulze-Bahr E, **Decher N** (2014) Gain-of-function mutation in TASK-4 channels and severe cardiac conduction disorder. *EMBO Mol Med* 6:937-951

Renigunta V, Fischer T, Zuzarte M, Kling S, Zou X, Siebert K, **Limberg M**, **Rinné S**, **Decher N**, Schlichthörl G, Daut, J. (2014) Co-operative endocytosis of the endosomal SNARE protein syntaxin-8 and the potassium channel TASK-1. *Mol Biol Cell* 25: 1877-1891

Rinné S, Renigunta V, Schlichthörl G, Zuzarte M, Bittner S, Meuth SG, **Decher N**, Daut J, Preisig-Müller R (2014) A splice variant of the two-pore domain potassium channel TREK-1 with only one pore domain reduces the surface expression of full-length TREK-1 channels. *Pflügers Archiv*, 66: 1559-1570

Research Group Professor D. Oliver

Main fields of research

1. Signaling by phosphoinositides and other membrane lipids. Development of methods for live-cell imaging with fluorescence microscopy and for acute manipulation of phosphoinositide concentrations by rapidly controllable enzymes.
2. Biophysics, molecular physiology and cellular regulation of ion channels, in particular potassium channels (Kv, KCNQ, K2P, Kir).
3. Physiology and pathophysiology of cochlear auditory hair cells and signal encoding by the peripheral auditory system.
4. Structure and molecular function of the membrane motor protein of outer hair cells, prestin (SLC26A5) and related anion transporters

Research projects

Title Compartment-specific phosphoinositide dynamics in a central neuron

Principal investigator(s) D. Oliver

Summary Phosphoinositides (PIs) control many cellular processes including synaptic function and ion channel activity. We use hippocampal pyramidal neurons as a model to investigate compartmentation of PI signaling. Changes in phosphatidylinositol (4,5)bisphosphate (PIP₂) and phosphatidylinositol-(3,4,5)trisphosphate levels in response to a variety of physiological stimuli will be examined using FRET imaging. Particular attention is paid to the highly compartmentalized dendritic compartments and postsynaptic spines.

Funded by DFG, SFB593, TP A12 – German Research Foundation, Collaborative Research Centre 593

Funding period 2011 – 2014

Title The mechanisms underlying receptor-mediated regulation of TASK and TREK channels

Principal investigator(s) D. Oliver

Summary

TASK- und TREK channels are leak potassium channels that are constitutively active at the resting potential, but are inhibited by a multitude of metabotropic neurotransmitter and hormone receptors. As these channels determine membrane potential and electrical signaling in many neurons and non-excitable cells, their inhibition results in depolarization and changes in excitability. Both channel types are inhibited by receptors that couple via heterotrimeric G-proteins of the Gq/11 class. In this project, we aim at elucidating the mechanisms and molecular components of this Gq-dependent signalling cascade that control TASK and TREK channels.

Funded by DFG, FOR 1086, TP 9; OL 240/3-1 – German Research Foundation, Research Unit Programme 1086

Funding period 2011 – 2014

Title Structure-based analysis of the molecular mechanisms of prestin-dependent cochlear amplification

Principal investigator(s) D. Oliver

Summary The exquisite acuity of mammalian hearing relies on active mechanical amplification and requires a process termed electromotility, i. e. voltage-driven ultrafast length changes of sensory outer hair cells (OHC). The elementary motor that generates motility is prestin (SLC26A5), an anion transporter-related, OHC-specific membrane protein. So far, analysis of the molecular mechanisms behind prestin's function has been hampered by a general lack of structural information about SLC26 transporters. By homology modeling we have now developed a structural model of prestin that is in excellent agreement with previous biophysical findings. We propose to validate and refine this structure and to use it as a template for elucidating the fundamental molecular features of prestin and related transporters.

Funded by DFG, SPP 1608 – German Research Foundation, Priority Programme

Funding period 2012 – 2015

Title Entwicklung einer Methodik zur automatisierten Untersuchung der Aktivität des Tumorsuppressors TEN in lebenden Zellen

Principal investigator(s) C. Halaszovich

Summary The tumor suppressor PTEN antagonizes the PI3K/Akt-pathway via its PI(3,4,5)P₃/PI(3,4)P₂-3-phosphatase activity. Recently, we were able to develop a PTEN-chimera (PTEN_{CIV}) that is controlled by membrane voltage. In this study we will develop methods that will allow the activation of this chimeric enzyme and the detection of its activity in living cells in a way that is amenable to automation.

Funded by UKGM – University Medical Centre Giessen / Marburg

Funding period 2011 – 2013

Title Interaction of KCNQ and Erg potassium channels in auditory hair cells

Principal investigator(s) M. Leitner

Summary The sensitivity of mammalian hearing depends on cochlear amplification that is facilitated by the outer hair cell current I_{K,n}. KCNQ4 K⁺ channels have been identified as molecular components, but cannot account for all properties of native currents. We identified Erg channel subunits as potential interaction partners of KCNQ4. Hypothesizing that heteromeric channels composed of KCNQ4 and Erg subunits determine the properties of the native current, we analyze this interaction in outer hair cells and heterologous expression systems.

Funded by UKGM – University Medical Centre Giessen / Marburg

Funding period 2014 – 2015

Title Homoclinic Bifurcations at Tonic-to-Bursting Transitions: Underlying Mechanisms and Impact on neuronal Synchronization

Principal investigator(s) U. Feudel (University of Oldenburg) & H. A. Braun

Summary Analyzing the bifurcation structure of a neuronal computer model which can reproduce physiologically and pathophysiologically most relevant impulse pattern, among them transitions from single-spike activity (tonic firing) to grouped discharges which are often accompanied by alterations of the neuronal synchronization state, for example, at wake-sleep transitions or during the development of epileptic seizures.

Funded by UKGM – University Medical Centre Giessen / Marburg

Funding period 2010 – 2013

Research group Professor A. del Rey

Main fields of research

Our research deals with interactions between the nervous, endocrine and immune systems under physiological and pathological conditions. During this period, we focused on six closely related aspects of these interactions: 1) the resetting of glucose homeostasis by brain-borne IL-1 β ; 2) bidirectional influences between non-neuronal acetylcholine and neuronal noradrenaline in lymphoid organs, 3) the contribution of glucocorticoids in the sensitivity to develop arthritis and to induce regulatory T cell apoptosis; 4) brain neurotransmitter and cytokines levels in a model of neurodevelopmental disorders; 5) the role of the sympathetic nervous system in a parasitic infection model; 6) neuro-endocrine disturbances in patients with tuberculosis

Research projects

Title Neuro-endocrine mechanisms of Interleukin-1 β -mediated resetting of glucose homeostasis

Principal investigator(s) A. del Rey

Summary We have shown that IL-1 β induces a prolonged and profound insulin-independent hypoglycemia without eliciting neurological symptoms, and mediated by peripheral and central effects of the cytokine. During this period, we concentrated on the molecular mechanisms by which brain-borne IL-1 β might resets glucose homeostasis by acting in the brain. Part of this work is included in the Doctoral Thesis of M. Verdenhalven.

Funded by DFG – German Science Foundation (RE 1451/3-1)

Funding period 2009 – 2013

Title Bidirectional communication between non-neuronal acetylcholine and neuronal noradrenaline in the spleen

Principal investigator(s) A. del Rey

Summary The main question addressed here is whether interactions between non-neuronal, lymphocyte-derived acetylcholine and noradrenaline from sympathetic nerves in lymphoid organs can affect the immune response. We focused on the spleen because this organ is not parasympathetically innervated in rodents. The results obtained emphasize the need to consider the balance between the effects of these mediators for the final immunoregulatory outcome.

Funded by LOEWE (NNCS 56200076)

Funding period 2012 – 2014

Title Counteracting the disruption of brain-immune system-joint communication: targeting the brain in arthritis

Principal investigator(s) A. del Rey - in collaboration with Prof. Dr. R. Straub, Dept. of Internal Medicine I, University Hospital Regensburg, Germany

Summary We have recently shown that the communication between the brain, the immune system, and the inflammatory, autoimmune process that occurs in the affected joints during arthritis is disrupted. During this period, we concentrated on studying the role that endogenous levels of glucocorticoids play in the susceptibility to develop arthritis in genetically resistant animals.

Funded by DFG – German Science Foundation (RE 1451/4-2)

Funding period 2009 – 2015

Title Immune-neuro-endocrine interactions during infections with parasites

Principal investigator(s) A. del Rey - in collaboration with Dr. E. Roggero, Open Interamerican University (UAI), Rosario, Argentina

Summary We have shown that interference with the functioning of the hypothalamus-pituitary-adrenal axis aggravates the disease in animals infected with *Trypanosoma cruzi*, the parasite that causes Chagas' disease in humans. During this period, we focused on the activity of the sympathetic nervous system in infected mice, and studied its contribution to the development of the disease.

Funded by Open Interamerican University, Argentina

Funding period 2012 – 2015

Title Endocrine responses during human tuberculosis

Principal investigator(s) A. del Rey - in collaboration with Dr. O. Bottasso, Institute of Physiology, Medical Faculty, Rosario, Argentina

Summary We have shown that patients with pulmonary tuberculosis have imbalanced endocrine and immune responses, associated with metabolic

alterations. During this period, we have: 1) continued the follow-up of patients with tuberculosis undergoing standardized long-term therapy, 2) identified TGF β as the most likely immune mediator that inhibits dehydroepiandrosterone (DHEA) secretion, one of the most marked alterations observed in patients with tuberculosis.

Funded by Argentinian Research Council

Funding period 2010 – 2014

Research group Professor J. Oberwinkler

Main fields of research

The group of Johannes Oberwinkler continued its long standing research focus on the functional characterization of TRPM3 and TRPM1 channels, by investigating the biophysical and pharmacological properties of these channels. Additionally, the regulation of activity by intracellular signaling cascades of these channels was investigated. These channels are highly interesting, because they have been implicated in a number of physiological and pathophysiological processes with important implications for common human diseases (TRPM3: insulin secretion, temperature and pain sensation; TRPM1: night blindness).

Research projects

Title Regulation of TRPM3 activity by noradrenaline in pancreatic beta cells

Principal investigator(s) J. Oberwinkler, F. Mohr & M. Behrendt

Summary TRPM3 channels are endogenously expressed in pancreatic beta cells, where they form ionotropic steroid receptors. Activation of these channels leads to Ca²⁺ influx and subsequent increase of glucose-evoked insulin release. However, it is still unclear how TRPM3 activity is regulated in vivo. We found that noradrenaline suppresses TRPM3 activity by activating α 2-adrenoreceptors and subsequently releasing beta/gamma-subunits from G α phai-proteins.

Funded by DFG (SFB 593, TP A16) – German Research Foundation, Collaborative Research Centre 593

Funding period 2009 – 2014

Title Regulation of TRPM3 activity by inositide phospholipids

Principal investigator(s) J. Oberwinkler, M. Konrad, B. Nickl & F. Mohr

Summary Many TRP channels, are regulated by phospholipids, most prominently by PIP2. In order to investigate whether also TRPM3 channels are regulated by PIP2, various enzymatic and pharmacological approaches are used in order to manipulate PIP2 and PIP3 levels in a controlled and precise way.

Funded by DFG (SFB 593, TP A16) – German Research Foundation, Collaborative Research Centre 593

Funding period 2012 – 2014

Title Regulation of TRPM3 in nociceptor neurons by opioids

Principal investigator(s) J. Oberwinkler, S. Dembla & M. Behrendt

Summary TRPM3 channels are expressed in nociceptor neurons, where these channels participate in the detection of noxious heat and in inflammatory responses. We found that the activation of mu-opioid receptors, targets of the most powerful analgesic drugs, leads to a strong inhibition of TRPM3 channels. We investigate the intracellular signaling pathways and the functional consequences of this clinically important regulatory mechanism.

Funded by UKGM – University Medical Centre Giessen / Marburg

Funding period 2012 – 2014

Title Regulation of TRPM1 by G-protein-coupled receptors and their signaling pathways

Principal investigator(s) J. Oberwinkler, M. Behrendt & F. Schneider

Summary Loss of function mutations of TRPM1 proteins (which are closely related to TRPM3 proteins) lead to nightblindness in humans and animal models. We study the functional properties of ion channels formed from TRPM1 proteins with respect to their pharmacology, biophysical properties and their regulation by intracellular signaling cascades.

Funded by DFG (SFB 593, TP A16) – German Research Foundation, Collaborative Research Centre 593

Funding period 2012 – 2014

Title Structure-affinity relationship of TRPM3 channels with their agonists and antagonists

Principal investigator(s) J. Oberwinkler, M. Behrendt & C. Goecke

Summary TRPM3 channels are potential therapeutic targets for diverse diseases such as diabetes and inflammatory pain. It is therefore important to better understand how agonists and antagonists interact with TRPM3 proteins. We study point mutations of TRPM3 channels and systematically modified small molecules in order to establish structure-activity relations with the aim of developing channel modulators with improved selectivity and usefulness.

Funded by DFG (SFB 593, TP A16) – German Research Foundation, Collaborative Research Centre 593

Funding period 2012 – 2014

Most important publications

Deng W, Nies F, Feuer A, Bocina I, **Oliver D**, Jiang D (2013) Anion translocation through an Slc26 transporter mediates lumen expansion during tubulogenesis. *Proc Natl Acad Sci USA* 110:14972-14977

Schiekel J, Lindner M, Hetzel A, Wemhoner K, Renigunta V, Schlichthorl G, **Decher N**, **Oliver D**, **Daut J** (2013) The inhibition of the potassium channel TASK-1 in rat cardiac muscle by endothelin-1 is mediated by phospholipase C. *Cardiovasc Res* 97:97-105

Straub I, Mohr F, Stab J, Konrad M, Philipp SE, **Oberwinkler J**, Schaefer M (2013) Citrus fruit and fabacea secondary metabolites potently and selectively block TRPM3. *Br J Pharmacol* 168(8):1835-50

del Rey A, Balschun D, Wetzel W, Randolph A, Besedovsky HO (2013) A cytokine network involving brain-borne IL-1 β , IL-1ra, IL-18, IL-6, and TNF α operates during long-term potentiation and learning. *Brain Behav Immun* 33:15-23

Wirth T, Westendorf AM, Bloemker D, Wildmann J, Engler H, Mollerus S, Wadwa M, Schäfer MK, Schedlowski M, **del Rey A** (2014) The sympathetic nervous system modulates CD4(+)Foxp3(+) regulatory T cells via noradrenaline-dependent apoptosis in a murine model of lymphoproliferative disease. *Brain Behav Immun* 38:100-10

Wilke BU, Lindner M, Greifenberg L, Albus A, Kronimus Y, Bünemann M, Leitner MG, **Oliver D** (2014) Diacylglycerol mediates regulation of TASK potassium channels by Gq-coupled receptors. *Nat Commun* 5:5540

Gorbunov D, Sturlese M, Nies F, Kluge M, Bellanda M, Battistutta R, **Oliver D** (2014) Molecular architecture and the structural basis for anion interaction in prestin and SLC26 transporters. *Nat Commun* 5:3622

Drews A, Mohr F, Rizun O, Wagner TF, Dembla S, Rudolph S, Lambert S, Konrad M, Philipp SE, Behrendt M, Marchais-Oberwinkler S, Covey DF, **Oberwinkler J** (2014) Structural requirements of steroidal agonists of transient receptor potential melastatin 3 (TRPM3) cation channels. *Br J Pharmacol* 171(4):1019-32

General information about the institute

Research funding 1.693.568,14 €

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Phone:++49 (0) 6421-28 66444
Director: Professor Dr. Dominik Oliver**

Department of Medical Psychology

Research Group Professor K. Thieme

Main fields of research

Our studies are experimental, interventional, translational science projects to investigate anatomical mechanisms - baroreflex and nucleus tractus solitarius (NTS) reflex arcs in chronic pain to define and to influence the disturbed pain inhibition mechanism. A new medical device and treatment method (SET) was developed and used for patients as well as a RCT study with 60 fibromyalgia patients who got the SET was executed to proof the therapy effects of pain freedom (Fig. 1).

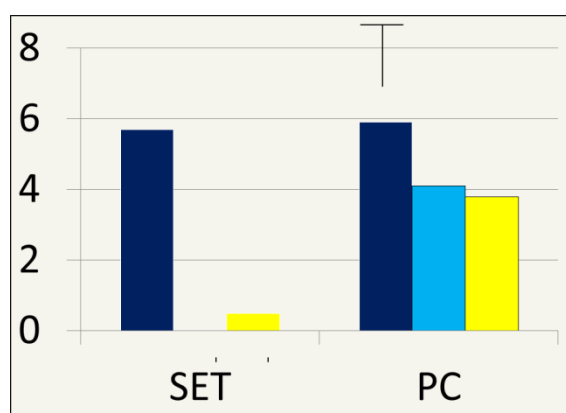


Figure 1 Changes of Clinical Pain immediately and 6-12 months after Systolic extinction training (SET) and Placebo Condition (PC)

Research projects

Title Mechanism of Baroreflexsensitivity in Fibromyalgia

Principal investigator(s) K. Thieme

Funded by UKGM – University Medical Centre Giessen/ Marburg

Funding period 2012 – 2014

Title Development of two computer supported instruments for screening and assessment of Fear Avoidance Beliefs in patients with low back pain older than 65 years (eAMICA-K and eAMIKA)

Principal investigator(s) S. Quint

Funded by Kempkes Foundation

Funding period 2012 – 2014

Title Mechanism of baroreflexsensitivity (BRS) – pathophysiology and treatment

Principal investigator(s) K. Thieme

Summary We developed a novel medical device and treatment method to increase the diminished BRS in chronic pain patients. Baroreceptors transmit pressure information to the nucleus tractus solitarius, which inhibits pain, blood pressure, sleep disturbances, anxiety, and hyperglycemia. When

combined with operant pain therapy, 100% of chronic pain patients achieved pain relief for 6 and 82% for 12 months.

Funded by DFG Th 899-7/1 – German Research Research Foundation, NIH – National Institute of Health & UKGM – University Medical Centre Giessen / Marburg

Funding period 2009 – 2015

Title Evaluation of the “Assertiveness Training for Medical Students”

Principal investigator(s) K. Thieme

Summary An interventional study with 1150 medical students was performed in order to improve their communication and empathy skills by using my manual “Self-assertiveness training for medical students”.

The interventional study investigates changes of anxiety, depression, empathy, sociopathy and training satisfaction as well as behavioral changes after the “Assertiveness training for medical students” in 1150 students of the 3rd semester. Standardized questionnaires and video-recorded behavioral observations of a role-play with an actor-patient were used to differ between 3 subgroups: empathy (36.85%), sociopathy (38.50%) and anxiety-depression (28.65%, Figure2).

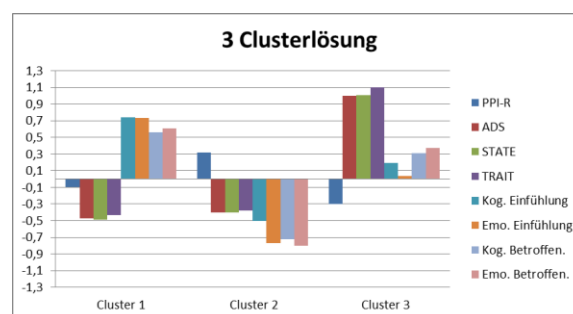


Figure 2 Subgroups in medical students (N = 767): Subgroup1: Empathy group (cluster1 36.85%), subgroup2: Soziopathy (cluster2, 38.50%), subgroup3: Anxiety-Depression-Group (cluster3. 24.65%)

Funded by Teaching Research Fond

Funding period 2012 – 2015

Title Stress and sensitization in medical students before the anatomy exam

Principal investigator(s) K. Thieme

Summary The multicenter study (UNC, ETH-Zürich) investigates the relationship between stress (anatomy-exam) and sensitization measured as vibrotactile discrimination capacity in 70 healthy individuals assuming a positive correlation because of GABAergic inhibition. Sensory thresholds in discrimination tasks, skin conductance level, cortisol

saliva and subjective ratings of stress and anxiety were recorded immediately before the oral anatomy exam controlled by a baseline situation.

Funded by CNS Therapy AG

Funding period 2013 – 2015

Note This research report does not include the not-funded projects such as “Characteristics of sleep pattern in fibromyalgia and their changes after systolic extinction training”, “Immunological changes in patients suffering from rheumatoid arthritis episode after systolic extinction training” as well as “Changes of sympathetic activity of fibromyalgia tested in LBNP after systolic extinction training – A microneurography study.”

General information about the institute

Research funding 33.146,05 €

Most important publications

Thieme K, Turk DC, Gracely RH, Maixner W, Flor H. The relationship among psychological and psychophysiological characteristics of fibromyalgia patients. *J Pain*. doi: 10.1016/j.jpain.2014.11.009. Epub 2014 Nov 26.

Posterabstracts (per-reviewed)

Flor H, **Thieme K**, Kleinböhl D, Kießling U, Wang H, Schiltenswolf M, Konrad Ch, Schmelz M. Enhancing extinction training by cannabis: A randomized controlled trial in patients with chronic musculoskeletal pain. 15th World Congress of the International Association for Study of Pain (IASP), Buenos Aires, Argentina, 2014

Lautenschlaeger G, Meller T, Malinowski R, Wilhelm K, Birklein F, Kaps M, **Thieme K**, Kraemer H. Sympathetic activity in patients with fibromyalgia – a microneurographic study. [Sympathische Nervenaktivität bei Fibromyalgie Patienten – eine Mikroneurographiestudie]. Meeting of the German Association for Study of Pain, Hamburg, Oktober 2014)

Meller T, Wolf S, Malinowski R, Maixner W, Gracely RH, **Thieme K**. Psychological pain treatment in fibromyalgia: Systolic extinction training (SET) and cardiovascular training restores baroreflex sensitivity, reduces pain sensitivity and clinical pain report. 15th World Congress of the International Association for Study of Pain (IASP), Buenos Aires, Argentina, 2014

Meller T, **Thieme K**. Pain inhibition after systolic extinction training. [Schmerzhemmung nach systolischer Extinktionstherapie (SET) bei Fibromyalgie.] Meeting of the German Association for Study of Pain, Hamburg, Oktober 2014

Thieme K, Kraemer H, Koehler U, Meller T, Maixner W, Gracely, RH. Psychological Pain Treatment in Fibromyalgia: Systolic Extinction Training (SET) Restores Baroreflex Sensitivity, Reduces Pain Sensitivity and Clinical Pain Report. 15th World Congress of the International Association for Study of Pain (IASP), Buenos Aires, Argentina, 2014

Thieme K, Maixner W, Gracely RH. Cardiac Gating of Peripheral Afferent Stimulation Restores Baroreflex Sensitivity, Reduces Pain Sensitivity and Clinical Pain Report in Fibromyalgia Patients. 15th World Congress of the International Association for Study of Pain (IASP), Buenos Aires, Argentina, 2014

Zeiler AL, Koehler W, Kesper K, Cassel W, **Thieme K**. Schlafmuster bei Fibromyalgie vor und nach systolischem Extinktionstraining (SET). *Somnologie* 2014, 18(1): R56 22nd Meeting of German Association for Sleep Research and Sleep Medicine

Book chapter

Finset A, **Thieme K**. (2014). Psychosocial Approaches in Rheumatic Diseases. In: Weller J (Ed.) *EULAR Textbook on Rheumatic Diseases - Online Course*.). Medwellmedia; Chapter 6, pp: 1 – 26

Thieme K. Fibromyalgie. In: Petermann F & Vaitl D (Hrsg.) *Entspannungsverfahren. Das Praxishandbuch*. 5. Auflage 2014, Beltz Verlag, Weinheim, Basel; S. 266 – 278

Patents

2013

Thieme K, Maixner W, Gracely RH. OLG 150/4 Prov

Thieme K, Maixner W, Gracely RH. OLG 150/4 Prov-2

Since it is a Translational Science Project, this study belongs to the most important research projects. It is a multicenter study and was supported by DFG (Th 899/7-1: “Pathways of chronic pain”) and the NIH (R01AR054895-01A1: “Mechanisms of sensory Processing in Fibromyalgia”) as well as the UKGM. It started in 2009 at the Center for Neurosensory Disorders, University of North Carolina (UNC), Chapel Hill, USA (director: Dr. William Maixner, PhD, DDS) and continued through 2011 as a collaboration between UNC (Dr. William Maixner, PhD, DDS), the Philipps University Marburg respective the Department of Medical Psychology (Director: Dr. Kati Thieme, PhD) and the CNS Therapy, AG, Switzerland (Director: Dr. Marc Mathys, PhD).

An important result of the study was the development of a new medical device - the systole-electrostimulator-synchronizer. The device treats pain and other chronic diseases. It allows the delivery of individual adjusted electrical stimuli dependent on cardiac cycle through the fingers. The cardiac gated electrical pulses stimulate the NTS reflex arcs, through the baro receptors and results in the long-term extinction of pain when the stimulation is combined with psychological pain therapy.

The new device was accepted by the Office of Technology and Discoveries (OTD) at the University of North Carolina (UNC), Chapel Hill, in 2011 for a submission of 2 provisional patents that the OTD supported in 2013. These provisional patents were then converted into the submission of a final patent in 2014.

The UNC has supported the submission of the provisional patents, only under the condition that I could find a sponsor who will commercialize the technology. Additionally to the costs of the patent submissions, UNC miniaturized the device at their own expense. After a 2 years search, the company 'CNS Therapy AG' (Director: Phd. Marc Mathys and investors) to sponsor the technology. Currently the sponsor is finding medtech companies in Germany and US that to prepare CE-certification and FDA.

UNC and CNS Therapy AG submitted final patent in 2014. Recently we have received a positive feedback to the patent filing by the American patent office. CNS Therapy, AG supported the RCT study at the University Marburg. Public and private investments together in the project exceed US\$ 3,000,000.

Until the submission of the final patent in March 2014, we were not allowed to submit or publish any research results in any papers or books.

2014

Thieme K, Maixner W, Monbureau O, Gracely RH.
OTD 12-0059 PCT/US14/26579

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Director: Professor Dr. Kati Thieme

Institute of Medical Sociology and Social Medicine

Research Group Professor U. Mueller

Main fields of research

- Medical Demography
- Epidemiology
- Health Care Research

Research projects

Title Computer-based Diabetes Risk-Management System (CDRM)

Principal investigator(s) U. Mueller

Summary The main purpose of the study yields on a science-based validation of the integrated health service model and the effectiveness of the computer-based risk-management-tools tested within a clinical study. The research project is proposed to evaluate cooperation of technical solutions according to methods of secondary prevention on a scientific background. The results should provide the efficiency of the already implemented disease management programs.

Funded by ICW - InterComponentWare AG, Roche Diagnostics Deutschland GmbH

Funding period 2007 –

Title Competence Center Mortality-Follow-Up of the German National Cohort

Principal investigator(s) U. Mueller

Summary The German National Cohort as an interdisciplinary research consortium includes scientists of the Hemholtz and Leibniz-community, universities and other research departments.

The major aim of the study is to search for causes and risk factors for the development of the most important chronic diseases, especially cardiovascular diseases, cancer, diabetes mellitus, neuro-degenerative and mental diseases, illness of the musculoskeletal system, respiratory tracts, infectious diseases and their grades in pre-clinical development and health related restraint over the life course. The study is based on a random sample of the total population in 18 study centers spread all over Germany, including 200.000 probands (100.000 female/ 100.000 male) aged between 20 and 69 years.

Funded by BMBF – Federal Ministry of Education and Research, Hemholtz u. Leibniz-Gemeinschaft

Funding period 2014 – 2018

General information about the institute

Research funding

62.789,45 €

Most important publications

Reese JP, Wienemann G, John A, Linnemann A, Balzer-Geldsetzer M, **Mueller UO**, Eienbröcker C, Tackenberg B, Dodel R (2014) Preference-based Health status in a German outpatient cohort with multiple sclerosis. *Health Qual Life Outcomes*. 11:162

Mazur A, **Westerman R**, **Werdecker A**, **Mueller U** (2014): Testosterone and type 2 diabetes in men. *Aging Male*. 17(1):18-24

Ng M, Fleming T, Robinson M, ..., **Werdecker A**, Lopez AD, Murray CJ, Gakidou E (2014) Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 384(9945):766-81

Kassebaum NJ, Bertozzi-Villa A, Coggeshall MS,..., **Mueller UO**,... ,**Westerman R**,..., Naghavi M, Murray CJ, Lozano R (2014) Global, regional, and national levels and causes of maternal mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 384(9947):980-1004

Wang H, Liddell CA, Coates MM, **Mueller UO**, ... , **Westerman R**, ..., Vos T, Lopez AD, Murray CJ (2014) Global, regional, and national levels of neonatal, infant, and under-5 mortality during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 384(9947):957-79

Murray CJ, Ortblad KF, Guinovart C, ... , **Westerman R**, ..., Zou XN, Lopez AD, Vos T (2014) Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 384(9947):1005-70

Naghavi M, **Wang H**, **Lozano R**, ..., Mueller U, ..., Westerman R, ..., Werdecker A, ..., Vos T, Lopez AD, Murray CJ (2014) Global, regional, and national age sex specific all-cause and cause-specific mortality for

240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. Dec 17. pii: S0140-6736(14)61682-2. [Epub ahead of print]

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Director: Professor Dr. Ulrich Mueller

Institute of General and Family Medicine, Preventive and Rehabilitative

Research Groups

Professor E. Baum, Professor A. Becker and Professor N. Donner-Banzhoff

Main fields of research

Cardiovascular Health: Diagnosis, Chronic Care, Prevention; Chronic Pain: Etiology, Treatment Strategies, Primary and Secondary Prevention; Clinical Decision Making: Cognitive Processes, Clinical Prediction Rules, Validity of the History and Physical Signs; Decision Support Technologies; Intercultural Primary Care; Professional Learning and Behavioural Change; Medical Care in rural regions.

Research projects

Title Transition from localized low back pain to chronic widespread pain in general practice: Identification of risk factors, preventive factors, and key elements for treatment

Principal investigator(s) A. Becker

Summary The aim of the study is to identify predictors of pain generalization in consulters for LBP in general practice and to identify individual resources for the prevention of the transition from chronic localized LBP to chronic widespread pain (CWP). These results provide the psychological background information on CWP patients which can be used for an intervention addressing resources and risk factors of this patient group. This intervention will be implemented and tested on clinical efficacy in the second phase of this research project. In summary this project aims at three main research objectives

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2011 – 2014

Title Developing and evaluation of a physical-activating therapy for low back pain in the elderly (graded activity & graded exposure principles) – STÄP [Schmerztherapie Ältere Patienten]

Principal investigator(s) A. Becker & S. Quint

Summary There is a lack of evidence-based therapy principles for low back pain in the elderly in primary care. This is a pre-study for an interventional project: Physiotherapy-manuals for two activating therapeutic approaches in older back pain patients are developed in cooperation with known experts. Pre-testing of the will be performed in a feasibility study.

Funded by DFG – German Research Foundation

Funding period 2011 – 2013



Title Diagnosis in primary care practice: cognitive strategies

Principal investigator(s) N. Donner-Banzhoff

Summary General Practitioners (GPs) are the most important point of entry into the health care system. They have to differentiate between frequently encountered benign problems and potentially serious conditions presented by their patients. Within this project, the cognitive strategies GPs use for their diagnostic assessment will be investigated in collaboration with the MPI for Human Development, Berlin. 300 consultations in 12 practices were videotaped and are being analysed.

Funded by DFG – German Research Foundation

Funding period 2011 – 2013

Title Center of Competence for General Practitioners' vocational training in the state of Hessen (middle and northern part)

Principal investigator(s) E. Baum

Summary Vocational training for general practitioners/family physicians (GPs) is often disrupted and uncoordinated. Germany is facing an increasing lack of young GPs. This programme helps to overcome barriers by initiating cooperations for the full time of vocational training and offers seminars, mentoring and evaluates each step. This is performed in close cooperation with the Competence Center in south Hessen and the other players in the system.

Funded by Social Ministry Hessen

Funding period 2013 – 2014

Title arriba-PRO

Principal investigator(s) N. Donner-Banzhoff

Summary The decision-support software "arriba" which has been developed within our department, is

being systematically implemented in Baden-Württemberg as part of a primary care gatekeeping scheme (Hausarztzentrierte Versorgung der AOK). Patients counseled by their General Practitioners using the software, form a virtual cohort. By assessing future cardiovascular events, we will be able to adjust the predictive algorithm underlying the prognosis provided by arriba.

Funded by GPZK

Funding period 2011 – 2014

Title *OptRisk: Optimisation of risk consultancy through presentation of changeability of individual life expectancy*

Principal investigator(s) N. Donner-Banzhoff

Summary The aim of this project is to improve the presentation of risks in a decision aid for cardiovascular diseases. Central to the research project is the comparison of the presentation on the basis of 1) the absolute risk employed so far (10-year prognosis), and 2) the event-free lifetime. Main question: Which presentations of prognosis and therapeutic effects are particularly suitable in patient consulting – absolute risk or lifetime?

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2011 – 2014

Title Community nurse in Muschenheim

Principal investigator(s) E. Baum & D. Kuhn

Summary Declining numbers of General Practitioners (GPs) in Germany and especially in rural regions lead to under-supply of the ageing population in these regions with respect to basic medical needs. This local and privately funded initiative introduces consulting hours and home visits run by community nurses living in the village and special offers like medication check and gymnastics for elderly people. The project is evaluated by qualitative and quantitative methods.

Funded by Private local sponsor Sauerborn, silver star prize

Funding period 2013 – 2014

Minor Project without External Funding 2014

- Bias-calculator
- Systematic reviews of symptom evaluating studies in primary care
- Qualitative studies about use of allopurinol, dermatological problems, leg edema und headache in primary care
- Evaluation of an OSCE about decision making in undergraduate training
- Impact evaluation of the seminar 'Differential diagnosis in Primary Care'

Minor Projects without External Funding or External Funding in Previous Years:

- Bias in CME-Journals
- Psychiatric treatment of immigrants from Turkey
- Prescribing of thyroid hormones in primary care
- Development and psychometric testing of a standardised instrument to assess the quality of vocational training
- Patient information leaflets disseminated in primary care practice
- Epidemiology of low back pain and coping strategies in elderly patients
- Geographical distribution of obesity
- Effectiveness of computer-based counselling for chronic low back-pain patients
- Implementation of a guideline about chest pain in primary care
- Diagnosis of headache in Primary Care
- Diagnosis of leg edema in Primary Care
- Chronic skin disease in Primary Care
- Teaching points and feedback during the mandatory general practice elective – an ethnographic study

General information about the institute

Research funding

893.138,75 €

Most important publications

Bösner S, Bönisch K, Haasenritter J, Schlegel P, Hüllermeier E and Donner-Banzhoff N (2013) Chest pain in primary care: is the localization of pain diagnostically helpful in the critical evaluation of patients? - A cross sectional study. *BMC Family Practice* 14:154

Bösner S, Hartel S, Diederich J, Baum E (2014) Diagnosing headache in primary care: a qualitative study of GPs' approaches. *Br J Gen Pract* 64:e532-7

Diederich J, Hartel S, Baum E, **Bösner S** (2014) Strategies for diagnosing leg oedema in primary care: A qualitative study of GPs' approaches. *Eur J Gen Pract* 17:1-7

Viniol A, Keunecke C, Biroga T, Stadje R, Dornieden K, Bösner S, Donner-Banzhoff N, Haasenritter J, **Becker A** (2014) Studies of the symptom abdominal pain - a systematic review and meta-analysis. *Fam Pract* 31:517-29

Viniol A, Jegan N, Leonhardt C, Brugger M, Strauch K, Barth J, Baum E, **Becker A** (2013) Differences between patients with chronic widespread pain and local chronic low back pain in primary care - a

comparative cross-sectional analysis. *BMC Musculoskelet Disord* 14:351

Hirsch O, Strauch K, Held H, Redaelli M, Chenot JF, Leonhardt C, Keller S, Baum E, Pfingsten M, Hildebrandt J, Basler HD, Kochen MM, Donner-Banzhoff N, **Becker A** (2014) Low back pain patient subgroups in primary care – pain characteristics, psychosocial determinants and health care utilization. *Clin J Pain* 30: 1023-32

Donner-Banzhoff N, Haasenritter J, Hüllermeier E, Viniol A, Bösner S, **Becker A** (2014) The comprehensive diagnostic study is suggested as a design to model the diagnostic process. *J Clin Epidemiology* 67:124 -132

Senge R, Bösner S, Dembczynski K, Haasenritter J, Hirsch O, **Donner-Banzhoff N**, Hüllermeier E (2014) Reliable classification: Learning classifiers that distinguish aleatoric and epistemic uncertainty. *Information Sciences* 255:16–29

Viniol A, Bösner S, Baum E, **Donner-Banzhoff N** (2013) Forgotten drugs: long-term prescriptions of thyroid hormones – a cross-sectional study. *Int J Gen Medicine* 6:329 – 334



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Director: Professor Dr. Erika Baum

Institute of Medical Biometry and Epidemiology

Research Group Jun.-Prof. Dr. Nina Timmesfeld (provisional Director)

Main fields of research

Statistical methods for genetic-epidemiological studies on complex diseases, particularly for genome-wide association analyses. Methodology of clinical studies, particularly adaptive statistical design methods and methods for data-dependent design changes.

Research projects

Title Central biostatistical support, data and data quality management for the research association on psychotherapy on eating disorders (Eating Disorders Diagnostic and Treatment Network, EDNET), subproject TP9

Principal investigator(s) N. Timmesfeld

Summary IMBE/KKS provide a biostatistical and data management unit for the EDNET-network. Our tasks, depending on single subprojects, comprise central randomization, data management, statistical design, monitoring and analysis, statistical supervision

Funded by BMBF, 01GV0623 – Federal Ministry of Education and Research

Funded period 2006 – 2013

Title R-package for optimal and flexible multistage designs for genetic-epidemiological studies

Principal investigator(s) H. Schäfer

Summary During the last years we developed optimal multistage designs for genome-wide association studies allowing a stepwise reduction of a genotyped markerset on promising markers during the course of a study. Also, we developed and enhanced the conditional rejection probability principle. Aim of this project is the development of a package for the statistical program system R implementing these procedures

Funded by BMBF, 01EZ0939 – Federal Ministry of Education and Research

Funded period 2010 – 2013

Title Molecular mechanisms on obesity – central statistical genomics and data management, subproject TP15a

Principal investigator(s) H. Schäfer

Summary With this subproject we provide biostatistical support for the genetic-epidemiologically orientated subprojects of the network. We provide genetic-statistical methods, particularly for the analysis of genome-wide association studies and the development and

implementation of reliable validation and replication strategies and gene-characterisation.

Funded by BMBF, 01GS0830 – Federal Ministry of Education and Research

Funded period 2008 – 2013

General information about the institute

Research Funding

96.658,30 €

Most important publications

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Institute of Pharmacology and Toxicology

**Professor R. Grosse, Professor F. Czubakyo
Professor T. Plant, Professor T. Worzfeld**

Main fields of research

We aim at understanding some of the principal cellular mechanisms that control cell shape and motility. Our goal is to identify and characterize relevant receptors and cytoskeletal signaling components that may represent novel molecular targets in particular for cancer and anti-invasive therapies. One focus of our institute is to study signal regulations of actin dynamics through Rho-GTPases and the formin family of actin nucleators and their interplay with nuclear actin dynamics and transcriptional events, which impinges on cancer cell behavior such as proliferation and invasiveness. Furthermore, current projects involve the analysis of calcium homeostasis and of plexin receptor signaling pathways to Rho proteins and the biological roles of plexins under physiological and pathophysiological conditions for the development of pharmacological agents, which target semaphorins and plexins.

Cytoskeletal Signaling

Dynamic rearrangement of the cytoskeleton regulates responses to a variety of extracellular signals that allow cells to move or to change shape. Actin dynamics is controlled by defined signaling pathways, which orchestrate the activity of distinct actin nucleation factors. The largest family of actin nucleators is represented by the formins, which are characterized by their highly conserved formin homology (FH) domain. Many diaphanous formins are regulated through physical interactions with Rho family proteins, which can function as molecular switches to relay signal instructions to various cellular responses. Interestingly, some formins such as mDia1 and mDia2 govern transcriptional activity of the Serum Response Factor (SRF) through their effects on actin polymerization. One current major focus of our lab is to understand formin-induced nuclear actin assembly for nuclear dynamics, which may have implications for cancer cell behavior, differentiation and nuclear architecture. For our investigations we employ or develop methods for 3D-collagen live cell assays, spatiotemporal optogenetic regulation of endogenous diaphanous or mDia formins as well as microscopy-based cytoskeletal analysis in living cells.

Function of nuclear actin in cancer cells

Recent progress in the field of nuclear actin dynamics has determined nuclear actin structures in somatic cells either under steady state conditions or

in response to extracellular signaling cues. Notably, these actin structures differ in size and shape as well as in their temporal appearance and dynamics. Thus, a picture emerges that suggests that mammalian cells may have different pathways and mechanisms to assemble specific nuclear actin filaments for distinct, yet mostly unknown functions. We investigate how growth factor receptors can trigger nuclear actin polymerization and how this impinges on the cancer cell phenotype. Some of these extracellular cues converge at the level of nuclear formin activity and subsequent regulation of transcriptional events.

Calcium Signaling

Properties and regulation of TRPC and TRPV channel subunits

The transient receptor potential (TRP) family of channel subunits is a relatively new and functionally diverse family of channel proteins with nearly 30 members in mammals. The subunits form cation channels, which are often Ca^{2+} permeable, and have a diversity of physiological roles ranging from sensory transduction to cation transport across epithelia. Because of these roles, TRP channels are putative pharmacological targets in a number of conditions. Our work focuses on the function, properties and regulation of members of the TRPC (canonical or classical) and TRPV (vanilloid) subfamilies of TRP channels. We study channels in native tissues, particularly neurons of the central nervous system, and channels formed by TRP subunits or mutants thereof after expression in mammalian cells.

Plexin Receptor Signaling

Plexins comprise a family of transmembrane proteins which serve as receptors for semaphorins. While they have initially been discovered as important axon guidance molecules during neural development, plexins are now recognized as key regulators of intercellular communication in many different organ systems. The current projects of the lab focus on the analysis of plexin signaling pathways and the biological role of plexins under physiological and pathophysiological conditions, particularly in cancer and during organ regeneration.

Research projects

Title The importance of formins for tumor progression and metastasis in vivo

Principal investigator(s) R. Grosse

Funded by DFG AI24/11-1 – German Research Foundation

Funding period 2009 – 2013

Title Signal transduction of diaphanous formins in tumor cell mobility and invasive cell migration

Principal investigator(s) R. Grosse

Funded by DFG GR 2111/2-1– German Research Foundation

Funding period 2010-2013

Title Ras-dependent pathways in human cancer“ Project A07: Die Rolle von CXorf22 in der Integrin-abhängigen Tumordinvasion

Principal investigator(s) R. Grosse

Funded by DFG, TR 17 – German Research Foundation, Transregional Collaborative Research Centre 17

Funding period 2011 – 2013

Title Mechanismus und Funktion von Plasmamembran Blebben und Freisetzung in Tumorzell-invasion

Principal investigator(s) R. Grosse

Funded by Deutsche Krebshilfe

Funding period 2012 – 2014

Title Mechanism of the Cellular Compartmentation and its relevance for Diseases – Project A14

Principal investigator(s) R. Grosse

Funded by DFG, Collaborative Research Centre 593 –

Funding period 2011 – 2014

Title Rolle von Plexinen für die Pathogenese des kolorektalen Karzinoms

Principal investigator(s) Grikscheit

Funded by Kempkes Foundation

Funding period 2014 – 2015

Title Die Bedeutung eines neu entdeckten dynamischen filamentösen Aktin-Netzwerks im Zellkern von Tumorzellen

Principal investigator(s) R. Grosse & F. Czubayko

Funded by Sander Foundation, No. 2013.149.1

Funding period 2014 – 2016

Title Nuclear actin turnover in cancer

Principal investigator(s) D. Brandt

Funded by UKGM – University Hospital Giessen and Marburg

Funding period 2014 – 2016

Title In vivo Bedeutung des MAL/SRF Repressors SCAI für die Tumormetastasierung

Principal investigator(s) R. Grosse

Funded by DFG GR 2111/2-2 – German Research Foundation

Funding period 2014 – 2017

Title Cdc42 signalling bei akutem Nierenversagen und Nierenfibrose

Principal investigator(s) T. Worzfeld

Funded by UKGM – University Hospital Giessen / Marburg

Funding period 2014 – 2016

Title Transmit-Einwerbung

Principal investigator(s) A. Aigner

Funded by Industry 2013.149.1

Funding period from 2009 on

Title Die Bedeutung eines neu entdeckten filamentösen Aktin-Netzwerks im Zellkern von Tumorzellen

Principal investigator(s) R. Grosse & F. Czubayko

Funded by Wilhelm Sander Foundation

Funding period 2014 – 2016

Most important publications

Nürnberg A, Kollmannsperger A, Grosse R (2014) Pharmacological Inhibition of Actin Assembly to Target Tumor Cell Motility. *Rev Physiol Biochem Pharmacol* 166:23-42

Grosse R, Vartiainen MK (2013) To be or not to be assembled: progressing into nuclear actin filaments. *Nat Rev Mol Cell Biol* 14(11):693-7

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Baarlink C, Grosse R (2014) Formin' actin in the nucleus. *Nucleus* 5(1):15-20

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Worzfeld T, Offermanns S (2014) Semaphorins and plexins as therapeutic targets. *Nat Rev Drug Discov* 13(8):603-21

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Research funding 649.145,09 €

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Emil von Behring-Library, Department of the History of Medicine

**Research Group Professor Dr. Sahmland,
Dr. K. Grundmann, Dr. U. Enke, N. Ulrich, M.A.**

Main fields of research

- Emil von Behring and his scientific work (Enke, Grundmann)
- History of Anatomy and the Anatomical Collection in Marburg (Grundmann, Ulrich)
- History of the Hessian High Hospitals (Sahmland)
- History of charitable and curing in-patient Treatment in Hesse (Sahmland)

Research projects

Title Provenience-research and digitalization of the objects of the Marburg Anatomical Collection

Principal investigator(s) N. Ulrich

Summary To this day, there has been no comprehensive digital collection catalogue of the Anatomical Collection at the University of Marburg. The aims of the project are to profoundly file the entire collection and to gather information about at least some prominent objects especially of the osteological collection. In cooperation with the Senckenberg-Museum in Frankfurt/M. these data are entered in the database Aquila.

Funded by FB 20, Philipps-University Marburg

Funding period 2013 – 2016

Title Analysis, Digitalization and online-Presentation of the heritage of Emil von Behring

Principal investigator(s) C. Friedrich, K. Grundmann, U. Enke & M. Kahler

Summary In the project central sources of the German history of medicine, pharmacy and science were presented to the public and researchers as an online-Database. Since May 2012, the digital copies of all hand-written manuscripts, pictures and historical business documents of the bacteriologist Emil von Behring (1854 – 1917) can be found on the internet (www.uni-marburg.de/behring-digital).

Funded by DFG, FR 887/4-1, 4-2, 4-3 – German Research Foundation

Funding period 2009 – 2013

Title Biography of Emil von Behring (1854-1917)

Principal investigator(s) U. Enke

Summary Based on the digitalized heritage of Emil von Behring a biography of him as a person, a scientist and an entrepreneur will be authored according to present scientific standards. Main focus will be laid on Behring's personality, considering the

background of the social, political, economical and scientific development in Germany's Imperial Era.

The constitution of a pharmaceutical corporation by a scientist (Behringwerk, 1904) is a unique considerable feature. Due to the vast source materials Behring's research can be newly evaluated in terms of *science studies* and become connected to a broadly based international scientist network.

Funded by DFG, EN 1068/2-1 – German Research Foundation

Funding period 2014 – 2017

General information about the institute

Research funding 15.689,12 €

Most important publications

Sahmland I (2013) Die Armenfürsorge in der Elisabeth-Rezeption des 16. Jahrhunderts, in: Klaus Bergdolt, Lothar Schmitt, Andreas Tönnemann (Hg.): Armut in der Renaissance (Wolfenbütteler Abhandlungen zur Renaissanceforschung, Bd. 30), Wiesbaden, S. 159-185

Sahmland I (2013) Die Erfassung des Vorkommens des Cretinismus in Kurhessen 1856, in: Schriftenreihe der Deutschen Gesellschaft für Geschichte der Nervenheilkunde, Bd. 19, 2013, S. 263-286

Konzeption und Ausführung einer neuen Behring-Ausstellung in der Bahnhofstraße 7 (Behring-Route): Blut ist ein ganz besonderer Saft – Emil von Behring (1854 – 1917). Eröffnung Dezember 2013 (Grundmann)

Enke U (2014): Joseph Benedikt Kurigers embryologische Wachstafel nach Soemmerring im Museum Anatomicum Marburg, in: Tote Objekte – lebendige Geschichten. Exponate aus den Sammlungen der Philipps-Universität Marburg, Hrsg. I. Sahmland und K. Grundmann, Petersberg: 2014: S. 152-175

Enke U (2014) Behrings Nachlässe – Behrings Biographien, in: Berichte zur Wissenschaftsgeschichte 37: S. 216-239

Grundmann K (2014) [...] durch das Schwert vom Leben zum Tode bringen [...] – Schädel und Totenmasken von hingerichteten Verbrechern in der Marburger Anatomischen Sammlung, in: Tote Objekte – lebendige Geschichten. Exponate aus den

Sammlungen der Philipps-Universität Marburg, Hrsg. I. Sahmland und K. Grundmann, Petersberg: S. 55-77

Grundmann K (2014) Gesammeltes Wissen – Zur Geschichte des Sammelns, in: Schätze der Wissenschaft. Die Sammlungen, Museen und Archive der Philipps-Universität Marburg, Hrsg. Ch. Otterbeck, J. Schachtner, Marburg 2014, S. 17-24

Sahmland I (2014) Die stationäre karitative und medizinisch-kurative Versorgungslandschaft in Hessen vom Mittelalter bis ins 20. Jahrhundert. Vorstellung eines Forschungsvorhabens, in: Arno Görgen, Thorsten Halling (Hrsg.): Verortungen des Krankenhauses (Kultur Anamnesen. Schriften zur Geschichte und Philosophie der Medizin und der Naturwissenschaften, Bd. 6), Stuttgart: Steiner, S. 101-115

Sahmland I (2014) Das Elend der menschlichen Kreatur: das hockende Skelett in der Anatomischen Sammlung der Philipps-Universität Marburg, in: Tote Objekte – lebendige Geschichten. Exponate aus den Sammlungen der Philipps-Universität Marburg, Hrsg. I. Sahmland und K. Grundmann, Petersberg: 2014, S. 125-151

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Institute of Clinical Cytobiology and Cytopathology

Research Groups Professor R. Lill Professor R. Jacob

Main fields of research

Research in the institute aims to elucidate molecular mechanisms of key cellular processes by using genetic, cell biological, biochemical and spectroscopic approaches. One focus of our work is on the biogenesis of iron-sulfur proteins in mitochondria, cytosol and nucleus and its links to cellular iron homeostasis and genome integrity. Another topic analyzes protein sorting to the apical membrane of polarized cells. Biochemical and microscopic techniques are applied to unravel cellular compartments, transport pathways and protein components involved in the trafficking of newly synthesized protein to the apical cell surface. Another focus is on the function of the transcription factor Miz1.

Research projects

Title The role of mitochondria in the maturation of cytosolic and nuclear iron-sulfur proteins

Principal investigator(s) R. Lill

Summary Mitochondria are essential cell organelles executing an indispensable function in the biogenesis of cytosolic and nuclear iron-sulfur (Fe/S) proteins. In this project we biochemically and structurally characterize the components involved in the transport of a sulfur- and glutathione-containing compound to the cytosol to support cytosolic-nuclear Fe/S protein maturation and other sulfur-requiring processes.

Funded by DFG, SFB593 TP A1 – German Science Foundation, Collaborative Research Centre 593

Funding period 2003 – 2014

Title Mechanism and Regulation of the Cellular Compartmentalization of Iron between Mitochondria and Cytosol

Principal investigator(s) U. Mühlenhoff

Summary The coordinated distribution of iron between intracellular compartments and the adaptation of iron uptake to intracellular demands are central for a balanced iron homeostasis. Mitochondria, the major iron-utilizing cell organelles, are critical regulators of cellular iron metabolism. This project focuses on the role of mitochondria in iron-responsive gene expression and the functional characterization of mitochondrial iron acquisition.

Funded by DFG, SFB593 TP A2 – German Research Foundation, Collaborative Research Centre

Funding period 2003 – 2014

Title Role of iron-sulfur protein biogenesis in the regulation of cellular iron uptake and intracellular iron distribution

Principal investigator(s) R. Lill

Summary The link between mitochondrial Fe/S proteins biogenesis, cellular iron uptake and intracellular iron distribution is poorly understood to date. In collaboration with TP A1 and A2 of SFB 593 this project tries to elucidate these connections using *Saccharomyces cerevisiae* and human cell culture as model systems.

Funded by DFG, Research Training Group 1216, Intra- and intercellular transport and communication

Funding period 2006 – 2015

Title Iron-sulfur protein biogenesis in eukaryotes

Principal investigator(s) R. Lill

Summary We biochemically elucidate the function of components involved in iron-sulfur cluster synthesis and insertion into apoproteins in mitochondria, cytosol and nucleus of eukaryotic cells. We investigate the link of Fe/S protein biogenesis to DNA damage repair and genome maintenance mediated by the presence of Fe/S clusters in DNA polymerases and helicases involved in the synthesis and repair of DNA.

Funded by Max-Planck Society, Fellowship

Funding period 2009 – 2014

Title Optimization of eukaryotic iron-sulfur protein biogenesis for biosynthetic purposes

Principal investigator(s) R. Lill

Summary Iron-sulfur (Fe/S) proteins are functional as enzymes, electron carriers and sensors in a multitude of metabolic and regulatory reactions. We try to better understand the function of the components involved in Fe/S protein biogenesis to use this knowledge for optimal maturation of Fe/S proteins that have been artificially introduced into cells as parts of newly constructed metabolic or regulatory pathways.

Funded by LOEWE Focus – Synthetische Mikrobiologie (SynMikro)

Funding period 2010 – 2015

Title Sensing and intracellular delivery of iron in fungi

Principal investigator(s) R. Lill & U. Mühlenhoff

Summary The iron metabolism in fungi is regulated on a transcriptional level and tightly linked to the biogenesis of iron-sulfur (Fe/S) proteins. We aim to elucidate the molecular basis of this link by studying how the iron-sensitive transcription factors respond

to changing iron concentrations. We have identified the cellular sensor for initiating the transcriptional program for fungal high iron detoxification.

Funded by DFG, SFB 987 TP B2 – German Research Foundation, Collaborative Research Centre

Funding period 2012 – 2016

Title Role of redox-active thiols in the biogenesis of cytosolic and nuclear iron-sulfur proteins

Principal investigator(s) R. Lill

Summary Fe/S protein biogenesis is a complex process requiring numerous components in mitochondria and cytosol. This proposal is centered on the thiol – metal-thiolate switch occurring during Fe/S protein assembly in the cytosol-nucleus of eukaryotes. In particular, the proposal addresses the role of a hyper-reactive Cys residue of the CIA protein Cia2 which is essential for cell viability.

Funded by DFG, SPP 1710 – German Research Foundation

Funding period 2012 – 2016

Title Identification of vesicle components involved in apical protein transport

Principal investigator(s) R. Jacob

Summary Polarized epithelial cells contain a plasma membrane that is divided into two separate compartments. Each membrane compartment is composed of distinct proteins and lipids, which are sorted by specific mechanisms into the correct membrane domain. Compartments that are traversed by these pathways as well as the implicated protein- and lipid-components will be analyzed in this project.

Funded by DFG, SFB593 TP A9 – German Research Foundation, Collaborative Research Centre

Funding period 2005 – 2014

Title Characterisation of motor proteins involved in apical targeting

Principal investigator(s) R. Jacob

Summary For apical protein trafficking lipid raft-dependent and -independent sorting has been described. The sorting mechanism itself, interactions between clusters within vesicular lumina and components on the cytosolic surface of newly formed vesicles are completely unknown. Especially motor proteins that are required for apical vesicle transport remain to be identified. Their characterization is the main focus of this research project.

Funded by DFG, Research Training Group 1216, Intra- and intercellular transport and communication

Funding period 2006 – 2015

Title Late onset neuropathy in mice lacking functional Miz1 in Schwann cells

Principal investigator(s) H.P. Elsässer

Summary Deletion of the Miz1 POZ domain in Schwann cells induces a neuropathy in three month old mice, with spontaneous partial remission after one month. We have documented the pathology of the nerve tissue. We unravel the molecular basis of this neuropathy to find target proteins for therapeutic approaches. We are interested in the regeneration of nerve tissue which accompanies dysmyelination.

Funded by DFG, EL 125/6-1 – German Research Foundation

Funding period 2013 – 2016

General information about the institute

Research funding 3.055.769,08 €

Most important publications

Stehling O, Mascarenhas J, Vashisht AA, Sheftel AD, Niggemeyer B, Röscher R, Pierik AJ, Wohlschlegel JA, Lill R (2013). Human CIA2A-FAM96A and CIA2B-FAM96B integrate iron homeostasis and maturation of different subsets of cytosolic-nuclear iron-sulfur proteins. *Cell Metab* 18: 187-198

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Weber M, Gawanbacht A, Habjan M, Rang A, Borner C, Schmidt AM, Veitinger S, Jacob R, Devignot S, Kochs G, García-Sastre A, Weber F (2013) Activation of RIG-I by incoming RNA virus nucleocapsids containing a 5'-triphosphorylated genome. *Cell Host & Microbe* 13: 336-346

Srinivasan V, Pierik AJ, Lill R (2014) Crystal structures of nucleotide-free and glutathione-bound mitochondrial ABC transporter Atm1. *Science* 343:1137-1140

Weber H, Freibert SA, Gallo A, Heidenreich T, Linne U, Amlacher S, Hurt E, Mühlenhoff U, Banci L, Lill R (2014) Functional reconstitution of mitochondrial Fe/S cluster synthesis on Isu1 reveals the involvement of ferredoxin. *Nat Commun* 5:5013

Paul V, Lill R (2014) Snapshot: Eukaryotic Fe-S Protein Biogenesis. *Cell Metab* 20:384

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Director: Professor Dr. Roland Lill

Institute of Immunology

**Research Groups Professor S. Bauer
Professor M. Schnare, Professor M. Bacher, Dr.
P. Yu, Dr. A. Kaufmann**

Main fields of research

Research activities of the Institute for Immunology encompass innate immune recognition of endogenous retroviruses and nucleic acids derived from pathogens, the function of antimicrobial proteins during inflammation, IgE regulation and immunological aspects of neuroinflammation in early Alzheimers disease.

Research projects

Title Generation and characterization of a RIG-I ligand derived from endogenous RNA by RNase digestion

Principal investigator(s) A. Kaufmann & S. Bauer

Summary RNase-digested self-RNA acts in addition to exogenous viral RNA as ligand for the cytoplasmic RNA sensor RIG-I. This immunostimulatory potential is triggered by a distinct structure generated by digestion with single-strand specific RNases (e.g. RNase L, RNase I). In this study we have started to identify the RIG-I-activating structure and sequence of self-RNA by next generation sequencing.

Funded by DZIF – German Centre for Infection Diseases

Funding period until 2015

Title Role of the RNA modifications 2'-O-methylation and N6-methyladenosine in viral pathogenicity

Principal investigator(s) S. Bauer

Summary Since RNA modifications such as 2'-O-methylation and N6-methyladenosine negatively modulate Toll-like receptor 7-mediated immune recognition of RNA, we will investigate if influenza virus genomic RNA is 2'-O-methylated and what role N6-methyladenosine in influenza mRNA may play for viral pathogenicity, infectivity and immune recognition. In addition, we will analyze a possible antagonistic function of 2'-O-methylated host cell tRNA associated with VSV or SeV in early immune escape from TLR7 recognition in plasmacytoid dendritic cells.

Funded by DFG, SFB 1021 – German Research Foundation, Collaborative Research Centre 1021

Funding period until 2016

Title Role of innate immune receptors in preventing hyper-inflammation and promoting repair during bacterial pneumonia

Principal investigator(s) S. Bauer & B. Opitz (Charité Berlin)

Summary This project focuses on the function of the TLR/interleukin-1 receptor / (TIR) family during pneumonia. ST2 and TIR8 (SIGIRR) have been implicated in the negative control of PRR-mediated inflammatory responses and/or promotion of repair processes. ST2 serves as a receptor for the DAMP IL-33 and is involved in recruiting type 2 innate lymphoid cells (ILC2) that in turn might regulate healing processes in the lung. We will investigate the role of ST2 in regulation the sub-acute phase of bacterial pneumonia after detection of the DAMP IL-33. Furthermore, the requirements and ligands for the immune-regulatory function of TIR8 during pneumonia will be analyzed.

Funded by DFG, SFB/TR84 – German Research Foundation, Transregional Collaborative Research Centre 84

Funding period 2014 – 2018

Title Development and function of respiratory macrophages and dendritic cell subsets during bacterial pneumonia

Principal investigator(s) S. Bauer, H. Hackstein (UKGM, Giessen) & J. Lohmeyer (UKGM, Giessen)

Summary Bacterial pneumonia is a leading cause of community acquired as well as nosocomial infections and death. Lung resident dendritic cells (DC) and macrophages (MP) recognize bacterial pathogens, initiate immune responses and regulate inflammation. Several DC subsets, such as CD103+ and CD103- conventional migratory DCs (cDCs), monocyte-derived DCs (moDCs) and plasmacytoid DCs as well as functionally distinct lung MP populations have been described but their precise contribution to the respiratory immune response during bacterial infections remains unresolved. We will address the role of DC and MP subsets and the mechanism of ADAR1-dependent DC and MP development in immune responses in the lung.

Funded by DFG, SFB/TR84 – German Research Foundation, Transregional Collaborative Research Centre 84

Funding period 2014 – 2018

Title Macrophage migration inhibitory factor and neuroinflammation in early Alzheimers disease

Principal investigator(s) M. Bacher

Summary One major aim of this proposal is to evaluate whether the early and sustained increase of MIF might be an important trigger for neuroinflammatory processes during the progress of the neurodegeneration in Alzheimer's dementia. To achieve this goal, we plan to use in vitro experiments with primary neuronal and microglia cell cultures, and we would like to substantiate our findings by

experiments using transgenic APP mouse models.

Funded by DFG – German Research Foundation

Funding period until 2015

Title The B cell response against Endogenous Retrovirus

Principal investigator(s) P. Yu

Summary We have demonstrated that nucleic acid recognizing Toll-like receptors (TLR) 3, -7 and -9 are an essential component of the defense against endogenous retroviruses. Surprisingly it seems that the TLR7 mediated activation of the endogenous retrovirus specific immune response is most essential for protection. We are currently establishing a in vitro B cell model to dissect the B cell receptor-TLR interactions, in order to understand the role of B cells in protection against endogenous and exogenous retroviruses.

Funded by DFG – German Research Foundation

Funding period 2014 – 2016

Title Analysis of the role of IgE in an in vivo model of systemic lupus erythematosus

Principal investigator(s) P. Yu

Summary IgE production is tightly regulated and normally associated with allergic diseases. However recently evidence in humans and mouse models arose, which suggests that IgE could play an effector or modulator role in autoimmunity. To study this hypothesis, we have generated double mutant mice, which display a genetically enhanced IgE immune response and are prone to develop lupus-like autoimmunity. We are currently studying the histochemical and immunological changes in the target organ kidney and secondary lymphatic organs. These studies have the potential to further our understanding of B cell mediated autoimmunity by establishing a pathogenic link between IgE and lupus inflammation.

Funded by Philipps University Marburg & Thyssen Foundation

Funding period 2013 – 2015

Title The influence of bactericidal/permeability-increasing protein (BPI) and BPI-related proteins on the infectivity on human pathogenic viruses

Principal investigator(s) M. Schnare

Summary The release of antimicrobial products prevents the uncontrolled growth and spread of pathogens within the host. Besides their well characterized function in controlling bacterial infections different antimicrobial proteins and peptides display antiviral activity as well.

We investigate the role of the antimicrobial protein BPI and BPI-related proteins in the control of virus replication and the underlying molecular mechanisms.

Funded by von Behring – Röntgen Foundation

Funding period until 2016

General information about the institute

Research funding

1.386.470,14 €

Most important publications

Lübben W, Turqueti-Neves A, Okhrimenko A, Stöberl C, Schmidt V, Pfeffer K, Dehnert S, Wünsche S, Storsberg S, Paul S, **Bauer S**, Riethmüller G, Voehringer D, **Yu P** (2013) IgE knock-in mice suggest a role for high levels of IgE in basophil-mediated active systemic anaphylaxis. *Eur J Immunol* 43 (5):1231-42

Noelker C, Stuckenholtz V, Reese JP, Alvarez-Fischer D, Sankowski R, Rausch T, Oertel WH, Hartmann A, van Patten S, Al-Abed-Y, **Bacher M** (2013) CNI-1493 attenuates neuroinflammation and dopaminergic neurodegeneration in the acute MPTP mouse model of Parkinson's disease. *Neurodeg Dis* 12:103-10

Czudai-Matwich V, **Schnare M**, Pinkenburg O (2013) A simple and fast system for cloning influenza A virus gene segments into pHW2000- and pCAGGS-based vectors. *Arch Virol* 58(10):2049-58

Atanasova S, Hirschburger M, Jonigk D, Obert M, Petri K, Evers A, Hecker A, Schmitz J, **Kaufmann A**, Wilhelm J, Chakraborty T, Warnecke G, Gottlieb J, Padberg W, Grau V (2013) A relevant experimental model for human bronchiolitis obliterans syndrome. *J Heart Lung Transplant* 32(11):1131-9

Roettger Y, Du Y, **Bacher M**, Zerr I, Dodel R, Bach JP (2013) Immunotherapy in Prion Diseases. *Nat Rev Neurol* 9:98-105

Reimer E, Somplatzki S, Zegenhagen D, Hänel S, Fels A, Bollhorst T, Hovest LG, **Bauer S**, Kirschning CJ, Böldicke T (2013) Molecular cloning and characterization of a novel anti-TLR9 intrabody. *Cell Mol Biol Lett* 18(3):433-46

Schwartz C, Turqueti-Neves A, Hartmann S, **Yu P**, Nimmerjahn F, Voehringer D (2014) Basophil-mediated protection against gastrointestinal helminths requires IgE-induced cytokine secretion. *PNAS* 111 (48):E5169-77

Martins M, McCarthy A, Baxendale R, Guichard S, Magno L, Kessar N, El-Bahrawy M, **Yu P**, Katan M (2014) Tumor suppressor role of phospholipase C epsilon in Ras-triggered cancers. *PNAS* 111 (11): 4239-44

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Director: Professor Dr. Stefan Bauer

Institute of Medical Microbiology and Hospital Hygiene

Research Group Professor M. Lohoff

Main fields of research

We are focused on the regulation CD4⁺ T-cell subset differentiation, particularly on the role of IRF transcription factors. We have previously shown that IRF4 is mandatory for generating the subsets Th2, Th9, Th17 and Tfh cells. During this research period, we have demonstrated a novel crucial role of IRF4 for developing the low cytotoxic CD8⁺ T cell subpopulation Tc17. Furthermore, we have delineated a reversed helper function of Tc17 cells for CD4⁺ T cells during autoimmunity of the central nervous system. Currently, we mutagenize IRF4 to test, if particular parts of IRF4 are responsible for selective functions among those mentioned.

Research projects

Title Analysis of the role of the transcription factor IRF4 for T lymphocyte subset differentiation

Principal investigator(s) M. Lohoff

Summary We have shown that IRF4 is crucial for developing the Tc17 subset among CD8⁺ cells, which lacks cytotoxicity but, as we showed, has an unexpected helper function for CD4⁺ T cells. These data reverse the common dogma of CD4⁺ helper function for development of CD8⁺ T cell functions.

Funded by DFG – German Research Foundation, von Behring-Röntgen Foundation

Funding period DFG until 2014

von Behring-Röntgen Foundation until 2016

Title Analysis of functional modules of IRF4 with mutually exclusive sub-functions in CD4⁺ T cells

Principal investigator(s) M. Lohoff

Summary We have shown that retroviral overexpression of IRF4 rescues the IRF4-dependent functions in T cells from IRF4-deficient mice. Currently, we attempt to insert mutations into the IRF4 gene and overexpress these altered IRF4 molecules in comparison to normal IRF4. The aim of the study is to identify critical functional modules of IRF4 which, if destroyed, create an IRF4 molecule with more specific sub-functions such as the capacity to support differentiation of only one T cell subset, but not others.

Funded by CholHo

Funding period 2014 – 2016

Most important publications

Huber M, Heink S, Pagenstecher A, Reinhard K, Ritter J, Visekruna A, Guralnik A, Bollig N, Jeltsch K, Heinemann C, Wittmann E, Buch T, Prazeres da Costa O, Brüstle A, Mak TW, Brenner D, Mittrücker HW,

Tackenberg B, Kamradt T, **Lohoff M** (2013) Pathogenic IL-17A-dependent help of Tc17 cells for Th17 cells to initiate autoimmune encephalomyelitis. *J Clin Invest* 123:247-260

Abass E, Bollig N, Reinhard K, Camara B, Mansour D, Visekruna A, **Lohoff M**, Steinhoff U (2013) rKLO8, a Novel *Leishmania donovani*-Derived Recombinant Immunodominant Protein for Sensitive Detection of Visceral Leishmaniasis in Sudan. *PLOS Neglected Tropical Diseases* 7:1-10

Huber M, **Lohoff M** (2013) IRF4 Provides Rations for Cytotoxic CD8(+) T Cell Soldiers. *Immunity* 39(5):797-9

Grusdat M, McIlwain DR, Xu HC, Pozdeev VI, Knievel J, Crome SQ, Robert-Tissot C, Dress RJ, Pandya AA, Speiser DE, Lang E, Maney SK, Elford AR, Hamilton SR, Scheu S, Pfeffer K, Bode J, Mittrücker H.-W., **Lohoff M**, Huber M, Haeussinger D, Ohashi PS, Mak TW, Lang KS, Lang PA (2014) IRF4 and BATF are critical for CD8T-cell function following infection with LCMV. *Cell Death and Differentiation* 21:1050-1060

Huber M, **Lohoff M** (2014) IRF4 at the crossroads of effector T-cell fate decision. *Eur J Immunol* 44(7):1886-95

Research Group PD M. Huber

Main fields of research

Our group is focused on the molecular regulation CD4⁺ and CD8⁺ T-cell differentiation and function in protective and pathologic immune responses. During the research period (2013/2014), our group has demonstrated a crucial role of the transcription factor interferon regulatory factor (IRF)4 for the development of the cytotoxic T lymphocytes (CTLs) and for “low” cytotoxic CD8⁺ T cell subpopulations including Tc9 and Tc17 cells. Furthermore, we have delineated the supportive function of low cytotoxic Tc9 and Tc17 cells for CD4⁺ T cell activity in allergic airway disease and autoimmunity of the central nervous system, respectively.

Research projects

Title Analysis of the role of the transcription factor IRF4 for cytotoxic T lymphocyte effector function and memory development

Principal investigator(s) M. Huber

Summary We have shown that IRF4 is crucial for the protective CD8⁺ T-cell response to the bacterium

Listeria monocytogenes (Lm). Although dispensable for early activation, IRF4 was essential for establishment of fully functional effector and memory pool. IRF4 regulated these functions, acting as both transcriptional repressor and activator. The direct positive regulation of *Prdm1* gene expression contributed to the IRF4 effects.

Funded by DFG – German Research Foundation

Funding period 2010 – 2015

Title Analysis of the role of the transcription factor IRF4 for Tc17 effector function in autoimmune encephalomyelitis

Principal investigator(s) M. Huber

Summary We have shown that IRF4 is required for the development of IL-17-producing CD8⁺ T (Tc17) cells. IRF4 regulated Tc17 differentiation by balancing the levels of TFs crucial for type 17, Treg and CTL- differentiation. A novel function of CD8⁺ T cells became obvious, because IRF4-sufficient Tc17 cells provided “reverse help” via cell-associated IL-17A to CD4⁺ T cells for Th17-mediated encephalomyelitis.

Funded by DFG – German Research Foundation and BiogenIdec

Funding period 2010-2015, 2014-2016

Title Analysis of the role of the transcription factor IRF4 for Tc9 effector function in allergic airway disease

Principal investigator(s) M. Huber

Summary We have demonstrated that murine CD8⁺ T cells activated in the presence of IL-4 plus TGF- β develop into transient IL-9 producers (Tc9 cells) characterized by low cytotoxic function. These cells required STAT6 and IRF4 for the differentiation and displayed a supportive function in Th2-dependent airway inflammation. This suggests that Tc9 cells might be a therapeutic target in allergic disorders.

Funded by DFG – German Research Foundation

Funding period 2010 – 2015

Most important publications

Huber M, Lohoff M (2013) IRF4 provides rations for cytotoxic CD8⁺ T cell soldiers. *Immunity* 39:797-59

Rackowski F, Ritter J, Heesch K, Schumacher V, Höcker L, Raifer H, Klein M, Bopp T, Harb H, Kesper DA, Pfefferle PI, Grusdat M, Lang PA, Mittrücker H-W and **Huber M** (2013) The transcription factor interferon regulatory factor 4 controls peripheral CD8⁺ T cell differentiation. *Proc Natl Acad Sci USA* 110:15019-24

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(2013) Tc9 cells, a new subset of CD8⁺ T cells, support Th2-mediated airway inflammation. *Eur J Immunol* 43:606-618 Article selected for “In this issue” section of *EJI*.

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Grusdat M, McIlwain DR, Xu HC, Pozdeev VI, Knievel J, Crome SQ, Robert-Tissot C, Dress RJ, Pandya AA, Speiser DE, Lang E, Maney SK, Elford AR, Hamilton SR, Scheu S, Pfeffer K, Bode J, Mittrücker HW, Lohoff M, **Huber M, Häussinger D, Ohashi PS, Mak TW, Lang KS, Lang PA** (2014) IRF4 and BATF are critical for CD8⁺ T-cell function following infection with LCMV. *Cell Death Differ* 21:1050-60

Research Group Professor Steinhoff

Main fields of research

Investigation of anti-inflammatory control mechanisms in the intestine. Our research focuses mainly on three main topics, i.e. a) the impact of normal dietary proteins on maintenance of intestinal homeostasis and regulation of inflammatory responses b) the effects of short chain fatty acids produced by intestinal bacteria on regulatory T cells and c) the importance of the intestinal microflora on intraluminal anti-bacterial defense against enteropathogenic *E. coli*.

Research projects

Title Control of intestinal inflammation by food and intestinal microflora

Principal investigator(s) A. Visekruna, Anton Volkov & U. Steinhoff

Summary Normal dietary proteins activate T cells predominantly in Peyer's patches of the gut. These cells remain innocuous because they will die after activation and removal of such dead T cells is crucial for the production of anti-inflammatory substances. Accordingly, animals fed with a protein-free diet proteins by amino acids are highly susceptible to inflammation.

Funded by von Behring-Röntgen Foundation –and LOEWE Centre – UGMLC; German Science Foundation – Collaborative Research Centre SFB 650

Funding period 2012 – 2015

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Tel.:++49 (0) 6421-28 66455
Director: Professor Dr. Michael Lohoff

Most important publications

Volkov A, Hagner S, Löser S, Raifer H, Hellhund A, Garn H, **Steinhoff U** (2013) β 5i Subunit Deficiency of the Immunoproteasome Leads to Reduced Th2 Response in OVA Induced Acute Asthma. *PLoS One* 4, 8(4):e60565

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Visekruna A, Linnerz T, Martinic V, Vachharajani N, Hartmann S, Harb H, Joeris T, Pfefferle P, Hofer J, **Steinhoff U** (2014) Transcription factor c-Rel plays a crucial role in driving anti-CD40-mediated innate colitis. *Mucosal Immunology* 8(2):307-15

Yun Y, Srinivas G, Kuenzel S, Linnenbrink M, Bruce K, **Steinhoff U**, Baines JF, Schaible U (2014) Environmentally determined differences in the murine lung microbiota and their relation to alveolar architecture. *PLoS One* 9 (12):e113466

Abass E, Martinkovic F, Semiao-Santos SJ, Sundar S, Walden P, Piarroux R, el Harith A, Lohoff M, **Steinhoff U** (2014) Heterogeneity of *Leishmania Donovanii* parasites complicates diagnosis of visceral Leishmaniasis: Comparison of different serological tests in three endemic regions. *Plos One* Accepted

General information about the institute

Research funding

496.707,62 €

Institute of Virology

Research group Professor Becker

Main fields of research

Research performed at the Institut für Virologie mainly focuses on highly pathogenic viruses that can be transmitted from animal to man. Examples are viruses causing fulminant hemorrhagic fevers, (Marburg virus, Lassa virus, Rift Valley Fever virus), highly pathogenic influenza virus (bird flu), Nipah virus, SARS and others. Work with those viruses is performed under highest safety conditions in a modern BSL-4 laboratory. With this laboratory, Marburg University represents a unique academic competence center for diagnostics and research on highly pathogenic viruses. Researchers at the Institut für Virologie are interested in interactions between viruses and the host that determine pathogenicity of the pathogen. The work group Parasitology within the Institut für Virologie carries out studies to characterize biosynthetic pathways in plasmodia, trypanosomes and toxoplasma.

Research projects

Title Deutsches Zentrum für Infektionsforschung (DZIF) – TTU Emerging Infections

Principal investigator(s) S. Becker

Summary The German Centre for Infectious research (DZIF) is one of the health centers for translational research funded by the federal ministry of research. The section Emerging Infections, coordinated by the Institute of Virology, focuses on the development of diagnostics, emergency vaccines and antivirals against novel viruses. In Marburg we develop and test two platforms for rapid vaccine development and establish animal models to be used in cases of emergencies under highest safety precautions (BSL-4). In the funding period 2013 - 2015 one vaccine platform (recombinant influenza virus) was established and emergency vaccines against MERS coronavirus were tested for immunogenicity and efficacy.

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2013 – 2015

Title The role of O-glycosylation of the Marburg virus surface glycoprotein GP

Principal investigator(s) S. Becker

Summary Viral surface glycoproteins represent the communication interface between the virus and the host. These molecules mediate receptor recognition and fusion with the host cell membranes. The surface glycoproteins of Marburg and Ebola virus are



highly O-glycosylated which is a rare feature. We produced a mutant surface protein missing the O-glycan attachment sites and test its function in cell culture. Surprisingly, the missing O-linked sugars which represent approximately 50% of the molecular mass did neither impair intracellular transport nor receptor recognition. Further on, recombinant Marburg virus missing the O-glycosylation was constructed and rescued. Characterization of the virus is ongoing.

Funded by Leibniz Graduate School for Emerging Infections (EIDIS)

Funding period 2012 – 2015

Title Morphogenesis and transport of filovirus nucleocapsids

Principal investigator(s) S. Becker & O. Dolnik

Summary Marburg virus replication in cells results in formation of inclusions in the cytoplasm. Inclusions represent sites of nucleocapsid morphogenesis, viral replication and transcription. We investigate the structure and formation of inclusions and nucleocapsids and how mature nucleocapsids are transported to the sites of budding. Live cell imaging was established for fluorescent viruses under BSL-4 conditions. Thereby identified interfaces between cellular and viral proteins may represent targets for antiviral intervention.

Funded by DFG, SFB 593, TPB12 – German Research Foundation, Collaborative Research Centre 593

Funding period 2011 – 2014

Title Quality Assurance Exercises and Networking on the Detection of Highly Infectious Pathogens (Quandhip)

Principal investigator(s) S. Becker & M. Eickmann

Summary The Joint Action (JA) aims to link and consolidate the objectives of two existing networks (EQADeBa and ENP4-Lab). The primary objective of the current application is to stabilise both network activities that link 33 partners from 21 European

countries highly specialised and advanced laboratories. This will ensure the universal exchange of best diagnostic strategies able to support a European response strategy to outbreaks of highly pathogenic infectious agents plus generating a biodiverse repository of reference materials. The JA will provide a supportive European infrastructure and strategy for bacterial antibiotic susceptibility testing, training, and external quality assurance exercises (EQAE) according to biosafety and biosecurity review of current practices.

Funded by EU

Funding period 2011 – 2014

Title European Infrastructure on highly pathogenic agents (ERINHA)

Principal investigator(s) S. Becker & M. Eickmann

Summary ERINHA aims to build a pan-European research infrastructure aiming to reinforce the European coordination and capacities for the study and the surveillance of highly pathogenic micro-organisms. The ERINHA infrastructure will provide access to state-of-the-art BSL4 facilities for the European scientific community to enhance basic and finalised research activities and diagnostic activities

Funded by EU

Funding period 2010 – 2013

Title Comparative analyses of nucleoproteins of Arenaviruses

Principal investigator(s) S. Becker & S. Wolff

Summary Characterisation of the nucleoprotein NP derived from Junin (JUNV) and Tacaribe (TCRV), which are closely related and prototypes for HF-causing and non-pathogenic New world arenaviruses. Main focus is the identification and analysis of motifs within NP for their effect on viral transcription/replication and budding, in particular with respect to the involvement of putative late domains and caspase cleavage sites.

Funded by Manchot-Foundation

Funding period 2010 – 2013

Title Analysis of host cell proteins for the intracellular transport of Marburg virus nucleocapsids

Principal investigator(s): S. Becker & M. Klüver

Summary The surface of Marburg virus nucleocapsids is covered with the proteins VP30, VP35, VP24 and L and it cannot be ruled out that one or more of these proteins is involved in transport processes and interactions with the cytoskeleton. Therefore this project focuses on identification of cellular interaction partners of the Marburg virus proteins VP30, VP35, VP24 and L by using yeast two-hybrid screenings. Special attention is paid on motor proteins and proteins involved in intracellular transport processes. Afterwards found interactions will be characterised more into detail.

Funded by: Manchot Foundation

Funding period: 2012 – 2015

Title Regulation der filoviralen RNA-Synthese

Principal investigator(s) S. Becker, R. Hartmann (Pharm. Chemie)

Summary: Filovirus transcription is dependent on a filoviral-specific transcription factor VP30. The mechanism of how VP30 regulates viral transcription and replication is unknown. This project aims at elucidating the composition and function of the viral transcriptase in complex with the viral genome. The focus of the current funding period is the interaction between VP30 and the viral RNA.

Funded by DFG, SFB 1021, TP A02 – German Research Foundation, Collaborative Research Centre 1021

Funding period 2013 – 2016

Title Die Adaption von Marburg Virus und Nagetiere als Modell für virale Pathogenese

Principal investigator(s) S. Becker

Summary: While Marburg virus is lethal for humans and non-human primates, infection of rodents results in no disease. Only after adaptation, Marburg virus becomes pathogenic for rodents. Using the guinea pig model, pathogenicity factors of Marburg virus are investigated comparing guinea pig adapted and non-adapted viruses.

Funded by DFG, SFB 1021, TP B03 – German Research Foundation, Collaborative Research Centre 1021

Funding period 2013 – 2016

Title Investigations of filovirus propagation and cellular defense mechanisms...

Principal investigator(s) S. Becker

Summary: Bats are considered to represent the natural reservoir of filoviruses. After infection, bats replicate and shed the filoviruses without developing disease. Humans, however, succumb to the disease. It is therefore of interest to compare the cellular response of bats and humans to filovirus infection in order to understand pathogenicity mechanisms that lead to the severe course of disease in humans.

Funded by DFG, Be 1325/6-1 – German Research Foundation

Funding period 2013 – 2015

Research group Dr. Friebertshäuser Professor Garten

Research projects

Title Proteases of the respiratory tract activating human influenza viruses: identification, characterization and cellular compartmentation

Principal investigator(s) E. Friebertshäuser & W. Garten

Summary The trypsin-like proteases HAT and TMPRSS2 activate human influenza viruses in the respiratory tract. TMPRSS2 cleaves the viral surface glycoprotein hemagglutinin (HA) intracellular before the virus is assembled, whereas HAT cleaves HA0 of virions upon entry into target cells and during HA is synthesized within the host cell. Moreover, TMPRSS2 and HAT differ in their distribution in the upper and lower respiratory tract with TMPRSS2 being present along the respiratory tract, whereas HAT is expressed in the upper airways, trachea and bronchi, but not in the lung. Using TMPRSS2-knockout mice we were able to demonstrate that TMPRSS2 is a host cell factor that is essential for pneumotropism and pathogenicity of human H1N1 and H7N9 influenza viruses in mice. Development of specific TMPRSS2 inhibitors is ongoing in our lab.

Funded by SFB 593 TP B2 – German Research Foundation, Collaborative Research Centre 593

Funding period 2011 – 2014

Title Proteolytic activation of influenza viruses by matriptase

Principal investigator(s) E. Friebertshäuser & A. Arendt

Summary Cleavage of the influenza virus surface glycoprotein hemagglutinin (HA) by host cell proteases is essential for virus infectivity. H9N2 viruses vary remarkably in the amino acid sequence at the HA cleavage site, and many isolates from Asia and the Middle East possess unusual multibasic motifs. The protease matriptase can activate H9N2 viruses at such motifs and thereby supports proteolytic activation in a wide range of tissues what may affect virus spread, tissue tropism and pathogenicity.

Funded by von Behring-Röntgen-Stiftung

Funding period 2012 – 2014

Title Activation of influenza viruses by proteases from host cells and bacteria in the human airway epithelium

Principal investigator(s) E. Friebertshäuser

Summary Bacterial co-infections by *S. aureus* or *S. pneumoniae* contribute significantly to morbidity and mortality of influenza infections. Interestingly, certain bacteria have been demonstrated to support activation of the influenza virus hemagglutinin (HA) either by secreting proteases that cleave HA or due to activation of cellular HA-cleaving proteases, and thereby may support virus spread and enhanced pathogenicity. We aim to identify bacterial proteases that support HA activation upon co-infection in the airway epithelium. Development of specific protease inhibitors may lead to novel drugs for the treatment of viral-bacterial co-infections.

Funded by Universities Giessen and Marburg Lung Center (UGMLC)

Funding period 2013 – 2015

Research group Professor Klenk

Research projects

Title New drugs targeting influenza virus polymerase

Principal investigator(s) H. D. Klenk

Summary Adaptation of avian influenza viruses to a mammalian host is mediated by mutations in the viral polymerase. Recombinant viruses have been generated to analyze the role of these mutations in the interaction with host proteins as well as their effects on polymerase activity, virus replication and pathogenicity.

Funded by EU (FLUPharm)

Funding period 2011 – 2014

Title Interaction of the influenza virus polymerase with host factors and its role in pathogenesis and host adaptation

Principal investigator(s) H. D. Klenk

Summary Host range and pathogenicity of influenza viruses depend on interactions of viral proteins with host factors preferentially at borders between different cell compartments. The project is focused on the interaction of the viral polymerase with the nuclear import machinery of the host cell and of the viral hemagglutinin with host proteases.

Funded by DFG, SFB 593, TP B1 – German Research Foundation, Collaborative Research Centre 593

Funding period 2011 – 2014

Research group Professor Maisner

Research projects

Title Role of the matrix protein in Nipah virus infection of polarized epithelial cells

Principal investigator(s) A. Maisner & Erik Dietzel

Summary Entry and exit from polarized epithelia in lungs and kidneys crucially influence spread of highly pathogenic Nipah viruses within the host, and determine host-to-host transmission. Aim of this project is to elucidate the molecular basis of the apical transport of the viral matrix protein leading to targeted apical virus release from polarized epithelia.

Funded by DFG, MA-1886/6-1 – German Research Foundation

Funding period 2010 – 2013

Title Role of the matrix protein in Nipah virus infection of polarized epithelial cells

Principal investigator(s) A. Maisner & Boris Lamp

Summary Entry and exit from polarized epithelia in lungs and kidneys crucially influence spread of highly pathogenic Nipah viruses within the host, and determine host-to-host transmission. Aim of this project is to elucidate the molecular basis of the apical transport of the viral matrix protein leading to

targeted apical virus release from polarized epithelia.

Funded by DFG, MA-1886/6-2

Funding period 2014 – 2016

Title Nipah virus infection of polarized epithelial cells

Principal investigator(s) A. Maisner & Laura Behner

Summary Nipah virus spread in polarized epithelial cell monolayers is always characterized by rapid virus-mediated cell-to-cell fusion. To elucidate the molecular mechanisms induced by the fusion-mediated cytopathic effect, the influence of NiV glycoproteins F and G on the actin cytoskeleton and the epithelial barrier function is analyzed.

Funded by DFG, GK 1216/2 (Project B.8) – German Research Foundation, Research Training Group 1216

Funding period 2011 – 2015

Title Nipah virus replication in bronchial epithelial cells from pigs and humans.

Principal investigator(s) A. Maisner & L. Sauerhering

Summary To answer the question why respiratory infections caused by highly pathogenic Nipah viruses (NiV) are generally observed in pigs but rarely seen in humans, this project compares the influence of NiV infection on cellular junction markers and cytokine production in primary bronchial epithelial cells from pigs and humans at different times p.i.

Funded by Manchot-Foundation

Funding period 2011-2013

Title Functional characterization of newly identified African Henipaviruses

Principal investigator(s) A. Maisner & M. Weis

Summary In recent years, novel Henipavirus-related sequences have been identified in bats in Africa. To evaluate the potential of cross-species infections of humans or livestock, biological functions of the new African Henipavirus glycoproteins are studied by quantitative binding, cleavage or fusion assays, and by infection competition studies in primary porcine and human cells.

Funded by Manchot-Foundation

Funding period 2012 - 2014

Title Role of the endosomal compartment in Nipah virus replication

Principal investigator(s) A. Maisner, S. Erbar & E. Dietzel

Summary Activation of the fusion glycoprotein F of highly pathogenic Nipah virus (NiV) by endosomal host cell proteases is an indispensable prerequisite for the generation of infectious virus and virus spread. This project focuses on role of transport sequences within the F cytoplasmic tail for endo-lysosomal trafficking and proteolytic activation by endosomal cathepsins.

Funded by DFG, SFB 593 (Project B11) – German Research Foundation, Collaborative Research Centre 593

Funding period 2011 – 2014

Title Proteolytic activation and endosomal trafficking of the Nipah virus fusion protein

Principal investigator(s) A. Maisner & T. Freitag

Summary To elucidate the molecular basis of the high pathogenicity of Nipah viruses, the project focus on the endosomal trafficking of the F protein and subsequent cathepsin cleavage in the absence or presence of other viral envelope proteins (G and M). Inhibitors either blocking F trafficking or the proteolytic activity of endosomal cathepsin L and B should be analyzed as a starting point for developing antivirals.

Funded by Leibniz Graduate School for Emerging Infectious Diseases (EIDIS)

Funding period 2012 – 2015

Title Characterization of matrix protein-mediated assembly of highly pathogenic Nipah viruses using a virus-like particle (NiVLP) system.

Principal investigator(s) A. Maisner & M. Ringel

Summary To study the role of the Nipah virus matrix protein during assembly in the absence of infectious virus replication, a virus-like particle (VLP) system with a minigenome encoding a reporter plasmid (luciferase, eGFP) should be established by coexpressing plasmid-expressed wildtype and mutant viral proteins.

Funded by Manchot-Foundation

Funding period 2014 – 2015

Title Nipah virus replication in respiratory epithelial cells: Influence of host factors and virus-strain specific sequence variations

Principal investigator(s) A. Maisner, L. Sauerhering & M. Zickler

Summary To answer the question why respiratory infections caused by highly pathogenic Nipah viruses are generally observed in pigs but rarely seen in humans, we want to elucidate the molecular requirements (host cell factors, virus variability) deciding on a productive replication in mucosal surfaces of the respiratory system which critically influence the pathogenicity and transmissibility of Nipah viruses via airway secretions.

Funded by DFG, SFB 1021 (Project B04) – German Research Foundation, Collaborative Research Centre 1021

Funding period 2013 – 2016

Research group Dr. Matrosovich

Research projects

Title RNA Viruses: the Metabolism of viral RNA, Immune Response of the Host Cells, and Viral Pathogenesis. Project B02: Role of receptor specificity of influenza viruses in host range, cell tropism and pathogenicity

Principal investigator(s) M. Matrosovich

Summary The project studies how natural variation of receptor-binding specificity, membrane-fusion and sialidase activity of surface glycoproteins of influenza viruses affects viral tropism, replication efficiency and pathogenicity in human respiratory tract. These questions are addressed by using recombinant influenza viruses with well-defined phenotypic characteristics and primary cultures of human tracheo-bronchial, alveolar and endothelial cells. The project will improve influenza surveillance and pandemic preparedness and may lead to the development of new approaches to influenza control and treatment.

Funded by DFG SFB 1021, Project B02 – German Research Foundation, Collaborative Research Centre 1021

Funding period 2013 – 2016

Title Role of receptor specificity of influenza viruses in lung tropism and pathogenicity

Principal investigator(s) M. Matrosovich & S. Herold (JLU-Giessen)

Summary This project studies influenza virus interactions with receptors in human lung using i) recombinant influenza viruses with well-defined receptor-binding specificity and ii) in vivo (mice) and in vitro (murine and human) models of infection in alveolar epithelium. The major aim is elucidation of mechanisms of virus-host interactions mediating viral entry, replication and host innate immune responses, which ultimately determine pathogenicity

Funded by Von Behring-Röntgen-Foundation

Funding period 2010 – 2013

Title Characterization of the neuraminidase of H1N1 2009 swine-origin influenza virus: functional properties and role in viral host range and pathogenicity

Principal investigator(s) M. Matrosovich & V. Czudai-Matwich

Summary The novel pandemic H1N1/09 virus is a reassortant with a unique gene constellation. It is thought that acquisition of a novel neuraminidase gene may have provided the emergent virus replicative advantage in humans. This project studies functional properties of the neuraminidase of H1N1/09 and tests whether they could have contributed to enhanced viral replication and transmission in humans.

Funded by FluResearchNet, a BMBF-sponsored network dedicated to research on the zoonosis influenza – Federal Ministry of Education and Research

Funding period 2010 – 2013

Title Pathogenesis and transmission of influenza in pigs (FLUPIG)

Principal investigator(s) M. Matrosovich

Summary The FLUPIG aims at a better understanding of the role of pigs in influenza pandemics. In particular, the consortium studies the nature of the genetic changes that are required for (a) efficient replication of an avian virus in pigs, (b) efficient transmission of avian viruses between pigs and (c) virus transmission from pigs to humans and between humans.

Funded by EU (7th Framework Programme)

Funding period 2010 – 2014

Title Influenza virus interactions with receptors and inhibitors in human airway epithelium

Principal investigator(s) M. Matrosovich

Summary The EIDIS partners German Primate Center, Göttingen, and Institute of Virology, Philipps-University Marburg, jointly investigate emerging infections at the molecular, cellular and organismic level, with a strong focus on highly pathogenic viruses. In particular, the group headed by M. Matrosovich studies mechanisms, by which hemagglutinin (HA) and neuraminidase (NA) of avian influenza virus limit their replication in the human airway epithelium. This is essential for the understanding of receptor-dependent mechanisms of zoonotic transmission of influenza viruses and barriers that prevent their pandemic spread.

Funded by Leibniz Graduate school for emerging infectious diseases (EIDIS)

Funding period 2012 – 2015

Title Prediction and prevention of emerging zoonotic viruses with pandemic potential using multidisciplinary approaches (PREDEMICS)

Principal investigator(s) M. Matrosovich

Summary PREDEMICS brings together 23 teams from 17 institutions in 8 countries with cross-disciplinary expertise in veterinary and human medicine. The aim of the project is to unravel the complex interactions between the factors involved in the four stages of emergence, i.e. exposure and introduction into a new host species, infection causing local chains of transmission, spread in human populations and post-transfer adaptation leading to widespread transmission and pandemics. The project will focus on the following zoonotic viruses with epidemic potential in Europe: influenza virus, hepatitis E virus, viruses of the Japanese encephalitis serocomplex and lyssaviruses.

Funded by EU (7th Framework Programme)

Funding period 2011 - 2016

Title Inactivated vaccine platforms for emerging viruses

Principal investigator(s) S.Becker, F.Weber & M. Matrosovich

Summary: The project develops a novel vaccine platform which is based on recombinant influenza virus expressing foreign protective antigen on the surface of viral particle. The main advantages of this approach are utilization of widely used technology, equipment and logistics of inactivated influenza vaccines. For the proof of principle, candidate vaccine against MERS coronavirus is being developed.

Funded by: German Center for Infection Research (DZIF), TTU Emerging Infections – Federal Ministry of Education and Research

Funding period 2013 – 2015

Research group Dr. Strecker

Research projects

Title Lassa virus: host cell tropism and molecular pathogenesis

Principal investigator(s) T. Strecker and S.K. Fehling

Summary The primary transmission route of Lassa virus from its rodent host to humans is by direct exposure to virus-containing rodent excretions. Therefore, the respiratory tract represents an important virus entry site. Aim of this project is to understand how Lassa virus overcomes the epithelial barrier and disseminates from the airway epithelium to other parts of the body through the blood or lymphatic system.

Funded by: DGF SFB 1021 TP B05, German Research Foundation, Collaborative Research Centre 1021 von Behring-Röntgen-Foundation

Funding period 2013-2016 DGF SFB 1021

2013 – 2014 von Behring-Röntgen-Foundation

Research group Professor Weber

Research projects

Title SARS coronavirus and the antiviral interferon system

Principal investigator(s) F. Weber

Summary Interferons (IFN-alpha/beta) are the only licenced drugs against SARS-coronavirus (SARS-CoV). We have previously shown SARS-CoV is sensitive to the antiviral action of IFN, but that infected cells are unable to secrete IFN. The aims of this project are (i) to identify the viral factor(s) which block IFN production, and (iii) to identify the IFN-stimulated antiviral factor responsible for inhibiting SARS-CoV.

Funded by BMBF, 01KI0705 – Federal Ministry of Education and Research

Funding period 2007 – 2010 & 2010 – 2013 (two funding periods)

Title Degradation of the antiviral interferon-effector PKR by the virulence factor NSs of Rift Valley fever virus

Principal investigator(s) F. Weber

Summary Rift Valley fever virus (RVFV) is responsible for large and recurrent outbreaks among animals and humans in Africa. We previously demonstrated that the virulence factor NSs induces the specific degradation of the antiviral host protein PKR. The aim of the present proposal is to elucidate the molecular mechanisms underlying NSs action.

Funded by DFG, We 2616/5-2 German Research Foundation

Funding period 2010 – 2013

Title Development of new vaccine candidates against CCH fever

Principal investigator F. Weber

Summary To this date, there is no research program on vaccine development for Crimean Congo Hemorrhagic fever virus (CCHFV). The aim of project is to develop conventional and novel vaccine candidates like recombinant antigens, DNA constructs, and virus-like particles, and to characterize the immune responses and protective capacity.

Funded by EU FP7 ("CCH Fever")

Funding period 2010 – 2014

Title Disturbance of the nuclear and nucleolar compartments by a viral interferon antagonist

Principal investigator F. Weber

Summary We found that the virulence factor NSs of the La Crosse encephalitis virus acts by degrading the host cell RNA polymerase II. The project is intended to determine the molecular mechanism (interaction partners, signaling pathways, protein domains)

Funded by DFG, SFB 593, TP B13 – German Research Foundation, Collaborative Research Centre 593

Funding period 2011 – 2014

Title Physiological function of the pathogen recognition receptor RIG-I

Principal investigator(s) F. Weber

Summary RIG-I is an intracellular pathogen sensor essential for the recognition of a wide array of viruses. The activation of RIG-I by viral RNA in infected cells activates an antiviral IFN response, but can also result in a storm of pro-inflammatory cytokines. Despite massive efforts by the research community, it remains unclear which viral RNA-containing structures are activating RIG-I. This project engages the latest tools and methods developed by us to solve this question.

Funded by UKGM – University Hospital Giessen and Marburg

Funding period 2012 – 2013

Title Recognition of zoonotic viruses by the pathogen sensor RIG-I.

Principal investigator(s) F. Weber

Summary This project includes the screening of a large set of zoonotic viruses to determine their RIG-I activating (or -dampening) structures.

Funded by Leibniz Graduate School for Emerging Infectious Diseases (EIDIS)

Funding period 2012 - 2015

General information about the institute

Research funding 5.658.983,09 €

Most important publications

Schudt G, Kolesnikova L, Dolnik O, Sodeik B, **Becker S** (2013) Live-cell imaging of Marburg virus-infected cells uncovers actin-dependent transport of nucleocapsids over long distances. *Proceedings of the National Academy of Sciences of the United States of America* 110(35), 14402-14407

Weber M, Gawanbacht A, Habjan M, Rang A, Borner C, Schmidt AM, Veitinger S, Jacob R, Devignot S, Kochs G, Garcia-Sastre A, **Weber F** (2013) Incoming RNA virus nucleocapsids containing a 5'-triphosphorylated genome activate RIG-I and antiviral signaling. *Cell host & microbe* 13(3), 336-346

Czudai-Matwich V, Otte A, **Matrosovich M**, Gabriel G, **Klenk HD** (2014) PB2 mutations D701N and S714R promote adaptation of an influenza H5N1 virus to a mammalian host. *Journal of virology* 88(16), 8735-8742

Dolnik O, Kolesnikova L, Welsch S, **Strecker T**, Schudt, G, **Becker S** (2014) Interaction with Tsg101 is necessary for the efficient transport and release of nucleocapsids in marburg virus-infected cells. *PLoS pathogens* 10(10), e1004463

Peitsch C, **Klenk HD**, **Garten W**, **Bottcher-Friebertshauser E** (2014) Activation of influenza A viruses by host proteases from swine airway epithelium. *Journal of virology* 88(1), 282-291

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Centre for Human Genetics

Research Groups Professor Bohlander (till October 2013)

Professor Grzeschik (emeritus)

Provisional Direction PD Dr. Fritz

Main fields of research

- Human genetics, dermatogenetics (Prof. Grzeschik)
- Human genetics, leukemia genetics (Prof. Bohlander)

Research projects

Title Identifizierung von genomischen, epigenomischen und proteomischen Zielen des CALM/AF10 Fusionsproteins

Principal investigator S. Bohlander

Summary This project seeks to elucidate the genomic targets (direct binding sites) of the CALM/AF10 fusion protein and tries to identify epigenetic changes mediated by the expression of CALM/AF10. Furthermore, we study the interaction network of CALM/AF10 with other proteins using a yeast-two hybrid screening approach. In addition, the infrastructure for the bioinformatics analysis of large of gene expression datasets and their correlation with clinical outcome in AML and CLL was established.

Funded by BMBF – Federal Ministry of Education and Research (Nationales Genomforschungsnetzwerk, NGFN)

Funding period 2002 – 2013

Title The role of TET proteins in myeloid neoplasia

Principal investigators S. Bohlander, K. Spiekermann & H. Leonhardt

Summary The TET (ten eleven translocation) proteins are oxygenases that convert 5 methylcytosine (5MC) into 5 hydroxymethylcytosine (5HMC). Mutations affecting TET2 and translocations resulting in an MLL/TET1 fusion protein are found in various types of myeloid leukemias. It is the aim of this project to study the correlation between TET2 mutations, TET2 expression levels, 5HMC levels and global gene expression level changes in myeloid neoplasms. In addition, we are establishing an MLL/TET1 murine bone marrow transplantation model to investigate the transforming potential of this fusion protein and its effect on 5MC and 5HMC levels.

Funded by DFG German Science Foundation, Priority Programme 1463

Funding period 2011 – 2013

Title Molecular genetical and functional analysis of ichthyoses caused by genetic defects in cholesterol biosynthesis

Principal investigator K.-H. Grzeschik

Summary CHILD-syndrome and Conradi-Hünemann-Happle-syndrome (CDPX2) are caused by deficiency in two successive steps of the cholesterol synthesis pathway. The project aimed at detecting mutated sites in the underlying genes and characterizing functionally their effect on the proteins NSDHL and EBP, respectively.

Funded by BMBF – Federal Ministry of Education and Research, DLR 01GM0903

Funding period 2009 – 2013

General information about the institute

Research funding 21.801,15 €

Most important publications

Diffner E, Beck D, Gudgin E, ... , **Bohlander SK**, Buske C, Burnett A, Ottersbach K, Vassiliou GS, Olivier J, Wong JW, Göttgens B, Huntly BJ, Pimanda JE (2013) Activity of a heptad of transcription factors is associated with stem cell programs and clinical outcome in acute myeloid leukemia. *Blood* 121:2289-2300

Li Z, Herold T, He C, ..., **Bohlander SK**, Chen J (2013) Identification of a 24-Gene prognostic signature that improves the European leukemia net risk classification of acute myeloid leukemia. *J Clin Oncol* 31:1172-1181

Meyer C, Hofmann J, Burmeister T, **Kakadia PM**, **Bohlander SK**, Ahlmann M, Choi JR, Gameiro P et al. (2013) The MLL recombinome of acute leukemias in 2013. *Leukemia* 27:2165-2176

Malik S, Percin FE, Bornholdt D, Albrecht B, Percesepe A, Koch MC, Landi A, Fritz B, Khan R, Mumtaz S, Akarsu NA, **Grzeschik KH** (2014) Mutations affecting the BHLHA9 DNA-binding domain cause MSSD, mesoaxial synostotic syndactyly with phalangeal reduction, Malik-Percin type. *Am J Hum Genet* 95(6):649-659

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Provisional Direction: PD Dr. Barbara Fritz

Institute of Pathology

Research Group Professor R. Moll

Main fields of research

The central research topics of the institute cover specific aspects of cell and tumor biology. A main research focus is related to the cytoskeleton and cellular adhesion mediated by desmosomes. As an important component of desmosomal architecture and function we are analyzing the regulation on transcriptional and post-translational level of plakophilin 3 (PKP3), an affiliate of the eponymous protein family. PKPs may also be involved in further cellular processes such as translational regulation, cellular stress response, malignant transformation and invasion of cells. Moreover, our institute served as a core facility on SFB Transregio 17 providing immunohistochemical staining and pathological evaluation of human and murine tissue samples. Histopathological and immunohistochemical services are granted as well for many scientific and clinical studies in collaboration with other departments of the Medical Faculty. The fetal pathology team correlates fetal malformations with genetic syndromes.

Research projects

Title Expression, posttranslational modifications and subcellular distribution of plakophilins: Significance in epithelial tumors

Principal investigator(s) A. Schmidt & R. Moll

Summary We identified a new protein variant of the human PKP3 gene - PKP3b - that is transcriptionally regulated by an independent promoter element and exhibits a restricted expression pattern in normal and transformed tissues compared to the regular variant PKP3a. Additionally, we analyzed a specific modification of PKP3 (phosphorylation of tyrosine-195) for its functional relevance in normal and malignant cells. We identified proto-oncogenic Src-kinase as one relevant enzyme catalyzing this modification and could show that this also takes place after epidermal growth factor receptor (EGFR) stimulation as a downstream event. This phosphorylation seems to be associated with a change of functional properties of PKP3. We could identify this modification also in some tumor entities such as poorly differentiated prostate cancer. Finally we are analyzing newly discovered interacting proteins with PKP3 identified during a two-hybrid screen on immunobiochemical and cell biological level in various diploma, bachelor or master theses.

Funded by Deutsche Krebshilfe – German Cancer Aid

Funding period 2009 – 2013

Title Tissue-based pathological analyses

Principal investigator(s) R. Moll

Summary The central pathology service project Z04 was responsible for tissue-based morphological investigations for the SFB Transregio 17 and its scientific projects. These comprised histological and immunohistochemical analyses of human and experimental animal tissues, tissue microarrays, morphometry, and characterization of antibodies on paraffin-embedded tissues.

Funded by DFG, SFB TR 17 – German Research Foundation, Transregional Collaborative Research Centre 17

Funding period 2008 – 2013

General information about the institute

Research funding 107.695,47 €

Most important publications

Bommert KS, Effenberger M, Leich E, Küspert M, Murphy D, Langer C, **Moll R**, Janz S, Mottok A, Weissbach S, Rosenwald A, Bargou R, Bommert K (2013) The feed-forward loop between YB-1 and MYC is essential for multiple myeloma cell survival. *Leukemia* 27:441-50

Makarova G, Bette M, **Schmidt A**, Jacob R, Cai C, **Rodepeter F**, Betz T, Sitterberg J, Bakowsky U, **Moll R**, Neff A, Sesterhenn A, Teymoortash A, Ocker M, Werner JA, Mandic R (2013) Epidermal growth factor-induced modulation of cytokeratin expression levels influences the morphological phenotype of head and neck squamous cell carcinoma cells. *Cell Tissue Res* 351:59-72

Schoner K, Kohlhasse J, Müller AM, Schramm T, Plassmann M, Schmitz R, Neesen J, Wieacker P, Rehder H (2013) Hydrocephalus, agenesis of the corpus callosum, and cleft lip/palate represent frequent associations in fetuses with Peters' plus syndrome and B3GALT1 mutations. Fetal PPS phenotypes, expanded by Dandy Walker cyst and encephalocele. *Prenat Diagn* 33:75-80

Bergs JW, Neuendorff N, van der Heijden G, Wassenaar E, **Rexin P**, Elsässer HP, **Moll R**, Baarends WM, Brehm A (2014) Differential expression and sex chromosome association of CHD3/4 and CHD5 during spermatogenesis. *PLoS One* 9(5):e98203

Mühmer M, Ditthardt D, Jäkel J, Wischmann V, Moll R, Schmidt A (2014) An alternative promoter of the human plakophilin-3 gene controls the expression of the new isoform PKP3b. *Cell Tissue Res* 355:143-162

Neuber S, Jäger S, Meyer M, Wischmann V, Koch PJ, Moll R, Schmidt A (2014) c-Src mediated tyrosine phosphorylation of plakophilin 3 as a new mechanism to control desmosome composition in cells exposed to oxidative stress. *Cell Tissue Res* Epub 2014 Dec 12

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Director: Professor Dr. Roland Moll

Division of Neuropathology

Research Group Professor Pagenstecher

Main fields of research

The Department's main research interest is in the fields of neuroimmunology and neurooncology. We are interested in the induction of immune reactions in the central nervous system (CNS) in animal models of inflammation such as experimental allergic encephalomyelitis, virus and bacterial infection and tumor rejection. Moreover, we investigate the factors that render astrocytes tumorigenic and lead to the infiltrative behaviour of these cells in the CNS. Main factors we are interested in are Matrix Metalloproteases and their inhibitors (MMPs, ADAMs and TIMPs), IRF-9 and IL-12.

Research projects

Title Initiation of immune responses in the CNS

Principal investigator(s) A. Pagenstecher

Summary We investigate whether it is possible to induce a specific immune reaction against MOG peptide in the CNS of mice deficient for IL-12 and IL23 that express IL-12 exclusively in the CNS under control of the GFAP promoter.

Title Effect of MT-MMPs in the infiltrative behaviour of astrocytes and glioma cells

Principal investigator(s) A. Pagenstecher

Summary Astrocytic tumors diffusely invade the surrounding brain. It is not fully understood which factors mediate this propensity. We have developed a new in vitro model that allows for the determination of the influence of single proteases for the infiltrative behaviour of astrocytes in the CNS.

Title Effect of TIMP-1 expression in cerebral ischemia

Principal investigator(s) A. Pagenstecher

Summary Tissue inhibitor of MMPs 1 (TIMP-1) has been shown to be neuroprotective on hypoxic neurons. In this project we determine in vivo and in vitro the effect of transgenic expression of TIMP-1 in the CNS in the course of cerebral ischemia following medial cerebral artery occlusion (MCAO).

Title Tumorigenicity of myc and Akt in astrocytes

Principal investigator(s) A. Pagenstecher

Summary In order to establish an animal model for glioma we transduce primary murine astrocytes with myc, Akt or both oncogenes and investigate the growth behaviour, phenotype and tumorigenicity of these cells.

Title Role of IRF9 in the infection of mice with Lymphocytic choriomeningitis virus (LCMV)

Principal investigator(s) M. Hofer & A. Pagenstecher

Summary We investigate the effects IRF9-deficiency has on the clinical course and immune response of mice infected with LCMV.

Funded by DFG – German Research Foundation

Funding period 2010 – 2014

Title Presence of persistent virus infections in the human CNS

Principal investigator(s) M. Hofer & A. Pagenstecher

Summary We aim to determine the presence of virus nucleic acid and protein in the non-inflamed human CNS.

Funded by Kooperationsvertrag

Funding period 2011 – 2012

General information about the institute

Research Funding 76.125,00 €

Most important publications

Stellzig J, Chariot A, Shostak K, Ismail Göktuna S, Renner F, Acker T, **Pagenstecher A**, Schmitz ML (2013) Deregulated expression of TANK in glioblastomas triggers pro-tumorigenic ERK1/2 and AKT signaling pathways. *Oncogenesis*: 2:e79

El Hindy N, Keyvani K, **Pagenstecher A**, Dammann P, Sandalcioğlu IE, Sure U, Zhu Y (2013) Implications of DLL4-Notch signaling activation in primary glioblastoma multiforme. *Neuro Oncol* 15(10):1366-78

Timofeev O, Schlereth K, Wanzel M, Braun A, Nieswandt B, **Pagenstecher A**, Rosenwald A, Elsässer HP, Stiewe T (2013) p53 DNA Binding Cooperativity Is Essential for Apoptosis and Tumor Suppression In Vivo. *Cell Rep* 3(5):1512-25

Radke J, **Bortolussi G**, **Pagenstecher A** (2013) Activated Akt and c-Myc induce a progenitor-like phenotype of mature primary p53^{-/-} astrocytes and render these cells gliomagenic in the brain of immunocompetent mice. *PLoS One* 8:e56691

Huber M, Heink S, **Pagenstecher A**, Reinhard K, Ritter J, Visekruna A, Guralnik A, Bollig N, Jeltsch K, Heinemann C, Wittmann E, Buch T, Prazeres O, Brüstle A, Brenner D, Mak TW, Mittrücker HW, Tackenberg B, Kamradt T, Lohoff M. (2013) Pathogenic IL-17A-dependent help of Tc17 cells for Th17-mediated autoimmune encephalomyelitis. *J Clin Invest* 123(1):247-60

Teymoortash A, Zieger L, Hoch S, **Pagenstecher A**, **Hofer MJ** (2014) Distinct microscopic features of perineural invasion in adenoid cystic carcinoma of the head and neck. *Histopathology* 64:1037-9

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Director: Professor Dr. Axel Pagenstecher

Institute of Laboratory Medicine and Pathobiochemistry, Molecular Diagnostics

Professor H. Renz

PD Dr. H. Garn, PD Dr. Dr. P. Pfefferle, PD Dr. A. Nockher, PD Dr. T. Stief, PD Dr. N. Al-Fakhri

Main fields of research

Major topic of research is the investigation of mechanisms of disease development, prevention and therapy of chronic inflammatory diseases, mainly allergic diseases of the lung. Therefore, several animal models are developed that mimic characteristic features and phenotypes of acute and chronic allergic airway inflammation. Additionally, investigations are extended to the participation in respective human cohort studies. A newly established lipidomics platform investigates fatty acid patterns during the course of inflammatory processes. Further projects focus on the role of neurotrophins on lung remodeling, angiogenesis and tumor development, role of endothelium in atherosclerosis and development of novel analytical systems for clotting cascade parameters.

Research projects

Title Epigenetic regulation of pre- and neonatal programming of allergic asthma

Principal investigator(s) H. Renz, P. Pfefferle

Summary Based on the results of the preceding project it is hypothesized that epigenetic regulation mechanisms are involved in the prenatal allergy protection by *Acinetobacter lwoffii* F78. This project investigates in detail DNA methylation and histone modification processes within candidate genes involved in the regulation of allergic immune responses and their importance for allergy protection.

Funded by DFG, SFB/TR22, TPA18 – German Science Foundation, Transregional Collaborative Research Centre 22

Funding period 2013 – 2014

Title Animal models for endotypes of allergic airway inflammation

Principal investigator(s) H. Garn

Summary This project is the continuation of the animal core facility of the SFB. It extends the line of animal models of inflammatory diseases of the lung by implementing models of non-eosinophilic airway inflammation. In addition, processes of disease chronification and their resolution are studied in different asthma phenotype models in comparison.

Funded by DFG, SFB/TR22, TPA18 – German Science Foundation, Transregional Collaborative Research Centre 22

Funding period 2013 – 2014

Title The role of viral influenza infection on the protection and exacerbation of acute and chronic allergic airway inflammation

Principal investigator(s) H. Renz

Summary Viral infections have been shown to may exert opposing effects on the development of allergies and asthma depending on virus type, dose, and time point of infection leading either to allergy protection or to disease progression and exacerbations. Vice versa, allergic inflammation within the lung may interfere with immune responses to viruses and viral infections. Thus, interrelationship of these conditions is investigated in this project.

Funded by DFG, SFB 1021, TP C04 – German Research Foundation, Collaborative Research Centre 1021

Funding period 2013 – 2016

Title Role of microRNA in the pathogenesis of bronchial asthma

Principal investigator(s) H. Renz in cooperation with T. Braun, Bad Nauheim

Summary MicroRNAs are small non-coding RNA molecules regulating gene expression on the post-transcriptional level. Their controlled expression is mandatory for normal immune function and an imbalance in microRNA expression is sufficient to cause disease. By studying distinct immune cell subsets and structural cells, we intend to identify specific microRNAs contributing to asthma pathology.

Funded by von Behring Röntgen Foundation

Funding period 2010 – 2013

Title Role of Th1 lymphocytes and the transcription factor Tbet for chronic inflammation initiation and/or maintenance in a COPD animal model

Principal investigator(s) H. Garn in cooperation with N. Weißmann, JLU Giessen

Summary It is postulated that Th1-driven autoimmune processes may contribute to the development of chronic obstructive pulmonary disease (COPD). The project investigates the role Th1 lymphocytes and their major transcription factor Tbet on initiation and development of chronic inflammation in a mouse smoke exposure model to evaluate the potential of Tbet as therapeutic target.

Funded by LOEWE Centre, UGMLC P9

Funding period 2013 – 2014

Title FP 7 – PreDicta

Principal investigator(s) H. Renz

Summary Development of a DNAzyme specific to human RV, analysis of antiviral effectiveness in vitro and in vivo, testing of DNAzymes for therapeutic potential in a murine RV model of asthma. The team will also participate in WP2 for the investigation of the role of the lung epithelial barrier in the interplay between RV infection and asthma.

Funded by EU FP7, PreDicta WP8 – European Union

Funding period 2010 – 2015

Title DZL Disease area AA

Principal investigator(s) H. Renz, H. Garn, P. Pfefferle, A. Nockher

Summary Multiplex cytokine, epigenetic and lipidomics analyses of samples from children and adult patients cohorts within the German Lung Center (DZL). Development and characterization of animal models of endophenotypes of asthma and analysis of underlying pathomechanisms.

Funded by DZL, BMBF – German Ministry of Education and Research

Funding period 2013 – 2015

Title DZL Disease area CF

Principal investigator(s) H. Garn in cooperation with M. Mall, University Heidelberg

Summary Generation of DNAzymes against the epidermal sodium channel (ENaC) family members as potential therapeutics for the treatment of CF. Characterization of these molecules in vitro using primary epithelial cell cultures and in vivo in cooperation with Heidelberg colleagues.

Funded by DZL, BMBF – German Ministry of Education and Research

Funding period 2013 – 2015

Title Plasmatic thrombin activity

Principal investigator(s) T. Stief

Summary Thrombin - Tests measuring thrombin in IU/ml instead of clotting seconds are much more refined than the usual clinical blunted assays. These new tests detect without problems even thrombin activities in the clinically so important 1-10 milli-IU/ml range and allow the early diagnosis of NIC→PIC changes. The trick consists in using the substrate in the approx. 1fold Km range together with supramolar arginine concentrations.

Funded by Industry, Fellowships

Funding period 2009 – 2014

Title Investigation of the protective effects of vascular endothelial growth factor (VEGF) on the endothelium through regulation of poly-[ADP-ribose]-polymerase (PARP) in the animal model

Principal investigator(s) N. Al-Fakhri in cooperation with T. Gerriets, JLU Giessen

Summary The pharmacological modulation of the VEGF system and of PARP through inhibitors and small molecules are tested in a rat model of cerebral

infarction to analyze effects on endothelial protection and on stroke.

Funded by Hans und Gertie Fischer Foundation

Funding period 2012 – 2013

Title The role of Factor VII activating protease (FSAP) in the pathogenesis of stroke

Principal investigator(s) N. Al-Fakhri in cooperation with S. Kanse and T. Gerriets, JLU Giessen

Summary The role of factor VII activating protease (FSAP), a circulating protease involved in the coagulation and fibrinolysis pathways, in stroke is investigated in an animal model.

Funded by von Behring Röntgen Foundation

Funding period 2011 – 2013

General information about the institute

Research funding

2.207.094,61 €

Most important publications

Turowska A, Librizzi D, Baumgartl N, Kuhlmann J, Dicke T, Merkel O, Homburg U, Höffken H, **Renz H, Garn H** (2013) Biodistribution of the GATA-3-specific DNAzyme hgd40 after inhalative exposure in mice, rats and dogs. *Toxicol Appl Pharmacol* 272(2):365-72

Garn H, Neves JF, Blumberg RS, Renz H (2013) Effect of barrier microbes on organ-based inflammation. *J Allergy Clin Immunol* 131(6):1465-78

Harb H, van Tol EA, Heine H, Braaksma M, Gross G, Overkamp K, Hennen M, Alrifai M, Conrad ML, **Renz H, Garn H** (2013) Neonatal supplementation of processed supernatant from *Lactobacillus rhamnosus* GG improves allergic airway inflammation in mice later in life. *Clin Exp Allergy* 43(3):353-64

Hagner S, Harb H, Zhao M, Stein K, Holst O, Ege MJ, Mayer M, Matthes J, Bauer J, von Mutius E, **Renz H, Heine H, Pfefferle PI, Garn H** (2013) Farm-derived Gram-positive bacterium *Staphylococcus sciuri* W620 prevents asthma phenotype in HDM- and OVA-exposed mice. *Allergy* 68(3):322-9

Pfefferle PI, Weber J, von Mutius E (2013) PASTURE Study Group. Atopic sensitization in the first year of life. *J Allergy Clin Immunol* 131(3):781-8

Pfefferle PI, Prescott SL, Kopp M (2013) Microbial influence on tolerance and opportunities for intervention with prebiotics/probiotics and bacterial lysates. *J Allergy Clin Immunol* 131(6):1453-63

Pfefferle PI, Renz H (2014) The mucosal microbiome in shaping health and disease. *F1000Prime Rep* 6:11

Alrifai M, Marsh LM, Dicke T, Kılıç A, Conrad ML, **Renz H, Garn H** (2014) Compartmental and temporal dynamics of chronic inflammation and airway remodelling in a chronic asthma mouse model. *PLoS One* 9(1):e85839

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Director: Professor Dr. Harald Renz

Institute for Lung Research

Research Group Professor B. T. Schmeck

Main fields of research

- chromatin modifications and microRNA regulating lung immunology
- Systems biology of lung diseases
- translational and clinical research (clinical studies: PhenoCOPD)

Research projects

Title microRNA-regulation in pulmonary inflammation (with *L. pneumophila*)

Principal investigators B. T. Schmeck & M. Vingron (Max-Planck-Institute for Molecular Genetics Berlin)

Summary Using the example of infection with *Legionella pneumophila* in human cell and tissue cultures as well as in mouse models, the relevance of small, non-protein coding RNAs from host and pathogen are analysed experimentally (e.g. Deep Sequencing) and bioinformatically modeled with Systems biological / mathematical methods.

Funded by DFG SFB/TR84 (German Research Foundation – Transregional Collaborative Research Center 84)

Funding period 2014 - 2018 (second funding period)

Title Epigenetic regulation of Influenza virus and *S. pneumonia* infection

Principal investigators B. T. Schmeck & A. Hocke, (Charité Universitätsmedizin Berlin)

Summary The process of respiratory infection can be affected by different predisposing factors. The impact of epigenetic regulations for post-influenza pneumonia (elicited by *S. pneumoniae*) is analysed among others with high-throughput and bio-informatical methods in human cell and tissue culture.

Funded by BMBF-Progress - Federal Ministry of Education and Research –

Funding period 2010 – 2013

Title microRNA as a biomarker for pulmonary inflammation and infection

Principal investigators B. T. Schmeck & S. Hippenstiel (Charité Universitätsmedizin Berlin)

Summary microRNA bears an important meaning for the differentiation and regulation of monocytic cells. In blood monocytes from patients with acute and chronic pulmonary infections in Germany and India, expression and mutations of microRNA are analysed as potential biomarkers.

Funded by DFG-GRK 1673 (German Research Foundation – International Research Training Group

1673 “Functional and Molecular Epidemiology Berlin-Hyderabad”)

Funding period 2010 – 2014

Title Regulation of pulmonary inflammation with the help of new therapeutical agents

Principal investigators B. T. Schmeck & S. Hippenstiel (Charité Universitätsmedizin Berlin)

Summary In animal and cell culture models, the anti-inflammatory and vasoprotective potential of new experimental COPD-drugs is evaluated.

Funded by Boehringer Ingelheim

Funding period 2010 -2014

Title PneumiR

Principal investigators B. T. Schmeck & K. Meyer (JLU Giessen)

Summary Infections and neoplasia of the respiratory tract and lung tissue are among of the most frequent causes of death worldwide and cause high socio-economic burdens. They pose a diagnostic and urgent challenge. The simple accessibility of exhalation air is a unique opportunity for non-invasive diagnosis with high compartment specificity. The analysis of exhaled air is both possible in children and patients who are critically ill. Own previous work show that in exhaled air, RNA is present in sufficient amount and quality so that miRNA can be detected. Therefore, the aim of the project is to look for the small RNAs in exhaled air condensate from patients with infections and malignancies of the respiratory tract and to validate them as biomarkers.

Funded by Collaborative project UKGM - University Hospital Giessen and Marburg

Funding period 2012 – 2014

Title DZL-Sysbio-Plattform

Principal investigator(s) B. T. Schmeck

Summary The aim of the project is to investigate the role of miRNA regulation in signalling and gene regulatory networks related to lung inflammation using an iterative approach of mathematical modelling, bioinformatics, and laboratory experiments. The project is to detect critical miRNAs for lung inflammation in pathological conditions associated to infection and cancer. Other objectives of the project are the development of bioinformatics methods for analysis and construction of miRNA related biochemical networks.

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2011 – 2015

Title Systems biology of pulmonary inflammation

Principal investigator B. T. Schmeck

Summary COPD, asthma and pneumonia are characterized by significantly different types of inflammation. A very important role of chromatin modification within the process of inflammation could be demonstrated in own investigations. The regulation of these different kinds of inflammation is analysed experimentally (ChIP-Seq) and bio-informatically and modeled with Systems biological / mathematical methods.

Funded by BMBF Forsys Partner Federal Ministry of Education and Research

Funding period 2008 – 2013

Title microRNA at the crossroad of lung inflammation, regeneration and cancer (miRSys)

Principal investigators B. T. Schmeck & J. Vera-Gonzalez (Friedrich-Alexander-Universität Erlangen-Nürnberg)

Summary Aim of this project is to understand the role of miRNA in the pathophysiological development of inflammation, regeneration and carcinogenesis in the lung. The basis is to develop a mathematical model that is supplemented with quantitative data in iterative cycles by modelling and experimental series. Afterwards, hypotheses concerning the structure of the model and the supposed role of feedback loops are integrated and tested by computer simulations. The results of these simulations are used to validate hypotheses about the miRNA-regulation in inflammation reactions in the lung. It will also be possible to predict the behaviour of the system in the complex biological context of lung inflammation.

Funded by BMBF Innovationswettbewerb Systembiologie - Federal Ministry of Education and Research

Funding period 2013 – 2015

Title Molecular regulation of iNOS in experimental and clinical emphysema

Principal investigator B. T. Schmeck

Summary In this project, the hypothesis that chromatin-status and miRNA-patterns are important regulators of (1) iNOS expression and (2) the subsequent development of emphysema and vascular remodeling in cigarette smoke induced lung disease. A comprehensive miRNA and mRNA pattern will be determined, and chromatin modifications at smoke-regulated genes in alveolar epithelial cells, endothelial cells and vascular smooth muscle cells at different time points in our murine model of chronic cigarette smoke exposure. Subsequent, knock-out and L-NIL treated mice will be analyzed. A comprehensive bioinformatics approach will be applied to cluster the results with respect to emphysema and vascular remodeling, and mRNA changes will be correlated with corresponding

histone acetylation and their predicted targeting miRNAs. As an outlook, promising synthetic miRs will be studied *in vivo*.

Funded by Collaborative project UGMLC – LOEWE Centre Universities of Giessen and Marburg Lung Center (UGLMC)

Funding period 2013 – 2014

Title Molecular characterization of macrophage phenotypes in pneumonia and asthma

Principal investigators B. T. Schmeck, H. Garn, A. Sittka & S. Herold

Summary The aim of this study is to test the hypothesis, that chromatin-status and miRNA-patterns are important regulators of macrophage polarization in different pulmonary disease settings. In detail, we will determine the genome-wide acetylation state of histone H4, and a comprehensive miRNA and mRNA pattern in a) human macrophages, differentiated and polarized from PBMCs, b) human alveolar macrophages from BAL, c) exudate macrophages from a mouse model of gram-negative pneumonia, and d) lung macrophages from a mouse model of allergic asthma. A comprehensive bioinformatics approach will be applied to cluster the results with respect to different macrophage subtypes, and mRNA changes will be correlated with corresponding histone acetylation and their predicted targeting miRNAs. Putative interaction partners will be validated and phenotypically characterized *in vitro*. As an outlook, promising synthetic miRs will be studied *in vivo*.

Funded by Collaborative project UGMLC – LOEWE Centre Universities of Giessen and Marburg Lung Center (UGLMC)

Funding period 2013 – 2014

Title Experimental modelling and validation of pneumonia pathophysiology

Principal investigators B. T. Schmeck & M. Witzenrath, (Charité Universitätsmedizin Berlin)

Summary Mathematical modelling on the basis of deeply phenotyped clinical cohorts is the central systems medicine approach in CAPSyS. This approach has to be complemented by goal-directed cutting edge *in vivo* and *in vitro* experiments, because (1) important features of pneumonia pathogenesis evade clinical observation as they happen too early, or are inaccessible in the required timely and spatial resolution in patients, and (2) concise model construction and validation requires manipulation of biological pathways, which is impossible in patients.

This subproject uses experimental models to focus on two aims: Central aspects of pneumonia pathology inaccessible to patient-centred research will be elucidated in highly standardized and well controlled experimental models *in vitro*, *ex vivo* and *in vivo*, to provide homogenous data as starting

points for mathematical modelling of pathophysiologic sequences. Important functional modules and hypotheses established from previous studies and the patient-centred part will be narrowed down by hypothesis-driven in vitro screening approaches, and analysed in depth by a process including model construction, optimization, and validation iterating between wet lab and mathematics.

Funded by BMBF CapSys – Federal Ministry of Education and Research

Funding period 2014 – 2017

Title Extracellular Ribonuclease1: A new protective factor for vascular diseases

Principal investigators B. T. Schmeck & K. T. Preissner (JLU Giessen)

Summary Recently, vascular Ribonuclease1 (RNase1) was characterized as a new, vessel-protective protein. It neutralizes or prohibits the procoagulant, oedema-promoting or hyper-inflammatory activities of extra-cellular RNA (eRNA) within the vessel system. In this project, regulatory mechanisms of RNase-expression and –secretion as well as its protective role in vessel diseases will be determined and further validated in animal models. In addition, in patient cohorts, we will investigate whether an RNase1-deficiency or –mutant can be presumed as a risk factor for the development of hyperinflammatory or thrombotic diseases.

Funded by von Behring-Röntgen Foundation

Funding period 2014 – 2016

Title The influence of the virulence factor pneumolysin on histone modifications in pneumococcal pneumonia

Principal investigator K. Seidel

Summary Pneumococcal pneumonia belongs to the leading causes of death worldwide. Its course is mainly determined by virulence factors of the bacterium *Streptococcus pneumoniae* (*S. pneumoniae*) and the immune response of the host, emerging from the bronchial epithelium of the lung. In animal models of severe infections, „epigenetic“ therapeutical strategies have been studied successfully. The aim of the proposed project is providing the scientific basis for better understanding of such therapy. Therefore histone modifications within pneumococcal infection, its underlying mechanisms and impacts is to investigate.

Funded by P. E. Kempkes Foundation

Funding period 2014 – 2015

Title The role of miRNA in the pathogenesis of post-influenza pneumococcal pneumonia **Principal investigator** Evelyn Vollmeister

Summary This project addresses the relevant clinical problem of post-influenza pneumonia with a mouse

model of post-influenza pneumococcal pneumonia and the analysis of exosomes from bronchoalveolar lavage. The translational potential of this project includes the identification of possible biomarkers for severe course of the disease.

Funded by DFG-SFB/TRR84 (internal competition)

Funding period: 2014

General information about the institute

Research Funding

1.336.742,95 €

Most important publications

Chillappagari S, Venkatesan S, Garapati V, Mahavadi P, Munder A, Seubert A, Sarode G, Guenther A, **Schmeck BT**, Tümmler B, Henke MO (2014) Impaired TLR4 and HIF expression in cystic fibrosis bronchial epithelial cells downregulates hemeoxygenase-1 and alters iron homeostasis in vitro. *Am J Physiol Lung Cell Mol Physiol* 307:L791-9.

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Smirnova L, Block K, **Sittka A**, Oelgeschläger M, Seiler AE, Luch A (2014) MicroRNA profiling as tool for in vitro developmental neurotoxicity testing: the case of sodium valproate. *PLoS One* 9(6):e98892

Haag T, **Herkt CE**, Walesch SK, Richter AM, Dammann RH (2014) The apoptosis associated tyrosine kinase gene is frequently hypermethylated

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Sittka A, Schmeck B (2013) MicroRNAs in the lung. *Adv Exp Med Biol* 774:121-34

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Zaade D, Schmitz J, Benke E, Klare S, **Seidel K**, Kirsch S, Goldin-Lang P, Zollmann FS, Unger T, Funke-Kaiser H (2013) Distinct signal transduction pathways downstream of the (P)RR revealed by microarray and ChIP-chip analyses. *PLoS One* 8:e57674

Zahlten J, Steinicke R, **Bertrams W**, Hocke AC, Scharf S, **Schmeck B**, Witzernath M, Hammerschmidt S, Suttorp N, Hippenstiel S (2013) TLR9- and Src-dependent expression of Krueppel-like factor 4 controls interleukin-10 expression in pneumonia. *Eur Respir J* 41:384-9

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Director: Professor Dr. Bernd T. Schmeck

Department of Anaesthesia and Intensive Care Therapy

Chair Professor H. Wulf

Main fields of research

- Regional Anaesthesia
- Perioperative Patient Safety, outcome and quality of life (including Pain, PONV)
- Hypothermia (Surgery, Trauma)
- Resuscitation
- Perioperative Quality of Life

Regional Anaesthesia

Prof. Dr. T. Steinfeldt, Prof. Dr. H. Wulf

Main fields of research

Safety in regional anesthesia. Experimental and clinical models for simulation, detection and prevention of nerve injury following several intervention as used in daily practice in patients. Topics: nerve localization, needle nerve proximity, nerve injury. Research projects in 2013 and 2014: Selective saphenous nerve block for prevention of motor weakness for knee arthroplasty. Supraclavicular blocks instead of interscalene block for shoulder surgery as a prevention of diaphragmatic paralysis by local anesthetics.

Title Prevention of side effects during regional anesthesia

Principal investigator(s) T. Steinfeldt & H. Hinnerk

Summary Peripheral nerve blocks are of fundamental relevance for postoperative analgesia in the postoperative phase after knee arthroplasty. Therefore femoral nerve blocks are commonly applied. Unfortunately motor weakness in the quadriceps muscle often results due to the femoral nerve block. Thereby it is suggested, that patients are at risk of unintentional falls and consecutive injuries. By selective blocking of the saphenous nerve we intended to prevent a severe motor weakness of the quadriceps muscle. Therefore we compared motor strength and pain quality in 50 patients following femoral nerve or saphenous nerve block for knee arthroplasty.

Funded by Institutional grant

Therapeutic hypothermia in polytrauma patients during intensive care therapy

Prof. Dr. T. Steinfeldt, Prof. Dr. H. Wulf

(Cooperation with the Department of Traumatology (Prof. Dr. Ruchholtz))

Main fields of research

Effects on therapeutic induced hypothermia on organ function in an experimental porcine polytrauma model.

Principal investigator(s) T. Steinfeldt

Summary Induced moderate hypothermia after cardiac arrest has been proven to be beneficial and is established in clinical practice. Therefore, in a porcine model, the effect of hypothermia after a combined trauma to head, thorax, liver and lower extremity was investigated regarding pulmonary, cardiac, cerebral and renal outcome and on systemic inflammatory reaction.

Funded by Reinfried-Pohl-Stiftung

Perioperative Patient Safety

Dr. HJ Aust, PD Dr. D. Rüscher, Prof. Dr. L. Eberhart, Prof. Dr. H. Wulf

Main fields of research

Perioperative patient safety ; preoperative anxiety

Research projects Preoperative risk evaluation of adult patients before elective non-cardiac surgery; Prevention of postoperative hypoxemia; Preoperative anxiety: incidence, predictors and manifestations; Coping strategies of preoperative anxiety; Postoperative nausea and vomiting (PONV): prophylaxis and treatment of PONV; Influence of anaesthesia on postoperative sleep patterns, perioperative hemodynamic monitoring by transthoracic echocardiography.

Principal investigator(s) H. Aust & D. Rüscher

Summary Hypoxemia in the period right after surgery under general anesthesia during patient transfer to the recovery room is still a frequent complication in patients breathing room air. Therefore, routine monitoring of SpO₂ during patient transfer in all patients and supplementary oxygen if necessary is recommended.

Survey on the incidence and manifestations of preanesthesia and preoperative anxiety as well as coping strategies regarding these anxieties in more than 3000 patients.

Results so far (analysis not entirely completed): Anxiety about surgery is slightly more pronounced than anxiety about anesthesia. Most important risk factors for preoperative anxiety are female gender and bad experience with a previous anesthetic. Type of surgery does not have a significant impact on preoperative anxiety.

Funded by Medtronic Inc. gave access to subcutaneous sensors, no further funding

Resuscitation

PD Dr. C. Kill, Dr. Dersch, Prof. Dr. H. Wulf

Title New techniques of combining ventilation and cardiac compression during cardiopulmonary resuscitation

Summary A synchronized ventilation and compression could have a positive influence on ROSC (re-occurrence of spontaneous circulation), oxygenation, hemodynamics and outcome after cardiopulmonary resuscitation in an experimental porcine model of cardiac arrest.

Funded by Federal Ministry of Economics No KF2502403FR0, KF2660001FR0

Perioperative Quality of Life

Prof. Dr. L. Eberhart, T. Koch, Prof. Dr. H. Wulf

Main fields of research

The research group "Perioperative quality of life" works on strategies to measure and improve quality of life of surgical patients in the perioperative period. In this contexts strategies against postoperative complications like postoperative nausea and vomiting, pain, shivering, confusion and fatigue are of major concern.

Clinical research, epidemiologic studies and meta-analyses are the methodological cornerstones for the group.

Title Amisulpirid alone or in combination for the prevention of postoperative nausea and vomiting Amisulpirid for the treatment of breakthrough postoperative nausea and vomiting

Principal investigator(s) L Eberhart

Summary The dopamine D₂-antagonist droperidol was frequently used to prevent postoperative nausea and vomiting until safety concerns limited its use. Amisulpirid, a D₂/D₃-antagonist has shown promising anti-emetic efficacy at very low doses. The drug given IV prior to surgery is safe and highly effective at reducing PONV in moderate/high-risk adult surgical patients. The optimal dose tested was 5 mg in previous trials. This dose will be used in the current study alone versus a combination group consisting of amisulpiride and another standard antiemetic drug. In addition we will perform a study were established nausea and vomiting that occurs despite of a prophylactic dose of an antiemetic will be treated with amisulpiride.

Funded by Accacia-Pharma Ltd.

Funding period 2014 – 2016

Most important publications

Steinfeldt T, Wiesmann T, Nimphius W, Cornelius V, Eismann D, Kratz T, Hadzic A, Wulf H, Werner T (2014) Perineural hematoma may result in nerve inflammation and myelin damage. *Reg Anesth Pain Med* 39(6):513-9

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Aust H, Dinges G, Nardi-Hiebl S, Koch T, Lattermann R, Schricker T, Eberhart LH (2014) Feasibility and precision of subcutaneous continuous glucose monitoring in patients undergoing CABG surgery. *J Cardiothorac Vasc Anesth* 28(5):1264-72

Rahe-Meyer N, Fennema H, Schulman S, Klimscha W, Przemeck M, Blobner M, Wulf H, Speck M, McCrary Sisk C, Williams-Herman Debora Woo T, Szegedi (2014) Armin Effect of Reversal of Neuromuscular Blockade with Sugammadex versus Usual Care on Bleeding Risk in a Randomized Study of Surgical Patients. *Anesthesiology* 121:969-77

Dette F, Cassel W, Urban F, Zoremba M, Koehler U, Wulf H, Graf J, Steinfeldt T (2013) Occurrence of rapid eye movement sleep deprivation after surgery under regional anesthesia. *Anesth Analg* 116(4):939-43

Kill C, Hahn O, Dietz F, Neuhaus C, Schwarz S, Mahling R, Wallot P, Jerrentrup A, Steinfeldt T, Wulf H, Dersch W (2014) Mechanical ventilation during cardiopulmonary resuscitation with intermittent positive-pressure ventilation, bilevel ventilation, or chest compression synchronized ventilation in a pig model. *Crit Care Med*. 42(2):89-95

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Director: Professor Dr. Hinnerk Wulf

General information about the institute

Research funding

339.139,73 €

Department of Diagnostic and Interventional Radiology

Chair Professor A. Mahnken

Main fields of research

Interventional Radiology
Computed Tomography

Research projects

Title Multicentric Non-Randomized Investigation of RESISTANT Camouflage Stent System in Peripheral Superficial Femoral Arteries

Principal investigator(s) A. Mahnken

Summary Non-randomized post-market clinical follow-up study to confirm long-term safety and effectiveness of the CE-approved Camouflage-coated self-expandable RESISTANT Camouflage stent system for revascularization of de novo stenotic lesions in superficial femoral arteries in compliant patients suitable for stent angioplasty.

Funded by Eucatech AG, 79618 Rheinfelden

Funding period 2013 – 2016

Title Image-Based Structural and Functional Phenotyping of the COSYCONET Cohort Using MRI and CT (MR COPD)

Principal investigator(s) A. Mahnken & P. Seyfer

Summary The medical problem addressed in this trial is the image-based phenotyping of COPD. The principal research question is whether magnetic resonance imaging (MRI) can replace CT for the characterization of COPD by “structural and functional phenotyping” on a regional basis. The sensitivity and specificity of MRI will be compared to CT serving as the gold standard.

Funded by Heidelberg – University Medical Centre

Funding period 2013 – 2015

Title Hepa Care CT Subtraction vs. Angiography - Vergleichende Studie zur Beurteilbarkeit der Unterschenkelgefäße mittels CT-Angiographie

Principal investigator(s) R. Tjong & J. Görlach

Summary Bei Patienten mit pAVK bei denen eine konventionelle Angiographie erfolgte, erfolgt eine CT-Angiographie incl. der Akquisition nativer CT-Daten des Unterschenkels. Die Daten der CT-Angiographie mit und ohne Subtraktionstechnik werden mit dem Befund der intraarteriellen Angiographie verglichen. Zielparameter: Stenosedetektion und Therapieentscheidung anhand der CT Daten im Vergleich zum Goldstandard. Ziel: Überlegenheit der Subtraktions CT-Angiographie gegenüber der Standard-CTA Technik zu zeigen.

Title High Resolution Topogramm

Principal investigator(s) R. Tjong

Summary Während Verbesserungen der Ortsauflösung meist sofort implementiert wurden, werden zu Beginn der Untersuchung durchgeführten Übersichtsaufnahmen mit einer unterlegenen Ortsauflösung rekonstruiert. Eine Rekonstruktion der Topogramme von 50 Patienten auf die mögliche Auflösung von 0.5 mm, soll zeigen welche Verbesserung in der Darstellung und Planung möglich sind. Hier ist eine Auswertung hinsichtlich Bildqualität als auch pathologischer Befunde v.a. in der Traumadiagnostik geplant.

Title Evaluation alternativer Response Kriterien

Principal investigator(s) Perla Seyfer

Summary Neue Responsekriterien (z.B. mRECIST, Cheson, usw.) gewinnen zunehmend an Bedeutung. Ziel ist der Transfer dieser Responsebewertungsalgorithmus auf neuroendokrine Tumoren (NET). In einer Studie mit syngo.via MM Oncology soll die Prognosebewertung von NETs unter Anwendung der hepaCARE Funktionalitaet beurteilt werden. Dazu werden die Daten von 25 Patienten mit hepatisch metastasiertem NET vor und nach Chemoembolisation beurteilt.

Title Establishment of in vivo C-13 magnetic resonance spectroscopy (MRS) for tumor metabolism investigation

Principal investigator(s) A. Mahnken & A. M. König

Summary With C-13 magnetic resonance spectroscopy (MRS) it is possible to monitor noninvasively the uptake of glucose and its conversion into metabolites such as lactate. This opens the way to assessing metabolic activity in tumor tissue. This could help to characterise the malignancy of tumors and their response of therapy.

Funded by P. E. Kempkes Foundation

Funding period 2013 – ongoing project

Title Development of a cryogenic RF coil for MRI

Principal investigator(s) D. Sasse & M. Völker

Summary The research objective is to develop a cryogenic RF coil for MRI with a reduced thermal noise contribution. Increasing the SNR provides a higher resolution and/or shorter measurement times, thus extending MRI capabilities.

Funded by Foundation of the Medical Faculty, Philipps University Marburg

Funding period 2014 – 2015

Title RF coils for dual frequency experiments in small animal MRI (PhD thesis Maximilian Völker)

Principal investigator(s) M. Völker & J.T. Heverhagen

Summary New RF coils were developed to increase the potential of small animal MRI. The coils are

optimized for dual frequency operation at mice. Phosphorus signal was used to get additional metabolic information of tissues. Specific coils for brain, abdominal and heart MRI on mice were developed.

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2009 – 2013

Title Semi-automatic lung segmentation method for mri based lung images

Principal investigator(s) S. Braun

Summary The development of MR imaging of the lung is an alternative application to computer tomography in clinical routine without the availability of computer-aided analysis for diagnose and treatment. We propose an alternative postprocessing method for lung segmentation based on a threshold algorithm for MR images of the lung that was verified with several imaging sequences and different magnetic field strength.

Title Mikrozirkulatorische und metabolische Veränderungen des Skelett- und Herzmuskels bei obstruktiver Schlafapnoe – von Genexpression und Signalling zum klinisch relevanten Readout

Principal investigator(s) W. Hildebrandt, R. Schulz (UKGM Giessen), U. Koehler, A. Kießling

Summary The highly prevalent obstructive sleep apnea syndrome (OSAS) is associated with adipositas, insulin resistance and hypertension and considered an independent cardiovascular risk factor. This project focusses on in-vivo and ex-vivo analyses of skeletal muscle microcirculation and metabolism in OSAS-patients compared to age-, gender- and BMI-matched healthy controls. Investigations include muscle biopsies for histo- and ultrastructural morphology and gene expression in combination with real-time contrast-enhanced ultrasound and Duplex-Doppler and ¹H-MRS in identical localisation beside clinical blood, MRT and other readouts.

Funded by von Behring-Röntgen Foundation

Funding period 2011 – 2014

Title MRT-Diagnostik von gentechnisch veränderten Tumorzellen

Principal investigator(s) J. Bartsch & M. Bauer (Neurosurgery)

Summary Im geplanten Projekt soll die Tumorprogression verschiedener Gliomzelllinien im Mausmodell umfassend untersucht werden. Hierbei steht die Entwicklung spezifischer molekularer Sonden, sowie die Entwicklung und Optimierung der MR-Sequenzen für die MR-Spektroskopie sowie die Anpassung der Analysesoftware im Vordergrund. Für dieses Vorhaben sollen die Sonden und die Spektroskopie ex vivo an den Gliomzelllinien untersucht und optimiert werden.

Funded by von Behring-Röntgen Foundation

Funding period 2014 – 2016

Title Intrafraktionale Prostata- und Rektumveränderung im MRT nach Fixierung der Prostata durch Positionierung eines Rektum-Doppelballon versus ohne Ballon für die Hochpräzisionsstrahlentherapie

Principal investigator(s) R. Engenhart-Cabillic, G. Straßmann & M. Thiemer

Summary Im vorliegenden Projekt soll das Ausmaß der intrafraktionalen Beweglichkeit der Prostata unter Einsatz eines endorektalen Doppelballons bestimmt werden. Die Messungen erfolgen in Zusammenarbeit mit der Klinik für Strahlendiagnostik MRT-gestützt. Ziel ist es nachzuweisen, dass die Prostatabeweglichkeit mit endorektalem Doppelballon durch die Fixation signifikant geringer ist als ohne Fixation.

Commissioned Research

Title Funktionelle Bildgebung von Stoffwechselvorgängen bei Zwerghamstern und Mäusen

Principal investigator(s) G. Heldmaier, FB Biology & K. Grimpo

Funding period 2010 – 2013

Title Analyse der Tumorprogression in Maus – Tumormordellen durch MRT Multimodale Analyse von Gliomen im Mausmodell

Principal investigator(s) J. Bartsch, Neusurgery

Title Oxygen damage at rat premature babies

Principal investigator(s) K. Stieger, M. Zenlin, R. F. Maier, Children's Hospital Marburg

Funding period 2012 – 2014

Title MRI at epileptic mice

Principal investigator(s) F. Rosenow & B. Norwood, Department of Neurology Marburg

Funding period 2013 – 2016

Title In vivo imaging of migration from dendritic cells in arthrosclerosis mouse model

Principal investigator(s) J. Schütt & B. Schieffer, Department of Internal Medicine: Division of Cardiology Marburg

Funding period 2014 – 2017

Title P53 – cooperation in therapy of thymus – lymphoma

Principal investigator(s) O. Timofeev & T. Stiewe, Institute of Molecular Biology and Tumorbiology Marburg

Funding period 2013 – 2016

Title Suppression Kras – induced lung cancer by p53

Principal investigator(s) T. Stiewe, O. Timofeev,

Institute of Molecular Biology and Tumorbiology
Marburg

Funding period 2013 – 2016

Title Shank1 and autism in mouse model

Principal investigator(s) S. Röskam & M. Wöhr,
Institute of Psychology Marburg

Funding period 2010 – 2014

Burbelko M, Kalinowski M, Heverhagen JT, Piechowiak E, Kiessling A, Figiel J, Swaid Z, Geks J, **Hundt W** (2014) Prevention of type II endoleak using the AMPLATZER vascular plug before endovascular aneurysm repair. *Eur J Vasc Endovasc Surg* 47(1):28-36

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General information about the institute

Research funding 180.185,95 €

Most important publications

Isfort P, Penzkofer T, Tanaka T, Bruners P, Westphal S, Kennes LN, Schmitz-Rode T, Kuhl CK, **Mahnken AH** (2013) Efficacy of antegrade pyeloperfusion to protect the renal pelvis in kidney microwave ablation using an in vivo swine model. *Invest Radiol* 48(12):863-8

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Department of Nuclear Medicine

Chair Professor M. Luster

Main fields of research

During the reporting period the capacity of the radiochemical laboratory was expanded by the installation of a Germanium/Gallium-68 radionuclide generator and a computer-controlled device for the automated synthesis of radiopharmaceuticals, in particular radiopeptides in the rapidly expanding field of “theranostics”. Thus the diagnostic spectrum could be complemented by Ga-68-DOTATOC-PET/CT for staging of neuroendocrine tumors and Ga-68-PSMA-PET/CT for imaging of prostate cancer. Furthermore the corresponding radiopharmaceuticals can be used for radionuclide therapy of metastases or in some cases primary lesions of the same entities by labeling the compounds with Lu-177 or Y-90. This approach also offers the possibility of an individual pretherapeutic dosimetry in order to optimize the absorbed radiation dose to the tumor while minimizing the radiation exposure of the patient i.e. the organs at risk. For this purpose appropriate novel software tools were introduced and their feasibility was investigated. Individual dosimetry could be already successfully established during the reporting period in the field of radioiodine therapy of thyroid cancer and in the management of neuroendocrine malignancies. A new field of research is the use of targeted therapies i.e. tyrosinekinase- inhibitors for the treatment of advanced thyroid tumors namely radioiodine refractory thyroid cancer.

Research projects

Title A Randomised, Double Blind Study of Compare the Complete Remission Rate Following a 5-Week Course of Selumetinib or Placebo and Single Dose Adjuvant Radioactive Iodine Therapy in Patients with Differentiated Thyroid Cancer (under review)

Principal investigator(s) M. Kreißl & M. Luster

Summary The study is designed to evaluate the clinical efficacy, safety and tolerability of selumetinib with radioactive iodine therapy in patients with differentiated thyroid cancer.

Funded by AstraZeneca AB, Södertälje, Schweden

Funding period 2013 – 2015

Title FOXFIREGlobal: Assessment of Overall Survival of FOLFOX6m plus SIR-Spheres microspheres versus FOLFOX6m alone as first-line treatment in patients with non-resectable liver metastases from primary colorectal carcinoma in randomised clinical study

Principal investigator(s) A. Pfestroff, H. Höffken & J.

Riera-Knorrenschild, Department of Hematology, Oncology and Immunology

Summary This study is a randomized, multi-center study that will compare the efficacy and safety of selective internal radiation therapy (SIRT) using SIR-Spheres microspheres plus a standard chemotherapy regimen of FOLFOX6m versus FOLFOX6m alone as first-line therapy in patients with non-resectable liver metastases from primary colorectal carcinoma.

Funded by Sirtex Technology, Sydney; Australia

Funding period 2013 – 2015

Title A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of ARN-509 in Men with Non-Metastatic (M0) Castration-Resistant Prostate Cancer

Principal investigator(s) J. Heinis, J. Olbert, Department of Urology and Paediatric Urology, University of Marburg & A. Heidenreich, Department of Urology, University of Aachen

Summary The purpose of this study is to evaluate the efficacy and safety of ARN-509 in adult men with high-risk non-metastatic castration-resistant prostate cancer.

Funded by Pharmaceutical Research Associates GmbH, Mannheim

Funding period 2013 – 2015

Title A Randomized, Double-blind, Phase 3 Efficacy Trial of PROSTVAC-V/F ± GM-CSF in Men With Asymptomatic or Minimally Symptomatic Metastatic, Castrate-Resistant Prostate Cancer

Principal investigator(s) J. Heinis & P. J. Olbert, Department of Urology and Paediatric Urology, Marburg

Summary The purpose of this study is to determine whether PROSTVAC alone or in combination with GM-CSF is effective in prolonging overall survival in men with few or no symptoms from metastatic, castrate-resistant prostate cancer.

Funded by Nordic, Inc.; PPD Immuno Therapeutics

Funding period 2011 – 2015

Title PRESENT: Prevention of Recurrence in Early Stage, Node-Positive Breast Cancer with Low to Intermediate HER2 Expression with NeuVax™ Treatment (Phase 3)

Principal investigator(s) D. Librizzi, & Dr. K. Baumann, Department of Gynecology, Gynecological Endocrinology and Oncology, Marburg

Summary Purpose of this trial: To assess the efficacy and safety of NeuVax™ administered with adjuvant Leukine® (sargramostim, GM-CSF). To evaluate and compare the disease free survival (DFS) in the vaccinated and control subjects

Funded by Galena Biopharma, Inc.

Funding period 2011 – 2015

Title QUEST Study: Quantitative Uptake Evaluation in SIR-Spheres Therapy

Principal investigator(s) A. Pfestroff

Summary The QUEST (Quantitative Uptake Evaluation in SIR-Spheres Therapy) study is an investigator based initiative to understand the dose-response relationship in Y-90 radioembolisation treatment of liver cancer. Based on results from the site assessment phase to characterize scanners, a clinical protocol is proposed for image acquisition and analysis in an attempt to standardize the approach to dosimetry in this study.

Funded by Sirtex Technology Pty Ltd, Sydney, Australia

Funding period 2013 – 2014

Title ReBeL study: A randomized phase I/II trial of lenalidomide and rituximab with or without bendamustine in patients ≥ 18 years with relapsed follicular lymphoma

Principal investigator(s) H. Höffken & C. Wilhelm, Department of Hematology, Oncology and Immunology, Marburg

Summary *For the phase I part of the study:* to determine the dose limiting toxicity (DLT) and recommended dose level (RDL) of lenalidomide and bendamustine given in combination with rituximab for the phase II part of the study *For the phase II of the study:* to determine the efficacy and toxicity of the two arms of the study (arm A: lenalidomide and rituximab, and arm B: lenalidomide, rituximab and bendamustine) in patients with relapsed follicular lymphoma

Funded by HOVON ClinAssess GmbH (Monitoring), Leverkusen

Funding period 2012 – 2015

Title SIRFLOX-Study: Randomised Comparative Study Of Folfox6m Plus Sir-Spheres® Microspheres Versus Folfox6m Alone As First Line Treatment In Patients With Nonresectable Liver Metastases From Primary Colorectal Carcinoma Primary

Principal investigator(s) A. Pfestroff, H. Höffken & J. Riera-Knorrenschild, Department of Hematology, Oncology and Immunology, Marburg

Summary The SIRFLOX study is an international research study designed to evaluate a new treatment option for patients with colorectal cancer that has undergone metastatic spread to the liver. The study is designed to evaluate whether FOLFOX chemotherapy in combination with Selective Internal Radiation Therapy is more effective than chemotherapy alone. This study represents the first time that these treatments have been assessed together as part of a randomized controlled study and as a first-line therapy (i.e. in patients who have

not previously received chemotherapy for their liver metastases).

Funded by Sirtex Medical

Funding period 2006 – 2018

Title Pilotprojekt zur Quantifizierung und Eindringtiefe von Radiopharmaka durch nächtliche nasale Langzeitinhalation (NLI) bei Patienten mit COPD

Principal investigator(s) D. Librizzi, Dr. Pfestroff, Prof. Groß (FH Gießen) & U. Koehler; Division of Pneumology Marburg

Summary Ventilationsszintigraphie mit nasalem Applikationsweg vs. oralem Applikationsweg. Zur Etablierung einer neuen Therapieform bei COPD.

Funded by LOEWE

Funding period 2011 – 2014

Title The Parkinson's Progression Markers Initiative (PPMI)

Principal investigator(s) H. Höffken & Prof. B. Mollenhauer, Paracelsus-Elena Clinic Kassel

Summary The mission of PPMI is to identify one or more biomarkers of Parkinson's disease progression. The discovery of a biomarker is a critical step in the development of new and better treatments for PD.

Funded by The Michael J. Fox Foundation for Parkinson's Research (MJFF)

Funding period 2010 – 2018

General information about the institute

Research funding 12.564,62 €

Most important publications

Hänscheid H, Canzi C, Eschner W, Flux G, **Luster M**, Strigari L, Lassmann M (2013) EANM Dosimetry Committee series on standard operational procedures for pre-therapeutic dosimetry II. Dosimetry prior to radioiodine therapy of benign thyroid diseases. *Eur J Nucl Med Mol Imaging* 40(7):1126-34

Weber T, Maier-Funk C, Ohlhauser D, Hillenbrand A, Cammerer G, Barth TF, Henne-Bruns D, Boehm BO, Reske SN, **Luster M** (2013) Accurate preoperative localization of parathyroid adenomas with C-11 methionine PET/CT. *Ann Surg* 257(6):1124-8

Pitoia F, Bueno MF, Abelleira E, Salvai ME, Bergoglio L, **Luster M**, Niepomnische H (2013) Undetectable pre-ablation thyroglobulin levels in patients with differentiated thyroid cancer: it is not always what it seems. *Arq Bras Endocrinol Metabol* 57(4):300-6

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Thies ED, Tanase K, Maeder U, **Luster M**, Buck AK, Hänscheid H, Reiners C, Verburg FA (2014) The number of ¹³¹I therapy courses needed to achieve complete remission is an indicator of prognosis in patients with differentiated thyroid carcinoma. *Eur J Nucl Med Mol Imaging* 41(12):2281-90

Schlumberger M, Brose M, Elisei R, Leboulleux S, **Luster M**, Pitoia F, Pacini F (2014) Definition and management of radioactive iodine-refractory differentiated thyroid cancer. *Lancet Diabetes Endocrinol* 2(5):356-8

Rossmann A, Mandic R, **Heinis J**, **Höffken H**, Küssner O, Kinscherf R, Weihe E, Bette M (2014) Intraperitoneal oxidative stress in rabbits with papillomavirus-associated head and neck cancer induces tumoricidal immune response that is adoptively transferable. *Clin Cancer Res* 20(16):4289-301

Luster M, Weber T, Verburg FA (2014) Differentiated thyroid cancer-personalized therapies to prevent overtreatment. *Nat Rev Endocrinol* 10(9):563-74

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Director: Professor Dr. Markus Luster

Department of Radiotherapy and Radiooncology

Chair Professor R. Engenhart-Cabillic

Main fields of research

Clinical focus

- Clinical application and technical development of stereotactic radiotherapy and other high precision techniques
- Adaptive radiotherapy planning for photon and particle therapy

Physical and Technical focus

- Monte Carlo methods for treatment planning and quality assurance
- Dosimetry and quality assurance in sophisticated radiotherapy techniques with emphasis on particle radiotherapy and irradiation of small targets

Biological focus

- Biological radiotherapy planning by means of biophysical modeling
- Methods to overcome resistance with focus on hypoxia
- Treatment response in human papilloma virus induced head and neck squamous cell cancer

Research projects

Title Union of Light-Ion Centers in Europe (ULICE)

Principal investigator(s) R. Orecchia, Centro Nazionale di Adroterapia Oncologica, Milan (project coordinator), Marburg: U. Jelen, F. Ammazalorso & A. Wittig

Summary ULICE comprises more than 20 academic and industrial partners, aiming at development of instruments and protocols for particle therapy and increase inter-facility clinical cooperation. Marburg participates in WP5 (Adaptive Treatment Planning), WP10 (European Standardization of Clinical Protocols) and WP11 (Transnational Access). In WP5 Marburg is involved with patient immobilization, dosimetric stability and tool development for particle therapy treatment planning and delivery.

Funded by European Commission (FP7)

Funding period 2009 – 2014

Title Radiation Oncology Collaborative Comparison (ROCO). In Silico clinical trial in lung, prostate and head cancer, comparing photons, protons and C-ion therapy treatment: a multicentric planning study based on a reference dataset of patients.

Principal investigator(s) P. Lambin, Maastricht Radiation Oncology, Maastricht, Marburg: U. Jelen & F. Ammazalorso & A. Santiago

Summary Evidence is needed to assess if particle therapy outperforms conventional radiotherapy. ROCOCO aims at demonstrating through *in silico* trials that particle therapy: (1) decreases irradiation of normal tissue and therefore risk of side effects and secondary tumors, (2) increases iso-toxic tumor control probability, hence local control and survival rates in head and neck, prostate and lung cancer.

Title Development of ultra-fast dose computation algorithms for radiotherapy

Principal investigator(s) U. Jelen & F. Ammazalorso

Summary The conformity of advanced radiotherapy modalities requires extensive dosimetric verification, potentially combined with on-line treatment plan adaptation. The prohibitive dose computation times have hinder the application of such techniques in the clinical routine. This project proposes an ultra-fast multi-modality (photon/proton/carbon-ion) analytical dose computation engine exploiting general purpose graphic processing units (GPGPU).

Funded by Parts of the project were funded:

DFG – German Research Foundation: *Support of the Initiation of International Collaboration*
Alfred und Ursula Kulemann Foundation support for hardware purchase

Title Biological radiotherapy planning by means of biophysical modeling of the tumor control probability in particle beam therapy

Principal investigator(s) A. Wittig, U. Jelen, A. Santiago & M.-A. Chanrion

For radiotherapy treatment planning, the increased biological effectiveness of carbon ions must be quantified through a biophysical model. One such model, is the local effect model (LEM). Purpose of this work is to validate the computational results obtained with the LEM model against the available clinical data and to provide the best estimate of the α/β , to be used as input for LEM, for tissues where the verification against the clinical follow-up data is not possible.

Funded by Anneliese Pohl Foundation

Funding period 2012 – 2014

Title Evaluation of the clinical outcome of high precision and stereotactic techniques in terms of tumor control and side effects

Principal investigator(s) A. Wittig, R. Engenhart-Cabillic, Prof. Fritz (Siegen)

Summary Highly precision radiotherapy techniques aim at conforming the dose to the target thus enabling escalation of the biologically effective dose in the tumor and/or sparing of normal tissues. The project aims at evaluation of clinical follow up data

with focus on mature long term data in patients treated with precision techniques for lung or brain lesions.

Title Study on the technical implementation of particle therapy for treatment of pulmonary lesions

Principal investigator(s) A. Wittig, U. Jelen, A. Santiago, R. Engenhardt-Cabillic & Prof. Fritz (Siegen)

Summary The challenge of particle therapy in the lung is the management of respiratory motion, due to the sensitivity of the ion range to changes in the water equivalent path length. The feasibility of High Frequency Jet Ventilation (HFJV) as compared to alternative techniques for breathing control is evaluated based on data of patients treated with stereotactic photon radiotherapy and the respective techniques for motion control.

Title Optimization of the dosimetric quality and stability of heavy ion therapy planning

Principal investigator(s) U. Jelen & F. Ammazalorso

Summary Conformity offered by particle therapy requires tighter tolerances for dosimetric uncertainties, e.g. patient setup, CT calibration. Tools for dosimetrically robust treatment plans, like the Port Homogeneity Index were developed in Marburg. In this project (1) a comprehensive study of the robustness problem, (2) substantial improvements to the PHI concept and (3) its complete software implementation, for clinical application, are proposed.

Title KoHaLa

Principal investigator(s) H. Vorwerk, G. Sakas MedCom GmbH, F. Wesang (Frauenhofer IGD), D. Baltas (Clinical Centre Offenbach)

Summary Development and testing of an automated contouring atlas for patients with head and neck cancer.

Funded by LOEWE

Funding period 2012 – 2014

Title Adaptive radiotherapy: daily patient related dose reconstruction in fluence modulated radiotherapy techniques

Principal investigator(s) H. Vorwerk, D. Wolff & D. Wolf (Gießen)

Summary The project aims at the evaluation of 3D-imaging for patient positioning at linear accelerators and includes the development of methods for calibration of conebeam-CTs for calculation of the photon dose distribution and methods for online measurements of the fluence in intensity modulated techniques. Such is used for calculation of the daily dose distribution in fractionated treatments. The clinical evaluation of reconstructed dose distributions helps in developing protocols for safety margins in image guided radiotherapy.

Funded by UKGM, University Medical Centre Giessen / Marburg

Funding period 2012 – 2014

Title Role of hypoxia-inducible transcription factors for the treatment efficacy of carbon ion radiation compared to photons in the lung cancer model

Principal investigator(s) F. Rose, J. Hänze & F. Subtil

Summary Radiation resistance of solid tumors towards photon irradiation is caused by attenuated amounts of DNA-damage in less oxygenated tumor areas and by increased Hypoxia-inducible factor 1 (HIF-1) signaling. We analyzed the effect of HIF-1 signaling after irradiation with photons in comparison to carbon ions using biological equivalent doses in a human non-small cell lung cancer model. Knockdown of HIF-1 α in vivo combined with photon irradiation delayed tumor growth. Photon irradiation induced HIF-1 α and target genes predominantly in oxygenated cells with subsequently enhanced tumor angiogenesis in contrast to carbon ion irradiation. Micro-DNA array analysis indicated that photons but not carbon ions induced components of the mTOR (mammalian target of rapamycin) pathway as relevant for HIF-1 α induction. Importantly after carbon ion irradiation in vivo, we observed substantially decreased HIF-1 α levels and drastically delayed tumor growth indicating a higher relative biological effectiveness than anticipated from the cell survival data. In conclusion, carbon ions mediate an improved therapeutic effectiveness without tumor promoting HIF-1 signaling.

Funded by DFG – German Research Foundation

Funding period 2009 – 2013

Title Role of bacterial pathogenicity in promoting mechanisms of radioresistance in NSCLC

Principal investigator(s) F. Subtil, K. Hattar (Gießen) & U. Grandel (Gießen)

Summary Lung cancer is frequently complicated by pulmonary infections which may impair prognosis of this disease. We hypothesize that purified endotoxin, the main pathogenicity factor of gram-negative bacteria, promotes radioresistance. Therefore, we investigated the effect of bacterial lipopolysaccharides (LPS) on tumor proliferation in combination with photon irradiation in different non-small cell lung cancer (NSCLC) cell lines. Further, we plan to investigate the molecular mechanism, which may be involved in this LPS-induced radioresistance.

Funded by von Behring-Röntgen Foundation

Funding period 2013 – 2015

Title Development of individualized treatment concepts in head and neck malignancies by combined modalities

Principal investigator(s) Prof. R. Dr. Engenhardt-Cabillic, Priv.-Doz. Dr. A. Wittig, Dr. A. Arenz, Dr. S. Wagner, Prof. Dr. C. Wittekind, Prof. Dr. J.P. Klußmann

Summary HPV related cancers of the oropharynx represent a different clinicopathological and molecular entity compared to not HPV-related tumors. Regardless of a superior treatment response in HPV-related tumors, both groups are treated with the same treatment regimes. Aim of the research projects is to elucidate the molecular mechanisms leading to a higher efficacy of ionizing irradiation in HPV-related cancer and to understand and overcome radioresistance in HPV negative tumors, mainly by using combined modalities.

Funded by UKGM – University Medical Centre Giessen / Marburg

Funding period 2012 – 2014

Title Optimization of the irradiation effect through modulation of autophagy in radioresistant tumor cell lines

Principal investigator(s) C. Akropowicz & A. Arenz

Summary Autophagy serves as a pro-death mechanism but also as a protective cell survival mechanism causing resistance to anticancer therapies. We investigate the effects of radiation- and hypoxia-induced autophagy on survival of cancer cells of different entities. Targeting the pro-death and pro-survival functions of autophagy we evaluate cellular survival after inhibition or induction of autophagy. Depending on the cellular features, either induction or inhibition of autophagy can provide therapeutic benefits in vitro offering opportunities to personalized medicine strategies.

Funded by P.E. Kempkes Foundation

Funding period 2012 – 2014

follow up in 164 patients of a single institution. *J Neurol* 260(8): 2156-2162

Ammazzalorso F, Graef S, Weber U, Wittig A, Engenhardt-Cabillic R, Jelen U: Dosimetric consequences of intrafraction prostate motion in scanned ion beam radiotherapy. *Radiother Oncol* 2014 May 12. pii: S0167-8140(14)00165-0 [Epub ahead of print]

Fokas E, Henzel M, Surber G, Hamm K, Engenhardt-Cabillic R. (2014) Stereotactic radiotherapy of benign meningioma in the elderly: clinical outcome and toxicity in 121 patients. *Radiother Oncol* 111(3):457-62.

Fokas E, Henzel M, Surber G, Hamm K, Engenhardt-Cabillic R. (2014) Stereotactic radiation therapy for benign meningioma: long-term outcome in 318 patients. *Int J Radiat Oncol Biol Phys* 89(3):569-75

Subtil FS, Wilhelm J, Bill V, Westholt N, Rudolph S, Fischer J, Scheel S, Seay U, Fournier C, Taucher-Scholz G, Scholz M, Seeger W, Engenhardt-Cabillic R, Rose F, Dahm-Daphi J, Hänze J (2014) Carbon ion radiotherapy of human lung cancer attenuates HIF-1 signaling and acts with considerably enhanced therapeutic efficacy. *FASEB J* 28(3):1412-21

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Tel.:++49 (0) 6421-58 66434

Director: Professor Dr. Rita Engenhardt-Cabillic

General information about the institute

Research funding 499.385,37 €

Most important publications

Santiago A, Jelen U, Ammazalorso F, Engenhardt-Cabillic R, Fritz P, Mühlnickel W, Enghardt W, Baumann M, Wittig A (2013) Reproducibility of target coverage in stereotactic spot scanning proton lung irradiation under high frequency jet ventilation. *Radiother Oncol* 2013 Oct 12. doi:pii: S0167-8140(13)00475-1. 10

Fokas E, Henzel M, Wittig A, Grund S, Engenhardt-Cabillic R (2013) Stereotactic radiosurgery of cerebral arteriovenous malformations: long-term

Department of Internal Medicine: Division of Gastroenterology, Endocrinology and Metabolism

Chair Professor T. Gress
Professor V. Ellenrieder

Main fields of research

Clinical and molecular gastrointestinal oncology, early detection of GI tumors, preneoplastic lesions of GI-tumours, endoscopy, chronic inflammatory bowel disease, acute and chronic pancreatitis, neuroendocrine tumours, functional genome analysis of GI tumors, molecular diagnosis and therapy, molecular mechanisms of cancerogenesis in GI-tract, hereditary disease of GI-tract, NFAT and TGF β -signal transduction, transcriptional regulation of gene expression, fibrogenesis in the pancreas.

Research projects

Title Role of transcription factors NFATc1 in the leukaemia genesis and therapy resistance of FLT3-ITD-positive AML

Principal investigator(s) A. Burchert & V. Ellenrieder

Funded by José Carreras Leukaemia Foundation

Funding period 2012 – 2015

Title NGFN-plus "Translational Genome Network for pancreas carcinoma"

Principal investigator(s) T. Gress, project coordinator

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2008 – 2013

Title KMU-innovativ-4: PakaNostra

Principal investigator(s) M. Buchholz

Summary TP6 Identification and validation of drug targets of pancreas carcinomas by innovative strategies

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2010 – 2013

Title Identification of new therapeutic targets using RNA interference library screens to resolve chemo resistance at pancreas carcinoma

Principal investigator(s) P. Michl

Funded by Deutsche Krebshilfe

Funding period 2010 – 2013

Title Mechanisms of the oncogenetic senescence overcoming in the transgenic mouse model of the pancreatic carcinogenesis

Principal investigator(s) S. Baumgart & V. Ellenrieder

Summary Mechanisms of the oncogenetic senescence overcoming in the transgenic mouse model of the pancreatic carcinogenesis

Funded by UKGM – University Medical Centre Giessen / Marburg

Funding period 2012 – 2013

Title Genome-wide analysis of the CUX1 transcriptional network mediating resistance to apoptosis in pancreatic cancer: Continuation of Clinical Research Group

Principal investigator(s) P. Michl

Funded by DFG – German Research Foundation

Funding period 2012 – 2015

Title EPC-TM-Net Targeting the tumor microenvironment to improve pancreatic cancer prognosis

Principal investigator(s) T. Gress

Funded by EU – European Research Council

Funding period 2011 – 2014

Title Analysis of microRNA profiles depending on K-ras and B-raf mutations in colon cancer: a combined assessment on the PETACC-2-trial

Principal investigator(s) P. Michl

Funded by EORTC – European organization for Research and Treatment of Cancer

Funding period 2012 – 2014

Title Characterization and therapeutic targeting of cathepsin activity in tumor-associated macrophages during pancreatic cancer development and progression

Principal investigator(s) P. Michl

Funded by DFG – German Research Foundation

Funding period 2014 – 2017

Title Interactions between SSTR modulation via lanreotide and TKIs in sequential and combination approaches *in vitro* and *in vivo*

Principal investigator(s) S. Krug & P. Michl

Summary

Funded by IPSEN Pharma GmbH

Funding period 2014 – 2016

Title Resistenzmechanismen auf antiangiogene Therapieansätze bei Neuroendokrinen Neoplasien - Charakterisierung molekularer Mechanismen u. Identifizierung prädiktiver Marker

Principal investigator(s) S. Krug & P. Michl

Funded by UKGM

Funding period 2014 – 2016

Title Pharmakologische Immunmodulation im transgenen RIP-Tag-Modell

Principal investigator(s) S. Krug & P. Michl

Funded by Theranostics Research Network

Funding period 2013 – 2014

Title Charakterisierung der molekularen Mechanismen der CUX1-induzierten Angiogenese bei Neuroendokrinen Neoplasien

Principal investigator(s) S. Krug & P. Michl

Summary WNT5A - mediator of resistance to apoptosis in pancreatic cancer

Funded by Röntgen-Behring Foundation

Funding period 2014 – 2016

Title Connective tissue growth factor (CTGF) im dukalen Pankreaskarzinom: Funktionelle und therapeutische Evaluation in Maus und Mensch

Principal investigator(s) A. Neese

Funded by UKGM – University Medical Centre Giessen / Marburg

Funding period 2013 – 2014

Title Analyse der extrinsischen (Anti-) Apoptosemechanismen des HCC in Abhängigkeit des Survival Faktors CUX1

- Zusammenhang des TRAIL Pathways und CUX1

Principal investigator(s) L. Doll & T. Wisiński

Funded by P.E. Kempkes Foundation

Funding period 2014 – 2015

Title CAM-PaC (Integrative Analysis of Gene Functions in Cellular and Animal Models of Pancreatic Cancer)

Principal investigator(s) M. Buchholz & T. M. Gress

Funded by EU – European Research Council

Funding period 2013 – 2018

Most important publications

Michl P, Gress TM (2013) Current concepts and novel targets in advanced pancreatic cancer. *Gut* 62: 317-26

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investigate safety and efficacy of gemcitabine combined with cetuximab as adjuvant therapy in pancreatic cancer (ATIP). *Ann Oncol* : 24, 2576-81

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Baumgart S, Chen NM, Siveke JT, König A, Zhang JS, Singh SK, Wolf E, Bartkuhn M, Esposito I, Hessmann E, Reinecke J, Nikorowitsch J, Brunner M, Singh G, Fernandez-Zapico ME, Smyrk T, Bamlet WR, Eilers M, Neesse A, **Gress TM**, Billadeau DD, Tuveson D, Urrutia R, **Ellenrieder V** (2014) Inflammation-induced NFATc1-STAT3 transcription complex promotes pancreatic cancer initiation by KrasG12D. *Cancer Discov* 4: 688-701

Kaistha BP, Honstein T, Muller V, Bielak S, Sauer M, Kreider R, Fassan M, Scarpa A, Schmees C, Volkmer H, **Gress TM, Buchholz M** (2014). Key role of dual specificity kinase TTK in proliferation and survival of pancreatic cancer cells. *Br J Cancer* 111: 1780-1787

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Hermann PC, Sancho P, Cañamero M, Martinelli P, Madriles F, **Michl P, Gress T**, de Pascual R, Gandia L, Guerra C, Barbacid M, Wagner M, Vieira CR, Aicher A, Real FX, Sainz B Jr, Heeschen C. (2014) Nicotine promotes initiation and progression of KRAS-induced pancreatic cancer via Gata6-dependent dedifferentiation of acinar cells in mice. *Gastroenterology* 147, 1119-33

**Professor P. Kann –
Endocrinology & Diabetology**

Main fields of research

- Pituitary Diseases: Growth Hormone Substitution, Pharmacogenetics, Somatotrophic Function and Cancer Risk
- Diabetes Mellitus: Epidemiology, Treatment, Hemochromatosis
- Osteology: Osteoporosis - Diagnosis and Treatment, Mechanical Properties of Bone Tissue, Migrants' Osteomalacia
- Neuroendocrine Tumors: Endocrine Imaging - Endoscopic Ultrasound, Multiple Endocrine Neoplasia, Insulinoma
- Diseases of the Adrenal Glands: Adrenal Incidentaloma, Primary Hyperaldosteronism, Pheochromocytoma
- Medical Anthropology: Cultural / Social Change and the Risk for Metabolic Diseases in Subsaharian Africa
- Laboratory Medicine

Research projects

Title Association of the GHRd3-polymorphism to risk and prognosis of breast cancer

Principal investigator(s) P. H. Kann

Summary Analysis of the association between the growth hormone receptor deletion exon 3 (GHRd3)-polymorphism with the development of breast cancer – a cross-sectional diagnostic study, molecular genetics

Funded by DFG – German Science Foundation

Funding period 2010 – 2013

Title Change in culture and lifestyle and the risk for diabetes mellitus, metabolic syndrome and osteoporosis

Principal investigator(s) P. H. Kann & P. Nyarango, University of Namibia, Windhoek, Namibia

Summary Do cultural change and the alteration of the style of living modulate the risk for diabetes mellitus type 2 and osteoporosis in subsaharian africa? A diagnostic study in cooperation with the Ovahimba people in Kunene / north-western Namibia

Funded by Novo Nordisk Pharma GmbH, International Diabetes Federation

Funding period 2011-2013

Title Growth hormone substitution in childhood and adulthood (NordiWin/GrowthWin)

Principal investigator(s) S. Meckes-Ferber, Mainz

Summary Observational Study - Effects and safety of growth hormone replacement in subjects with growth hormone deficiency due to an organic disease of the pituitary gland

Funded by Novo Nordisk Pharma GmbH

Funding period 2003 – 2015

Title Development of a multimodal score to monitor the effects of growth hormone substitution in hypopituitarism

Principal investigator(s) P. H. Kann

Summary Observational, prospective clinical study - Growth hormone deficiency and efficacy of treatment (GET), Study: to develop and establish a score that integrates the multimodal effects of growth hormone substitution.

Funded by Novo Nordisk Pharma GmbH

Funding period 2009 – 2015

Title Seascape Study

Principal investigator(s) G. K. Stalla, Munich

Summary An open-label, multi-center, expanded access study of pasireotide s.c. in patients with Cushing's disease (IIIb)

Funded by Novartis Pharma GmbH

Funding period 2011 – 2013

Title KIMS Pharmacogenetics Study – Pharmacogenetics of growth hormone substitution

Principal investigator(s) P. H. Kann

Summary Aim of this study is to correlate genetic features with clinical data and responsiveness to the individually required recombinant human growth hormone dose of adult patients with pituitary growth hormone deficiency caused by trauma, tumor, surgery, inflammation or idiopathic origin collected in the international long-term follow-up study KIMS (Pfizer International Metabolic Database).

Funded by Pfizer Pharma GmbH

Funding period 1999 – 2013

Title GHRd3 gene polymorphism and IGF1 serum concentration at baseline in the German KIMS cohort

Principal investigator(s) P. H. Kann

Summary Non-interventional diagnostic study to investigate whether the GHRd3 polymorphism which has been shown to be related to the responsiveness to GH treatment previously might be related to basal IGF1 serum concentrations in the KIMS cohort and explain the prevalence of subjects with IGF1 serum concentrations within the age- and sex-related normal range at baseline in a cohort of patients with growth hormone deficiency / hypopituitarism.

Funded by Pfizer Pharma GmbH

Funding period 2012 – 2015

Title Pituitary function in patients with hereditary hemochromatosis

Principal investigator(s) P. H. Kann

Summary Cross-sectional diagnostic study to determine the prevalence of deficiencies of pituitary

functions in patients with genetically determined hemochromatosis

Funded by Novo Nordisk Pharma

Funding period 2008 – 2014

Title Endoscopic ultrasound of pancreatic neuroendocrine tumors – evaluation of diagnostic criteria

Principal investigator(s) P. H. Kann,

Summary prospective diagnostic study to establish diagnostic and prognostic criteria for pancreatic neuroendocrine tumors occurring sporadically and in genetic diseases, especially MEN1.

Funded by funded by Novartis Pharma GmbH 1995-2005, at this time not funded

Project period 1995-2014

Title In vitro assessment of mechanical properties of bone tissue

Principal investigator(s) S. Ruchholtz, Professor of Surgery, Marburg

Summary In vitro study to determine whether embalmed and/or fresh frozen human bones in orthopaedic cadaveric studies are authentic and feasible to describe mechanical properties of bone tissue.

Title Evaluation of ultrasound transmission velocity and 3-dimensional radiology in different bone types for dental implantology: a comparative ex vivo study

Principal investigator(s) B. Al-Nawas, Professor of Orofacial Surgery, Mainz

Summary Characterization of mechanical properties of bone tissue by ultrasound to determine an appropriate diagnostic procedure to plan surgical strategies in orofacial surgery.

Funded by Johannes Gutenberg University Mainz

Funding period 2006 – 2013

Title Partial pancreaticoduodenectomy in duodenal gastrinoma associated with multiple endocrine neoplasia type 1

Principal investigator(s) D. K. Bartsch, Professor of Surgery, Marburg

Summary Long-term monitoring and therapeutical decision-making processes in patients with MEN1

Title Relation between bone quality values from ultrasound transmission velocity and implant stability parameters – an ex vivo study

Principal investigator(s) B. Al-Nawas, Professor of Orofacial Surgery, Mainz

Summary Ex vivo study to characterize mechanical properties of bone tissue by ultrasound to determine appropriate diagnostic procedures to plan surgical strategies in orofacial surgery

Funded by funded by IGEA Italy 1998-2002, at this time not funded

Project period 1998 – 2014

Title Zoledronic acid versus alendronate in postmenopausal osteoporosis

Principal investigator(s) P. Hadji, Professor of Gynecology, Marburg

Summary Prospective clinical study to determine fracture risk, quality of life and health status under treatment with zoledronic acid and generic alendronate in postmenopausal women with low bone mass

Funded by Novartis Pharma GmbH

Funding period 2007-2013

Title Pituitary adenylate cyclase activating polypeptide in stressed patients with multiple sclerosis (MS) or clinically isolated syndrome suggestive for MS under treatment with glatiramer acetate (PACAMUS)

Principal investigator(s) B. Tackenberg, Marburg

Summary Prospective clinical study to collect data on biological and psychological stress parameters and their influence on neuroendocrine circuits in patients with multiple sclerosis

Funded by Sanofi Aventis

Funding period 2009 – 2015

Title Cultural Neuroscience – neuronal processes, social interactions and conflicts

Principal investigator(s) T. Kircher, Professor of Psychiatry, Marburg; U. Wagner, Professor of Psychology, Marburg

Summary Experimental study to investigate neuronal correlates of processes of social categorization including endocrine parameters

Funded by LOEWE

Funding period 2010 – 2015

Title Study on migrants' osteomalacia

Principal investigator(s) U. Lange, Professor of Rheumatology, Bad Nauheim

Summary Experimental study on molecular genetics of migrants' osteomalacia – characterization of polymorphisms of specific candidate genes for osteoporosis/osteomalacia, a comparison between Germans and Turkish immigrants living in Germany

Funded by Justus Liebig University Gießen

Funding period 2011 – 2016

Title Tumors of the adrenal glands – hormonally inactive and subclinical Cushing's syndrome not requiring surgical treatment: a longitudinal follow-up study using endoscopic ultrasound

Principal investigator(s) P. H. Kann

Summary This study addresses adrenal masses detected incidentally characterized as hormonally inactive or subclinical Cushing's Syndrome not requiring surgical treatment in a follow-up period up to 15 years using endoscopic ultrasound.

Title Diagnostic and therapy of the primary hyperaldosteronism

Principal investigator(s) P. H. Kann

Summary Diagnostic study to establish appropriate diagnostic strategies to identify patients with primary hyperaldosteronism which may be treated causally by minimal-invasive resection of a Conn's adenoma. This study focuses on the role of endoscopic ultrasound of the adrenals.

Title The value of different imaging techniques including endoscopic ultrasound in the diagnosis of primary hyperaldosteronism

Principal investigator(s) P. H. Kann

Summary Patients with primary hyperaldosteronism are studied, including the performance of different imaging techniques like magnetic resonance imaging (MRI), computed tomography (CT) and endoscopic ultrasound. A lot of patients had undergone adrenal vein sampling (AVS). The aim of the study is to compare these examination methods and to evaluate the therapeutic impact of adrenalectomy and antimineralocorticoid treatment, respectively. Therefore different clinical and laboratory parameters are investigated.

Title Long-term evaluation of adrenal tumors

Principal investigator(s) P. H. Kann

Summary Using endoscopic ultrasound, morphological characteristics of adrenal tumors are investigated. The objective of this study is to examine whether there is a tumor progression or a change of the endocrine status over time. Additionally numerous laboratory and clinical parameters are analyzed.

Title Lithium-induced, MEN1-associated and sporadic primary hyperparathyroidism. A comparative study

Principal investigator(s) P. H. Kann

Summary This study addresses the prevalence and special clinical and prognostic characteristics of Lithium-induced primary hyperparathyroidism.

Funded by not funded

Project period 2013 – 2016

Title Localisation of MEN1-associated pNETS in the ventral and dorsal origin of the pancreas

Principal investigator(s) P. H. Kann

Summary MEN1-associated pNETS do not seem to occur equally distributed in the ventral and dorsal origin of the pancreas. This study aims to quantify the regional incidence and prevalence.

Funded by not funded

Project period 2014 – 2016

Most important publications

Uitz PM, Hartleb S, Schaefer S, AL-Fakhri N, Kann PH (2013) Pituitary function in patients with hereditary haemochromatosis. *Horm Metab Res* 45: 54-61

Lopez CL, Falconi M, Waldmann J, Boninsegna L, Fendrich V, Goretzki PK, Langer P, **Kann PH**, Partelli S, Bartsch DK (2013) Partial pancreaticoduodenectomy can provide cure for duodenal gastrinoma associated with multiple endocrine neoplasia type 1. *Ann Surg* 257: 308-314

Unger MM, Ekmann R, Björklund AK, Karlsson G, Andersson C, Mankel K, Bohne K, Tebbe JJ, Stiasny-Kolster K, Möller JC, Mayer G, **Kann PH**, Oertel WH (2013) Unimpaired postprandial pancreatic polypeptide secretion in Parkinson's disease and REM sleep behaviour disorder. *Mov Disord* 28: 529-533

Bartsch DK, Albers M, Knoop R, **Kann PH**, Fendrich V, Waldmann J (2013) Enucleation and limited pancreatic resection provide long-term cure für insulinoma in multiple endocrine neoplasia typ 1. *Neuroendocrinology* 98: 290-298

Kann PH, Hadji P, **Bergmann RS** (2014) Pharmakogene Osteoporose jenseits von Kortison. Protonenpumpenhemmer, Glitazone, Diuretika. *Z Rheumatol* 73: 323-328

Hadji P, Kauka A, Ziller, M, Birkholz K, Baier M, Muth M, **Kann PH** (2014) Effect of adjuvant endocrine therapy on hormonal levels in premenopausal women with breast cancer: the ProBONE II study. *Breast Cancer Res Treat* 144: 343-351

Tamagno G, Fedtke K, Eidenmüller M, Geks J, Hamann A, Langer K, **Kann PH** (2014) The polymorphism of type 1 collagen (COL1A1) gene does not correlate with an increased risk of foot ulcers in patients with diabetes mellitus. *Exp Clin Endocrinol Diabetes* 122: in press

General information about the institute

Research funding 1.965.917,42 €

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Director: Professor Dr. Thomas Gress

Department of Internal Medicine: Division of Hematology, Oncology and Immunology

Chair Professor A. Neubauer

Research projects

Title Genetics of drug resistance in cancer

Principal investigator(s) A. Neubauer & A. Burchert

Summary Cancer is a major threat to human society in industrialized countries. Only 50% of all cancers can be cured by local therapies such as surgery or radiation therapy. Current evidence supports the growing importance of systemic therapies even in cancers, which were curatively operated on (so-called adjuvant therapies). However, only a minority of patients' cancer is diagnosed at an advanced stage where systemic therapies (i.e. chemotherapy and immunotherapy) are not expected to cure the patients, but primarily to prolong life or treat symptoms. Only a minority of cancers can be cured in an advanced stage by chemotherapy. In addition, in recurrent cancers response to systemic chemotherapy is mainly poor. As a consequence, resistance to systemic therapy is one of the major problems in medical oncology. Most programs to influence primary or secondary resistance to chemotherapy have failed and not entered clinical practice. Therefore, this proposal heads for a detailed molecular understanding of resistance. To discover new candidate genes, we will take advantage of functional RNA interference based sh-RNA libraries, which have been established in our groups. Drugs such as platinum, cytarabine as well as doxorubicine will be used to uncover novel genes and pathways responsible for resistance in leukemia, lung and pancreatic cancer. We will also use sophisticated cell sorting techniques to address the question of in vivo resistance in leukemias. In addition, we will work on already established resistance genes such as NFAT and p73. We believe that this approach will lead to a better understanding of molecular pathways of resistance in cancer and enable the development of new drugs influencing these pathways.

Funded by DFG, Clinical Research Unit, KFO 210

Funding period 2012 – 2016 (2. funding period)

Title A synthetic lethal screen to identify novel targets for therapy in acute myeloid leukemia

Principal investigator(s) A. Neubauer

Summary Acute myeloid leukemia (AML) is a model disease in cancer research. As in other cancer types, most AML patients still die of their disease, most frequently because of drug resistance. In our previous work we have shown that oncogenic *RAS*

modulates drug sensitivity by interacting with a DNA-damage program that is p53 dependent and causes cellular differentiation, thereby leading to decrease of immature leukemia stem cells and significant less relapses (Meyer et al, 2009; Neubauer et al, 2008). Our project intended to study drug resistance in cancer cells by using a synthetic lethal screen with cytarabine and daunorubicine (drugs that are frequently used in the therapy of AML). We took advantage of a DNA-repair siRNA library, as drug resistance frequently is caused by a change in DNA-repair. To this end, we have used a siRNA screening consisting of 437 siRNA probes specific for DNA-repair genes and applied this to U2OS osteosarcoma cells (as proposed, because expression of siRNA libraries into AML cells is rather difficult). So far, we have identified several candidate genes, which sensitize cells to cytarabine-treatment when knocked-down. Some of these genes have been implicated in drug resistance, and some are also "druggable". Currently, we are validating these candidate genes. We now want to analyze genes in human primary AML samples and correlate these data with clinical parameters. Our goal therefore is to overcome drug resistance in AML. Ultimately, these data may lead to a more individualized AML therapy, resulting in better treatment outcome.

Funded by DFG, Clinical Research Group, KFO 210 - Genetics of drug resistance in cancer

Funding period 2012 – 2015 (2. funding period)

Summary Transregio TRR17 (Würzburg – Marburg) has the background that we are far from completely understanding the single mechanisms leading to malignant transformation. Oncogenic Ras, or other proteins activating important signaling pathways mediated by Ras, plays a key role in transformation in many tumor cells. In TRR17 we sought to mechanistically understand how cancer – related perturbed signaling is influenced by Ras. There are three separated parts in this transregio: A) Signal Transduction through the Ras Pathway. The second part tries to discern how cells respond to oncogenic Ras: Cellular Responses to Ras and their Genetic Control. The third is translational and asks how Ras modulates response e.g. to certain chemotherapeutic drugs: Ras-dependent signalling in Human Tumors.

Funded by DFG, SFB/Transregio 17 – German Research Foundation, Transregional Collaborative Research Centre 17: Ras-dependent pathways in human cancer

Funding period 2008 – 2012, Final period 2012 – 2014

Project C2 Cooperation of *Ras* induced signaling and the nuclear oncogene *Ski* in acute myeloid leukemia (AML) and malignant melanoma

Principal investigator(s) A. Neubauer, U.-M. Bauer & C. Brendel

Summary Part 1: We ask the following questions:

1. What is the relationship between DNA-damage checkpoints and the differentiation observed after activation the Ras-pathway?
 2. Is p53 needed in this differentiation program?
 3. What role do repair enzymes play in this respect?
- We have recently published our main observations (Meyer et al, 2009; Neubauer et al, 2008) and concentrate now on part 2 of the project, *Ski*.

Summary Part 2: *Ski* and *Ras* in AML

By performing gene array analyses in AML, we discovered the nuclear repressor protein *Ski* as up-regulated in AML, especially in AML with -7 / del7q. Interestingly, *Ski* and *Ras* were the two most up-regulated genes in In this paper, we also have shown that *Ski* represses retinoic acid signaling in AML (Ritter et al, 2006). Recently we showed that micro-RNA miR-29a regulates *Ski* on a post-transcriptional level (Teichler et al, 2011). The project now aims to better understand the molecular interactions between *Ras* signal transduction and *Ski* using a mouse model. To this end we will collaborate with Prof. Zuber of Vienna. In this model we will try to analyse the oncogenic cooperativity between FLT3-ITD (activating *Ras*-signaling) and *Ski*.

Title Vitamin A-Resistenz in der akuten myeloischen Leukämie: Die Rolle des nukleären Repressors *Ski* und funktionelle shRNA Barcode Screens in myeloischen Zellen im Verbundvorhaben „Akute Leukämie“

Principal investigators (s) A. Neubauer

Summary This project will be ending in 2013. Several papers have been published (Metzelder et al, 2009; Teichler et al, 2011; Teichler et al, 2008).

Funded by NGFN-plus Verbund: Akute Leukämien (Deutsches Zentrum für Luft- und Raumfahrt e.V., Projektträger für das BMBF)

Funding period 2008 – 2013

Title Epigenetics of the nuclear oncogene *Ski* in AML

Principal investigator (s) A. Neubauer,

Summary In this DFG program we are currently investigating the epigenetic role of *Ski* in leukemogenesis. Specifically, we are interested which genes are regulated in leukemic transformation by the nuclear repressor *Ski*. We perform ChIP – Seq on a genome wide level and are currently validating some of the genes. Also, we try to correlate these findings with expression data obtained in leukemia cells. This project will hopefully

help us to better understand the role *Ski* plays in normal and malignant hematopoiesis.

Funded by DFG – German Research Foundation, Priority Programme SPP 1463: Epigenetics in myeloid neoplasias

Funding period 2012 – 2015

Title Signaling in persisting leukemic stem cells in acute myeloid leukemia

Principal investigator (s) C. Brendel

Funded by DFG, KFO210 – German Science Foundation, Clinical Research Unit KFO 210

Funding period 2012 – 2014

Title Immunmodulation und experimentelle Therapie der bakteriellen Pneumonie durch mesenchymale Stammzellen

Principal investigator (s) C. Brendel

Funded by UGMLC – Universities of Giessen and Marburg Lung Center, SFB/TR22 – Transregional Collaborative Research Centre 22, Project 12

Funding period 2012 – 2013

Title Interaction of pro-inflammatory signals in gastric MALT-Lymphomas

Principal investigator (s) A. Neubauer

Funded by LOEWE – Graduate School: Tumor and Inflammation

Funding period 2008 – 2013

Most important publications

Serve H, Krug U, Wagner R, Sauerland MC, Heinecke A, Brunnberg U, Schaich M, Ottmann O, Duyster J, Wandt H, Fischer T, Giagounidis A, **Neubauer A**, Reichle A, Aulitzky W, Noppeney R, Blau I, Kunzmann V, Stuhlmann R, Krämer A, Kreuzer K-A, Brandts C, Steffen B, Thiede C, Müller-Tidow C, Ehninger G, Berdel WE (2013) Sorafenib in combination with intensive chemotherapy in elderly patients with acute myeloid leukemia: results from a randomized, placebo-controlled trial. *J Clin Oncol* 31(25):3110-8

Schaich M, Parmentier S, Kramer M, Illmer T, Stölzel F, Röllig C, Thiede C, Hänel M, Schäfer-Eckart K, Aulitzky W, Einsele H, Ho AD, Serve H, Berdel WE, Mayer J, Schmitz N, Krause SW, **Neubauer A**, Baldus CD, Schetelig J, Bornhäuser M, Ehninger G (2013) High-dose cytarabine consolidation with or without additional amsacrine and mitoxantrone in acute myeloid leukemia: results of the prospective randomized AML2003 trial. *J Clin Oncol* 31(17): 2094-102

Hoffmann JC, Stabla K, Burchert A, Volkmann T, Bornhäuser M, Thiede C, **Neubauer A**, Brendel C (2014) Monitoring of acute myeloid leukemia patients after allogeneic stem cell transplantation

employing semi-automated CD34+ donor cell chimerism analysis. *Ann Hematol* 93(2):279-85

Huynh MQ, Goßmann J, Gattenlöhner S, Klapper W, Wacker HH, Ramaswamy A, Bittner A, Kaiser U, **Neubauer A** (2014) Expression and pro-survival function of phospholipase Cy2 in diffuse large B-cell lymphoma. *Leuk Lymphoma* 2014 Sep 8:1-8. [Epub ahead of print]

Hanfstein B, Lauseker M, Hehlmann R, Saussele S, Erben P, Dietz C, Fabarius A, Proetel U, Schnittger S, Haferlach C, Krause SW, Schubert J, Einsele H, Hänel M, Dengler J, Falge C, Kanz L, **Neubauer A**, Kneba M, Stegelmann F, Pfreundschuh M, Waller CF, Spiekermann K, Baerlocher GM, Pfirrmann M, Hasford J, Hofmann WK, Hochhaus A, Müller MC; SAKK and the German CML Study Group (2014) Distinct characteristics of e13a2 versus e14a2 BCR-ABL1 driven chronic myeloid leukemia under first-line therapy with imatinib. *Haematologica* 99(9):1441-7

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Hehlmann R, Müller MC, Lauseker M, Hanfstein B, Fabarius A, Schreiber A, Proetel U, Pletsch N, Pfirrmann M, Haferlach C, Schnittger S, Einsele H, Dengler J, Falge C, Kanz L, **Neubauer A**, Kneba M, Stegelmann F, Pfreundschuh M, Waller CF, Spiekermann K, Baerlocher GM, Ehninger G, Heim D, Heimpel H, Nerl C, Krause SW, Hossfeld DK, Kolb HJ, Hasford J, Sauße S, Hochhaus A (2014) Deep molecular response is reached by the majority of patients treated with imatinib, predicts survival, and is achieved more quickly by optimized high-dose imatinib: results from the randomized CML-study IV. *J Clin Oncol* 32(5):415-23

Professor A. Burchert

Title Modulation of the p19^{Arf}-p53 tumor suppressor response to overcome persistence in CML

Principal investigators (s) A. Burchert

Drug resistance in CML – It will be studied whether BCR-ABL expression level control elicitation of the p19^{Arf}-p53-mediated tumor suppressive response,

and thus enable persistence in CML. Secondly, we will study the hypothesis that IFN amplifies via induction of IRF8 sensing of oncogenic stress signals initiated by BCR-ABL.

Funded by DFG, Clinical Research Group – KFO 210 Genetics of drug resistance in cancer, TP 1

Funding period 2008 – 2015 (second funding period)

Title Functional genomic analysis of Sorafenib resistance in human FLT3-ITD-positive AML,

Principal investigators (s) A. Burchert

Summary Mechanism of Sorafenib resistance will be studied.

Funded by DFG, Clinical Research Group – KFO 210 Genetics of drug resistance in cancer, TP 7

Funding period 2013 – 2017 (second funding period)

Title Studium eines neuen Imatinib-Persistenzmodells bei der chronischen myeloischen Leukämie DJCLS R 09/04

Principal investigators (s) A. Burchert

Funded by Deutsche José Carreras-Leukämie-Stiftung e. V.

Funding period 2009 – 2013

Title Rolle des Transkriptionsfaktors NFATc1 in der Leukämogenese und Therapieresistenz der FLT3-ITD-positiven akuten myeloischen Leukämie DJCLS R 12/12

Principal investigators (s) A. Burchert

Funded by Deutsche José Carreras-Leukämie-Stiftung e. V.

Funding period 2013 – 2016

Title Identifikation von Prädiktoren von CML Persistenz vor und nach Pausieren einer TKI / Interferon alpha Kombinationstherapie bei chronischer myeloischer Leukämie DJCLS R 14/07

Principal investigators (s) A. Burchert

Funded by Deutsche José Carreras-Leukämie-Stiftung e. V.

Funding period 2014 – 2017

Title Isolation and genetic analysis of individual persisting clones in CML: Role of Jak2 signaling for survival

Principal investigators (s) A. Burchert

Funded by UKGM, University Medical Centre Giessen / Marburg

Funding period 2010 – 2013

Title Elucidation of mechanisms of tumor stem cell drug resistance and persistence

Principal investigators (s) A. Burchert

Summary shRNA screen in lung cancer and study of resistance mechanisms in CML.

Funded by Behring-Röntgen Foundation

Funding period 2008 – 2013

Title Interference of ICSBP deficiency with p53 function in the regulation of BCR/ABL induced transformation and kinase inhibitor resistance

Principal investigators (s) A. Burchert

Funded by DFG, SFB/TR 17 –German Research Foundation, Transregional Collaborative Research Centre 17: Ras-dependent pathways in human cancer, Project C2

Funding period 2008 – 2012, Final period 2012 – 2013

Most important publications

Hoffmann JC, Stabla K, **Burchert A**, Volkmann T (2013) *Ann Hematol* 93(2):279-85 Kröger N, Zabelina T, Klyuchnikov E, Kropff M, Pflüger KH, **Burchert A**, Stübiger T, Wolschke C, Ayuk F, Hildebrandt Y, Bacher U, Badbaran A, Schilling G, Hansen T, Atanackovic D, Zander AR (2013) Toxicity-reduced, myeloablative allograft followed by lenalidomide maintenance as salvage therapy for refractory/relapsed myeloma patients. *Bone Marrow Transplant* 48(3):403-7

Hassan I, Brendel C, Zielke A, **Burchert A**, Danila R (2014) Immune regulatory plasmacytoid dendritic cells selectively accumulate in perithyroidal lymph nodes of patients with Graves disease: implications for the understanding of autoimmunity. *Rev Med Chir Soc Med Nat Iasi* 117(1):46-51

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Hoffmann JC, Stabla K, **Burchert A**, Volkmann T, Bornhäuser M, Thiede C, **Neubauer A**, **Brendel C** (2014) Monitoring of acute myeloid leukemia

patients after allogeneic stem cell transplantation employing semi-automated CD34+ donor cell chimerism analysis. *Ann Hematol* 93(2):279-85

Professor T. Stiewe

Main fields of research

Cancer is caused by the accumulation and selection of genome mutations that disrupt tissue homeostasis resulting in uncontrolled cell proliferation. The most commonly mutated gene in cancer patients is the p53 tumor suppressor gene, which normally functions as a guardian of the genome to prevent cancer development. Recently, two other genes – p63 and p73 – have been identified that are remarkably similar to p53. The role of these genes in cancer development is yet unclear. Using classical molecular biology as well as cutting-edge functional genomics we aim to delineate the contribution of the p53 family genes to cancer development, progression and therapy resistance and identify novel targets for cancer therapy.

Research projects

Title P73CANCER – p73 dependence in cancer: from molecular mechanisms to therapeutic targeting

Principal investigator(s) T. Stiewe

Summary Cancer cells frequently overexpress the p73 gene suggesting that p73 is beneficial for tumor growth. Since p73 also has profound tumor suppressive functions, p73 overexpressing tumor cells are likely to be critically dependent on cooperating factors which keep the tumor suppressive function of p73 in check. It is the goal of this project to identify these essential survival factors using high-throughput loss-of-function screens as interesting novel targets for cancer therapy.

Funded by EU – European Research Council, FP7 ERC Starting Grant

Funding period 2010 – 2015

Title Role of p53 core domain interactions for target gene selection and tumor suppression

Principal investigator(s) T. Stiewe

Summary The tumor suppressive transcription factor p53 limits the expansion of precancerous cells by inducing either cell-cycle arrest or apoptosis. The mechanism by which the tetrameric p53 protein distinguishes functionally different target genes in this cell fate decision is only poorly understood. In this project we investigate p53 interactions within the p53 tetramer as a critical determinant of p53 functions in tumor suppression.

Funded by DFG, SFB/TR 17 – German Research Foundation, Transregional Collaborative Research

Centre 17: Ras-dependent pathways in human cancer, Project B2

Funding period 2008 – 2013

Title Role of DNA binding cooperativity for tumor suppression by p53

Principal investigator(s) T. Stiewe

Summary p53 acts as a tumor suppressor by inducing apoptosis in incipient cancer cells. We have shown previously in cell lines that cooperative DNA binding by p53 is required for its apoptotic function. Using a p53 cooperativity mutant mouse model we explore the functional role of DNA binding cooperativity for tumor suppression in vivo.

Funded by DFG ST182/-1 – German Research Foundation

Funding period 2013 – 2016

Title Role of p73 for drug resistance

Principal investigator(s) T. Stiewe

Summary Cancer cells frequently overexpress the p73 gene and this is clinically correlated with increased tumor aggressiveness and therapy resistance leading to an inferior patient outcome. It is the goal of this project to understand in molecular terms how increased expression of p73 promotes tumor progression to a drug resistant state.

Funded by DFG/KFO210, Clinical Research Group: Genetics of Drug Resistance in Cancer, Project B5

Funding period 2008 – 2015

Title Exploring cancer therapies based on p53-reactivating drugs using shRNA barcode screening

Principal investigator(s) M. Wanzel

Summary Pharmacological inhibitors of the MDM2 oncogene induce tumor cell death by reactivating the tumor suppressor p53. This project uses an RNAi screening approach to genetically pinpoint a subset of cancer patients that profits from MDM2 inhibitor therapy.

Funded by DFG/KFO210, Clinical Research Group: Genetics of Drug Resistance in Cancer DFG/KFO210, Clinical Research Group: Genetics of Drug Resistance in Cancer

Funding period 2012 – 2016

Title Mechanisms of gene silencing by the p53 family inhibitor $\Delta Np73$

Principal investigator(s) T. Stiewe

Summary Transcription factors of the same gene family often bind to similar sequence motifs, yet can generate opposite chromatin states. One example is the p53 family of tumor suppressors. Tumors frequently express the transcriptionally repressive p73 isoform $\Delta Np73$, which inhibits the transactivating p53 family members and contributes to the establishment of a repressive chromatin structure leading to reduced patient survival. In this project we characterize genome-wide $\Delta Np73$ -

induced chromatin changes to better understand how $\Delta Np73$ contributes to epigenetic reprogramming during tumorigenesis.

Funded by DFG/SFB/TR 81 – German Research Foundation, Transregional Collaborative Research Centre: Chromatin changes in differentiation and malignancies; Project A10

Funding period 2010 – 2014, 2014 – 2018

Title Role of the Myc/Miz1 interaction in the co-operation of Ras and Myc

Principal investigator(s) M. Wanzel, H.-P. Elsässer & M. Eilers (Würzburg)

Funded by DFG, SFB/TR 17 – German Research Foundation, Transregional Collaborative Research Centre 17: Ras-dependent pathways in human cancer

Funding period 2008 – 2013

Title Gene Expression Profiling and Functional Genomics

Principal investigator(s) M. Krause

Funding by DFG, SFB/TR 17 – German Research Foundation, Transregional Collaborative Research Centre 17: Ras-dependent pathways in human cancer

Funding period 2008 – 2013

Title PhD program Molecular Cancer Biology

Principal investigator(s) T. Stiewe and S. Gaubatz

Funded by DFG, SFB/TR 17 – German Research Foundation, Transregional Collaborative Research Centre 17: Ras-dependent pathways in human cancer, Project Z5

Funding period 2008 – 2013

Title Modulation of p53 DNA binding cooperativity for improved lung cancer therapy

Principal investigator(s) T. Stiewe

Funded by Deutsche Krebshilfe

Funding period 2013 – 2016

Title Role of the tumor suppressor p73 for B-cell neoplasia

Principal investigator(s) T. Stiewe, C. Brendel & A. Rosenwald

Funded by Deutsche José Carreras Leukämie Foundation

Funding period 2010 – 2014

Title Genetic mechanisms of nutlin-resistance in acute myeloid leukemia

Principal investigator(s) T. Stiewe & J. Cinatl (Frankfurt)

Funded by Deutsche José Carreras Leukämie Foundation

Funding period 2012 – 2015

Title Identification of p53-dependent tumor suppression pathways relevant for chemotherapy response in Acute Myeloid Leukemia (AML)

Principal investigator(s) O. Timofeev & T. Stiewe

Funded by Deutsche José Carreras Leukämie Foundation

Funding period 2014 – 2017

Most important publications

Schlereth K, Heyl C, Krampitz AM, Mernberger M, Finkernagel F, Scharfe M, Jarek M, Leich E, Rosenwald A, **Stiewe T** (2013) Characterization of the p53 cistrome – DNA binding cooperativity dissects p53's tumor suppressor functions. *PLoS Genetics* 9: e10003726

Maas AM, Bretz AC, Mack E, **Stiewe T** (2013) Targeting p73 in cancer. *Cancer Letters* 332: 229–236

Pribluda A, Elyada E, Wiener Z, Hamza H, Goldstein RE, Biton M, Burstain I, Morgenstern Y, Brachya G, Billauer H, Biton S, Snir-Alkalay I, Vucic C, Schlereth K, Mernberger M, **Stiewe T**, Oren M, Alitalo K, Pikarsky E, Ben-Neriah Y (2013) A senescence-inflammatory switch from cancer-inhibitory to cancer-promoting mechanism. *Cancer Cell* 24:242–256

Timofeev O, Schlereth K, **Wanzel M**, Braun A, Nieswandt B, Pagenstecher A, Rosenwald A, Elsässer HP, **Stiewe T** (2013) p53 DNA Binding Cooperativity is Essential for Apoptosis and Tumor Suppression *In vivo*. *Cell Reports* 3: 1512–1525

Charles JP, Fuchs J, Hefter M, Vishedyk JB, Kleint M, Vogiatzi F, Schäfer JA, Nist A, **Timofeev O**, **Wanzel M**, **Stiewe T** (2014) Monitoring the dynamics of clonal tumour evolution in vivo using secreted luciferases. *Nature Communications* 5: e3981

General information about the institute

Research funding 3.016.423,95 €

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Director: Professor Dr. Andreas Neubauer

Department of Internal Medicine: Division of Cardiology

Chair Professor B. Schieffer
Professor J. Schäfer

Main fields of research

The major focus is the pathogenesis of atherosclerotic plaque development and associated pathological remodeling in the vessel wall. The role of cells and components of innate and adaptive immunity and their interaction with endothelial cells is of special interest. In this context, vascular inflammation and its mediators (cells, cytokines and chemokines) and their role in the formation of atherosclerotic plaques are studied in animal models and patients with coronary heart disease. The aim is to identify innovative therapeutic interventions for interfering with plaque development, plaque instability and vascular maladaptation.

Research projects

Title Impact of SOCS-1 on the differentiation status of Ly6C^{high}- and Ly6C^{low} monocytes in an atherosclerotic mouse model

Principal investigator(s) J. Schuett

Summary Within this fellowship the SOCS-1-mediated impact on Ly6C-expression of monocytes and its capacity to regulate monocyte differentiation is investigated. Based on the current knowledge it is hypothesized that SOCS-1 influences gene expression patterns on mRNA and miRNA levels and thus regulates monocyte differentiation and that the Ly6C-expression on monocytes is subjected to different classical pro-inflammatory as well as pro-atherosclerotic stimuli.

Funded by DGK fellowship

Funding period 2014 – 20115

Title Atherosclerosis and its consequence: From proteomics and genomics towards optimized risk stratification and individualized prevention and therapy – Bio-NRW

Principal investigator(s) B. Schieffer

Summary Genetic and genomic characterization of patients with coronary artery diseases and their affected relatives using 660W Infinium SNP chips and the HumanWG-6 v3.0 expression BeadChips in addition to identification of biological mechanisms and key proteins using next generation sequencing.

Funded by ISAS- Institute for analytical sciences

Funding period 2012 – 2016

Title Characterization of the expression and activation of “early growth response-1 (Egr-1)” signaling pathways in arteriogenesis *in vivo*

Principal investigator(s) M. Schoppet, KT. Preissner (JLU Giessen) & E. Deindl (LMU München)

Summary The transcription factor “early growth response-1 (Egr-1) is a crucial regulator of arteriogenesis, which induces adhesion receptors and proteases. The upstream signal transduction of arteriogenesis is incompletely understood. In a murine model of arteriogenesis, which uses the ligation of the femoral artery, the signaling cascades leading to Egr-1 activation will be investigated.

Funded by Behring-Röntgen Foundation

Funding period 2010 – 2013

Title Inflammatory / familial dilated cardiomyopathy: Is there a link to autoimmune diseases? - IKARIUS -

Principal investigator(s) B. Schieffer & S. Pankuweit

Summary The original aims of the project were: 1) The inclusion of patients within the cohort of the network with dilated cardiomyopathy (ejection fraction <45%, left ventricular enddiastolic diameter > 56mm) and in addition the 2) inclusion of all relevant data regarding a possible familial, infectious or autoimmune etiology of the disease. This should help us get for the first time data on the proportion of patients with sporadic or familial inflammatory or not inflammatory DCM within the cohort of patients with DCM. Derived from the data base, the biopsy and serum bank further aims of the project are 1) the search for a genetic link to autoimmune diseases in patients with familial / inflammatory DCM and the 2) the search for a genetic predisposition for autoimmune diseases in patients with DCM, especially inflammatory diseases.

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2004 – 2017

Title Clinical and prognostic relevance of beta1-adrenoceptor autoantibodies in human heart disease: Etiology, Titer-Course, and Survival BetaAb-HF (ETiCS)

Principal investigator(s) B. Schieffer, S. Pankuweit & R. Jahns, Würzburg

Summary The first aim is to clarify the pathophysiological sequence of events leading to generation of anti-beta1-Ab in humans by prospectively analyzing the potential links between (a) acute myocardial inflammation or (b) first acute myocardial ischemia and autoimmunity. The second goal is to retrospectively determine the titer-course of activating anti-beta1-Ab in large patient-populations with heart failure of known etiology compared with that in healthy subjects (a.

idiopathic/inflammatory, b. ischemic cardiomyopathy, and c. hypertensive heart disease *versus* d. healthy controls). The final aim of both studies is to evaluate the prognostic value of activating anti-beta1-Ab in heart failure dependent on heart failure origin (a. idiopathic/inflammatory, b. ischemic cardiomyopathy, c. hypertensive heart disease, d. healthy subjects).

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2009 – 2013

Title Effects of selective serotonin re-uptake inhibition on MOrbidity, mOrtality and mood in Depressed Heart Failure patients (MOOD-HF)

Principal investigator(s) B. Schieffer, S. Pankuweit & C. Angermann, Würzburg

Summary To investigate the effects of treatment with the SSRI *escitalopram* compared to *placebo* on morbidity and mortality in CHF patients with a current episode of major depression. To estimate the improvement of depression by *escitalopram* compared to placebo in depressed CHF patients. To assess whether possible reduction of morbidity and mortality (see primary objective) might be attributable to the improvement of depression.

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2007 – 2013

General information about the institute

Research funding 836.294,14 €

Most important publications

Westhoff-Bleck M, **Schieffer B**, Tegtbu U, Meyer GP, Hoy L, Schaefer A, Tallone EM, Tutarel O, Mertins R, Wilmink LM, Anker SD, Bauersachs J, Roentgen P (2013) Aerobic training in adults after atrial switch procedure for transposition of the great arteries improves exercise capacity without impairing systemic right ventricular function. *Int J Cardiol* 170(1):24-9

Grote K, Sonnenschein K, Kapopara PR, Hillmer A, Grothausen C, Salguero G, Kotlarz D, **Schuett H**, Bavendiek U, **Schieffer B** (2013) Toll-like receptor 2/6 agonist macrophage-activating lipopeptide-2 promotes reendothelialization and inhibits neointima formation after vascular injury. *Arterioscler Thromb Vasc Biol* 33(9):2097-104

Eberhard J, **Grote K**, **Luchtefeld M**, Heuer W, **Schuett H**, Divchev D, Scherer R, Schmitz-Streit R, Langfeldt D, Stumpp N, Staufenbiel I, **Schieffer B**, Stiesch M (2013) Experimental gingivitis induces systemic inflammatory markers in young healthy individuals: a single-subject interventional study. *PLoS One* 8(2):e55265

Lukasz A, Beutel G, Kümpers P, Denecke A, Westhoff-Bleck M, **Schieffer B**, Bauersachs J, Kielstein JT, Tutarel O (2013) Angiopoietin-2 in adults with congenital heart disease and heart failure. *PLoS One* 8(6):e66861

Caforio AL, **Pankuweit S**, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Heliö T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM; European Society of Cardiology Working Group on Myocardial and Pericardial Diseases (2013) Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 34(33):2636-48

Grimm W, Timmesfeld N, Efimova (2013) ELeft ventricular function improvement after prophylactic implantable cardioverter-defibrillator implantation in patients with non-ischaemic dilated cardiomyopathy. *Europace* 15(11):1594-600

Dahms K, **Sharkova Y**, Heitland P, **Pankuweit S**, **Schaefer JR** (2014) Cobalt intoxication diagnosed with the help of Dr House. *Lancet* 383(9916):574

Meder B, Rühle F, Weis T, Homuth G, Keller A, Franke J, Peil B, Lorenzo Bermejo J, Frese K, Hüge A, Witten A, Vogel B, Haas J, Völker U, Ernst F, Teumer A, Ehlermann P, Zugck C, Friedrichs F, Kroemer H, Dörr M, Hoffmann W, Maisch B, **Pankuweit S**, **Ruppert V**, Scheffold T, Kühl U, Schultheiss HP, Kreutz R, Ertl G, Angermann C, Charron P, Villard E, Gary F, Isnard R, Komajda M, Lutz M, Meitinger T, Sinner MF, Wichmann HE, Krawczak M, Ivandic B, Weichenhan D, Gelbrich G, El-Mokhtari NE, Schreiber S, Felix SB, Hasenfuß G, Pfeufer A, Hübner N, Käb S, Arbustini E, Rottbauer W, Frey N, Stoll M, Katus HA (2014) A genome-wide association study identifies 6p21 as novel risk locus for dilated cardiomyopathy. *Eur Heart J* 35(16):1069-77

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Department of Internal Medicine: Division of Pneumology

Chair Professor C. Vogelmeier

Main fields of research

The main focus of clinical research is COPD. Various groups in our institution work on either clinical aspects (e.g. drug effects, comorbidities, new therapies and diagnostic methods) or basic research related to these topics.

Another important field is sleep medicine, as well as emergency and intensive care medicine. The main focus in these fields is related to clinical (e.g. ventilation procedures/techniques) and technical topics (biosignal analysis).

In further projects markers of exhaled breath condensate are analyzed. These projects try to answer, if diseases like COPD or Alzheimer can be diagnosed early with this simple technical procedure.

Research projects

Title COSYCONET (German COPD and Systemic Consequences – Comorbidities Network)

Principal investigator(s) C. Vogelmeier

Summary This huge multicenter cohort study aims to build a national COPD cohort of 3000 patients, which then serves as a basis for future studies. Subprojects will characterize the patients over 18 months, analyze the individual pattern of comorbidities, compare the data with other control cohorts and focus on specific clinically important topics relevant for the progression of COPD.

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2009 – 2014

Title SFB Transregio 22 – Pulmonary Allergies

Principal investigator(s) H. Renz (Institute of Laboratory Medicine and Pathobiochemistry) & C. Vogelmeier

Summary Researchers from Marburg, Borstel and Munich collaborate to use their unique competence in performing huge cross-sectional and longitudinal cohort studies determining the risk factors for the development of allergies and asthma. Based on these studies the partners will develop a natural scientific understanding of cellular and molecular mechanisms.

Funded by DFG, SFB/TR 22 – German Research Foundation, Transregional Collaborative Research Centre 22

Funding period 2005 – 2014

Title LOEWE Center "UGMLC - Universities of Giessen and Marburg Lung Center: Inflammatory and

Hyperproliferative Diseases of the Lung and Respiratory Tract"

Principal investigator(s) W. Seeger (University of Giessen) & C. Vogelmeier

Summary In this LOEWE Center the Justus Liebig University, the Philipps University Marburg and the Max Planck Institute for Heart and Lung Research (MPI) Bad Nauheim are participating. The goal is to become an internationally leading center in the area of lung and respiratory tract disease by grouping the experimental and clinical research in Giessen, Marburg, and Bad Nauheim together.

Funded by Hessisches Ministerium für Wissenschaft und Kunst (2010-2012) / Behring Röntgen Foundation (follow-up funding)

Funding period 2010-ongoing

Title DZL – German Center for Lung Research

Principal investigator(s) W. Seeger (University of Giessen) & C. Vogelmeier

Summary The German Center for Lung Research (DZL) is an association of the leading university and non-university institutions dedicated to lung research in Germany. Using translational research methods, the DZL seeks to jointly develop new approaches for the prevention, diagnosis and therapy of serious lung diseases such as asthma, COPD, diffuse parenchymal lung disease or pulmonary hypertension and lung cancer.

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2011-ongoing

Title German central lab for the diagnosis of alpha-1 antitrypsin deficiency

Principal investigator(s) C. Vogelmeier, T. Greulich & R. Koczulla

Summary We provide high level laboratory analysis for the diagnosis of alpha-1 antitrypsin deficiency. In the last 9 years, 18.000 samples have been analyzed.

Funded by Grifols

Funding period 2003 – 2013

Title A Phase II/III, Double-Blind, Randomized, Placebo-Controlled, Multicenter, International Study Evaluating the Safety and Efficacy of Inhaled, Human, Alpha-1 Antitrypsin (AAT) in Alpha-1 Antitrypsin Deficient Patients with Emphysema

Principal investigator(s) C. Vogelmeier & T. Greulich

Summary In this phase II/III clinical trial the safety and efficacy of inhaled AAT is compared to placebo. We participate as one of two German centers in the German sub-study where the IMP is in addition to intravenous augmentation therapy with alpha-1 antitrypsin, making this population unique.

Funded by Kamada Ltd.

Funding period 2010-ongoing

Title Comparison Of An Individualized Outpatient Exercise Training Versus A Standardized Outpatient Exercise Training In Patients With Moderate To Very Severe Chronic Obstructive Pulmonary Disease

Principal investigator(s) A.R. Koczulla & T. Greulich

Summary The purpose of this study is to compare the effects of different outpatient exercise training programs in COPD patients. Patients will be trained for 3 – 5 months. Extensive assessment (including exercise testing, muscle strength, inflammatory markers) are performed before and after the program.

Funded by GlaxoSmithKline

Funding period 2011 – 2013

Title Extracellular Matrix in patients with COPD

Principal investigator(s) C. Vogelmeier

Summary Pilot study to investigate the changes of extracellular matrix in patients with COPD.

Funded by LOEWE Centre UGMLC – Universities of Giessen and Marburg Lung Center

Funding period 2010-ongoing

Title INHALE

Principal investigator(s) C. Vogelmeier

Summary This study investigates the effect of the LABA application with AKITA inhalation system in patients with severe asthma.

Funded by LOEWE Centre UGMLC – Universities of Giessen and Marburg Lung Center

Funding period 2010-ongoing

Title Effect of Roflumilast on Exacerbation Rate in Patients With COPD Treated With Fixed Combinations of LABA and ICS. A 52-week, Randomised Double-blind Trial With Roflumilast 500 µg Versus Placebo. The REACT Trial

Principal investigator(s) C. Vogelmeier

Summary The REACT trial is a 52-week, randomised, double-blind, multi-centre study which investigates roflumilast when used in patients concomitantly treated with fixed combination treatment or triple therapy.

Funded by Nycomed: A Takeda Company

Funding period 2010 – 2014

Title Serve-HF

Principal investigator(s) U. Koehler

Summary The purpose of this trial is to evaluate the long-term effects and cost-effectiveness of adaptive servo-ventilation on the mortality and morbidity of patients with stable heart failure due to left ventricular systolic dysfunction, already receiving optimal medical therapy, who have sleep disordered breathing (SDB) that is predominantly central.

Funded by ResMed GmbH & Co.KG, München

Funding period 2008 – ongoing

Title Telemonitoring in patients with COPD - TeleTherapeut

Principal investigator(s) U. Koehler

Summary The project aims to improve medical care of patients with chronic obstructive lung disease (COPD). A system will be developed that incorporates different signals like heart rate, oxygenation, lung sounds and pulse transit time. Another system will be developed for instruction and monitoring of patients training measures.

Funded by Hessenagentur LOEWE III

Funding period 2012 – 2014

Title Discriminating factors for assessment of daytime sleepiness in patients with obstructive sleep apnea and obesity

Principal investigator(s) U. Koehler

Summary The project aims to determine, how obese patients with obstructive sleep apnea (OSA) and daytime sleepiness differ from obese patients with OSA without daytime sleepiness.

Funded by Reinhard Löwenstein Foundation

Funding period 2012 – 2014

Title ENCORE: Effects of Neupro on Cardiovascular Observations in Patients with Restless Legs Syndrome

Principal investigator(s) U. Koehler

Summary Multicenter, double-blind, placebo-controlled, two-arm, randomized, parallel, treatment intervention, sleep lab phase IV study to assess the effect of rotigotine on nocturnal blood pressure in patients with idiopathic restless legs syndrome.

Funded by UCB Biosciences

Funding period 2011 – 2013

Title Effects of Neupro on PLMs in Patients with secondary Restless Legs Syndrome

Principal investigator(s) U. Koehler

Summary A multi-center, randomized, double-blind, placebo-controlled, parallel-group polysomnography study to investigate safety and efficacy of the rotigotine transdermal patch in subjects with restless legs syndrome and end-stage renal disease requiring hemodialysis.

Funded by UCB Biosciences

Funding period 2011 – 2013

Title REFRESH-PD: Randomized evaluation for rotigotine's efficacy in sleep in idiopathic PD patients

Principal investigator(s) U. Koehler

Summary A multi-center, randomized, double-blind, placebo-controlled study to evaluate the effects of rotigotine on sleep efficiency in patients with advanced Parkinson's disease.

Funded by UCB Celltech

Funding period 2011 – 2013

Title Support for MPG-approval of a product for precise detection of body position

Principal investigator(s) U. Koehler

Summary In this project the system of IfM GmbH will be prepared for MPG-approval.

Funded by Ingenieurbüro für Medizintechnik GmbH (IfM)

Funding period 2012 – 2013

Title Motivational influences on the results of vigilance measurements

Principal investigator(s) U. Koehler

Summary In this project the motivational influences on the results of vigilance measurements are determined.

Funded by Reinhard Löwenstein Foundation

Funding period 2013 – 2014

Title Development of an algorithm to detect Cheyne-Stokes breathing patterns in patients with chronic heart failure

Principal investigator(s) U. Koehler

Summary In this project an algorithm will be development to detect Cheyne-Stokes breathing patterns out of PSG-data.

Funded by Ingenieurbüro für Medizintechnik GmbH (IfM)

Funding period 2013 – 2014

Title Validation and optimization of an algorithm to detect Cheyne-Stokes breathing pattern

Principal investigator(s) U. Koehler

Summary In this project a developed algorithm to detect Cheyne-Stokes breathing pattern will be validated and optimized.

Funded by Ingenieurbüro für Medizintechnik GmbH (IfM)

Funding period 2014 ongoing

Title Toxicology of Carbon Black Nanoparticles (CBNP) on Type II Pneumocytes and Clara Cells

Principal investigator(s) B. Müller

Summary Increasing development and application of carbon nanoparticles bears the risk of toxicity, especially upon inhalation. Depending on CBNP characteristics the project aims to evaluate the pathomechanisms of impairment of surfactant- and antioxidant-metabolism as well as inflammation in type II pneumocytes and the clara cells. The overall aim is to categorize CBNP characteristics and their corresponding toxicologic potential.

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2010 – 2013

Title Long Term Toxicology of Modified Carbon Black Nanoparticles (CBNP) on Normal and Preinjured Lungs (NanoCOLT)

Principal investigator(s) B. Müller

Summary Increasing development and application of inhalable carbon nanoparticles (CBNP) bears the risk of toxicity, especially on the lung. However long term effects still are unknown and will be evaluated in this project. The overall aim is to study the deleterious long term effects of CBNP on normal and preinjured lungs.

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2014 – 2017

Title PostDoc Stipendium to Dr. Shashi Pavan Chillappagari

Principal investigator(s) M. Henke

Summary Cystic fibrosis leads to compromised congenital and adaptive immune reactions of the respiratory epithelium due to reduced expression of TLR-4 on the cell surface. This is likely to be relevant for the chronic inflammation of the airways.

Funded by LOEWE – ECCPS

Funding period 2010 – 2013

Title AST@home

Principal investigator(s) A. R. Koczulla

Summary In this project a COPD Exacerbation will be developed.

Funded by LOEWE III

Funding period 2014 – 2016

Title Effects of Prolastin® therapy on peripheral blood monocyte populations

Principal investigator(s) A. R. Koczulla & S. Janciauskiene (MHH)

Summary In this project the augmentation of AAT and its function on neutrophil and macrophage regulation in AAT and COPD patients and samples will be evaluated.

Funded by Grifols

Funding period 2014 – 2016

General information about the institute

Research funding 3.928.839,96 €

Most important publications

Kratzer A, Salys J, Nold-Petry C, Cool C, Zamora M, Bowler R, **Koczulla AR**, Janciauskiene S, Edwards MG, Dinarello CA, Taraseviciene-Stewart L (2013) Role of IL-18 in second-hand smoke-induced emphysema. *Am J Respir Cell Mol Biol* 48(6): 725-732

Greulich T, Hattesoehl A, Grabisch A, Koepke J, Schmid S, **Noeske S**, **Nell C**, Wencker M, Jörres RA, **Vogelmeier CF**, **Köhler U**, **Koczulla AR** (2013)

Detection of obstructive sleep apnoea by an electronic nose. *Eur Respir J* 42(1): 145-155

Hoogendoorn M, Al MJ, Beeh KM, Bowles D, Graf von der Schulenburg JM, Lungershausen J, Monz BU, Schmidt H, **Vogelmeier C**, Rutten-van Mölken MP (2013) Cost-effectiveness of tiotropium versus salmeterol: the POET-COPD trial. *Eur Respir J* 41(3): 556-564

Alter P, Luetteken L, **Nell C**, Haid D, Kehr K, **Greulich T**, Apelt S, Langenhan K, Hohmann C, **Vogelmeier CF**, **Koczulla AR** (2014) Exercise training leads to physiological left ventricular hypertrophy in COPD. *Int J Cardiol* 174(1): 156-157

Grimm W, **Hildebrandt O**, **Nell C**, **Koehler U** (2014) Excessive daytime sleepiness and central sleep apnea in patients with stable heart failure. *Int J Cardiol* 176(3): 1447-1448

Kill C, Hahn O, Dietz F, Neuhaus C, Schwarz S, Mahling R, Wallot P, **Jerrentrup A**, Steinfeldt T, Wulf H, Dersch W (2014) Mechanical ventilation during cardiopulmonary resuscitation with intermittent positive-pressure ventilation, bilevel ventilation, or chest compression synchronized ventilation in a pig model. *Crit Care Med* 42(2): e89-95

Frenzel E, Wrenger S, Immenschuh S, **Koczulla R**, Mahadeva R, Deeg HJ, Dinarello CA, Welte T, Marcondes AM, Janciauskiene S (2014) Acute-phase protein α 1-antitrypsin--a novel regulator of angiopoietin-like protein 4 transcription and secretion. *J Immunol* 192(11): 5354-5362

Rogosch T, Herrmann N, Maier RF, Domann E, Hattesoehl A, **Koczulla AR**, Zemlin M (2014) Detection of bloodstream infections and prediction of bronchopulmonary dysplasia in preterm neonates with an electronic nose. *J Pediatr* 165(3): 622-624

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Department of Internal Medicine: Division of Psychosomatic Medicine and Psychotherapy

Chair Professor J. Kruse

Main fields of research

Psychotherapy / Psychosomatic interventions for chronic physical illnesses with mental co-morbidity, especially in diabetology, oncology, cardiology, and neurology. Psychosomatic treatment of somatoform disorders, especially somatoform pain disorders, psychotherapy of posttraumatic stress disorders as a result of extreme traumatic incidents (abuse, violence), the effects of chronic stress experiences and extreme violence experienced in childhood and adulthood on the development of chronic physical illnesses, including the psychoneuroimmunologic changes, Health Care Research.

Research projects

Title Randomized controlled study to investigate effect mechanisms of EMDR (Eye Movement Desensitization and Reprocessing) treatment

Principal investigator(s) M. Sack, J. Kruse

Summary The effect mechanisms of EMDR treatment are examined within the context of an RCT in patients with uncomplicated PTSD. The standard protocol is compared with a simple focus on attention and the narration of trauma.

Funded by DFG – German Research Foundation

Funding period 2010 – 2013

Title The course of mental disorders and their predictors

Principal investigator(s) J. Kruse, F. Leichsenring

Summary Based on a systematic literature analysis, the project aims to determine the current scientific level of knowledge on the course of mental disorders and relevant factors. It shall also be studied which influence psychotherapy is having on the long-term course of mental disorder.

Funded by Dr. Karl Wilder Foundation

Funded period 2010 – 2013

Title The return of torture? – An interdisciplinary study on an extreme form of violence, its media representation, and its ostracism

Principal investigator(s) J. Kruse, C. Altenhain & G. Göring

Summary The aim is a) to examine in systematic reviews the effects of extreme violence on health, b) to clarify historically how psychotherapy and psychosomatics handled the issue of extreme violence experience and c) to analyse the current

medical assessment of refugees with PTSD in legal residence procedures.

Funded by VW Foundation

Funded period 2009 – 2013

Title The psychosomatic / psychotherapeutic care in health insured care in Germany

Principal investigator(s) J. Kruse

Summary The study aims:

- a) to describe the current reality of care in outpatient psychosomatic / psychotherapeutic care
- b) to examine the different areas of care by psychotherapeutic / psychosomatic physicians and psychologists
- c) and to analyse the differential effectiveness / efficiency of these structures

Funded by Kassenärztliche Bundesvereinigung

Funded period 2010 – 2014

Title Integrated psychosocial treatment program for patients with type 2 diabetes (psy-PAD) - Evaluation of an interdisciplinary psychosocial care model

Principal investigator(s) J. Kruse

Summary The aim of the project is the implementation and evaluation of an integrated collaborative care (psy-PAD), which is conducted by a consulting psychotherapist in specialized diabetic outpatient clinics in cooperation with the diabetologist.

Funded by Bundesärztekammer

Funded period 2010 – 2014

Title Chronic stress, anxiety and diabetes – The impact of chronic psychological distress on the onset and course of Type 2 Diabetes (DIAMANT-CAD)

Principal investigator(s) J. Kruse, K.H. Ladwig

Summary Based on population-based data from cross sectional and prospective studies within the MONICA/KORA research platform, the project aims (a) to describe the prevalence of anxiety, posttraumatic stress disorder (PTSD) in subjects with normal glucose metabolism, pre-diabetes and type 2 diabetes (T2DM), (b) to study the synergistic effect sizes of adverse sub-threshold psychosocial conditions to predict subsequent onset of T2DM, as well as onset of complications and mortality in previously diabetic individuals (c), to establish an allostatic load model to estimate the effect size of psycho-biological and behavioural mechanisms on T2DM onset, complications onset, and mortality.

Funded by BMBF – Federal Ministry of Education and Research: Kompetenznetz Diabetes

Funded period 2011 – 2014

Title Effectiveness of a step care approach for diabetic patients with subthreshold depression, diabetes related distress and/or poor glycemic control

Principal investigator(s) B. Kulzer, J. Kruse

Summary The overall objective of this study is to develop a step care approach and evaluate the effectiveness of such a step care approach versus a treatment as usual in diabetic patients with poor glycemic control and elevated depressive symptoms or specific diabetes related stress in a randomised controlled trial.

Funded by BMBF – Federal Ministry of Education and Research: Kompetenznetz Diabetes

Funded period 2011 – 2014

Most important publications

Baumert J, Lukaschek K, **Kruse J**, Emeny RT, Koenig W, von Känel R, Ladwig KH; KORA investigators (2013) No evidence for an association of posttraumatic stress disorder with circulating levels of CRP and IL-18 in a population-based study. *Cytokine* 2013;63(2):201-8

Hofmann M, Hagemeyer I, Altenhain K, **Kruse J** (2013) Evaluation ärztlicher und psychologischer Bescheinigungen in asyl- und aufenthaltsrechtlichen Verfahren. *Psychother Psych Med* DOI: 10.1055/s-0033-1347254

Hofmann M, Köhler B, Leichsenring F, **Kruse J** (2013) Depression as a Risk Factor for Mortality in Individuals with Diabetes: A Meta-Analysis of Prospective Studies. *Plos One* 8(11)

Icks A, Albers B, Haastert B, Pechlivanis S, Bokhof B, Slomiany U, Erbel R, Jöckel KH, **Kruse J**, Nowotny B, Herder C, Giani G, Moebus S (2013) Diabetes incidence does not differ between subjects with and without high depressive symptoms – 5-year follow-up results of the Heinz Nixdorf Recall Study. *Diabetic Medicine* 30(1): 65-69

Kruse J, Larisch A, Hofmann M, Herzog W (2013) Ambulante psychosomatische und psychotherapeutische Versorgung in Deutschland – Versorgungsprofile abgebildet durch Daten der Kassenärztlichen Bundesvereinigung (KBV). *Psychother Psych Med* 59: 254-272

Lukaschek K, Baumert J, **Kruse J**, Emeny RT, Lacruz ME, Huth C, Thorand B, Holle R, Rathmann W, Meisinger C, Ladwig KH; KORA Investigators (2013) Relationship between posttraumatic stress disorder and type 2 diabetes in a population-based cross-

sectional study with 2970 participants. *J Psychosom Res* 74(4):340-5

Peters EM, Liezmann C, Spatz K, Ungethüm U, Kuban RJ, Danilchenko M, **Kruse J**, Imfeld D, Klapp BF, Campiche R (2013) Profiling mRNA of the Graying Human Hair Follicle Constitutes a Promising State-of-the-Art Tool to Assess its Aging: An Exemplary Report. *J Invest Dermatology* 133: 1150-1160

Huth C, Thorand B, Baumert J, **Kruse J**, Emeny RT, Schneider A, Meisinger C, Ladwig KH (2014) Job strain as a risk factor for the onset of type 2 diabetes mellitus: findings from the MONICA/KORA Augsburg cohort study. *Psychosom Med* 76(7):562-8

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Director: Professor Dr. Johannes Kruse

Department of Cardiovascular Surgery

Chair Professor R. Moosdorf

Principal investigator Professor S. Vogt

Main fields of research

1. Regulation of Respiration

During evolution from prokaryotes to eukaryotes, the main function of cytochrome c oxidase (COX), i.e., the coupling of oxygen reduction to proton translocation without the production of ROS (reactive oxygen species) remained unchanged demonstrating its robustness. A new regulation of respiration by the ATP/ADP ratio was introduced in eukaryotes based on nucleotide interaction with the added COX subunit IV. This allosteric ATP-inhibition was proposed to keep the mitochondrial membrane potential ($\Delta\Psi(m)$) at low healthy values and thus prevents the formation of ROS at complexes I and III. ROS have been implicated in various degenerative diseases. The allosteric ATP-inhibition of COX is reversibly switched on and off by phosphorylation of COX at a serine or threonine. In more than 100 individual preparations of rat heart and liver mitochondria, prepared under identical conditions, the extent of allosteric ATP-inhibition varied. This variability correlates with the variable inhibition of uncoupled respiration in intact isolated mitochondria by ATP. It is concluded that in higher organisms the allosteric ATP-inhibition is continually switched on and off by neuronal signalling in order to change oxidative phosphorylation from optimal efficiency with lower rate of ATP synthesis under resting conditions (low $\Delta\Psi(m)$ and ROS production) to maximal rate of ATP synthesis under active (working, stress) conditions (elevated $\Delta\Psi(m)$ and ROS production).

2. Strain Analysis of the Aortic Wall

Aortic wall strains are indicators of biomechanical changes of the aorta due to aging or progressing pathologies such as aortic aneurysm. We investigated the potential of time-resolved three-dimensional ultrasonography coupled with speckle-tracking algorithms and finite element analysis as a novel method for noninvasive in vivo assessment of aortic wall strain. Three-dimensional volume datasets of 6 subjects without cardiovascular risk factors and 2 abdominal aortic aneurysms were acquired with a commercial real time three-dimensional echocardiography system. Longitudinal and circumferential strains were computed offline with high spatial resolution using a customized commercial speckle-tracking software and finite

element analysis. Indices for spatial heterogeneity and systolic dyssynchrony were determined for healthy abdominal aortas and abdominal aneurysms. All examined aortic wall segments exhibited considerable heterogeneous in-plane strain distributions. Higher spatial resolution of strain imaging resulted in the detection of significantly higher local peak strains ($p \leq 0.01$). In comparison with healthy abdominal aortas, aneurysms showed reduced mean strains and increased spatial heterogeneity and more pronounced temporal dyssynchrony as well as delayed systole. Three-dimensional ultrasound speckle tracking enables the analysis of spatially highly resolved strain fields of the aortic wall and offers the potential to detect local aortic wall motion deformations and abnormalities. These data allow the definition of new indices by which the different biomechanical properties of healthy aortas and aortic aneurysms can be characterized.

3. Calcification Studies in Arteriosclerosis

The knowledge available to the field of arterial calcification and vascular mineral metabolism has grown in the recent years. Our understanding of this disease biology has been enabled by incredible advancements in bone and mineral research that occurred alongside innovative investigation in cardiovascular medicine. As in bone, mechanistic heterogeneity exists in the different forms of vascular mineral deposition. There is heterogeneity in the sources and mechanisms of mineralizing vascular cell types: osteochondrocytic VSMC transdifferentiation, VSMC apoptosis, and osteochondrocytic lineage allocation of multipotent mesenchymal cells all contribute but to varying extents dependent on pathophysiologic setting and disease stage. It has been posited that marrow derived circulating osteoprogenitors may also contribute to vascular mineralizing cell types. The knowledge about the ectopic bioapatite crystals is not complete, despite of well defined phase composition and general crystal chemical characteristics.

The aim of this study describes a proven technique and method of sample preparation for the undisputed assessment of ultrastructural characteristics in nanostructured calcified pathological deposits. The primary objective comprises characterizing the structure of the calcification down to nanoscale in terms of composition, crystallography and grain size in an ex-vivo calcified [coronary artery](#). An approach common

to material science, but rather novel to life science, was utilized.

Electron Back Scatter Diffraction (EBSD) and Transmission Kikuchi Diffraction (TKD) analysis in the scanning electron microscope (SEM) were used, just as well as elemental analysis (EDX) and viscoelastic mapping by AM-FM technique. The AM-FM technique provides stiffness or Young's modulus maps of the sample surface along with topography information. The vascular calcification was compared to a trabecular bone sample as control. Similarities in chemistry were analysed but slightly differences in crystallography.

Research projects

Title Study on different working states of the mitochondrial enzyme complex IV for understanding ROS production in myocardial ischemia and reperfusion

Principal investigator(s) S. Vogt, R. Moosdorf, N. Mirow, A. Wittek, Ch. Blasé & R. Ramzan

Summary 1.

Funded by DFG – German Research Foundation, VO809/4-1

Funding period 2006 – 2013

Title Aortic wall strain measurements with three-dimensional ultrasound speckle tracking and fitted finite element analysis

Principal investigator(s) S. Vogt, R. Moosdorf, N. Mirow, A. Wittek, Ch. Blasé & R. Ramzan

Summary 2.

Funded by DFG – German Research Foundation, VO809/4-1

Funding period 2006 – 2013

Title Vascular Calcification Analysis: An approach common to material science, but rather novel to life science

Principal investigator(s) S. Vogt, R. Moosdorf, N. Mirow, A. Wittek, Ch. Blasé & R. Ramzan

Summary 3.

Funded by BMBF – Federal Ministry of Education and Research, FKZ:01M3198D

Funding period 2012 – 2016

Most important publications

Ramzan R, Weber P, Linne U, Vogt S (2013) GAPDH: the missing link between glycolysis and mitochondrial oxidative phosphorylation? *Biochem Soc Trans* 41(5):1294-7

Karatolios K, Wittek A, Nwe TH, Bihari P, Shelke A, Josef D, Schmitz-Rixen T, Geks J, Maisch B, Blase C, **Moosdorf R, Vogt S** (2013) Method for aortic wall strain measurement with three-dimensional ultrasound speckle tracking and fitted finite element analysis. *Ann Thorac Surg* 96(5):1664-71

Vogt S, Ramzan R, Weber P, Troitzsch D, Rhiel A, Sattler A, Iqrsusi M, Ruppert V, Moosdorf R (2013) Ischemic preconditioning results in an ATP-dependent inhibition of cytochrome C oxidase. *Shock* 40(5):407-13

Kadenbach B, **Ramzan R, Vogt S** (2013) High efficiency versus maximal performance—the cause of oxidative stress in eukaryotes: a hypothesis. *Mitochondrion* 13(1):1-6

Wittek A, Karatolios K, Bihari P, Schmitz-Rixen T, Moosdorf R, Vogt S, Blase C (2013) In vivo determination of elastic properties of the human aorta based on 4D ultrasound data, in: *J Mechanical Behavior of Biomedical Materials* 27: 167-83

Wittek A, Karatolios K, Vogt S, Moosdorf R, Schmitz-Rixen T, Blasé C (2013) Use of time resolved 3D ultrasound data for the determination of the anisotropic elastic properties of the human aorta: *Ultraschall in der Medizin* 10/2013. 34, 1

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General information about the institute

Research funding

185.055,73 €

Department of Neurosurgery

Chair Professor C. Nimsky
Head Lab Research Group:
Professor J.-W. Bartsch

Main fields of research

Image processing & imaging analysis:

- Visualization of eloquent brain areas by using state-of-the-art methods of neuronavigation and intra-operative imaging, including MRI, fiber tractography, ultrasound, and confocal laser endoscopy to optimize the extent of tumor resection with preservation of function
- Analysis of tumor properties and determination of tumor grading using MR spectroscopy, correlation imaging to histology
- Optimization of functional clinical MR imaging protocols and analysis strategies for intraoperative use
- Imaging of tumor pattern and tumor growth in glioma mouse models

Molecular/Cell Biology:

- Identification of proteolytic processes for growth and invasiveness of tumor cells
- Mechanisms of chemoresistance in gliomas
- Rational design of specific protease inhibitors as anti-tumor drugs
- Photodynamic therapy of gliomas

Research projects

Title Tractography for visualization of fiber bundles in the proximity of primary brain tumours

Principal investigator(s) M. Bauer, D. Kuhnt & Ch. Nimsky

Summary This project aims to reliably visualize subcortical fiber bundles as risk structures in the proximity of gliomas with perifocal edema. This is important in the context of maximum safe tumor resection without new postoperative neurological deficits, which serves as positive predictive factor for extended patient survival, within the interdisciplinary concept combining microsurgery, multimodal navigation, intraoperative imaging, radiation, and chemotherapy.

Funded by Behring-Röntgen Foundation No. 58-0044
Funding period 2011 – 2013

Title Optimizing intraoperative visualization of the optic radiation for neurosurgical interventions

Principal investigator(s) D. Kuhnt & M. Bauer

Summary This project aims to improve the visualization of the optic radiation which is heavily influenced by the MRI acquisition protocol. To

optimized the scan protocol due to optimization of the reconstruction of the optic radiation several acquisition schemes are tested and evaluated with respect to clinical constraints.

Funded by UKGM – University Medical Centre Giessen / Marburg

Funding period 2013 – 2015

Title Screening of drug candidates for inhibition of ADAM8

Principal Investigator(s) J.-W. Bartsch

Summary These proposals aim to identify novel candidate cyclic peptides for ADAM8 inhibition by large-scale screen of phage display libraries. Novel peptides will be tested in preclinical phase studies.

Funded by Bicycle Therapeutics, Inc., Cambridge, UK CRT/Medivir

Funding period 2012 – 2013

Title A randomized, double-blinded and placebo-controlled phase 3 study to investigate the efficacy and the safety of progesterone in patients with traumatic brain injury (TBI)

Principal Investigator(s) Ch. Nimsky

Summary SyNAPSe is a global, Phase 3, multi-center pivotal trial to evaluate the effectiveness of BHR-100, a proprietary progesterone formulation, in treating severe Traumatic Brain Injury (TBI). Previous clinical trials have shown that progesterone has neuroprotective properties for both males and females. Traumatic brain injury (TBI) is a major cause of death and disability worldwide. Among TBI victims injuries result from automobile crashes, sports accidents, assaults and injuries sustained on the battlefield.

Funded by: BHR Pharma, LLC.

Funding period 2012 – 2013

Title Development of a concept for combined intraoperative multimodal spectroscopy with digital image processing for resection of malignant Gliomas

Principal Investigator(s) F. Duffner, R. Kessler, R. Ritz & J.W. Bartsch

Summary This project aims to use fluorescence, UV/VIS and s-NIR absorption spectroscopy to visualize malignant tumor tissue. Multidimensional absorptions spectra can be acquired and combined with complex data analysis to provide reliable prediction of tumor grading.

Funded by: Baden-Württemberg Foundation

Funding period: 2013 – 2014

Title Validation of the metalloprotease ADAM8 as biomarker in primary tumors and metastases

Principal Investigator(s) C. Conrad & J.W. Bartsch

Summary Malignant breast tumors are the most common incident form of cancer and cause of cancer-related death in women worldwide (IARC report, 2008). In this project, the role of the Metalloprotease ADAM8 is investigated to validate ADAM8 as a tumor target in malignant breast tumors.

Funded by Alfred und Ursula Kulemann Foundation
Funding period 2013

Title: Multimodal analysis of glioma growth in a mouse model

Principal Investigator M. Bauer

Summary The aim of this project is to establish multimodal methods (MR Imaging, biomarkers, tracers) for the detection and analysis of tumor growth, hypoxia, and angiogenesis *in situ* using a mouse model for gliomas.

Funded by Behring-Röntgen Foundation
Funding period 2014 – 2016

progesterone for severe traumatic brain injury. *N Engl J Med* 371(26):2467-76

Brüssler J, Marxer E, Becker A, Schubert R, Schümmelfeder J, **Nimsky C**, Bakowsky U (2014) Correlation of structure and echogenicity of nanoscaled ultrasound contrast agents in vitro. *Colloids Surf B Biointerfaces* 117:206-15

Romagnoli M, Mineva ND, Polmear M, Conrad C, Srinivasan S, Loussouarn D, Barillé-Nion S, Georgakoudi I, Dagg Á, McDermott EW, Duffy MJ, McGowan PM, Schlomann U, Parsons M, **Bartsch JW**, Sonenshein GE (2014) ADAM8 expression in invasive breast cancer promotes tumor dissemination and metastasis. *EMBO Mol Med* 6(2):278-94.

Noell S, Beschorner R, Bisdas S, Beyer U, Weber RG, Fallier-Becker P, **Ritz R** (2014) Simultaneous subependymomas in monozygotic female twins: further evidence for a common genetic or developmental disorder background. *J Neurosurg* 121(3):570-5

General information about the institute

Research funding 168.155,25 €

Most important publications

Bauer MH, Kuhnt D, Barbieri S, Klein J, Becker A, Freisleben B, Hahn HK, **Nimsky C** (2013) Reconstruction of white matter tracts via repeated deterministic streamline tracking--initial experience. *PLoS One* 8(5):e63082

Egger J, Kapur T, Fedorov A, Pieper S, Miller JV, Veeraraghavan H, Freisleben B, Golby AJ, **Nimsky C**, Kikinis R (2013) GBM volumetry using the 3D Slicer medical image computing platform. *Sci Rep* 3:1364

Kuhnt D, Bauer MH, Egger J, Richter M, Kapur T, Sommer J, Merhof D, **Nimsky C** (2013) Fiber tractography based on diffusion tensor imaging compared with high-angular-resolution diffusion imaging with compressed sensing: initial experience. *Neurosurgery* 72 Suppl 1:165-75

Tonge D, Zhu N, Lynham S, Leclere P, Snape A, Brewer A, Schlomann U, Ferdous T, Tennyson C, **Bartsch JW**, Ward M, Pizzey J (2013) Axonal growth towards *Xenopus* skin in vitro is mediated by matrix metalloproteinase activity. *Eur J Neurosci* 37(4):519-31

Skolnick BE, Maas AI, Narayan RK, van der Hoop RG, MacAllister T, Ward JD, Nelson NR, Stocchetti N, **SYNAPSE Trial Investigators** (2014) A clinical trial of

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Department of Orthopaedics and Rheumatology

Chair Professor S. Fuchs-Winkelmann

Main fields of research

The focus of the research group of the department of Orthopedics and Rheumatology is set on origin of musculoskeletal diseases as well as their treatment options. In this connection, both clinical issues as well as aspects of basic research were considered and linked with each other. Therefore the impact of commercial available tissue replacement materials (endoprosthesis and biological transplants) on healing and patient satisfaction as well as their application is analyzed and new scaffolds for bone and tendon healing were developed. The research is supplemented by analysis of various aspects of bone tumors with respect to their metastasis.

Research projects

Title Tissue engineering based on electro spun nanofibers

Principal investigator(s) J.R. Paletta & S. Fuchs-Winkelmann

Summary Previous studies showed that Nanoscaffolds represent suitable matrices for bone tissue engineering. The aim of the current investigations is to combine multi-jet electrospinning with electrospraying of MSC in order to achieve cell seeded scaffolds. Environmental conditions within the process were optimized with respect to cell survival. By variations of the polymer used for nanofiber scaffold production, mechanic as well as osteoinductive properties should be enhanced.

Funded by AO Foundation

Funding period 2013 – 2015

Title Expression of MMP-1, 3, 9, 13 and their regulators NGAL and RECK in Chondrosarcoma"

Principal investigator(s) D. Malcherczyk & J. R. Paletta

Summary Chondrosarcoma is the second most common bone tumor in population older than 50 years. Because of their heterogeneity, with differences in invasive and metastatic behavior, it is important to identify biological markers for accurate estimation of patient prognosis. In this project the influence of MMP-1, MMP-3, MMP-9 and MMP-13 as well as their regulators NGAL and RECK on metastatic potential of chondrosarcoma is investigated.

Funded by AXIS Foundation

Funding period 2014-2015

Title Prospective, multicenter, randomized, double-blind, parallel-group, dose-response study of three

doses Xeomin® (incobotulinumtoxin A, NT 201) for the treatment of lower limb spasticity in children and adolescents (age 2-17 years) with cerebral palsy

Principal investigator C.-D. Peterlein

Summary In this clinical study, the effect of botulinum toxin injections in children and adolescents with cerebral palsy is examined. Main focus is set on spasticity, locomotion, and the sensation of pain.

Funded by Merz Pharmaceuticals GmbH

Funding period 2013 – 2016

Title Open-label, non-controlled, multicenter long-term study to investigate the safety and efficacy of Xeomin® (incobotulinumtoxin A, NT 201) for the treatment of spasticity of the lower limb(s) or of combined spasticity of upper and lower limb in children and adolescents (age 2-17 years) with cerebral palsy.

Principal investigator C.-D. Peterlein

Summary In this clinical study, the influence of repeated botulinum toxin injections on pain and locomotion in children and adolescents with cerebral palsy is analysed (with special focus on the upper extremity).

Funded by Merz Pharmaceuticals GmbH

Funding period 2013 – 2016

Title Clinical and radiological evaluation of cell free collagen type I transplants

Principal investigator(s) T. Efe

Summary A new cell-free collagen type I gel (CaReS®-1S, Arthro Kinetics, Krems/Donau, Austria) has been introduced for the treatment of smaller local cartilage defects. Within an ex vivo model different parameters of transplant stability were analyzed. Furthermore in a clinical study, long time stability of the transplant is analyzed and demonstrates good clinical and radiological results.

Funded by Arthro Kinetics, Krems/Donau, Austria

Funding period 2008 – 2015

Title Multicenter Clinical Observation Using the Nanos femoral neck prosthesis

Principal investigator(s) T. Efe

Summary Prospective, multi center, observational study focusing on effectiveness and safety of calcium phosphate coated NANOS short stem prosthesis with respect to clinical and radiological long term (10 years) outcome.

Funded by Smith & Nephew

Funding period 2010 – 2021

Title Multicenter Clinical Observation Using the Cementless Version of the POLARSTEM

Principal investigator(s) T. Efe

Summary The prospective randomized trial is part of a multicenter study focusing on the long term results of the cement less, hydroxyapatite coated version of the Polarstem. Clinical and radiological data were collected 3 month, 1, 3, 5 and 10 years after implantation and analyzed with respect to Harris Hip Scores, WOMAC and radiolucent lines according to Gruen

Funded by Smith & Nephew

Funding period 2010 – 2021

Title Biomechanical evaluation after unicompartmental knee arthroplasty

Principal investigator(s) T.J. Heyse, B.F. El Zayat & S. Fuchs-Winkelmann

Summary In vitro knee kinematics was investigated before and after unicompartmental knee arthroplasty (UKA). It was shown that UKA kinematics is close to native kinematics in different loading regimes.

Funded by Smith & Nephew

Funding period 2009 – 2015

Title Influence of lateral facetectomy on retropatellar contact pressure after knee TKA

Principal investigator(s) B.F. El Zayat, T.J. Heyse & S. Fuchs-Winkelmann

Summary Within this study the kinematics and influence on retropatellar contact pressure after knee TKA through lateral patella facetectomy is analyzed.

Funded by Smith & Nephew

Funding period 2009 – 2015

Title Kinematic investigations on the impact of femoral component rotation in total knee arthroplasty

Principal investigator(s) T.J. Heyse, B.F. El-Zayat & S. Fuchs-Winkelmann

Summary In vitro knee kinematics were investigated for natural knees and after implantation of normal as well as internally and externally malrotated femur components in TKA.

Funded by Smith & Nephew

Funding period 2009 – 2015

Title Influence of different inlay sizes on knee kinematics after unicompartmental knee arthroplasty

Principal investigator(s) T.J. Heyse, B.J El-Zayat & S. Fuchs-Winkelmann

Summary In vitro knee kinematics investigated a natural knee as well as after unicompartmental knee arthroplasty (UKA). Evaluation of different inlay sizes (optimal, one size upgraded and one size downgraded) on knee kinematics were observed.

Funded by Smith & Nephew

Funding period 2009 – 2015

Title Biomechanical and kinematic evaluation after unicompartmental and patellofemoral joint knee arthroplasty

Principal investigator(s) T.J. Heyse, B.J El-Zayat & S. Fuchs-Winkelmann

Summary In vitro knee kinematics as well as loading pressure in the lateral component were investigated before and after medial unicompartmental knee arthroplasty (UKA). Subsequently influence of additional patellofemoral joint arthroplasty was evaluated.

Funded by Smith & Nephew, Röhn-Klinikum

Funding period 2009 – 2015

Title Analysis of different stem lengths and fixation techniques in hinged Total Knee Arthroplasty

Principal investigator(s) Bilal Farouk El-Zayat & T.J. Heyse

Summary A numerical model, coupling rigid body kinematics and finite element analysis, was developed to evaluate and compare the effect of the fixation technique and stem length in a hinged TKA

Funded by Smith&Nephew

Funding period 2010 – 2015

Title Biomechanical and kinematic evaluation after Mobile bearing unicompartmental knee arthroplasty

Principal investigator(s) T.J. Heyse & S. Fuchs-Winkelmann

Summary In vitro knee kinematics as well as loading pressure in the lateral component are investigated before and after mobile bearing medial unicompartmental knee arthroplasty (UKA). Data will be compared with those of fixed bearing UKA.

Funded by Deutsche Knie-Gesellschaft, Biomet

Funding period 2014 – 2016

Title Biomechanical and kinematic evaluation after bicruciate retaining total knee arthroplasty

Principal investigator(s) T.J. Heyse & S. Fuchs-Winkelmann

Summary In vitro knee kinematics as well as loading pressures are investigated before and after a novel total knee arthroplasty (TKA), that preserves both cruciate ligaments.

Funded by Biomet

Funding period 2014 – 2016

Title Laser scanning retrieved TKA polyethylene inlays: Oxidized zirconium vs. conventional CoCr

Principal investigator(s) T.J. Heyse

Summary A retrieval analysis will be performed to compare PE damage with femoral components from the two different materials.

Funded by Smith & Nephew

Funding period 2014 – 2016

General information about the institute

Research funding 99.746,22 €

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Director: Professor Dr. Susanne Winkelmann

Most important publications

El-Zayat BF, Efe T, Heidrich A, Anetsmann R, Timmesfeld N, Fuchs-Winkelmann S, Schofer MD (2013) Objective assessment, repeatability, and agreement of shoulder ROM with a 3D gyroscope. *BMC Musculoskelet Disord* 14:72

Lakemeier S, Lind M, Schultz W, **Fuchs-Winkelmann S**, Timmesfeld N, Foelsch C, **Peterlein CD** (2013) A comparison of intraarticular lumbar facet joint steroid injections and lumbar facet joint radiofrequency denervation in the treatment of low back pain: a randomized, controlled, double-blind trial. *Anesth Analg*. 2013 Jul;117(1):228-35.

Heyse TJ, Figiel J, Hähnlein U, Schmitt J, Timmesfeld N, **Fuchs-Winkelmann S, Efe T** (2013) MRI after unicondylar knee arthroplasty: rotational alignment of components. *Arch Orthop Trauma Surg* 133(11):1579-86

Struewer J, Roessler PP, Schuettler KF, Ruppert V, Stein T, Timmesfeld N, **Paletta JR, Efe T** (2014) Influence of cyclical mechanical loading on osteogenic markers in an osteoblast-fibroblast co-culture in vitro: tendon-to-bone interface in anterior cruciate ligament reconstruction. *Int Orthop* 8(5):1083-9

Heyse TJ, El-Zayat BF, De Corte R, Scheys L, Chevalier Y, **Fuchs-Winkelmann S**, Labey L (2014) Biomechanics of medial unicondylar in combination with patellofemoral knee arthroplasty. *Knee* 21 Suppl 1:S3-9

Eberhardt O, Fernandez FF, Gabriel H, Wirth T, **Fuchs-Winkelmann S, Peterlein CD** (2014) Clubfoot associated with preaxial polydactyly. *J Pediatr Orthop B* 23(6):505-11

Heyse TJ, El-Zayat BF, De Corte R, Chevalier Y, Scheys L, Innocenti B, **Fuchs-Winkelmann S**, Labey L (2014) UKA closely preserves natural knee kinematics in vitro. *Knee Surg Sports Traumatol Arthrosc*. 2014 Aug;22(8):1902-10

Heyse TJ, Haas SB, Drinkwater D, Lyman S, Kim HJ, Kahn BA, Figgie MP (2014) Intraarticular fibrinogen does not reduce blood loss in TKA: a randomized clinical trial. *Clin Orthop Relat Res* 472(1):272-6

Department of Trauma-, Hand- and Reconstructive Surgery

Chair Professor S. Ruchholtz

Main fields of research

Research in the Department of Trauma- Hand- and Reconstructive Surgery is dedicated to preclinical and clinical investigations in the fields of a) multiple injury, b) geriatric trauma and c) sports injuries.

- Healing of tendons into bone (Schwartz, Lechler, Frink et al.)
- Healing of osteoporotic fractures (Wack, Wirries, Aigner et al.)
- Hypothermia (Eschbach, Frink et al.)
- Biomechanics in fracture treatment (Frink, Bliemel, et al.)
- Minimal-invasive spine surgery (Krüger, Oberkircher, et al.)
- Minimal-invasive trauma surgery (Ruchholtz, Zettl, Aigner et al.)
- Geriatric fractures (Bücking, Eschbach, et al.)
- TraumaNetwork DGU (Kühne, Ruchholtz, et al.)

Research projects

Title Effects of bone morphogenetic protein 2 and 7 (BMP-2; BMP-7) onto the process of tendon-bone-integration in a vitro Co-Culture model

Principal investigator(s) T. Schwartz, P. Lechler & M. Frink

Summary Graft incorporation and ligamentization are high critical factors in anterior cruciate ligament surgery, related to the biological processes at tendon-bone interface. Aim of the present project is to investigate the influence of growth factors like bone morphogenetic protein (BMP-2; BMP-7) on murine osteoblasts and fibroblasts within an *in vitro* co-culture model and its influence onto the tendon-bone-healing. Furthermore, the influence of COX-1 and-2 inhibition was elucidated.

Funded by Intramural funding

Funding period since 2013

Title Effects of local application of osteoanabolic substances in osteoporotic fracture healing

Principal investigator(s) C. Wack, A. Wirries & R. Aigner

Summary This project studies the effects of established as well as promising new osteoanabolic substances on bone fracture healing in vivo. Experiments are carried out in a rat-fracture model comparing normal to osteoporotic (ovariectomized) rats applying substances locally in the fracture or systemically by subcutaneous injection and comparing healing results through radiological, biomechanical and histological findings.

Funded by Kempkes Foundation

Funding period until 2013

Title Effects of induced hypothermia in a multiple trauma model in pig

Principal investigator(s) D. Eschbach, J. Mohr & M. Frink

Summary Accidental hypothermia represents a leading cause of death in severely injured patients. Therapeutic hypothermia, however, is commonly used after cardiac arrest. Therefore, the effects of therapeutic hypothermia following multiple trauma with severe lung injury, abdominal trauma, hemorrhagic shock and fracture in combination with induced hypothermia after cardiopulmonary stabilization is evaluated in pigs over 48 hours in order to proof survival.

Funded by Reinfried Pohl Foundation

Funding period since 2014

Title Biomechanics in fracture treatment

Principal investigator(s) R. Zettl, C. Bliemel, Th. Müller & M. Frink

Summary The studies performed in this research project deal with the effect of valgisation in proximal femur fractures, the biomechanical testing of two established osteosyntheses (nailing vs. plating and cement augmented vs. non-cement augmented) in a human cadaver model and with the question if plate fixation in acetabular fractures need screw fixation in the symphysis or if supraacetabular fixation and support is sufficient.

Funded by Fa. Zimmer

Funding period 2014

Title Minimal-invasive spine surgery

Principal investigator(s) A. Krüger, L. Oberkircher, M. Bergmann, F. Floßdorf & C. Dorschel

Summary The treatment of osteoporotic vertebral fractures by cement augmenting procedures is well accepted in spine surgery. Different procedures and their biomechanical performance are evaluated. A fracture model has been standardized and the first biomechanical tests have been performed. In addition, a survey among german surgeons regarding the use of cement augmentation procedures in spine surgery was conducted and published.

Title Minimal invasive trauma surgery: fracture stabilization in geriatric trauma patients

Principal investigator(s) S. Ruchholtz, R. Zettl, B. Bücking, C. Bliemel & J. Mohr

Summary Along with the increase of the aging society higher rates of complex osteoporotic fractures of the humerus, the pelvic ring, the acetabulum and in peri-prosthetic or peri-implant situations are seen. Our study group follows new techniques of minimal invasive stabilization of these complicated fractures within prospective clinical studies.

Title Geriatric fractures

Principal investigator(s) C. Bliemel, B. Bücking, S. Ruchholtz, D. Eschbach & J. Mohr

Summary We investigate the role of the rehabilitation after hip fracture with a prospective observational study. In addition, we evaluate fixation of trochanteric fractures with a new anatomical shaped proximal femoral nail and compare the effects of Teriparatide with those of Risedronate on lumbar spine bone mineral density in osteoporotic patients with low bone mass and a recent pertrochanteric hip fracture.

Funded by Fa. Zimmer, Fa. Lilly

Funding period 2010 – 2013

Title TraumaNetwork DGU

Principal investigator(s) C. Kühne, S. Ruchholtz, F. Debus & C. Mand

Summary In order to guarantee an optimum of nationwide severe trauma care in 2006 the TraumaNetwork DGU® - project of the German Society of Trauma Surgery (Deutsche Gesellschaft für Unfallchirurgie - DGU) was initiated. The working group in our department analyses the impact of this project on the quality of trauma care in our country.

Funded by DGU (German Society of Trauma Surgery); GDV (Gesamtverband Deutscher Versicherer)

Funding period 2011 – 2013

Frühe geriatrische Mitbehandlung in der Alterstraumatologie. Eine systematische Literaturanalyse. *Dtsch Arztebl Int* 110(15):255-62

Eschbach DA, Oberkircher L, Bliemel C, Mohr J, Ruchholtz S, Buecking B (2013) Increased age is not associated with higher incidence of complications, longer stay in acute care hospital and in hospital mortality in geriatric hip fracture patients. *Maturitas* 74(2):185-9.

Buecking B, Struwer J, Waldermann A, Horstmann K, Schubert N, Balzer-Geldsetzer M, Dodel R, Bohl K, Ruchholtz S, Bliemel C (2014) What determines health-related quality of life in hip fracture patients at the end of acute care? - a prospective observational study. *Osteoporos Int* 25(2):475-84

Buecking B, Eschbach D, Bliemel C, Oberkircher L, Struwer J, Ruchholtz S, Sachs UJ (2014) Effectiveness of vitamin K in anticoagulation reversal for hip fracture surgery - A prospective observational study. *Thromb Res* 133(1):42-7

Schüttler KF, Strüwer J, Roessler PP, Gesslein M, Rominger MB, **Ziring E**, Efe T (2014) Patellofemoral osteoarthritis after Insall's proximal realignment for recurrent patellar dislocation. *Knee Surg Sports Traumatol Arthrosc* 22(11):2623-8

Buecking B, Mohr J, Bockmann B, Zettl R, Ruchholtz S (2014) Deltoid-split or Deltopectoral Approaches for the Treatment of Displaced Proximal Humeral Fractures? *Clin Orthop Relat Res* 472(5):1576-85

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Director: Professor Dr. Steffen Ruchholtz

General information about the institute

Research funding 190.569,02 €

Most important publications

Mand C, Müller T, Lefering R, **Ruchholtz S**, Kühne CA (2013) A Comparison of the Treatment of Severe Injuries Between the Former East and West German States- Vergleich der Schwerverletztenversorgung in den neuen und alten deutschen Bundesländern. *Dtsch Arztebl Int* 110(12):203-10

Buecking B, Timmesfeld N, Riem S, Bliemel C, Hartwig E, Friess T, Liener U, Ruchholtz S, Eschbach D (2013) Early Orthogeriatric Treatment of Trauma in the Elderly: A Systematic Review and Metaanalysis-

Department of Urology and Pediatric Urology Prostate Cancer Centre

Chair Professor R. Hofmann

Main fields of research

Oncology

Addressing possible actions of BCG immunotherapy in bladder cancer, the functions of TLR-4/9 were investigated as possible targets in bladder cancer cells [1]. A related project focussed on the responses of the cells towards inhibition of receptor tyrosine kinases that can be aberrantly activated in bladder cancer. An ongoing project deals with RNA biomarkers in prostate cancer.

Overactive bladder syndrome (OAB)

The role of prostaglandin E2 (PGE2) in patients with idiopathic overactive bladder syndrome was investigated supporting its possible value to objectify clinical diagnosis and responsiveness towards botulinum toxin A (BoNT-A) therapy [2].

Kidney injury

An experimental study identified TLR-3 as critical component for the pathomechanism of acute kidney injury following ischemia and reperfusion (IR) [3]. In a clinical study, certain profiles of NGAL and KIM-1 in serum and urine were recognized as promising valuable markers for postrenal kidney injury [4].

Research projects

Title Effects of TKI258 on bladder cancer cell lines with different EMT pattern

Principal investigator J. Hänze & P. Olbert

Summary Aberrant cellular processes in bladder cancer comprise altered signaling of receptor tyrosine kinases. Here we demonstrated that the cellular epithelial-mesenchymal transition status is associated with responses towards tyrosine kinase inhibition by dovitinib (Novartis). Dovitinib was more effective in epithelial-like than in mesenchymal-like bladder cancer cells. Therefore, determination of the EMT status may offer to predict treatment response [2].

Funded by Novartis Institutes for Biomedical Research

Title Evaluation of PGE2 in overactive bladder syndrome (OAB)

Principal investigator(s) A. Hegele

Summary PGE2 has been noticed as critical mediator being involved in OAB. Here, we analyzed serum PGE2 levels in OAB patients receiving intravesical BoNT-A administration representing a safe and effective therapy for refractory idiopathic OAB. In

sum, sPGE2 was increased in patients with OAB and decreased after BoNT-A treatment. Thus, sPGE2 may serve as biomarker in diagnostic and therapy monitoring [3].

Funded by Ipsen Pharma

General information about the institute

Research funding 58.996,60 €

Most important publications

Hänze J, Henrici M, Hegele A, Hofmann R, Olbert, PJ (2013) Epithelial mesenchymal transition status is associated with anti-cancer responses towards receptor tyrosine-kinase inhibition by dovitinib in human bladder cancer cells. *BMC Cancer* 13, 589

Hegele A, Knippschild S, Frohme C, Hänze J, Olbert P, Hofmann R (2014) Changes in prostaglandin E2 in patients with idiopathic overactive bladder syndrome after botulinum toxin type A treatment: is there a clinical benefit? *BMC Urol* 14, 85

Urbschat A, Gauer S, Paulus P, Reissig M, Weipert C, Ramos-Lopez E, Hofmann R, Hadji P, Geiger H, Obermuller N (2014) Serum and urinary NGAL but not KIM-1 raises in human postrenal AKI. *Eur J Clin Invest* 44, 652-659

Paulus P, Rupprecht K, Baer P, Obermuller N, Penzkofer D, Reissig C, Scheller B, Holfeld J, Zacharowski K, Dimmeler S, Schlammes J, **Urbschat, A.** (2014) The early activation of toll-like receptor (TLR)-3 initiates kidney injury after ischemia and reperfusion. *PLoS One* 9, e94366

Frohme, C., Ludt, F., Varga, Z., Olbert, P. J., Hofmann, R., and Hegele, A. (2014) TOT approach in stress urinary incontinence (SUI) - outcome in obese female. *BMC Urol* 14, 20

Hegele A, Goebell P, Matz U, Neuhaus T (2014) Monotherapy with intravenous vinflunine in patients with advanced or metastatic urothelial cancer after failure of a platinum-containing regimen: a retrospective analysis of German routine data. *Urol Int* 92, 174-179

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Director: Professor Dr. Rainer Hofmann

Department of Visceral-, Thoracic and Vascular Surgery

Chair Professor D. Bartsch

Main fields of research

AG Bartsch: familial pancreatic cancer, neuroendocrine tumors of the GI –tract

Our department has a broad spectrum of all kind of surgical, molecular and genetic research. In our main focus is to understand the development and progression of pancreatic tumor. A sort of tumor which had still a bad prognosis instead of all research and clinical efforts. Also we want to become more informations about the relative rare forms of familial pancreatic cancer. Together with the Deutsche Krebshilfe we work on a national database on this topic. Further we want to establish and develop modern surgical procedures for robotic –assisted operations of the goiter, pancreas. In thoracic surgery we evaluate the use of new laser systems in lung metastases surgery.

Research projects

Title Molecular mechanisms in the development of pancreatic cancer

Principal investigator(s) Trilateral project, together with Dr. Areej Alkahtib, Bethlehem University and Dr. Yuval Dor, The Hebrew University of Jerusalem

Summary Pancreatic cancer has a poor long term survival. This trilateral project wants to evaluate the origin cell for this disease. So by analysis of the cell methylation patterns, the researchers are able to distinguish the different cell types. An additional project should concentrate on molecular mechanisms in the development of pancreatic cancer, like for example the dysfunction of the gene BRCA2.

Funded by DFG – German Research Foundation

Funding period 2014 – 2016

Title Role of Rac1b and MMP-3 for the development and progression of pancreatic cancer

Principal investigator(s) J. Waldmann

Summary Matrix metalloproteinases (MMP) are known as key drivers of tumor progression that originate primarily from stromal cells activated by the developing tumor. In pancreatic cancer it was found that MMP – 3 was expressed together with Rac1b. In this study we want to know what is the role of both MMP-3 and Rac1b for the development and maybe the progression of pancreatic cancer.

Funded by Deutsche Krebshilfe

Funding period 2013 – 2015

Title Clinical and genetic evaluation of familial pancreatic cancer

Principal investigator(s) D. Bartsch, E. P. Slater & V. Fendrich

Summary Familial pancreatic cancer (FPC) is defined by families with at least two first- degree relatives with confirmed pancreatic ductal adenocarcinoma (PDAC). We want to explore a screening program with a multidisciplinary approach under research protocol conditions. Further research will done in establish new biomarkers for screening of individuals at risk. A national database will build up.

Funded by Deutsche Krebshilfe

Funding period 2013 – 2016

Title INTRANS Study

Principle investigators K. Manschuw & D. K. Bartsch

Summary Surgical site infections are the third most frequent type of nosocomial infections. Literature data for skin closure in elective abdominal surgery are still deficient. This project is designed as a prospective randomized controlled single center study in order to define the gold standard for wound closure in elective abdominal surgery (intracutaneous suture vs. transcutaneous skin stapling).

Funded by UKGM – University Medical Centre Giessen and Marburg

Funding period 2013 – 2016

Title Chemoprevention with Enalapril, ASS and a Somatostatinanalog in MEN 1 knockout mice

Principle investigator (s) C. Lopez

Summary To evaluate the longterm outcome of a medical treatment with enalapril or ASS or a somatostatinanalog in an MEN 1 Knockout mouse modell.

Funded by Anneliese Pohl Foundation

Funding period 2013 – 2016

Title The role of SNAIL as a key protein in epithelial to mesenchymal transition (EMT) in pancreatitis in a transgene mouse model

Principal investigator(s) M. Albers

Summary SNAIL is a key protein in EMT. Aim of the study is to evaluate the role of SNAIL in the course of pancreatitis in terms of severity of inflammation, necrosis and regeneration in a mouse model of genetically abrogation and chemical inhibition of SNAIL. Pancreatitis is provoked by intraperitoneal application of cerulean.

Funded by Cooperation between Hessen and Rhön Klinikum

Funding period 2013 – 2015

Title Marburg surgical curriculum

Principle investigator A. Damanakis

Summary The Marburg surgical curriculum (Marburger chirurgisches Weiterbildungscurriculum MCW) wants to improve residents training. With a focus on the first 2 years of residency (common trunk) it offers high quality courses by experienced clinicians of various disciplines. Topics covered are perioperative management of a surgical patient (perioperative management of coagulation, sepsis, standard antibiotic therapy etc.) and surgical basic skills (knot tying, suturing, laparoscopy basics, operation techniques for starters). The duration of the course is two years and apart from residents currently undergoing training at the Marburg University hospital, residents from associated hospitals are invited to take part.

Funded by Mittelhessische Medizin Stiftung, Behandlungsexzellenz und Netzwerkmedizin of the Rhön Klinikum AG

Funding period 2013 – 2015

General information about the institute

Research funding 451.825,78 €

Most important publications

Bartsch DK, Albers M, Knoop R, Kann PH, Fendrich V, Waldmann J (2013) Enucleation and limited pancreatic resection provide long-term cure for insulinoma in multiple endocrine neoplasia type 1. *Neuroendocrinology* 98(4):290-8

López CL, Langer P, Waldmann J, Fendrich V, Sitter H, Nies C, Bartsch DK (2013) Shortness: an unknown phenotype of multiple endocrine neoplasia type 1. *Eur J Endocrinol* 169(1):133-7

Heeger K, **Fendrich V, Waldmann J, Langer P, Kanngießer V, Bartsch DK** (2013) Reduced complication rate after modified binding purse-string-mattress sutures pancreatogastrostomy versus duct-to-mucosa pancreaticojejunostomy. *Surgeon* 11(5):246-52

Lopez CL, Falconi M, Waldmann J, Boninsega L, Fendrich V, Goretzki PK, Langer P, Kann PH, Partelli S, Bartsch DK (2013) Partial pancreaticoduodenectomy can provide cure for duodenal gastrinoma associated with multiple endocrine neoplasia type 1. *Ann Surg* 257(2):308-14

Bartsch DK, Slater EP, Albers M, Knoop R, Chaloupka B, Lopez CL, Fendrich V, Kann PH, Waldmann J (2014) Higher risk of aggressive pancreatic neuroendocrine tumors in MEN1 patients with MEN1 mutations affecting the CHES1 interacting MENIN domain. *J Clin Endocrinol Metab* 99(11):E2387-91

Di Dalmazi G, Kisker C, Calebiro D, Mannelli M, Canu L, Arnaldi G, Quinkler M, Rayes N, Tabarin A, Laure Jullié M, Mantero F, Rubin B, **Waldmann J, Bartsch DK, Pasquali R, Lohse M, Allolio B, Fassnacht M, Beuschlein F, Reincke M** (2014) Novel somatic mutations in the catalytic subunit of the protein kinase A as a cause of adrenal Cushing's syndrome: a European multicentric study. *J Clin Endocrinol Metab* 99(10):E2093-100

Knoop RF, Sparn M, **Waldmann J, Plassmeier L, Bartsch DK, Lauth M, Hudemann C, Fendrich V** (2014) Chronic pancreatitis and systemic inflammatory response syndrome prevent impact of chemotherapy with gemcitabine in a genetically engineered mouse model of pancreatic cancer. *Neoplasia* 16(6):463-70

Assié G, Letouzé E, Fassnacht M, Jouinot A, Luscip W, Barreau O, Omeiri H, Rodriguez S, Perlemoine K, René-Corail F, Elarouci N, Sbiera S, Kroiss M, Allolio B, **Waldmann J, Quinkler M, Mannelli M, Mantero F, Papathomas T, De Krijger R, Tabarin A, Kerlan V, Baudin E, Tissier F, Dousset B, Groussin L, Amar L, Clauser E, Bertagna X, Ragazzon B, Beuschlein F, Libé R, de Reyniès A, Bertherat J** (2014) Integrated genomic characterization of adrenocortical carcinoma. *Nat Genet* 46(6):607-12

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Department of Gynaecology, Gynaecological Endocrinology and Oncology

Chair Professor U. Wagner

Main fields of research

The main focus of research is placed on basic and clinical research in gynaecologic oncology, ovarian and breast cancer, cancer therapy related osteoporosis. Basic research comprises the evaluation of immunological regulation in cancer development and progression. In Obstetrics research is focussed on preeclampsia and the development of new methods in prenatal diagnosis.

Research projects

Title Transcriptional Signal pathways for the polarization of tumor-associated Macrophages in Ovarian Cancer

Principal investigator(s) U. Wagner & R. Müller

Summary Tumor-associated macrophages (TAM) seem to have a strong impact on the development and progress of cancer. We demonstrated that ovarian cancer patients could be divided into two subgroups based on the TAM phenotype in ascites. In the present study, the project focusses on the evaluation of the transcriptional signal pathways in the tumor associated macrophages from human ovarian carcinomas. Main focus lies on the transcription factors IL-1 β and IL-6 and the genome wide sequencing of the chromatin binding areas in contrast to normal macrophages.

Funded by Anneliese Pohl Foundation

Funding period 2014 – 2015

Title Lymphadenectomy In Ovarian Neoplasms – LION

Principal investigator(s) U. Wagner, Prof. Dr. A. du Bois and Dr. P. Harter (Kliniken Essen-Mitte (KEM), Evang. Huyssens-Stiftung/Knappschaft GmbH, Klinik für Gynäkologische Onkologie

Summary Pelvic and para-aortic lymphadenectomy (LNE) is well established as surgical staging in early stage ovarian cancer. The role of LNE in advanced ovarian cancer is unclear. Retrospective analyses indicate a potential benefit of LNE in patients with macroscopically complete intraabdominally resection. However, prospective randomized trials are lacking. The lack of sound evidence in this area is reflected by the heterogeneous LNE usage in Germany. This prospectively randomized controlled multicentre phase III trial will clarify the role of LNE in advanced ovarian cancer, thereby either establish LNE as evidence-based part of ovarian cancer surgery in routine care or disregard its use. Both results would provide benefit for the patient by

either stopping overtreatment or withheld of optimal surgical care. Endpoints include overall survival, quality of life and tolerability.

Funded by DLR, BMBF – Federal Ministry of Education and Research

Funding period 2008 – 2017

Title Stealth liposomal doxorubicin versus carboplatin/paclitaxel in patients with ovarian cancer recurrence between six and twelve months after previous platinum based chemotherapy (MITO-8)

Principal investigator(s) Dr. Sandro Pignata (Italy), U. Wagner & K. H. Baumann

Summary Ovarian cancer is the second most frequent gynaecological neoplasm but it is the first in order of mortality. Following initial surgical and systemic therapy, 70% of patients with ovarian cancer in an advanced stage and 25% of patients with early stage (FIGO I and II) will have disease progression or recurrence and require a second line chemotherapy. In patients with progression or recurrence more than 12 months after completion of first-line therapy, reinduction with carboplatin/paclitaxel is regarded as standard treatment. But in patients with progression or recurrence between 6 and 12 months, the evidence is not as clear-cut. It has been hypothesized that these patients might benefit from an artificial prolongation of the platinum-free interval through the use of an on-platinum agent. The proposed prospectively randomized and controlled multicenter phase III trial MITO-8 will test the hypothesis whether the treatment sequence 'stealth liposomal doxorubicin followed on further progression by carboplatin/paclitaxel' is superior to the reverse sequence in patients with ovarian cancer recurrence between 6 and 12 months after previous platinum based chemotherapy. The study will evaluate overall survival but will also focus on quality of life and tolerability. The Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) Study Group will take part in MITO-8 within the framework of the Gynecologic Cancer Intergroup (GCIg), an international network of gynaecologic oncology study groups.

Funded by DLR, BMBF – Federal Ministry of Education and Research

Funding period 2010 – 2016

Title Function and therapeutic potential of PPAR β / δ in tumor-associated macrophages in human ovarian cancer

Principal investigator(s) S. Müller-Brüsselbach & S. Reinartz

Summary Tumor-associated macrophages (TAM) seem to have a strong impact on the development and progress of cancer. We demonstrated that ovarian cancer patients could be divided into two subgroups based on the TAM phenotype in ascites. In the present study, the clinical relevance of TAM subtypes and the role of ligand-regulated transcription factor PPAR β / δ in functional TAM polarization should be investigated.

Funded by Wilhelm-Sander Foundation

Funding period 2011 – 2016

Title Regulation of glucose metabolism by PPAR β / δ ligands in ovarian carcinoma: Mechanism and therapeutic potential

Principal investigator(s) V. Rohalter, S. Müller-Brüsselbach & S. Reinartz

Summary The PPAR β / δ target gene PDK4 (Pyruvate dehydrogenase-Kinase 4) is overexpressed in tumor-associated macrophages (TAM) and tumor-initiating cells (TIC) in ascites of ovarian cancer patients. PDK4 plays a central role in glucose metabolism and favours glycolysis which is essential for the survival of TICs under hypoxia. In this study, we test the hypothesis if inverse PPAR β / δ -agonists can block induction of glycolysis by PDK4, thereby influencing survival / stem cell properties of TIC as well as protumorigenic functions of TAM.

Funded by UKGM – University Hospital Giessen and Marburg

Funding period 2014 – 2015

Title Differential chromatin signatures and expression pattern of tumor-associated macrophages in ovarian cancer

Principal investigator(s) T. Adhikary & S. Reinartz

Summary Tumor-associated macrophages (TAM) play a pivotal role in tumor development and progression, but little is known about regulation of TAM polarization. In this study we focus on epigenetic markers essential for stability and reversibility of TAM polarization in ovarian cancer. Ovarian cancer is often associated with malignant ascites which contains large amounts of TAM sufficient for genome-wide sequencing and expression analysis. Correlation of epigenetic markers with clinical data should provide new insights in clinically relevant mechanisms in TAM.

Funded by UKGM – University Hospital Giessen and Marburg

Funding period 2013 – 2014

Title A prospective randomized Phase III trial of carboplatin / gemcitabine/bevacizumab vs. carboplatin /pegylated liposomal doxorubicin

bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. An ENGOT/GCIG Trial.

Principal investigator(s) I. Pfisterer (International Coordinator & K. Baumann (PI Germany)

Summary Patients with first recurrence of epithelial ovarian cancer (EOC), fallopian tube carcinoma (FTC) or primary peritoneal carcinoma (PPC) and sensitive to platinum-based treatment regardless of FIGO stage, histological grades and types. So far, carboplatin/pegylated liposomal doxorubicin was one of the options with the best therapeutic index for patients with platinum-sensitive recurrence and carboplatin/gemcitabine/bevacizumab has shown a dramatic improvement in PFS, the rationale of this clinical trial is to evaluate the best platinum-based regimen in combination with bevacizumab in platinum-sensitive recurrence. The question would be answered whether the addition of bevacizumab to pegylated liposomal doxorubicin (cin/carboplatin is superior to bevacizumab combined with gemcitabine/carboplatin. TRIAL DESIGN of this academic trial: Prospective, open-label, multinational, randomized, two arm, superiority Phase III trial. 654 patients will be enrolled (327 per arm). Primary objective: The primary efficacy outcome measure for this clinical trial is investigator-determined progression-free survival (PFS). Recruitment: N=654 patients will be recruited into this clinical trial over a period of 30 months. Primary analysis will be done after 564 PFS events achieved. The analysis with respect to OS will be done after the last patient randomized has completed the 30 month follow-up (corresponds to 60 months after the randomization of the first patient).

Funded by AGO Research GmbH (an academic research group), Wiesbaden

Funding period 2012 – 2017

Title S3-Guideline on Diagnostics, Therapy and Follow-up of Malignant Ovarian Tumours

Principal investigator(s) U. Wagner

Summary The guideline was compiled with the aim of providing high-risk groups with advice on diagnostics, surgical and systemic therapy in early and advanced stages of disease in ovarian cancer. A lot of emphasis has been placed on follow-up care, rehabilitation, palliative therapy and psycho-oncological counselling. The recommendations are for physicians working both in hospitals and outpatient clinics, nursing staff and other medical partners involved in treating patients with malignant ovarian tumours. As it also covers the topics 'Screening' and 'Follow-up', registered physicians working in their own practice are also an important target audience of this guideline. It is additionally intended to offer guidance to affected patients and persons seeking more information as well as providing a basis for the gynaecological cancer centres currently being set up in Germany.

Funded by Deutsche Krebshilfe

Funding period 2012 – 2014

Title Angiogenic factors in early –versus late onset preeclampsia(PE) and HELLP-Syndrome

Principal investigator(s) M. Kühnert

Summary Prognosis of patients with symptoms of preeclampsia and HELLP-Syndrome. Correlation of worsening clinical course with early and late onset. PE with changes in the angiogenic profile and implications in identification of the women for appropriate patient management and possible future therapies on the reduction of s Ftt-1 levels.

Title Prognostic value of quantitative fibronectin in Preterm Birth

Principal investigator(s) M. Kühnert

Summary Eurofibronectin Study: Prognostic value of quantitative fibronectin, cervical length and vaginal exam in women with preterm contractions.

Funded by Hologic (test will be reimbursed)

Funding period 2013 – 2014

Title EPICE-Study

Principal investigator(s) S. Schmidt (retired) & R. F. Maier

Summary Health service research in obstetrics concerning mode of delivery of preterm birth (until 12/2015).

Funded by EU

Funding period 2011 – 2015

General information about the institute

Research funding 1.189.500,73 €

Most important publications

Adhikary T, Brandt DT, Kaddatz K, Stockert J, Naruhn S, Meissner W, Finkernagel F, Obert J, Lieber S, Scharfe M, Jarek M, Toth PM, Scheer F, Diederich WE, **Reinartz S**, Grosse R, Müller-Brüsselbach S, Müller R (2013) Inverse PPAR β/δ agonists suppress oncogenic signaling to the ANGPTL4 gene and inhibit cancer cell invasion. *Oncogene* 32(44):5241-52

du Bois A, Floquet A, Kim JW, Rau J, del Campo JM, Friedlander M, Pignata S, Fujiwara K, Vergote I, Colombo N, Mirza MR, Monk BJ, Kimmig R, Ray-Coquard I, Zang R, Diaz-Padilla I, **Baumann KH**, Mouret-Reynier MA, Kim JH, Kurzeder C, Lesoin A, Vasey P, Marth C, Canzler U, Scambia G, Shimada M, Calvert P, Pujade-Lauraine E, Kim BG, Herzog TJ, Mitrica I, Schade-Brittinger C, Wang Q, Crescenzo R, Harter P (2014) Incorporation of pazopanib in maintenance therapy of ovarian cancer. *J Clin Oncol* 32(30):3374-82

Reinartz S, Schumann T, Finkernagel F, Wortmann A, Jansen JM, Meissner W, Krause M, Schwörer AM, **Wagner U**, Müller-Brüsselbach S, Müller R (2014) Mixed-polarization phenotype of ascites-associated macrophages in human ovarian carcinoma: correlation of CD163 expression, cytokine levels and early relapse. *Int J Cancer* 134(1):32-42

Trillsch F, Mahner S, Woelber L, Vettorazzi E, Reuss A, Ewald-Riegler N, de Gregorio N, Fotopoulou C, Schmalfeldt B, Burges A, Hilpert F, Fehm T, Meier W, Hillemanns P, Hanker L, Hasenburg A, Strauss HG, Hellriegel M, Wimberger P, **Baumann K**, Keyver-Paik MD, Canzler U, Wollschlaeger K, Forner D, Pfisterer J, Schroeder W, Muenstedt K, Richter B, Kommos F, Hauptmann S, du Bois A (2014) Age-dependent differences in borderline ovarian tumours (BOT) regarding clinical characteristics and outcome: results from a sub-analysis of the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) ROBOT study. *Ann Oncol* 25(7):1320-7

Hadji P, Jackisch C, Bolten W, Blettner M, Hindenburg HJ, Klein P, König K, Kreienberg R, Rief W, Wallwiener D, Zaun S, Harbeck N (2014) COMPLIANCE and Arthralgia in Clinical Therapy: the COMPACT trial, assessing the incidence of arthralgia, and compliance within the first year of adjuvant anastrozole therapy. *Ann Oncol* 25(2):372-7

Kann PH, Münzel M, **Hadji P**, Daniel H, Flache S, Nyarango P, Wilhelm A (2014) Alterations of Cortisol Homeostasis May Link Changes of the Sociocultural Environment to an Increased Diabetes and Metabolic Risk in Developing Countries: A Prospective Diagnostic Study Performed in Cooperation With the Ovahimba People of the Kunene Region/Northwestern Namibia. *J Clin Endocrinol Metab* 2014 Dec 18:jc20142625. [Epub ahead of print].

Würstlein R, Degenhardt F, **Duda V**, Madjar H, Merz E, Mundinger A, Ohlinger R, Peisker U, Schulz-Wendtland R, Warm M, Hahn M (2014) [Evaluation of the nationwide DEGUM breast ultrasound training program]. *Ultraschall Med* 35(4):345-9

Axt-Fliedner R, Tenzer A, Kaweck A, Degenhardt J, Schranz D, Valeske K, Vogel M, Kohl T, **Enzensberger C** (2014) Prenatal assessment of ventriculocoronary connections and ventricular endocardial fibro-elastosis in hypoplastic left heart. *Ultraschall Med* 35(4):357-63

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Director: Professor Dr. Uwe Wagner

Children's Hospital

Chair Professor R. F. Maier

Prof. Dr. M. Zemlin – “Allergy and Developmental Immunology”

Prof. Dr. R. F. Maier – “Neonatology and Neuroprotection”

Dr. A. Renigunta – “Pediatric Nephrology”

Main fields of research

The research areas of the Children's Hospital Marburg are allergy, developmental immunology, neonatology, neuroprotection, and pediatric nephrology. We pursue clinical research as well as basic research based on a broad spectrum of techniques such as molecular biology, electrophysiology, cellular biology, mass spectrometry and others. Our research projects are funded by the European Union, the German Research Council (DFG), the State Hessen, the von-Behring-Röntgen-Stiftung, and several other institutions.

Research projects

Title Effective Perinatal Intensive Care in Europe - Translating knowledge into evidence-based practice (EPICE)

Principal investigator(s) R. F. Maier, Germany (Steering Committee)

Summary The EPICE project uses quantitative and qualitative approaches to build a knowledge base about the adoption of evidence-based medical interventions for the care of very preterm babies in 18 regions from 12 European countries.

Funded by EU – European Union

Funding period 2011 - 2015

Title Characterization of plasma cell subsets in allergic bronchial asthma

Principal investigator(s) M. Zemlin

Summary This project is part of the Transregio/SFB 22 “Allergic diseases of the lung” and aims to better understand the factors that lead to the migration, differentiation and survival of plasma blasts and plasma cells to produce IgE antibodies against allergens.

Funded by DFG – German Research Council

Funding period 2009 –2014

Title Effects of transfusion thresholds on neurocognitive outcome of extremely low birth weight infants (ETTNO)

Principal investigator(s) R. F. Maier (Steering Committee) & M. Zemlin

Summary Blinded randomized multicenter trial to compare the effect of restrictive versus liberal red blood cell transfusion thresholds on long-term neurodevelopmental outcome in extremely low birth weight infants.

Funded by DFG – German Science Foundation

Funding period 2011 – 2015

Title Sauerstoff-abhängige Schädigung des unreifen Gehirns und der unreifen Retina und die Schutzwirkung von Erythropoietin

Principal investigator(s) R. F. Maier (Marburg) & B. Lorenz (Giessen)

Summary The aim of this animal study is to investigate the effect of hypoxia and hyperoxia on the immature brain and retina as well as the neuroprotective effects of erythropoietin.

Funded by von Behring-Röntgen Foundation

Funding period 2011 – 2013

Title Prevention of chronic lung disease in very low birth weight neonates by inhaled NO (INOT-27-Studie)

Principal investigator(s) R. F. Maier & M. Zemlin

Summary In this European multicenter randomized controlled clinical trial, the efficacy and safety of inhaled NO to prevent chronic lung disease in very low birth weight infants is studied.

Funded by Industry

Funding period 2006 –2015

General information about the institute

Research funding 715.389,87 €

Most important publications

Gabler J, Wittmann J, Porstner M, Renz H, Jäck HM, Abram M, Zemlin M (2013) Contribution of microRNA 24-3p and Erk1/2 to interleukin-6-mediated plasma cell survival. *Eur J Immunol* 43(11):3028-37

Wagner JJ, Bedarf JR, Russ M, Grosch-Ott S, Keckel T, Hiebl B, Schell H, Unger JK (2013) Adverse Influence of Mixed Acidemia on the Biocompatibility of Continuous Veno-Venous Hemofiltration With Respect to the Lungs. *Artif Organs* 37(12):1049-58

Dorn F, Wirth L, Gorbey S, Wege M, Zemlin M, Maier RF, Lemmer B (2014) Influence of acoustic

stimulation on the circadian and ultradian rhythm of premature infants. *Chronobiol Int* 31(9):1062-74

Leonhardt C, Margraf-Stiksrud J, **Badners L**, Szerencsi A, **Maier RF** (2014) Does the 'Teddy Bear Hospital' enhance preschool children's knowledge? A pilot study with a pre/post-case control design in Germany. *J Health Psychol* 19(10):1250-60

Rogosch T, **Herrmann N**, **Maier RF**, Domann E, Hattesoht A, Koczulla AR, **Zemlin M** (2014) Detection of bloodstream infections and prediction of bronchopulmonary dysplasia in preterm neonates with an electronic nose. *J Pediatr* 165(3):622-4

Rogosch T, **Kerzel S**, **Dey F**, **Wagner JJ**, Zhang Z, **Maier RF**, **Zemlin M** (2014) IgG4 and IgE Transcripts in Childhood Allergic Asthma Reflect Divergent Antigen-Driven Selection. *J Immunol* 193(12):5801-8

Watzer B, Lusthof KJ, **Schweer H** (2014) Abortion after deliberate Arthrotec® addition to food. Mass spectrometric detection of diclofenac, misoprostol acid, and their urinary metabolites. *Int J Legal Med* 2014 Dec 19

Peters DM, Vadász I, Wujak L, Wygrecka M, Olschewski A, Becker C, Herold S, Papp R, Mayer K, Rummel S, Brandes RP, Günther A, **Waldegger S**, Eickelberg O, Seeger W, Morty RE (2014) TGF- β directs trafficking of the epithelial sodium channel ENaC which has implications for ion and fluid transport in acute lung injury. *Proc Natl Acad Sci USA* 111(3):E374-83

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Director: Professor Dr. Rolf F. Maier

Department of Otolaryngology, Head & Neck Surgery

Chair Professor J. A. Werner

Main fields of research

Our research is mainly focusing on aspects relating to the progress and the development of head and neck cancer as well as on pathomechanisms underlying the development of vascular anomalies in the head and neck area. The goal of the investigations is to better understand the biology of these important diseases and to identify and develop new therapeutic approaches that can be used in their treatment.

Research projects

Title Investigations regarding a possible association of vascular anomalies with human papilloma virus infection

Principal investigator(s) N. Franke & R. Mandic

Summary The pathogenesis of vascular anomalies (VA) of the head and neck area is only incompletely understood. Preliminary immunohistochemical studies point to the presence of human papilloma virus (HPV) E6 oncoproteins in nerves and endothelial cells present in VAs. Other groups attributed a pro-angiogenic function to HPV E6, which is mediated by its ability to upregulate VEGF121. Interestingly, own studies found VEGF121 to be significantly upregulated in VAs. The aim of this project is to evaluate if HPV is implicated in the pathogenesis of head and neck VAs.

Funded by P. E. Kempkes Foundation

Funding period 2014 – 2015

Title The chorion allantoic membrane (CAM) assay as a model system to study vascular anomalies

Principal investigator(s) R. Mandic, J. Jedelská-Keusgen, B. Eivazi, S. Wiegand, U. Bakowsky & J.A. Werner

Summary No reliable model systems exist for the study of vascular anomalies such as arterio-venous or lymphatic malformations. For decades, the CAM assay was successfully used in cancer research, investigating tumor growth and angiogenesis. The aim of this project is to assess the suitability of the CAM assay for studies of vascular anomalies.

Title Evaluation of ANCROD in Therapy of the sudden hearing loss

Principal investigator(s) C. Gueldner

Summary STUDY PHASE: Phase II. DESIGN: This is a randomized, double-blind, multicenter, placebo controlled, parallel-group phase II proof-of-concept study comparing Ancrod treatment versus placebo in patients with unilateral sudden sensorineural

hearing loss (SSHL). Patients presenting with unilateral SSLH within 7 days after onset and meeting all in- and exclusion criteria will be randomized into 2 cohorts in a ratio of 2:1 between active treatment and placebo. Study treatment and all study assessments will be performed in an outpatient setting at designated clinical study sites. OBJECTIVES/AIM OF THE STUDY: The aim of this study is to evaluate the efficacy of Ancrod treatment on hearing ability in patients suffering from SSLH.

Funded by Nordmark GmbH

Funding period 2013 – 2015

Title Immunohistochemical differentiation of vascular anomalies of the head and neck – with emphasis on GLUT-1, D2-40 and WT-1

Principal investigator(s) B. Eivazi

Summary Differentiation among distinct entities within vascular anomalies is essential for proper clinical management. Up to date, no specific marker could become established for differential diagnosis. Glucose-transporter-1 protein (GLUT-1), which is evident in placenta tissue, has been found to be present also on infantile hemangiomas. Wilms-tumor protein 1 (WT-1) has been found to be present in hemangiomas and arteriovenous malformations, whereas a role of D2-40 (podoplanin) for lymphatic malformations is discussed. The aim of this study is to identify and evaluate the role of these markers not only for the differential diagnosis, but also for conclusive studies on the pathogenesis of these entities.

Title Evaluation of artifacts and intracochlear placement of different cochlear electrodes in various radiologic modalities (X-Ray, CBCT, CT and MRI)

Principal investigator(s) C. Gueldner

Summary Phase 1: All patients with a radiological dislocation between the scales will undergo further investigations. The profile of the intracochlear position of the electrode will be correlated to the profile of the intraoperative biophysical measurements (NRTs, impedances). Phase 2: The possibilities of visualization of the different intracochlear positions of the electrodes (vestibular scale, tympanic scale, dislocation between scales) of the different radiological tools (X-Ray, CT, CBCT, MRI) will be analyzed. Phase 3: The different electrodes are implanted as full implants into human cadaveric heads. To have comparable results, the typical different locations of insertion of the electrode are planned to be performed. So, each electrode will be implanted via cochleostomy, round window and enlarged round window approach.

Radiological imaging will be performed using conventional X-Ray-examination and CT (64 slice, Siemens). Afterwards, diameters at different points of the electrodes will be measured in every diagnostic tool. This will result in a rate of artifacts individual for each combination of electrode and radiologic diagnostic tool.

Funded by Cochlear Europe

Funding period 2014 – 2016

Title Candidate genes involved in cisplatin resistance of head and neck cancer.

Principal investigator(s) R. Mandic

Summary Sensitivity to chemotherapeutic agents such as cisplatin correlates with the overall survival of head and neck cancer patients. This study is focusing on the functional characterization of previously identified candidate genes (initial funding by UKGM) that are differentially expressed in cisplatin-resistant HNSCC cells. These candidate genes could serve as potential therapeutic targets to overcome cisplatin resistance.

Title Role of adenosine receptors in chemotherapy resistance of regulatory T cells in patients with head and neck cancer

Principal investigator(s) M. Mandapathil

Summary The aim of this project is to study the role of adenosine receptors in the resistance of regulatory T cells (Treg) to chemotherapeutic drugs in HNC patients. Treg maintain profound immunosuppression in HNC patients, also following chemotherapy, as they persist in the peripheral blood of these patients after treatment. The underlying mechanisms are yet unknown, but there is evidence that paracrine adenosinergic effects in Treg contribute to their chemoresistance. Manipulation of this pathway could improve immune responses and therefore prognosis of HNC patients.

Funded by Foundation Tumorforschung Kopf/Hals (Alexander-Karl-Prize)

Funding period 2012 – 2013

Title Significance of the localized intravascular coagulopathy and marker function of D-dimers in venous malformations of the head and neck

Principal investigator(s) B. Eivazi

Summary A size-dependent increase in D-dimer- and a decrease of fibrinogen levels as a sign of localized intravascular coagulopathy (LIC) are observed in extensive venous malformations. Furthermore, the D-dimers are considered as a reliable marker for this particular entity. Since venous malformations of the head and neck are already relevant at much smaller size, the extent of the LIC and the significance of D-dimer as a potential marker are to be clarified. The aim of this study is to identify and evaluate the role of LIC for following purposes: firstly to improve the

understanding of the clinical course, secondly to integrate this fact into the therapeutic scheme and into the differential diagnosis, and thirdly to improve the safety of surgical procedures on venous malformation by early detection of LIC.

Title Intraperitoneal oxidative stress as an oncolytic immunomodulator

Principal investigator(s) R. Mandic & M. Bette

Summary Intraperitoneal oxidative stress effectively converts the immune response against the papillomavirus-associated rabbit VX2 carcinoma from tumor permissive to tumoricidal and leads to a sustainable oncolytic immune response that can be adoptively transferred. This study aims to further dissect the immunological and molecular mechanisms underlying the immune recognition of VX2 tumor cells leading to tumor regression and how this information can be applied in the treatment of human HNSCC patients.

Title Design and development of a disease-specific questionnaire for the assessment of quality of life in patients with arteriovenous malformations of the head and neck

Principal investigator(s) A. Zimmermann

Summary Arteriovenous malformations (AVM) of the head and neck are characterized by specific symptoms and problems that significantly affect the quality of life and that are not covered by the existing quality of life questionnaires such as bleeding, pulsations, sensations of heat, distortion / deformation, paraesthesia, and many more. The aim of our study is to analyze the quality of life of patients with AVMs, especially in terms of the question if a specific questionnaire for AVMs is reasonable.

Title The role of regulatory T cells in the lymphogenic metastasis of patients with head and neck cancer

Principal investigator(s) M. Mandapathil

Summary The involvement of immunosuppressive Treg in the formation of metastasis to the cervical lymph nodes is not fully understood. The frequency and activity of Treg is increased in cancer patients and positively correlate with the disease stage. Therefore, it is likely that Treg play a key role in the formation and occurrence of lymphogenic metastasis in head and neck cancer.

Funded by Alfred und Ursula Kulemann Foundation

Funding period 2012 – 2013

General information about the institute

Research funding 82.307,83 €

Most important publications

Mandapathil M, Visus C, Finn OJ, Lang S, Whiteside TL (2013) Generation and immunosuppressive functions of p53-induced human adaptive regulatory T cells. *Oncoimmunology* 2(7):e25514

Jedelská J, Strehlow B, Bakowsky U, Aigner A, Höbel S, Bette M, Roessler M, **Franke N**, **Teymoortash A**, **Werner JA**, **Eivazi B**, **Mandic R** (2013) The chorioallantoic membrane assay is a promising ex vivo model system for the study of vascular anomalies. *In Vivo* 27(6):701-5

Teymoortash A, Bohne F, Jonsdottir T, Hoch S, **Eivazi B**, Roessler M, **Werner JA**, **Mandic R** (2013) Human papilloma virus (HPV) is not implicated in the etiology of Warthin's tumor of the parotid gland. *Acta Otolaryngol* 133(9):972-6

Wiegand S, Wiemers C, Murthum T, **Zimmermann AP**, Bette M, **Mandic R**, **Werner JA** (2013) Risk of lymph node metastases after en bloc cold steel, en bloc laser-, and piecemeal laser surgical resection of auricular VX2 carcinoma. *Lasers Med Sci* 28(4):1137-41

Makarova G, Bette M, Schmidt A, Jacob R, Cai C, Rodepeter F, Betz T, Sitterberg J, Bakowsky U, Moll R, Neff A, Sesterhenn A, **Teymoortash A**, Ocker M, **Werner JA**, **Mandic R** (2013) Epidermal growth factor-induced modulation of cytokeratin expression levels influences the morphological phenotype of head and neck squamous cell carcinoma cells. *Cell Tissue Res* 351(1):59-72

Güldner C, Heinrichs J, Weiß R, **Eivazi B**, Bien S, **Teymoortash A**, **Werner JA**, Diogo I (2013) Prospective evaluation of reliability of cone-beam computed tomography in detecting different position of vibroplasty middle ear implants. *Clin Otolaryngol* 38(3):217-24

Tonigold M, Rossmann A, Meinold M, Bette M, Märken M, Henkenius K, Bretz AC, Giel G, Cai C, Rodepeter FR, Beneš V, Grénman R, Carey TE, Lage H, Stiewe T, Neubauer A, **Werner JA**, Brendel C, **Mandic R** (2014) A cisplatin-resistant head and neck cancer cell line with cytoplasmic p53(mut) exhibits ATP-binding cassette transporter upregulation and high glutathione levels. *J Cancer Res Clin Oncol* 140(10):1689-704

Rossmann A, **Mandic R**, Heinis J, Höffken H, Küssner O, Kinscherf R, Weihe E, Bette M (2014) Intraperitoneal oxidative stress in rabbits with papillomavirus-associated head and neck cancer induces tumoricidal immune response that is

adoptively transferable. *Clin Cancer Res* 20(16):4289-301.

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Chair Professor W. Sekundo

Main fields of research

- Refractive surgery (ReLEX/SMILE)
- Lamellar corneal transplantation (DMEK)
- Glaucoma
- Vitreous and vitreoretinal diseases

Research projects

Title BLUE-RAY

Principal investigator(s) W. Sekundo

Summary Clinical evaluation of the efficacy of IOL calculation using raytracing - toric IOLs.

Funded by Zeiss Meditec AG

Funding period 2013 – 2016

Title PERSEUS

Principal investigator(s) T. Bertelmann

Summary A prospective non-interventional study to assess the effectiveness of aflibercept (Eylea®) in routine clinical practice in patients with wet age-related macular degeneration.

Funded by Bayer Pharma AG

Funding period 2013 – 2014

Title SALT

Principal investigator(s) T. Bertelmann

Summary A 12-month, phase IV, randomized, open label, multicenter study to compare efficacy of 0.5 mg ranibizumab PRN compared to 2 mg aflibercept bimonthly intravitreal injections on retinal thickness stability till month 6 of treatment and explore correlated functional outcomes up to month 12 in patients with neovascular (wet) age-related macular degeneration (AMD).

Funded by Novartis Pharma GmbH

Funding period 2013 – 2015

Title INJECT

Principal investigator(s) T. Bertelmann

Summary Investigation of Jetrea in patients with confirmed vitreo-macular traction.

Funded by Alcon Pharma GmbH

Funding period 2014 – 2017

Title C12-II

Principal investigator(s) W. Sekundo

Summary Clinical evaluation of the femtosecond laser system VisuMax® for treatment of hyperopic eyes with lenticule extraction.

Funded by Zeiss Meditec AG

Funding period 2013 – 2014

Title OCEAN

Principal investigator(s) T. Bertelmann

Summary A multicentre, open-label, non-interventional study to observe treatment patterns in patients with wet age-related macular degeneration (wAMD), with visual impairment due to diabetic macular edema (DME), due to macular edema following retinal vein occlusion (RVO) or due to choroidal neovascularization following pathologic myopia (mCNV) with repeated intravitreal injections of Lucentis® (Ranibizumab) including optional OCT monitoring over a 24 months observational period under real life conditions.

Funded by Novartis Pharma GmbH

Funding period 2012 – 2016

Title PRIDE

Principal investigator(s) T. Bertelmann

Summary Multicenter 12-months clinical study to evaluate efficacy and safety of Ranibizumab alone or in combination with laser photocoagulation vs. laser photocoagulation alone in proliferative diabetic retinopathy.

Funded by Novartis Pharma GmbH

Funding period 2012– 2014

Title CONSTANCE

Principal investigator(s) T. Bertelmann

Summary This study is a multicenter, prospective, observational study to evaluate the long-term safety of OZURDEX® in patients with macular oedema following central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO) or patients with non-infectious posterior segment uveitis in real-world clinical practice.

Funded by Pharm-Allergan GmbH

Funding period 2012 – ongoing

Title Intraocular fibrinolysis study group

Principal investigator(s) T. Bertelmann

Summary Detection of intravitreal activities and/or concentrations of the fibrinolytic system components in eyes with diabetic macular edema and wet age-related macular degeneration.

Funded by IIT, Novartis Pharma GmbH

Funding period 2013 – 2015

Title Intraocular opsin study group

Principal investigator(s) T. Bertelmann

Summary Detection of intravitreal opsin concentrations in eyes with and without disturbance of the blood-retina-barrier.

Funded by IIT

Funding period 2014 – 2017

Title Intraocular neurotrophins study group

Principal investigator(s) T. Bertelmann

Summary Detection of intravitreal neurotrophin concentrations in eyes with and without disturbance of the blood-retina-barrier.

Funded by IIT

Funding period 2014 – 2015

Title OCTAVIAN

Principal investigator(s) T. Bertelmann

Summary Use of optical coherence tomography (OCT) to objectively assess the vitreomacular interface.

Funded by IIT, Novartis Pharma GmbH

Funding period 2014 – 2016

Bertelmann T, Stief T, **Sekundo W** (2014) Soluble opsin is present in human vitreous. *Exp Eye Res* 121:23-5

Bertelmann T, Schulze S, Bölöni R, **Sekundo W**, Irle S, Stief T, Mennel S (2014) Intravitreal vascular endothelial growth factor. *Graefes Arch Clin Exp Ophthalmol* 252(4):583-8

Blum M, Flach A, Kunert KS, **Sekundo W** (2014) Five-year results of refractive lenticule extraction. *J Cataract Refract Surg* 40(9):1425-9

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Director: Professor Dr. Walter Sekundo

General information about the institute

Research funding 101.259,91 €

Most important publications

Blum M, Kunert KS, Voßmerbäumer U, **Sekundo W** (2013) Femtosecond lenticule extraction (ReLEx) for correction of hyperopia - first results. *Graefes Arch Clin Exp Ophthalmol* 251(1):349-55

Meyer CH, Kaymak H, Liu Z, Saxena S, Rodrigues EB (2014) Geometry, penetration force, and cutting profile of different 23-gauge trocars systems for pars plana vitrectomy. *Retina* 34(11):2290-9

Monnereau C, Quilendrino R, Dapena I, Liarakos VS, Alfonso JF, Arnalich-Montiel F, Böhnke M, Pereira NC, Dirisamer M, Parker J, **Droutsas K**, Geerling G, Gerten G, Hashemi H, Kobayashi A, Naveiras M, Oganessian O, Orduña Domingo E, Priglinger S, Stodulka P, Torrano Silva J Jr, Venzano D, Vetter JM, Yiu E, Melles GR (2014) Multicenter study of descemet membrane endothelial keratoplasty: first case series of 18 surgeons. *JAMA Ophthalmol* 132(10):1192-8

van Dijk K, **Droutsas K**, Hou J, Sangsari S, Liarakos VS, Melles GR (2014) Optical quality of the cornea after Descemet membrane endothelial keratoplasty. *Am J Ophthalmol* 158(1):71-79

Koss MJ, Hoffmann J, Nguyen N, Pfister M, Mischak H, Mullen W, Husi H, Rejdak R, Koch F, Jankowski J, Krueger K, **Bertelmann T**, Klein J, Schanstra JP, Siwy J (2014) Proteomics of vitreous humor of patients with exudative age-related macular degeneration. *PLoS One* 9(5):e96895

Department of Dermatology and Allergology

Chair Professor M. Hertl

A. Bender M.D., R. Eming M.D., C. Möbs PhD, W. Pfützner M.D., T. Schmidt PhD

Main fields of research

1. Autoimmune dermatoses: autoimmune bullous disorders, lichen planus, collagen vascular diseases, vasculitides (R. Eming M.D., M. Hertl, M.D., T. Schmidt, PhD)
2. Allergology: respiratory allergies, hymenoptera venom allergy, immune mechanisms of specific immunotherapy, tolerance induction in allergy, atopic eczema, drug allergy (W. Pfützner M.D., C. Möbs PhD)
3. Dermatooncology: Human malignant melanoma in basic and clinical research, focusing on immune modulation by regulatory CD4+ T cells and immunotherapy which might result in advanced vaccine strategies (A. Bender M.D.)
4. Psoriasis (C. Möbs PhD)

Research projects

Autoimmune bullous disorders

Title Charakterisierung regulatorischer T-Zellen beim Pemphigus

Principal investigator(s) R. Eming & M. Hertl

Summary Pemphigus is probably among other factors a result of a dysregulation of peripheral tolerance. The role of autoantigen specific CD4+ regulatory T-cells in maintaining peripheral tolerance to the autoantigen desmoglein 3 in pemphigus is investigated in this project.

Funded by DFG (He 1602/7-1, 7-2, 7-3) – German Research Foundation

Funding period 2004 – 2014

Title Efficacy and safety of adjuvant immunoabsorption in pemphigus vulgaris and pemphigus foliaceus. A randomized, prospective, multi-center, parallel-group study (IA-Pem-study)

Principal investigator(s) R. Eming

Summary Aim of the study is to investigate whether adjuvant immunoabsorption is superior to standard immunosuppressive treatment in inducing clinical remission in pemphigus.

Funded by DFG (Em 80/2-1) / BMBF – German Science Foundation / Federal Ministry of Education and Research

Funding period 2010 – 2015

Title Entwicklung pathogener Autoimmunreaktionen beim bullösen Pemphigoid

Principal investigator(s) M. Hertl & C. Sitaru

Summary In this joint project, the immune mechanisms leading to clinically overt autoimmune diseases will be studied in elderly patients with pruritic dermatoses. Previous studies have shown that a significant number of elderly patients have IgG autoantibodies against the autoantigens of bullous pemphigoid, BP180 and BP230, but do not yet fulfill all the criteria of the autoimmune bullous skin disorder, bullous pemphigoid

Funded by DFG (He 1602/13-1) – German Research Foundation

Funding period 2012 – 2015

Title Clinical Trial „Effect of simvastatin in combination with a superpotent topical corticosteroid in bullous pemphigoid“

Principal investigator(s) M. Hertl, M. Goebeler & M. Behzad

Summary In this tri-center trial (Marburg, Würzburg, Wuppertal), the anti-inflammatory properties of the statins will be investigated in a cohort of patients with bullous pemphigoid. The clinical efficacy of the statins will be evaluated by the cumulative dose of topically applied clobetasol until clinical remission is reached.

Funding period 2013 – 2015

Title Preclinical validation, development and clinical testing of a tolerance inducing immunotherapy (phase Ib) in pemphigus vulgaris

Principal investigator(s) M. Hertl & C. Schade-Brittinger

Summary This proposal deals with the creation of an extensive project proposal for the early development and testing of an innovative treatment of the potentially life-threatening autoimmune disease pemphigus vulgaris. The central project goal is to establish a balanced consortium that combines all expertise necessary for the successful implementation of this innovation project with a project strategy that meets the complex technical and regulatory requirements involved in the development of a nanoparticle-based treatment. The project plan provides for two stages: at first, safety and efficacy of the application of proteins coupled with nanoparticles is examined in an HLA-transgenic mouse model before it will then be examined in pemphigus patients. According to the results in pemphigus, the nanoparticle-based immunotherapy may also be an option for the specific treatment of other autoimmune diseases in humans.

Funded by BMBF (01EK1418) – Federal Ministry of Education and Research
Funding period 2014

Title Rolle der Flotilline bei der Zell-Zelladhäsion in Epithelzellen

Principal investigator(s) R. Eming & M. Hertl & R. Tikkannen

Summary Cell-cell adhesion plays an important role in the development and maintenance of multicellular structures. This project focuses on the molecular pathways involved in the assembly and maintenance of two major adherence structures in the epidermis, i.e. desmosomes and adherence junctions. The role of lipid raft-associated proteins called flotillins in cell-cell adhesion of epidermal keratinocytes is investigated. Previous results suggest that flotillins interact with the cell adhesion molecule gamma-catenin; furthermore the expression of adhesion proteins in flotilline-2 knock-out mice is altered. One goal of this collaborative project is to investigate whether flotillins demonstrate a regulatory function in the assembly of desmosomes and whether they might play a role in the pathogenesis of the blistering autoimmune disorder, pemphigus.

Funded by Von-Behring-Röntgen Foundation
Funding period 2012 – 2015

Title Rolle extra- und intradesmosomaler Cadherine beim Pemphigus

Principal investigator(s) M. Hertl, R. Eming, R. Jacob & J. Hoyer

Summary The loss of cell-cell adhesion of epidermal keratinocytes is a pathogenic hallmark in pemphigus, an organ-specific autoimmune disease of the skin and mucous membranes. The exact molecular mechanisms leading to the loss of keratinocyte adhesion are still incompletely understood. This project aims at characterizing the role of intra- and extradesmosomal cadherins, especially desmoglein 1, 3 and desmocollin 1, 3 in the process of keratinocyte detachment. The hypothesis that extradesmosomal cadherins might provide a crucial target in the autoantibody response in pemphigus thereby interrupting the constant recruitment of extradesmosomal cadherins into the desmosome is being investigated. Moreover, the function of E-cadherin, a non-desmosomal important component of adhesion junctions, in the process of keratinocyte detachment in pemphigus is examined. Molecular events such as Src-signaling pathways and alterations in two-pore domain potassium channels (K2P-TREK/TWIK) in epidermal keratinocytes after binding of pemphigus autoantibodies are investigated in cultured keratinocytes. Finally, changes in the cytoskeleton of epidermal keratinocytes and alterations in the polarization of these epithelial cells, e.g. changes in the distribution

of membrane proteins such as ATP-binding cassette sub-family A member 12 (ABCA12), are addressed in this project.

Funded by Internal Funding of the Faculty
Funding period 2012 – 2014

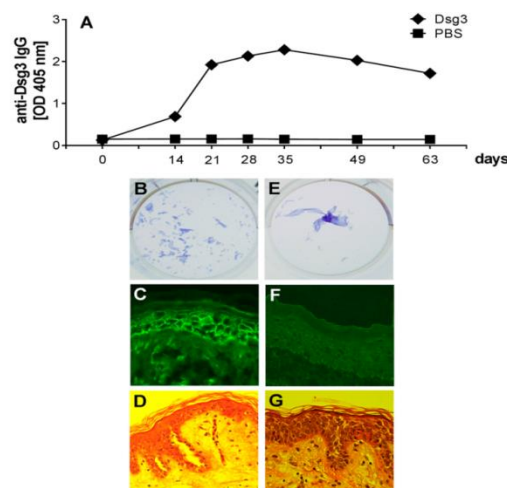


Fig. 1: In vivo induction of pathogenic IgG autoantibodies in an HLA class II transgenic pemphigus mouse model

Title Depression und Lebensqualität bei Pemphigus-Patienten

Principal investigator(s) R. Eming & R. Dodel

Summary Pemphigus represents a rare chronic organ-specific autoimmune disorder affecting skin and mucous membranes. Due to severe blister formation and widespread erosions pemphigus patients are heavily impaired in their daily life. Only few investigations have addressed the aspects of quality of life and psychiatric disorders such as depression in pemphigus patients so far. However, previous results suggest that these parameters are severely affected by the autoimmune disease and its therapy, respectively. The aim of this nation-wide cross-sectional study is to characterize the incidence, the severity and the treatment options of depressive disorders in a cohort of pemphigus patients. Various parameters such as quality of life, comorbidities, pemphigus disease activity, treatment and severity of depression (Beck Depression Inventory (BDI-II)) are investigated.

Funded by UKGM – University Medical Centre Giessen / Marburg

Funding period 2011 – 2013

Title Validation of serological diagnostics in the detection of IgG autoantibodies against human collagen type VII in epidermolysis bullosa acquisita (EBA)

Principal investigator(s) M. Hertl & M. Behzad

Summary The purpose of this project is to validate *in vitro* diagnostic products for epidermolysis bullosa acquisita (EBA). It aims at comparing the sensitivity

and specificity of four different diagnostic procedures in the detection of serum IgG autoantibodies against human collagen type VII. The analysis includes validation of the MESACUP anti-type VII collagen Test for diagnosis and monitoring disease activity of EBA.

Funded by MBL, Nagoya, Japan

Funding period 2014 – 2016

Allergology

Title Cellular and humoral mechanisms of specific immunotherapy (SIT) of respiratory type-I-allergies

Principal investigator(s) W. Pfützner & M. Hertl,

Summary Characterization of humoral (e.g. specific antibody concentrations, blocking capacity) and cellular parameters (e.g. specific T cell and cytokine responses) in patients with birch pollen allergy treated with specific immunotherapy. Comparison of alternative treatment routes (subcutaneous, sublingual) and allergen preparations (native allergen, modified allergoids).

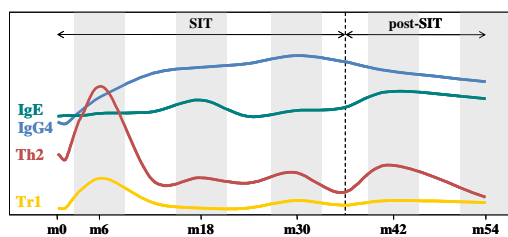


Fig.: Specific immunotherapy (SIT)-induced alterations in patients with birch pollen allergy

Funded by DFG HE 1602/10-1, SFB/TR22 – German Research Foundation, Transregional Collaborative Research Centre 22

Funding period 2007 – 2009; 2009 – 2013, 2013 – 2014

Title B-zelluläre Regulation der Allergentoleranz bei spezifischer Immuntherapie IgE-vermittelter Respirationsallergien

Summary Aim of this study is to characterize if allergen-specific B cells serve as mediators of allergen tolerance by production of allergen-blocking antibodies and/or secretion of regulatory cytokines during the course of allergen-specific immunotherapy (ASIT). Furthermore, the role of both different modes of allergen application (subcutaneous vs. sublingual ASIT) in modifying the B cellular immune response and allergen-specific memory B cells in maintaining long-term tolerance is addressed.

Principal investigator(s) W. Pfützner & C. Möbs,

Funded by DFG (PF 344/3-1/MO 2076/3-1) – German Research Foundation

Funding period 2014 – 2017

Title Charakterisierung ASIT-induzierter, blockierender IgG-Antikörper bei Hymenopteren-giftallergien

Principal investigator(s) C. Möbs

Summary Cross-sectional study to analyze the occurrence and long-term maintenance of hymenoptera venom-specific IgG blocking antibodies after successful allergen-specific immunotherapy (ASIT). Evaluation of the ASIT-induced allergen blocking capacity of IgG antibodies and correlation of its inhibitory activity with clinical tolerance.

Funded by Internal Funding of the Faculty

Funding period 2014 – 2016

Title Modulation humoraler und T-zellulärer Faktoren durch allergenspezifische Immuntherapie (ASIT) mit einer rekombinanten, hypoallergen Vakzine

Principal investigator(s) C. Möbs & W. Pfützner

Summary Characterization of a peptide carrier-based, recombinant, hypoallergenic grass pollen allergy vaccine in comparison to allergen-specific immunotherapy with conventional, native grass pollen extract. Analysis of effector and regulatory T cell subsets and allergen-specific antibody concentrations in peripheral blood and nasal secretion of grass pollen allergic patients.

Funded by UKGM – University Medical Center Giessen/Marburg)

Funding period 2014 – 2016

Title Impaired immune regulation in hymenoptera venom allergy and its correction by specific immunotherapy

Principal investigator(s) W. Pfützner

Summary Analysis of immunological tolerance induction (i.e. alterations in allergen-specific antibody concentrations and T cell subsets) in patients with bee and wasp venom allergy treated by allergen-specific immunotherapy and impact of treatment on patients' quality-of-life (questionnaires).

Title Immunological pathomechanisms of delayed-type allergies induced by beta-lactam antibiotics

Principal investigator(s) W. Pfützner

Summary Identification of distinct subsets of beta-lactam specific T cell frequencies in patients with drug-induced delayed-type-hypersensitivity. Subcategorization of T cell-mediated drug-induced type-IV-reactions according to their cytokine pattern (type-IVa to type-IVd).

Title Diffusion Tensor Imaging (DTI) in patients with atopic eczema

Principal investigator(s) W. Pfützner

Summary Characterization of neuronal mechanisms in the pathogenesis of atopic eczema and their

correlation to defined genetic and immunological parameters.

Non-investigator initiated clinical trials:

Title APPLES "A prospective pediatric longitudinal evaluation to assess the long-term safety of tacrolimus ointment for the treatment of atopic dermatitis" (FHI 03-0-161/FG-506-06-37)

Principal investigator(s) W. Pfützner

Funded by Astellas

Title XOLAIR Q4883g "A phase III, multicenter, randomized, double-blind, placebo-controlled safety study of xolair (omalizumab) in patients with chronic idiopathic urticaria who remain symptomatic despite treatment with H1 antihistamines, H2 blockers and/or leucotriene receptor antagonists"

Principal investigator(s) W. Pfützner

Funded by Genentec

Title BIOMAY CS-BM-32-003 "Phase IIb study on the safety and efficacy of BM32, a recombinant hypoallergenic vaccine for immunotherapy of grass pollen allergy"

Principal investigator(s) W. Pfützner

Funded by Biomay AG

Title Allergovit "Double-blind phase IV multicenter clinical trial to evaluate and compare specific and non-specific effects of SCIT by use of an Environmental Challenge Chamber after treatment with Allergovit® grasses or Allergovit® birch in patients with grass and birch pollen allergy"

Principal investigator(s) W. Pfützner

Funded by Allergopharma

Title AWARE „Nicht-interventionelle chronische Urtikaria-Studie zur Erfassung von klinischen Daten aus der täglichen Praxis“

Principal investigator(s) W. Pfützner

Funded by Novartis

Dermatooncology

Non-investigator initiated clinical trials for treatment of early and progressing malignant melanoma:

Title DERMA trial "Adjuvant immunotherapy with MAGE-A3 in melanoma (Stage IIIB-IIIC)"; COMBI-AD trial "A Phase III Randomized Double Blind Study of Dabrafenib (GSK2118436) in COMBination With Trametinib (GSK1120212) Versus Two Placebos in the ADjuvant Treatment of High-risk BRAF V600 Mutation-positive Melanoma After Surgical Resection"

Principal investigator(s) A. Bender

Funded by Glaxo Smith Kline

Title MO25616 (Vismodegib) "A single arm, open-label, phase II, multicentre study to assess the safety of vismodegib (GDC-0449) in patients with locally advanced or metastatic basal cell carcinoma (BCC); MO25515 (Vemurafenib) "An open-label, multicenter expanded access study of RO5185426 in patients with *metastatic melanoma*

Principal investigator(s) A. Bender

Funded by Roche

Title IMAGE (CA184143) "A Multi-National, Prospective, Observational Study in Patients with Unresectable or Metastatic Melanoma

Principal investigator(s) A. Bender

Funded by Bristol-Myers Squibb

Title PO-Studie Melanom "Die neuroimmunologischen Auswirkungen von Stress und ihre Rolle beim Melanom (Psychoonkologie-Studie)"

Principal investigator(s) A. Bender

Funded by UKGM – University Medical Centre Giessen / Marburg

Psoriasis

Title CD4+CD25+ regulatorische T-Zellen bei Psoriasis vulgaris

Principal investigator(s) A. Jacobi

Summary Characterization of the impact of biologics on the cellular immune response in psoriasis under treatment with TNF- α blockers and Fumaric acid esters.

Funded by Biogen Idec

Funding period 2014

Title Systemische Entzündungsprozesse bei chronisch entzündlichen Erkrankungen der Haut - Psoriasis

Principal investigator(s) A. Jacobi, R. Mößner & M. P. Schön

Funded by Universitätsklinik Göttingen

Funding period 2012 – 2016

Title Epidemiologische Studie "Predictors of psoriasis on response to systemic therapy (PREDICT)

Principal investigator(s) A. Jacobi

Funded by AbbVie Deutschland

Funding period 2012 – 2016

General information about the institute

Research funding

1.281.920,57 €

Most important publications

Subbarayal B, Schiller D, **Möbs C**, de Jong NW, Ebner C, Reider N, Bartel D, Lidholm J, **Pfützner W**, Gerth van Wijk R, Vieths S, Bohle B (2013) Kinetics, cross-reactivity, and specificity of Bet v 1-specific IgG4 antibodies induced by immunotherapy with birch pollen. *Allergy* 68(11):1377-86

Colliou N, Picard D, Caillot F, Calbo S, Le Corre S, Lim A, Lemerrier B, Le Mauff B, Maho-Vaillant M, Jacquot S, Bedane C, Bernard P, Caux F, Prost C, Delaporte E, Doutre MS, Dreno B, Franck N, Ingen-Housz-Oro S, Chosidow O, Pauwels C, Picard C, Roujeau JC, Sigal M, Tancrede-Bohin E, Templier I, **Eming R**, **Hertl M**, D'Incan M, Joly P, Musette P (2013) Long-term remissions of severe pemphigus after rituximab therapy are associated with prolonged failure of desmoglein B cell response. *Sci Transl Med* 5(175):175ra30

Kurrl N, Völlner F, **Eming R**, **Hertl M**, Banning A, Tikkanen R (2013) Flotillins directly interact with γ -catenin and regulate epithelial cell-cell adhesion. *PLoS One* 8(12):e84393

Rafei-Shamsabadi D, Müller S, **Pfützner W**, Spillner E, Rüeff F, Jakob T (2014) Recombinant allergens rarely allow identification of Hymenoptera venom-allergic patients with negative specific IgE to whole venom preparations. *J Allergy Clin Immunol* 134:493-494
Letter to the Editor

Schmidt T, Sitaru C, Amber K, **Hertl M**. (2014) BP180 and BP230 specific IgG autoantibodies in pruritic disorders of the elderly - a pre-clinical stage of bullous pemphigoid? *Br J Dermatol* 171(2):212-9

Eming R, Hennerici T, Bäcklund J, Feliciani C, Visconti KC, Willenborg S, Wohde J, Holmdahl R, Sørenstrup G, **Hertl M** (2014) Pathogenic IgG antibodies against desmoglein 3 in pemphigus vulgaris are regulated by HLA-DRB1*04:02-restricted T cells. *J Immunol* 193(9):4391-9

Nagel A, **Möbs C**, Raifer H, Wiendl H, **Hertl M**, **Eming R** (2014) CD3-positive B cells: a storage-dependent phenomenon. *PLoS One* 9(10):e110138

Wambre E, DeLong JH, James EA, Torres-Chinn N, **Pfützner W**, **Möbs C**, Durham SR, Till SJ, Robinson D, Kwok WW (2014) Specific immunotherapy modifies allergen-specific CD4(+) T-cell responses in an epitope-dependent manner. *J Allergy Clin Immunol* 133(3):872-9.e7

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Director: Professor Dr. Michael Hertl

Department of Neurology

Chair Professor W. H. Oertel (until June 30th, 2014)

Professor R. Dodel (since July 1st, 2014)

- **Apl. Prof. Dr. med. K. Bürk**
- **Therapeutic Research and Dementia (AG Prof. Dodel)**
- **German Parkinson Study Group (PD Dr. Eggert)**
- **Hertie-Senior Research Professorship (AG Prof. Oertel)**
- **Movement Disorders - Experimental Neurology (PD Dr. Ries/PD Dr. Depboylu/Prof. Höglinger)**
- **Working Group on Clinical and Experimental Epileptology (AG Prof. Rosenow)**
- **Neuro-Oncology (Prof. Strik)**
- **Clinical Neuroimmunology Group (AG PD Dr. Tackenberg)**

Main fields of research

Apl. Prof. Dr. med. K. Bürk

Movement disorders, especially ataxic, spastic and hyperkinetic movement disorders including Spinocerebellar ataxias, recessive ataxias, spastic paraplegias and Huntington's disease (HD). Description of phenotypical presentations and genotyping including identification of new mutations causing hereditary movement disorders.

Therapeutic Research and Dementia (AG Prof. Dodel)

Autoimmunity in neurodegenerative disorders; Translational research; investigator-initiated clinical trials; Health-economic evaluations in neurological disorders

German Parkinson Study Group (PD Dr. Eggert)

Design, execution and analysis of pharmacological multicenter trials on motor and non-motor symptoms in patients with Parkinson's disease and atypical Parkinson-Syndromes. Development of new study designs for disease modifying or neuroprotective agents in Parkinson's disease

Hertie-Senior Research Professorship (AG Prof. Oertel)

Neurodegeneration - neuroprevention - translational neurology: new preclinical diagnostic procedures, disease modifying and neuropreventive therapy research: on prodromal stages of neurodegenerative

disorders (alpha-synucleinopathy; REM sleep behavior disorder (RBD), Parkinson disease, multiple system atrophy(MSA), dementia Lewy body type(DLB); tauopathies; progressive supranuclear palsy) - hyposmia, depression, stomach-gut function
Methods: cell culture, stem cell research, animal models for Parkinson disease, microbiomics, neuropsychology, autonomic, oculomotor, sensorimotor control, phase II and III randomized controlled therapeutical trials, magnetresonance tomography (VBM, resting state, diffusion tensor, functional MRI, others), nuclear medicine imaging (SPECT, PET), long term follow-up

Neurological sleep research: restless legs syndrome, narcolepsy, REM sleep behavior disorder

Movement Disorders - Experimental Neurology (PD Dr. Ries/PD Dr. Depboylu/Prof. Höglinger)

Mechanisms of endogenous brain repair processes. Experimental modeling of neurodegeneration and study of endogenous neurogenesis. Development of novel protective or restorative treatments.

Working Group on Clinical and Experimental Epileptology (AG Prof. Rosenow)

Clinical and experimental epileptology, epilepsy genetics, cognitive neurology, neuroimaging motor cortex physiology, The role of micro RNA, neuropeptides and cytokines in pathophysiology, treatment and prevention of epilepsy, health economy.

Neuro-Oncology (Prof. Strik)

Glioma biology; CSF involvement in neoplastic diseases; Supportive care in neurooncology

Clinical Neuroimmunology Group (AG PD Dr. Tackenberg)

Treatment predictors for Multiple Sclerosis; Immunotherapy of Multiple Sclerosis and other neurological autoimmune diseases; T-cell/B-cell interaction in autoimmunity

Research projects

Apl. Prof. Dr. med. K. Bürk

Title Identification of novel mutations causing hereditary ataxia

Principal investigator(s) K. Bürk in cooperation with Prof. Dr. C. Zühlke, University of Lübeck

Summary Phenotypical description of patients with hereditary ataxias and identification of novel underlying mutations and their pathogenic impact

Title EFACTS: European Friedreich Ataxia Consortium of Translational Studies

Principal investigator(s) K. Bürk, multicenter study, principal investigator Prof. Dr. M. Pandolfo, University of Brussels and Prof. Dr. J. B. Schulz, University of Aachen

Summary EFACTS assembles a body of expertise to adopt a translational research strategy for the rare autosomal recessive *Friedreich's ataxia* (FRDA). This project aims to establish a European FRDA database, linked to a bio bank, define a panel of clinical assessment tools and to build on the knowledge base of frataxin structure and function.

Funded by EU FP7 – European Union

Funding period 2011 – 2015

Title RISCA: Risk of spinocerebellar ataxia

Principal investigator(s) K. Bürk, multicenter study, principal investigator Prof. Dr. M. Pandolfo, University of Brussels and Prof. Dr. J. B. Schulz, University of Aachen

Summary Prospective observational study of individuals at risk for the most common SCA disorders, SCA1, SCA2, SCA3 and SCA6 (RISCA). The study aims to define the incidence of disease manifestation in mutation carriers, clinical signs precede the onset of manifest ataxia, the prevalence and incidence of preceding signs.

Funded by Former FP6 project

Funding period No financial support

Title Enroll-HD

Principal investigator(s) K. Bürk, multicenter study, principal investigator Prof. Dr. B. Landwehrmeyer, University of Ulm

Summary Enroll-HD is a longitudinal, observational, multinational study that will integrate two existing Huntington's Disease (HD) registries, REGISTRY in Europe and COHORT in North America and Australia, while also expanding to include sites in Latin America and Asia. This database will serve as a basis for future studies aimed at developing tools and biomarkers for progression and prognosis.

Funded by CHDI Foundation

Funding period 2014, unlimited

Therapeutic Research and Dementia – AG Prof. Dodel

Title Dementia in Parkinson's disease: Future Challenges (Landscape)

Principal investigator(s) R. Dodel

Summary The consortium established a large cohort of patients with PD/PDD. The patients will undergo repeated clinical examination, detailed neuropsychological testing including investigation of cognitive reserve as well as morphological/functional

MRI studies. It is our aim to study the evolution of dementia in PD, to determine the conversion rate to PDD, and to identify clinical, biochemical and genetic risk factors.

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2011 – 2017

Title Health Service Analysis in Patients with advanced Parkinson-Syndrom

Principal investigator(s) J.-P. Reese & R. Dodel

Summary The aim of the study is to get conclusion about the actual health care situation for patients with advanced Parkinson-Syndrom in Germany and possible use of alternative treatment options next to oral polytherapy.

Funded by Abbott Arzneimittel GmbH

Funding period 2012 – 2013

Title Cloning, Expression and Efficacy Evaluation of Naturally Occurring Autoantibodies against beta-Amyloid

Principal investigator(s) J.-P. Bach & R. Dodel

Summary There is increasing evidence that nAbs are playing an important role in the development of neurodegenerative disorders. To date, not much is known regarding the development and physiological and pathophysiological role of nAbs. The aim is to isolate B-cells responsible for producing nAbs-A β , the cloning of these autoantibodies and to test their efficacy in respective models.

Funded by Baxter Healthcare

Funding periods 2012 – 2015

Title Double-blind, randomized, two-arm study of the efficacy of bupropion in the treatment of apathy in patients with Alzheimer's disease (APA-AD)

Principal investigator(s) R. Dodel

Summary This multicenter-double-blinded randomized clinical trial investigates the effect of bupropion on apathy in patients with Alzheimer's disease.

Funded by BMBF, through study centre Bonn – Federal Ministry of Education and Research

Funding period 2012 – 2014

Title Multi-site randomised controlled REDALI-DEM trial. The effects of structured Relearning methods on Daily Living task performance of persons with Dementia

Principal investigator(s) R. Dodel

Summary To assess the efficacy and safety of errorless learning hypothesizing a significant difference in the task performance scale 1, 6 and 16 weeks after treatment completion in favour of the experimental group with at least moderate effect sizes.

Funded by BMBF, through study centre Freiburg – Federal Ministry of Education and Research

Funding period 2012 – 2015

Title Development and Validation of an Instrument to forecast Assessments of Rehabilitation after Proximal Femur Fractor (Reprof)

Principal investigator(s) B.Bücking & R. Dodel

Funded by UKGM –University Hospital Giessen / Marburg

Funding period 2013

Title Long-term Follow-up on a Cohort of Parkinson Patients

Principal investigator(s) M. Balzer-Geldsetzer & R. Dodel

Summary The project is a naturalistic observational multi-center cohort study (follow-up at 6 years post baseline) in a stratified sample of outpatients (office-based neurologists) with Parkinson's disease. The objectives are to re-evaluate this large cohort and to re-characterize these patients in a standardized manner by clinical and neuropsychological testing as well as assessment of health-related quality of life and depression.

Funded by International Parkinson Fonds (IPF)

Funding period 2013 – 2014

Title Joint Programme - Neurodegenerative Disease Research. Care for Late Stage Parkinsonism (Clasp)

Principal investigator(s) R. Dodel (in Germany)

Summary The aim of this project is to evaluate the needs and provision of care for patients with late stage Parkinsonism and their carers in six European countries, compare the effectiveness of different health and social care systems, and to lay the foundation for improved outcomes in this population.

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2014 – 2017

German Parkinson Study Group – PD Dr. Eggert

Pharmacological multicenter trials on motor and non-motor symptoms in patients with Parkinson's disease and atypical Parkinson-Syndromes
Impact of patient education and psychological factors in Parkinson's disease quality of life
Evaluation of jaw movement dysfunction related to Parkinson's disease

Title German Parkinson Study Group, multicenter trials on Parkinson's disease

Principal investigator(s) K. Eggert & H. Pape

Summary The GPSG has established as one of the leading groups in Europe for conducting industry-sponsored clinical trials and investigator-initiated trials. In 2013/2014 numerous controlled trials assessing new compounds were performed. Studies on the impact of patient education and psychological factors in PD quality of life were carried out. Furthermore, an evaluation of jaw

movement dysfunction in PD-patients was conducted.

Funded by Pharmaceutical industry, Willy Robert Pitzer Foundation, Hessen

Funding period 2013 – 2014

Hertie-Senior Research Professorship – AG Prof. Oertel in cooperation with PD Dr. Depboylu and PD Dr. Ries

Title Effect of nicotinic drugs and other compounds on the toxicity of alpha-synuclein overexpression onto dopaminergic neurons in a protein-aggregation mouse-model of Parkinson disease

Principal investigator(s) W. H Oertel

Summary To test the potentially disease-modifying effect of nicotinic drugs (and other compounds) on the protein aggregation induced unilateral Parkinson model in mouse – developing an animal test model for new therapeutical developments.

Funded by Hertie-Senior-Research Professorship and Novartis Deutschland GmbH

Funding period 2013 – 2015

Title Pupillary assessment as an indicator of brain stem function in REM-sleep behavior disorder (RBD = prodromal Parkinson's disease (PD)), Parkinson disease (PD) and healthy control.

Principal investigator(s) W. H. Oertel

Summary To develop a test for the function of brain stem nuclei in neurodegenerative disorders

Funded by DFG – German Research Foundation, International Research Training Group - IRTG

Funding period 2013 – 2016

Title Real time video MRI imaging of gastric motility in REM-sleep behavior disorder (RBD = prodromal Parkinson's disease (PD), de novo PD and healthy controls

Principal investigator(s) W. H. Oertel

Summary To analyse the gastric motility in vivo without a radioactive method in neurodegenerative disorders as a indicator for affection of the motor dorsal nucleus of the vagal nerve.

Funded by International Parkinson Fonds (IPF)

Funding period 2012 – 2014

Title REM-PET - Fluorodesoxy-Glucose-Positron-Emissions-Tomography (FDG-PET) – differential diagnostic study between alpha-synucleinopathies – predictive value of FD-PET (pilot study) for conversion of RBD to PD

Principal investigator(s) W. H Oertel &, Prof. Klaus Leenders, (Groningen, Holland

Summary recognition of "specific patterns of glucose consumption in the CNS" in alpha-synucleinopathies

(RBD, PD DLB, MSA) as a differential indicator and predictor for conversion from RBD to PD, MSA or DLB

Funded by International Parkinson Fonds (Dutch-German-study) (IPF)

Funding period 2013 – 2015

Title CouragePD - genetic-environmental analysis of risk factors of Parkinson disease

Principal investigator(s) T. Gasser, Tübingen

Summary providing biosamples for a large scale analysis of risk factor genes of Parkinson disease – in relation to environmental factors.

Funded by Joint Programming Neurodegeneration (JPND-EU)

Funding period 2014 – 2016

Title PPMI – Parkinson progression marker initiative

Principal investigator(s) K. Marek, New Haven, USA

Summary Search for biomarkers in early motor stage Parkinson patients

Funded by Michael J Fox Foundation (MJFF)

Funding period 2013 – 2016

Title PPPMI-RBD – prodromal Parkinson progression marker initiative

Principal investigator(s) W. H. Oertel, G. Mayer and K. Marek, New Haven, USA

Summary Search for biomarkers in prodromal stage Parkinson patients, i.e. REM-sleep behavior disorder (RBD)

Funded by Michael J Fox Foundation (MJFF)

Funding period 2013 – 2015

Title Nicotine patch (NIC-PD) in de novo Parkinson's disease

Principal investigator(s) W. H Oertel

Summary Testing the potentially disease modifying effect of nicotine on the progression of early (de novo) Parkinson patients – double blind placebo controlled randomized clinical trial

Funded by International Parkinson Fonds (IPF), Michael J Fox Foundation (MJFF), German Parkinson Study Group (German-USA-trial)

Funding period 2013 – 2016

Movement Disorders - Experimental Neurology

PD Dr. Ries/PD Dr. Depboylu/Prof. Höglinger

Title Modulation of adult neurogenesis in the olfactory bulb in a rodent toxin model of Parkinson's disease

Principal investigator(s) V. Ries, C. Depboylu & G. Höglinger

Summary Dopamine depletion in the regions of adult neurogenesis leads to a reduction of newborn stem cells in the adult mammalian brain. In this study we investigated, if direct or indirect

dopaminergic stimulation can modulate the survival and cell fate of neural stem cells in the olfactory bulb in an acute mouse model of PD.

Funded by Pharmaceutical Industry

Funding period 2010 – 2013

Title Effect of neuregulin-1 β 1 in MPTP mouse models of Parkinson's disease

Principal investigator(s) V. Ries, C. Depboylu & G. Höglinger

Summary Extracellular domain of neuregulin-1 β 1 (Nrg1 β 1), a nerve growth and differentiation factor, passes the blood-brain barrier and rescues dopaminergic neurons of substantia nigra in the 6-hydroxydopamine-mouse model of Parkinson's disease (PD). In another toxin-based mouse model of PD. We found that Nrg1 β 1 significantly reduced the loss of nigral dopaminergic neurons in both intoxication paradigms. Neuroprotective properties of Nrg1 β 1 on nigral dopaminergic neurons are specifically mediated by ErbB4 as revealed through the study of ErbB4 knockout mice. In conclusion, systemically administered Nrg1 β 1 protects midbrain dopaminergic neurons against this PD-related toxic insult. Thus, Nrg1 β 1 may have a benefit in the treatment of PD patients.

Funded by Pharmaceutical industry, UKGM

Funding period 2011 – 2013

Working Group on Clinical and Experimental Epileptology – AG Prof. Rosenow

Title EpimiRNA: Micro-RNA in the pathophysiology, treatment and prevention of epilepsy (www.epimirna.eu)

Principal investigator(s) F. Rosenow; K. M. Klein; S. Knake, A. Strzelczyk, K. Menzler, B. Norwood & S. Bauer

Summary EpimiRNA: Through highly collaborative, inter-disciplinary and inter-sectorial research, EpiMiRNA will explain the mechanism by which miRNAs contribute to epileptogenesis, characterize genetic variation of miRNA in patients, evaluate seizure-suppressing effects of miRNAs in experimental models, identify novel miRNA modulatory molecules as potential future therapeutics, and develop miRNAs as prognostic markers to identify patients who respond to novel, non-pharmacological therapeutic interventions including brain-stimulation.

Funded by EU within FP7 (Grant agreement number 602130) – European Union

Funding period 2013 – 2018

Title EuroEPINOMICS-RES: Genetics of rare epilepsy syndromes (www.euroepinomics.org)

Principal investigator(s) F. Rosenow; K. M. Klein; S. Knake, A. Strzelczyk, K. Menzler, B. Norwood & S. Bauer

Summary EuroEPINOMICS-RES: The strategy of this RES-CRP is to create a 4-stage pipeline for tackling the genetics of RES starting with (1) sample collection and systematic assessment of phenotypic data, (2) screening of known genes, (3) novel gene discovery, by genome-wide screening for novel genetic risk factors using high-throughput CNV analysis and Next-Generation Sequencing and (4) genotype-phenotype correlation/diagnostic guidelines / functional studies.

Funded by DFG – German Research Foundation and ESF (RO 3396/2-1)

Funding period 11-2011 to 6-2014

Neuro-Oncology – Prof. Strik

Title Internet-based registry of brain tumors and neoplastic meningitis

Principal investigator(s) H. Strik

Summary Primary CNS neoplasms and neoplastic meningitis, neoplastic CSF involvement, are rare. Building up a solid database on treatment results with a sufficient size of cases even in subgroups requires a multicentric registry. We are designing an internet-based registry on CNS neoplasms with special respect on neoplastic meningitis that enables to document cases within an international network of interested centres.

Funded by Barbara und Wilfried Mohr Foundation; Medac GmbH; Mundipharma; Riemser Pharma

Funding period 2011 – 2016

Clinical Neuroimmunology Group – AG PD Dr. Tackenberg

Title Clinical Trial Center Neuroimmunology

Principal investigator(s) B. Tackenberg

Summary External (industrial sponsored) and internal Phase I-III RCTs were conducted and performed on the basis of the Marburg Outpatient Neuroimmunology Clinic (MONC) with its 5,500 patient contacts per year.

Funded by Industry

Funding period 2008 – ongoing

Title Krankheitsbezogenes Kompetenznetzwerk Multiple Sklerose (KKNMS)

Principal investigator(s) B. Tackenberg (local)

Summary The Clinical neuroimmunology Group Marburg is member of the KKNMS and participates in the nationwide 10-year prospective early MS Cohort study (n=1,100) and its treatment registry project “REGIMS”.

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2012 – 2015

Title T-cell/B-cell interactions in antibody dependent autoimmune diseases (Myasthenia gravis, CIDP)

Principal investigator(s) B. Tackenberg

Summary Activated epitope specific Th-cells provide signals to B lymphocytes for differentiation and subsequent antibody production by direct interaction through receptor/ligand systems co-mediated by members of the TNF super-family crucial for survival signalling and apoptosis. Autoantibody mediated autoimmune diseases (MG; CIDP) miss regulated Th-cell activation and migration which might lead to positive feedback through TC/BC interaction resulting in auto-antibody production.

Funded by various

Funding period 2013 – ongoing

Title Prospective identification and biomaterial characterization of a cohort with active disease using 1.5 T vs. 3.0 T MRI in RR-MS under standard immune treatment

Principal investigator(s) B. Tackenberg

Funded by Industry

Funding period 2013 – 2016

Title Functional anatomic correlates of working-memory, interhemispheric interactions, visual motion and motor functions in 3.0 T fMRI during fampridine treatment in Multiple Sclerosis patients with concomitant cognitive impairment and motor dysfunction

Principal investigator(s) B. Tackenberg

Funded by Industry

Funding period 2012 – 2015

General information about the institute

Research funding 4.706.463,29 €

Most important publications

Jacobi H, Reetz K, du Montcel ST, Bauer P, Mariotti C, Nanetti L, Rakowicz M, Sulek A, Durr A, Charles P, Filla A, Antenora A, Schöls L, Schicks J, Infante J, Kang JS, Timmann D, Fabio RD, Masciullo M, Baliko L, Melegh B, Boesch S, **Bürk K**, Peltz A, Schulz JB, Dufaure-Garé I, Klockgether T (2013) Biological and clinical characteristics of individuals at risk for spinocerebellar ataxia types 1, 2, 3, and 6 in the longitudinal RISCA study: analysis of baseline data. *Lancet Neurol* 12:650-8

Wenning GK, Geser F, Krismer F, Seppi K, Duerr S, Boesch S, Köllensperger M, Goebel G, Pfeiffer KP,

Barone P, Pellecchia MT, Quinn NP, Koukouni V, Fowler CJ, Schrag A, Mathias CJ, Giladi N, Gurevich T, Dupont E, Ostergaard K, Nilsson CF, Widner H, **Oertel W**, **Eggert KM**, Albanese A, Del Sorbo F, Tolosa E, Cardozo A, Deuschl G, Hellriegel H, Klockgether T, **Dodel R**, Sampaio C, Coelho M, Djaldetti R, Melamed E, Gasser T, Kamm C, Meco G, Colosimo C, Rascol O, Meissner WG, Tison F, Poewe W; European Multiple System Atrophy Study Group (2013) The natural history of multiple system atrophy: a prospective European cohort study. *Lancet Neurol* 12(3):264-74

Roettger Y, Du Y, **Bacher M**, Zerr I, **Dodel R**, **Bach JP** (2013) Immunotherapy in prion disease. *Nat Rev Neurol* 9(2):98-105

Eggert K, Öhlwein C, Kassubek J, Wolz M, Kupsch A, Ceballos-Baumann A, Ehret R, Polzer U, Klostermann F, Schwarz J, Fuchs G, Jost W, **Albert A**, **Haag A**, **Hermesen A**, Lohmüller K, Kuhn K, Wangemann M, **Oertel WH**; In Cooperation With the German Competence Network on Parkinson's Disease (2014) Influence of the nonergot dopamine agonist piribedil on vigilance in patients With Parkinson Disease and excessive daytime sleepiness (PiViCog-PD): an 11-week randomized comparison trial against pramipexole and ropinirole. *Clin Neuropharmacol* 37: 116-22

Sanchez-Padilla J, Guzman JN, Ilijic E, Kondapalli J, Galtieri DJ, Yang B, Schieber S, **Oertel W**, Wokosin D, Schumacker P, Surmeier DJ (2014) Mitochondrial oxidant stress in locus coeruleus is regulated by activity and nitric oxide synthase. *Nat Neurosci* 2014; 17(6): 832-840

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Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy

Chair Professor K. Becker

Professor H. Remschmidt (Emeritus),

Professor I. Kamp-Becker (W2 . since 2014)

Main fields of research

Research in child and adolescent psychiatry and (neuro)developmental psychopathology, basic research in neuropsychology, therapy, and genetics in autism spectrum disorders and ADHD and comorbid conditions; fMRI studies; therapy evaluation, early childhood research, research in eating disorders (obesity, anorexia nervosa), transcranial direct current stimulation (tDCS), gene-environment interaction, longitudinal research, psychopharmacoepidemiology, health economics, medical education.

In addition to the selection of research projects listed below, we are part of the German anorexia-register study initiated in 2014 (PI B. Herpertz-Dahlmann, Aachen; local PI's K. Becker, J. Pfeiffer) and involved in different groups drawing up or revising medical guidelines in the field of child and adolescent psychiatry (e.g. suicidality, non-suicidal self-injurious behavior, autism, conduct disorder).

Research projects

Research group Autism Spectrum Disorders

Title Search and analyses of candidate genes for autism spectrum disorders especially for high-functioning autism spectrum disorders

Principal investigators A. K. Wermter, I. Kamp-Becker & K. Becker

Summary This project aims at the identification of candidate genes and genetic variants, influencing particular core symptoms of the autism spectrum disorders (ASD). The analyses were performed in a sample of individuals with high-functioning ASD (Asperger syndrome, high-functioning autism, and atypical autism) and their parents. Under consideration of the hypothesis that the mental retardation of the majority of patients with autism considerably hampers the detection of candidate genes for ASD, the investigated sample of individuals with high-functioning ASD has a potential to elucidate genes underlying the susceptibility to ASD.

Title Etiological, diagnostic, differential diagnoses and therapeutic aspects of autism spectrum disorder

Principal investigators I. Kamp-Becker & K. Becker

Summary This project aims at the investigation of genetic, neuronal, diagnostic as well as differential diagnostic aspects of autism spectrum disorders.

Emotion recognition deficits were examined in a large sample of children and adolescents with autism spectrum disorders and other psychiatric disorders. A short questionnaire with few interview questions for screening of ASD was developed. The effectiveness of the Parenting Program „Stepping Stones/Triple P“ for children diagnosed with autism spectrum disorder was evaluated.

Title Neurobiological principles of social emotions

Principal investigators S. Krach, I. Kamp-Becker, S. Knake (Dept. of Neurology), W. Einhaeuser-Treyer (Working Group Neurophysics) & A. Jansen (Working Group Brain Imaging)

Summary The multimodal project evaluates basic and clinical aspects of development, processing as well as regulation of social emotions.

Funded by Philipps-University Marburg (Research Promotion Fund)

Funding period 2012 – 2014

Title The female variant of Asperger's syndrome

Principal investigators Kamp-Becker, L. Paye, S. Fraessle, L. Rademacher, C. Kauschke (Institute for Linguistics, Marburg) & K. Becker

Summary The research project investigates the characteristics of female individuals with Asperger's Syndrome or a high-functioning autism spectrum disorder. Complex social emotions ("social pain"), communicative and narrative skills, as well as the ability to verbalize internal conditions ("Internal State Language") are analyzed in female children and adolescents with autistic disorders. Both the neuronal correlates of social emotions and their verbalization on a behavioural level are examined.

Funded by Philipps University Marburg

Title Empathy, Autism and Oxytocin – an investigation by means of functional magnetic resonance imaging and molecular genetic analyses

Principal investigators A.-K. Wermter, I. Kamp-Becker & S. Krach

Summary This project aimed for the first time at investigating the ability for empathy in adolescents with high-functioning ASD in a wide battery of paradigms using fMRT and analyzing the modulating effect of intranasal oxytocin. Additionally, the influence of the SNP rs53576 in the oxytocin receptor gene (*OXTR*) on the empathy and the activation pattern in the neural network of empathy should be investigated.

Funded by DFG (WE5076/1-1) – German Research Foundation

Funding period 2014 – 2016

Title Scientific Accompanying Study ADHD Care Concept (Wissenschaftliche Begleitevaluationsstudie zum BKK-Versorgungskonzept ADHS)

Principal investigators K. John, F. Matthejat & K. Becker

Summary The study analyzed the effectiveness of the newly established outpatient treatment care concept “ADHD” for ADHD-patients between the ages of 4 and 17 insured by BKK insurance funds in Baden-Wuerttemberg in comparison to Treatment as Usual.

Funded by German Federal Ministry of Health

Funding period 2010 – 2013

Health economics

Title Psychopharmacoeconomics in child & adolescent psychiatry

Principal investigators C. Bachmann & F. Hoffmann (University Bremen)

Summary This project aims to analyze the prescription of psychotropic substances for children and adolescents in Germany, mainly based on secondary data from health insurance funds (e.g. BARMER GEK, AOK). So far, several articles on utilization of antidepressants and antipsychotics and on outpatient treatment (Pharmacotherapy and/or psychotherapy) of children and adolescents with ADHD, tic disorders, eating disorders and depression have been published.

Title Health economics of conduct disorder

Principal investigators C. Bachmann

Summary Patients with conduct disorder constitute a large portion of child and adolescent psychiatric inpatients and outpatients. For Germany, to date there is almost no data on health services utilization of this group and the resulting economic consequences. Based on health insurance data (AOK Nordost), our research evaluates health insurance expenses for these patients, also considering regional and socio-economic influencing factors.

Teaching/Research projects

Title Teaching child and adolescent psychiatry in German medical schools

Principal investigators K. Becker

Summary The current scope of teaching in the field of child and adolescent psychiatry (CAP) in German medical schools was investigated. All chairs of child and adolescent psychiatry were asked to provide detailed information on involvement in compulsory and non-compulsory medical training, scope of lectures in CAP and courses for students of other disciplines. In 25 out of 26 medical schools with a chair for CAP, the medical specialty of CAP is already

part of compulsory medical training. CAP is either taught in independent lectures or integrated in lectures on psychiatry, pediatrics and/or psychosomatics. CAP is often taught for students of other disciplines as well, e.g. psychology or education.

Title Medical education in child & adolescent psychiatry

Principal investigator C. Bachmann & T. Lempp (CAP, University of Frankfurt)

Summary It is unclear, whether the current German child and adolescent psychiatry (CAP) medical school curriculum is helpful for future primary care doctors regarding evaluation and management of children and adolescents with mental health problems. To address this question, 500 GPs and 348 pediatricians were surveyed, asking them to rate the relevance of CAP-related skills and knowledge for their daily practice.

Funded by Excellence-in-teaching award (Goethe-University Frankfurt) and research grant from Actelion Pharmaceuticals

Funding period 2014

Research Group Developmental Psychopathology

Title Neuropsychological basic deficits and developmental pathways in children at risk of developing attention deficit/hyperactivity disorder (ADHD) – The AUFMERKSAM Longitudinal Study

Principal investigators K. Becker, U. Pauli-Pott

Summary Inhibitory control and delay aversion have been supposed to underlie the complex ADHD symptoms, to be involved in their developmental trajectories, and, thereby, to moderate the effects of environmental risk factors. Empirical research on these issues is scant. We conduct a longitudinal study on the putative basic deficit-environment interactions involving 210 preschoolers (70% thereof at an increased risk of developing ADHD).

Funded by DFG – German Research Foundation

Funding period 2012 – 2015

Title Attention deficit/hyperactivity (ADHD) symptoms, eating behaviors, and body weight at age 6

Principal investigators U. Pauli-Pott & K. Becker

Summary Overweight and obesity represent serious, health threatening conditions that are prevalent already in early school-age. In this project we analyze the associations between early psychopathological symptoms, impulsive eating, physical activity, and body weight in children at primary school enrollment. The study is conducted in cooperation with the Health Department of the Marburg-Biedenkopf district (Fachbereich Gesundheit des Landkreises Marburg-Biedenkopf, Dr. B. Wollenberg, A. Schroer)

Title Psychiatric disorders in preschool years

Principal investigators I. Kamp-Becker & K. Becker

Summary There is increasing awareness in the field of child and adolescent psychiatry of the existence of psychiatric disorders in preschool-aged children. This research projects aims to evaluate diagnostic as well as therapeutic options in this age range. A standardized observation method for parent-child interaction will be developed and evaluated.

Research group Social Neuroscience

Main fields of research

Social emotions in autism spectrum disorders; neural correlates and multimodal data integration in social neuroscience of neuropsychiatric conditions;

We use fMRI, pupillometry, eyetracking, personality and behavior observation to disentangle the neural architecture of (dys)functional processes of social interaction in clinical samples (autism) and healthy controls.

Title Social interaction with human robots in Asperger syndrome

Principal investigator S. Krach & I. Kamp-Becker

Summary In cooperation with Bielefeld University (faculty of technology, faculty of linguistic) vision behaviour and dilatations of pupils during interaction with human robots were examined in patients with Asperger syndrome.

Funded by DFG – German Research Foundation

Funding period 2010 – 2013

Title Neural foundations, plasticity and regulation of embarrassment in social anxiety

Principal investigators S. Krach, B. Hanewald, S. Westermann & F. Paulus

Summary Social phobia ranges among the most often diagnosed psychiatric conditions (life-time prevalence of 8-10%). The fear of public failure and accordingly to overtly get stuck into embarrassing situations can be such strong that people with social phobia entirely avoid social interactions. In the context of neuroscientific studies the social emotion of embarrassment and its underlying neural foundations have not been studied so far. In the present project we investigate the multimodal dynamics of the embarrassment experience and try to disentangle how this process is affected in (subclinical) patients with social anxiety.

Funded by BR-Stiftung

Funding period 2012 – 2015

Title Emotion regulation and its neural correlates in the process of transition to psychosis

Principal investigators T. Lincoln (Hamburg), S. Krach & A. Jansen (Psychology, Marburg)

Summary The processes underlying transition into a first psychotic episode or relapse are not yet well understood. Although a state of heightened

emotionality precedes psychotic episodes, we do not know why individuals fail to regulate these emotions effectively. The project aims to identify difficulties in emotion regulation (ER) that constitute the unknown links between stressors, negative emotions, and psychotic symptoms in persons at risk of developing a first psychotic episode or relapse. The project involves testing the effect of different ER-strategies on emotions, psycho-physiological reactions and symptoms. In addition, functional magnetic resonance imaging (fMRI) is employed to test whether difficulties in down-regulating distressing emotions are associated with stronger activations of cortico-limbic structures including PFC and amygdala.

Funded by German Research Foundation (DFG)

Funding period 2013 – 2016

Other Research Projects

Title Transcranial direct current stimulation (tDCS) – a possible new treatment option in child and adolescent attention deficit /hyperactivity disorder (ADHD)

Principal investigators A. Sotnikova, C. Soff, K. Becker, M. Siniatchkin (Kiel)

Summary ADHD is characterized by an underactivation of the neuronal networks playing a role in the regulation of attention, executive functions and control of impulsivity. The dorsolateral prefrontal cortex is one of the main components of these networks. This study aimed to investigate a possible therapeutic influence of the anodal tDCS on the dorsolateral prefrontal cortex in order to restore the deficient neuronal activation by means of a non-invasive brain stimulation.

Funded by UKGM – University Hospital Giessen and Marburg

Funding period 2011 – 2013

Title Non suicidal self-injury with regard to resilience in a school sample.

Principal investigator(s) A. Thum, J. Pfeiffer & K. Becker

Summary Aim of this survey is to investigate the relationship between non-suicidal self-injury and resilience in adolescents. A school sample of more than 500 ninth graders of different schools and schooltypes (Haupt-/Realschule as well as Gymnasium) of Marburg-Biedenkopf district were investigated. They were asked inter alia for self-harm behaviour (using as instruments the Self-Harm-Behavior-Questionnaire and the modified Ottawa/Ulm Self-Harm Inventory MOUSI), as well as for depressive symptoms (Allgemeine Depressions-skala ADS), drug use and resilience (German translation of the Resilience Scale, RS-25). First results show that 23% of the investigated adolescents reported self-harm behavior at least

once in the past, 10% had shown self-harm behavior four times or more. Mean age of starting self-harm was about 13 years. Male adolescents started at an earlier age, whereas girls showed increased incidence of self-harm. There is a positive correlation of depressive symptoms and self-harm behavior.

Title Psychosocial Development of Adolescents with Hearing Impairment

Principal Investigators M. Pinquart (Psychology, Marburg) & J. Pfeiffer

Summary We examined psychosocial development (developmental tasks, alcohol consumption, bullying, and psychological problems) of adolescents with hearing impairment in comparison to adolescents without HI. The studies assessed 181 adolescents from schools for students with HI and 259 hearing peers from regular schools. It is concluded that adolescents with acquired deafness are in a particular need for reducing emotional and behavioral problems.

Title Psychosocial Development of Adolescents from Boarding Schools

Principal Investigators J. Pfeiffer & M. Pinquart (Psychology, Marburg)

Summary Adolescents who attend boarding schools share more time with peers than students from regular schools. This might lead to a different development (own behaviour, socialization). Therefore, we examined the development of 706 German adolescents at boarding and regular schools in a cross-sectional design. We conclude that anti-bullying-interventions are needed to help boarding schools.

Title Violent crime perpetrated by young people – results of a 13-year longitudinal study

Principal investigator H. Remschmidt

Summary 114 offenders (103 male, 11 female), whose age at the time of the offense was 17.6 ± 1.9 years (mean, standard deviation) were investigated. They underwent assessment in an overall period of nearly 31 years after taking the lives of 70 persons. In 96 cases (84.2%), a psychiatric diagnosis was made at the time of assessment; this was not the case for only 18 individuals (15.8%), 20 (17.5%) were admitted to a psychiatric hospital or drug withdrawal clinic. 44 (38.6%) developed into chronic criminal offenders who continued to commit crimes after the index offense.

Funded by Scientific Association for Child and Adolescence Psychiatry (Berlin)

Funding period 2008 – 2013

Most important publications

Pauli-Pott U, Roller A, Heinz-Gutenbrunner M, Mingeback T, Dalir S, Becker, K (2014) Inhibitory control and delay aversion in unaffected preschoolers with a positive family history of attention deficit hyperactivity disorder. *Journal of Child Psychology and Psychiatry*, 55: 1117-1124

Pauli-Pott U, Dalir S, Mingeback T, Roller A, Becker K (2013) Do different ADHD-related etiological risks involve specific neuropsychological pathways? An analysis of mediation processes by inhibitory control and delay aversion. *Journal of Child Psychology and Psychiatry* 54:800-809

Sprenger L, Bühler E, Poustka L, Bach C, Heinz-Gutenbrunner M, Kamp-Becker I, Bachmann C (2013) Impact of ADHD symptoms on Autism Spectrum Disorder Symptom Severity. *Research in Developmental Disabilities* 34:3545–3552

Bachmann C, Manthey T, Kamp-Becker I, Glaeske G, Hoffmann F (2013) Psychopharmacological treatment in children and adolescents with autism spectrum disorders in Germany. *Research in Developmental Disabilities* 34:2551–2563

John K, Becker K, Matthejat F (2013) Impact of family-oriented rehabilitation and prevention: An inpatient program for mothers with breast cancer and their children. *Psycho-Oncology*, 22:2684-2692

Pinquart M, Pfeiffer JP (2014) Change in psychological problems of adolescents with and without visual impairment. *European Child and Adolescent Psychiatry*, 23, 571–578

Nikitopoulos J, Zohsel K, Blomeyer D, Buchmann AF, Schmid B, Jennen-Steinmetz C, Becker K, Schmidt MH, Esser G, Brandeis D, Banaschewski T, Laucht M (2014) Are infants differentially sensitive to parenting? Early maternal care, DRD4 genotype and externalizing behavior during adolescence. *Journal of Psychiatric Research* 59:53-59

Schulte-Rüther M, Greimel E, Piefke M, Kamp-Becker I, Remschmidt H, Fink GR, Herpertz-Dahlmann B, Konrad K (2014). Age-dependent changes in the neural substrates of empathy in autism spectrum disorder. *Social Cognitive and Affective Neuroscience* 9:1118-1126

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419.221,03 €

Department of Psychiatry and Psychotherapy

Chair Professor T. Kircher

Professor Dr. Dr. U. Dannlowski, Professor Dr. A. Jansen, Professor Dr. C. Konrad

Main fields of research

Research group Prof. Dr. Dr. Dannlowski

Imaging in Psychiatry

The section „Imaging in Psychiatry“ investigates the neurobiology of emotions and affective disorders by using multimodal neuroimaging techniques. Affective disorders, i.e. major depressive disorder and bipolar disorder, are complex and heterogeneous phenotypes with genetic and environmental risk factors interacting in their etiology. The neurobiological mechanisms by which these risk factors exert their detrimental influence on brain structure and function are poorly understood. The aims of the section “imaging in psychiatry” are to integrate clinical and neurobiological determinants of interacting genetic and environmental risk factors involved in the etiology, onset and the course of affective disorders.

Research group Prof. Dr. Jansen

Multimodal Imaging in Cognitive Neuroscience

One of the primary research goals is to understand the basic principles underlying hemispheric lateralization. This question is addressed using multimodal imaging techniques, in particular magnetic resonance imaging, aiming at characterizing the principles of hemispheric lateralization in terms of asymmetries in brain connectivity. In the research team, there are further developed methods to improve the quality of the data acquisition, to assess the reliability of imaging data, to integrate different imaging modalities, and to advance data analysis techniques. These methods are applied in various research projects in cognitive and clinical neuroscience, for instance in the field of imaging genetics and in multicenter studies on psychiatric disorders.

Research group Prof. Dr. Kircher

Systems Neuroscience

Systems neuroscience encompasses molecular and cognitive neuroscience. Its goal is to further our understanding of the relationship between cognitive phenomena and the physical matter of the brain. Using a combination of genetics, behavioral testing, and advanced brain imaging, our cognitive neuroscience research endeavors seek to elucidate how high-level functions, such as psychopathological

phenomena, language, social and cultural behaviour, expectations and motivational states relate to specific neural networks in the brain.

Focus of research:

- Schizophrenia, affective disorders, anxiety disorders
- Neuroimaging
- Genetic imaging
- Neurobiology of Psychotherapy

Research group Prof. Dr. Konrad

Cognitive Neuropsychiatry

The main focus of the research group is the exploration of the neurobiology of affective disorders as well as mechanisms of therapy in affective disorders. Emotional and cognitive brain-functions are investigated. As methods of brain-imaging, functional and structural MRI as well as electroencephalography (EEG) are applied. The anatomy and function of the human brain, especially hippocampus, and genetic influences on the cognitive functions and brain structures are areas of special interest. Psychotherapy such as CBASP for chronic depression and CBT for anxiety orders are explored in large national cooperations.

Core-Unit Brainimaging Prof. Dr. Jansen

The Core-Unit Brainimaging is a core resource that offers technical and administrative assistance to permit scientists of the University Marburg and their collaborators to conduct human brain imaging research. This will be accomplished by offering access to state of the art imaging technology, infrastructure, and personnel assistance. We use various magnetic resonance imaging methods, including functional and structural magnetic resonance imaging, diffusion tensor imaging and magnetic resonance spectroscopy. Our highly experienced team is composed of physicists, computer scientists, and radiographers. The laboratory is equipped with a 3 T Siemens scanner, two EEG systems and various MR compatible eye-tracker systems.

Research projects

Title Language in the predictive brain: Using naturalistic stimuli to assess forward models of language processing and their neural implementation

Principal investigator(s) I. Bornkessel-Schlesewsky, T. Kircher & R. Wiese

Summary Prediction has been termed a possible unifying concept of brain function. It is also

pervasive in language, where upcoming input is anticipated at various levels (from sound to discourse). By using fMRI to examine several of these levels of prediction in naturalistic stories, this project aims to illuminate possible unified neural bases for prediction in language and beyond.

Funded by Philipps-University of Marburg (ExIn-Sondermittel)

Funding period 2012 – 2015

Title High Paternal Age as a Risk Factor for Social Deficits in Neuropsychiatric Disorders: Genes, Brain and Behavior - A Translational Approach

Principal investigator(s) R.K.W. Schwarting, T. Kircher, A. Krug, & M. Wöhr

Summary High paternal age is a risk factor for neurodevelopmental disorders such as schizophrenia. Using a rat model, effects of high paternal age on behaviors with relevance to schizophrenia-related social deficits and associated candidate genes will be examined. Such candidate genes will then be used for the characterization of genotype-dependent differences in brain activation during social tasks in healthy human subjects.

Funded by Philipps-University of Marburg (ExIn-Sondermittel)

Funding period 3 years

Title Verbundprojekt: Verbund Psychotherapie Panik BMBF multi-center project: Psychotherapy in panic disorder

Principal investigator(s) T. Kircher

Summary In context of the clinical multi-center Project, funded by the German Federal Ministry of Education and Research, fMRI data of patients with panic disorder are acquired before and after cognitive behavioural therapy (CBT). Three different paradigms have been implemented: Semantic, interoceptive and subliminal priming. We expect that the construction of new, not anxiety-related neural networks is an important component of CBT.

Funded by: BMBF – Federal Ministry of Education and Research

Funded period: 2006 – 2013

Title Core Facility for neuro-scientific research

Principal investigator(s) T. Kircher, W. Oertel & G. Heverhagen

Summary Neuroscientific research for MRI is provided and administrated by a core facility at the Dept. of Psychiatry and Psychotherapy. The core facility is responsible for scan time allocation as well as for the maintaining of technical equipment and know-how that is needed for planning, executing and evaluating neuropsychological experiments in the MRI. In this project, a position for a computer scientist is funded for 3 years.

Funded by von Behring-Röntgen Foundation

Funded period 2009 – 2013

Title Neural correlates of human-robot communication

Principal investigator(s) S. Krach, I. Kamp-Becker, B. Wrede & A. Jansen

Summary Aim of the project is to investigate healthy subjects and persons with the diagnosis of Autism Spectrum Disorders (ASD) with regard to their ability to take the perspective of another person or humanoid robot, respectively. Therefore N = 15 persons with the diagnosis of ASD will be examined by means of functional MRI, eyetracking and optotracking techniques. Forms of perspective-taking will be investigated by addressing the participants' ability to empathically feel pain of others, experience vicarious embarrassment and to maintain joint attention. These parameters will be correlated with individual differences in personality traits. First results of the current study are expected in spring 2012.

Funding by DFG – German Research Foundation

Funded period 2010 – 2013

Title Correlative imaging of molecular-genetic risk variants for schizophrenia and bipolar disorder

Principal investigator(s) A. Krug, T. Kircher & M. Rietschel

Summary In this project, effects of genetic variation, environmental effects as well as their interactions on brain activation and brain structure are investigated in patients with schizophrenia, bipolar disorder and healthy controls.

Funded by DFG – German Research Foundation

Funding period 2010 – 2015

Title The neural correlates of natural social-communicative perception in healthy subjects and patients with schizophrenia: Comprehension, detection and interpretation of verbal and non-verbal information

Principal investigator(s) T. Kircher & B. Straube

Summary Patients with schizophrenia show dysfunctional communication skills. The DFG-funded fMRI-project is focussed on three important levels of natural social communication: (1) The comprehension of non-verbal information, (2) the detection of social-affective content and (3) the interpretation of social cues. Beside the general difficulties for patients with schizophrenia, we expect symptom specific dysfunctions in the three different experimental tasks.

Funded by DFG – German Science Foundation

Funded period 2010 – 2015

Title Functional and structural connectivity of patients with schizophrenia

Principal investigator(s) T. Kircher & A. Jansen

Summary The causes of schizophrenia have been the subject of much debate. One prominent hypothesis is that alterations in both structural and functional brain connectivity are responsible for various symptoms associated with schizophrenia. In the present project we use structural and functional MR-techniques to investigate alterations of brain connectivity patterns in specific subgroups of patients with schizophrenia.

Funded by: DFG – German Research Foundation

Funded period 2011 – 2015

Title Effects of meditation on functional and structural connectivity of the brain: A combined fMRI and DTI study

Principal investigator(s) A. Jansen, J. Sommer, D. Laneri, U. Ott & B. Hölzel

Summary Little is currently known about the cerebral characteristics that underlie the complex processes of meditation. The present project combines for the first time both functional and structural MR techniques to determine simultaneously whether the practice of meditation produces structural changes in the white matter and/or in the functional network connectivity at rest. The combined results of these two approaches will show which regions of the brain are involved in meditation.

Funded by von Behring-Röntgen Foundation

Funded period 2012 – 2014

Title Neural correlates of reward anticipation in patients with Major Depression: Pathophysiological relevance and therapeutic implications

Principal investigator(s) I. Falkenberg, S. Krach, A. Nagels & T. Kircher

Summary Anhedonia is a prominent feature of Major Depressive Disorder (MDD). Previous research suggests that anhedonia may be the endophenotype of a dysfunctional mesolimbic dopaminergic reward system. The aim of this project is to promote the patients hedonic abilities by means of a specific training using humor related techniques and to characterize the effects of such training on the neural correlates of reward processing in MDD.

Funded by von Behring-Röntgen Foundation

Funded period 2011 – 2014

Title Innovative psychotherapy techniques in the maintenance therapy of Major Depression

Principal investigator(s) I. Falkenberg & A. Nagels

Summary Major Depressive Disorder (MDD) is associated with reduced stress tolerance and dysfunction of the HPA axis. The latter is related to an increased risk of depressive relapse. The aim of this study is to test the influence of a training of humor related abilities on stress tolerance, HPA

function and risk of depressive relapse in MDD.

Funded by UKGM – University Medical Centre Giessen and Marburg

Funded period 2012 – 2014

T Title Genetic variants and risk of brain structure as predictors of treatment success in recurrent depressive disorders

Principal investigator(s) A. Krug & C. Konrad

Summary In this project, genetic variation as well as brain structure in patients with major depression is investigated. The main purpose of the study is to estimate the predictive value of these variables on therapy outcome and maintenance of therapeutic effects.

Funded by UKGM – University Medical Centre Giessen and Marburg

Funded period 2010 – 2014

Title Delusions and hallucinations in patients with schizophrenia: is cognitive behavioural therapy (CBTp) or acceptance-oriented therapy (ACT) more effective in reducing positive symptoms in patients with schizophrenia?

Principal investigator(s) S. Mehl & D. Leube

Summary 80 patients with schizophrenia are included in a randomized controlled trial in order to compare the effectiveness of traditional cognitive behavioural therapy (CBTp) and acceptance-oriented therapy (ACT) in order to reduce delusions and hallucinations. First, patients psychopathological symptoms are assessed, then patients are randomized and receive either 20 individual sessions of CBT or ACT and are examined, again.

Funded by UKGM – University Medical Centre Giessen and Marburg

Funded period 2012 – 2015

Title Emotion Regulation and its Neural Correlates in the Process of Transition to Psychosis

Principal investigator(s) S. Krach, T. Lincoln, A. Jansen & S. Westermann

Summary In this project we have finished the process of fMRI paradigm development and already successfully piloted the experiments in N = 10 healthy control participants. We applied two fMRI experiments, one on the regulation of basic emotions such as fear and a second one to study the regulation of social emotions, here social exclusion. In a next step we will include patients with a diagnosis of schizophrenia in the study protocol.

Funded by DFG – German Research Foundation

Funded period: 2012 – 2015

Title Simultaneous measurement of EEG and fMRI: establishing the methodology for testing the

'dysconnectivity hypothesis' in patients with schizophrenia

Principal investigator(s) B. Straube, G. Sammer & H. Gebhardt

Summary Patients with schizophrenia show dysfunctional integration of information from different sensory channels. It has been hypothesized that this dysfunction is a result of dysconnectivity between disparate brain regions. To test this "dysconnectivity hypothesis" with temporal and spatial accuracy the project focuses on establishing the methodology for simultaneous measurement of EEG and fMRI in healthy subjects and patients with schizophrenia.

Funded by von Behring-Röntgen Foundation

Funded period 2012 – 2015

Title Neural foundations, plasticity, and regulation of embarrassment in social anxiety

Principal investigator(s) D. Krach, B. Hanewald, S. Westermann & F. Paulus

Summary In this project we develop and apply an fMRI paradigm to induce first-person feelings of embarrassment in a social interaction with other participants. In a second step we will investigate persons with social anxiety with this paradigm.

Funded by von Behring-Röntgen Foundation

Funded period 2012 – 2015

Title Neural mechanisms and predictors of affect regulation improvement induced by psychotherapy

Principal investigator(s) C. Konrad (Marburg), K. Schnell (Heidelberg) & H. Walter (Berlin)

Summary Patients undergoing two forms of psychotherapy for chronic depression (CBASP vs. supportive psychotherapy) are examined by MRI before and after therapy using paradigms reflecting unspecific, symptom-related changes and specifically targeted by CBASP. The hypotheses are tested that both groups show unspecific, symptom related changes in the first paradigms, while changes in specific paradigms will be significantly larger under CBASP-treatment.

Funded by DFG – German Research Foundation

Funded period 2010 – 2013

Title Group intervention to improve stigmatization-management competence and empowerment in psychiatric disease (STEM)

Principal investigator(s) C. Konrad (Marburg) & W. Gaebel (Düsseldorf)

Summary A group psychotherapy to improve quality of life and empowerment, to manage disease stigmatization and reduce self-stigmatization is tested in a multicenter setting, including 512 patients from 24 institutions.

Funded by BMBF – Federal Ministry of Education and Research

Funded period 2011 – 2014

Title Ultra-early relapse detection in schizophrenia: a modern approach using ecological momentary assessment and dynamic system modeling

Principal investigator(s) S. Westermann, A. Jansen & S. Krach

Summary The successful development and setup of the technical infrastructure (ecological momentary assessment, text messaging webservice, etc.) was followed by a pilot study with N=31 healthy participants, which revealed associations between the dynamics of emotionality and non-clinical positive symptoms. Currently, the main pilot study with patients with a diagnosis of schizophrenia is underway.

Funded by UKGM – University Medical Centre Giessen and Marburg

Funding period 2013 – 2015

Title Imaging Epigenetics - Assoziation epigenetischer Marker mit limbischer Responsivität auf aversive Stimuli

Principal investigator(s) U. Dannlowski

Summary The study aims at investigating the neurobiological underpinnings of DNA methylation at the 5-HTT and BDNF gene in a healthy human sample using functional and structural MRI. First results show a strong association of methylation rates at the 5-HTT gene and hippocampal volumes. The data suggest that epigenetic processes alter brain structure with relevance to psychiatric disorders such as major depression.

Funded by UKGM – University Medical Centre Giessen and Marburg

Funding period 2013 – 2015

Title Longitudinal study on brain structure and function in patients with major depression and healthy subjects

Principal investigator(s) A. Krug & C. Konrad

Summary Within this project, a sample of healthy subjects and patients with major depression is to be re-investigated three years after initial investigation. All subjects are being scanned with structural and functional MRI and these measures will be correlated with course of illness, genetic and environmental risk factors. In 2014, 71 subjects were re-investigated.

Funded by von Behring-Röntgen Foundation

Funding period 2014 – 2017

Title The dysconnectivity hypothesis of schizophrenia: Determination of test-retest reliability of fMRI paradigms

Principal investigator(s) A. Jansen & S. Westermann

Summary Functional imaging paradigms that are used in clinical cohorts should yield robust activation

and tap into cognitive and affective processes that are important for the understanding of the clinical disorder. A further important aspect, in particular with regard to the longitudinal aspect of the study design, is the reliability of brain activation measures. In the present project, we aim to further understand how the reliability of fMRI imaging markers can be improved.

Funded by Else Kröner-Fresenius Foundation
Funding period 2013 – 2016

Title Neural processes of social interaction in people with genetic and environmental risk factors for schizophrenia

Principal investigator(s) T. Kircher & B. Straube

Summary Social categorization mediates behaviour during interpersonal interaction. The neural processes and the interaction of these environmental factors with genetic risk for schizophrenia has not yet been explored. In this project the influence of environmental (immigration status) and genetic risk factors (relatives of patients with schizophrenia) for schizophrenia on neural mirror neuron and Theory of Mind (ToM) networks will be investigated.

Funded by DFG (KI588 16-1) – German Research Foundation

Funding period 2014 – 2017

Title Neural processes of social interaction in people with genetic and environmental risk factors for schizophrenia

Principal investigator(s): B. Straube, T. Kircher

Summary: Social categorization mediates behaviour during interpersonal interaction. The neural processes and the interaction of these environmental factors with genetic risk for schizophrenia has not yet been explored. In this project the influence of environmental (immigration status) and genetic risk factors (relatives of patients with schizophrenia) for schizophrenia on neural mirror neuron and Theory of Mind (ToM) networks will be investigated.

Funded by DFG (STR 1146/4-1) – German Research Foundation

Funding period 2014 – 2017

Title Intermodal integration of perception of one's own actions – Cardinal mechanisms of perception: Prediction, valuation, categorization (Coordinator: Prof. Dr. Karl Gegenfurtner)

Subproject A3: Predictive perception: multisensory consequences of one's own actions

Principal investigator(s) T. Kircher, D. Leube & B. Straube

Summary The investigations will focus on three different aspects of predictive mechanisms relevant

for the perception of the multisensory consequences of one's own actions. 1) supramodal vs. unimodal effects of action-sensory feedback matching processing, 2) the neural correlates of supramodal predictive mechanisms and their consequences and, 3) predictive mechanisms during tool-use actions and the perception of related multisensory consequences.

Funded by DFG SFB/TR 135 TP A3 – German Research Foundation, Transregional Collaborative Research Centre

Funding period 2014 – 2017

Title International Research Training Group (IRTG) "The Brain in Action"

Principal investigator(s): T. Kircher

Summary This project is focused on the neural systems and processes that underlie perception and action in everyday living. Especially predictive mechanisms for the multisensory perception of action consequences as well as multisensory integration processes are investigated to understand how we perceive and adequately interact with the world.

Funded by DFG (GRK 1901/1) – German Research Foundation

Funding period 2013 – 2018

Title Science and Development Contract

Principal investigator(s) T. Kircher

Summary Variations in specific genetic polymorphisms might contribute to neurophysiological differences and therapeutic outcomes within subgroups of patients with panic disorder and agoraphobia. Here, we test this hypothesis by combining genetic with behavioural techniques and neuroimaging in a clinical multicentre trial, where patients receive 12 sessions of manualized cognitive-behavioural therapy and were genotyped for specific candidate genes.

Funded by BMBF

Funding period 2013 – 2014

Title Social Networks and the Brain

Principal investigator(s) J. Sommer & P. Kenning

Summary Social Network Sites (SNS) play a major role in modern technology-bounded societies. Fostering connectivity in SNS is essential for achieving individual benefits such as enhanced information access. The effects of taking part in social networks are under investigation.

Funded by Zeppelin University Friedrichshafen

Funding period until depletion of funding

Title Integrative analyses of genetic, epigenetic and environmental risk-factors of affective disorders

Principal investigator(s) A. Krug, M. Rietschel, S. Witt & M. Nöthen

Summary Within this FOR, a large sample of healthy subjects and different patient groups is being investigated. This sub-project will perform genome-wide genotyping, methylation analyses etc. As the sample is being investigated at the moment within WP1, no analyses have been performed yet.

Funded by DFG (FOR 2107) – German Research Foundation, Research Unit

Funding period 2014 – 2017

Title Methodological aspects of longitudinal imaging genetics MRI studies: reliability, quality assurance, statistical genetics and genetic epidemiology

Principal investigator(s) A. Jansen, A. Dempfle

Summary Within this FOR, a large sample of healthy subjects and different patient groups is being investigated. This sub-project will perform genome-wide genotyping, methylation analyses etc. As the sample is being investigated at the moment within WP1, no analyses have been performed yet.

Funded by DFG (FOR 2107) – German Research Foundation, Research Unit

Funding period 2014 – 2017

Title Dissecting the neurobiology in the course of affective disorders – the Marburg affective disorders cohort study (MACS)

Principal investigator(s) U. Dannlowski, C. Konrad & T. Kircher

Summary This Project constitutes the human backbone study of the DFG-research group. N=2500 human subjects (N=1000 patients suffering from affective disorders, N=1000 healthy subjects, N=500 subjects at risk) will be recruited in a longitudinal design and will undergo 1. Functional and structural magnetic resonance imaging, 2. Biomaterial assessment, 3. Deep clinical phenotyping. Follow-up sessions are scheduled 2 years after first participation.

Funded by DFG (FOR 2107, WP 1) – German Research Foundation, Research Unit

Funding period 2014 – 2017

Title Management and Administration

Principal investigator(s) T. Kircher, K. Konrad & U. Dannlowski

Summary Core project 2 (CP2) constitutes the administrative and coordinative core of the FOR 2107. The main objectives are administration and coordination, organization of meetings and public relations. For example, CP2 organises administrative contacts, manages and assigns rotational positions (GEROK), organizes meetings, conferences, and an annual research retreat. Public visibility of the FOR and transfer of research results will be granted by CP2.

Funded by DFG (FOR 2107, CP2) – German Research Foundation, Research Unit

Funding period 2014 – 2017

General information about the institute

Research funding 1.458.627,69 €

Most important publications

Lueken U, **Straube B**, **Konrad C**, Wittchen HU, Ströhle A, Wittmann A, Pfeleiderer B, Uhlmann C, Arolt V, **Jansen A**, Deckert J, **Kircher T** (2013) Neural Substrates of Treatment Response to Cognitive-Behavioral Therapy in Panic Disorder With Agoraphobia. *American Journal of Psychiatry* 170:1345-1355

Kircher T, Arolt V, **Jansen A**, Pyka M, Reinhardt I, Kellermann T, Konrad C, Lueken U, Gloster A, Gerlach AL, Ströhle A, Wittmann A, Pfeleiderer B, Wittchen HU, **Straube B** (2013) Effect of cognitive behavioural therapy on the neural correlates of fear conditioning in panic disorder. *Biological Psychiatry* 73:93-101

Krug A, **Krach S**, **Jansen A**, Nieratschker V, Witt SH, Shah NJ, Nöthen MM, Rietschel M, **Kircher T** (2013) The effect of Neurogranin on neural correlates of episodic memory encoding and retrieval. *Schizophrenia Bulletin* 39:141-150

Straube B, Lueken U, **Jansen A**, **Konrad C**, Gloster AT, Gerlach AL, Ströhle A, Wittmann A, Pfeleiderer B, Gauggel S, Wittchen HU, Arolt V, **Kircher T** (2014) Neural correlates of procedural variants in cognitive behavioral therapy: A randomized, controlled multicentre fMRI study. *Psychotherapy and Psychosomatics* 83:222-233

Mehl S, Landsberg MW, Schmidt AC, Cabanis M, Bechdorf A, Herrlich J, Loos-Jankowiak S, **Kircher T**, Kiszkenow S, Klingberg S, Kommescher M, Moritz S, Sartory G, Müller BW, Wiedemann G, Wittorf A, Wölwer W, Wagner M (2014) Why do bad things happen to me? Attributional style, depressed mood, and persecutory delusions in patients with schizophrenia. *Schizophrenia Bulletin* 40:1338-1346

Straube B, Green A, Sass K, **Kircher T** (2014) Superior temporal sulcus disconnectivity during processing of metaphoric gestures in schizophrenia. *Schizophrenia Bulletin* 40:936-944

Opel N, Redlich R, Zwanzger P, Grotegerd D, Arolt V, Heindel W, **Konrad C**, Kugel H, **Dannlowski U** (2014) Hippocampal Atrophy in Major Depression-a Function of Childhood Maltreatment Rather Than Diagnosis? *Neuropsychopharmacology* 39:2723-2731

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Tilo Kircher

Department of Oral and Maxillofacial Surgery, Oral Surgery and Implantology

Chair Professor A. Neff

Professor C. Knabe-Ducheyne – Endowed Professorship of Experimental Orofacial Medicine

The Endowed Professorship of Experimental Orofacial Medicine has an equal association with the Dept of Prosthodontics and the Dept. of Maxillofacial Surgery.

Dept. of Prosthodontics (U. Lotzmann) and Oral and Maxillofacial Surgery (Professor A. Neff)

Department of Oral and Maxillofacial Surgery

Main fields of research

Development and evaluation of innovative osteosynthesis procedures (endoscopic assistance, condylar process and head fractures), TMJ disorders and chronic pain, bisphosphonate associated osteonecrosis (BRONJ) and osteonecrosis after irradiation (ORN), speech improvement in cleft patients, bone microsection and bone histochemistry, mandibular tumor invasion

Research projects

Title pN1-study: efficacy of postoperative irradiation in patients with squamous cell carcinomas of the mouth or oropharynx and simultaneously secured solitary ipsilateral lymph node metastasis (pN1) - a multi-centre clinical study

Principal investigator(s) Mainz, Berlin, Hamburg, Regensburg, Gießen, Marburg, Frankfurt, Tübingen, Heidelberg, Rostock, Düsseldorf, Lübeck, Ulm, Wien

Summary Objective: assessment of the benefit of postoperative irradiation in patients with SCC. Patient selection: pT1 or pT2 tumours of the oral cavity and oropharynx with histological verification of a singular ipsilateral lymph node metastasis (pN1) and after R0-resection, are divided into two groups (irradiation vs wait and see), then the survival time is measured.

Title Surgical versus conservative therapy in head fractures of the mandible - a multi-centre study

Principal investigator(s) Berlin, Dresden, Innsbruck, Leeds, Marburg, Oxford, Wien

Summary Objective: assessment of conservative versus surgical therapy options in condylar head fractures. Conservative treatment of head fractures is associated with a high rate of malfunction and adverse late sequelae. Surgical therapy has not been shown to be efficient in a randomized study yet. This first multicenter study compares the functional and

subjective outcome parameters after surgical or conservative treatment.

Title Efficacy and mechanisms of biofeedback based behavioural therapy compared to dental splint therapy in the treatment of craniomandibular disorders

Principal investigator(s) A. Neff, U. Lotzmann (Dental School) & U. Rief (Clinical Psychology)

Summary This prospective randomized study deals with the interdisciplinary evaluation of specific therapy approaches in craniomandibular dysfunction (CMD) and evaluates the therapeutic standard options and their interdisciplinary combination. First results show profits for patients with muscle pain in a biofeedback setting.

Title Laser-enhanced cytotoxicity of zoledronic acid and cisplatin on primary human fibroblasts and head and neck squamous cell carcinoma cell line UM-SCC-3

Principal investigator(s) Heymann PG, Mandic R, Kämmerer PW, Kretschmer F, Saydali A, Neff A, Draenert FG

Summary The purpose of this study was to investigate the combination of laser therapy with chemotherapy. Fibroblasts and tumour cells were treated with zoledronic acid or cisplatin and irradiated with a laser. Cell viability was tested by XTT. Irradiation alone increased bioviability, but under chemotherapy it lowered viability significantly. In conclusion, radiation is able to raise the cytotoxicity of chemotherapeutic drugs.

Funded by Research Foundation Dental e. V.

Funding period 2013 – 2014

Title Development of a floor of the mouth squamous cell carcinoma rabbit animal model

Principal investigator(s) R. Mandic, Dept. of ENT, C. Knabe-Ducheyne, Dr. Bette, Dept. of Anatomy & Dr. P. Heymann, Dept. of Oral and Maxillofacial Surgery

Summary This pilot study seeks to establish a floor of the mouth squamous cell carcinoma rabbit animal model.

Most important publications

Hansen PJ, Knitschke M, Draenert FG, Irle S, Neff A (2013) Incidence of bisphosphonate-related osteonecrosis *Clin Oral Invest* 17(8):1829-37

Shedden Mora MC, Weber D, **Neff A ***, Rief W * (2013) Biofeedback-based cognitive behavioral treatment *Clin J Pain* 29(12):1057-65, *shared senior authorship

Makarova G, Bette M, Schmidt A, Jacob R, Cai C, Rodepeter F, Betz T, Sitterberg J, Bakowsky U, Moll R, **Neff A**, Sesterhenn A, Teymoortash A, Ocker M, Werner JA, Mandic R (2013) Epidermal growth factor-induced modulation of cytokeratin expression levels influences the morphological phenotype of head and neck squamous cell carcinoma cells. *Cell Tissue Res* 351(1):59-72

Neff A, Chossegros C, Blanc JL, Champsaur P, Cheynet F, Devauchelle B, Eckelt U, Ferri J, Gabrielli MF, Guyot L, Koppel DA, Meyer C, Müller B, Peltomäki T, Spallaccia F, Varoquaux, , Wilk A, Pitak-Arnop P (2014) Position paper from the IBRA Symposium on Surgery of the Head - The 2nd International Symposium for Condylar Fracture Osteosynthesis, Marseille, France 12. *J Craniomaxillofac Surg* 67:292-304

Heymann PG, Mandic R, Kämmerer PW, **Kretschmer F**, **Saydali A**, **Neff A**, **Draenert FG** (2014) Laser-enhanced cytotoxicity of zoledronic acid and cisplatin on primary human fibroblasts and head and neck squamous cell carcinoma cell line UM-SCC-3. *J Craniomaxillofac Surg* 42(7):1469-74

Wang S, Wang X, **Draenert FG**, Albert O, Schröder HC, Mailänder V, Mitov G, Müller WE (2014) Bioactive and biodegradable silica biomaterial for bone regeneration. *Bone* 67C:292-304

Bhattacharyya S, Agrawal A, **Knabe C**, Ducheyne P (2014) Sol-gel silica controlled release thin films for the inhibition of methicillin-resistant *Staphylococcus aureus*. *Biomaterials* 35(1):509-17

Stiller M, Kluk E, Bohner M, **Lopez-Heredia MA**, Müller-Mai C, **Knabe C** (2014) Performance of β -tricalcium phosphate granules and putty, bone grafting materials after bilateral sinus floor augmentation in humans. *Biomaterials* 35(10):3154-63

Research funding

217,511.16 €*

*The funding obtained for instituting the Endowed Professorship of Experimental Orofacial Medicine has been raised by the Departments of Prosthodontics and Maxillofacial Surgery (50% each, i.e. 100,000 € annually).

Endowed Professorship of Experimental Orofacial Medicine – Professor C. Knabe-Ducheyne

Main fields of research

Regenerative medicine, bone regeneration, bioactive calcium phosphate bone grafting materials, bone-tissue engineering utilizing resorbable calcium alkali phosphate scaffolds produced by 3D printing, mesenchymal stem cell and microvascular techniques, moldable calcium alkali phosphate bone grafting cements, individualized medicine, antibacterial & bactericidal implant materials

Research projects

Title Rapidly resorbable calcium alkali orthophosphate scaffolds for bone tissue engineering.

Principal investigator(s) C. Knabe & Dr. G. Berger, Federal Institute for Materials Research and Testing, Berlin

Summary The objective of this project is to develop an adequate approach for regenerating large segmental bone defects. To this end, three dimensional scaffolds with varying porosity are fabricated from rapidly resorbable calcium alkali orthophosphates by 3 D printing or applying the Schwarzwald-Somers technique which utilizes combustible polyurethane foam templates. In a first step the material and the printing process are optimized. Mesenchymal stem cells are then cultured on these scaffolds for two weeks under perfusion. Subsequently the scaffolds are implanted in segmental defects in the rat femur in conjunction with a microvascular surgical technique in order to achieve adequate vascularization, which is of paramount importance when regenerating segmental defects.

Funded by German Research Foundation-KN 377/8-1, Federal Institute for Materials Research and Testing

Funding period 2011 – 2015

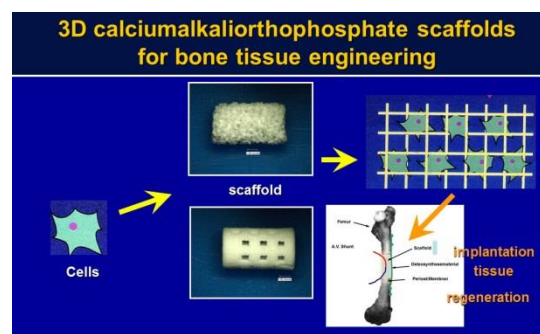


Fig. 1 Tissue engineering approach and animal model using 3 D scaffolds and mesenchymal stem for regeneration of segmental defects in the rat femur



Fig. 2 Animal model using 3 D scaffolds and mesenchymal stem cells for regeneration of segmental defects in the rat femur in combination with a microvascular technique

Title The effect of hormone status on bone regeneration after sinus floor augmentation with porous tricalcium phosphate particles

Principal investigator(s) C. Knabe & PD. Dr. Dr. M. Stiller, Charité University Medical Center Berlin

Summary This study elucidates the effect of age, BMI and gender related parameters such as hormone status on bone regeneration after sinus floor augmentation with porous tricalcium phosphate particles in humans.

Funded by Robert Mathys Foundation

Funding period 2008 – 2014

Title BioMin II – Biofunctionalized calcium phosphate surfaces: adsorption mechanisms of bone morphogenetic proteins to the surfaces of calcium phosphate bone grafting materials

Principal investigator(s) C. Knabe & PD Dr. Ch. Müller-Mai, Medical Faculty, University Bochum

Summary This study evaluates the effect of bone morphogenetic proteins, which are adsorbed onto the surface of bioactive glass 45S5 cylinders, on bone osteoblast differentiation and bone formation after implantation in the rabbit femur.

Funded by Federal Ministry for Research and Technology

Funding period 2011 – 2014

Title Effect of various tricalcium calcium phosphate-based mesh and paste-like bone grafting materials on osteogenesis and bone regeneration after implantation in critical-size defects in the sheep scapula

Principal investigator(s) C. Knabe

Summary This study evaluates the effect of various tricalcium calcium phosphate-based mesh and paste-like bone grafting materials on osteoblast differentiation and bone regeneration after implantation in critical-size defects in the sheep scapula.

Funded by Corporate Sponsor, Curasan

Funding period 2013 – 2014

Title BioMimetic Bone - Biofunctionalized calcium phosphate scaffolds for fracture repair - Histologic evaluation.

Principal investigator(s) C. Knabe-Ducheyne & PD Ch. Dr. Müller-Mai, Medical Faculty, University Bochum

Summary This study evaluates the effect of tricalcium phosphate based scaffolds to whose surface bone morphogenetic proteins are adsorbed on bone regeneration of segmental defects after implantation in the rabbit ulna.

Funded by Federal Ministry for Research and Technology

Funding period 2012 – 2014

Title Effect of a silica containing calcium alkali orthophosphate ceramic as compared to silicon doped tricalcium phosphate on bone formation and osteogenic marker expression after sinus floor augmentation in humans."

Principal investigator(s) C. Knabe & Dr. Stiller

Summary This study evaluates the effect of a silica containing calcium alkali orthophosphate ceramic as compared to silicon doped tricalcium phosphate on bone formation and osteogenic marker expression after sinus floor augmentation in humans.

Funded by Zimmer Foundation

Funding period 2013 – 2014

Title Effect of silk-based periodontal membranes on guided bone regeneration

Principal investigator(s) C. Knabe

Summary This study evaluates the effect of a silk-based periodontal membranes on bone formation and osteogenic marker expression after implantation in an rabbit calvarial defect model.

Funded by Corporate Sponsor, BLS Preclinical Services

Funding period 2011 – 2013

Title Infected fractures – Treatment and Mitigation of Biofilm Formation

Principal investigator(s) C. Knabe & Prof. Paul Ducheyne, Dept. of Bioengineering, University of Pennsylvania, Dr. J. Garino, Dept. of Orthopaedic Surgery, University of Pennsylvania

Summary This study evaluates the efficacy of bactericidal sol-gel coatings on intramedullary fracture fixation pins with controlled release of vancomycin for preventing infection in a sheep model after inoculation with *Staph. aureus*.

Funded by US Department of Defense

Funding period 2010 – 2013

Title Preclinical Testing of Microparticle Ceramic Urethral Bulking Agents in a rat model

Principal investigator(s) P. Zvara, Dept. of Surgery / Urology, University of Vermont, C. Knabe-Ducheyne, Philipps University Marburg, A. El-Ghannam, Dept. of

Mechanical Engineering and Engineering Science,
The University of North Carolina at Charlotte

Summary This study evaluates the efficacy of micro particle ceramic urethral bulking agents in a rat model

Funded by University of Vermont

Funding period 2014 – 2015

Title Bone Tissue Engineering in Implant Dentistry

Principal investigator(s) C. Knabe-Ducheyne

Summary The objective of this project is to develop an adequate approach for regenerating large segmental bone defects. To this end, three dimensional scaffolds with varying porosity are fabricated from rapidly resorbable calcium alkali orthophosphates by 3 D printing or applying the Schwarzwald-Somers technique which utilizes combustible polyurethane foam templates. In a first step the material and the printing process are optimized. Mesenchymal stem cells are then cultured on these scaffolds for one to two weeks under perfusion and the cellular response is characterized. Subsequently the scaffolds are implanted in segmental defects in the rat femur in conjunction with a microvascular surgical technique in order to achieve adequate vascularization, which is of paramount importance when regenerating segmental defects.

Funded by DAAD – German Academic Exchange Service

Funding period 2014

Title Development of a floor of the mouth squamous cell carcinoma rabbit animal model

Principal investigator(s) R. Mandic, Dept. of ENT, C. Knabe-Ducheyne, Dr. Bette, Dept. of Anatomy & Dr. P. Heymann, Dept. of Oral and Maxillofacial Surgery

Summary This pilot study seeks to establish a floor of the mouth squamous cell carcinoma rabbit animal model.

Title The effect of tricalcium phosphate ceramic particles and a tricalcium phosphate hyaluronic acid-based putty bone grafting material on bone regeneration after sinus floor augmentation using a split mouth design

Principal investigator(s) C. Knabe & PD Dr. M. Stiller, Charité University Medical Center Berlin

Summary This study elucidates the effect of tricalcium phosphate ceramic bone grafting particles and a tricalcium phosphate hyaluronic acid-based putty bone grafting material on bone regeneration and volume stability of the grafted area after sinus floor augmentation in human using a split mouth design.

Funded by Robert Mathys Foundation

Funding period 2009 – 2013

Most important publications

Stiller M, Kluk E, Bohner M, **Lopez-Heredia MA**, Müller-Mai C, **Knabe C** (2014) Performance of β -tricalcium phosphate granules and putty, bone grafting materials after bilateral sinus floor augmentation in humans. *Biomaterials* 35(10):3154-63

Bhattacharyya S, Agrawal A, **Knabe C**, Ducheyne P (2014) Sol-gel silica controlled release thin films for the inhibition of methicillin-resistant *Staphylococcus aureus*. *Biomaterials* 35(1):509-17

Qu H, **Knabe C**, Burke M, Radin S, Garino J, Schaer T, Ducheyne P (2014) Bactericidal micron-thin sol-gel films prevent pin tract and periprosthetic infection. *Mil Med* 179(8 Suppl):29-33

Qu H*, **Knabe C***, Radin S, Garino J, Ducheyne P. Percutaneous external fixator pins with bactericidal micron-thin sol-gel films for the prevention of pin tract infection. *Biomaterials* in press

*authors have contributed equally

Knabe C, **Lopez Heredia MA**, Barnemitz D, Genzel A, Peters F, Hübner WD (2014) Effect of silicon-doped calcium phosphate bone substitute materials on bone formation and osteoblastic phenotype expression in vivo. *Key Engineering Materials* 614:31-14

Lopez-Heredia MA, Barnewitz D, Genzel A, Stiller M, Peters F, Huebner W-D, Stang B, Kuhr A, **Knabe C** (2014) In vivo osteogenesis assessment of a tricalcium phosphate paste and a tricalcium phosphate foam bone grafting materials. *Key Engineering Materials* 631:426-429

Mann-Gow TK, Blaivas JG, King BJ, El-Ghannam A, **Knabe C**, Lam MK, Kida M, Sikavi CS, Plante MK, Krhut J, Zvara P. Rat animal model for preclinical testing of microparticle urethral bulking agents. *Int J Urol* in press

Research funding

260,872.73 €

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Phone:++49 (0) 6421-58 61784

Prof. Christine Knabe-Ducheyne

Department of Orthodontics

Chair Professor H. M. Korbmacher-Steiner

Main fields of research

- Relation of form and function
- Effects of RME (wanted and unwanted)
- Enamel conditioning, sealing and bonding
- New strategies of bracket bonding techniques
- Impact of orthodontic therapy on cervical spine posture
- 3D-Evaluation of CBCT including superimpositioning

Research Projects

Title Laboratory evaluation of toothbrush / toothpaste abrasion resistance after smooth enamel surface sealing

Principal investigator(s) H. M. Korbmacher-Steiner, A. Hellak & M. Schauseil

Title Density of the midpalatal suture after RME treatment - a retrospective comparative low-dose CT-study

Principal investigator(s) H. M. Korbmacher-Steiner, A. Hellak & M. Schauseil

Title Einfluss der chirurgisch unterstützten Hyrax-GNE und Hybrid-GNE auf die Weichteil-Morphologie der Nase – eine prospektive 3D RCT-Studie

Principal investigator(s) H. M. Korbmacher-Steiner, A. Hellak & M. Schauseil

Title Influence of RME treatment on the postpubertal midpalatal suture – a comparative Low-Dose CT-study on sufficient retention time

Principal investigator(s) H. M. Korbmacher-Steiner, A. Hellak & M. Schauseil

Title Einfluss unterschiedlicher Methoden des interproximalen Polishings auf das Demineralisationsverhalten des Zahnschmelzes

Principal investigator(s) H. M. Korbmacher-Steiner, A. Hellak & M. Schauseil

Title Einfluss der Hybrid-GNE versus der konventionellen GNE auf die Hart- und Weichteilveränderungen der Nase – eine retrospektive 3D Low-Dose-CT Studie an einem postpubertalen Patientenkollektiv

Principal investigator(s) H. M. Korbmacher-Steiner, A. Hellak & M. Schauseil

General information about the institute

Research funding 2.343,60 €

Most important publications

Laboratory evaluation of toothbrush/toothpaste abrasion resistance after smooth enamel surface sealing (2013) *Clin Oral Investig*

Therapeutic effects of functional orthodontic appliances on cervical spine posture: a retrospective cephalometric study (2014) *Head Face Med*

Density of the midpalatal suture after RME treatment - a retrospective comparative low-dose CT-study (2014) *Head Face Med*

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Georg-Voigt-Str. 3, 35039 Marburg

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Director: Professor Heike Korbmacher-Steiner

Department of Periodontology

Chair Professor N. Arweiler

Main fields of research

In the frame of infection biology and infection control, microbiology of the oral cavity and the influence of systemic diseases on oral health are examined clinically, radiologically and immunologically. Health services research deals with the primary and secondary care as well as the prevention of periodontal and perimplant disease especially aggressive forms. Especially new antibacterial agents and oral hygiene in vitro or clinically tested.

Research projects

Title The effect of different cleaning modalities on biofilm and inflammation in maintenance care of dental implants

Principal investigator(s) N. Arweiler

Summary Biofilm formation and inflammation is the main factor for peri-implant diseases and failures. Due to similarities to periodontitis, similar treatment principles are suggested. However their effect on surface characteristics of implants has not yet investigated clinically. Possibly treatment can harm or roughen the surface of teeth or implants and promotes biofilm formation. Recent findings – however on teeth - showed that after instrumentation with different curettes a rougher surface did not enhance microbial adhesion but lead to an improved attachment of PDL fibroblasts. So the aim of the study is to investigating three different treatment modalities and a control on clinical, microbial and immunological parameter.

Funded by Grant from Camlog Foundation

Funding period 2012 – 2014

Title In vitro-Study to evaluate the antibacterial effect of Salviacur in comparison to a control solution and chlorhexidine (0.2%) on an established ex vivo plaque biofilm

Principal investigator(s) N. Arweiler

Summary Aim of the in vitro study was the first evaluation of an antibacterial effect of a new dental, antibacterial gel in comparison to a control/saline solution and chlorhexidine.

Funded by Rottapharm, Madaus GmbH D-51101 Köln

Funding period 2014

Title Double-blind, prospective, randomized, clinical cross-over study to evaluation the plaque reducing and antibacterial effect of a new dental gel

(Salviatop®) compared to another gel (Parodur®) and a chlorhexidine mouthrinse (Meridol®med CHX 0,2%)

Principal investigator(s) N. Arweiler

Summary Aim of the blinded, randomized, four-cell, crossover study was the clinical evaluation of the antibacterial effect of a new dental, antibacterial gel in comparison to another gel (Parodur®) and a chlorhexidine mouthrinse (Meridol®med CHX 0,2%) solution. In a 4 day plaque regrowth study 24 subjects refrained from all oral hygiene measurements for the following 96 hours and applied instead one of the gels or rinsed with the chlorhexidine solution.

Funded by Rottapharm, Madaus GmbH D-51101 Köln

Funding period 2014 – 2015

Title Antibacterial effect and substantivity of toothpaste slurries in vivo

Principal investigator(s) N. Arweiler

Summary The aim of this blinded, randomized, four-cell, crossover study was to assess the antibacterial effect and substantivity of toothpastes applied as slurries on established dental biofilms over 24h.

Meridol® toothpaste was compared to a benchmark toothpaste and a positive and negative control after a single application on mature biofilm over an observation period of 24 hours. For this purpose, twenty-four subjects were selected to participate in four test cycles. For each test cycle the subjects were requested to discontinue all oral hygiene measures for a period of 48 hours. The participants were then required to rinse their mouth for one minute with one of the randomly allocated test or control solutions. A plaque sample was taken from a defined pair of teeth every second hour up to 14 hours as well as 24 hours after application of the test product. Vital staining of the sample was performed each time to assess the vitality of the bacterial biofilm.

Funded by GABA International AG, 4106 Therwil, Switzerland

Funding period 2014

Title In situ evaluation of the antibacterial effect of different restorative materials on in situ biofilm formation: A controlled clinical study

Principal investigator(s) T. M. Auschill & N. Arweiler

Summary The purpose of the clinical study was to investigate the influence of different composite materials as well as glass-ionomer cements on the in situ biofilm formation using an intraoral splint model

and to compare it to enamel. Vitality of the biofilm as well as plaque coverage of the slabs was examined after 72 biofilm development

Funded by VOCO GmbH, Cuxhaven, Germany

Funding period 2014 – 2015

Title Effectivity and immunological mechanism of photodynamic therapy on oral lichen planus

Principal investigator(s) R. Cosgarea, N. Arweiler & M. Hertl

Summary Lichen planus (LP) is an inflammatory disease, which shows characteristic clinical and histopathological features and involves skin and various mucous membrane. Although LP is known to be triggered by various factors, including drugs, viruses and oral metals, pathogenic mechanisms is still unknown. Oral mucosal lesions of LP are called oral LP (OLP) and are characterized clinically by erythemas and reticular lace-like whitish coating with erosions and ulcers on the oral mucosa and lips, and histopathologically by massive infiltrates of lymphocytes beneath basement membrane zone (BMZ). OLP is occasionally intractable to various treatments, including topical steroids, topical antifungals, various types of gurgles and oral health care, however none of these approaches can so far resolve these inflammatory lesions. The photodynamic therapy (PDT) could be a treatment option but is relatively unknown. The study includes 24 patients suffering from OLP and receiving 5 treatment applications of PDT. Both clinical and immunohistological parameters will be assessed before and after PDT-treatment.

Funded by UKGM – University Hospital Giessen and Marburg

Funding period 2014

Arweiler NB, Pietruska M, Pietruski J, Skurska A, Dolińska E, Heumann C, **Auschill TM**, Sculean A (2014) Six-month results following treatment of aggressive periodontitis with antimicrobial photodynamic therapy or amoxicillin and metronidazole. *Clin Oral Investig* 18(9):2129-35

Netuschil L, **Auschill TM**, Sculean A, **Arweiler NB** (2014) Confusion over live/dead stainings for the detection of vital microorganisms in oral biofilms--which stain is suitable? *BMC Oral Health* 14:2

Arweiler NB, **Netuschil L**, Beier D, Grunert S, Heumann C, Altenburger MJ, Sculean A, Nagy K, Al-Ahmad A, **Auschill TM** (2014) Action of food preservatives on 14-days dental biofilm formation, biofilm vitality and biofilm-derived enamel demineralisation in situ. *Clin Oral Investig* 18(3):829-38

Bassetti M, Schär D, Wicki B, Eick S, Ramseier CA, **Arweiler NB**, Sculean A, Salvi GE (2014) Anti-infective therapy of peri-implantitis with adjunctive local drug delivery or photodynamic therapy: 12-month outcomes of a randomized controlled clinical trial. *Clin Oral Implants Res* 25(3):279-87

Polonyi M, Prenninger N, **Arweiler NB**, Haririan H, Winklehner P, Kierstein S (2013) Assessment of viable periodontal pathogens by reverse transcription quantitative polymerase chain reaction. *J Periodontol Res* 48(5):671-6

Döri F, **Arweiler N**, Húszár T, Gera I, Miron RJ, Sculean A (2013) Five-year results evaluating the effects of platelet-rich plasma on the healing of intrabony defects treated with enamel matrix derivative and natural bone mineral. *J Periodontol* 84(11):1546-55

General information about the institute

Research funding 188.463,46 €

Most important publications

Auschill TM, Schmidt KE, **Arweiler NB** (2014) Resin Infiltration for Aesthetic Improvement of Mild to Moderate Fluorosis: A Six-month Follow-up Case Report. *Oral Health Prev Dent* 2014 Sep 18. doi: 10.3290/j.ohpd.a32785

Sculean A, **Cosgarea R**, Stähli A, Katsaros C, **Arweiler NB**, Brex M, Deppe H (2014) The modified coronally advanced tunnel combined with an enamel matrix derivative and subepithelial connective tissue graft for the treatment of isolated mandibular Miller Class I and II gingival recessions: a report of 16 cases. *Quintessence Int* 45(10):829-35

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Director: Professor Nicole Arweiler

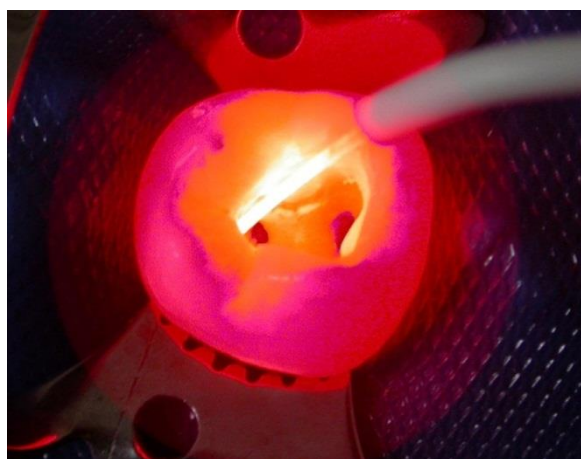
Department of Operative Dentistry and Endodontics

Chair Professor Dr. R. Frankenberger
Professor Dr. A. Braun, Dr. M. J. Roggendorf

Main fields of research

Operative Dentistry

- a. Preclinical laboratory evaluation of dental biomaterials for restorative techniques: Artificial mouth simulation of resin composite materials, glass ionomer cements, postendodontic restoratives and techniques in order to predict their clinical behavior. Analyses using scanning electron microscopy.
- b. Randomized prospective clinical long-term trials as university based expert studies or practice based research investigations nationwide.
- c. Laser Dentistry (caries diagnosis and treatment Fig. 1).



Laser irradiation during antimicrobial photodynamic root canal treatment (Fig. 1)

Endodontology

- a. Strategies for optimization of endodontic treatment, retreatment, and adhesive coronal seal.
- b. Evaluation of crack formation due to endodontic treatment. μ -CT evaluations of retreatment efficacy in endodontics (Fig. 2). Development of new root canal preparation and obturation instruments.

Research projects

Title Development of low-shrink resin composites for dental applications

Principal investigator(s) R. Frankenberger

Summary Innovative polymerization strategies for resin composite restorations in conservative dentistry in order to reduce marginal gap formation and recurrent caries.

Funded by BMWi ZIM/AiF FKZ KF2967801AK2

Funding period 2012 – 2014

Title Microparticulate silver for antimicrobial dental applications

Principal investigator(s) R. Frankenberger

Summary Modification of resin-based adhesives, resin composites, and laquers with microparticulate silver additions for use in conservative dentistry in order to prevent initial caries and to reduce recurrent caries.

Funded by EU – European Research Council, EFRE Grant 1330/68562, Industry

Funding period 2009 – 2012, ongoing

Title Preclinical evaluation of adhesion, marginal quality, crack formation and flexural fatigue behavior

Principal investigator(s) R. Frankenberger

Summary Intraoral simulation of different dental biomaterials in the artificial mouth using microtensile testing, thermomechanical loading, and wear determination, SEM margin analysis, handling properties, gap width, and dentists' perception.

Funded by Industry

Funding period 2013 – 2014

Prospective clinical trials

Clinical studies concerning resin-based biomaterials as both Dental School single and multi-center project as well as practice based research multi-center studies nationwide.

Funded by Industry

Title Laser disinfection of root canals

Principal investigator(s) A. Braun & F. Schelle

Summary The aim of the study was to evaluate different treatment protocols for root canal disinfection. Root canals of extracted teeth were prepared and inoculated with *Enterococcus faecalis* (*E.f.*). Root canals were cleaned using diode laser irradiation at different wavelengths and conventional rinsing with sodium hypochlorite. Colony forming units of *E.f.* were assessed before and after treatment by a culturing procedure

Funded by Sirona Dental Systems GmbH

Title Ultrasonical removal of subgingival calculus

Principal investigator(s) A. Braun & F. Schelle

Summary Efficiency evaluation of a novel ultrasonic system for calculus removal. Extracted human teeth were treated in vitro using the ultrasonic device with different power settings. Calculus removal was assessed at constant intervals using an artificial periodontal pocket model. Residual calculus was evaluated by means of digitized planimetry

Funded by Sirona Dental Systems GmbH

Title Microhardness of cavity walls after fluorescence aided caries excavation (FACE)

Principal investigator(s) A. Braun & R. Frankenberger

Summary The aim of the study was to compare the microhardness of cavity walls after fluorescence aided (FACE) and conventional caries removal. Extracted carious teeth were excavated with a bur. The endpoint of caries removal was determined either with a probe or using a fluorescence device. After treatment, teeth were cross sectioned through the prepared cavity and dentine microhardness was determined.

Title Laser disinfection of periodontal tissues

Principal investigator(s) A. Braun & M. Krech

Summary The aim of the study was to compare different treatment protocols for disinfection of artificial periodontal lesions in vitro. Pig jaws were used to prepare artificial periodontal pockets. After inoculation with a variety of periopathogenic microorganisms the lesions were cleaned using diode laser irradiation at different wavelengths and conventional rinsing. Bacterial counts were assessed before and after treatment.

Funded by Sirona Dental Systems GmbH

Title Crack formation during postendodontic treatment regimens

Principal investigator(s) M. J. Roggendorf

Summary Influence of different intracanal medications on tightness and bond strength of endodontic sealers

Funded by Grant/Dental Chamber Hessen, Industry

(USPL) system. *Lasers Med Sci* [Epub ahead of print]. DOI 10.1007/s10103-013-1344-z

Braun A, Beisel C, Brede O, Krause F (2013) Laser fluorescence of dentin caries covered with a novel nano-filled sealant. *Lasers Med Sci* 28:133-138

Bitter K, Gläser C, Neumann K, Blunck U, **Frankenberger R** (2014) Analysis of resin-dentin interface morphology and bond strength evaluation of core materials for one stage post-endodontic restorations. *PLoS One* 28:e86294

Braun A, Kecsmar S, Krause F, Berthold M, Frentzen M, **Frankenberger R**, **Schelle F** (2014) Effect of simulated pulpal fluid circulation on intrapulpal temperature following irradiation with an Nd:YVO4 laser. *Lasers Med Sci* [Epub ahead of print]. DOI 10.1007/s10103-014-1540-5

Frankenberger R, Reinelt C, Krämer N (2014) Nanohybrid vs. fine hybrid composite in extended class II cavities: 8-year results. *Clin Oral Investig* 18:125-137

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Director: Professor Roland Frankenberger

General information about the institute

Research funding 327.714,91 €

Most important publications

Frankenberger R, Hehn J, Hajtó J, Krämer N, Naumann M, Koch A, **Roggendorf MJ** (2013) Effect of proximal box elevation with resin composite on marginal quality of ceramic inlays in vitro. *Clin Oral Investig* 17:177-183

Pontius V, Pontius O, **Braun A**, **Frankenberger R**, **Roggendorf MJ** (2013) Retrospective evaluation of perforation repairs in 6 private practices. *J Endod* 39:1346-1358

Braun A, Krillke RF, Frentzen M, Bourauel C, Stark H, **Schelle F** (2013) Heat generation caused by ablation of dental hard tissues with an ultrashort pulse laser

Department of Pediatric and Community Dentistry

Chair Professor K. Pieper

Main fields of research

Most of the multicenter studies carried out by the Department of Pediatric Dentistry are focusing on the changes of oral health in children and adolescents over time. In retrospective and prospective studies we examine which measures have contributed to the caries decline as a prerequisite for optimizing preventive programs. As a foundation for these surveys several in-vitro and in-vivo studies have been performed dealing with different diagnostic tools such as the International Caries Detection and Assessment System (ICDAS) for the visual diagnosis of dental caries, laser devices, fluorescence based cameras and impedance spectroscopy.

Research projects

Title Prevention in Primary Schools with Elmex Gelee®

Principal investigator(s) K. Pieper

Summary A preventive program utilizing Elmex Gelee® was introduced in primary schools consecutively to the Kindergarten program performed in Northern Hesse. The study carried concomitantly analyses the effect of this intensified preventive program. Additionally we are investigating the question whether an intensified preventive programme in Kindergartens has a long lasting effect on oral health of school children.

Funded by GABA International

Funding period 2013 – 2015

Title Effect of Curodont TM Protect on prevention of artificial carious lesions of bovine enamel-an in-situ study

Principal investigator A. Jablonski-Momeni

Summary Initial carious lesions in enamel may progress towards dentine caries with decay without any prevention. While an initial lesion can be arrested with preventive measures, this is seldom the case in cavitations. The aim of this study is to evaluate whether different measurements are able to arrest enamel lesions of further development. Two different methods serve as test group 1: the established Duraphat varnish, 2: the newly developed Curodont Protect. The human saliva serves as control group without any intervention. For each participant an individual removable resin appliance is prepared. In each appliance demineralized bovine enamel specimens (sterilized, BSE free) will be inserted. The specimen will be

demineralized in a solution in order to simulate initial caries lesions.

Funded by DGPZM-CP GABA Wissenschaftsfond

Funding period 2014 – 2015

Title Detection of interproximal carious lesions using the NIR based camera VistaCam iX Proxi

Principal investigator (s) A. Jablonski-Momeni

Summary Interproximal carious lesions are usually detected by x-rays. Recently an X-ray-free method for proximal caries detection was introduced to the market (VistaCam iX with the Proxi Head). The method is based on the near-infrared light transillumination technology. The aim of this clinical study is to evaluate the diagnostic accuracy of the camera with respect to visual and radiographic findings.

Funded by Dürr Dental AG, Germany

Funding period 2014 – 2015

General information about the institute

Research funding 34.413,51 €

Most important publications

Pieper K, Weber K, Margraf-Stiksrud J, Heinzel-Gutenbrunner M, Stein S, **Jablonski-Momeni A** (2013) Evaluation of a preventive program aiming at children with increased caries risk using ICDAS II criteria. *Clin Oral Invest* 17: 2049-2055

Jablonski-Momeni A, Liebegall F, Stoll R, Heinzel-Gutenbrunner M, **Pieper K** (2013) Performance of a new fluorescence camera for detection of occlusal caries in vitro. *Lasers Med Sci* 28: 101-109

Pieper K, Lange J, **Jablonski-Momeni A**, Schulte AG (2013) Caries prevalence in 12-year-old children from Germany: results of the 2009 national survey. *Community Dent Health* 30: 138-142

Stoll R, Urban-Klein B, Giacomini P, Loukas A, **Jablonski-Momeni A** (2013) In vivo assessment of caries excavation with a fluorescence camera compared to direct bacteriological sampling and quantitative analysis using flow cytometry. *Lasers Med Sci*, DOI 10.1007/s10103-013-459-2

Jablonski-Momeni A, Winter J, Petrakakis P, Schmidt-Schäfer S (2014) Caries prevalence (ICDAS)

in 12-year-olds from low caries prevalence areas and association with independent variables. *Int J Paediatric Dentistry* 24: 90-97

Jablonski-Momeni A, Heinzel-Gutenbrunner M, Klein SMC (2014) In-vivo performance of the VistaProof fluorescence based camera for detection of occlusal lesions. *Clinical Oral Invest* 18, 1757-1762

Jablonski-Momeni A, Heinzel-Gutenbrunner M (2014) Efficacy of the "Self-assembling peptide P11-4" in the formation of a remineralization scaffold on artificially induced enamel lesions on smooth surfaces. *J Orofac Orthop* 75, 175-189

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Director: Professor Klaus Pieper

Department of Prosthodontics and Craniomandibular Function

Chair Professor U. Lotzmann

Professor M. Gente, Professor R. Mengel

Professor C. Knabe-Ducheyne – Endowed Professorship of Experimental Orofacial Medicine

The Endowed Professorship of Experimental Orofacial Medicine has an equal association with the Dept of Prosthodontics and the Dept. of Maxillofacial Surgery.

Main fields of research

1. Risk factors affecting the success of dental implants and dental implant superstructures.
2. Histological, immunological and molecular biological characterization of the genesis of peri-implant diseases.
3. Preventive measures and methods of treatment for per-implant disease.
4. Influence of the intermaxillary relation and stabilization on masticatory muscle activity and athletic performance.
5. Occlusal support and chewing efficiency
6. Application of eye-tracking in dentistry
7. Regenerative medicine, bone regeneration, bioactive calcium phosphate bone grafting materials, bone-tissue engineering utilizing resorbable calcium alkali phosphate scaffolds produced by 3D printing, mesenchymal stem cell and microvascular techniques, moldable calcium alkali phosphate bone grafting cements, individualized medicine, antibacterial & bactericidal implant materials.

Research projects

Title Establishment of a scientific database documenting data on patients with periodontal disease and dental implants

Principal investigator(s) R. Mengel & C. Schade-Brittinger (KKS Marburg)

Summary The objective of this research project involves the documentation and scientific analysis of clinical, microbiological, radiological and immunological data from patients with periodontal disease and dental implants using a newly developed scientific database.

Funded by Nobel Biocare (Zürich, Switzerland)

Funding period 2010 – 2016

Title Comparison of 2 electric toothbrushes. An experimental gingivitis trial

Principal investigator(s) R. Mengel

Summary The objective of this study is to directly examine and compare electric toothbrushes from

Oral B and Philips using the experimental gingivitis model.

Funded by Philips Oral Health Care, USA

Funding period 2010 – 2015

Title Vascular and nonvascular innervation of periodontal and periimplant tissue

Principal investigator(s) R. Mengel & E. Weihe (Institute of Anatomy and Cell Biologie, Marburg)

Summary Chemical coding of vascular and nonvascular innervation in young and old human gingiva and periimplant soft tissue.

Funded by GABA Lörrach

Funding period 2008 – 2016

Title Periodontitis as a risk factor for preterm birth

Principal investigator(s) R. Mengel, M. Kühnert (Obstetrics and Perinatal Medicine, Marburg)

Summary A long-term clinical study researching the influence of periodontal disease on the prevalence of preterm births.

Funded by DGP/ARPA Foundation

Funding period 2009 – 2015

Title Efficacy and mechanisms of biofeedback based behavioural therapy compared to dental splint therapy in the treatment of craniomandibular disorders

Principal investigator(s) A. Neff & U. Lotzmann (Dental School), U. Rief (Clinical Psychology), Philipps University Marburg

Summary This prospective randomized study deals with the interdisciplinary evaluation of specific therapy approaches in craniomandibular dysfunction (CMD) and evaluates the therapeutic standard options and their interdisciplinary combination. First results show profits for patients with muscle pain in a biofeedback setting.

Title Influence of Implants und Locators for improved retention of mandibular full dentures on patient's quality of life and oral function. A controlled an prospective study

Principal investigator(s) R. Mengel & U. Lotzmann

Summary In the controlled and prospective study the influence of Implants and Locators for improved retention of mandibular full dentures on patient's oral function and quality of life will be examined.

Funded by GC Europe (Leuven, Belgium)

Funding period 2014 – 2016

Most important publications

Thöne-Mühling M, Peleska B, Gockel F, Lotzmann U, Mengel R (2013) Template-guided flapless implant insertion and prosthetic rehabilitation with telescopic crowns in a patient with treated generalized aggressive periodontitis: a case report. *Quintessenz International* 43:179-185

Swierkot K, Brusius M, Leismann D, Nonnenmacher C, Nüsing R, Lubbe D, Schade-Brittinger C, **Mengel R** (2013) Manual versus sonic-powered toothbrushing for plaque reduction in patients with dental implants – an explanatory randomized controlled trial. *Eur J Oral Implantol* 6(2): 133 – 144

Lopez-Heredia MA, Pattipeilohy J, Hsu S, Grykien M, van der Weijden B, Leeuwenburgh SCG, Wolke JGC and Jansen JA (2013) Bulk physicochemical, interconnectivity and mechanical properties of calcium phosphate cements – fibrin glue composites for bone substitute applications. *J Biomed Mater Res A* 101(2):478-90

Eberle JC, **Schneider J, Lotzmann U** (2013) Initial effects of reduced vertical dimension on the projection of body's center of gravity on a standing surface – a pilot study. *J Craniomandib Function* 5(2): 151-161

Shedden Mora MC, **Weber D**, Neff A, Rief W (2013) Biofeedback-based cognitive-behavioral treatment *Clin J Pain* 29(12):1057-65

Bhattacharyya S, Agrawal A, **Knabe C**, Ducheyne P (2014) Sol-gel silica controlled release thin films for the inhibition of methicillin-resistant *Staphylococcus aureus*. *Biomaterials* 35 (1):509-17

Stiller M, Kluk E, Bohner M, **Lopez-Heredia MA**, Müller-Mai C, **Knabe C**. (2014) Performance of β -tricalcium phosphate granules and putty, bone grafting materials after bilateral sinus floor augmentation in humans. *Biomaterials* 35(10):3154-63

Knabe C, Lopez Heredia MA, Barnemitz D, Genzel A, Peters F, Hübner WD (2014) Effect of silicon-doped calcium phosphate bone substitute materials on bone formation and osteoblastic phenotype expression in vivo. *Key Engineering Materials* 614:31-14

Research funding

215,304.43 €*

*The funding obtained for instituting the Endowed Professorship of Experimental Orofacial Medicine has been raised by the Departments of Prosthodontics and Maxillofacial Surgery (50% each, i.e. 100,000 € annually).

Experimental Orofacial Medicine – Professor C. Knabe-Ducheyne

Main fields of research

Regenerative medicine, bone regeneration, bioactive calcium phosphate bone grafting materials, bone-tissue engineering utilizing resorbable calcium alkali phosphate scaffolds produced by 3D printing, mesenchymal stem cell and microvascular techniques, moldable calcium alkali phosphate bone grafting cements, individualized medicine, antibacterial & bactericidal implant materials

Research projects

Title Rapidly resorbable calcium alkali orthophosphate scaffolds for bone tissue engineering.

Principal investigator(s) C. Knabe & Dr. G. Berger, Federal Institute for Materials Research and Testing, Berlin

Summary The objective of this project is to develop an adequate approach for regenerating large segmental bone defects. To this end, three dimensional scaffolds with varying porosity are fabricated from rapidly resorbable calcium alkali orthophosphates by 3 D printing or applying the Schwarzwald-Somers technique which utilizes combustible polyurethane foam templates. In a first step the material and the printing process are optimized. Mesenchymal stem cells are then cultured on these scaffolds for two weeks under perfusion. Subsequently the scaffolds are implanted in segmental defects in the rat femur in conjunction with a microvascular surgical technique in order to achieve adequate vascularization, which is of paramount importance when regenerating segmental defects.

Funded by German Research Foundation-KN 377/8-1, Federal Institute for Materials Research and Testing

Funding period 2011 – 2015

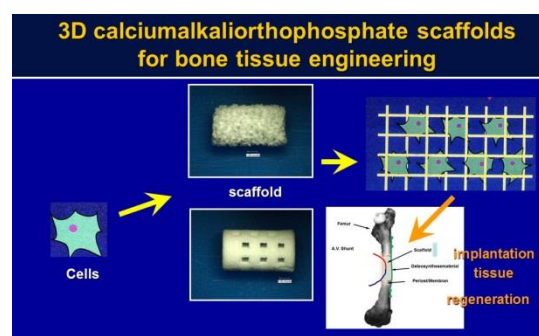


Fig. 1 Tissue engineering approach and animal model using 3 D scaffolds and mesenchymal stem for regeneration of segmental defects in the rat femur

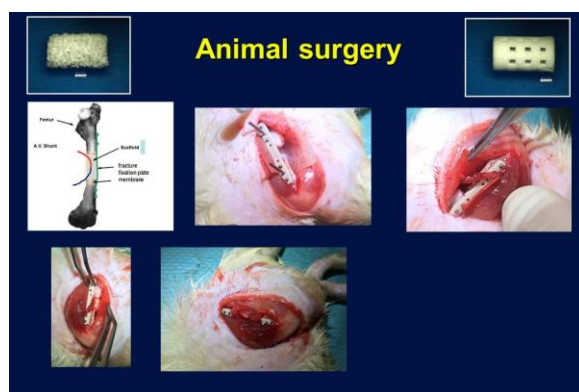


Fig. 2 Animal model using 3 D scaffolds and mesenchymal stem cells for regeneration of segmental defects in the rat femur in combination with a microvascular technique

Title The effect of hormone status on bone regeneration after sinus floor augmentation with porous tricalcium phosphate particles

Principal investigator(s) C. Knabe & PD. Dr. Dr. M. Stiller, Charité University Medical Center Berlin

Summary This study elucidates the effect of age, BMI and gender related parameters such as hormone status on bone regeneration after sinus floor augmentation with porous tricalcium phosphate particles in humans.

Funded by Robert Mathys Foundation

Funding period 2008 – 2014

Title BioMin II – Biofunctionalized calcium phosphate surfaces: adsorption mechanisms of bone morphogenetic proteins to the surfaces of calcium phosphate bone grafting materials

Principal investigator(s) C. Knabe & PD Dr. Ch. Müller-Mai, Medical Faculty, University Bochum

Summary This study evaluates the effect of bone morphogenetic proteins, which are adsorbed onto the surface of bioactive glass 45S5 cylinders, on bone osteoblast differentiation and bone formation after implantation in the rabbit femur.

Funded by Federal Ministry for Research and Technology

Funding period 2011 – 2014

Title Effect of various tricalcium calcium phosphate-based mesh and paste-like bone grafting materials on osteogenesis and bone regeneration after implantation in critical-size defects in the sheep scapula

Principal investigator(s) C. Knabe

Summary This study evaluates the effect of various tricalcium calcium phosphate-based mesh and paste-like bone grafting materials on osteoblast differentiation and bone regeneration after implantation in critical-size defects in the sheep scapula.

Funded by Corporate Sponsor, Curasan

Funding period 2013 – 2014

Title BioMimetic Bone - Biofunctionalized calcium phosphate scaffolds for fracture repair - Histologic evaluation.

Principal investigator(s) C. Knabe-Ducheyne & PD Ch. Dr. Müller-Mai, Medical Faculty, University Bochum

Summary This study evaluates the effect of tricalcium phosphate based scaffolds to whose surface bone morphogenetic proteins are adsorbed on bone regeneration of segmental defects after implantation in the rabbit ulna.

Funded by Federal Ministry for Research and Technology

Funding period 2012 – 2014

Title Effect of a silica containing calcium alkali orthophosphate ceramic as compared to silicon doped tricalcium phosphate on bone formation and osteogenic marker expression after sinus floor augmentation in humans."

Principal investigator(s) C. Knabe & Dr. Stiller

Summary This study evaluates the effect of a silica containing calcium alkali orthophosphate ceramic as compared to silicon doped tricalcium phosphate on bone formation and osteogenic marker expression after sinus floor augmentation in humans.

Funded by Zimmer Foundation

Funding period 2013 – 2014

Title Effect of silk-based periodontal membranes on guided bone regeneration

Principal investigator(s) C. Knabe

Summary This study evaluates the effect of a silk-based periodontal membranes on bone formation and osteogenic marker expression after implantation in an rabbit calvarial defect model.

Funded by Corporate Sponsor, BLS Preclinical Services

Funding period 2011 – 2013

Title Infected fractures – Treatment and Mitigation of Biofilm Formation

Principal investigator(s) C. Knabe & Prof. Paul Ducheyne, Dept. of Bioengineering, University of Pennsylvania, Dr. J. Garino, Dept. of Orthopaedic Surgery, University of Pennsylvania

Summary This study evaluates the efficacy of bactericidal sol-gel coatings on intramedullary fracture fixation pins with controlled release of vancomycin for preventing infection in a sheep model after inoculation with *Staph. aureus*.

Funded by US Department of Defense

Funding period 2010 – 2013

Title Preclinical Testing of Microparticle Ceramic Urethral Bulking Agents in a rat model

Principal investigator(s) P. Zvara, Dept. of Surgery / Urology, University of Vermont, C. Knabe-Ducheyne, Philipps University Marburg, A. El-Ghannam, Dept. of

Mechanical Engineering and Engineering Science,
The University of North Carolina at Charlotte

Summary This study evaluates the efficacy of micro particle ceramic urethral bulking agents in a rat model

Funded by University of Vermont

Funding period 2014 – 2015

Title Bone Tissue Engineering in Implant Dentistry

Principal investigator(s) C. Knabe-Ducheyne

Summary The objective of this project is to develop an adequate approach for regenerating large segmental bone defects. To this end, three dimensional scaffolds with varying porosity are fabricated from rapidly resorbable calcium alkali orthophosphates by 3 D printing or applying the Schwarzwald-Somers technique which utilizes combustible polyurethane foam templates. In a first step the material and the printing process are optimized. Mesenchymal stem cells are then cultured on these scaffolds for one to two weeks under perfusion and the cellular response is characterized. Subsequently the scaffolds are implanted in segmental defects in the rat femur in conjunction with a microvascular surgical technique in order to achieve adequate vascularization, which is of paramount importance when regenerating segmental defects.

Funded by DAAD – German Academic Exchange Service

Funding period 2014

Title Development of a floor of the mouth squamous cell carcinoma rabbit animal model

Principal investigator(s) R. Mandic, Dept. of ENT, C. Knabe-Ducheyne, Dr. Bette, Dept. of Anatomy & Dr. P. Heymann, Dept. of Oral and Maxillofacial Surgery

Summary This pilot study seeks to establish a floor of the mouth squamous cell carcinoma rabbit animal model.

Title The effect of tricalcium phosphate ceramic particles and a tricalcium phosphate hyaluronic acid-based putty bone grafting material on bone regeneration after sinus floor augmentation using a split mouth design

Principal investigator(s) C. Knabe & PD Dr. M. Stiller, Charité University Medical Center Berlin

Summary This study elucidates the effect of tricalcium phosphate ceramic bone grafting particles and a tricalcium phosphate hyaluronic acid-based putty bone grafting material on bone regeneration and volume stability of the grafted area after sinus floor augmentation in human using a split mouth design.

Funded by Robert Mathys Foundation

Funding period 2009 – 2013

Most important publications

Stiller M, Kluk E, Böhner M, **Lopez-Heredia MA**, Müller-Mai C, **Knabe C** (2014) Performance of β -tricalcium phosphate granules and putty, bone grafting materials after bilateral sinus floor augmentation in humans. *Biomaterials* 35(10):3154-63

Bhattacharyya S, Agrawal A, **Knabe C**, Ducheyne P (2014) Sol-gel silica controlled release thin films for the inhibition of methicillin-resistant *Staphylococcus aureus*. *Biomaterials* 35(1):509-17

Qu H, **Knabe C**, Burke M, Radin S, Garino J, Schaer T, Ducheyne P (2014) Bactericidal micron-thin sol-gel films prevent pin tract and periprosthetic infection. *Mil Med* 179(8 Suppl):29-33

Qu H*, **Knabe C***, Radin S, Garino J, Ducheyne P. Percutaneous external fixator pins with bactericidal micron-thin sol-gel films for the prevention of pin tract infection. *Biomaterials* in press

*authors have contributed equally

Knabe C, **Lopez Heredia MA**, Barnemitz D, Genzel A, Peters F, Hübner WD (2014) Effect of silicon-doped calcium phosphate bone substitute materials on bone formation and osteoblastic phenotype expression in vivo. *Key Engineering Materials* 614:31-14

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Mann-Gow TK, Blaivas JG, King BJ, El-Ghannam A, **Knabe C**, Lam MK, Kida M, Sikavi CS, Plante MK, Krhut J, Zvara P. Rat animal model for preclinical testing of microparticle urethral bulking agents. *Int J Urol* in press

Research funding

260,872.73 €

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Main fields of research

The KKS Marburg with its 30 staff members (www.kks.uni-marburg.de) is member of the KKS-Network, a consortium of currently 19 German clinical trial units at university hospitals. All requirements according to GCP are well established including administration as well as central randomization, data management, statistics, quality management and monitoring. KKS Marburg is the legal representative of the University for investigator initiated trials and the global contract management office of the University for all patient-related trials. Currently, KKS is in charge of more than 30 running multi-center clinical trials and also engaged in training related to scientific and organizational aspects of trials.

Research projects

Title Promid

Principal investigator(s) R. Arnold

Summary Untersuchung des Gesamtüberlebens von Patienten, die an der PROMID-Studie teilgenommen haben, nachdem Sandostatin® abgesetzt wurde

Funded by Industry

Funding period 2001 – 2013

Title MAGIKA

Principal investigator(s) B. Maisch

Summary Umsetzung des Behandlungspfades zur Diagnostik und Therapie der DCM mit und ohne Inflammation in der integrierten Struktur eines Klinikkonzerns (Rhön AG) unter Berücksichtigung eines universitären Zentrums

Funded by Industry

Funding period 2009 – 2013

Title SELECT A

Principal investigator(s) Prof. Wolf

Summary TS stratified Chemotherapy and VEGF Inhibition in Non-Squamous Non-Small Cell Lung Cancer - Stage IV

Funded by Aktion Bronchialkarzinom (ABC) e.V.

Funding period 2012 – 2013

Title VENUS-1

Principal investigator(s) Prof. Wolf

Summary An open label phase I dose escalation of oral BIBF 1120 in combination with intravenous vinorelbine in elderly patients with advanced Non-Small Lung Cancer - Stage VI

Funded by Aktion Bronchialkarzinom (ABC) e.V

Funding period 2012 – 2013

Title VENUS-2

Principal investigator(s) Prof. Wolf

Summary An open label phase I dose escalation of oral BIBF 1120 in combination with intravenous carboplatin and vinorelbine in elderly patients with advanced Non-Small Lung Cancer - Stage VI

Funded by Aktion Bronchialkarzinom (ABC) e.V

Funding period 2012 – 2013

Title GYN-7

Principal investigator(s) P. Harter

Summary Phase II-Studie zum Einsatz der Kombinationschemotherapie PegLiposomales Doxorubicin (PLD) und Carboplatin bei gynäkologischen Sarkomen und gemischt epithelial-mesenchymalen Tumoren.

Funded by AGO Study Group

Funding period 2008 – 2014

Title Ovar 16

Principal investigator(s) A. du Bois

Summary A Phase III Study to evaluate the efficacy and safety of Pazopanib monotherapy versus placebo in women who have not progressed after first line chemotherapy for Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal.

Funded by AGO Study Group

Funding period 2010 – 2014

Title Desktop III

Principal investigator(s) P. Harter

Summary Eine randomisierte, multizentrische Studie zum Vergleich der Wirksamkeit einer zusätzlichen Tumordebulking-Operation gegen eine alleinige Chemotherapie bei Patientinnen mit einem platin-sensiblen Ovarialkarzinom-rezidiv.

Funded by AGO Study group

Funding period 2010 – 2015

Title ATIP

Principal investigator(s) T. Gress

Summary Multicentre Phase II-trial to investigate the safety and the effects of ERBITUX® and Gemcitabine in Patients with R0 resected Adenocarcinoma of the pancreas.

Funded by Industry

Funding period 2005 – 2013

Title BIOPACE

Principal investigator(s) R. Funck

Summary Biventricular Pacing for Atrioventricular Block in Left Ventricular Dysfunction to Prevent Cardiac Desynchronization

Funded by Industry

Funding period 2001 – 2015**Title** Sormain**Principal investigator(s)** A. Burchert**Summary** Eine doppelblinde, Placebo-kontrollierte, randomisierte, multizentrische Phase II Studie zur Untersuchung der Wirksamkeit und Sicherheit einer Sorafenib Erhaltungstherapie bei Patienten mit Flt3-ITD positiver AML in kompletter hämatologischer Remission (CHR) nach allogener Stammzelltransplantation (allo-SCT).**Funded by** Industry**Funding period** 2009 – 2015**Title** OVAR 12**Principal investigator(s)** A. du Bois**Summary** Multicenter, randomised, double-blind Phase III trial to investigate the efficacy and safety of BIBF 1120 in combination with carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in patients with advanced ovarian cancer.**Funded by** AGO Study group**Funding period** 2012 – 2015**Title** OVAR 17**Principal investigator(s)** J. Pfisterer**Summary** A prospective randomised Phase III trial to evaluate optimal treatment duration of first-line bevacizumab in combination with carboplatin and paclitaxel in patients with primary epithelial ovarian, fallopian tube or peritoneal cancer. The BOOST (Bevacizumab Ovarian Optimal Standard Treatment) Trial.**Funded by** AGO Study group**Funding period** 2011 – 2016**Title** GYN-8**Principal investigator(s)** G. Emons**Summary** Wirksamkeit, Verträglichkeit und Sicherheit von Temsirolimus beim platinrefraktären Ovarialkarzinom und beim fortgeschrittenen oder rezidierten Endometriumkarzinom.**Funded by** AGO Study group**Funding period** 2011 – 2015**Title** OVAR 2.15 Aurelia**Principal investigator(s)** F. Hilpert**Summary** A multi-centre, open-label, randomised, two-arm Phase III trial of bevacizumab plus chemotherapy versus chemotherapy alone in patients with platinum-resistant, epithelial ovarian, fallopian tube or primary peritoneal cancer.**Funded by** AGO Study group**Funding period** 2013**Title** GEIS-Liposarcom**Principal investigator(s)** C. Valverde Morales**Summary** Phase II Clinical Trial of Pazopanib to evaluate the activity and tolerability in patients with

advanced and/or metastatic liposarcoma who have relapsed following standard therapies or for whom no standard therapy exists.

Funded by Onkologisches Liposarkom-Netz, Spanien**Funding period** 2012 – 2015**Title** Earlystim-PSFU**Principal investigator(s)** G. Deuschl**Summary** Post Study follow-up to the study: The effect of deep brain stimulation of the Subthalamic Nucleus (STN-DBS) on quality of life in comparision to best medical treatment in patients with complicated Parkinson's disease and preserved psychosocial competence (EarlyStim).**Funded by** Industry**Funding period** 2007 – 2018**Title** EDNET**Principal investigator(s):** B. Herpertz-Dahlmann (ANDI), Prof. Zipfel; Prof. Herzog (ANTOP), C. Jacobi (INA), M. de Zwaan (Interbed)**Summary** Zentrale biostatistische Betreuung, Daten- und Datenqualitätsmanagement für den Forschungsverbund zur Psychotherapie bei Essstörungen, gemeinsam mit dem Institut für Med. Biometrie und Epidemiologie (Eating Disorders Diagnostic Treatment Network, EDNET)**Funded by** BMBF – Federal Ministry of Education and Research**Funding period** 2006 – 2013**Title** Ovar 2.16 (Mito-8)**Principal investigator(s)** K. Baumann**Summary** Stealth Liposomal Doxorubicin vs Carboplatin/Paclitaxel in Patients With Ovarian Cancer Recurrence Between Six and Twelve Months After Previous Platinum Based Chemotherapy: Phase III Multicenter Randomized Study (MITO-8; AGO-OVAR).**Funded by** BMBF - Federal Ministry of Education and Research**Funding period** 2010 – 2014**Title** LION**Principal investigator(s)** U. Wagner**Summary** An open randomized prospective multicenter-trial "Lymphadenectomy in ovarian neoplasms (LION)"**Funded by** DFG – German Science Foundation**Funding period** 2008 – 2017**Title** IA-Pem**Principal investigator(s)** R. Eming & E. Schmidt**Summary** Efficacy and safety of adjuvant immuno-adsorption in pemphigus vulgaris and pemphigus foliaceus (IA-pem-study).**Funded by** DFG – German Research Foundation**Funding period** 2010 – 2015

Title UGMLC

Summary Clinical Trial unit for the UGMLC – Module Lung

Funded by State Hessen – LOEWE Centre

Funding period 2010 – 2015

Title BILANZ

Principal investigator(s) Prof. Dr. Pfeilschifter

Summary Randomisierte, partiell doppelblinde, placebokontrollierte, multizentrische Studie zur Evaluation der Wirksamkeit und Sicherheit von Bisphosphonaten in der Langzeittherapie der Osteoporose (BILANZ).

Funded by BMBF

Funding period 2012 – 2013

Title NIC-PD

Principal investigator(s) W. Oertel

Summary A randomized, placebo-controlled, double-blind, multi-centre trial to assess the disease-modifying potential of transdermal nicotine in early Parkinson's disease in Germany and the USA

Funded by Michael J. Fox Foundation

Funding period 2009 – 2017

Title FirstMapp

Principal investigator(s) M. Fassnacht

Summary First International Randomized Study placebo in Malignant Progressive

Pheochromocytoma and Paraganglioma (PPGL)

Funded by BMBF – Federal Ministry of Education and Research

Funding period 2013 – 2020

Title PATENT

Principal investigator(s) L. Eberhart

Summary

Funded by Industry

Funding period 2013 – 2015

Title OVAR 2.21

Principal investigator(s) K. Baumann

Summary A prospective randomized Phase III trial of carboplatin/gemcitabine/bevacizumab vs. carboplatin/pegylated liposomal doxorubicin/bevacizumab in patients with platinum-sensitive recurrent ovarian cancer.

Funded by AGO Study Group

Funding period 2013 – 2019

Title OVAR 2.20

Principal investigator(s) C. Kurzeder

Summary A two-part, randomized phase II, double-blind, multicenter trial assessing the efficacy and safety of Pertuzumab in combination with standard chemotherapy vs. placebo plus standard chemotherapy in women with recurrent platinum

resistant epithelial ovarian cancer and low HER3 mRNA expression.

Funded by AGO Study group

Funding period 2013 – 2016

Title LDE225

Principal investigator(s) T. Gress

Summary Phase I Trial with Post-Study Follow-up to Evaluate the Safety and Tolerability of LDE225 and Octreotide LAR in Patients with Progressive Neuroendocrine Tumors.

Funded by Industry

Funding period 2013 – 2016

Title AGO-TR 1

Principal investigator(s) P. Harter

Summary BRCA-Screening in Ovarian Cancer (Protocol ID: AGOTR-1). Incidence of BRCA in tumor samples in Ovarian Cancer.

Funded by: AGO Study group

Funding period: 2014-2019

Title CORSETT

Principal investigator(s) P. Harter

Summary CORSETT - Current Ovarian germ cell and Sex cord Tumor Treatment strategies - An observational retrospective study of treatment strategies for ovarian germ cell and sex cord-stromal tumors in Germany.

Funded by Uniklinikum Freiburg

Funding period 2014 – 2016

Title Alphasom

Principal investigator(s) W. Rief

Summary Alternative dosing regimens in the pharmacotherapy of mild to moderate insomnia

Funded by DFG – German Research Foundation

Funding period 2013 – 2014

Title CORRA

Principal investigator(s) J. Braun

Summary Comparison of the efficacy and safety of two starting dosages of prednisolone in early active rheumatoid arthritis: a randomized, placebo controlled trial

Funded by BMBF – Federal Ministry of Education and Research über Universität Bochum

Funding period 2013 – 2016

Title INTRANS

Principal investigator(s) D. K. Bartsch

Summary Fortlaufende Intrakutannaht oder transkutaner Klammernahtverschluss bei elektiven abdominal chirurgischen Eingriffen - Eine prospektive, randomisierte, kontrollierte, monozentrische, klinische Studie zur Evaluierung des postoperativen oberflächlichen Wundinfekts.

Funded by UKGM – University Hospital Giessen and Marburg

Funding period 2013 – 2015**Title** ADIUVO Ens@t-Cancer**Principal investigator(s)** M. Fassnacht**Summary** Efficacy of adjuvant mitotane treatment in prolonging recurrence-free survival in patients with adrenocortical carcinoma at low-intermediate risk of recurrence.**Funded by** EU – European Union**Funding period** 2010 – 2015**Title** ENCERT**Principal investigator(s)** Prof. Dr. med. Winfried Rief**Summary** Enriching Cognitive-behavioral Therapy (CBT) with Emotion Regulation Training (ERT) in Patients with Multiple Somatoform Symptoms: ENCERT**Funded by** DFG**Funding period** 2013 – 2016**Title** COPD SB010**Principal investigator(s)** C. Vogelmeier**Summary** Clinical study to investigate safety, tolerability, efficacy, pharmacokinetics and pharmacodynamics of inhaled multiple doses of the human GATA-3-specific DNzyme solution SB010 in patients with moderate to severe COPD – A randomised, double-blind, parallel group, multicenter, phase IIa pilot study.**Funded by** BMBF – Federal Ministry of Education and research, Helmholtz und Industry**Funding period** 2013 – 2015**Title** HD-DBS Huntington II**Principal investigator(s)** J. Vesper**Summary** Deep Brain Stimulation (DBS) of the Globus pallidus (GP) in Huntington's disease (HD): A prospective, randomised, controlled, international, multi-centre study**Funded by** DFG – German Research Foundation, über Universität Düsseldorf**Funding period** 2014 – 2016**Title** CLaSP**Principal investigator(s)** R. Dodel**Summary** JPND Verbundprojekt CLaSP, Versorgung von Patienten im fortgeschrittenen Stadium der Parkinson-Krankheit, TP**Funded by** BMBF – Federal Ministry of Education and Research**Funding period** 2014 – 2017**Most important publications**

Fensterer H, **Schade-Brittinger C**, Muller HH, Tebbe S, Fass J, Lindig U, Settmacher U, Schmidt WE, Marten A, Ebert MP, Kornmann M, Hofheinz R, Endlicher E, Brendel C, Barth PJ, Bartsch DK, Michl P, Gress TM (2013) Multicenter phase II trial to investigate safety and efficacy of gemcitabine combined with cetuximab as adjuvant therapy in pancreatic cancer (ATIP). *Ann Oncol* 24(10):2576-81

Schuepbach WMM*, **Rau J***, Knudsen K*, Volkmann J, Krack P, Timmermann L, Hälbig TD, Hesekamp H, Navarro SM, Meier N, Falk D, Mehdorn M, Paschen S, Maarouf M, Barbe MT, Fink GR, Kupsch A, Gruber D, Schneider G-H, Seigneuret E, Kistner A, Chaynes P, Ory-Magne F, Brefel Courbon C, Vesper J, Schnitzler A, Wojtecki L, Houeto J-L, Bataille B, Maltête, D, Damier P, Raoul S, Sixel-Doering F, Hellwig D, Gharabaghi A, Krüger R, Pinsker MO, Amtage F, Régis J-M, Witjas T, Thobois S, Mertens P, Kloss M, Hartmann A, Oertel WH, Post B, Speelman H, Agid Y*, **Schade-Brittinger C***, Deuschl G* (2013) Neurostimulation for Parkinson's Disease with Early Motor Complications. *New England Journal of Medicine* 368(7): 610-622; *shared authorship

Zipfel S, Wild B, Groß G, Friederich H-C, Teufel M, Schellberg D, Giel KE, De Zwaan M, Dinkel A, Herpertz S, Burgmer M, Löwe B, Tagay S, Von Wietersheim J, Zeeck A, **Schade-Brittinger C**, Schauenburg H, Herzog W (2014) Focal psychodynamic therapy, cognitive behaviour therapy, and optimised treatment as usual in outpatients with anorexia nervosa (ANTOP study): randomised controlled trial. *Lancet* 383(9912):127-37

Du Bois A, Floquet A, Kim JW, **Rau J**, Del Campo JM, Friedlander M, Pignata S, Fujiwara K, Vergote I, Colombo N, Mirza MR, Monk BJ, Kimmig R, Ray-Coquard I, Zang R, Diaz-Padilla I, Baumann KH, Mouret-Reynier MA, Kim JH, Kurzeder C, Lesoin A, Vasey P, Marth C, Canzler U, Scambia G, Shimada M, Calvert P, Pujade-Lauraine E, Kim BG, Herzog TJ, Mitrica I, **Schade-Brittinger C**, Wang Q, Crescenzo R, Harter P (2014) Incorporation of Pazopanib in Maintenance Therapy of Ovarian Cancer. *J Clin Oncol* 32(30):3374-82

Herpertz-Dahlmann B, Schwarte R, Krei M, Egberts K, Warnke A, Wewetzer C, Pfeiffer E, Fleischhaker C, Scherag A, Holtkamp K, Hagenah U, Buhren K, Konrad K, Schmidt U, **Schade-Brittinger C**, Timmesfeld N, Dempfle A (2014) Day-patient treatment after short inpatient care versus continued inpatient treatment in adolescents with anorexia nervosa (ANDI): a multicentre, randomised, open-label, non-inferiority trial. *Lancet* 383(9924): 1222-9

General information about the institute**Research funding** 1.826.640,37 €

Schüpbach W.M.M., **Rau J**, Houeto J-L, Krack P, Schnitzler A, **Schade-Brittinger C**, Timmermann L, Deuschl G (2014) Myths and facts about the EARLYSTIM study. *Mov Disord* 29(14):1742-50

Pujade-Lauraine E, Hilpert F, Weber B, **Reuss A**, Poveda A, Kristensen G, Sorio R, Vergote I, Witteveen P, Bamias A, Pereira D, Wimberger P, Oaknin A, Mirza MR, Follana P, Bollag D, Ray-Coquard I (2014) Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. *J Clin Oncol* 32(13):1302-8

Trillsch F, Mahner S, Woelber L, Vettorazzi E, **Reuss A**, Ewald-Riegler N, de Gregorio N, Fotopoulou C, Schmalfeldt B, Burges A, Hilpert F, Fehm T, Meier W, Hillemanns P, Hanker L, Hasenburg A, Strauss HG, Hellriegel M, Wimberger P, Baumann K, Keyver-Paik MD, Canzler U, Wollschlaeger K, Forner D, Pfisterer J, Schroeder W, Muenstedt K, Richter B, Kommos F, Hauptmann S, du Bois A (2014) Age-dependent differences in borderline ovarian tumours (BOT) regarding clinical characteristics and outcome: results from a sub-analysis of the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) ROBOT study. *Ann Oncol* 25(7):1320-7

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