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It is well established, that University Medical Centers in Germany receive inadequate compensation for their numerous services in patient care. In spite of these difficult financial conditions, the University Medical Center Mainz successfully continued its course of economic consolidation commenced two years earlier. We concluded the year 2014 with a 6.5 million euro deficit, cutting the negative result of the previous year almost in half. To foster scientific progress and development in this financially restrictive environment proved to be a challenging task.

In 2014, the University Medical Center realized investments of 35.5 million euros. Around 15 million of these funds were invested in current and new construction projects, in particular the new Paul-Klein-Center for Immune Intervention (PKZI) – a new, highly modern building for immunological research located on the southwest side of the Medical Center’s campus – and the construction of a new linear accelerator for radiotherapy. In the coming three years, the University Medical Center will invest an additional 150 million euros in the construction of a new Transfusion Center and Dental Clinic, as well as a new building for the Institutes of Theoretical Medicine and the Neuroimaging Center (NIC).

Over the last couple of years, the University Medical Center has developed a distinct and visible research profile. Also in 2014, we focused our limited resources on these core competencies, the Research Center for Immunotherapy (FZI), the Focus Program Translational Neurosciences (FTN), the Center for Translational Vascular Biology (CTVB) and the Key Research Area Biomaterials, Tissues and Cells in Science (BiomaTICS). These research areas received funds from the Research Initiative of the State of Rhineland-Palatinate and additional support from the Faculty of Medicine.

Formally established in July 2014, the German Resilience Center’s (DRZ) tripartite approach, combining basic neuroscience, clinical neuroscience and social science, uniquely addresses one of the most important public health challenges of modern, knowledge-based societies. The DRZ is a central research institution of the Johannes Gutenberg
University Mainz (JGU) and the first dedicated research institution in Europe that aims to tackle these challenges and to fill an important gap in our knowledge and understanding of resilience. In September, the Gutenberg Brain Study, as a platform project of the Focus Program Translational Neuroscience (FTN) and the Mainz Resilience Project, launched a study on resilience mechanisms in the brain, thereby developing a new platform for translational, genetic and resilience-based neurological research. A large, population-based pool of volunteers with corresponding biobank will be established for long-term studies on brain structure and function. The study aims to improve prevention and treatment of mental disorders. More precisely, it shall be discovered which strains of everyday life figure prominently into mental disorders and when. Moreover, the role of genetic predispositions will be explored.

Individual medicine and strategic patient care are only two exemplary sub-areas of a variety of translational research at the University Medical Center Mainz. To name one pioneering project in this field, the University Cancer Center Mainz (UCT) started sampling cancer patients’ biomaterials for tissue and liquid biobanks in March. The tissue biobank will store up to 14,000 samples and thereby help develop novel treatment options.

Our research profile is a significant factor in the selection and hiring of new faculty. In July, the German Research Foundation (DFG) selected Professor Krishnaraj Rajalingam, a fellow of the Boehringer Ingelheim Foundation-PLUS3 program, for the prestigious W3 Heisenberg professorship in Cell Biology. He joined the Research Center for Immunotherapy (FZI) at the University Medical Center to establish a cell biology unit. One of his main research interests is the defective signal transduction in cells and its influence on chronic diseases such as infections, cancer and autoimmune disorders. Additionally, Professor Ulrich Hink was appointed the first professorship in the nation for Interventional Heart Valve Therapy. Interventional heart valve therapy is a minimally invasive procedure to treat valve insufficiency.

In 2014, we successfully realized several research outreach projects that brought our work closer to the people. Under the reoccurring program University in the Town Hall, we presented a series of events within the core topic Medicine in the 21st Century. The feedback, after the first talk on the revolutionary developments in drug treatment since 1900 proved the audience fascination and the demand for more presentations on behalf of the public. Consequently, the further presentations were all well visited and the whole series proved successful. Additionally, the Summer University Immunology and Biomedicine enabled a group of high school students to gain insights into the daily routines of our researchers.

Finally, regional and international collaboration strengthened the University Medical Center’s reputation and cross-border visibility in 2014. We maintained our collaboration with the Goethe University of Frankfurt through the Rhine-Main Neuroscience Network (rmn²), the German Cancer Consortium (DKTK) and the German Center for Cardiovascular Research (DZHK). At the international level, we signed an agreement with the Hebrew University of Jerusalem in June. This collaboration is intended to propose joint research projects, foster regular exchange of experience and develop a joint training program.

The present research report provides you with the overall performance of the University Medical Center Mainz, enables you to take a closer look at our different departments and calls back to mind past accomplishments. Concurrently, we want to inform you of the institutes’ and departments’ future directions. I hope you enjoy reading this year’s edition.

With best regards,

Ulrich Förstermann
Mainz, December 2015
MILESTONES

NEW YEAR RECEPTION AT THE UNIVERSITY MEDICAL CENTER

The New Year Reception at the University Medical Center offered a special occasion to not only consider future prospects, but also to review past accomplishments: The hospital celebrated its 100th year in existence. After a turbulent history including its closing in the 19th century and refoundation in 1946, the fusion of the preclinical departments, the KTI and the clinic established the University Medical Center as its own independent public corporation on January 1, 2009. With its emphasis on the Research Center for Immunotherapy, Research Center for Translational Neurosciences and the Center for Translational Vascular Biology, as well as the new focus program Biomaterials, Tissues and Cells in Science (BiomATiCS), the University Medical Center is well equipped for the future.

FIRST STONE LAYING OF THE PAUL-KLEIN-CENTER FOR IMMUNE INTERVENTION (PKZI)

The foundation of the seven-story PKZI building was laid on February 14th. The new building will be home to most of the research groups in the fields of immunology and immunotherapy. The total costs add up to € 34 million and are financed jointly by the Federal Government and the State of Rhineland-Palatinate. By the end of 2016, scientists in different fields of expertise will be jointly working in the PKZI and under the umbrella of the Research Center of Immunotherapy. The center is named after Professor Paul Klein who researched in the field of Medical Microbiology and Immunology from 1961 until his retirement in 1990. He was involved in the institute’s first two collaborative research centers, “Executive mechanisms of immune reaction” (CRC 107, 1973-1984) and “Immunopathogenesis” (CRC 311, 1987-1999) and was a long-standing director of the institute.

PROFESSOR WERNER E.G. MÜLLER RECEIVES THE ORDER OF MERIT OF THE FEDERAL REPUBLIC OF GERMANY

On February 21st, Professor Werner E. G. Müller was honored with the Order of Merit of the Federal Republic of Germany by Doris Ahnen (at that time Rhineland-Palatinate’s Minister of Science). He received this tribute for his dedication to international research collaborations and groundbreaking findings in context of his research on marine sponges.

RESTAFFING OF THE MANAGEMENT BOARD

Two important personnel decisions were made in context of a special session of the University Medical Center’s supervisory board. Professor Babette Simon was appointed to take up the positions of Chairwoman and Chief Medical Officer from April 2014 onwards. Moreover, the supervisory board chose Marion Hahn as Evelyn Möhlenkamp’s replacement in the position of Chief Care Officer from February 2014 onwards. Both will have five-year terms.

January

February

Doris Ahnen (Finance Minister of Rhineland-Palatinate), Professor Georg Krausch (President of the Johannes Gutenberg University), Dr. Waltraud Kreutz-Gers (Chancellor of Johannes Gutenberg University), Univ.-Prof. Dr. med. Ulrich Förstermann (Dean and Chief Scientific Officer), Götz Scholz (Chief Financial Officer), Marion Hahn (Chief Nursing Officer), Univ.-Prof. Dr. med. Norbert Pfeiffer (Director of the Department of Ophthalmology) at the New Year Reception

Doris Ahnen (Finance Minister of Rhineland-Palatinate), Professor Georg Krausch (President of the Johannes Gutenberg University), Professor Ulrich Förstermann (Dean and Chief Scientific Officer of the University Medical Center Mainz), Professor Norbert Pfeiffer (Director of the Department of Ophthalmology)
BUILDING REFURBISHMENT
At the end of March, new plans for the refurbishment of Duesbergweg 6 were presented. A biomedical research center that pools the University Medical Center’s neuroscientific fundamental research will be created. The refurbishment is jointly financed by the Federal Government and the State of Rhineland-Palatinate with a budget of € 42 million. The project aims to enable biomedical neuroscientific research according to the most modern standards.

NEW VICE DEANS
During a constitutive faculty board meeting on April 29, 2014, Professor Stephan Letzel and Professor Manfred Beutel were elected as Vice Dean for Learning and Teaching and Vice Dean for Research.

ADVANCED THERAPY FOR VALVULAR HEART DISEASE
Univ.-Prof. Dr. Ulrich Hink of the University Medical Center of Johannes Gutenberg-University Mainz is appointed to the first professorship for Interventional Heart Valve Therapy nationwide. The interventional heart valve therapy is a minimal-invasive procedure, to treat valve insufficiency.

NEW HIGH TECH TISSUE BIOBANK
The University Center of Tumor Diseases (UCT) established a new high tech tissue biobank in the rooms of the Institute of Pathology. It stores up to 14,000 tissue samples and thereby serves as a foundation of cancer research.
MILESTONES

FIRST HEISENBERG PROFESSORSHIP FOR THE UNIVERSITY MEDICAL CENTER MAINZ

Professor Krishnaraj Rajalingam won the prestigious Heisenberg Professorship of the German Research Foundation (DFG) and has started off as a tenured cell biology professor at the University Medical Center Mainz. One of his main research interests is the defective signal transduction in cells and its influence on chronic diseases such as infections, cancer and autoimmune disorders.

Krishnaraj Rajalingam, a group leader from IBCII and a BIF-PLUS3 fellow has been selected for the prestigious W3 Heisenberg professorship in Cell Biology by the DFG. With this award, he joins the Research Center for Immunotherapy (FZI) at the Johannes Gutenberg-University Mainz (JGU) to establish a cell biology unit.

SUMMER UNIVERSITY OF RESEARCH CENTER FOR IMMUNOTHERAPY

For the eighth time, the Research Center for Immunotherapy hosted a Summer University. The focus topics were immunology and biomedicine. Twenty-four high school students were able to gather information and gain insights into laboratory work. The project aims to arouse their spirit for research.

COOPERATION AGREEMENT WITH HEBREW UNIVERSITY JERUSALEM

At the beginning of June, a group of scientists from the Hebrew University Jerusalem came to visit the University Medical Center Mainz. During this meeting, valuable contacts were established and a closer collaboration was encouraged. These intentions were consolidated through a cooperation contract.

Professor Shlomo Sasson (Vice Dean for Research of the Medical Center of the Hadassah Medical Center of the Hebrew University of Jerusalem and Professor Ulrich Förstermann (Dean and Chief Scientific Officer of the University Medical Center Mainz).

Professor Babette Simon (Chief Medical Officer, CEO) Professor Ulrich Förstermann (Chief Scientific Officer, Dean), Professor Hansjörg Schild (Director of the Institute of Immunology) welcome Professor Krishnaraj Rajalingam to the University Medical Center Mainz.

JUNE

Professor Detlef Schuppan of the University Medical Center of the Johannes Gutenberg-University Mainz was awarded the "Maki Celiac Disease Tampere Prize", worth €15,000, from the University of Tampere in Finland. The jury defended their decision in July stating that in 1997 the gastroenterologist had a successful breakthrough in celiac research.

JULY

SEPTEMBER
PROFESSORS RECEIVE ORDER OF MERIT OF RHINELAND-PALATINATE

Malu Dreyer, Prime Minister of Rhineland-Palatinate, honored Professor Thomas Münzel and Professor Jörg Michaels with the Order of Merit of Rhineland-Palatinate. Professor Münzel received the tribute due to his groundbreaking research on cardiovascular diseases and his dedication in raising public awareness of these diseases. Professor Michaels was honored for decades of research work in several positions and the promotion of science.

INSPECTION OF TRANSREGIO INITIATIVE 156

At the beginning of December, the Transregio Initiative 156 began. The skin as a sensor and effector organ orchestrating local and systemic immune responses was explored. Several working groups from the University Medical Center Mainz’ research focus immunology participate in this research center.

ACKNOWLEDGEMENT OF YOUNG RESEARCHERS WITHIN THE CONVENTIO MEDICINAE

For the fifth time, the University Medical Center of the Johannes Gutenberg-University honored top young scientists at the Conventio Medicinae, the central academic ceremony of the department. More than 30 young scientists were recognized. They received prizes, stipends and other exceptional distinctions for outstanding scientific performance.

MILESTONES
RESEARCH ACTIVITIES

This section provides the Key Performance Indicators (KPIs) for all research activities of the University Medical Center Mainz (UMC). It aims to give an in-depth analysis of the national and international standing of the University Medical Center. The statistics can be divided into the following four categories: funding, publications, technology transfer and promotion of young researchers.

I. FUNDING

Figure 1 shows the third-party funding expenditures from 2010 to 2014. Compared to 2013, funding expenditures increased slightly by 2.1% in 2014. They amounted more than 55 million euros. Therefore, 2014’s third-party funding expenditures again make for an all-time high for the University Medical Center Mainz. This development is mainly attributable to a rise in funding for the pre-clinical and clinical-theoretical medical units.

The different medical units of the University Medical Center Mainz have always had different amounts of third-party funding. Those differences result from the unequal conditions in number of funding programs for the different units, as well as diverging effort spent on funding applications.

The ongoing rise in third-party funding expenditures enables researchers at University Medical Center Mainz to invest more in their scientific projects and increase the number of publications.

FIG. 1: Development of Third-party Funding Expenditures
Figure 2 shows the allocation of sources of the third-party funding expenditures in 2014. The development from 2010 to 2014 documents that the funding of public sponsors (e.g., European Union and German Research Foundation) increased steadily, while private sponsoring (e.g., industrial project partners) stayed the same level in the last years.

Figure 3 shows the annual amount (~3.6 million euro) for individual grants funded by the German Research Foundation (DFG) in 2014. This period the annual amount of granted collaborative projects was 31% higher (~5.3 million euro), which means that synergies could be used efficiently at the UMC.
II. PUBLICATIONS

One important KPI regarding the University Medical Center’s publications is the number of publications with Impact Factor Points (Figure 4). The overall number for the University Medical Center in 2014 is 1027 and therefore nearly on the same level in comparison to 2013. The large amount of publications strengthens the national and international standing of the University Medical Center Mainz.

Figure 5 shows that the sum of impact factors for all publications in 2014 is 4218. Although the number of publications was only slightly different, it is clear in fig. 5 that a few publications, which were published in journals with higher impact factor points make a big difference.

Impact Factor Points (IF)
Person-related cumulative impact factors (CIF) have been used to evaluate the overall performance of scientists within an institute. In doing this, the impact factor points from all publications (regardless of their date) were compiled for each area and are shown as a value of each institute. The calculation was based on the German Council of Science and Humanities’ guidelines. The cumulative impact factors are determined on an institute-by-institute basis and these in turn are the basis for internal performance-based fund allocation (PBFA).

Figure 6 shows, that the “General Medicine” unit had a significant CIF increase of 60.1% from 2013 in 2014. Similarly, the Dental Clinic saw a 35.1% increase and the Clinical-Theoretical Institutes a 37.9% increase. Although the University Medical Center reported fewer publications, there was no significant decrease of CIF in any of the units. In addition, the development illustrates an increase of CIF-points from 2013 (1, 5) to 2014 (1, 6) related to any individual publication.
Figure 7 shows the number of staff with publications. The number increased this year from 1136 in 2013 up to 1166 in 2014, which is even higher than the 1151 reported in 2012. These numbers show that the scientists at the University Medical Center are extremely dedicated to their work in research and continue to make progress despite large workloads.

Number

FIG. 7: Number of Staff with Publications
Open Access-Publications are digital publications which are free to users to read, download, and reproduce. Open Access provides the worldwide community of scientists with the newest research results more quickly than traditional journals, thereby promoting not only international, but also interdisciplinary cooperation. The University Medical Center (UMC) and the Johannes Gutenberg-University (JGU) Mainz have adopted an open-access policy to support open access publishing of research data. In 2012, UMC and JGU built up an Open Access Publication fund to sponsor the publication of its employees’ research results in Open Access journals. For three years in a row now, UMC and JGU were able to apply successfully for DFG-grants to increase the Open Access Publication fund. The diagram shows the development of Open Access-Publications at the UMC from 2010 to 2014. The number of Open Access publications rose from just 68 in 2010 (4 % of all publications of the UMC) to 156 by 2014 (9 % of all publications). By increasing the Open Access publication output, UMC is positively contributing to the exchange of information among scientists and is making its research known to the public.

Figure 9 depicts the top scientists of the University Medical who achieved a cumulative impact factor of more than 15. Although the number of authors remained the same in 2014 from 2013, the overall CIF of the authors increased.
III. TECHNOLOGY TRANSFER

While the key performance indicators in the category publications show the scientific standing of the University Medical Center Mainz, the category technology transfer rather focuses on the transferability of projects to medical practice.

With 19 inventions in 2014 the number of disclosed inventions is slightly below the average of the past five years, which can be seen as a normal fluctuation. Nevertheless, even more effort has been made in 2015 to further the University Medical Center’s technology transfer. The number of 17 disclosed inventions by midyear 2015 indicates a first positive result of the measures.

Figure 10 shows, that the number of patent registrations decreased compared to 2013. However, this development should not be assessed too negative, because 2013’s number was comparatively high. After the initial patent application, which establishes priority (usually for the EU states), patent protection is often extended to new regions via additional patent applications in countries such as the United States and Japan. These additional applications are not included in the figures presented here.

Next to the patent registrations the transfer of intellectual property rights is a key performance indicator regarding successful technology transfer. In 2014, eight inventions of University Medical Center’s researchers were transferred to pharmaceutical enterprises, which shows a strong incline compared to the previous years.
IV. PROMOTION OF YOUNG RESEARCHERS

The University Medical Center Mainz places strong emphasis on fostering and developing young research talent. One way to measure the success of young researchers is to take a look at the awards bestowed upon them. Once again, the number of doctorates awarded was upheld. In 2014, 287 doctorates were conferred at the University Medical Center. Human medicine received 220 awards and 62 went to dentistry. Five outstanding candidates received the title „summa cum laude“ (Figure 11). Moreover, 15 scientists successfully completed their postdoctoral lecturing qualification. It is important to consider that the number of persons who are currently registered for this qualification is much higher than the number of those who already finished. Firstly, this difference is caused by both the scientists’ academic diligence and their involvement in the hospital’s daily routines. Secondly, high-quality scientific thesis require a larger period of preparation and more time. In summary, the number of doctorates remained at a constantly high level.

![Chart showing the number of awards by year and category](chart)

**FIG. 11:** Young Scientists that received their doctoral and postdoctoral degrees

Thanks to the dedication of the Committee on Equal Opportunities, the University Medical Center is able to constantly improve gender equality throughout the different units of this institution. 2014’s statistics on graduated young scientists gives evidence of the success of the endeavors so far: 172 women and 115 men received their doctoral degree.
NEW FACULTY

PROFESSOR PHILIPP DREES
CENTER FOR ORTHOPEDICS AND TRAUMA SURGERY
University Medical Center of the Johannes Gutenberg-University Mainz
Full Professorship (W3) for Orthopedics, Orthopedic and Rheumatoid Surgery

PROFESSOR SERGIU GROPPA
DEPARTMENT OF NEUROLOGY
Christian-Albrechts-University of Kiel
Full Professorship (W2) for Neurology with Focus on Movement Disorders

PROFESSOR ULRICH HINK
DEPARTMENT OF MEDICINE II
University Medical Center of the Johannes Gutenberg-University Mainz
Full Professorship (W2) for Interventional Cardiac Valve Therapy

PROFESSOR ALEXANDER HOFMANN
CENTER FOR ORTHOPEDICS AND TRAUMA SURGERY
University Medical Center of the Johannes Gutenberg-University Mainz
Full Professorship (W2) for Special and Reconstructive Trauma Surgery

PROFESSOR CHRISTOPH MATTHIAS
DEPARTMENT OF OTORHINOLARYNGOLOGY, HEAD- AND NECK SURGERY
Georg-August-University Göttingen
Full Professorship (W3) for Otorhinolaryngology

PROFESSOR OLIVER MUNSTERER
DEPARTMENT OF PEDIATRIC SURGERY
New York Medical College Valhalla (USA)
Full Professorship (W3) for Pediatric Surgery
NEW FACULTY

PROFESSOR MARIANNE MÜLLER-SITZ
DEPARTMENT OF PSYCHIATRY AND PSYCHOTHERAPY
Max Planck Institute of Psychiatry
Full Professorship (W2) for Experimental Psychiatry

PROFESSOR KRISHNARAJ RAJALINGAM
INSTITUTE OF IMMUNOLOGY
Goethe University Medical School Frankfurt
Heisenberg Professorship of the German Research Foundation (W3) for Cell Biology

PROFESSOR SIMON RUMPPEL
INSTITUTE OF PHYSIOLOGY
Research Institute of Molecular Pathology Vienna
Full Professorship (W2) for Systemic Neurophysiology

JUNIOR PROFESSOR MAIK STÜTTGEN
INSTITUTE OF PATHOPHYSIOLOGY
Junior Professorship (W1) for Molecular Neurophysiology
Ruhr University Bochum

PROFESSOR GER VAN ZANDBERGEN
INSTITUTE OF IMMUNOLOGY
Paul-Ehrlich-Institute Langen
Full Professorship (W2) for Molecular Immunology of Infections

PROFESSOR ULRICH ZECHNER
INSTITUTE OF HUMAN GENETICS
University Medical Center of the Johannes Gutenberg-University Mainz
Full Professorship (W2) for Human Molecular Genetics and Epigenetics
SPECIAL AWARDS

DR. ANDREAS BARDENS
INSTITUTE OF MEDICAL MICROBIOLOGY AND HYGIENE
Award of the Johannes Gutenberg University Mainz

DR. MONIKA BJELOPAVLOVIC
DEPARTMENT OF PROSTHODONTICS
Peers Promotional Award

PROFESSOR PETER BROCKERHOFF
DEPARTMENT OF OBSTETRICS AND GYNECOLOGY
Teaching Award Rhineland Palatinate

DR. UTE DIESTLER
INSTITUTE OF IMMUNOLOGY
Boehringer Ingelheim Prize

DR. DOMINIC DOCTER
DEPARTMENT OF OTORHINOLARYNGOLOGY, HEAD- AND NECKSURGERY
Award of the Scientific Medical Research Center (NMFZ) for Interdisciplinary Research

DR. DOMINIC DOCTER
DEPARTMENT OF OTORHINOLARYNGOLOGY, HEAD- AND NECKSURGERY
Fellowship of the Walter and Sibylle Kalkhof Rose Foundation

DR. JÖRN DOPHEIDE
DEPARTMENT OF MEDICINE II
Research Fellowship of the Margarete Waitz Foundation

DR. CHRISTINA ERBE
DEPARTMENT OF ORTHODONTICS AND DENTOFACIAL ORTHOPEDICS
Invisalign Research Award

DR. ALEXANDER GAWLITZA
INSTITUTE OF MEDICAL MICROBIOLOGY AND HYGIENE
Dr. med. Erich and Ella Tancré Foundation

DR. SARAH GRIMM
DEPARTMENT OF ORTHODONTICS AND DENTOFACIAL ORTHOPEDICS
Martin Herrmann Science Award

DR. COLLIN JACOBS
DEPARTMENT OF DENTOFACIAL ORTHOPEDICS
Teaching Award of the Johannes Gutenberg University Mainz

PROFESSOR BERND JANSEN
INSTITUTE FOR MEDICAL MICROBIOLOGY UND HYGIENE
Gütesiegel of the MRE Network Rhine-Main

DR. WOLFGANG JÄGER
DEPARTMENT OF UROLOGY
DGU Innovation and Research Prize

PROFESSOR ANNEROSE KEILMANN
DEPARTMENT OF OTORHINOLARYNGOLOGY, HEAD- AND NECKSURGERY
Award of the German Society of Phoniatics and Pediatric Audiology

PROFESSOR ANNEROSE KEILMANN
DEPARTMENT OF OTORHINOLARYNGOLOGY, HEAD- AND NECKSURGERY
Award of the Union of the European Phoniaticians

PROFESSOR ANNEROSE KEILMANN
DEPARTMENT OF OTORHINOLARYNGOLOGY, HEAD- AND NECKSURGERY
Karl Storz Prize

DR. SEBASTIAN KLOBUCH
DEPARTMENT OF HEMATOLOGY, PNEUMOLOGY, AND ONCOLOGY
Award of the Hedwig St. Denis Foundation

HANNAH KÖHRING
DEPARTMENT OF DERMATOLOGY
Junior Members poster award of the DGAKI
DR. ULRRIKE KRAHN  
INSTITUTE OF MEDICAL BIOMETRY, EPIDEMIOLOGY AND INFORMATICS (IMBEI)  
Gustav Adolf Lienert Award

DR. NINA-KIM KRÖHER  
DEPARTMENT OF PSYCHIATRY AND PSYCHOTHERAPY  
Edith Heischkel Mentoring Program

DR. JULIA LAMPERTER  
DEPARTMENT OF OPHTHALMOLOGY  
Glucoma Research Award of the German Ophthalmology Society

DR. VOLKER LENNERZ  
DEPARTMENT OF MEDICINE III  
Award of the CIMT-association

DIANE LUDWIG  
DEPARTMENT OF MEDICINE II  
Award “Studying as a parent” of the University Medical Center’s Foundation

PROFESSOR WERNER E.G. MÜLLER  
INSTITUTE OF PHYSIOLOGICAL CHEMISTRY  
The Order of Merit of the Federal Republic of Germany

PROFESSOR THOMAS MÜNZEL  
DEPARTMENT OF MEDICINE II  
Paul Morawitz Award 2014

DR. ANDREAS NEISIUM  
DEPARTMENT OF UROLOGY  
Werner Stähler Commemorative Prize

DR. AXEL NEULEN  
DEPARTMENT OF NEUROSURGERY  
Foundation for Neurosurgical Research of the DGNC

NATARAJAN PERUMAL  
DEPARTMENT OF OPHTHALMOLOGY  
Dry Eye Award 2014

PROFESSOR NORBERT PFEIFFER  
DEPARTMENT OF OPHTHALMOLOGY  
Anagnostakis-Trantas Award of the Greek Glaucoma Society

PROFESSOR KRISHNARAJ RAJALINGAM  
INSTITUTE OF IMMUNOLOGY  
Heisenberg Professorship

PROFESSOR POL M. ROMMENS  
CENTER FOR ORTHOPEDICS AND TRAUMA SURGERY  
Johann-Friederich Dieffenbach Bust from the German Society of Trauma Surgery (DGU)

DR. RICHARD SCHELL  
DEPARTMENT OF MEDICINE II  
Promotional Award of the Margarete Waitz Foundation 2014

PROFESSOR DETLEF SCHUPPAN  
INSTITUTE OF TRANSLATIONAL IMMUNOLOGY  
Maki Celiac Disease Tampere Prize

DR. SERGE THAL  
DEPARTMENT OF ANESTHESIOLOGY  
Heinrich Dräger Prize

DR. SIMON THEISS  
TEACHING DEPARTMENT OF GENERAL MEDICINE  
Prize of the German General Practitioners’ Association Rhineland-Palatine e.V.

DR. LEA VON BIALY  
Prize of the German General Practitioners’ Association Rhineland-Palatine e.V.

DR. CHRISTIAN WALTER  
DEPARTMENT OF ORAL AND MAXILLOFACIAL SURGERY  
Teaching Prize 2014

DR. JULIA WEINMANN-MENKE  
DEPARTMENT OF MEDICINE I  
Boehringer Ingelheim Prize 2014

ELENA WÜSTENHAGEN  
INSTITUTE FOR MEDICAL MICROBIOLOGY UND HYGIENE  
PhD Stipend Max Planck Graduate Center

DR. TIM ZIMMERMANN  
DEPARTMENT OF MEDICINE II  
Prize of the German Transplant Society (DTG)
RESEARCH ENTITIES

Key Research Center of Translational Medicine
Key Research Area
Research Cluster
German Center of Health Research
Profile Centers
Key Scientific Research Platforms
Key Scientific Teaching Platform
The vertebrate immune system has developed to protect the organism against infections. This is supported by the finding that congenital or acquired immunodeficiencies increase susceptibility to infections. However, immune responses need to be carefully calibrated as hyper-reactivity towards environmental or “self” antigens causes allergic and autoimmune diseases. The common denominator in the pathogenesis of these widespread human diseases is a dysregulated immune system. Therefore, understanding the basic principles of immunity and their dysregulation in pathogenesis of disease is of fundamental importance for the development of immunointervention strategies. Their translation into clinical practice represents the ultimate goal of our activities. Major advances in different fields of immunological research in recent years have provided a foundation of knowledge that puts this goal within reach.

The complex mechanisms involved in inflammatory processes, in the control of tumor development and in the interaction of pathogens with the immune system still pose a major challenge to immunologists and clinicians. In this key research field, investigators with multifaceted expertise in basic and clinically oriented immunological research strive to combine and coordinate their activities in an effort to further improve our understanding of the immunological basis of infectious, allergic, autoimmune and neoplastic diseases, with the ultimate aim of developing novel strategies for immune intervention. Our activities are funded by the collaborative research centers SFB1066 “Nanodimensional polymer therapeutics for tumor therapy” and TR128 „Initiating/effector versus regulatory mechanisms in Multiple Sclerosis – Progress towards unraveling and treating the disease“ (speaker Frauke Zipp) of the DFG and by the European Union with the ERC Advanced Grant “Quantitative Imaging of Liver Fibrosis and Fibrogenesis” (Detlef Schuppan) and the ERC Starting/Consolidator Grant „NutrImmune - Nutrient-controlled molecular pathways instructing development and function of mucosa-associated innate lymphocytes“ (Andreas Diefenbach) and the NeuroKine Project (EU FP7 Integrated Training Network – coordinator Ari Waisman).

In addition, we receive support from the Government of the State of Rhineland-Palatinate as one of the research centers of the University of Mainz. Within the research center for immunotherapy, which was founded in 2008, we have established several research programs supporting collaborative research projects and various technology platforms. These platforms, which include core facilities for asthma research, confocal microscopy, immunohistochemistry, flow cytometry, conditional gene targeting and protein biochemistry and mass spectrometry, are available to researchers of the University Medical Center and the Johannes Gutenberg University (www.fzi.uni-mainz.de). In 2014, two new leading scientists could be recruited, Prof. Dr. Krishnaraj Rajalingam and Prof. Dr. Ger van Zandbergen (both Institute for Immunology). Prof. Rajalingam received the first Heisenberg-Professorship of the University Medical Center in Mainz. Ute Distler - a member of the working group from the FZI-core facility protein biochemistry and mass spectrometry Stefan Tenzer - received the Boehringer Ingelheim Prize 2014.

In February 2014, there was the laying of the foundation stone of the Paul Klein Center for Immunointervention (PKZI), where the research activities within the FZI will be centralized. In 2014, the FZI with Prof. Dr. Frauke Zipp and Prof. Dr. Ari Waisman as congress chairs organized the 12th International Neuroimmunology Congress (ISNI) in Mainz. Other scientific meetings such as the NextGen Genomics & Bioinformatics Technologies (NGBT) and the 2nd Waldthausen-Castle Symposium were (co-)organized by FZI members. Additionally, the FZI supported and organized the 8th SommerUni Immunology and Biomedicine at the University Medical Center Mainz. Members of the key research area immunology published more than 350 original papers and articles, were invited to about 140 talks during scientific conferences, filed several patent applications and, in addition to the funding by coordinated research programs, they received support through individual grants from the DFG, the European Union and other organizations.
FUTURE DIRECTIONS

The characterization of target structures recognized by immune effector mechanisms, the discovery of pathogen-derived pattern recognition by cells of the innate immune system, the identification of cytokines controlling and coordinating innate and adaptive immunity, the redirection and amplification of adaptive immune responses and the discovery of networks involved in the regulation of immune responses have significantly improved our understanding of the immune system. In 2014 two initiatives for collaborative research centers were reviewed positively. One of them, the CRC/TR 156 „The Skin as Sensor and Effector Organ Orchestrating Local and Systemic Immune Responses“, a collaboration project with the Universities of Heidelberg and Tübingen, will be funded by the DFG from July 2015 on for 4 years initially. The main objectives of the consortium are the better understanding of the skin as an innate immune barrier and the influence of skin immune reactions on systemic immunity and vice versa. Additionally it is the aim of the CRC to provide knowledge about the cells and molecules orchestrating the intracutaneous immune cross talk.

In 2015 a new CRC initiative that will be focused on immune intervention regarding the convergent mechanisms of inefficient immunity in tumors and chronic infections will be initiated by FZI-members. The FZI started to support 9 translational research groups with the long-term aim to transfer the knowledge of immunological oriented basic research to clinical applications. In the future, these groups could request a proposal for a clinical research unit.
In 2014, the Focus Program Translational Neuroscience (FTN) continued to push its activities in appointing outstanding scientists in strategic important positions such as systems neurophysiology, pathophysiology, translational psychiatry, neurogenetics, and neurobiology of resilience. By such strategic planning, the FTN made further progress to establish neuroscience research in Mainz as a center of national and international importance. Established collaboration research continued in DFG-funded CRCs (SFB 1080 and SFB/TR 128). Research within the FTN is supported by several research platforms and uses close collaborations with researchers in the rhine main neuroscience network (rmn2). To further focus and prioritize its research within the area of network homeostasis and prevention of disease, the FTN has formally established the “Deutsches Resilienz-Zentrum” (DRZ) in July 2014.

Based on extensive research efforts on network homeostasis in the brain, resilience research has become a major research focus within the FTN since more than three years. This resulted in the formal establishment of the “Deutsches Resilienz-Zentrum” (DRZ) in July 2014 (spokespersons Robert Nitsch and Klaus Lieb). The DRZ’s tripartite approach of combining basic neuroscience, clinical neuroscience and social science provides a comprehensive scientific basis to address one of the most important challenges of modern, knowledge-based societies, i.e. how people and the society can be resistant to stress, i.e. resilient, in a dramatically changing environment. By doing so, the DRZ aims to advance the paradigm shift from disease-oriented towards health- and prevention-oriented research.

In addition to the well established FTN platforms such as the human neuroimaging center (NIC) or the mouse behavioral unit (MBU), the FTN has established another major platform project in 2014, the “Gutenberg Brain Study” (GBS). The GBS is in the process of establishing a population-based sample of 5,000 subjects from Mainz and the surrounding area in order to address important questions at the heart of neuroscience research in the FTN. The overall research theme of this platform is the explanation of molecular aspects of brain structure and function in line with the research focus of FTN in network homeostasis and resilience. In addition to the study of the normal brain principles, in particular those that enable the human brain to respond to environmental influences (e.g. stress) in order to preserve function and structural integrity will be explained.
FUTURE DIRECTIONS

One major objective of the FTN is to further position neurosciences at the University Medical Center and at the Johannes Gutenberg-University in Mainz among the five most important neuroscience locations in Germany. We would like to enhance our profile by our research on resilience which is unique in Europe and clearly differentiates ourselves from other neuroscience centers in Europe which focused their research on certain mental disorders like Alzheimer’s disease or bipolar disorder. Therefore, we closely co-operate with many important institutes within the rhine-main neuroscience network (rmn2) like the MPI for Brain Research or the MPI for Empirical Aesthetics.

Special focus is also laid on the further development of the newly formed research center on resilience (the DRZ) at the JGU. It is an interdisciplinary integrative attempt initiated by neuroscientists, psychologists, clinicians and social scientists to advance mental health by preventing stress-related diseases. The DRZ aims to provide a structural and long-term perspective for research on resilience and for attracting further structural funding from federal sources. A CRC-initiative on “Neurobiology of Resilience” (Spokesperson: Beat Lutz) was submitted to the DFG in April 2014, and the full proposal will be evaluated in early 2016 by the DFG. The current personnel provides an excellent basis for the DRZ, providing promising long-term perspectives for the planned projects and research strategies.
OVERVIEW

Cardiovascular Research is one of the three main research areas in the University Medical Center Mainz and is coordinated by the Center for Translational Vascular Biology (CTVB). The research center bundles all institutions and working groups dedicated to the research field and represents an interdisciplinary platform that strategically structures and sustainably establishes large-scale research efforts and promotes educational programs and career paths at the UMCM.

HIGHLIGHTS

Research activities are focused on the following three interdisciplinary large-scale areas:

The Gutenberg-Health Study (GHS), one of the largest single center epidemiological population-based cohort studies world-wide was initiated in 2007 primarily focusing on cardiovascular epidemiology. The GHS offers interfaces to other research areas, especially research in ageing and maladaptation of human health. In this context, the CTVB has large-scale high-quality biodatabases available as research resource not only from the population, but also various clinical conditions.

In 2010, the BMBF-funded Center for Thrombosis and Hemostasis (CTH) was founded as integrated research and treatment center addressing translational science in thrombosis and hemostasis with interfaces to the fields of immunology and oncology. The CTH provides an integrated basic and clinical research structure with capabilities for national and international multicenter trials.

Last, the UMC Mainz contributes with these unique facilities as member to the BMBF-funded German Center for Cardiovascular Research (Deutsches Zentrum für Herz-Kreislauf-Forschung, DZHK) since 2011. The translational research program of the DZHK-Center Rhein-Main (together with the Goethe University Frankfurt and Max-Planck Institute Bad Nauheim) covers the exploration of the interaction between myocardium and vasculature.

In 2014, the CTVB strengthened its translational research portfolio and the structures within these areas by supporting the initiation of further professorships within the field (W2 professorship for translational vascular biology, W3 professorship clinical epidemiology), focused translational research projects (Departments of Ophthalmology, Pharmacology and IMBEI), as well as investments in technology (intravital microscopy, CTH).

After external review, the working program at the UMCM within the Center Rhein-Main of the German Center for Cardiovascular Research was approved for funding by the BMBF from 2014 to 2018 (budget: 2.2 Mio EUR). The appointment of a new W3-professorship for „Myocardial und Vascular Interaction“ will be supported by a BMBF budget of 680,000 EUR. The position was advertised in late 2014 and is envisaged to start its work in late 2015.

The CTH was initially funded from September 2010 to August 2015 and was successfully evaluated for continuation of the scientific working program and structural concept for a second 5-year funding period by an international panel of experts in October 2014. The board approved the institutional funding with a budget of approximately 24 Mio EUR from September 2015 to August 2020.
FUTURE DIRECTIONS

SCIENTIFIC AIMS
The CTVB’s mission is to investigate the dynamic adaptation of the cardiovascular system to ageing processes, environmental factors and metabolic and inflammatory changes that contribute essentially to the maintenance of organ functions and therefore physical and mental health. Special interest is set on the failure of the homeostatic regulation against the background of genetic predisposition and epigenetic malfunction that play pivotal roles in the development of chronic cardiovascular, thromboembolic and metabolic diseases.

STRUCTURAL AIMS
• To establish further large scale research initiatives for a sustainable development of the research area
• To foster young researchers in a career in cardiovascular research
• To develop a common regional concept for cardiovascular science with the Goethe University Frankfurt for future sustainability
• To strengthen the visibility of the research within the CTVB on a national and international level
In 2014, BiomaTiCS continued its established collaboration projects in the area of „smart materials“ and „individualized materials“ and pushed its activities forward with the partners of the Max-Planck Institute of Polymer Research (Prof. Landfester and Dr. Frederik Wurm), the Department of Physiological Chemistry (Prof. Müller, Prof. Schröder, Prof. Wang) and the Department of Chemistry (Prof. Tremel and Prof. Frey). On the fundamentals of these interdisciplinary cooperation projects BiomaTiCS published 45 publications and was able to submit several patents. Five representative publications are listed below:


Important milestones have been the granted scientific proposal at the European Research Council (ERC) of Professor Müller and the 6th International Pectus Symposium & Live Surgery Workshop together with the BiomaTiCS-Symposium in November 2014. With this international congress it was possible to integrate more surgical disciplines such as the pediatric surgery with Professor Turial into the network of BiomaTiCS. In order to strengthen the linkage between the material scientists and the Max Planck-Institute for Polymer Research, the integration into the Mainz Research School of Translational Biomedicine (Transmed) was demonstrated by the contribution to the Transmed Science Day 2014 and the series of lectures that were carried out by principle investigators of BiomaTiCS (Prof. Al-Nawas, Prof. Brieger, Prof. Hofmann, Prof. Mailänder).
It has already been demonstrated that especially the translation between surgeons and material scientist leads to a new quality of smart and individual material design and helps to improve difficult clinical situations with the medical and material expertise of BiomaTiCS. The aims of BiomaTiCS will be the integration and establishment of new surgical disciplines and material scientists in their network and to use the generated synergies for the development of promising collaborations with the focus on “new and intelligent materials” in regenerative medicine.
**OVERVIEW**

The CRC 1066 “Nanodimensionale polymere Therapeutika für die Tumortherapie” addresses the development of a nanoparticle based tumor immune therapy.

**HIGHLIGHTS**

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<td>Mini-Symposium: Imaging-Methods in the Tumour Therapy</td>
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<td>Joint seminar of the Graduate School and Students of Prof. Kataoka, University of Tokyo</td>
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FUTURE DIRECTIONS

Within a highly interdisciplinary course, the SFB 1066 is directed to combine (i) innovative therapy approaches arising from the immunology and oncology with (ii) the synthesis of a variety of well characterized and adapted functionalized nanoparticles and (iii) an evident characterization of the nanomaterial under biological relevant environment. The expertise of the Johannes Gutenberg Universität Mainz (JGU) and the Max-Planck Institute for Polymer Research (MPIP), which is together a leading location for polymer science in Germany, as well as offering an excellent research structure in the field of tumor immune therapy of the University Medical Center, are combined. Therefore, scientist from the fields of chemistry, immunology and biomedicine develop novel, multifunctional nano-dimensional therapeutics, providing cell specific drug release as well as rendering sensitive active ingredients (eg. RNA) applicable.

For the chemists, the challenge is to synthesize well-defined polymeric carrier systems and to modify them, render them functional, and to load them with suitable therapeutic agents. Building on these synthetic steps, the scientists will go on to test these carrier systems in cross-sectional projects with respect to their interactions in extracellular media, cellular uptake, and distribution in the body. Thereafter the biomedical specialists will then test these systems in combined tumor immunotherapy based on the targeted induction of inflammation in the tumor, stimulation of the immune response, and neutralization of tumor tolerance.
OVERVIEW

In recent years, research into homeostasis in the nervous system has gathered significant momentum. What is more, with its move to the centre stage of scientific research, it is now considered by many to be a “hot topic”. With this in mind our initiative has tasked itself with gaining a new understanding of the molecular and cellular mechanisms underlying the ability of the nervous system to maintain a balanced and stable internal state (homeostasis) when faced with constant input from an everchanging environment. This ability is undoubtedly the most remarkable feature of the nervous system and by unraveling the mechanisms involved, we will provide a new basis for research into regeneration that will factor in both the attempt of neural tissue to regain its equilibrium in reaction to an insult, as well as the failure of these stabilizing mechanisms in progressive disorders. Our initiative is confident in its research and scientific discussions making a significant contribution to a clearer understanding of the concept of neural homeostasis. Moreover, this new understanding of the impact of homeostatic mechanisms and their potential pharmacological regulation will provide a solid basis for novel therapeutic strategies.

Spokesperson:
Professor
Robert Nitsch

Nett A, Mergia E, Neubacher U et al. NO regulates the strength of synaptic inputs onto hippocampal CA1 neurons via NO-GC1/cGMP signalling. *PFLÜGERS ARCHIV-EUROPEAN JOURNAL OF PHYSIOLOGY*. 2014; 467(6), 1383-1394.


**HIGHLIGHTS**

**STEERING COMMITTEE:**
- Robert Nitsch (spokesperson): Johannes Gutenberg University Mainz
- Amparo Acker-Palmer (deputy spokesperson): Goethe University Frankfurt
- Heiko Luhmann: Johannes Gutenberg University Mainz
- Jochen Roeper: Goethe University Frankfurt
- Mirko HH Schmidt: Johannes Gutenberg University Mainz
- Erin Schuman: Max Planck-Institute for Brain Research

**PARTICIPATING INSTITUTES:**
- Johannes Gutenberg University Mainz
- Goethe-University Frankfurt
- Max Planck-Institute for Biophysics
- Max Planck-Institute für Brainresearch
- Institute of Molecular Biology Mainz (IMB)

**PROJECTS:**

**A1** Activity-Dependent Regulation of Apoptosis in Developing Rodent: Heiko Luhmann

**A2** Bioactive Phospholipid Signaling in Homeostatic Regulation of Neuron Numbers and Connections: Johannes Vogt/ Robert Nitsch

**A3** EGFL7: A Novel Modulator of Neural Homeostasis in the Hippocampus: Mirko HH Schmidt/Stephan Schwarzacher

**A4** Homeostasis of the Main Olfactory Epithelium in Mouse: Peter Mombaerts

**A5** Defining the impact of newborn neurons in mouse olfactory bulb on neural homeostasis by combining optogenetics with in vivo imaging: Albrecht Stroh/ Benedikt Berninger

**A6** Epigenetic DNA Demethylation in Adaptation and Stability Processes of the Nervous System: Christof Niehrs/Beat Lutz

**A7** Functional Role of the Proteasome and Autophagic Protein Degradation System in Neuronal Homeostasis Following Traumatic Brain Injury: Kristin Engelhard/Thomas Mittmann/Christian Behl

**A8** Stabilization of the Neuronal Homeostasis by Adaptation of Chaperone Activity to Long Term Proteotoxic Stress in vivo: Albrecht Clement/ Christian Behl

**A9** Progranulin in the Adaptive Response of the Nociceptive System to Damage: Irmgard Tegeder

**A10** G2A1 is a redox sensor that controls cellular redox homeostasis by altering mitochondrial shape and function: Axel Methner

**B1** Decoding Neural Activity by Snyaptic Proteome Remodeling: Erin Schuman

**B2** Optogenetic and Ultrastructural Analysis of Synaptic Vesicle Homeostasis at Hyper-stimulated Synapses in Caenorhabditis elegans: Alexander Gottschalk

**B3** Molecular Mechanisms of Synaptic Adaptation after Denervation: Andreas Vlachos/Thomas Deller

**B4** Molecular Mechanisms of Dendritic Development and Maintenance: Amparo Acker-Palmer

**B5** Plasticity Related Gene 1: Functional Role in Homeostasis of Synapse Formation and Maintenance: Robert Nitsch/Jisen Huai

**B6** Molecular mechanisms of neuronal homeostasis during inflammatory processes in the CNS: Michael Schäfer/Frauke Zipp

**B7** Mechanisms of Homeostatic and Allostatic Electrophysiological States of Dopaminergic Midbrain Neurons in Aging and Models of Parkinson’s Disease: Jochen Roeper

**B8** Endocannabinoids in Negative Feedback Mechanisms: Involvement of Epigenetic Mechanisms Underlying Homeostasis and the Shift to Allostasis: Beat Lutz
OVERVIEW

Multiple sclerosis (MS) is the most common chronic inflammatory disease of the central nervous system in the western world and it leads to devastating disability in young adults, with only limited treatment options currently available. The socioeconomic burden of this disease is tremendous, since healthcare costs are very high and it affects decisions young patients must make for the rest of their lives. Findings in patients are a complex composite of inflammation (with demyelination, remyelination, axonal/neuronal damage) typically in subcortical, but also cortical, disseminated lesions and neurodegeneration. Remissions of clinical relapses point to the repair capacity of the CNS, which exhibits strong interindividual and course-dependent differences.

HIGHLIGHTS

The Transregional Collaborative Research Center (CRC/TRR 128) is divided into two parts. Project area A focuses on the elucidation of innate and adaptive mechanisms related to the etiology, onset and course of chronic neuroinflammation. Important intracellular functions as well as antigen recognition and differentiation or shaping of relevant pro-inflammatory or regulatory lymphocyte subpopulations are the focus of these projects. Project Area B addresses significant processes related to transmigration and infiltration of immune cells into the CNS as well as lesion development, lesion resolution and the impact for the overall functional outcome. These approaches often combine molecular and cellular mechanisms with innovative imaging tools, both in rodent experimental systems and in humans.

The University Medical Center plays a central role in the CRC/TRR 128 with Prof. Frauke Zipp (Department of Neurology) acting as its spokesperson, as well as the principal investigators Prof. Ari Waisman (Institute of Molecular Medicine), Prof. Tobias Bopp (Institute for Immunology), Prof. Helmut Jonuleit (Dermatological Clinic), Dr. Volker Siffrin (Department of Neurology) and Dr. Florian Kurschus (Institute of Molecular Medicine) being based here.

In 2014, Mainz was host to the 12th International Congress of Neuroimmunology with Prof. Zipp and Prof. Waisman acting as Conference Chairs. The CRC/TRR 128 was centrally involved in supporting and organizing this event, which attracted approximately 1000 scientists and clinicians to Mainz from around the world. In addition to a session sponsored by the CRC/TRR 128, many of our principal investigators and young researchers presented their work as posters or presentations.
**FUTURE DIRECTIONS**

The CRC/TRR 128 is a consortium of scientists from institutions in the Rhine-Main Neuroscience Network (www.rmn2.de), Münster, Bochum and Munich, who are sharing their complementary scientific expertise and experimental resources as well as their clinical experience to achieve the goal of gaining novel insights into the pathology of MS and ultimately translating this to therapeutic improvements for patients.

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**IMPORTANT PUBLICATIONS // MAX. 5**


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**FIG. 1:** Project area A focuses on the elucidation of innate and adaptive mechanisms related to the etiology, onset and course of chronic neuroinflammation.

**FIG. 2:** Project Area B addresses significant processes related to transmigration and infiltration of immune cells into the CNS as well as lesion development, lesion resolution and the impact for the overall functional outcome. These approaches often combine molecular and cellular mechanisms with innovative imaging tools, both in rodent experimental systems and in humans.
FOR926 “Physiology and Pathophysiology of the Endocannabinoid System” was established in 2008 and prolonged for another three years in 2011. The two joint spokespersons are Prof. Andreas Zimmer (Bonn) and Prof. Beat Lutz (Mainz). FOR926 assembles groups from Mainz, Mannheim, and Bonn. One central project in Mainz involves measurements of endocannabinoids using mass spectrometry. The Research Unit’s aims at examining the principle of the functionality of the endocannabinoid system in a multidisciplinary approach in various model systems (e.g. memory processing, inflammation, pain, Alzheimer’s disease, bone homeostasis, heart and lung functions). In addition, the pharmacological modulation of the system offers new therapeutic possibilities to treat various pathologies.

**HIGHLIGHTS**

Schneider et al., (2014) investigated the modulatory role of the endocannabinoid system on hedonic perception, measured by the pleasure attenuated startle (PAS) paradigm for a palatable food reward. In this paradigm, a conditioned odor is thought to induce a pleasant affective state that attenuates an aversive reflex — the acoustic startle response. Using pharmacological and genetic intervention, the authors found that the CB1 receptor signaling is central for the mediation of hedonic aspects of reward processing. Hiebel et al. (2014) sought to examine the role of CB1 receptor in the context of the evolutionarily conserved autophagic machinery, a main constituent of the regulation of the intracellular energy status. Manipulating CB1 receptor function by siRNA knockdown in mammalian cells caused an elevated autophagic flux, while the expression of autophagy-related genes remained unaltered. Altogether, this study concluded that CB1 receptor activity affects the autophagic flux independently of the two major canonic regulation complexes controlling autophagic vesicle formation (i.e., mTOR and BECLIN1 complex). Duerr et al. (2014) investigated the role of the CB2 receptor in a model of ischemia. The data obtained indicate that CB2 receptor-endocannabinoid axis constitutes a protective mechanisms against several hallmarks of ischemic cardiomyopathy (including apoptosis, inflammatory responses, and collagen deposits). Further studies are needed to explore the underlying mechanisms. Gaffal et al. (2014) characterized the function of CB1 receptor specifically in keratinocytes in a model of CB1 atopic-like dermatitis. They found that CB1 receptor-deficient keratinocytes secreted increased levels of thymic stromal lymphopoietin, a proinflammatory mediator that drives Th2-type skin inflammation in atopic dermatitis, under basal and Th2-type inflammatory conditions. In conclusion, these projects illustrate the broad function of the endocannabinoid system in physiological and pathophysiological processes, both in the nervous system and the many peripheral organ systems. It is hoped that these investigations are able to fuel novel pharmacological approaches to tackle pathologies investigated in FOR926.

**5 MOST IMPORTANT PROJECTS**

- Beat Lutz, Kristzina Monory (Mainz): Characterization of cell type-specific endocannabinoid signaling at biochemical and behavioral level
- Andreas Zimmer (Bonn): The role of the CB2 receptor and human CB2 receptor variants in neuropathic pain
- Oliver Dewald, Daniela Wenzel, Bernd Fleischmann (Bonn): Role of the endocannabinoid system in homeostasis and adaptation to pathological conditions in the cardiopulmonary system
- Christian Behl (Mainz): Analysis of the detrimental effects of Cnr1-/- mice in an Alzheimer’s mouse model and of the interplay between CB1 receptor function and amyloid precursor protein processing
- Beat Lutz (Mainz): Detection and quantification of endocannabinoids and related lipids by LC-MS/MS

Jergas B, Schulte K, Bindila L et al. O-2050 facilitates noradrenaline release and increases the CB1 receptor inverse agonistic effect of rimonabant in the guinea pig hippocampus. NAUNYN SCHMIEDEBERGS ARC PHARMACOL. 2014; 387:621-8.


Duerr GD, Heinemann JC, Suchan G et al. The endocannabinoid-CB2 receptor axis protects the ischemic heart at the early stage of cardiomyopathy. BASIC RES CARDIOL. 2014; 109:425.


FIG. 1: Cannabinoid CB2 receptor protects ischemic heart at early stage of cardiomyopathy. Repetitive ischemia and reperfusion (I/R) episodes leads to aggravated interstitial fibrosis in CB2 receptor-deficient mice (B, Cnr2-/-) as compared to wild-type controls (A), and also to altered levels of the endocannabinoid anandamide in the ischemia/ reperfusion model, indicating a dysregulated endocannabinoid signaling in CB2 receptor-deficient mice. (from: Duerr et al. Basic Res Cardiol 2014; 109:425)

FUTURE DIRECTIONS

FOR926 has finished in the course of 2014. Still, many collaborations have continued. In particular, the mutual exchange of mutant mouse lines targeting components of the endocannabinoid system, and the determination of levels of endocannabinoid / endocannabinoid-like compounds and other lipid signaling systems by LC-MS/MS will continue to set tight bands for future projects. It is aimed at establishing a lipidomic platform / core unit in Mainz, and the acquisition of advanced technologies, including mass spectroscopy imaging, enabling to analyze lipid contents on histological sections at high spatial resolution.
OVERVIEW

The research unit FOR 1341 „Barrel Cortex Function“ began in 2010. This project is supported by the German Research Foundation (DFG) and the Swiss National Science Foundation.

The spokesmen are: Prof. Heiko Luhmann (Mainz) and Prof. Fritjof Helmchen (Zürich).

- Prof. Dirk Feldmeyer (Jülich)
- Prof. Carl Petersen (Lausanne)
- Dr. Poulet / Prof. Brecht (Berlin)
- Prof. Schwarz (Tübingen)
- Prof. Luhmann (Mainz)
- Prof. Helmchen (Zürich)

HIGHLIGHTS

The cerebral cortex is organised horizontally in layers and vertically in cortical columns. Although the structural and functional properties of a cortical column have been intensively studied in a variety of mammalian species, the „canonical circuit“ of a cortical column and the interaction between different columns is still largely unknown. Over the past few years, it has become clear that understanding neocortical information processing does not only require a detailed knowledge of the synaptic circuitry at the single cell level, but also an in-depth analysis of the columnar network activity at the population level. The rodent barrel cortex offers unique opportunities for studying sensory processing in a cortical column and for correlating whisker-related behaviour with neuronal activity in a well-defined cortical map.
FUTURE DIRECTIONS

The overall aim of this Swiss-German Research Unit is: Understanding the function of a neocortical column by using the rodent barrel cortex as a model for neuronal information processing within a neocortical module.

THE SPECIFIC OBJECTIVES ARE:

- To describe the inhibitory and excitatory synaptic circuitry within a barrel-related cortical column and to understand the general principles of neuronal information processing, i.e. excitatory feedback circuits within a cortical column.
- To study large-scale network activity in order to reveal the role of intracolumnar and intercolumnar interactions in spontaneous and sensory-driven activity patterns.
- To examine defined synaptic microcircuits and large-scale neocortical networks during UP and DOWN states in order to elucidate state-dependent modifications of neuronal information processing.
- To understand the neocortical network mechanism participating in or generating a distinct sensor-related behaviour.
- To understand the activity-dependent mechanisms that lead to the formation of a cortical column during the precritical period and its modification during subsequent developmental stages.
- To develop, test and install novel behavioural tasks which will allow detailed electrophysiological or population imaging analyses of behaviourally relevant neocortical circuits.
OVERVIEW

The graduate program converges the areas of life sciences and life writing and sees them as complementary approaches to understand, explain and act in boundary experiences of human life. To achieve this convergence, joint concepts need to be established. The graduate program focuses on three research areas – corporeality, ability, temporality.

The interdisciplinary approaches are linked by narrative practices, which function as the conceptual and methodological background against which boundary experiences of human life are studied from diverse disciplinary angles, such as medicine, neonatology, psychotherapy, pharmaceutical biology, molecular biology, social sciences, cultural anthropology, history, philosophy, ethics, German studies and American studies.

HIGHLIGHTS

The GRK started in April 2014. Since then, we managed to publish 14 papers in national and international peer review journals respectively for those areas with a focus on the humanities in highly ranked book publications. By forging a close cooperation with clinical disciplines, new horizons of our research “from books to bedside” could be implemented.

1) The unfortunate Ebola-outbreak provided us with the empirical data to explore the narrative negotiation of epidemic and pandemic risk. One publication on the topic has been accepted, a second one is under review.

2) The second highlights is constituted by the use of historical findings to unveil culturally contingent practices of organ harvesting. We joined an international group of scientists from the US, Canada and Germany addressing unethical historical and contemporary practices of organ harvesting in China. In this context, four collaborative publications were prepared and submitted and we are awaiting the commentaries of the reviewers and publication within 2015. The main partner and driving force for this project is Prof. Li from the Pharmacological Institute of the Johannes Gutenberg University Medical Center.

3) Last not least, one highlight of our research was brought about by collaborations which made clear, that translational approaches do not only work “from books to bedside” but also vice versa. What has been well established knowledge for translational clinical research in other areas (such as experimental research driven by clinical entities) had yet to be proven for our field. In a close collaboration with the Neonatal Intensive Care Unit of our Medical Center (Prof. Mildenberger), we established first approaches to gauge the clinical impact of narrativity with regard to a) the narrative co-construction of evidence in a field that is characterized by small sample sizes and b) the narrative co-construction of knowledge-based clinical judgments. The first topic has been published in a review-paper while the second issues had been exemplified on a case of Osteogenesis imperfect and will be published in 2015 (submission complete). Beyond working on publications, we organized a number of workshops and conferences to prepare new grant initiatives in order to sustain the momentum of our research and to connect to scholars in the field. We put a focus on the Rhein-Main-Region in order to get prepared for a regional initiative, most likely within the national programs of excellence. We are happy that Prof. Lemke and Prof. Habermas, both Frankfurt, joined our initiative as associate members of the GRK supporting us in transforming our narrative approaches into a future oriented approach to immaterial issues (primarily communication) and materialities of human life at the interface of biomedicine, individuals, and society.
FUTURE DIRECTIONS

The research and training program of the graduate college aims at establishing mutually shared methodological pathways to topics in life sciences and life writing related to boundary experiences of human life. The graduate college proceeds from the hypothesis that in their explanations of boundary experiences of human life, life sciences and biomedicine on the one hand and the humanities and cultural sciences on the other hand approach the same subject of man in his life-world from different angles. If we assume that life sciences and life writing can each be understood as a specific set of narrative practices, in which the significance of explanations and models depend to a large degree on the ways in which empirical data, explanations, and experiences are narrativized, what emerges then is an approach for establishing common methodological perspectives on man in his life-world.
OVERVIEW

Biomineralization has become a fascinating topic of research, at the cutting edge between inorganic and organic world, also in view of its numerous applications from nanotechnology to biomedicine. One animal species has gained special attention: marine sponges, the oldest Metazoan, which have a biosilica skeleton, a unique material consisting of polymeric silica. The special feature of biosilica is that it is synthesized via a biocatalytic mechanism. The silicateins are the first enzymes that catalyze the formation of an inorganic polymer, biosilica, a breakthrough discovery in material sciences. Moreover, the sponge skeleton formation is the first biomineralization process that can be described from gene level to protein level and finally the hierarchically ordered biosilica structures.

FUTURE DIRECTIONS

The aim of this project is to understand the biomineralization process in the most basal animal phylum, the siliceous sponges, in order to acquire new knowledge for application in therapy of human bone diseases and biotechnology. For that purpose, the genes/cDNAs involved in sponge biosilification shall be isolated and characterized. In addition to silicatein, the silicatein interactors shall be identified and the posttranslational modifications of silicatein investigated. The sequential expression of the genes involved in biosilica formation and the morphology and composition of this inorganic-organic hybrid material, as well as the cellular and molecular factors involved in the spatio-temporal control of spicular morphogenesis shall be elucidated. Novel scaffold/composite materials based on silicatein and biosilica shall be designed and fabricated. The self-healing properties of biosilica and the physico-chemical characteristics of the biosilica-based materials, including their mechanical properties, shall be analyzed. The mechanism of hardening of the soft matter biosilica material initially formed by silicatein shall be elucidated. Biomimetic light waveguides shall be constructed. First prototype implant/scaffold materials will be prepared and the effect of biosilica on osteoblasts and osteoclasts, including the expression of specific proteins will be analyzed.

HIGHLIGHTS

Based on studies on biomineral formation in calcareous sponges, considerable progress has been made in understanding the initial steps of human bone formation. Unexpectedly we found that hydroxyapatite formation is initiated by the synthesis of calcium carbonate bioseeds. This process turned out to be enzyme-mediated, catalyzed by carbonic anhydrases, like silicatein-mediated sponge biosilica formation. This discovery and the discovery of the decisive role of a second enzyme, alkaline phosphatase, and certain morphogenetically active, high-energy polymers, inorganic polyphosphates, allowed new applications of the knowledge derived from sponges, the evolutionary oldest biomineral forming animal system, in therapy of human bone disorders. New results were presented suggesting that the sponge spicules act as a light-transmitting, nerve-like system. The introduction of specific mutations allowed the dissection of the structure-forming and structure-guiding functions of silicatein and the generation of light transmitting fibers. Moreover, biosilica was used as morpho-active component of novel scaffolds for bone repair. First materials were successfully tested in animal experiments. Besides his first ERC Proof-of-Concept (PoC) grant “Si-Bone-PoC”, W.E.G. Müller succeeded to apply for a second PoC grant “MorphoVES-PoC” on artificial active blood vessels that started in 2015.


Wang XH, Schröder HC, Müller WEG. Enzyme-based biosilica and biocalcite: biomaterials for the future in regenerative medicine. TRENDS IN BIOTECHNOLOGY. 2014; 32: 441-447.


Wang XH, Schröder HC, Schlossmacher U et al. Modulation of the initial mineralization process of SaOS-2 cells by carbonic anhydrase activators and polyphosphate. CALCIFIED TISSUE INTERNATIONAL. 2014; 94: 495-509.

**FIG. 1:** Potential application of morphogenetically active biosilica in distraction osteogenesis.

**FIG. 2:** Increased carbon content of mineral nodules onto bone-forming SaOS-2 cells after incubation with a carbonic anhydrase activator. Element mapping studies.

**FIG. 3:** Formation of light-transmitting fibers based on the structure-forming and structure-guiding properties of silicatein.

**FIG. 4:** Biosilica coated nanofibers fabricated by electrospinning procedure. (A) Electrospun fiber mats. (B and C) Fiber mats without or with a silica precursor layered in a microtiter well. (D - F) SEM images of electrospun nanofibers without (D) or with a silica precursor (F and E).
OVERVIEW

The European Research Council (ERC) has earmarked about € 2.5 million to fund the research being conducted by gastroenterologist and biochemist Professor Dr. Dr. Detlef Schuppan at Mainz University Medical Center. Professor Schuppan is a specialist in intestinal and liver diseases ranging from inflammation to fibrosis and organ failure and cancer. Among others, his aim is to develop therapeutic strategies that will slow or even reverse the pathological deposition of fibrous connective tissue (scarring) in various organs. Many patients could benefit from this development, because the advanced stages of fibrosis can currently not be treated and represent the main cause of death in those suffering from chronic inflammatory diseases of the liver and other organs.

HIGHLIGHTS

Ongoing inflammation usually leads to replacement of functional tissue by excess connective tissue (scarring) and the failure of organs like liver, lungs, kidneys or skin. Antifibrotic therapies to treat progressive fibrosis are lacking. While several antifibrotic drug candidates have been found in cell and animal studies, none has entered an advanced clinical phase. A major reason is the usually slow progression of fibrosis and the unreliability of follow up tissue biopsy for the assessment of fibrosis and fibrosis progression (fibrogenesis). With current efficacy measures, “proof of concept” antifibrotic drug trials will have to include several hundred patients and to last at least 2 years, which incurs a high risk for patients and unacceptable costs for drug developers. Therefore, sensitive and specific non-invasive biomarkers are urgently needed. The project aims at the development of a quantitative imaging technology that permits the quantification of fibrous tissue deposition over the whole liver. The feasibility of this approach has been shown by research conducted by Prof. Schuppan in collaboration with Prof. John Frangioni at Harvard Medical School, Boston (Prof. Schuppan who was appointed at Mainz University Medicine still holds a professorship at Harvard). They developed an imaging agent (radiotracer) that binds to the fibrogenic cells in the liver. Injection of this radiotracer could visualize the activity of fibrosis progression in this organ. In collaboration with Prof. Frank Rosch and Junior Prof. Tobias Ross of the Institute of Nuclear Chemistry at Mainz University these and several other fibrosis imaging agents will be further developed and optimized, with the final aim of application in patients in 3-5 years from now. Notably, this method will allow 1) clinical efficacy testing of antifibrotic therapies in only a few patients within a few days to weeks, 2) an individualized dose adjustment of such therapies according to the therapy response.


**FIG. 1:** Causes of chronic liver diseases

**FIG. 2:** Strategies pursued to develop quantitative molecular Imaging of liver fibrosis (targeting scar tissue collagen) and liver fibrosis Progression (fibrogenesis, targeting activated cholangiocytes and activated myofibroblasts).
Further work was done on the ERC Grant LiPsyD, awarded to Professor Robert Nitsch, during its second funding year in 2014.
OVERVIEW

The last decade has witnessed an explosion of research into the molecular networks ensuring maintenance of a mutualistic relationship between microbes and host cell systems such as epithelia and the immune system at mucosal surfaces. Failure of such homeostatic programs leads to susceptibility to intestinal infection or to chronic inflammation causing debilitating human diseases such as inflammatory bowel diseases (e.g., ulcerative colitis, Crohn’s disease) or inflammation-induced intestinal cancer. Much has been learned about how the microbiota contributes to intestinal homeostasis through the identification of host molecules sensing microbiota and even of specific microbiota controlling distinct aspects of immune cell function. In contrast to the role of the microbiota, the role of nutrients for development and function of the intestinal immune system has been a matter of speculation owing to the fact that molecular sensors of dietary molecules are widely unknown. Given the broad role of nutrients in metabolic diseases and the impact of intestinal cancer on human health, research into the question of how the power of nutrients can be harnessed for improving human health and for the prevention of disease is much warranted.

HIGHLIGHTS

1. IDENTIFICATION OF A T-BET-EXPRESSING ILC3 SUBSET THAT REQUIRES THE ARYL HYDROCARBON RECEPTOR (AHR) FOR DEVELOPMENT.

We had previously found that the maintenance of ILC3 depended on signaling of the AhR (Kiss, Science 2011). However, not all ILC3 populations were equally dependent on the presence of AhR signals which may indicate the existence of AhR-dependent and AhR-independent ILC3 subsets. We found that a subset of ILC3 expressed the transcription factor T-bet. This subset was characterized by low level expression of CCR6 and it contained the Nkp46-positive population of ILC3. T-bet instructed the expression of T-bet target genes such as interferon-γ (IFN-γ) and of the natural cytotoxicity receptor Nkp46. Mice genetically lacking T-bet showed normal development of RORγt+ ILC3, but CCR6-ILC3 did not up-regulate Nkp46 and failed to produce IFN-γ. The production of IFN-γ by T-bet-expressing CCR6-ILC3 was essential for the release of mucus-forming glycoproteins required to protect the epithelial barrier during \textit{Salmonella enterica} infection. \textit{Salmonella} infection also causes severe enterocolitis that is at least partly driven by IFN-γ. Thus, graded expression of T-bet in CCR6-ILC3 facilitates the differentiation of IFN-γ-producing CCR6-ILC3 required to protect the epithelial barrier against \textit{Salmonella} infections. Co-expression of T-bet and RORγt, which is also found in subsets of T, cells, may be an evolutionary conserved transcriptional program that originally developed as part of the innate defence against infections but that also confers an increased risk for immune-mediated pathology.

2. IDENTIFICATION OF A CLONAL PROGENITOR TO ALL HELPER-LIKE ILC, THE COMMON HELPER-LIKE ILC PROGENITOR (CHILP).

ILCs have been categorized into three distinct groups, transcriptional circuitry and effector functions of which strikingly resemble the various T helper cell subsets. We identified a common, Id2-expressing progenitor to all IL-7 receptor-expressing, ‘helper-like’ ILC lineages, the CHILP. Interestingly, the CHILP differentiated into ILC2 and ILC3 lineages but not into conventional natural killer (NK) cells that have been considered an ILC1 subset. Instead, the CHILP gave rise to a peculiar Nkp46+ IL-7Rα+ ILC lineage that required T-bet for specification and was distinct of cNK cells or other ILC lineages. Such ILC1s co-produced high levels of IFN-γ and TNF and protected against infections with the intracellular parasite \textit{Toxoplasma gondii}. Our data significantly advances our understanding of ILC differentiation and presents evidence for a new ILC lineage that protects barrier surfaces against intracellular infections.
FUTURE DIRECTIONS

We have recently found that the aryl hydrocarbon receptor (AhR), a ligand-inducible transcription factor, is required for the development of innate immune system components (Kiss, Science 2011). The AhR serves as a sensor for dietary AhR ligands that are contained in high concentrations in vegetables of the Brassicaceae family (e.g., broccoli, Brussel’s sprouts). Specifically, a subset of innate lymphocytes (ILC) referred to as lymphoid tissue inducer (LTi) cells or RORγt+ ILC3 that is involved in maintaining epithelial barrier function and resistance to intestinal infections, required diet-induced AhR signals for its maintenance and expansion. We found that AhR directly regulates expression of the receptor tyrosine kinase Kit which may be the key regulator for the maintenance of ILC3. The data established the first molecular link between diets and the development of immune system components. Based on these preliminary data, we aim to systematically define the role of diet-induced changes for the function and differentiation of mucosa-associated innate lymphocytes and to uncover how innate lymphocytes regulate epithelial adaptation by controlling niche support for intestinal epithelial stem cells. We propose to address the following three specific aims: (1) to interrogate the role of ILC3 in controlling the intestinal stem cell niche, (2) to test the role of diet-controlled, tunable Kit signals for maintenance and function of ILC3 and (3) to probe the role of dietary phytochemicals for plasticity of transcriptional programs controlling ILC3 effector fates. To achieve these goals we will combine mouse genetics, complex phenotyping, state-of-the-art multicolor fate labeling and pre-clinical disease models.

These aims will for the first time allow to test the role of nutrients in a defined molecular pathway for human health. They have the potential to unravel an entire regulatory niveau in mucosal biology and may reveal new potential therapeutic or prophylactic strategies for intestinal infections, inflammation and cancer.
Upon the framework “Cancer Prevention, Early Detection and Outcome Research”, Frankfurt/Mainz has focused on outcome research. A new study was initiated in 2014, investigating long-term Quality of Life (QoL) and psychosocial rehabilitation status of patients who were diagnosed with lung cancer and have survived for at least one year - the LARIS Study (Quality of Life and Psychosocial Rehabilitation in Lung Cancer Survivors).

CCP-IT

This study is the establishment of an IT backbone for connecting all DKTK sites. Some of the already running IT components are a bridgehead, running at each partner’s site, consisting of a local data management (“CentraXX Light” from Kairos GmbH) to store data and a “Teiler” to make it available to the consortium (“Samply.Share”: Client from IMBEI). As central components, there are a central search tool from the DKFZ, the decentral search broker (“Samply.Share”: Server) and several kinds of identity management tools based on the OpenSource software “Mainzelliste” to support privacy-preserving record linkage. Lastly, a metadata repository (“Samply.MDR”) provides a “common tongue” and semantic interoperability among the consortium’s sites.

IMMUNOTHERAPY

Malignant melanoma is an immunogenic skin tumor with increasing incidence for the last decades. Especially advanced stages have a poor prognosis and a long-term survival despite metastatic disease is still a rare event. Although approaches have been made to overcome immune tolerance by immune checkpoint inhibitors like CTLA-4 or anti-PD1/PDL1 antibodies only a minority of patients will respond to therapy. To obtain insight into the mechanisms of tumor progression in non-responding patients compared to responders and in search of new prognostic markers protein expression profiling in patients undergoing therapy with different immunotherapeutic agents is performed.

TCR

The overall aim is to develop an effective adoptive T cell-based tumor immunotherapy for widespread use in cancer patients by generating novel optimized specific TCR with enhanced tumor recognition as well as reduced potential for ON- and OFF-target toxicity and defining the T-cell subsets that can most effectively promote long-lived functional memory T-cell response for tumor eradication.
Haehnel PS, Enders B, Sasca D et al. Targeting components of the alternative NHEJ pathway sensitizes KRAS mutant leukemic cells to chemotherapy. BLOOD. 2014; 123 (15): 2355-2366


Rudolph BM, Loquai C, Gerwe A et al. 2014. Increased frequencies of CD11b(+) CD33(+) CD14(+) HLA-DR(low) myeloid-derived suppressor cells are an early event in melanoma patients. Exp. Dermatol. 23: 202-204


**FUTURE DIRECTIONS**

**CANCER PREVENTION**
This study is a cooperation between Mainz and Frankfurt; the expected total study time is 36 months, and funding has been granted by the DKTK. The study has progressed to the point that questionnaires have been pilot tested and the first 50 survivors are enrolled.

**CCP-IT**
As result of the first funding period (2012-2015), the CCP-IT bridgehead architecture includes routine data of 267,000 patients. Thanks to the bridgehead architecture and the decentral search, these data are highly detailed: Based on the ADT dataset [4], they are just as detailed as each partner’s tumor documentation.

**IMMUNOTHERAPY**
Melanoma. In a next step, identified proteins and marker molecules will then be correlated to clinical response, incidence of autoimmune side effects, and overall survival.

TCR. To overcome TCR mispairing, our group designed a single chain (sc) TCR format by connecting the variable TCRα domain to the TCRβ chain via a short peptide linker co-expressed with a TCRα constant domain. During the first DKTK funding period we demonstrated the improved safety and therapeutic efficacy of a high-affinity scTCR specific for the broadly expressed tumor-associated antigen p53 for T cell-based immunotherapy of p53-associated malignancies. We successfully applied the scTCR format to HLA-A2.1-restricted MDM2 oncogene-specific TCR as promising antigen-driven immunotherapy for both melanoma and hematologic malignancies such as multiple myeloma.
OVERVIEW

The “German Center for Cardiovascular Research (DZHK)” is one of the six German centers of health research (Deutsche Zentren der Gesundheitsforschung (DZG)) established by the German Federal Ministry of Education and Research. The University Medical Center of the Johannes Gutenberg-University Mainz (UMCM) is part of the Center Rhine-Main of the German Center for Cardiovascular Research (DZHK). The UMCM has set itself the goal of identifying markers and mediators of cardiovascular disease, especially in the interaction between blood vessels and myocardial tissue. Another focus is the investigation of thrombosis mechanisms and platelet function. Modern imaging techniques shall help researchers to better understand the molecular mechanisms of cardiovascular disease.

HIGHLIGHTS

STRUCTURE

In 2014, DZHK researchers at the UMCM comprise the working groups of 4 Principal Investigators and 10 DZHK researchers. A DZHK W3-Professorship "Vascular and Myocardial Interaction" at the UMCM was advertised in late 2014. The professorship will have a translational and patient-oriented research approach to improve the diagnostics, therapy and prognosis of cardiovascular disease. Its working program will focus on the macro- and microcirculation with focus on the peripheral and coronary vascular function. The candidate will bring additional expertise in state-of-the-art of ischemic cardiovascular disease and intravascular imaging. The professorship will be integrated in the Department of Medicine 2 and is envisaged to be installed in 2015.

The local research program was successfully reviewed by an external review panel and is further funded by the BMGF until 12/2018 with a budget of 2.886.000 EUR. An additional laboratory for investigating vascular function by ultrasound was established by a DZHK investment grant (100.000 EUR).

SCIENTIFIC WORKING PROGRAM

Myocardial disorders appear in varying clinical phenotypes ranging from subclinical changes to terminal heart failure with preserved or reduced contractile function and sudden cardiac death. The vascular system is a central player and mediator of the development and course of myocardial disease. The MyoVasc-Cohort Study makes use of high-dimensional data from a large sample including biobanking and focusses on the transition from asymptomatic to symptomatic heart failure. In January 2014, the one-year follow-up examination was initiated and in July 2014, the 1000th participant was recruited. With this milestone, the first interim analysis timepoint will soon be reached. After data reading and quality control, the biodatabase will be available for researchers to analyze first data in 2015.

In June 2014, a prospective cohort study for the evaluation of diagnostic and therapeutic strategies in the Chest Pain Unit (ProsPECTUS-Study) was initiated. The project includes a comprehensive biobanking a detailed and structured follow-up investigation of patients. Data will also available for consortial projects with other DZHK sites. Similarly, cooperation has been started with regards to studies involving platelet function diagnostics as well as intracoronary imaging.

The DZHK strongly supports national collaboration within the network by sharing scientific competences or methods. Currently nine projects are ongoing as cooperation projects within the funding program “Shared Expertise”.

The UMCM joined the DZHK Clinical Study Group (CSG) and will contribute two several collaborative multicenter studies within the DZHK.

EARLY CAREER SUPPORT

The Young DZHK supports the personal and professional development of 13 young scientists at the UMCM on their way to becoming independent, successful investigators in cardiovascular research. Four DZHK doctoral candidate fellowships were established.
FUTURE DIRECTIONS

SCIENTIFIC AIMS
- To investigate the interaction of myocardial and vascular disease by especially focusing on molecular mechanism and cells,
- To analyze mechanisms involved in thrombosis, and in-stent thrombosis,
- To explore the transition from asymptomatic to symptomatic heart failure, and how this impacts on vascular homeostasis,
- To examine and improve the diagnostics, treatment and outcome of patients with acute coronary syndrome, and
- To investigate at a molecular, functional and structural level myocardial infarction in low-risk individuals.

STRUCTURAL AIMS
- To strengthen the visibility and the research program of the UMCM within the DZHK by establishing the DZHK.W3 Professorship “Vascular and Myocardial Interaction”
- To extend the scientific collaboration within the DZHK network
- To foster the young researchers in the career in cardiovascular research
- To develop a common regional concept for cardiovascular science with the Goethe University Frankfurt for future sustainability
The Center for Thrombosis and Hemostasis Mainz (CTH) was established in 2010 as an Integrated Research and Treatment Center (IFB) funded by the German Ministry for Education and Research (BMBF). The CTH provides a unique interdisciplinary environment that facilitates basic research, innovative patient care and the development of new diagnostic approaches and therapies. The CTH fosters translational research from bedside-to-bench and vice versa in the field of thrombosis and hemostasis and career development of physician scientists and biomedical researchers.

**OVERVIEW**

The CTH Professorships and Junior groups pursue a broad range of clinical and translational research projects in close association with several clinical departments and institutes, including Internal Medicine II (Cardiology and Vascular Medicine) and III (Hematology and Oncology), Dermatology, Ophthalmology, Pharmacology, Laboratory Medicine and Clinical Chemistry, Biostatistics-Epidemiology-Informatics (IMBEI), and the Interdisciplinary Center for Clinical Studies (IZKS) Mainz. The experimental and clinical research platforms offer state-of-the-art technologies to the CTH members and external cooperation partners and support the training of pre- and postdoctoral fellows. These platforms cover cardiovascular disease models including cardiac ischemia and vascular remodeling, invasive and non-invasive imaging methods of thrombus formation and resolution as well as multicellular interactions at the vascular interface, advanced molecular and platelet diagnostics, genetic model organisms, biobanking, and bioinformatics. CTH research aims to understand mechanisms of thrombotic and inflammatory processes in experimental cellular and animal models, linked to validation in population and patient studies. The CTH is devoted to translational studies and interventional multicenter trials with the ultimate goal to contribute to the improvement of patient care. In the current year, studies of the Junior group of M. Bosmann provided evidence that neutralizing IL-27 ameliorates the course of polymicrobial sepsis in mice. The Junior group of C. Reinhardt found that gut microbiota regulates intestinal integrity in a TLR-2-dependent manner. The Junior group of P. Wenzel showed that monocytes contribute to eNOS uncoupling and nitro-oxidative stress in vascular inflammation. The Professorship Clinical Trials (S. Konstantinides) published the results of the landmark international ‘Pulmonary Embolism Thrombolysis’ trial (PEITHO) that provides guidance for risk-adjusted treatment of acute pulmonary embolism. The ongoing ThrombEVAL study conducted by the Professorship Clinical Epidemiology (P. Wild) yielded new insights that clinically significant depression impaired several aspects of anticoagulation treatment.
FUTURE DIRECTIONS

In 2014, the CTH was externally reviewed for continuation of funding by the BMBF. The structural and scientific concept for further development of the center was evaluated on site and approved by a panel of internationally recognized experts. The implementation of this concept and additional recommendations by the external scientific advisory board will begin with the start of the second funding period in the fall of 2015. The recent advances and future perspectives of thrombosis research, as well as the contribution of the CTH to the field will be highlighted by a CTH organized scientific symposium on “Thrombosis and Inflammation”. The major goals for the second funding period are to create a sustainable translational center and develop the national and international profile of the CTH as a reference center for integrated multidisciplinary patient care and translational Thrombosis and Hemostasis research in Germany.

FIG.: Poster session at Spring School organized by CTH / Professorship Clinical Trials

IMPORTANT PROJECTS // MAX. 5

The Professorship Clinical Trials Konstantinides and the Juniorgroups Group Lankeit address risk stratification in anticoagulant therapy and the discovery and validation of new biomarkers in venous thromboembolic disease.

The Humboldt Professorship Ruf and the Professorship Experimental Hemostasis and Laboratory Medicine Danckwardt study disease mechanisms of the hemostatic system beyond the traditional roles in thrombosis.

The Professorship Clinical Epidemiology investigates interrelationships between thrombosis and metabolic and cardiovascular diseases in large populations.

The Juniorgroups Reinhardt, Bosmann and Wenzel study inflammatory circuits of the hemostatic system in host-microbiome interactions, sepsis and vascular inflammation.

CTH translational research projects are focused on platelet contributions to various pathologies, including myelodysplastic syndromes, TTP and rare bleeding disorders.
The University Cancer Center (UCT Mainz) provides the framework for diagnosis, treatment and psychosocial care for cancer patients. It constantly seeks to improve the education of all persons involved. It also provides the organization of interdisciplinary tumor boards, therefore laying a basis for rational and individual diagnostic and therapeutic decisions. Founded in 2011, the UCT not only connects cancer care across the university medical center, but also supports clinical, translational and basic scientific cancer research, as well as local, regional and national outreach projects in oncology. A clinical cancer registry responsible for data collection and evaluation is also part of the UCT Mainz. Furthermore, the UCT Mainz is a partner within the German Cancer Consortium (DKTK).

One of the main goals for 2014 was the establishment of an interdisciplinary outpatient cancer clinic. This unit could be opened in the fall, thus providing standardized, high quality care for outpatients. In 2014, a lot of preparatory work in view of the forthcoming application as a cancer center (CC) in 2015 has been carried out. This includes the further development of cancer tissue and liquid biobanking, which will finally start in 2015. Furthermore, structural requirements and resources for the certification or recertification of centers for various cancer entities have been set up, therefore laying an excellent foundation for the forthcoming tasks in 2015.

The major aim of the UCT Mainz is the constant improvement of patient care. In order to make progress towards achieving this objective, the certification of centers is a leading goal for 2015. The existing centers for breast cancer, gynecological cancers and skin cancer will be applying for re-certification in 2015. Furthermore, a center for visceral oncology and prostate cancer are in preparation and will seek for certification in 2015. As a following step, a cancer center, combining all these centers and providing excellent transdisciplinary care for all cancer patients is also planned to be certificated in 2015.

Also in 2014, clinical trial management within the different departments will be centrally harmonized and standardized, providing another step towards high quality clinical cancer research. Furthermore, translational and potentially interdisciplinary projects will be collected centrally. The support of translational research will be one of the major points in focus in 2015, also thinking ahead to the potential application as comprehensive cancer center (CCC) even further ahead.


Marquardt JU, Seo D, Andersen JB et al. Sequential transcriptome analysis of human liver cancer indicates late stage acquisition of malignant traits. JOURNAL OF HEPATOLOGY. 2014; 60 (2): 346-353 Article

Rudolph BM, Loquai C, Gerve A et al. Increased frequencies of CD11b(+) CD33(+) CD14(+) HLA-DR(low) myeloid-derived suppressor cells are an early event in melanoma patients. EXP DERMATOL. 2014 Mar; 23(3):202-4.


Functional significance and regulation of CTGF (connective tissue growth factor) in the context of stroma-mediated drug resistance in acute myeloid leukemia
FUNDING: German José Carreras Leukemia Foundation
PROJECT DURATION: 2014-2017

Continuous intraoperative monitoring of the pelvic autonomic nerves during Total Mesorectal Excision (TME) for the prevention of urogenital and anorectal dysfunction in patients with rectal cancer
PROJECT DURATION: 2009-2015

Comparative genomic and epigenomic characterization of hepatobiliary cancer stem cells and identification of new therapeutic targets
FUNDING: German Research Foundation (DFG)
SUM: € 152,410
PROJECT DURATION: 2012-2014

Characterization of the immunoglobulin repertoire of tumor-infiltrating plasma cells and correlation of factors within the plasma with prognosis in early breast cancer
FUNDING: Bayer Technology Services GmbH
SUM: € 35,000
PROJECT DURATION: 2011-2016

Identification of functionally relevant regulatory key molecules and signal pathways of malignant melanoma to optimize therapeutic immunological approaches
PROJECT DURATION: 2012-2014
KEY SCIENTIFIC RESEARCH PLATFORMS

HIGHLIGHTS

• The IZKS was funded by the German Federal Ministry of Education and Research (BMBF) for continuous optimization of multicenter clinical trials, for building regional trial networks, and for improving qualification of study personnel until April 2015.
• In 2014, the database of the IZKS contained 333 studies including 70 Investigator Initiated Trials; in 54 of these studies, part of the sponsor responsibilities was taken by the IZKS.
• Efficient and quality-oriented support for clinical trials was offered by the IZKS in a high number of professional clinical trial units: Anaesthesia, Cardiology, Dermatology, Gynaecology, Gastroenterology, Hepatology/Infectiology, Immunology/Haematology, Mental Disorders, Neurology, Oncology, Ophthalmology, Paediatrics, Pulmonology, Radiology, and Rheumatology.
• Seven draft proposals from various fields were supported as part of the “Clinical Trials Programme” from the German Research Foundation (DFG) resulting in two full proposals. In the new European funding program HORIZON 2020, two proposals were developed and, due to successful evaluation, the full proposals were submitted, respectively. In addition, funding proposals for the BMBF call „Deutsche Zentren der Herzkreislaufforschung e.V.” were submitted.
• The accreditation for the electronic reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) to the European Medicines Agency (EMA) has been extended to other European countries as a precondition for acquisition of safety management tasks in multinational studies.
• An extensive, well evaluated training program was offered to clinical trial staff (i.e., investigators, scientists, study nurses, monitors, and students), including information on the upcoming new EU Clinical Trials Regulation.
• New activities together with the Chief Scientific Officer of the UMC and the Dean of the Faculty of Medicine were started to optimize clinical trials in Mainz.
• In October 2014, Prof. Annegret Kuhn became Head of the IZKS and followed Prof. Monika Seibert-Grafe who had established the IZKS in 2007. Prof. Kuhn had worked at University Medical Centers and Scientific Institutions, such as the Max-Planck-Institute for Molecular Biomedicine, Muenster, and the German Cancer Research Center, Heidelberg. She is dermatologist and has long-term experience in the transfer of technologies from basic science to pharmaceutical applications by conducting Investigator Initiated Trials and Sponsor Initiated Trials.
• The IZKS has more than 45 trained and experienced medical, scientific, and technical employees contributing to planning, coordination, evaluation, and publication of clinical trials. The employees are organized in four areas: Study Coordination and Clinical Monitoring, Safety Management and Regulatory Affairs, Statistics and Data Management, and Study Systems and Processes.
• At the end of 2014, the IZKS temporarily moved from the Langenbeckstrasse 2 to the Isaac-Fulda-Allee 5. In spring 2016, the IZKS will relocate to the new building 508 at the campus of the UMC.


**IMPORTANT PROJECTS // MAX. 5**

**CERTIFY** – Cerament treatment of fracture defects: A prospective, multicenter, randomized study investigating the use of CERAMENT™BONE VOID FILLER as bone graft substitute in tibia plateau fractures

**PROJECT MANAGER:**
Prof. PM Rommens
Dr. S Gorbulev

**FUNDING:**
BONESUPPORT GmbH
SUM: € 720,000

**PROJECT DURATION:** 2012-2014

**EVITA** – Effect of vitamin D as add-on therapy for vitamin D insufficient patients with severe asthma: A randomized, doubleblind, placebo-controlled trial

**PROJECT MANAGER:**
PD Dr. S Korn
Prof. R Buhl

**FUNDING:**
Federal Ministry of Education and Research (BMBF)
SUM: ca. € 850,000

**PROJECT DURATION:** 2013-2017

**HotPE** – Home treatment of patients with low-risk pulmonary embolism with the oral factor xa inhibitor rivaroxaban

**PROJECT MANAGER:**
Prof. S Konstantinides

**FUNDING:**
Federal Ministry of Education and Research (BMBF)
SUM: € 150,000

**PROJECT DURATION:** 2013-2016

**RELATED AF** – Resolution of left atrial-appendage thrombus: Effects of dabigatran in patients with atrial fibrillation

**PROJECT MANAGER:**
Prof. T Münzel
Prof. T Rostock
Dr. O Deuster et al.

**FUNDING:**
Boehringer Ingelheim GmbH & Co. KG
SUM: ca. € 650,000

**PROJECT DURATION:** 2013-2018

**IZKS:** Interdisciplinary Center for Clinical Trials

**PROJECT MANAGER:**
Prof. M Seibert-Grafe
Prof. A. Kuhn

**FUNDING:**
Federal Ministry of Education and Research (BMBF)
SUM: € 8,780,000

**PROJECT DURATION:** 2007-2015

**FUTURE DIRECTIONS**

- To provide full service according to the requirements of clinical trials at the UMC including all aspects of clinical research.
- To fulfill ICH-GCP guidelines with focus on conception, planning, organization, and analysis of innovative clinical trials by investigating drugs, medical devices, and other interventions, e.g., psychotherapeutic and surgical procedures.
- To enhance quality, quantity, and efficacy of clinical trials with emphasis on prospective, randomized, controlled clinical trials, health care research, registries, and EU-research projects resulting in European-wide collaborations.
- To further include special expertise for Investigator Initiated Trials and the respective sponsor duties according to regulations, e.g., study coordination, regulatory affairs, clinical monitoring, quality management, data and safety management, biostatistics, and electronic trial systems and processes.
- To successfully apply for grant applications in cooperation with clinical scientists to i.e. Federal Ministry of Education and Research (BMBF), German Research Foundation (DFG), Germany Cancer Aid (DKH), European Commission, and pharmaceutical and medical device industry.
- To expand national and international trial networks and to further improve the qualification of study personnel.
- To continue the new activities together with the Chief Scientific Officer and the Dean of the Faculty of Medicine in order to optimize clinical trials at the UMC.
The NIC has at its disposal research-only scanning time on a 3 Tesla Siemens TIM TRIO magnetic resonance (MR) scanner (located in building 605 on medical campus), equipment for peripheral stimulation, psychophysiological recordings, eye-tracking, transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), combined MRI-EEG (256 channels), two fully equipped psychophysiological laboratories for behavioral studies (in building 503), dedicated Unix and Windows servers, analysis software, and an office suite with terminals for data analysis in building 701. Services include advice with study design, ethics applications, stimulus presentation, sequence selection, data analysis, and bi-weekly discussion meetings. Regular methods teaching activities include an annual course in design and analysis of functional MRI experiments and bi-annual courses in Matlab and Presentation programming.

FOCUS ON NEUROIMAGING

Imaging the human brain is a way to study the neural basis of human cognition and behavior, to unravel mechanisms of neurological or psychiatric disorders, and to develop methods for the prevention and treatment of those conditions. We mainly use magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS), non-invasive, safe and comparatively inexpensive techniques that exploit the natural presence in the body of protons and other nuclei with a “spin”, that is, which we can see by applying phasic radiofrequency pulses while the body is in a strong static magnetic field (e.g., 3 Tesla). We thus generate images of brain structure (grey and white matter, cerebrospinal fluid, fiber tracts), brain chemistry (concentrations of certain brain metabolites), and brain function (changes in perfusion when brain areas are active during certain experimental conditions). Especially functional imaging allows us to observe the living human brain “in action” and relate those measures to behavior, learning and memory, subjective experience such as perception, thoughts or feelings, to personality, genotype, or pathology. We can also assess changes in brain structure, chemistry or function as a result of pharmacological, psychological-behavioral, neurotechnological or therapeutic interventions.

NIC users investigate questions like multiple sclerosis, stress resiliency, aging and dementia, addiction, impulse control, emotion regulation, executive function, fear and anxiety, and aesthetics.
**FUTURE DIRECTIONS**

**INFRASTRUCTURE AND COLLABORATIONS**

From 2018, the NIC will be housed in a new dedicated neuroimaging building that will harbor a new 3 Tesla MR scanner, an EEG suite, other laboratories and office space for imaging groups from the faculty and FTN. Our goal is to become a home for human systems and cognitive neuroscience in Mainz and to closely interlink the Mainz human neuroscience community with our partners in the rhine-main neuroscience network (rmn2), in particular the Brain Imaging Center Frankfurt (BIC).

**RESEARCH**

The NIC professorship (Raffael Kalisch) has a particular interest in the topic of resilience. Resilience describes the process of maintaining or regaining one’s mental health during or after severely stressful life situations. Traditionally, psychiatric research has focused on mechanisms that make people vulnerable and lead to disease and on ways of treating mental illness. Interestingly, however, many people do not or only temporarily become mentally ill despite significant burden from psychological or physical adversity. This suggests the existence of protective mechanisms that can prevent the development of stress-related conditions like anxiety, post-traumatic stress, depression or addiction. Our approach is to understand these resilience mechanisms and to harness them in the service of better disease prevention. Here, neuroimaging is a key tool to gain insight into the brain mechanisms underlying and promoting resilience.

**IMPORTANT PUBLICATIONS**


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**IMPORTANT PROJECTS**

**Mainz Resilience Project (MARp) (Stiftung RLP)**

**PROJECT MANAGER:**

Prof. R Kalisch,
Prof. K Lieb,
Prof. R Nitsch et al.

**FUNDING:**

Rheinland-Palatinate Foundation for Innovation

**SUM:** € 249,633

**PROJECT DURATION:**

2013-2016

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**FIG. 1**

Brain activation in response to vertigo (courtesy of P. zu Eulenburg, Neurology).

**FIG. 2**

Resting-state functional connectivity between the ventromedial prefrontal cortex (vmPFC), a key area for remembering experiences of safety from threat, and the ventral tegmental area (VTA), an area that provides neurotransmitter input (dopamine) to the vmPFC. The degree of connectivity between both areas after the learning experience predicts how well subjects remember their safety experience, suggesting it is important for memory consolidation. (Haaker et al., PNAS 2013)
The main focus of our research is on the 3R principles. The 3R (Replace, Reduce and Refine) principles serve as a framework for human animal research and are embedded in legislation defining the use of animals for scientific purposes. The 3rd R, Refine, which includes the minimization of suffering and especially the improvement of animal welfare, is our primary concern.

In this area several new projects, partially in collaboration with the Institute of Animal Welfare, Animal Behavior and Laboratory Animal Science at the FU Berlin, are planned. In the first row we are interested in how to measure animal well-being. This is particularly interesting because well-being is a multifactorial, not at all levels objective and easy to capture variable. Following up on this, we aim to assess and improve well-being of laboratory animals in regard to different environmental conditions. Because it is known that the well-being of a mouse is not only influenced by the cage environment but also by the interaction with the animal caretaker and researcher and that stress triggered by experimental procedures can influence animal research, the improvement of handling in the animal facility to reduce stress in the experiment is a further approach.

An additional perspective is the provision of our skills, starting from support for preparing Animal Study Proposals to surgical techniques like the in utero electroporation for researchers at the University Medical Center Mainz.

**OVERVIEW**

The TARC is responsible for all aspects of housing and breeding of laboratory animals at the University Medical Center Mainz.

One central part is our transgenic facility, where we generate genetically modified mouse strains. We provide a variety of state of the art services such as the use of the Cas9/CRISPR system and further support researcher at the University Medical Center Mainz in several areas.

Another key area of the TARC is the educational training of the scientist. In our courses we teach researchers the responsible handling of laboratory animals in accordance with the 3R principle and the legal aspects for working with laboratory animals.

We consider ourselves as a central point of contact for all researchers of the University Medical Center working with animals.

**FUTURE DIRECTIONS**

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**TRANSLATIONAL ANIMAL RESEARCH CENTER (TARC)**

University Medical Center Mainz
Langenbeckstr. 1
D-55128 Mainz
Phone: +49 (0) 6131 17 21332
jan.baumgart@unimedizin-mainz.de

**OVERVIEW**

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**FUTURE DIRECTIONS**

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An additional perspective is the provision of our skills, starting from support for preparing Animal Study Proposals to surgical techniques like the in utero electroporation for researchers at the University Medical Center Mainz.

**FIG. 1:** Handling of experimental animals in a responsible and caring manner.

**FIG. 2:** Getting familiar with a rat in our educational courses.

**FIG. 3:** Mouse surgery setup.

**FIG. 4:** Mouse surgery.
KEY SCIENTIFIC RESEARCH PLATFORMS

BIOMATERIALS IN MEDICINE
(BioAPP)

Head:
Professor Bilal Al-Nawas

University Medical Center Mainz
Department of Oral and Maxillofacial Surgery
phone: +49 (0) 6131 17 3083
al-nawas@mkg.klinik.uni-mainz.de
Website BioMATICS:
www.unimedizin-mainz.de/biomatics
Website BioAPP:
www.unimedizin-mainz.de/biomatics/
organisationsstruktur/wissenschaftliche-
plattformen.html#c136615

OVERVIEW

Emerged from the previously established Applied Structure- and Microanalysis (ASMA) the analytical performance platform resume most of the introduced well known methods of analytical surface science.

The BioAPP is primarily designed to support the medical researchers of BiomaTiCS, (University Medical Center) and the interdisciplinary network of material scientists at the University of Mainz with specialized analytical methods not available in the standard laboratory equipment.

The micro-chemical investigation of the outermost surface area with X-ray photoelectron spectroscopy (XPS) as well as the structural and chemical composition analysis with the mean of scanning electron microscopy (SEM, EDX) are the main resources for surface science available at BioAPP. Further applications provided by BioAPP includes confocal laser scanning microscopy (CLSM) and X-ray microtomography (µCT).

HIGHLIGHTS

The BioAPP provides several techniques and knowledge for studying different kinds of surface and material characterization. Following some ongoing projects are listed:

- General characterization of biological hard tissues (bone, teeth, cartilage) by means of confocal laser scanning microscopy (CLSM), µCT, XPS, ESEM/EDX
- Characterization of Bone graft materials and collage membranes
- Treated and untreated metallic implants
- Characterization of the polymeric coating of implants by means of XPS
- Characterization of newly ceramic implants
- Finite elements model simulation with µCT-Data. Enhanced mesenchymal stem cell differentiation on load-bearing trabecular Nitinol scaffolds by medium perfusion (T.Böse, RepairLAB Mainz)
- In-vitro and in-vivo characterization of biocompatibility and biomechanical properties of a new acellular collagen matrix (PD Dr. A.Kasaj, ZMK Mainz)
- Opacification of hydrophilic acrylic intraocular lens attributable to calcification (PD Dr.med. B.Stoffelns, FEBO, Department of Ophthalmology UMC Mainz)
**IMPORTANT PUBLICATIONS**


Neulen A, Gutenberg A, Kosterhon M et al. Micro computed tomography for quantification of vasospasms in a Murine model of subarachnoid hemorrhage., *65. JAHRESTAGUNG DER DEUTSCHEN GESELLSCHAFT FÜR NEUROCHIRURGIE (DGNC); 20140511-20140514; Dresden; DOCDL.11.06 /20140513/.


**IMPORTANT PROJECTS**

Projects with the Center for Orthopaedics and Traumatology, Prof. Dr.med. Dr. h.c. P. M. Rommens (AG Prof. A. Hofmann):

- In-vivo analyses of pre-vascularized bone substitute material — cranial defect model with defects of critical sizes in mice, collagen-gels pre-vascularized with mono- and co-cultures of endothelial cells and primary osteoblasts, analyses of fracture healing Prof. A. Hofmann, Dr. U. Ritz, J. Hertweck
- In-vivo analyses of silicatein biomaterials as bone substitutes in bone defects of critical sizes, cooperation with Prof. W.E.G Müller, Physiologische Chemie, Mainz, Prof. A. Hofmann, Dr. U. Ritz, M. Eberhardt
- Heterotopic ossification after surgical intervention at the hip in a rat model – possible reasons and the role of bone morphogenic proteins – Dr. J. Anthonissen, T. Steffens
- Role of endogenous osteoinductive markers in the development of heterotopic ossification after cranio-cerebral injury, Dr. J. Anthonissen, J. Hoock
- Evaluation of Bone Sialoprotein (BSP)-functionalized ceramic bone substitute materials in bone defects of critical sizes in a murine cranial defect model, analogous to 1. With hydroxyapatatite scaffolds with and without BSP-coating, Prof. A. Hofmann, A. Klein, Dr. A. Baranowski
- Development of pre-vascularized dextran hydrogel scaffolds as bone substitute, analogous to 1. instead of collagen gels with dextran hydrogels, cooperation with Prof. U. Jonas, Makromolekulare Chemie, Uni Siegen, Dr. U. Ritz

Projects with the Neurosurgical Center at the Medical University of Mainz, Prof. Dr. med. A. Giese.

- Quantification of Vasospasm by Micro Computed Tomography in a Murine Model of Subarachnoid Hemorrhage – a Feasibility Study, Dr. A. Neulen

External projects with Johannes Gutenberg University Mainz, Institute of Inorganic Chemistry and Analytical Chemistry, Group of Prof. Dr. Wolfgang Tremel:

- Design of Functional Membranes by Anodization of Valve MetalsSynthesis and Application for the Anodization of Tin and Iron (Dr. H. Kerschbaumer).
- Calciumcarbonate as Bone Substitute Material (R. Schröder).
- Metal Oxide Nanoparticles (Dr. Muhammad Nawaz Tahir).
- Inorganic Nanoparticles as Enzyme Mimics (Ruben Ragg).
- Synthesis and Application for the Anodization of Tin and Iron (Dr. N. Mohri)

**BIOAPP SERVICES**

A: Determination of structure and chemical composition

- Micro-Computer_Tomography µCT (Scanco Medical µCT40)
- Scanning Electron Microscopy FEI Quanta 200 FEG)
- Energy dispersive X-Ray analysis (Oxford Inst. INCA 350 Energy)
- Wavelength dispersive X-Ray analysis (Oxford Inst. Wave 700)
- Ar Sputter Coating (Bal-Tec Sputter Coater SCD 050)
- Confocal Laser Scanning Microscopy CLSM (Leica TCS SP2)
- Epifluorescence Microscopy incl. “Life on Stage” (Leica DM IRE2)
- Stereo Light Microscopy (Leica MZ 16A)
- UV-VIS Spectrophotometer (Thermo Scientific™ Evolution 600)
- Electrophotoscoppectroscopy XPS (Physical Electronics ESCA PHI 5600)
- Optical Near Field Microscopy (Omicron TwinSNOM) + CLSM (Nikon C1)
- Image Processing, Leica QWin Pro, ImageJ, OsiriX
- At external partnerships of the JGU Mainz:
  - X-Ray Diffraction (XRD), Bruker Advance D8 with GADDS. (Group of Prof. Dr. W.Tremel)
  - FT-Raman, FT-IR, IR-Microscopy (Group of Prof. Dr. E Rentschler)
  - Trenn-
  - Dünnschlifftechnik, EXACT 300CP (MKG)

B: Cell Biology

- CO2 Incubator (Thermo Scientific™ Heracell™ 240i)
- Class II Biological Safety Cabinets (Thermo Scientific™ Safe 2020)
- Centrifuge (Thermo Scientific™ Heraeus™ Megafuge™ 16R)
- Waterbath WNB 22 (Memmert)
- Laboratory refrigerator-freezer (Liebherr LCv 4010 MediLine)
- Microscope (Olympus CK 40)
- Benchtop shaking (Sartorius CERTOMAT®MO II)
- Heated Magnetic Stirrer (Schott Model SLR)
- Micro-, Analytical-, and Precision Balances (Sartorius)
KEY SCIENTIFIC TEACHING PLATFORM

OVERVIEW

The main purpose of the autonomous training platform for general medicine (Teaching Department for General Medicine) under its director Prof. Michael Jansky, is, as the name suggests, to provide teaching. The training platform concentrates on the main activities of a general practitioner providing care to a non-specialized group of patients. The areas covered and forms of training provided are: Career exploration, an introduction to clinical medicine, Family medicine for pre-clinical, interdisciplinary subject Q12 (rehabilitation, manual therapy and complementary medicine), clinical week in General Medicine, course in general medicine, a block internship as well as a year’s practice in general medicine.

HIGHLIGHTS

The main research projects of the Teaching Department: General Medicine include a practice-oriented health care research program (in cooperation with the Institute of Medical Psychology and Medical Sociology and the Rhineland Palatinate Association of Statutory Health Insurance Physicians), post-graduate training programs and educational research (concentrating on the assimilation of clinical and preclinical training and interactive teaching).

EDUCATIONAL RESEARCH

Last year’s project on the subject of ‘Use of a voting system in seminars on general medicine’ has in 2014 finalized. Another educational research project currently at the planning stage concerns the integration of preclinical and clinical training (Family medicine for pre-clinical). One of the most important tasks of general practitioners is to explain, in simple terms, the often complex situations that arise in medicine. This very often requires basic knowledge in the fields of physiology, anatomy and physiological chemistry. In collaboration with the Institute of Physiology and the Rudolf Frey Learning Clinic, a corresponding learning/teaching concept for the new preclinical course is currently in the progress of being prepared.

FUTURE DIRECTIONS

The main objective of the Institute is to improve the research and more focus on practice-oriented teaching in general medicine. The planned institutionalization opens up new possibilities in the implementation of new research projects in the field of General Medicine. The aim is to strengthen research in the field of prevention opportunities in general practice.

DEPARTMENT OF GENERAL MEDICINE

Head:
Professor
Michael Jansky

University Medical Center Mainz
Langenbeckstr. 1
D-55101 Mainz
phone: +49 (0) 6131 17-7082
jansky@uni-mainz.de
www.unimedizin-mainz.de/allgemeinmedizin
FIG. 1: Pictures from the course: Introduction to Clinical Medicine
FIG. 2: Image from the course: family medicine for pre-clinical
FIG. 3: Picture from clinical week in General Medicine

IMPORTANT PROJECTS // MAX. 5

- HIV in general practice
  PROJECT MANAGER: Prof. B Schappert, Prof. M Jansky
  PROJECT DURATION: 2010 - 2015

- Improve teaching in general medicine
  PROJECT MANAGER: Prof. M Jansky, Prof. B Schappert
  PROJECT DURATION: 2010 - 2014

- Integration of preclinical and clinical teaching
  PROJECT MANAGER: Prof. M Jansky, Prof. R Haidmayer
  PROJECT DURATION: 2011 - 2014

- Postgraduate training
  PROJECT MANAGER: Prof. M Jansky, Prof. B Schappert
  PROJECT DURATION: 2011 - 2015
SPECIAL ADVANCEMENT OF YOUNG SCIENTISTS

Mainz Research School of Translational Biomedicine (TransMed)
OVERVIEW

The Mainz Research School of Translational Biomedicine (TransMed) and its doctoral degree regulation “PhD-MD/PhD in Translational Biomedicine” were jointly established in 2012 by four faculties of the Johannes Gutenberg University (JGU) Mainz, the University Medical Center, Biology, Chemistry/Pharmaceutical Sciences/Geosciences and Social Sciences/Media/Sports.

TransMed plays a multifaceted role for the promotion of young scientists in life sciences at JGU Mainz and at cooperating institutions in the Rhine-Main area. TransMed serves as the graduate school for the Research Center “Translational Medicine”. Beyond this, TransMed is the umbrella organization for all training groups within the area of biomedicine at JGU.

HIGHLIGHTS

In 2014, another three TransMed Fellows have been selected through a competitive application procedure. The TransMed Fellow community now consists of seven scientists, three of them are physician scientists who perform a MD/PhD thesis in parallel to their specialist training. The support by TransMed allows them protected time to perform their research project for half of the duration of the fellowship. The other four TransMed Fellows are natural scientists performing a PhD or Dr. rer. nat. thesis. They will be familiarized with the workflow at a clinical institution and introduced to the regulatory issues of patient-oriented research. The fellows are co-supervised by a clinician and a basic research scientist.

In November 2014, the first TransMed Science Day brought together more than hundred participants (doctoral students, postdoctoral fellows and senior scientists) working in translational medicine. Doctoral students gave short talks on their project. The participants discussed about scientific publications and “bench-to-beside” approaches with the pharmaceutical industry. Special Editor & Speaker sessions facilitated the informal exchange.
FIG. 1: TransMed Program Director Prof. Dr. med. Esther von Stebut-Borschitz (r.), TransMed Program Coordinator Dr. rer. nat. Petra Schwarz (l.) and the seven TransMed Fellows (from left to right) Klytaimnista Kiouptsi, Dr. med. Joanna Wegner-Kops, Cornelia Schätzel, Anna Gerlicher, Anke Werner, Dr. med. Alexander Ziebart and Dr. med. Daniel Teschner.

FIG. 2: The recipients of the Best Presentation Awards Maximilian Kopp, Radhika Menon, Dr. Martin Heller and Melanie Flach together with the organizers of the First TransMed Science Day, Prof. Dr. Krishnaraj Rajalingam, Dr. Petra Schwarz and Prof. Dr. Esther von Stebut-Borschitz.
PRE-CLINICAL

Institute of Functional and Clinical Anatomy
Institute of Microscopic Anatomy und Neurobiology
Institute of Physiology
Institute of Pathophysiology
Institute of Physiological Chemistry
Institute of Pathobiochemistry
The research carried out focussed on the subjects angiogenesis, wound healing and tumour growth, as well as circadian systems, the retina, gene expression and the daily dynamics of the photoreceptor cells. The methodical repertoire of the research groups includes a wide spectrum of microscopic techniques (e.g., scanning electron microscopy, transmission electron microscopy, laser scanning microscopy, in addition to biochemical (e.g., Western blot, Southern blot) and molecular-biological techniques (e.g., Real-time-PCR, gene-deficient mouse models).

RESEARCH GROUP SPESSERT:
The retina is subject to a daily rhythm with regard to numerous parameters. This diurnal regulation is - in the case of the vertebrates - highly conserved and functional - and can be understood as an adaptation to the changing light intensity which occurs more than 100 times over the 24-hour daily cycle. The daily adaptation of the retina also applies to the photoreceptors (rods and cones). In this way they show a 24-hour rhythm with regard to their morphology (e.g., renewal and phagocytosis of the membrane discs in the outer segment, ultrastructure of the ribbon synapse) and physiology (e.g., synthesis of melatonin, visual signal processing). The daily changes in the photoreceptors are partly directly regulated through the outer light conditions and partly through the retina’s own molecular clocks (oscillators), which on their part are influenced by the outer light conditions. In the research group, the daily adaptation of the photoreceptors is being investigated at the gene level. Here, the working hypothesis is tested that the survival of photoreceptors under changing light intensities is promoted by the daily regulation of genes possessing protective power.

RESEARCH GROUP ACKERMANN:
The reparative and regenerative wound healing depends, among other things, on the induction of blood vessels. New vessels are formed either through the sprouting of pre-existing vessels or through intussusceptive angiogenesis (IA). Within the framework of a NIH-RO1 cooperative project, our group investigated to what extent the IA is involved in the new formation of murine lung tissue after pneumonectomy and whether it can be influenced. The mechanisms of lung growth, and in particular the participation of endothelial progenitor cells are being investigated together with our cooperation partners at the Brigham and Women’s Hospital of the Harvard Medical School and the Harvard School of Public Health. In addition, the influence of micromechanical forces during regeneration was investigated using a unilateral phrenic exeresis. The Ackermann research group also further investigated the effects of angiogenesis in Alzheimer’s disease and its therapeutic influence. Clinical questions concerning the biomechanics of the ventral body wall, the integration of hernia meshes or jamming injuries are being worked on in various clinical cooperations.

OVERVIEW
The Institute of Functional and Clinical Anatomy has three areas of focus:

1. Teaching The Institute offers various events for students of medicine and dentistry, such as a macroscopic anatomy course (dissection), a course on microscopic anatomy (histology course), lectures and seminars. The head of the department is one of the authors of the “Prometheus Lernatlas Anatomie”.

2. Research The research focuses on various scientific questions concerning angiogenesis and wound healing (research group Ackermann), “Circadian system” and “Retina” (research group Spessert).

3. Body donation Within the framework of their studies, students are given an extensive training in the anatomy of the human body. The study of the bodies takes place in accordance with the testamentary disposal at the institute.
**FUTURE DIRECTIONS**

**RESEARCH GROUP SPESSERT:**

The energy metabolism of the mammalian retina has to comply with daily changes in energy demand and its impairment contributes to diabetic retinopathy - one of the most common causes of blindness in Europe and USA. To gain a view of the regulation of the energy metabolism of the retina, future investigation of our group will focus on circadian regulation of retinal energy metabolism and its dysregulation in diabetic retinopathy.

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**IMPORTANT PUBLICATIONS // MAX. 5**


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**IMPORTANT PROJECTS // MAX. 5**

**Adult tissue morphogenesis:**

Functional regulation of intussusceptive angiogenesis

**PROJECT MANAGER:** Dr. M Ackermann

**FUNDING:** National Institutes of Health (NIH) USA

**SUM:** € 200,000

**PROJECT DURATION:** 2009 - 2016

**Auto-immune diseases and the effects on the morphology and architecture of the human lung**

**PROJECT MANAGER:** Dr. M Ackermann, PD Dr. D Jonigk

**PROJECT DURATION:** 2014 - 2014

**Impact of vascular morphology and architecture on the fibrogenesis of the liver**

**PROJECT MANAGER:** Dr. M Ackermann, Prof. D Schuppan, Dr. Y Kim

**PROJECT DURATION:** 2014 - 2014

**The molecular oscillator of the photoreceptor cell**

**PROJECT MANAGER:** Prof. R Spessert, Dr. T Wolloscheck

**FUNDING:** Intramural Funding

**SUM:** € 20,000

**PROJECT DURATION:** 2010 - 2014

**Which genes enable the morphological adaptation of the receptor cells during light and dark.**

**PROJECT MANAGER:** Prof. R Spessert

**FUNDING:** NMatZ

**SUM:** € 55,000

**PROJECT DURATION:** 2011 - 2015

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**FIG. 1:** Retina of wild-typ mice - fluorescence microscope image - AG Spessert
The scientific focus of the research groups of Robert Nitsch are on I) the role of bioactive phospholipid signaling in the nervous system, II) axonal outgrowth & reorganization plus neuroimmune interactions and III) neuroaesthetics. I) A precise understanding of the molecular mechanisms of layer formation and connectivity in the developing brain or the homoeostatic control of signaling in the adult brain can provide a basis for possible therapeutic interventions in brain disorders. We analyze LPA-synthetizing enzymes such as autotaxin and the postsynaptic regulators PRG-1/2 using a broad range of techniques. II) The question of the involvement of non-neuronal cells in the process of CNS reorganization arose as in recent years it has become evident that a specific modulated form of immune response occurs in the CNS. Understanding the mechanisms of axonal transport and signaling is thus a main focus of our research. III) This new field of research addresses cognitive processes underlying adaptation in the arts. A combined view from humanities and neuroscience on recognition and perception of adaptations is pursued. Neuronal correlates are studies using functional imaging using various perception paradigms.

The "Molecular Signal Transduction" labs (MS labs) of Mirko HH Schmidt focus on the analysis and cure of CNS diseases. Questions of life sciences and translational research approaches are applied to contribute to the cure of patients. In particular, researchers in the lab analyze I) how malignant brain tumors, e.g., glioma are formed and how they can be treated beyond conservative medicine. Further, it is studied II) how neural stem cells are regulated in the adult brain, whether these cells can be exploited for the cure of neurodegenerative diseases, e.g., Alzheimer’s disease and which influence newborn neurons have for the homeostasis and allostatics of the adult brain. Last, the molecular causes of III) neurovascular diseases, such as stroke, are explored and it is studied how these diseases can be prevented, cured or at the least, how their detrimental effects can be attenuated. The MS labs study molecular signal cascades involving proteins, which are either secreted or localized at the plasma membrane and are therefore druggable from the cellular exterior such as EGFL7/Notch, EGF/EGFR or integrins by the application of a broad range of life science techniques ranging from biochemical analyses via advanced imaging and lab animal models to the analysis of human specimens.

The Research Group “Molecular Imaging and Optogenetics” of Albrecht Stroh focuses on combining state-of-the-art optogenetic techniques with optical neuroimaging. Advancement of our understanding of neuronal network dynamics in health and disease requires the investigation of defined populations of neurons and their interactions in the intact CNS. Probing the specific contribution of genetically defined neuronal cell populations in vivo is pivotal for furthering our knowledge of impairment of network dynamics and for the development of effective therapy strategies. The discovery of a rapidly gated light-sensitive cation channel channelrhodopsin-2 (ChR2) suitable for noninvasive control of neuronal activity has made it possible to optically control membrane depolarization on the millisecond timescale in genetically defined neurons. Recent developments of the optogenetic toolbox allow for the effective inhibition of genetically defined neuronal cell populations in vivo.
**PRE-CLINICAL INSTITUTES**

**RESEARCH REPORT 2014**

**IMPORTANT PUBLICATIONS // MAX. 5**


**FUTURE DIRECTIONS**

**Goal I:** To explore the basis of brain development and function
**Goal II:** To understand CNS diseases in order to develop novel therapies
**Goal III:** To observe and illustrate neural processes *in vivo*

**IMPORTANT PROJECTS // MAX. 5**

<table>
<thead>
<tr>
<th>Project Name</th>
<th>Project Manager</th>
<th>Duration</th>
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<tr>
<td>The role of bioactive phospholipid signaling in the nervous system</td>
<td>Prof. R. Nitsch, Dr. Johannes Vogt, Dr. Jisen Huai, Dr. Sebastian Richers</td>
<td>2011-2017</td>
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<td>Role of bioactive phospholipid signaling in the developing nervous system</td>
<td>Prof. R. Nitsch, Dr. Johannes Vogt</td>
<td>2011-2017</td>
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<tr>
<td>Mechanisms of Axon Regeneration</td>
<td>Prof. R. Nitsch, Dr. Tineke Vogelaar</td>
<td>2012-2016</td>
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<td>Neuroaesthetics and adaptation in cultural and neuronal networks</td>
<td>Prof. R. Nitsch, PD Dr. Nicklas</td>
<td>2013-2016</td>
</tr>
<tr>
<td>Notch signaling in neural stem cells</td>
<td>Prof. Mirko HH Schmidt, Dr. Frank Bicker</td>
<td>2013-2016</td>
</tr>
</tbody>
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OVERVIEW

The work group of Prof. Luhmann is interested in the development and physiology of cortical structures with a strong focus on the somatosensory system. The lab of Prof. Mittmann studies adaptive and homeostatic processes at synapses in the neocortex after traumatic brain injury. The subgroup of PD Dr. Kilb is also studying the development of the cerebral cortex, but with respect to the GABAergic inhibition as well as network interactions. The subgroup of PD Dr. Kirischuk has a focus on neuron-glia interactions in the cerebral cortex and a special focus on chloride-transporters in neurons and in glial cells. The subgroup of Dr. White is also studying glial cells, while the subgroup of Dr. Hedrich has a focus on the function of the blood-brain-barrier in rodents.

HIGHLIGHTS

The group of Prof. Luhmann studies with in vitro and in vivo electrophysiological and imaging techniques the development and physiology of neocortical networks in rodents. The goal is to understand the function and dysfunction of neuronal networks from the subcellular level to large-scale network interactions.

The group of Prof. Mittmann studies the question how does activity from intracellular proteasome and autophagy signal cascades mediate adaptation and homeostasis in the somatosensory cortex following traumatic brain injury in mice. Another project addresses the function of GABAergic synaptic inhibition in the vicinity of focal lesions in the visual cortex.

The group of Prof. Rumpel focuses on two fundamental questions: How are sounds perceived and represented in the neocortex? How are these representations transformed into a long-term memory? In order to address these questions we use molecular biology and genetics to target neurons in the living, behaving mouse with modern optical and physiological methods for observation and manipulation.

The group of PD Dr. Kilb investigates the cellular physiology of the immature cerebral cortex and the role of developmental disorders in the generation of neuronal pathologies.

The group of PD Dr. Kirischuk investigates the information flow in the brain as a combination of ”digital” (synaptic) and ”analog” (volume) transmissions by the use of electrophysiological, but also microfluorimetric, immunohistochemical and molecular methods.

The group of Dr. White studies with molecular biological methods myelination and remyelination processes.

The group of Dr. Hedrich investigates the physiology and pathophysiology of the blood-brain-barrier in different in vitro models.

FUTURE DIRECTIONS

The overall aim of our research is a better understanding of physiological and pathophysiological processes in the brain. Our new findings might be used by clinical researchers to develop new and innovative-therapeutical strategies to treat disorders in brain development and rehabilitation therapies after traumatic brain injuries. Furthermore, our research results shine some new light on the causes of diseases of the central nervous system like in epilepsy and neurodegenerative disorders like Multiple sclerosis.


**FIG. 1:** Electrophysiological and morphological properties of Cajal-Retzius cells with different ontogenetic origins.

A: Cajal-Retzius cells originating from the pallial-pulvillar border are permanently labelled by YFP expression in transgenic Dbx1cre;ROSA26YFP mice (black arrowhead). Inset illustrates the electrophysiological responses in this cell upon injection of de- and hyperpolarizing responses

B: A YFP- Cajal-Retzius cell (gray arrowhead) shows comparable electrophysiological properties.

C: Action potential waveform is similar in YFP+ (black trace) and YFP- (gray trace) Cajal-Retzius cells.

D: Phase-plane plots illustrating that the kinetic properties of action potentials are similar between YFP+ (black trace) and YFP- (gray trace) Cajal-Retzius cells.

E: Neurolucida reconstruction of the axonal (yellow) and somatodendritic (red, with filopodia colored cyan) compartment of a YFP+ Cajal-Retzius cell.

F: Neurolucida reconstruction of a YFP- Cajal-Retzius cell. Scale bars for E and F represent 100 µm.
Cancer cells are able to escape from the immune defense of the tumor host as well as from therapeutic attacks, and they may ultimately cause the death of the cancer patient. Besides other mechanisms, specific properties of tumor metabolism contribute to this immunological and therapeutic resistance of tumor cells. The malignant transformation of normal cells in the human body is associated with a multiple increase in the cellular glucose uptake rate. Simultaneously, the malignant cells produce large or variable amounts of lactic acid and lactate, respectively, independent of the oxygenation status. This so-called aerobic glycolysis leads to an accumulation of lactate in solid malignancies, which in turn is influencing biological and therapeutic properties of tumor tissue.

HIGHLIGHTS

Our research team has developed a new method, called induced metabolic Bioluminescence Imaging (imBI), for the systematic analysis of tumor metabolism in snap-frozen tissue biopsies. Rapid freezing by immersion into liquid nitrogen of biopsies acutely removed from normal and diseased tissue represents a technique feasible in both the experimental and clinical setting for the appropriate cryo-fixation of the momentary metabolic status of live tissue. We have demonstrated by long-term storage in liquid nitrogen, that the metabolic status in such biopsies can be preserved for at least 10 years which can be of high relevance for tissue banking under these conditions.

The imBI technique can be used for the quantitative assessment of metabolite distributions within tissue cryosections at a microscopical level in relation to the histological structure of the tissue. Computerized image analysis makes it possible to determine tissue concentrations of metabolites, such as ATP, glucose, lactate, pyruvate and others, in selected histological regions within solid tumors, e. g. in areas containing viable malignant cells, in stromal or necrotic regions, or in areas with infiltrated defense cells. The application of imBI in numerous experimental tumor systems and in a number of clinical studies has substantially increased our knowledge on mechanisms of metabolic resistance in malignant disease. It has been shown in several tumor entities, such as squamous cell carcinoma of the uterine cervix or of the head and neck and in rectal adenocarcinomas, that the level of lactate accumulation in primary lesions is positively correlated with the incidence of metastasis and with the resistance to a conventional radiotherapy, and is negatively correlated with the overall or disease-free survival of the cancer patients. Mechanisms underlying these correlations include an activation of tumor cell migration by an acidic and high lactate environment with a simultaneous inactivation of macrophages, dendritic cells and cytotoxic T cells with regard to migration and cytokine release in such an environment. Furthermore, de-regulated tumor glycolysis is associated with an increased antioxidative defense, neutralizing reactive oxygen species (ROS), which are required for an effective radiation treatment. We were able to show that a combined non-cytotoxic inhibition of oxidative phosphorylation and glycolytic flux can radio-sensitize human cancer cells to a clinically relevant extent.


**IMPORTANT PROJECTS** // MAX. 5

**Combining cells and behavior: neuronal foundations of extinction and renewal (DFG FOR 1581 TP 1)**

**PROJECT MANAGER:** Prof. O Güntürkün, h.c., Junior Professor MC Stüttgen

**FUNDING:** German Research Foundation (DFG)

**PROJECT DURATION:** 2014 - 2016

**FUTURE DIRECTIONS**

Besides an increase in our scientific knowledge, research on tumor metabolism can be expected to give access to novel therapeutic strategies in oncology by a sophisticated and personalized manipulation of tumor metabolism. Unlike most molecular strategies that are directed towards a specific receptor or signaling molecule, such a “metabolic targeting” aims at the global metabolic status of the cancer cell. Since methods are available for the characterization of this metabolic status in individual patients in the clinic, metabolic targeting may be used for a personalization of therapeutic approaches. Such research concepts are currently under development worldwide, and numerous promising metabolic approaches have already entered phase I and II clinical trials.
The group of Beat Lutz in conjunction with long-term collaborators advanced the understanding of the roles of the endocannabinoid system in several aspects. The following new insights should be highlighted. (i) This lipid neuromodulatory system is involved in the control of feeding behavior, whereby the CB1 cannabinoid receptor in the olfactory system was shown to be crucial. (ii) The role of the CB1 receptor in oxidative phosphorylation processes in mitochondria was substantiated. This modulatory function is proposed to be mediated by the CB1 receptor localized in the inner mitochondrial membrane. (iii) Neuroprotective functions of telencephalic CB1 receptor in mouse models of the neurodegenerative disorders Huntington Disease and multiple sclerosis were defined. (iv) The dynamics of the endocannabinoid system in a mouse model of cardiomyopathy was evidenced using mass spectrometry methods.

A main focus of the Berninger lab concerns the possibility of reprogramming endogenous glia into induced neurons as a potential novel approach towards a cell-based therapy of neurological disorders. Earlier work of the group showed that in vitro cultured glia can be converted into functional neurons by forced expression of defined transcription factors that play key roles during embryonic neurogenesis (reviewed by (Arlotta and Berninger, 2014)). In the last year we could now show that such glia-to-neuron reprogramming is also possible in the adult cerebral cortex in vivo (Heinrich et al., 2014). We found that Sox2 can reprogram so called NG2 glia into induced neurons expressing the early neuron marker doublecortin. Intriguingly, these induced neurons were found to express active conductances and to receive synaptic input from the pre-existing neuronal network. Surprisingly, Sox2-induced reprogramming only occurred in the context of an acute lesion of the cerebral cortex but not in the intact cortex. Our new data provide in vivo evidence for the feasibility of glia-to-neuron conversion for brain repair.

Highlights of the group of W.E.G. Müller, H.C. Schröder and X.H. Wang were (i) the elucidation of the crucial role of enzymes during biomineralization in general and bone formation in particular, as well as the identification of the first morphogenetically active inorganic polymers, inducing the synthesis of bone-related growth factors/cytokines, (ii) the functional dissection of silicatein, the first enzyme that forms an inorganic material for exploitation in micro-optics and nanomedicine, (iii) the development of the first morphogenetically active and regenerative bio-scaffolds for bone disease, even customized implants by 3D-(cell)-printing techniques, and (iv) the fabrication of small diameter artificial blood vessels, allowing endothelial cells to grow. These results were obtained in the frame of the ERC Advanced grant BIOSILICA (W.E.G. Müller) and the EU FP7 projects BlueGenics, Bio-Scaffolds, CoreShell, as well as MarBioTec.
FUTURE DIRECTIONS

The Lutz group aims at defining critical functions of the CB1 receptor regarding several behaviors, including fear memory, anxiety, stress resilience, feeding behaviors and energy balance. Thereby, we apply genetic complementation experiments, which enables us to determine sufficient CB1 receptor functions. Second, we investigate the protective roles of brain derived neurotrophic factor in neurodegeneration and injury mouse models. Third, we wish to advance our lipidomic platform towards mass spectrometry imaging.

A main goal of the Berninger group is to improve glia-to-neuron reprogramming in the adult brain in vivo in order to obtain specific subtypes of neurons and to assess their functional contribution to the pre-existing neural circuit. Our second focus concerns the functional integration of adult-born neurons in the hippocampus using rabies-virus mediated tracing of synaptic connectivity. Using this approach we also hope to address the role of adult hippocampal neurogenesis as a resilience-conducive mechanism.

Taking nature as a blueprint, the group of Müller/Schröder/Wang develops new biomaterials composed of polymers which are morphogenetically active and induce proliferation and differentiation of human cells, especially of bone cells. These polymers can be organized into biocompatible and biodegradable scaffolds that can be biointegrated and used for various tissue implants. The new implants are superior to current implants in the market.

IMPORTANT PUBLICATIONS // MAX. 5


Soria-Gomez E, Belloccchio L, Reguero L et al. The endocannabinoid system controls food intake via olfactory processes. NATURE NEUROSCIENCE. 2014; 17 (3).

Wang X, Schroeder HC, Mueller WEG. Enzyme-based biosilica and biocalcite: biomaterials for the future in regenerative medicine. TRENDS IN BIOTECHNOLOGY. 2014; 32 (9): 441-447.


EU ERC Advanced Grant BIOSILICA (Grant agreement no.: 268476): From gene to biomineral: Biosynthesis and application of sponge biosilica

EU FP7 – BlueGenics (Grant Agreement no.: 311848) Large-scale integrating project: BlueGenics – From gene to bioactive product: (coordinator: W.E.G. Müller)


Lineage reprogramming of astroglia into distinct glutamatergic neuron subtypes


Molecular and Cellular Mechanisms of Neural Homeostasis 1080 (B08)

PROJECT MANAGER: Prof. B Lutz FUNDING: German Research Foundation (DFG) SUM: € 357,700 PROJECT DURATION: 2013 - 2016

Fear, anxiety and anxiety disorders, SFB/TRR 58 (A04-2)

PROJECT MANAGER: Prof. B Lutz FUNDING: German Research Foundation (DFG) SUM: € 279,400 PROJECT DURATION: 2013 - 2016
OVERVIEW

The research of the Institute of Pathobiochemistry is dedicated to the biochemistry of neurodegenerative disorders and aging. The three groups (Behl: Biochemistry of Neurodegeneration and Aging; Moosmann: Evolutionary Biochemistry and Redox Medicine; Pietrzik: Molecular Neurodegeneration) are working complementary with respect to their particular research content and strategies with many overlaps, including technologies and model systems used. It is the ultimate research goal of the institute by effectively using this synergy to create a full picture of the addressed human age-related neurodegenerative disorders leading to novel strategies for prevention and therapy. Currently, basic processes and mechanisms of Alzheimer’s disease (AD), amyotrophic lateral sclerosis (ALS) and Parkinson’s disease combined with evolutionary aspects of these disorders are intensively studied.

HIGHLIGHTS

The Behl group aims to decipher the role of proteostasis in neuronal function and dysfunction with a special focus on the process of autophagy. In 2014, Dr. Andreas Kern with his team has discovered a novel regulator of macroautophagy, RAB3GAP1/2, by studying the molecular players in C.elegans and the mammalian system. In a research project of Dr. Albrecht Clement molecular details on a calcium-sensing protein (visinin-like protein1) triggered by oxidative stress and its link to ALS were described. Finally, Dr. Parvana Hajieva and her co-workers have revealed that it is in fact the process of membrane protein oxidation that determines the extent of neuronal degeneration.

Based on its seminal finding that long-lived animals including humans strictly avoid the otherwise essential amino acid cysteine in membranes, the Moosmann group has been able to delineate a novel biochemical reaction that appears to be at the heart of the aging process: the intramembrane formation of thiyl radicals.

The Pietrzik group has identified a novel enzyme, meprin β, involved in the processing of the amyloid precursor protein which is linked to familial AD. Additionally, they were able to demonstrate the importance of the Low Density Lipoprotein Receptor-related Protein 1 in the clearance pathway of the amyloid β peptide across the blood brain barrier. Both findings may be of importance for the understanding of AD development.

FUTURE DIRECTIONS

Under the umbrella of the general research topic of the institute the three research groups have individual plans to further successfully follow their projects. The Behl group will intensify its studies on the role of macroautophagy in neuronal function by analyzing regulators of this pathway (Rab GTPase activating proteins - RABGAPs, estrogen receptors, cannabinoid receptors), selective macroautophagy mechanisms (e.g. BAG3-pathway) and their link to disease. These studies are complemented by investigations of the molecular consequences of hypoperfusion of the brain with a special look into the role of mitochondria.

The Moosmann group currently is investigating the mechanisms by which thiyl radicals induce premature aging and tissue dysfunction. Knowledge about these mechanisms might be very valuable in the development of therapies against degenerative diseases of old age. The Pietrzik group plans to influence the enzymatic activity of the novel enzyme involved in amyloid precursor processing to potentially influence amyloid β production. Using our amyloid β clearance model we will try to increase amyloid β efflux from the brain to reduce amyloid β burden and hopefully reduce the risk for AD development.
**IMPORTANT PUBLICATIONS // MAX. 5**


Liebl MP, Kaya AM, Tenzer S et al. Dimerization of visinin-like protein 1 is regulated by oxidative stress and calcium and is a pathological hallmark of amyotrophic lateral sclerosis. FREE RADICAL BIOLOGY AND MEDICINE. 2014; 72: 41-54.


**FIG. 1:** Schematic representation of the proteolytic cleavage of APP by meprin β. We found molecular interaction of APP and the metalloprotease meprin β in the secretory pathway and at the cell surface. On the right site, specific antibodies for APP/ APP fragments and their epitopes are marked.

**FIG. 2:** RAB3GAP1/2 are positive modulators of autophagy. siRNA-mediated deficiency of RAB3GAP1 and RAB3GAP2 decreases autophagic activity as shown by immunostainings of human fibroblasts. The observed green dots correspond to autophagic vesicles (autophagosomes) and their amount is reduced after knockdown of RAB3GAP1/2 at control conditions and after inhibition of lysosomes (Bafi).

**IMPORTANT PROJECTS // MAX. 5**

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<tr>
<th>Project</th>
<th>Description</th>
<th>Project Manager</th>
<th>Funding</th>
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<td>„Stabilization of Neuronal Protein Homeostasis by Adaptation of Chaperone Activity to Long Term Proteotoxic Stress in vivo” (SP A08) - SFB 1080/1 „Molecular and Cellular Mechanisms of Neural Homeostasis”</td>
<td>Functional Role of the Proteasome and Autophagic Protein Degradation System in Neuronal Homeostasis Following Traumatic Brain Injury (SP A07) - SFB 1080/1 „Molecular and Cellular Mechanisms of Neural Homeostasis”</td>
<td>Prof. C Behl, Dr. AM Clement</td>
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<td>Bioinformatic analysis of fully sequenced proteomes</td>
<td>Prof. B Moosmann</td>
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<td>The role of meprin beta in Alzheimer’s Disease</td>
<td>Prof. CU Pietrzik, Prof. Dr. C Becker-Pauly</td>
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<td>2013 - 2016</td>
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**RESEARCH REPORT 2014**
INSTITUTES OF THEORETICAL MEDICINE

Institute of Occupational, Social and Environmental Medicine
Institute of the History, Philosophy and Ethics of Medicine
Institute of Immunology
Institute of Medical Microbiology and Hygiene
Institute of Pharmacology
Institute of Legal Medicine
Institute of Toxicology
Institute of Virology
Institute of Translational Immunology
OVERVIEW

The Institute of Occupational, Social, and Environmental Medicine represents the corresponding disciplines in research as well as teaching and provides consultancy service in the health care sector. Since 2011 a specialized advisory Institute for Teachers’ Health (IfL) was integrated in the institute.

The independent disciplines Occupational, Social, and Environmental Medicine are subdivided into the working groups “Occupational Medicine”, “Occupational Toxicology and Laboratory Diagnostics”, “Occupational Physiology”, “Public Health/Social Medicine”, “Occupational and Social Psychology”, “Environmental Medicine”, and “Teachers’ Health”.

HIGHLIGHTS

MAIN RESEARCH PROJECTS OF THE WORKING GROUPS:

OCCUPATIONAL TOXICOLOGY AND LABORATORY DIAGNOSTICS
Assessment of internal chemical exposure and potentially related health effects associated with introduction of new technologies (e.g. use of carbon fibre reinforced plastics in car body construction, application of permethrin on clothing for tick protection); release of hazardous substances and concomitant exposure of nursing staff as a consequence of handling pharmaceuticals.

OCCUPATIONAL MEDICINE
Pressure pain thresholds of 100 healthy subjects were measured with a force-controlled automatic algometer at 29 body sites. The measured values have been passed on to the International Committee for Standardization. They will revise an ISO norm for collaborative robot systems, which will regulate maximum force and peak pressures in case of a collision between human and robot. Robotics suppliers and users will be given a basis for the safe construction and application.

OCCUPATIONAL AND SOCIAL PSYCHOLOGY
Research activities in 2014:
- Occupational health of nurses: In this area, two projects on working conditions and occupational health of more than 100 nurses working in geriatric and palliative care were carried out.
- Occupational health management: Within the scope of a project funded by the European Social Fund Rhineland-Palatinate, an internet platform (www.gesundekmu.de) was created providing a guideline regarding occupational health management in small and medium-sized enterprises.

PUBLIC HEALTH/SOCIAL MEDICINE
The Pink-Study – Couples Undergoing Fertility Treatment
Assisted reproductive technologies are increasingly used to overcome infertility. The first prospective cohort study on the patient’s perspective on fertility treatment in Germany aims at a better understanding of the situation of couples with an unfulfilled desire for a child, pathways leading to fertility treatment as well as psychological and social consequences of the experience of infertility and treatment. In 2014, data collection of the one-year follow-up was completed.

TEACHERS’ HEALTH
The Institute for Teachers’ Health as a part of the ASU is responsible for occupational health and safety counseling of more than 45,000 teachers and educational staff in Rhineland-Palatinate. Current research activities include a cross-sectional study on occupational strain and stress of staff working at inclusive primary schools with handicapped pupils. The project focuses particularly on burden of teachers and educational staff caused by infectious, musculo-skeletal, and psychological factors. Results will lead to eligible measures of occupational health prevention. The annual report on the health status of teachers and educational staff in Rhineland-Palatinate for the school year 2013/2014 is currently in press.
**FUTURE DIRECTIONS**

Current and future developments and changes in work and society like demographic change, new technologies, and inclusion, require continued efforts in the field of preventive occupational medicine. With a special focus on teachers’ health and new technologies, the generation of knowledge within the scope of basic and applied research is one of the institute’s main goals. Thereby, we try to contribute to the reorganization and further development of occupational healthcare for employees. 

Regarding Social Medicine / Public Health, future research activities aim to continue research on migration, inclusion and palliative medicine, under special consideration of population and supply-relevant aspects. Based on the planned Prevention Act, possible measures to improve preventive healthcare of employees, especially in small and medium-sized enterprises, shall be evaluated. It is further intended to build and scientifically support additional supply structures (e.g. occupational telemedicine).

Furthermore, the institute aims to integrate new scientific knowledge into basic and advanced professional training as well as teaching. This includes the development of new teaching and learning methods (e.g. game-based learning).

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**IMPORTANT PROJECTS // MAX. 5**

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<th>Collaborative robots - Assessment of pain sensibility at the human-machine interface</th>
<th>Couples undergoing fertility treatment (Pink-Study)</th>
<th>Evaluation of occupational stress and strain in teachers and educational staff working at inclusive primary schools</th>
<th>Provision of safety-related information on pharmaceuticals and associated tasks - BESI</th>
<th>UV-radiation-induced malignant skin tumors – Development and evaluation of legally relevant criteria to distinguish occupational and non-occupational causation</th>
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<td><strong>PROJECT MANAGER:</strong> Prof. S Letzel, Prof. A Muthray, Dr. B Geißler</td>
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HIGHLIGHTS

GRK 2015/1 „Life Sciences - Life Writing: Boundary Experiences of Human Life between Biomedical Explanation and Lived Experience“ (funded by the German Research Foundation) Man’s embeddedness in a socio-cultural context on the one hand and in a sphere of materiality on the other hand has given rise to the differentiation of the sciences into the natural sciences and humanities, now understood as the life sciences and the social and cultural sciences. In the field of biomedicine, which explains and sustains human life through the use of empirical methodologies and frameworks, the search for rational explanations for decision-making and action have resulted in the dominance of natural scientific models as the leading perspective on man as an organism. In contrast, the humanities and cultural sciences have been increasingly concerned with the role of the individual and his or her manifold forms of access to the world. The fact that new possibilities in the field of biomedicine have caused new boundary experiences of human life (from technologically assisted reproduction to ways of dying accompanied by intensive care), challenging the humanities and cultural sciences to contribute of complementary interpretations of those boundary experiences. The Research Training Group, approved in 2013, aims for the development of joint methodological approaches to established subject areas on human boundary experiences in Life Sciences and Life Writing on the level of human corporeality, temporality and ability.

Discours historiques, sociologiques, philosophiques et éthiques. German-French graduate college with Université de Strasbourg The German-French graduate college is a transdisciplinary training program for PhD students of medicine, the humanities and cultural studies, which focuses on the intersections of medicine, philosophy, ethics and culture.
FUTURE DIRECTIONS

FUTURE AIMS AND SCOPE OF RESEARCH:

NARRATIVITY:
The findings generated within the DFG Research Training Group 2015/1 „Life Sciences - Life Writing: Boundary experiences of human life between biomedical explanation and lived experience“ are indicative for the fact, that deliberation in clinical ethics lends itself to concepts of narrativity and narratability as well. This requires a re-assessment of the praxeology and methodology of clinical ethics in the light of narrative practices and determines one of our major research goals.

INDIVIDUALITY:
One of our research goals is to explain the historical roots of concepts of individuality in medicine and follow the development from an epistemological and ethical perspective into the plausible future.

MEDICINE AND THE PUBLIC:
The societal impact, the migration of biomedical knowledge and information, the evaluation of medicine in the public sphere and the shaping of that sphere through biomedical knowledge and practices is an overarching goal of our research.

MATERIALITY:
To understand the ways in which materiality is addressed, shaped and reshaped at the interface of medicine an human life is one of the main future goals of research.

TEMPORALITY:
Experimental systems, however, are often designed to overcome biological timing. The impact of „wild types“ of time and technologically constructed time on the materiality of humans are thus consequently our third research focus.

IMPORTANT PROJECTS // MAX. 5

Assessment of teaching success in History, Theory, and Ethics (HTE)
PROJECT MANAGER: Prof. L Pruell
FUNDING: MAICUM
SUM: € 53,469
PROJECT DURATION: 2012 - 2014

DFG Research Training Group 2015/1 „Life Sciences - Life Writing: Boundary experiences of human life between biomedical explanation and lived experience“
PROJECT MANAGER: Prof. NW Paul, Prof. M Banerjee
PROJECT DURATION: 2014 - 2018

Gender-specific aspects and prevention concepts for cardiovascular diseases in Germany, 1949-2000
PROJECT MANAGER: Prof. L Pruell
FUNDING: German Research Foundation (DFG)
PROJECT DURATION: 2011 – 2014

Narrative Practices in Medicine. Historical, Sociological, Philosophical and Ethical Discourses
PROJECT MANAGER: Prof. NW Paul, C Buir
PROJECT DURATION: 2012 - 2014

Patients, The Public and Medicine in West Germany
PROJECT MANAGER: Prof. L Pruell
PROJECT DURATION: 2009 - 2014

IMPORTANT PUBLICATIONS // MAX. 5


The research activities realized at the Institute for Immunology concern various aspects of the induction of innate and adaptive immune responses. As part of our investigations of the innate immune system we analyze the function and regulation of mast cells and neutrophils as well as their interaction within the framework of the induction of inflammatory reactions and in the development of airway hypersensitivity. Our work on the activation of cells of the innate immune system and their effect on the induction of adaptive immune responses addresses particularly the use of ligands for Toll-like receptors in the development and optimization of vaccination protocols, especially for transcutaneous applications. Of particular interest are the activities of different populations of dendritic cells in the skin and in peripheral lymphoid organs where tolerance and induction of antigen-specific immunity is established. The studies on the activation of adaptive immune responses are completed by projects that attend on one hand to the role of different cytokines in the differentiation of T-cells and on the other hand to the function of regulatory T cells. The analysis of T-cell differentiation is focused on regulatory mechanisms which modulate the expression of individual genes, such as transcription factors. These genes control the influence on the development and function of different T helper cell populations, such as Th2, Th9, Th17 cells. With respect to the function of regulatory T cells, the role of this T-cell subpopulation is analysed in a tissue-specific manner with the goal to understand their specific roles in different organs and also diseases. Studies that lead to a better understanding of antigen processing and presentation of MHC Class I ligands in tumors and virus-infected cells complete projects aiming at a better understanding of the activation of adaptive immune responses.

Through local but also international cooperations, we are particularly interested in the correlation of protein expression and degradation rates and the production of MHC class I ligands. Furthermore, we analyse the specificity of the proteasome system and cytosolic and ER-resident aminopeptidases in the generation of MHC class I ligands in the context of HIV infection.
**FUTURE DIRECTIONS**

Research at the Institute for Immunology aims at a better understanding of immune regulatory mechanisms controlling both the interactions of cells of the innate immune system with each other and cells of the innate and adaptive immune system. The goal is to identify mechanisms and pathways that allow the manipulation of immune responses. This knowledge will be used to develop therapeutic approaches for the treatment of allergic and autoimmune diseases as well as tumor-specific immunotherapies. After preclinical validation, clinical trails will be planned and initiated with the help of clinical partners. All this is impossible without continuous improvement of the unit infrastructure to ensure state-of-the-art research and goes in hand with the recruitment and support of young, well-trained and motivated scientists. Therefore, the Institute for Immunology provides immunological teaching programs within the studies of molecular medicine, biology, pharmacy and biomedical chemistry.

**IMPORTANT PUBLICATIONS**

- Ebert S, Becker M, Lemmermann NAW et al. Mast Cells Expedite Control of Pulmonary Muirine Cytomegalovirus Infection by Enhancing the Recruitment of Protective CD8+ T Cells to the Lungs. PLOS PATHOGENS. 2014; 10 (4).

**IMPORTANT PROJECTS**

- **CRC-TR-128, Project B4**: Impact of antigen-presenting cells on T cell responses in chronic neuroinflammation
  - **PROJECT MANAGER**: Prof. T Bopp, Prof. F Zipp
  - **PROJECT DURATION**: 2012 - 2016
  - **FUNDING**: German Research Foundation (DFG)
  - **SUM**: € 450,900
  - **PROJECT DURATION**: 2012 - 2015

- **Identification and characterization of L. major T cell epitopes based on quantitative proteomics (DFG)**
  - **PROJECT MANAGER**: Prof. S Terzer, Prof. IE von Stebut-Borschitz
  - **FUNDING**: German Research Foundation (DFG)
  - **SUM**: € 191,200
  - **PROJECT DURATION**: 2012 - 2015

- **Interactions between mast cells and neutrophils in murine models of acute inflammation**
  - **PROJECT MANAGER**: PD Dr. M Stassen
  - **FUNDING**: German Research Foundation (DFG)
  - **SUM**: € 414,700
  - **PROJECT DURATION**: 2013 - 2017

- **Polymer-mediated in situ activation of dendritic cells for tumor immunotherapy**
  - **PROJECT MANAGER**: Prof. H Schild, Prof. S Grabbe
  - **FUNDING**: German Research Foundation (DFG)
  - **SUM**: € 193,745
  - **PROJECT DURATION**: 2014 - 2016

**FUTURE DIRECTIONS**

Research at the Institute for Immunology aims at a better understanding of immune regulatory mechanisms controlling both the interactions of cells of the innate immune system with each other and cells of the innate and adaptive immune system. The goal is to identify mechanisms and pathways that allow the manipulation of immune responses. This knowledge will be used to develop therapeutic approaches for the treatment of allergic and autoimmune diseases as well as tumor-specific immunotherapies. After preclinical validation, clinical trails will be planned and initiated with the help of clinical partners. All this is impossible without continuous improvement of the unit infrastructure to ensure state-of-the-art research and goes in hand with the recruitment and support of young, well-trained and motivated scientists. Therefore, the Institute for Immunology provides immunological teaching programs within the studies of molecular medicine, biology, pharmacy and biomedical chemistry.

**IMPORTANT PUBLICATIONS**

- Ebert S, Becker M, Lemmermann NAW et al. Mast Cells Expedite Control of Pulmonary Muirine Cytomegalovirus Infection by Enhancing the Recruitment of Protective CD8+ T Cells to the Lungs. PLOS PATHOGENS. 2014; 10 (4).
HIGHLIGHTS

The Diefenbach laboratory studies development and function of the innate immune system. A focus has been the analysis of transcriptional programs controlling lineage specification, commitment and function of innate lymphoid cells (ILC), a recently identified group of innate lymphocytes located at barrier surfaces. ILC have been categorized into three distinct groups, transcriptional circuitry and effector functions of which strikingly resemble the various T helper cell subsets. We identified a common, Id2-expressing progenitor to all interleukin 7 receptor-expressing, 'helper-like' ILC lineages, the CHILP. Interestingly, the CHILP differentiated into ILC2 and ILC3 lineages but not into conventional natural killer (cNK) cells that have been considered an ILC1 subset. Instead, the CHILP gave rise to a peculiar NKp46+ IL-7Rα+ ILC lineage that required T-bet for specification and was distinct of cNK cells or other ILC lineages. Such ILC1 co-produced high levels of IFN-γ and TNF and protected against infections with the intracellular parasite Toxoplasma gondii. Our data significantly advance our understanding of ILC differentiation and presents evidence for a new ILC lineage that protects barrier surfaces against intracellular infections (Klose, Flach, Cell 2014; Diefenbach, Immunity 2014; Gasteiger & Rudensky, Nat Rev Immunol 2014; Figure 1).

The Florin laboratory investigates human papillomavirus (HPV) cell entry, cellular defence-mechanisms and antiviral strategies. HPV is a non-enveloped DNA tumor virus that infects skin and mucosa and its oncogenic subtypes (e.g., HPV16) cause various types of cancer (e.g., cervical, anal, and head-and-neck cancer). During the multistep process of infection, numerous host proteins are required for the delivery of virus genetic information into the nucleus of target cells. Over the last two decades, host-cell receptors, enzymes, and transcriptional regulators have been described to be involved in HPV infection. Previous studies of the group have revealed the role of these host cell proteins during infection and their potential as new antiviral targets. After cell entry and virus disassembly, the HPV L2 protein accompanies the viral DNA to promyelocytic leukaemia nuclear bodies (PML-NBs) within the host nucleus enabling viral transcription and replication. Multiple components of PML-NBs are regulated by small ubiquitin-like modifiers (SUMOs) either based on covalent SUMOylation, or based on non-covalent SUMO interaction via SUMO interacting motifs (SIMs). Our study has identified an L2 SIM that is important for L2 interaction with SUMO and/or SUMOylated proteins, which is indispensable for the delivery of viral DNA to PML-NBs and efficient HPV infection (Bund, Cell Microbiol 2014).
Bund T, Spoden GA, Koyov K et al. An L2 SUMO interacting motif is important for PML localization and infection of human papillomavirus type 16. CELLULAR MICROBIOLOGY. 2014; 16 (8): 1179-1200.


**FUTURE DIRECTIONS**

**AIMS**

The aims of the Diefenbach laboratory can be found in the context of the ERC Grant NutrImmune (see page 52-53 of the Scientific Report 2014).

The Husmann laboratory continues to investigate cell autonomous defense mechanisms against bacterial pore forming toxins (PFT). They discovered basal nutrient stress as a novel mechanism conferring cellular tolerance to a-toxin of Staphylococcus aureus by modulating expression of its receptor. These are ideal tools to study membrane repair and subversion of these processes by pathogens.

The evolutionarily conserved Tid proteins, encoded by the Tid (tumorous imaginal discs) tumor suppressor gene, have been identified as physiological partners of many tumor suppressors, oncoproteins and of tumor-related signaling molecules. Future analyses of the Kurzik laboratory concern the role of Tid proteins in maintaining the homeostasis of central signaling pathways (e.g., Ptc, Wnt and NF-κB) during normal development and tumor formation and progression.

The hepatitis B virus (HBV) is an enveloped pararetrovirus that causes acute and chronic liver inflammation. Persistent HBV infections often result in fatal liver failure that is currently incurable. With the aim to improve knowledge of the biology of HBV infection and to identify novel antiviral targets, the Prange laboratory studies HBV particle morphology and its coordination by host factors.

**IMPORTANT PROJECTS**

**MAPK-mediated defense pathways against pore-forming toxins**

**PROJECT MANAGER:** Prof. M Husmann

**Subrecipient PI**

**FUNDING:** National Institutes of Health (NIH) USA

**SUM:** € 895,000

**PROJECT DURATION:** 2011 - 2015

**Molecular networks determining co-evolution and adaptation of commensal microflora and innate lymphocytes**

**PROJECT MANAGER:** Dr. L Britanova

**FUNDING:** Volkswagen Foundation

**SUM:** € 232,000

**PROJECT DURATION:** 2013 - 2015

**NutrImmune: Nutrient-controlled molecular pathways instructing development and function of mucosa-associated innate lymphocytes**

**PROJECT MANAGER:** Prof. A Diefenbach

**FUNDING:** European Research Council (ERC)

**SUM:** € 1,500,000

**PROJECT DURATION:** 2013 - 2018

**Reciprocal interactions between the intestinal microbiota and RORγt-expressing innate lymphoid cells (TP im SPP 1656)**

**PROJECT MANAGER:** Prof. A Diefenbach

**FUNDING:** German Research Foundation (DFG)

**SUM:** € 426,450

**PROJECT DURATION:** 2013 - 2015

**IMPORTANT PUBLICATIONS**

Bund T, Spoden GA, Koyov K et al. An L2 SUMO interacting motif is important for PML localization and infection of human papillomavirus type 16. CELLULAR MICROBIOLOGY. 2014; 16 (8): 1179-1200.


**HIGHLIGHTS**

**MOLECULAR CARDIOVASCULAR PHARMACOLOGY**

The targets of our research are the roles of nitric oxide (NO) in vascular function, enzyme systems generating and scavenging reactive oxygen species (ROS), and strategies for the reversal and prevention of vascular oxidative stress.

We could show that betulinic acid protected against cerebral ischemia-reperfusion injury in mice by reducing oxidative and nitrosative stress (ROS/RONS). Betulinic acid prevented the ischemia reperfusion-induced upregulation of NOX2, nNOS and iNOS. This was associated with reduced infarct volume and amelioration of neurological deficit.

We have demonstrated that resveratrol is a compound combining these two actions in one single molecule. Resveratrol recouples eNOS by stimulating tetrahydrobiopterin biosynthesis and preventing tetrahydrobiopterin oxidation. Resveratrol upregulates eNOS expression by activating SIRT1 and FOXO transcription factors.

**CELL AND REDOX SIGNALING**

As dysregulation of ROS production is intimately linked to human diseases, we analyze the regulation, mechanism and function of the anti-oxidative enzymes paraoxonases PON2/3 in vitro and in vivo.

**MOLECULAR PHARMACOLOGY/IMMUNOPHARMACOLOGY**

Chronic inflammatory diseases are characterized by the overexpression of pro-inflammatory genes. We analyze the molecular mechanisms involved in the transcriptional and post-transcriptional regulation of these genes. We could show that resveratrol reduces pro-inflammatory gene expression by enhancing the activity of KSRP a RNA-binding protein that negatively regulates the mRNA stability of these genes.

**CLINICAL PHARMACOLOGY AND PHARMACOGENETICS**

CYP3A enzymes are central for the metabolism of drugs and toxins. We analyze the mechanisms involved in the marked differences in CYP3A expression in the general population.

Anthracyclines are efficacious antineoplastic agents with severe side effects. We recently identified risk genes for anthracycline-induced heart failure. Current work focuses on the verification of these data in animal studies and on the apoptotic mechanisms of anthracyclines. We focus on the importance of the anthracycline target topoisomerase IIb and on the mechanism of the cardioprotective drug dexrazoxane.

**SOLUTE TRANSPORT THROUGH BIOLOGICAL MEMBRANES**

Membrane transporter proteins mediate the transport of hydrophilic, charged and bulky molecules across the membrane of cells. We analyze the expression, regulation and structure of cationic amino acid transporters (CATs) and the lysosomal transporter involved in cysteamine-mediated cystine efflux. In addition we analyze the mechanisms of intracellular accumulation of the NOS inhibitor asymmetrical L-Arginine, and the role of arginine transport in human T-Lymphocytes.

**GENDER-SPECIFIC MEDICINE**

Women have a higher probability to develop autoimmune, pro-inflammatory diseases. We analyze the gender-specific differences in the expression of pro- and anti-inflammatory gene in cellular and animal models.
**Important Publications** // Max. 5

| --- | --- |

**Future Directions**

A major research focus of Molecular Cardiovascular Pharmacology is oxidative stress in the vasculature: We investigate the role of endothelium-derived nitric oxide in vascular function, enzyme systems generating and scavenging reactive oxygen species and pharmacological approaches to reduce/revert vascular oxidative stress in vivo (Ulrich Förstermann, Huige Li, Sven Horke, and collaborators). Projects in Molecular Pharmacology/Immunopharmacology investigate molecular mechanisms regulating the expression of inflammatory genes. This includes analyses of transcriptional mechanisms and proteins regulating the stability of specific mRNAs (Hartmut Kleinitz, Andrea Pautz, and collaborators).

The Clinical Pharmacology and Pharmacogenetics Group (Leszek Wojnowski) investigates the impact of the individual genetic makeup on response to drugs. Specifically, the Group focuses on the variable expression of cytochrome P450 3A (CYP3A) and on the genetic predisposition to drug-induced cardiotoxicity (Leszek Wojnowski and collaborators).

Biochemical and Cellular Pharmacology focus on biochemical pathways controlling amino acid levels in cells (amino acid transporters/exchangers, intracellular pathways of amino acid generation and metabolism; Ellen I. Closs, Jean-Paul Boissel, and collaborators).

**Important Projects** // Max. 5

<table>
<thead>
<tr>
<th>Effects of the Crataegus extract WS1442 on eNOS activity</th>
<th>PROJECT MANAGER: Prof. H Li</th>
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<tr>
<td>FUNDING: Dr. Willmar Schwabe GmbH &amp; Co. KG</td>
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<td>PROJECT DURATION: 2013 - 2015</td>
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<td>Importance of the RNA binding protein KSRP for the pro-inflammatory gene expression</td>
<td>PROJECT MANAGER: Prof. W Wojnowski</td>
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<td>FUNDING: International PhD Programme (IPP) by Institute of Molecular Biology Mainz (IMB)</td>
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<td>PROJECT DURATION: 2014 - 2017</td>
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<td>Mechanisms and multi-generational effects of transient xenosensor activation</td>
<td>PROJECT MANAGER: Prof. L Wojnowski</td>
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<td>FUNDING: German Research Foundation (DFG)</td>
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<td>SUM: € 199,825</td>
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<td>PROJECT DURATION: 2013 - 2016</td>
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<td>Regulation and role of arginine transport in human T-Lymphocytes</td>
<td>PROJECT MANAGER: PD Dr. M Munder, Prof. Dr. EI Closs</td>
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<tr>
<td>FUNDING: Dr. Willmar Schwabe GmbH &amp; Co. KG</td>
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<td>PROJECT DURATION: 2012 - 2015</td>
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**Figure Legends**

- **Fig. 1:** Levels of the regulation of human iNOS expression.
- **Fig. 2:** Enzymes involved in the generation and inactivation of reactive oxygen species (ROS).
- **Fig. 3:** Role of vascular oxidative stress in atherosclerosis.
- **Fig. 4:** Resveratrol (a compound of red wine) inhibits the generation of inflammatory mediators crucially involved in the pathophysiology of cardiovascular diseases.
The highlight in research this year was the multi-center study, initiated by the legislative discussion of decreasing the critical value for drunken cyclists, which brought together scientists from the Institute of Legal Medicine in Mainz and the Universiti Teknologi Mara, Shah Alam, Malaysia.

We investigated the performance and the deficits of performance of drunken driving cyclists in concrete and reality near driving experiments similar to the investigations of SCHEWE et al. 1980 and 1984 from those derived the drunk-drive limit of 1,60 per mill. The parcours parts were chosen to give evidence of the motoric coordination and flexibility, the sense of distances, the reaction time, and the ability to maintain concentration on different tasks at the same time (multitasking). The driving mistakes, the uncertainty, and „accidents“ were assessed under the aspect of their importance for traffic safety.

The BAC levels „sober“, 0,5 per mill, 1,0 per mill und 1,5 per mill of ethanol were investigated with in total 197 test persons. Beside typical alcohol-induced effects as loss of impulse control and carelessness at low BAC levels (significant decrease of driving time) there was an abrupt rise of error values -- around 100 % increase -- at BAC level of 1,0 per mill (group of 0,9-1,1 per mill). At the goal BAC level 1,5 per mill (group of 1,4-1,6 per mill) there was an additional increase of error values between 34 % and 113 %. Obviously due to a very much higher-than-average alcohol tolerance 43 test persons, that means 24,9 % (n = 173) showed an individual increase of error value which were at the level of the error values of 50 % of the sober test persons. At BAC level 1,5 per mill (group of 1,4-1,6 per mill) still 17, which means 10,4 % of the test persons who were still able to drive through the parcours showed a driving performance with error values within the values of the upper quartile of the sober test persons. These results were monitored even in the most complex challenge of unexpected obstacles and traffic light circuit.

The conclusion of an inability of driving by the judge with the standard not to disadvantage anyone (BGH 1963, BGH 1986) in every possible case will be therefore a problematic task. The abrupt increase of error value in the predominant part of the test persons prove a limit range for no more acceptable alcohol related impairment to maintain traffic safety around 0,9 – 1,1 per mill, and should give reason to discuss the actual legal limit of driving ability of 1,6 per mill.

The results are just now in review for the publication in "Blutalkohol" and were together with a similar study in Düsseldorf and their results the basis for an interdisciplinary discussion of during the "Verkehrsgerichtstag" in Goslar in January and the still going on political discussion in the Ministry of Justice of the Federal Republic of Germany in Berlin.


FUTURE DIRECTIONS

Research is first and foremost applied research derived from questions arising in expert opinion request, partly also triggered by changes in legal regulations. The main topics in research are the following, most of them in cooperation projects with clinical colleagues:

- Analytical method validation in Forensic Toxicology,
- Donor-/acceptor-chimerism research after T-cell depleted allogenic stem-cell transplantation and administration of CD8-deleted donor lymphocytes,
- Post-mortem re-distribution processes of drugs,
- Method validation of screening tests for drug detection in sweat and oral fluid,
- Time table of ossification of the medial epiphysis of clavicle for the estimation of the biological age of persons with different imaging procedures,
- Advanced GC-/LC-MS-search- and analysis-procedures for detection of ko-drugs and the endless number of synthetic illicit drugs,
- Investigation of critical values of blood drug concentrations for driving ability testing,
- Epidemiology of child maltreatment and sexual abuse to develop prevention strategies.

The goals will be the improving of knowledge in Forensic Science and the ability to solve forensic problems or questions more efficiently and with more reliability.
WE HAVE SHOWN THAT

the B-Raf inhibitor vemurafenib is highly toxic for B-Raf mutated malignant melanoma cells and does not interfere with the cytotoxic activity of temozolomide, which is being used for melanoma therapy. The data suggest that vemurafenib and temozolomide (or dacarbazine) can be administered concomitantly or consecutively, without detrimental drug interactions (Roos et al., Oncotarget, 5, 12607-12620, 2014).

p53 mediated induction of the translesion polymerase eta (POLH) is involved in the repair of DNA crosslinks, which protects tumor cells against the cytotoxic effect of crosslink-inducing anticancer drugs. The data suggest POLH as an important novel target for anticancer therapy (Tomicic et al., Cancer Res., 74, 5585-5596, 2014).

the phosphorylation of histone 2AX (γH2AX) is induced by genotoxic agents, but not by non-genotoxins, and correlates with loss of viability. Our results support the notion that γH2AX foci are a reliable bioindicator for pretoxic DNA damage (Nikolova et al., Toxicol Sci., 140, 103-117, 2014).

the bacterial genotoxin CDT induces an ATM- and ATR-mediated DNA damage response (DDR), similar to ionizing radiation. Our findings suggest that CDT is an attractive tool to induce DNA double-strand breaks (Fahrer et al., DNA Repair, 18, 31-43, 2014).

DNA double-strand breaks arise when DNA replication meets base excision repair. We conclude that BER is a double-edged sword: it is required for removing deleterious lesions from DNA but, following collision with the replication fork, it can also result in severe genomic changes (Ensminger et al., J. Cell Biol., 6, 29-43, 2014).

the ubiquitin ligase SIAH2 and its induction by the tumor suppressor p53 promote the proteasomal degradation of the tyrosine kinase TYK2 and its activating effect on the cancer relevant transcription factor STAT3. We conclude that this novel signaling pathway is relevant for the growth and development of lung cancers, which are typically associated with smoking (Müller et al., Oncotarget., 5, 3184-3196, 2014).

mimicking acetylation of STAT3 within its DNA binding domain alters STAT3 activities and location within prostate cancer cells. We conclude that this may contribute to the acetylation dependent control of STAT3 (Ginter et al., Cell Signaling., 26, 1698-1706, 2014).

the transcription factor STAT1, which controls immunity and cancer growth, is cleaved by certain caspases in leukemic cells when they are treated with epigenetic drugs belonging to the group of histone deacetylase inhibitors. We conclude that such agents affect tumorigenesis through the proteolysis of STAT1 (Licht et al., Oncotarget., 5, 2305-2317, 2014).
The main goals of the Institute of Toxicology is to gain a better understanding of the mechanisms that protect us from environmental, food-borne and endogenously formed carcinogens, exploiting the mechanisms of anticancer drug action for improving cancer chemotherapy, and preparing the next generation of clinicians and scientists for a challenging future. The scientists at the ITOX are focusing on the regulation of DNA repair and signaling of genotoxic therapeutics in cancer, e.g. colon, skin, blood and brain, and normal tissue, e.g. hematopoietic system, apoptosis, DNA damage-induced survival mechanisms, e.g. autophagy and senescence, mechanism of toxic single-ended DNA double-strand break formation as well as thresholds for genotoxic carcinogens. The 7 working groups in the Institute address fields of research at the heart of modern day toxicology. The exploration of DNA repair functions and their regulation and consequences in relevant normal and cancer tissue model systems affords students at the Institute of Toxicology the opportunity for being exposed to the cutting edge of current and future techniques and will prepare them for a productive career in the bio-medical sciences.
INSTITUTE OF VIROLOGY

INSTITUTES OF THEORETICAL MEDICINE

OVERRVIEW

Research at the institute flanks the focus areas of the medical service by specialisation on Cytomegalovirus (CMV) infections in immunocompromised hematopoietic cell transplantation (HCT) patients and corresponding mouse models. As CMV infection does not cause overt clinical symptoms in immunocompetent persons, there is little public awareness of CMV in Germany, unlike in the United States where CMV infection of the fetus is recognized as the major viral cause of birth defects with a significant impact on the health system. Therefore, high priority is given to developing a vaccine for protecting adolescent women. In addition, CMV infection is a major complication in the therapy of hematopoietic malignancies by HCT in that it causes graft failure and life-threatening interstitial pneumonia.

HIGHLIGHTS

CMV belongs to the herpesvirus family. A key feature of CMV infection is its efficient immune control in the immunocompetent, healthy host that prevents disease and terminates productive infection, leading to a state of mainten-ance of viral genome in absence of virus production, a state known as ‘latency’. Clinical problems arise when such latent viral genomes reactivate to productive infection under conditions of a weakened immune system.

The Institute for Virology is internationally renowned for basic research on the molecular virology and immunology of CMV infection as well as for translational research aimed at developing a CMV vaccine based on recombinant subviral particles.

The Institute for Virology is part of the Research Center for Immunotherapy of the Johannes Gutenberg-University and of the priority research field ‘Immunology’ of the University Medical Center.

SPECIFIC RESEARCH TOPICS:

Topic 1: Optimization of a subviral particle vaccine against human CMV infection

Aims at the development of a particulate vaccine, based on subviral Dense Bodies (DBs). Recent experiments focused on the interaction of DBs with professional antigen presenting cells and on the interference of human CMV with MHC class I mediated antigen presentation.

Topic 2: Establishing a challenge model for optimizing CMV-specific immunotherapy

Aims at developing novel strategies for CMV therapeutic vaccination of HCT recipients based on human CMV DBs. Antigenicity-optimized, recombinant DBs will be evaluated for their protection-inducing capacity in a murine model of CMV infection with recombinant murine CMVs. We successfully established immunotherapy with human CD8 T cells in the model of HLA-transgenic mice.
### IMPORTANT PUBLICATIONS // MAX. 5


### IMPORTANT PROJECTS // MAX. 5

**Analysis of particle morphogenesis of human cytomegalovirus to develop a strategy for safe vaccine production**

**PROJECT MANAGER:** Prof. B Plachter  
**FUNDING:** Else-Kröner-Fresenius Foundation  
**SUM:** € 252,000  
**PROJECT DURATION:** 2014 - 2016

**Development of an amniocyte cell culture system for human CMV propagation and vaccine production**

**PROJECT MANAGER:** Prof. B Plachter  
**FUNDING:** CAP-CMV GmbH Cologne  
**SUM:** € 118,500  
**PROJECT DURATION:** 2011 - 2014

**Influence of latency-associated mCMV gene-expression on memory inflation of virus-specific CD8 T cells**

**PROJECT MANAGER:** Dr. N Lemmermann  
**FUNDING:** MAIFOR  
**PROJECT DURATION:** 2013 - 2015

### FUTURE DIRECTIONS

**AIM 1:** Improvement of immunotherapy of CMV disease after hematopoietic cell transplantation by evaluating the function of human CD8 T cells in HLA-transgenic mouse models.

**AIM 2:** Initiation of phase1/2 clinical studies to evaluate tolerability and immunogenicity of a vaccine against infections with the human cytomegalovirus.

**AIM 3:** Identification of the molecular mechanism by which CMV triggers mast cell degranulation.

**AIM 4:** Identification of the role of type-I interferon-signaling to promoters of viral immune evasion genes in CMV evasion of natural killer cells.

**AIM 5:** Immunomodulation of cytomegalovirus latency and reactivation by regulatory T cells and dendritic cells.

**AIM 6:** Pathophysiologic interaction between CMV infection and allergic airway disease.

### Topic 3: Development of an amniocyte cell culture system for human CMV propagation and vaccine production.

In collaboration with CAP-CMV GmbH, Cologne, this translational project deals with the establishment of a cell culture for the large-scale production of DBs. For this, the amniocytic CAP-cell line is being evaluated. We could demonstrate that CAP-cells are readily infectible with human CMV and release DBs into the culture supernatant. Current work focusses on the optimization of the infection condition for vaccine production.

### Topic 4: Role of mast cells (MC) in the control of CMV infection.

We could show that CMV activates degranulation of MC. Release of chemokine CCL5 by MC attracts CD8 T cells to the lungs, a key target organ of CMV disease, and thereby limits the infection.

### Topic 5: Pathophysiologic interaction between chronic CMV infection and allergic airway disease.

Data provide first indication for a synergy between CMV and an allergen (ovalbumin, OVA) administered to the airways. Both entities induce an enhanced immunological reaction in a mutual manner. CMV promotes an OVA-specific CD8 T-cell response, and OVA administration enhances the CMV-specific CD8 T-cell response.

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The molecular and cell biology of chronic liver diseases. Exploration of the cellular, molecular and signaling mechanisms of excess scar tissue deposition in fibrosis and cirrhosis and mechanisms of its dissolution (fibrolysis). These studies are linked to translational projects that are aimed at:

1. Study of the mechanisms underlying chronic inflammation and its resolution, liver and other organ fibrosis. Characterization and validation of antifibrotic and fibrosis reversal-inducing molecular and cellular therapies. Here, human and experimental in vitro and vivo models of liver fibrosis, inflammation, and oxidative stress are exploited, such as primary and secondary biliary fibrosis, lobular fibrosis and especially non-alcoholic steatohepatitis (NASH), including novel predictive mouse models for primary liver cancer and liver and lung metastasis. In vitro studies are performed with activated hepatic stellate cells, myofibroblasts, Kupffer cells/macrophages, dendritic and myeloid precursor cells, lymphocytes, progenitor and cancer cells. Specific projects explore modulation of hepatic progenitor/oval cells and macrophages to induce fibrosis reversal and cancer regression. Moreover, in collaboration with nanochemistry groups and biotech, organ and cell specific nanoparticles for effective delivery of therapeutic small molecules, siRNA and antisense oligonucleotides are evaluated. We also develop transgenic mice that harbor e.g. myofibroblast specific inducible promoters for the knockdown of potential fibrosis- or immune-system-relevant genes, or transgenic mice for the study of cancer related mechanisms and therapies.

2. The molecular pathogenesis and immunology of chronic intestinal diseases, including celiac disease wheat sensitivity, food allergies and inflammatory bowel disease. Prior and current research has lead to the identification of the celiac disease autoantigen, tissue transglutaminase (TG2), and focused on exploring the role of TG2 in celiac disease pathogenesis, including the clinical development of a TG2 inhibitor as novel treatment for celiac disease within the CI3 excellence cluster. As one of the beacon projects "KETI-Clinical development of transglutaminase-inhibitors for treating celiac disease", in conjunction with Zedira GmbH, Darmstadt, and Falk Pharma, Freiburg, is financed jointly by the Federal Ministry for Education and Research and the European Regional Development Fund (ERDF). Due to a successful phase 1 clinical study the second funding phase of this project will begin in October of 2015. The CI3 cluster’s strong networking capability is reflected in research and development projects in which partners of the cluster region collaborate in the field of individualized immune intervention. The TIM also develops a mouse model for celiac disease, including mice with a humanized immune system, a collaboration with the Dept. of Dermatology, to allow the preclinical testing of non-dietary and immune modulatory therapies for celiac disease. The Schuppan lab has recently identified amylase trypsin inhibitors (ATIs) of wheat/barley/rye as triggers of nonceliac/ non-allergy wheat sensitivitiy that after oral ingestion uniquely activate intestinal myeloid cells via toll like receptor 4 and thus intestinal and extraintestinal immune stimulation. Numerous preclinical studies of the TIM in collaboration with others have demonstrated a worsening of mouse models of autoimmunity, allergy and chronic inflammation with diets containing wheat or purified ATIs. Clinical studies in patients with autoimmune and allergic diseases are planned to begin in 2015. Finally, the Max-Planck Institute of Chemistry/Multiphase Chemistry and the Tim have entered a longterm partnership to study the role of environmental gases and particulate factors on airway and nutritional allergies.
3. The role and modulation of innate immunity in cancer. Several projects investigate and target macrophages, dendritic and myeloid suppressor cells in various cancers, including metastatic melanoma, primary liver and non small cell lung cancer. These studies are interconnected with projects studying adaptive immunity in cancer within other institutions.

4. Another new focus is the role of macronutrients and the microbiota in intestinal and extraintestinal inflammatory diseases. Major emphasis is on common carbohydrates, ATIs in gluten containing cereals, and major lipids, their interaction with the intestinal microbiota and the immune system. Diseases assessed in rodent models and possibly clinical studies are inflammatory bowel disease, irritable bowel syndrome, NASH/ type 2 diabetes, and cardiovascular disorders, in collaboration with e.g. cardiology and the CTH.

5. Identification, preclinical and clinical validation of novel biomarkers of inflammatory and neoplastic diseases. The aim is a better the development of better tools for diagnosis, prognosis and especially therapy control. There is a focus on the development of the development of non-invasive techniques for monitoring (liver) fibrogenesis and fibrolysis, including serum protein and microparticle markers (funded by the National Institutes of Health and the Foundation of the Rhineland-Palatinate), and for the design and validation of quantitative (PET and MR) imaging agents to quantitate tissue fibrogenesis (fibrosis progression), funded by an ERC Advanced Grant. Other projects develop proteomic and lipidomic serum biomarkers for celiac disease activity, non-celiac wheat sensitivity and inflammatory bowel diseases.

**IMPORTANT PROJECTS / MAX. 5**

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Project Manager(s)</th>
<th>Funding</th>
<th>Sum</th>
<th>Project Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of Serum Markers for the Assessment of Liver Fibrosis Progression and Reversal</td>
<td>Prof. D Schuppan</td>
<td>Rhineland-Palatinate Foundation for Innovation</td>
<td>€ 249,259</td>
<td>2013 - 2015</td>
</tr>
<tr>
<td>Quantitative Imaging of Liver Fibrosis and Fibrogenesis</td>
<td>Prof. D Schuppan</td>
<td>European Union (EU)</td>
<td>€ 2,000,000</td>
<td>2012 - 2017</td>
</tr>
<tr>
<td>Therapy of Metastatic Melanoma by Adressing Tolerance Inducing Macrophages</td>
<td>PD Dr. A Tüttenberg, Prof. D Schuppan</td>
<td></td>
<td></td>
<td>2013 - 2017</td>
</tr>
<tr>
<td>Use of human and animal tissue slices for the development of anti-fibritic compounds</td>
<td>Prof. D Schuppan</td>
<td></td>
<td></td>
<td>2014 - 2018</td>
</tr>
</tbody>
</table>
CONSERVATIVE MEDICINE

Department of Dermatology
Department of Medicine I
Department of Medicine II
Department of Medicine III
Department of Psychiatry and Psychotherapy
Department of Child and Adolescent Psychiatry and Psychotherapy
Department of Psychosomatic Medicine and Psychotherapy
Department of Neurology
Center for Childhood and Adolescent Medicine
OVERVIEW

The Department of Dermatology is one of the largest dermatology Hospitals of the Rhine-Main area with 45 beds on two wards for inpatient treatment of skin disorders and also offers a variety of outpatient clinics. 5 professors, 8 senior physicians and 15 specialists and junior doctors ensure medical diagnostics and therapy on the highest level. The Department has medical staff with special knowledge in allergy, occupational dermatology, medical tumor therapy, palliative care, diagnostic ultrasound, proctology, phlebology, plastic surgery, alternative medicine and medical quality management. The Department hosts a basic research laboratory with >50 researchers, and we also conduct >50 clinical trials on innovative therapies in dermatology in our Clinical Research Center.

HIGHLIGHTS

Renowned scientists with their employees investigate immunobiological causes of skin diseases and autoimmunity and allergy. The clinical research unit allergology with research for the development of allergic diseases, is the focus of Prof. Dr. Saloga and PD Dr. Bellinghausen. How dendritic cells in interaction with T cells control immune response and prevent allergies, but simultaneously fight against infectious agents is the research focus of Prof. Dr. Steinbrink and Prof. Dr. Stebut-Borschitz. The molecular characterization of dendritic cells will be investigated by Dr. Bros. The focus of the working group of HD Dr. Jonuleit is the study of the regulatory T cells, immune cells that prevent autoaggressive and allergic immune responses. The molecular characterization of T cell function and dysfunction in autoimmune and allergic diseases is the focus in the research group of PD Dr. Becker. Another important focus of our basic research is the black skin cancer, melanoma (Prof. Dr. Grabbe, PD Dr. Tüttenberg). For a better understanding and the development of new treatments for melanoma patients, we successfully established in strong collaboration with clinical colleagues, chemists and the Max-Planck-Institute for Polymer Research the new collaborative research center (CRC 1066) “Nanodimensional polymer therapeutics for tumor therapy”.

FUTURE DIRECTIONS

Our research is integrated in the Research Center for Immunotherapy (FZI) in Mainz. In close collaboration with other scientists of different disciplines we define the basic mechanisms of skin-associated immunological diseases and develop new therapeutic strategies for treatment of autoimmune diseases, allergies and skin cancer.

OUR RESEARCH TOPICS:

- Identification of molecular and cellular processes that trigger and control the induction of type I allergy (Prof. Dr. Reske-Kunz, Prof. Dr. Saloga, PD Dr. Bellinghausen)
- Functional and molecular characterization of T lymphocytes and regulatory T cells (HD Dr. Jonuleit, PD Dr. Becker, Prof. Dr. Steinbrink) and the investigation of dendritic cells as modulators of tolerance and immunity (Prof. Dr. Grabbe, Prof. Dr. Steinbrink, HD Dr. Jonuleit, Prof. Dr. Reske-Kunz)
- New multifunctional polymers for immunotherapeutic treatment of melanoma (Prof. Dr. Grabbe, Dr. M. Bros, Prof. Dr. K. Steinbrink, HD Dr. Jonuleit PD Dr. Tüttenberg, PD Dr. Becker, Prof. Dr. Reske-Kunz)
- The role of dendritic cells and Langerhans cells in the development of protective immune responses against cutaneous leishmaniasis (Prof. Dr. von Stebut-Borschitz)
- Clinical research and trials on innovative therapies in dermatology in our Clinical Research Center (CRC, PD Dr. Staubach, Dr. Loquai), which acts as an interface between clinical basic and applied research.


Rudolph BM, Loquai C, Gervé A et al. Increased frequencies of CD11b(+) CD33(+)/HLA-DRlow myeloid-derived suppressor cells are an early event in melanoma patients. EXPERIMENTAL DERMATOLOGY. 2014; 23 (3): 202-204.


FIG. 1: Media for tissue culture
FIG. 2: Histology
FIG. 3: Dendritic cells

IMPORTANT PROJECTS // MAX. 5

Analysis and modulation of allergic immune responses in an established humanized mouse model (DFG-Projekt BE 4504/2-2)
PROJECT MANAGER: PD Dr. I Bellinghausen
FUNDING: German Research Foundation (DFG)
Sum: € 283,050
PROJECT DURATION: 2013 - 2016

Analysis and therapeutic modification of T cell responses in multiple sclerosis
PROJECT MANAGER: PD Dr. H Jonuleit
FUNDING: German Research Foundation (DFG)
SUM: € 520,800
PROJECT DURATION: 2012 - 2016

Analysis of interaction between innate and adaptive immunity in contact allergen-specific inflammation (DFG-Einzelantrag STE 791/6-1)
PROJECT MANAGER: Prof. K Steinbrink
FUNDING: German Research Foundation (DFG)
SUM: € 465,150
PROJECT DURATION: 2013 - 2016

Mast-cells - promoters of health and modulators of disease
PROJECT MANAGER: Prof. RE von Stebut-Borschitz
FUNDING: German Research Foundation (DFG)
SUM: € 414,700
PROJECT DURATION: 2013 - 2017

Polymer-mediated in situ activation of dendritic cells for tumor immunotherapy
PROJECT MANAGER: Prof. H Schild, Prof. S Grabbe
FUNDING: German Research Foundation (DFG)
SUM: € 414,700
PROJECT DURATION: 2013 - 2017
The biomedical research of the I. Department of Internal Medicine focuses on a diverse range of diseases in the gastrointestinal tract, the kidney, the endocrine and musculoskeletal system as well as infectious diseases. The Department aims at dissecting the complex molecular mechanisms of the different diseases by using various in vitro and in vivo model systems as well as systems biological approaches. Major areas of scientific interest are cancer research as well as immune responses in the context of acute and chronic inflammatory processes. The goal of our studies is to build a strong scientific foundation for highly translational projects and to develop new innovative diagnostic as well as therapeutic strategies that complement currently used clinical approaches.

### HIGHLIGHTS

The scientific focus of our Gastroenterology/Gastrointestinal (GI) Oncology section are the molecular pathogenesis and treatment of chronic inflammatory bowel diseases (IBD) as well as GI tumors. Particular interests are gastric cancer and hepatocellular carcinoma (HCC) where the department cultivates a large translational research program. Clinical research in this area involves systemic therapies including new biological agents and targeted therapies. Additionally, innovative immunotherapeutic approaches including immune oncology and oncolytic virus therapy are pursued.

Our Interdisciplinary endoscopy performs several cutting-edge endoscopic procedures including novel approaches for the management of Barrett’s esophagus (e.g., radiofrequency ablation), spy-glass cholangioscopy, endosonography-guided interventions, and confocal laser chromoendoscopy. Application and systematic analyses of these procedures serves as the backbone of our research goals in this area.

Our research in Hepatology/Infectiology is aimed at understanding the pathogenesis and treatment of a large spectrum of chronic liver diseases including alcoholic, metabolic as well as autoimmune disorders. Another major focus of this section are epidemiological and translational investigations on non-alcoholic steatohepatitis (NASH). Our comprehensive studies further include novel antiviral therapies with concomitant monitoring of immune responses in hepatitis B and C virus infection. We have recently established the Cirrhosis Center Mainz (CCM) which will provide an interdisciplinary platform and network for the treatment of all complications of end-stage liver disease including fibrogenesis as well as tumorigenesis. We further conduct several investigator-initiated studies in the context of liver transplantation/immunosuppression and multidisciplinary treatment of HCC.

The Imaging Core Facility supports laboratories within and beyond the I. Department of Internal Medicine with expertise in the field of microscopy and with high-resolution confocal laser scanning techniques.

Our basic research program in Nephrology focuses on the mechanisms of kidney fibrosis and other consequences of progressive chronic kidney diseases as well as the development of organ dysfunction after kidney transplants. Clinical research projects deal with risk factors influencing the outcomes after kidney transplantation with a specific focus on psychosomatic questions as well as immunosuppression.

The „Adapthera” project in Rheumatology involves a well-established network of joint research studies across different partners in Rhineland-Palatinum. This network examines the individualized, risk-adapted rheumatism therapy. Further work is focused on the pathogenesis of systemic lupus erythematoses.

The research in the Endocrinology area is directed at endocrine tumors and immune mediated thyroid disorders. Islet cell transplantation offers a promising strategy for the treatment of diabetes.
**IMPORTANCE OF PUBLICATIONS**


**FUTURE DIRECTIONS**

Our translational research in the field of hepatic tumorigenesis will be significantly expanded with the overall goal to identify clinically relevant molecular subtypes of liver cancer using next-generation technologies. This precision medicine approach includes the identification of predictive and prognostic molecular profiles and will be the focus of a newly established Lichtenberg professorship from the Volkswagen Foundation awarded to Dr. Jens U Marquardt. Another professorship on Molecular Hepatology (Prof. Susanne Strand), supported by the “Professorinnenprogram” of the BMBF, focuses on the identification of epigenetic modulators and related molecular mechanisms involved in the development of different liver diseases. Unlike genetic alterations, epigenetic changes are reversible events, which make them attractive targets for therapeutic modulation. Clinical research in the field of Hepatology will be advanced by further expansion of the CCM and complemented by clinical databases from the Clinical Registry Unit (CRU).

**IMPORTANT PROJECTS**

**Core-Facility: Imaging Center**
PROJECT MANAGER: Dr. D Strand
FUNDING: FZI
SUM: € 320,000
PROJECT DURATION: 2012 - 2015

**Role of SIRT6 during cellular differentiation and cancer**
PROJECT MANAGER: Prof. S Strand
FUNDING: Boehringer Ingelheim Foundation
GRK Dynamics of Gene Regulation, Epigenetics and DNA Damage Response
SUM: € 108,000
PROJECT DURATION: 2012 - 2018

**Pathophysiological role of the two ligands of the CSF-1R CSF-1 and IL-34 in systemic lupus erythematoses.**
PROJECT MANAGER: PD Dr. J.Weinmann-Menke
FUNDING: German Research Foundation (DFG)
SUM: € 351,000
PROJECT DURATION: 2014 - 2017

**Pharmacogenomic-based targeting of Cancer Stem Cells in hepatocellular cancers: implications for relapse formation**
PROJECT MANAGER: Dr. JU Marquardt
FUNDING: German Cancer Aid
SUM: € 197,208
PROJECT DURATION: 2013 - 2016

**Role of the proto-oncogene Bcl-3 during initiation and progression of hepatocellular carcinoma (HCC)**
PROJECT MANAGER: PD Dr. M Wörns, PD Dr. J Schattenberg
FUNDING: German Cancer Aid
SUM: € 364,000
PROJECT DURATION: 2013 - 2016

**FIG. 1:** Interaction of two epigenetic factors (red) in the nucleus (blue) of a hepatocyte, detected by proximity ligation assay.
**FIG. 2:** Confocal laser scanning image of macrophages (green) in the liver (red).
OVERVIEW

The Department of Medicine 2 is the leading cardiology center in Rhineland-Palatinate and the metropolitan Rhine-Main area. The clinic has 86 beds on 3 wards, of which 24 beds can be monitored. We have an intensive care unit with a total of 20 beds and a Chest Pain Unit with 10 monitored beds. We have also established the first atrial fibrillation unit in Germany. The clinic also has the organizational responsibility for the emergency department. The main focuses of the clinic are treatment of patients with acute coronary syndromes and chronic coronary artery disease, interventional valve therapy including transcatheter aortic valve implantation (TAVI), mitral valve clipping and interventional electrophysiology including ablation of paroxysmal and persistent atrial fibrillation.

HIGHLIGHTS

SCIENTIFIC WORKING PROGRAM

The key research areas focus on the identification of causes leading to vascular damage. In preclinical and clinical studies we investigate the influence of genes and traditional risk factors but also new risk factors such as (aircraft noise) and the diagnostic value of biomarkers with respect to cardiovascular disease. Furthermore, we focus on the mechanisms of improvement of vascular damage by drug therapy. In particular, we explore these relationships in the Gutenberg Health Study (GHS), one of the largest prospective population-based cohort trials worldwide. The GHS included 15,010 participants from the population since 2007 and is currently in the follow-up investigation. The research program includes a standardized, detailed examination program over 6 hours. The Department of Medicine 2 is part of the successfully established Centre of Thrombosis and Hemostasis (CTH), an integrated research and treatment center, and also of the German Center for Cardiovascular Research (DZHK), where the research group focuses on the interaction between myocardial and vascular disease.

Recent findings established the crucial role of inflammatory cells in causing vascular damage and arterial hypertension in an animal model of psoriasis. New antidiabetics such as the gliptins (DPP-4) inhibitors were characterized to have potent anti-inflammatory and vascular-protective properties not only in the setting of diabetes mellitus but also in animal models of septic shock. The group is focused on the role of AMPK and PGC-1alpha in the regulation of vascular homeostasis. A recently developed key area of research comprises the effects of nighttime aircraft noise on endothelial (vascular) function, neurohormonal parameters, sleeping quality and generation of annoyance in healthy subjects and in patients with established coronary artery disease. This translational research combining techniques of sleep research and vascular function studies tries to figure out, why people living close to airports are suffering from cardiovascular disease, arterial hypertension, myocardial infarction and stroke.

FUTURE DIRECTIONS

On 1 October 2015 the Center for Cardiology at the University Medical Center Mainz will start officially. The Center for Cardiology will be visible from afar with the completion of the extension building which is announced for the end of the year 2015.

The center consists of Cardiology I (general and interventional Cardiology, Angiology and Intensive Care Medicine; Director: Prof. Dr. Thomas Münzel) and Cardiology II (Rhythmology; Director: Prof. Dr. Thomas Rostock). The spokesman of the center rotates annually.


**FIG. 1:** Aortic valve for catheter-based transarterial valve implantation (TAVI)
**FIG. 2:** Interventional cardiologists preparing for percutaneous coronary intervention (PCI)
**FIG. 3:** The Department of Medicine 2– Building 605

**IMPORTANT PROJECTS // MAX. 5**

**Cardiac and vascular late sequelae in long-term survivors of childhood cancer**” (CVSS-study)
PROJECT MANAGER: Prof. P Wild, Prof. J Faber, PD Dr. C Spix
FUNDING: German Research Foundation (DFG)
SUM: € 1,142,680
PROJECT DURATION: 2013 - 2017

**Effects of endothelial PGC-1 alpha on the modulation of vascular function**
PROJECT MANAGER: Dr. S Kröller-Schön
PROJECT DURATION: 2012 - 2015

**Impact of in-vivo ablation of myelomonocytic cells on vascular function and arterial hypertension induced by Angiotensin-II infusion**
PROJECT MANAGER: PD Dr. P Wenzel
FUNDING: German Research Foundation (DFG)
SUM: € 310,000
PROJECT DURATION: 2008 - 2014

**Importance of perivascular adipose tissue for vascular remodeling processes**
PROJECT MANAGER: Prof. K Schäfer
FUNDING: German Research Foundation (DFG)
SUM: € 383,850
PROJECT DURATION: 2011 - 2014

**Role of Interferon-gamma in Angiotensin-II induced vascular dysfunction inflammation**; DFG WE 4361/4-1
PROJECT MANAGER: Dr. P Wenzel
FUNDING: German Research Foundation (DFG)
PROJECT DURATION: 2012 - 2016
CONSERVATIVE MEDICINE

DEPARTMENT OF MEDICINE III

Director:
Professor
Matthias Theobald

University Medical Center Mainz
Langenbeckstr. 1
D-55131 Mainz
phone: +49 (0) 6131 17-7281
direktor-3med@unimedizin-mainz.de
www.unimedizin-mainz.de/3-med

OVERVIEW

The Department of Hematology, Medical Oncology & Pneumology provides state-of-the-art facilities for comprehensive consultation, diagnosis and treatment of patients suffering from hematologic disorders, solid tumors and airway and lung disease. A major effort in our department includes the immediate transfer of innovative findings in basic science into novel therapeutic strategies. To achieve this goal, the clinic is member of the German Cancer Research Center, the Center for Thrombosis and Hemostasis, the Research Center for Immunotherapy and contributes to several collaborative initiatives. A phase I clinical research unit of the department provides the basis for early, first-in-man clinical evaluation of novel compounds and offers service to the entire University Cancer Center.

HIGHLIGHTS

CLINICAL RESEARCH
Clinical research is key to the rational improvement of therapeutic options for patients. Our study section (PI: G. Hess) on hematology, oncology, infectious disease, hemostaseology, and palliative care is responsible for the due comprehensive clinical trial management with an emphasis on early, phase I/II trials. It provides 24-7 service and ensures that international ethics and scientific standards are met. Our pneumology study section (PIs: R. Buhl, S. Korn) has an emphasis on airway disease and provides equivalent service. In 2014 the department successfully performed more than 70 clinical trials.

BASIC RESEARCH
The foci of basic research within the department range from tumor immunology (PIs: H. Echchannaoui, U. Hartwig, M. Munder, M. Radsak, M. Theobald, T. Wölfl), immunobiology of stem cell transplantation (PI: E. Wagner), nanoparticles (PI: V. Mailänder), immunobiology of airway disease (PIs: R. Buhl, S. Reuter), the molecular basis of malignant hemopoiesis (PI: T. Kindler) to translational research in hemostaseology (PI: C. von Auer). The research groups are actively involved in international and national research programs, and are further part of collaborative research programs and graduate schools within both, the UM and the Johannes Gutenberg-University Mainz. In 2014 more than 70 articles were published in high-ranking, peer-reviewed journals.

FUTURE DIRECTIONS

The Department of Hematology, Medical Oncology & Pneumology is in a continuous process to improve its high clinical and scientific standards. In 2015, two important goals will be in the focus of our interest. First, we aim at establishing all requirements necessary for the approval as a cancer center of excellence provided by the German Cancer Society (Deutsche Krebshilfe). Second, we will continue our efforts required for the accreditation of the hematopoietic stem cell transplantation unit (JACIE) provided by the European Society for Blood and Marrow Transplantation (EBMT). Both certifications will be essential to improve cancer therapy and to maintain high quality standards of patient care and also function as backbone for translational and basic research. Further, several groups of the department are participating in ongoing research collaborative initiatives (SFBs), which will be evaluated in 2015. Finally, an important goal of the department will be the initiation of investigator initiated trials emerging from our clinical trial unit.


CONSERVATIVE MEDICINE

OVERVIEW

The Department of Psychiatry and Psychotherapy provides basic and specialized mental health services for more than 200,000 people of the city of Mainz as well as throughout the state of Rhineland-Palatinate, the Rhine- Main metropolitan area and Germany. Our therapies are based on a multidimensional disease conceptualization and involve pharmacological, psychotherapeutic, neurophysiological and psychosocial treatment methods. Highest standard of care is achieved by the implementation of Evidence Based Medicine (EBM) as well as national and international guidelines into routine treatment. The scientific vision of the Department is hence to advance evidence based psychiatric treatment and prevention by translational research.

HIGHLIGHTS

The Department of Psychiatry and Psychotherapy is a highly active and productive research institution with over 50 publications in 2014 as well as a well-rated education and training center for undergraduate, graduate and advanced medical training in close collaboration with other departments of the University Medical Center and as member of the Focus Program Translational Neurosciences (FTN). Research activities are focused within the following areas:

AFFECTIVE DISORDERS
The research focus concentrates on translational strategies to improve and accelerate the therapy of patients with affective disorders. Biochemical, genetic, neuropsychological and brain functional markers of successful treatments are identified validated and transferred into clinical practice.

COGNITIVE ENHANCEMENT
The research group uses innovative attempts to investigate neuroscientific aspects of cognitive enhancement by means of randomized controlled trials investigating the efficacy of putative cognitive enhancers, of studies assessing the prevalence of the use of cognitive enhancers in different populations as well as several interdisciplinary research projects supported by the German Federal Ministry of Education and Research (BMBF).

EMOTION REGULATION AND IMPULSE CONTROL
The research focus “Emotion Regulation and Impulse Control (ERIC)” uses a wide variety of functional neuroimaging methods (fMRI, MEG, EEG-fMRI) and genetic information to characterize the neurobiological foundations of two cognitive functions - emotion regulation and impulse control - which are key for normal psychological functioning and are often altered in psychiatric disorders such as Attention Deficit Hyperactivity Disorder (ADHD) and Borderline Personality Disorder (BPD).

FORENSIC PSYCHIATRY UND PSYCHOTHERAPY
The clinical and research section for Forensic Psychiatry und Psychotherapy is the most recent addition to the Department. Aside from its main task providing forensic assessment for local and regional courts, Forensic Psychiatry investigates the neurobiology of disorders often found to be associated with disruptive behaviors like ADHD in close collaboration with ERIC.

NORMAL AGING AND PATHOLOGICAL NEURODEGENERATION
The research focus “normal aging and pathological neurodegeneration” uses a wide spectrum of methods from biochemistry via mice to men (PET, MRI, DTI) to translationally understand the neuropathology of Alzheimer’s disease as well as the neurophysiology of normal aging and to develop new therapeutic strategies and substances which are immediately tested in clinical studies (for an example see Fig.).

PSYCHOPHARMACOLOGY AND MOLECULAR BIOLOGY
Psychopharmacology has a long-standing tradition at the Department focusing on Therapeutic Drug Monitoring (TDM) in psychiatry and is e.g. concerned with drug-drug interactions (www.psiac.de), behavioral pharmacology and transport of psychotropic drugs across the blood-brain barrier. The Molecular Biology research group focuses on the GABAA receptor, a GABA-gated chloride channel.

DEPARTMENT OF PSYCHIATRY AND PSYCHOTHERAPY

University Medical Center Mainz
Untere Zahlbacher Str. 8
D-55131 Mainz
phone: +49 (0) 6131 17-7336
klaus.lieb@unimedizin-mainz.de
www.unimedizin-mainz.de/psychiatrie

Director:
Professor
Klaus Lieb


The prevention of stress-related mental disorders is becoming increasingly important in western societies affecting each year approximately 120 million European Union citizens. The term resilience describes the ability of many people not to become mentally ill despite significant psychological or physical burdens. Examining the underlying mechanisms of resilience and developing measures to secure and promote optimal functioning of these mechanisms is an innovative and promising approach for psychiatric research. Hence, the German Resilience Center (Deutsches Resilienz Zentrum, DRZ) Mainz has been established in July 2014 as a central research institution of the Johannes Gutenberg University Mainz (JGU) and its University Medical Center. The DRZ pursues a tripartite approach, which combines basic neuroscience, clinical neuroscience and social science. Aside from the chairman of the Department of Psychiatry, Prof. Klaus Lieb, who serves as a Deputy Spokesperson of DRZ, Prof. Lieb also leads, together with Prof. Michele Wessa of the Institute of Psychology, the Resilience Health Care Center which offers professional counseling services tailored to those employees suffering from acute or chronic stress reactions and systematically develops resilience fostering trainings using modern evidence based medicine approaches.

**FUTURE DIRECTIONS**

**IMPORTANT PROJECTS // MAX. 5**
OVERVIEW

The Department for Child and Adolescent Psychiatry and Psychotherapy is primarily a science and teaching orientated institution, continually developed since 2007 under the direction of Prof. Dr. Dipl.-Psych. Michael Huss. The department’s major research fields are in child and youth psychiatry with the additional link to psychiatry in adults (adult ADHD and Fragile-X-Syndrome).

With the first compulsive teaching model in medicine in Germany we transfer this knowledge with an innovative teaching concept.

A cooperation with the Rheinhessen-Fachklinik Mainz, Child and Adolescent Psychiatry, Psychotherapy and Psychosomatic, which is also headed by Prof. Dr. Dipl.-Psych. Michael Huss, provides both outpatient treatment and inpatient treatment for 40 patients.

HIGHLIGHTS

EATING DISORDERS:
The MaiStep-project (Mainzer Schultraining für Essstörungsprävention) was started in cooperation with the insurance group KKH (Kaufmännische Krankenkasse), the Department of Social Issues, Employment, Health and Demography (MSAGD), the Department of Education, Science, Qualification and Culture (MBWWK) and the Association for Facilitating Feminist Social Work for Girls (FEMMA).

ADHD:
The PAD study seeks to analyse treatment outcomes with polyunsaturated fatty acids like fish oil. The ASTA study measures the adherence to standard treatment with methylphenidate using an electronic Medication Event Monitoring System (MEMS).

FRAGILE-X-SYNDROME:
A new new drug is being tested in phase-III-trials for adolescent as well as adult patients with this disorder.

HEALTHY SUBJECTS (MEDICINE AND DENTAL STUDENTS):
In cooperation with the dean of the University Medicine Mainz we established a mindfulness based stress prevention program. „MediMind” is based both on Mindfulness issues and strategies extracted from Cognitive-Behavioral therapy.
FUTURE DIRECTIONS

Future research goals of the Department for Child and Adolescent Psychiatry and Psychotherapy are improvement and evaluation of universal prevention and integration of research into treatment processes. With a new healthcare law, adopted 2015, concerning prevention assisted by health insurances research in prevention will be aimed at complementing primary prevention of eating disorders with universal prevention of psychiatric disorders. This future facet of research will consist of two steps with a representative evaluation of prevalence in psychiatric disorders in adolescents and the subsequent development of a universal prevention program.

For integration of research in treatment, an innovative approach is aimed at the use of smartphone-based monitoring of aversive tension of patients with eating disorders over the course of the day. A next level would be including ambulatory monitoring in the therapy process, both facilitating treatment progress and evaluating these amendments. This approach should be integrated with the onset of a new specialized inpatient treatment unit for eating disorders in cooperation with the Rheinhessen-Fachklinik Mainz, Child and Adolescent Psychiatry, Psychotherapy and Psychosomatic.

IMPORTANT PROJECTS // MAX. 5

**MaiStep - primary and secondary prevention**  
PROJECT MANAGER: A Bürger, F Hammerle  
FUNDING: Ministry for Social Work, Health and Demography of Rhineland-Palatinate (MSADG)  
SUM: € 49,500  
PROJECT DURATION: 2011 - 2015

**MediMind: A mindfulness-based stress prevention training for medical students**  
PROJECT MANAGER: A Bürger, F Hammerle  
FUNDING: University Medical Center Mainz  
SUM: € 120,000  
PROJECT DURATION: 2012 - 2015

**PAD-Studie - Nutritional Efficacy of Polysaturated Fatty Acids (Omega-3 and Omega-6) in combination with Zinc and Magnesium versus Placebo in Children and Adolescents with Attention Deficit/ Hyperactivity Disorder (ADHD)**  
PROJECT MANAGER: Prof. M Huss, Dr. M Stauss-Grabo  
FUNDING: Engelhard pharmaceuticals GmbH & Co. KG  
SUM: € 300,000  
PROJECT DURATION: 2010 - 2015

**A Phase 4, Open-label, Multicentre, 2-Year Safety Study of Lisdexamfetamine Dimesylate in Children and Adolescents Aged 6-17 Years with Attention-Deficit/ Hyperactivity Disorder (ADHD)**  
PROJECT MANAGER: Prof. M Huss  
FUNDING: Shire  
SUM: € 42,440  
PROJECT DURATION: 2011 - 2014

**MaiStep - primary and secondary prevention**  
PROJECT MANAGER: A Bürger, F Hammerle  
FUNDING: Ministry for Social Work, Health and Demography of Rhineland-Palatinate (MSADG)  
SUM: € 49,500  
PROJECT DURATION: 2011 - 2015

**MediMind: A mindfulness-based stress prevention training for medical students**  
PROJECT MANAGER: A Bürger, F Hammerle  
FUNDING: University Medical Center Mainz  
SUM: € 120,000  
PROJECT DURATION: 2012 - 2015

**PAD-Studie - Nutritional Efficacy of Polysaturated Fatty Acids (Omega-3 and Omega-6) in combination with Zinc and Magnesium versus Placebo in Children and Adolescents with Attention Deficit/ Hyperactivity Disorder (ADHD)**  
PROJECT MANAGER: Prof. M Huss, Dr. M Stauss-Grabo  
FUNDING: Engelhard pharmaceuticals GmbH & Co. KG  
SUM: € 300,000  
PROJECT DURATION: 2010 - 2015

**A Phase 4, Open-label, Multicentre, 2-Year Safety Study of Lisdexamfetamine Dimesylate in Children and Adolescents Aged 6-17 Years with Attention-Deficit/ Hyperactivity Disorder (ADHD)**  
PROJECT MANAGER: Prof. M Huss  
FUNDING: Shire  
SUM: € 42,440  
PROJECT DURATION: 2011 - 2014

**FUTURE DIRECTIONS**

Future research goals of the Department for Child and Adolescent Psychiatry and Psychotherapy are improvement and evaluation of universal prevention and integration of research into treatment processes. With a new healthcare law, adopted 2015, concerning prevention assisted by health insurances research in prevention will be aimed at complementing primary prevention of eating disorders with universal prevention of psychiatric disorders. This future facet of research will consist of two steps with a representative evaluation of prevalence in psychiatric disorders in adolescents and the subsequent development of a universal prevention program.

For integration of research in treatment, an innovative approach is aimed at the use of smartphone-based monitoring of aversive tension of patients with eating disorders over the course of the day. A next level would be including ambulatory monitoring in the therapy process, both facilitating treatment progress and evaluating these amendments. This approach should be integrated with the onset of a new specialized inpatient treatment unit for eating disorders in cooperation with the Rheinhessen-Fachklinik Mainz, Child and Adolescent Psychiatry, Psychotherapy and Psychosomatic.

**IMPORTANT PROJECTS // MAX. 5**

**FUTURE DIRECTIONS**

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OVERVIEW

The clinic provides inpatient multimodal treatment with 24 beds and day hospital treatment for 28 patients, taking into account acute and chronic physical, mental and social causes of disease.

Specialized outpatient units offer assessment, consultation and treatment, esp. for the depersonalization-derealization syndrome, posttraumatic stress disorders, behavioral addictions and sleep disorders. Consultation-liaison services are provided to all patients of the UM Mainz supporting patients to cope with stressful medical disorders or procedures.

Our postgraduate curriculum qualifies psychologists and physicians as psychodynamic psychotherapists or psychoanalysts.

The institute of medical psychology and sociology has focused on neuroscience research, and research on improving medical training.

HIGHLIGHTS

CENTER FOR TRANSLATIONAL VASCULAR BIOLOGY
As one of the core units of the Gutenberg Health Study, the department of psychosomatic medicine investigates the interaction of personality, mental disorders, cognitive function, health behavior and cardiovascular disease. Specific treatment approaches have been developed and tested for patients with cardiovascular disease.

TRANSLATIONAL NEUROSCIENCE
In neuroimaging studies (fMRI, PET, EEG) we investigate biological mechanisms of mental disorders, e.g. emotion regulation in collaboration with the Center for Translational Neuroscience. In a shielded EEG laboratory we study attention and emotional processing in psychosomatic and addictive disorders.

PSYCHOONCOLOGY
The department of psychosomatic medicine combines psychooncological treatment in the University Cancer Center (UCT).

PSYCHOTHERAPY RESEARCH
We have been conducting numerous RCTs to establish the efficacy of psychodynamic short-term outpatient treatments of anxiety disorders and depression. A special expertise is related to quality assurance (competence and adherence ratings of video recordings of sessions, process research) and to manualized psychodynamic treatments (published in a new series). Our postgraduate psychotherapy training program aims at establishing practice-research networks. In the DFG funded Graduate College Life Sciences- Life Writing we study patients’ narratives undergoing psychotherapy.

ATTACHMENT RESEARCH
In multidisciplinary studies we determine associations between childhood trauma, attachment patterns, emotion regulation, gene toxicity and mental representation and biological markers of oxytocine, and postpartum mother–child attachment.
E MENTAL HEALTH AND REHABILITATION RESEARCH GROUP

In an RCT we have tested the effect of a psychodynamic online intervention on vocational reintegration, and we are currently developing novel online approaches on preparing patients for psychotherapy and on supplementing self-guided online support to inpatient psychotherapy. A junior research group has dedicated itself to the development of e-mental-health.

SABINE M. GRÜSSER-SINOPOLI OUTPATIENT CLINIC FOR BEHAVIORAL ADDICTION

The clinic has been active defining standards for research, diagnosis, care and prevention in the rapidly evolving field of behavioral addictions. The clinic offers the whole range of medical care for behavioral addictions: an anonymous and free hotline, assessment, consultation, innovative and psychological, resp. sociological aspects and teaching research. Our department is closely connected to the translational research centers of the University Medicine.

OUR GOALS ARE:

- To advance the understanding of the interaction of psychological and social processes, health behavior and medical disease (e.g. long-term health consequences of childhood adversities)
- To examine complex planning skills (from early childhood to late adulthood) and working memory processes on a neuronal and behavioral level
- To advance evidence-based prevention and psychotherapeutical treatment in mental and psychosomatic disorders
- To translate basic science and clinical research into innovative psychotherapy treatments
- To develop and evaluate new models of integrative patient care
- To disseminate new findings in teaching and psychotherapy training
- To develop methods for excellent medical education: improving knowledge and communication skills

FUTURE DIRECTIONS

Psychosomatic medicine and psychotherapy endorses a holistic and interdisciplinary model of patient care. Medical Psychology and Sociology focuses on the neuronal and behavioral development of cognitive functioning across the lifespan, the interface between medical and psychological, resp. sociological aspects and teaching research. Our department is closely connected to the translational research centers of the University Medicine.

Development and evaluation of an internet-based aftercare programme to improve vocational reintegration after inpatient medical rehabilitation

Development of practical online aftercare interventions for patients of inpatient medical rehabilitation with vocational strains

Effects of a manualized Short-term Treatment of Internet and Computer game Addiction (STICA)

Enhancing Inpatient Psychotherapeutic Treatment With Online Self-help: Acceptance and Efficacy

Is psychic trauma genotoxic? Pilot-study funded by the intern research funding-program of the JGU

PROJECT MANAGER:
PD Dr. C Schür- Wrana, Prof. M Beutel, Prof. B Kaina
FUNDING: Intramural funding
PROJECT DURATION: 2013 - 2014

PROJECT MANAGER:
PD Dr. R Zwerenz, Prof. M Beutel
FUNDING: German pension insurance
SUM: € 243,010
PROJECT DURATION: 2010 - 2014

PROJECT MANAGER:
Dr. R Zwerenz, Prof. M Beutel
FUNDING: Federal Ministry of Education and Research (BMBF)
SUM: € 901,769
PROJECT DURATION: 2011 - 2016

PROJECT MANAGER:
Prof. M Beutel, Dr. Wölfling
FUNDING: Federal Ministry of Education and Research (BMBF)
SUM: € 46,500
PROJECT DURATION: 2014 - 2015
The primary focus of our research is in the field of neuroimmunology – classical inflammatory diseases as well as inflammatory and defense mechanisms in strokes and brain tumors. As part of this research, we are investigating the pathogenesis of such diseases using cell-culture and animal-model experiments, patient examinations, imaging, and genetics. An example of this research is the use of two-photon laser scanning microscopy to directly investigate the interaction of immune cells in inflammatory lesions in the brains of living organisms. Research is conducted in close collaboration with other scientists in the University through our active participation in the Focus Program for Translational Neurosciences (FTN), Research Center for Immunotherapy (FZI) and German Resilience Center (DRZ), as well as with neuroscientists in the Rhine-Main region as part of the Rhine-Main Neuroscience Network (rmn2). Together with the Universities of Munich and Munster, we are part of a DFG-funded Collaborative Research Center on Multiple Sclerosis, which aims to elucidate the foundations of multiple sclerosis to better understand its pathophysiology with the goal of finding new treatment targets. We are also aligned with the other specialist centers for Multiple Sclerosis in Germany as part of the BMBF-funded patient-oriented “Competence Network for Multiple Sclerosis (KKNMS),” whose purpose is to improve treatment of MS patients as well as strengthen clinical research through multi-center cooperation.

The mechanisms of neuroprotective medications, the modes of action of proteins and signaling pathways represent another important research area. We utilize models to study the cellular and molecular foundations of hereditary and acquired neurodegenerative illnesses, for example, in hereditary polyneuropathy.

A further important area of neurological research is pain research. In the Department of Neurology, this is based predominantly on psychophysical and functional-imaging methods, as well as using microneurography which can be performed at only a few centers worldwide. Financial support for this research has been received from the EU and DFG.

The neurovascular team is primarily involved with interdisciplinary projects, of which the principal aim is the development of optimized clinical treatments for patients. The detection of auricular fibrillations, interventional acute treatment of strokes and the long-term observation of patients with extra- and intracranial stents are examples of some of our research interests.

The neurostimulation and movement disorders group investigates how different regions of the brain interact, focusing on connectivity and reorganization in healthy and diseased individuals. Imaging, non-invasive stimulatory and electrophysiological methodologies are employed to explore the physiology and pathophysiology of the human motoric system, particularly in Parkinson’s disease and multiple sclerosis.
The overall research goal of the Department of Neurology is to advance the understanding of neurological diseases and improve the treatment of patients. All of our group leaders are both physicians and scientists, thus having a complete overview of the research process from bench to bedside. Together with our Clinical Study Center, they conduct investigator-initiated trials to bring the benefits of our research to patients as efficiently as possible.

Furthermore, we actively promote interdisciplinary research and collaboration, which we believe to be central to successful scientific research. This can be seen both within the university through our involvement in the FTN, FZI, DRZ and UCT, among others, as well as nationally and internationally in our role as the spokesperson of a national collaborative research center on multiple sclerosis, as a member of the KKNMS, CRC-1080 on neural homeostasis, an EU project on pain research as well as various international study groups investigating the efficacy of new medications and treatments as well as the genetic origins of neurological disorders. We aim to continue to conduct and secure funding for cutting-edge research projects nationally and internationally, disseminating our research findings in high-ranking publications and at international congresses. Ultimately, we want to use this knowledge to further the treatment of multiple sclerosis, stroke, Parkinson’s, chronic pain, epilepsy, and other neurological disorders.

FIG. 1 + 2: Neuroimmunological research laboratories

FIG. 3: Two-photon microscope image of mouse brain for stroke research

FIG. 4: MRI analysis of brain affected by multiple sclerosis
OVERVIEW

The Center for Childhood and Adolescent Medicine at the University Medical Center Mainz serves as a hospital for supra-maximum medical care and is the only academic child health institution in the state of Rhineland-Palatinate. The children’s hospital provides comprehensive pediatric care for the population of Mainz and the surrounding regions. In addition, state-of-the-art medical treatment is available for all relevant pediatric subspecialties. Beyond that, numerous research projects funded by national and international organizations are conducted. The clinic is highly reputed for its expertise in clinical trials comprising investigator initiated and externally sponsored clinical trials following GCP and GLP standards.

HIGHLIGHTS

Neonatology: Sponsored by the German Federal Ministry of Education and Research, the section of neonatology contributes to the development of a device for telemetric monitoring of cortical functions of newborns. 3 prospective studies investigate the duration of weaning preterm infants from CPAP, bacterial colonization and viral nosocomial infections in newborns.

Birth Registry Mainz Model: Teratogenic effects of new drugs (EUROCAT), Cohort changes (ART, c-section on request), Congenital anomalies and cancer and Congenital anomalies and maternal occupational radiation exposure.

Metabolism (Villa Metabolica): Research focuses on the investigation of the pathogenesis, clinical presentation and new treatment options in patients with lysosomal storage diseases.

The Molecular Pediatrics research group investigates the chromatin architecture of regulatory regions responsible for imprinted gene expression and disease associated defects by 4C and T2C techniques.

Pediatric Infectious Disease: The research focuses on epidemiologic studies of respiratory pathogens, the microbiome and pathogenesis of chronic inflammatory bowel diseases, and nanocarriers and experimental vaccinology.

Pediatric Immunology: The research group studies the biology of IL-27 and has characterized IL-27 as a highly expressed Th1 cytokine in newborn immunity, replacing IL-12, not secreted by neonatal dendritic cells. In addition, a specific role of IL-27 in puberty has been demonstrated.

Pediatric Rheumatology: The projects study phenotypic differentiation of T and B cells and the expression of pro- and anti-inflammatory cytokines on mRNA and protein levels. Actually, the epigenetic regulation by identifying JIA-specific micro-RNA using “next generation sequencing” is investigated.

Oncology: The interdisciplinary “Cardiac and vascular late sequelae in long-term survivors of childhood cancer (CVSS-) study” investigates the current health status of 1000 former pediatric oncology patients.


Kirchner M, Strothmann L, Sonnenschein A et al. Distinct Cytokine Profiles in Patients with Oligoarticular Juvenile Idiopathic Arthritis after in Vitro Blockade of Interleukin (IL)-1 and Tumor Necrosis Factor (TNF)-α. WORLD JOURNAL OF VACCINES. 2014; 4: 110-122.


FUTURE DIRECTIONS

Metabolism: Main focus is the development of new genetic engineering methods for therapy with enzyme replacement and/or substrate reduction in mucopolysaccharidoses, Fabry, Gaucher, Pompe and Niemann Pick disease. Molecular Pediatrics: Key research aims of the group are uncovering the molecular basis of imprinting disorders and the disease associated physiological role of ion channels TRPMS/TRP7 to improve diagnostics and therapy. Pediatric Infectious Disease: Development of a respiratory array-based detection platform. Microbiome studies in children with chronic inflammatory bowel diseases. Investigation of polymeric nanocarriers as novel vaccine platform. Pediatric Immunology: Role of IL-27 in neonatal sepsis. Relevance of the gut microbiota for the neonatal immune system. Inflammatory effect of rapamycin on tuberous sclerosis patients. Pediatric Rheumatology: The group researches immunological mechanisms and regulations in the pathogenesis of juvenile idiopathic arthritis (JIA) as well as of auto-inflammatory bone disease (CRMO). Oncology: Current projects investigate clinical, epidemiological and genetic aspects of late sequelae in long-term survivors of childhood cancer and related therapy. Neonatology: Interdisciplinary basic and clinical research. Birth Registry Mainz Model: Estimate prevalence of congenital anomalies, health effects and risk factors. Detect relevant changes (e.g. trends/regions), develop preventive measures and evaluate health campaigns.
Surgery

Center of Orthopedics and Trauma Surgery
Department of Ophthalmology
Department of Oto-Rhino-Laryngology, Head- and Neck Surgery
Department of General-, Abdominal and Transplantation Surgery
Department of Obstetrics and Gynecology
Department of Cardiothoracic and Vascular Surgery
Department of Pediatric Surgery
Department of Neurosurgery
Department of Urology
Department of Anaesthesiology
The research activities of the Department of Orthopedics and Traumatology continue to focus on two main directions in the field of reconstructive surgery – biomechanical research (i) and fracture healing & biomaterials (ii). Our “biomechanics” research team focuses on investigation and development of improved fracture fixation methods especially in the upper extremity and in the distal tibia. One of the important highlights of the “biomechanics” group headed by Prof. Rommens, PD Dr. Nowak and Dr. Kuhn was the development and proof of concept of a novel nailing system for distal tibia fractures. Due to associated soft tissue damage and limited soft tissue coverage of the bone, distal tibia fractures are associated with a high risk for different types of complications such as cortical necrosis, delayed healing and non-union, or infection. The team developed a minimally invasive surgical method for fixation of such types of fractures using an interlocked retrograde intramedullary nail. In a series of publications in 2014, they showed that the newly developed retrograde tibial nail possesses favorable biomechanical properties in comparison to all other methods of fixation while maintaining a maximum soft tissue protection.

Our “biomaterials” team headed by Prof. Hofmann, Dr. Ritz, and Prof. Rommens finished and published the first study on CD34+ progenitor cells in polytrauma patients. They found that numbers of these cells is significantly increased in patients with major trauma. Isolated and subcultured CD34+ cells were capable to differentiate into endothelial cells and mediated the osteoblast differentiation in a co-culture model with human osteoblasts. One of the most important findings of the experiments was the observation of increased new bone formation in a critical-size bone defect in athymic mice. These results open new perspectives for development of novel cell-based approaches in the field of regenerative medicine. The group successfully established an animal model for future research projects, which allows for a precise analysis of the osteogenic activity of different materials and cells in vivo using modern techniques (µCT, animal imaging).
FUTURE DIRECTIONS

The upcoming projects of the “biomaterials” group will focus on investigations of mobilization kinetics of CD34+ cells in patients with major trauma. A recent project deals with characterization of their different fractions and their differentiation capacity. We aim to investigate the impact of these subpopulations on fracture healing and to define their prognostic role with regard to clinical outcome. The second key area of research is the CERTiFy-study, which is a prospective, randomized, clinical trial investigating treatment outcomes in patients with fractures of the tibial plateau. In this study with 19 participating centers all across Germany, fracture-associated bone defects are treated either with autologous bone grafts or a bone substitute (CERAMENT BVF). With our department being the principle investigator center, we aim to complete the recruitment of patients within the next year.

In 2014, a new radiation-free analysis system of the human gait and spine (DIERS) was built in our department. This system allows for a precise analysis of different morphologic parameters of the spine and pelvis. The technology is based on a proven physical principle of photogrammetry and optical triangulation. The clinical use was originally designed for follow-up of therapeutic procedures of the spine by avoiding repeated radiological examinations. With this system, we plan to establish a solid base for future research.

FIG. 1: DIERS 4DmotionLab

FIG. 2: Novel olecranon tension plate compared to a tension band wiring in a biomechanical cadaver complex fracture model. X-ray after the implantation of the standard tension band wiring with a lag screw: A: antero-posterior view, B: lateral view. The olecranon tension plate: C: antero-posterior view D: lateral view.


IMPORTANT PROJECTS // MAX. 5

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Project Manager(s)</th>
<th>Funding Agency</th>
<th>Duration</th>
<th>Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of a patient-friendly tourniquet through FEM simulation of pressure transfer on soft tissue of the thigh</td>
<td>Prof. A. Hofmann, Prof. PM Rommens, h.c.</td>
<td>The Central Innovation Program for SME (ZIM)</td>
<td>2013 - 2016</td>
<td>€ 165,012</td>
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<tr>
<td>CERAMENT treatment of fracture defects (CERTiFy): a prospective, multicenter, randomized study</td>
<td>Dr. KE Roth</td>
<td>The Central Innovation Program for SME (ZIM)</td>
<td>2013 - 2016</td>
<td>€ 750,000</td>
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<tr>
<td>Novel olecranon tension plate compared to a tension band wiring in a biomechanical cadaver complex fracture model</td>
<td>PD Dr. T. Nowak, Dr. D. Gruszka</td>
<td>The Central Innovation Program for SME (ZIM)</td>
<td>2013 - 2014</td>
<td>€ 250,000</td>
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<tr>
<td>Surface functionalization of titanium implants with bone sialoprotein (BSP) for enhanced osseointegration</td>
<td>Prof. A. Hofmann, Dr. A. Baranowski</td>
<td>The Central Innovation Program for SME (ZIM)</td>
<td>2013 - 2015</td>
<td>€ 90,000</td>
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<tr>
<td>The Retrograde Tibial Nail – A new implant concept for distal tibia fractures</td>
<td>Dr. S. Kuhn, Prof. PM Rommens, h.c.</td>
<td>The Central Innovation Program for SME (ZIM)</td>
<td>2010 - 2015</td>
<td>€ 90,000</td>
</tr>
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</table>
OVERVIEW

The Department of Ophthalmology is one of the largest facilities of its kind in Germany in terms of health care services as well as research and teaching. Besides offering a broad range of diagnostic methods and treatment options of ocular diseases, the Department operates a large research facility and the associated Clinical Trial Site. Basic and clinical research aim to unravel pathogenesis and optimize diagnosis and therapeutic treatment of ocular diseases, including glaucoma, dry eye disease, and age-related macular degeneration. Furthermore, the Department of Ophthalmology conducts numerous research projects as part of the large-scale Gutenberg Health Study (GHS) with the goal to collect clinical, laboratorial, chemical, and epidemiological data on ocular diseases.

HIGHLIGHTS

One major strength of our clinical as well as our basic research is the great interdisciplinary networking between different researchers and institutes. This enables participation in various national and international projects and greatly contributes towards knowledge exchange.

Within the GHS the working group “Ophthalmological Epidemiology” focuses on prevalence survey and epidemiological genetics. One of the recent research highlights has been well recognized amongst researchers and non-scientists and is of great relevance to a vast number of people: myopia. About one third of the German population suffers from myopia and its causes remain to be fully understood. Within the GHS our scientists were able to find out that myopia increases significantly in correlation with the years spent in school. And even after school the effect remains: the higher their professional qualification the more short-sighted the Germans are. This work, published in the renowned journal "Ophthalmology", has been mentioned in the media many times, even the New York Times commented on these discoveries. So what can one do to fight myopia? Two hours a day spend outdoors during childhood can reduce the tendency.

The Clinical Trial Site of the Department of Ophthalmology is certified within the framework of the European Vision Institute Clinical Research Network (EVICR.net). In 2014 numerous clinical studies and scientifically initiated clinical studies were performed with great success. Amongst others, the Trial Site coordinates the multi-national FP7-Project “STRONG” which is funded by the European Commission and investigates the prevention of neovascular glaucoma following an ischemic central retinal vein occlusion. The study receives a total of 5.7 Mio Euro funding from the EU. Moreover, the Clinical Trial Site collaborates with various institutes from the University Medical Center Mainz.

The “Experimental and Translational Ophthalmology” focuses on clinic-related basic research while using state-of-the art analysis methods. The main research focus examines the immunological aspects of glaucoma and possible diagnosis and treatment options arising from changes in antibody patterns. Besides a large proteomics unit with mass spectrometric and antigen-microarray techniques, the laboratory work also includes cell culture, retinal organ culture and experimental glaucoma animal models.

The Cornea Bank of Rhineland-Palatinate, operated by the Department of Ophthalmology, is among the three largest facilities of its kind in Germany. In 2014 it was possible to obtain a total of 699 cornea of which 369 could be used as cornea transplants.

Further research projects include the investigation of protective characteristics and possible therapeutic use of antibodies, the morphological and functional characterization of intraocular pressure fluctuations or the characterization of the human tear proteome.
Important Publications // Max. 5


**Minshahi A, Ponto KA, Hoehn R et al.** Myopia and Level of Education Results from the Gutenberg Health Study. OPHTHALMOLOGY. 2014; 121 (10): 2047-2052.


**Wilding C, Bell K, Beck S et al.** gamma-Synuclein Antibodies Have Neuroprotective Potential on Neuroretinal Cells via Proteins of the Mitochondrial Apoptosis Pathway. PLOS ONE. 2014; 9 (3).

**Future Directions**

Our many publications in high ranked scientific journals confirm the success of our research projects and the relevance of our findings. The ongoing and future research projects include the investigation of molecular biomarkers in glaucoma, prevalence and causes of amblyopia, correlations between oxidative stress and glaucoma or the regulation of ocular pressure through muscarinic acetylcholine receptor subtypes, and the influence of resveratrol and betulinic acid on the development of a retinal ischemic-reperfusion injury. The ophthalmological epidemiology will continue its cooperation with the GHS to further investigate prevalence and incidences of ophthalmological risk factors and diseases. Moreover they aim to demonstrate interdisciplinary correlations and their genetic basis. The Clinical Trial Site currently performs and monitors 20 clinical studies, while another 12 studies are being prepared. A total of 10 employees, including 3 permanent trial physicians and further trial physicians on call, contribute to the success of the trial site. Within the Experimental Ophthalmology, recently established methods, like retinal organ culture, and a new experimental animal model for glaucoma will be used to elucidate the functional relevance of molecular biomarkers in glaucoma. The overall goal of our research projects is to gain a better understanding of pathogenesis and characteristics of ocular diseases and to develop new diagnostic and therapeutic options.

**Important Projects // Max. 5**

**Autoantibodies in glaucoma: Relevance for early diagnosis and therapy**

**Project Manager:** Prof. F Grus, Prof. N Pfeiffer

**Funding:** Rhineland-Palatinate Foundation for Innovation

**Sum:** € 207,975

**Project Duration:** 2014 - 2015

**Investigation of the protective effect of antibodies on neuroretinal cells (MAIFOR project)**

**Project Manager:** Dr. R Bell

**Funding:** MAIFOR

**Sum:** € 49,250

**Project Duration:** 2013 - 2014

**Oxidative stress and glaucoma**

**Project Manager:** Dr. A Gerick

**Funding:** Science Transfer Program of the University Medical Center Mainz

**Sum:** € 88,000

**Project Duration:** 2012 - 2014

**Testing of the peripheral and central vestibular system in patients with genetically diagnosed Gaucher type 3 disease, Niemann-Pick type C and phenylketonuria**

**Project Manager:** Dr. S Ashayer, Prof. S Pitz, Dr. S Hopf

**Project Duration:** 2014 - 2016

**The Gutenberg Health Study: Ophthalmological section**

**Project Manager:** Prof. N Pfeiffer, Dr. R Höhn, Dr. S Nickels et al.

**Project Duration:** 2005 - 2017

**Fig:** Microscopic image of stained neuroretinal cells
OVERVIEW

In order to guarantee an optimal and innovative patient care now and in the future, ENT typical disease patterns are explored. Microsurgical operations of the nose and paranasal sinuses and minimally invasive laser surgical procedures and open surgical procedures are applied. About 4,000 patients are treated each year. In the operating rooms over 6,000 surgeries are performed per year. Surgically, the entire field of ear, nose, and throat medicine is covered. Another clinical focus are cochlear implant (CI) operations in children and adults. Key research areas are oncology of the head and neck and hearing rehabilitation, considered as continuous translational developmental processes beginning from open operations to molecular-based treatment-, and prevention methods.

HIGHLIGHTS

ONCOLOGY AND NANOBIO MEDICINE
The mission of translational oncology is to exploit our comprehensive knowledge from basic research for the prevention and therapy of patients with head and neck cancer. Cellular mechanisms regulating survival and damage-repair are key for tumor development and progression. As such, these molecular regulations significantly impact also response to therapy, quality of life and survival of cancer patients. Hence, we specialize on the identification of mechanisms contributing to irradiation- and/or chemo-resistance of tumors as well as on the development of (nanomedical- and chemical-based) interference strategies, including the exploitation of natural products. Research is performed in close collaboration with UMM’s main research areas. Besides key publications in leading journals, including Nature Nanotechnology, the success of our work is underlined by patent application of novel anti-tumoral drugs and the implementation of the “Core facility for systematic cell analysis” supported by the Carl-Zeiss-Foundation, DFG, BMBF, and the Innovation Foundation Rheinland Pfalz and a variety of other foundations, resulting in extramural research funding of >200,000 EUR/year. To evaluate and further promote the clinical transfer of our knowledge, we are interacting with the CHIR-Net and IZKS in order to optimally design and execute (pre)clinical trials. The generated knowledge will improve our understanding of basic processes at the molecular level for a better prevention and therapy of patients with head and neck cancer.

MINIMAL AND FUNCTIONAL RECONSTRUCTIVE SURGERY
The trend to apply better and more sophisticated minimal invasive surgery to increase treatment and convalescence is still ongoing. Major emphasis is also put in functional aspects applying especially endoscopic and laser applications as well as plastic reconstructive measures. Besides improvements of surgical navigation our research centers on methods to improve organ preservation and quality of life for patients. As part of the BiomaTiCS group, we work on the development of functional or plastic implants.

RHINOLOGY
Allergies are increasingly occurring and have a significant socio-economic impact. Our research centers on the identification of main factors and disease mechanisms involved in chronic inflammation of the nose. Besides the sensitivity towards aspirin, various air pollutants, including nanoparticles, are investigated.
FUTURE DIRECTIONS

OTOLOGY AND COMMUNICATION DISORDERS

With the aim to improve hearing impairments we analyze the molecular causes and optimize treatment strategies by introduction of novel therapies in daily clinical practice. In the future, increasingly the body’s own molecular protection mechanisms, such as the cytoprotective protein survivin, will be recruited for prevention and treatment of hearing loss. Own data suggest specific proteins such as the cellular protective protein survivin, which ensures the survival of auditory cells, as a potential candidate. The findings from basic research should ultimately be the key of new otologic therapy principles. Hearing improving operations and innovative cochlear implants (CIs) could also be complemented in future by drug-mediated modulation of regulatory cellular circuits.

In the division of communication disorders clinical research focuses on hearing aid and cochlear implant fitting as well as on developmental speech disorders in collaboration with the Institute of Human Genetics. Thus, we found that children with hearing loss demonstrate very different speech and language development, which does not depend solely on the degree of hearing loss, but also on various other factors. We investigate in a prospective study the effectiveness of intensive stuttering therapy using the DOLPHIN by Sabine Schütz supported by the Kester Haeusler Foundation.

FIG.: Chemical Biomedicine: Core facility for systematic cell analysis in the search for Cancer Medicine of the Future.

IMPORTANT PROJECTS // MAX. 5

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Project Manager</th>
<th>Project Duration</th>
<th>Funding</th>
<th>SUM</th>
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<tbody>
<tr>
<td>Analysis of ZnO nanoparticles as a potential mutagen of respiratory epithelia</td>
<td>Prof. J Brieger, J Heim</td>
<td>2012 - 2014</td>
<td>Max-Planck</td>
<td>€ 75,000</td>
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<tr>
<td>Core facility for systematic cell analysis</td>
<td>Prof. R Stauber</td>
<td>2014 - 2018</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
In addition to the development, evaluation and implementation of innovative surgical procedures our research focus is mainly oncology. The characterization of the biology of primary tumors and metastases is analyzed by molecular biology and many clinical analyses in order to identify prognostic markers and targets for future treatments. The section of Endocrine Surgery focuses on the treatment of benign and especially malignant thyroid diseases as well as diseases of the parathyroids, adrenals, endocrine pancreas, neuroendocrine tumors of the gastrointestinal tract and paragangliomas. Beside established laparoscopic methods all kinds of minimal-invasive techniques like thyroidectomy, parathyroidectomy, partly resection of pancreas are performed, prospectively documented and analyzed. Intraoperative neuromonitoring is routinely used and advanced techniques developed in cooperation with international study groups. The genetic characterization of thyroid carcinomas as well as other endocrine tumors is one of the main research areas. In the sense of translational medicine the results are used to identify thyroid carcinomas preoperatively and to optimize postoperative treatment strategies.

The molecular research laboratory focuses on the regulation of the organic cation transporters 1 and 3 (OCT1/OCT3) as well as the tumor suppressor gene insulin-like growth factor receptor 2 (IGF2R) in human hepatocellular and cholangiocellular carcinoma (HCC/CCA). Transplantation research focuses on the treatment after liver transplantation (e.g. immunosuppression), long-term results of patients with hepatocellular cancer, prevention of bile duct damage and arterial thrombosis. Continuous intraoperative monitoring of pelvic autonomic nerves during total mesorectal excision (TME) to prevent urogenital and anorectal dysfunction in rectal cancer patients is one of the key projects; this import topic will be further developed and tested in future studies. The AVTC provides oncologic surgery for the full spectrum of abdominal tumor entities. The main focus is liver surgery for all primary and secondary malignancies, which is also offered laparoscopically as for most other entities. Moreover, the AVTC belongs to the pioneers of computer-assisted intraoperative navigation, which is routinely used for open and laparoscopic liver resections. The development of this novel technique, which allows the resection of predefined areas of the liver on a 3D-reconstructed computed tomography examination by preserving vascular structures, was supported by a former BMBF grand (“Fusion”). It is currently used for resections of diminished metastases or those with close relationship to important vessels. Also, the technique helps planning liver resections which may result in borderline liver volumes, since it simulates blood supply and venous drainage of remnant liver volume.

Virtual reality simulation of laparoscopic surgery is not only used for quality assurance at his high level of laparoscopic expertise. It is also used for educational research using four virtual reality laparoscopic simulators with residents and medical students to evaluate different learning strategies, proficiency levels and didactic approaches.


**IMPORTANT PROJECTS**

**autoPIN: Laparoscopic-assisted system for stimulation of autonome pelvic nerves during continuous intraoperative monitoring (autoPIN) – sub-project: methodic animal experimental and clinic evaluation for minimal-invasive neuro-monitoring (BMBF)**

**PROJECT MANAGER:** Prof. W Kneist
**FUNDING:** Federal Ministry of Education and Research (BMBF)
**SUM:** € 301,560
**PROJECT DURATION:** 2013 - 2016

**Intraoperative Monitoring of the Pelvic Autonomic Nerves (NEUROS)**

**PROJECT MANAGER:** Prof. W Kneist, Dr. S Gorbulev
**FUNDING:** German Research Foundation (DFG)
**SUM:** € 1,100,000
**PROJECT DURATION:** 2009 - 2015

**Prospective Evaluation of the Predictive Value of Intraoperative Vagus Nerve Amplitude Recovery after Loss of Signal during Thyroid Surgery (PREC)**

**(Version 1.0), International IONM Study Group**

**PROJECT MANAGER:** Prof. T Musholt, F Angeletti, Dr. A Gohrbandt et al.
**PROJECT DURATION:** 2013 - 2015

**Computer-assisted planning and image-guided interventions in hepatobiliary surgery**

**PROJECT MANAGER:** Prof. H Lang, Prof. S Weber
**PROJECT DURATION:** 2012-2016

**IMPORTANT PUBLICATIONS**


OVERVIEW

The Department of Obstetrics and Gynecology covers all aspects of this area including obstetrics and general gynecology as well as gynecological endocrinology, gynecological oncology and urogynecology. A main focus of the department is the treatment of patients with gynecological cancers. It is also an integral part of the cancer center (UCT) of the Universitätsmedizin Mainz. Besides the well-documented clinical and scientific focus in gynecological oncology, the department has a proven expertise in urogynecology. Beyond that, obstetrics is an essential part. To complete the field of activity, the division of gynecological endocrinology treats patients with disorders in reproductive endocrinology and infertility.

HIGHLIGHTS

A main focus of research is the examination of prognostic and predictive factors in breast and ovarian cancer. Based on these results, a gene-expression signature for risk assessment in estrogen receptor (ER) positive and human epidermal growth factor receptor 2 (HER2) negative is already commercialized and in routine use (EndoPredict®, Sividon GmbH, Köln, Germany). Furthermore, we could show the prognostic influence of inflammatory markers like COX-2 and CRP in breast cancer. Beyond that, we were the first to describe the prognostic and predictive influence of tumor-infiltrating B-cells and especially plasma cells in breast cancer. These novel findings will be extended both to other entities like ovarian and endometrial cancer as well as to breast cancer patients treated with adjuvant therapy. In addition to gene-expression analyses and immunohistochemistry we performed next generation sequencing on well-characterized breast cancer specimens in collaboration with the Institute of Translational Oncology (TRON), Universitätsmedizin Mainz, Germany. In addition to the participation in numerous multicenter studies in gynecological malignancies, we conducted the neoadjuvant EXPRESSION study in breast cancer to develop a predictive gene-expression signature and we are currently conducting a multicentric psychoeducative group intervention study to support the patient’s competence. In gynecological endocrinology, a field of special research interest is the Times Laps-system which allows the accurate determination of parameters of the embryonic division and growth behavior which will provide new insights into the biological behavior of fertilized eggs and embryos by non-invasive techniques. They are characterized by image analysis techniques of texture, growth curves and kinetic datas and are used to estimate prognosis. The aim is to predict implantation and thus the possibility to achieve pregnancy by a single transfer, which lead to a decrease in multiple births.
**FUTURE DIRECTIONS**

Building on our results showing the strong prognostic impact in breast cancer, we are collaborating with BioNTech AG, Mainz, Germany, to take a novel individualized vaccination strategy aiming at tumor-associated antigens in triple-negative breast cancer (TNBC) to the clinic. Another advancement of our research dealing with the prognostic and predictive capabilities of tumor-infiltrating plasma cells is collaboration with Bayer Technology Services GmbH, Leverkusen, Germany. Here, we aim to isolate tumor-infiltrating lymphocytes, especially plasma cells, and amplify and characterize their immunoglobulin repertoire with single-cell RT-PCR to develop an antibody library. In a next step, we are conducting a study to characterize antibodies in the plasma of breast cancer patients and examine correlations of the antibody profile and pathological characteristics of the breast cancer as well as the outcome of the patients. Another project is the characterization of the secretion and activation mechanisms of human granulosa cells gained during follicular puncture. We are measuring receptors for growth factors, steroids and proteohormons such as Inhibin B, activin A and follistatin as a function of stimulation protocol and patient population. In addition, a further focus of research is the level of anti-Müllerian hormone (AMH) which has a regulative function in the activation of folliculogenesis and is considered as a marker for the ovarian reserve.

**IMPORTANT PROJECTS**

- **Characterization of lymphocytic infiltrates as prognostic and predictive markers in breast cancer**
  - **PROJECT MANAGER:** Prof. M Schmidt
  - **PROJECT DURATION:** 2010 - 2016

- **Characterization of the immunoglobulin repertoire of tumor-infiltrating plasma cells and correlation of factors within the plasma with prognosis in early breast cancer**
  - **PROJECT MANAGER:** Prof. M Schmidt
  - **FUNDING:** Bayer Technology Services GmbH
  - **SUM:** € 35,000
  - **PROJECT DURATION:** 2011 - 2016

- **EXPRESSION**
  - **PROJECT MANAGER:** Prof. M Schmidt
  - **FUNDING:** Sanofi-Aventis
  - **SUM:** € 150,000
  - **PROJECT DURATION:** 2010 - 2016

- **Gene-expression analysis as prognostic factor in node-negative breast cancer**
  - **PROJECT MANAGER:** Prof. M Schmidt
  - **PROJECT DURATION:** 2004 - 2016

- **Identification of prognostic and predictive factors in breast cancer using Next-Generation Sequencing (NGS)**
  - **PROJECT MANAGER:** PD Dr. M Schmidt, Prof. U Sahin, Dr. C John
  - **FUNDING:** Federal Ministry of Education and Research (BMBF)
  - **SUM:** € 170,000
  - **PROJECT DURATION:** 2012 - 2016
RESEARCH:
The research focuses on “Minimally Invasive Surgery” and “Vascular Therapy- and Research”. Within the activities of the Cardiothoracic and Vascular research we distinguish “function, tissue and material”. For Germany innovative ways are scientifically processed like the aortic register; Mainz is one of the reference centers. Under the subpriority “function” especially the process of intra-and intercellular signaling is systematically explored. Prototypically the Department of Cardiothoracic and Vascular Surgery has a special position, because of methods for the measurement of intracellular calcium, pH and sodium on the vital human heart muscle are offered under various model conditions. In a model of “skinned fiber” of the heart muscle different projects are running. Patients with mucopolysaccardidosis are investigated regarding to Ca-sensitivity and force capacity. Another research focus of this working group is the diastolic dysfunction and cardiac mechanics of myxoid mitral valve degeneration. Furthermore, the working group examined gender-specific characteristics of the contraction dynamics of human tissues and the transferability of experimentally gained results to the clinical reality in terms of individualized patient concepts. The understanding of the mechanical properties of the arterial vessel wall is becoming more important in our increasingly aging society. In our laboratory we succeeded to establish a method for determining the isometric force and dynamic stiffness of vital human strip preparations of the internal mammary artery by the use of force-clamping technique. The results suggest that patients may need to be differentiated with coronary heart disease in subpopulations that may benefit from preoperative and postoperative stiffness reduction with different medication. A highly respected group with prices from the field vascular surgery developed pioneering prototypical three-dimensional models for the development of arteriosclerosis and biological vascular grafts using marine-sponge polymers in conjunction with the institute of biochemistry (ERC-grant sponsored). This should be an essential step on the pathway to biological implants. In addition, a basic research project funded by the german research foundation is directed towards assessing the role of proteases in endothelial cell apoptosis. Similar pathways are done in cardiac surgery in the context of optimization of biological prosthesis. An important and young research area is the area of obesity research. It is of particular interest because it offers from the view of cardiac and vascular surgery the same clinical and scientific perspectives. The night lecture series continue to enjoy great popularity, so that research focus “media convergence” has developed together with the Mainz Institute for Book Sciences. The night lecture is considered the largest and most sustainable prevention project in the region.
The strategic goals for our department are linked to the different divisions: For cardiac surgery, the further implementation of techniques for minimally-invasive aortic, valve and coronary surgery is planned. In addition, the generation of a dedicated unit for the treatment of acute severe myocardial insufficiency including extracorporal life support-systems is in progress.

For vascular surgery, the armamentarium of techniques for endovascular aortic surgery is further to be expanded including complex cases of thoracoabdominal aneurysms and dissections. This includes introduction of novel endograft devices as well as specialized 3D-imaging modalities for planning and follow-up of endografts.

For thoracic surgery, minimally-invasive video-assisted techniques for lung resection as well as treatment of recurrent pneumothorax and pleural effusion have been established and will be further refined.

Research projects in the cardiac experimental laboratory are focused on the examination of the contractile functions of human myocardium in diabetic and obese patients and patients with intracellular storage diseases (mucopolysaccharidosis). Furthermore, an ERC-Proof-of-concept-Grant could be successfully obtained by Prof. Dorweiler as cooperating partner of Prof. W.E.G. Müller (Institute of Biochemistry, University of Mainz) that is focused on the development of tissue-engineered small-caliber blood vessels based on novel marine-based biodegradable polymers.
OVERVIEW

The key research project of the Dep. of Ped. Surgery is the invention and development of innovative techniques that make the daily pediatric surgical work less invasive, more efficient, and safer. Besides the establishment of the single-incision pediatric endosurgery (SIPES) for a variety of new indications, new combined endoscopic-endosurgical techniques were developed as well. Google Glass, as a type of wearable technology with an optical head-mounted display, could successfully be tested in clinical work in 2014 by members of our team. Various projects on the use of telemedicine in the field of pediatric surgery have been launched. Our translational research focuses on the examination of tissue samples from tumors in childhood and in Hirschsprung’s disease using multiphoton microscopy.

HIGHLIGHTS

SINGLE-INCISION PEDIATRIC ENDO SURGERY (SIPES)

SIPES is accomplished through only a single small incision in the navel, minimizing the visible scar and potentially reducing incisional pain associated with the multiple points of entry used during traditional laparoscopic surgery. Within our department, a variety of novel laparoscopic procedures were first described early childhood, and are now routinely and safely performed with this method. The aim of a new research project is to establish this method for minimal invasive tumor surgery in comparison to standard laparoscopy.

GOOGLE GLASS

Personal portable information technology is advancing at a breathtaking speed. Last year, Google introduced Glass, a device that is worn like conventional glasses, but that combines a computerized central processing unit, touchpad, display screen, high-definition camera, microphone, bone-conduction transducer, and wireless connectivity. We have obtained a Glass device through Google’s Explorer program and have tested its applicability in our daily pediatric surgical practice and in relevant experimental settings. Glass has some clear utility in the clinical setting. At this time, we are using it for photo- and videodocumentation, and are working on overcoming specific drawbacks such as the lack of specialized medical applications, or issues of patient data protection.

TELEMEDICINE

Telemedicine is the use of telecommunication and information technologies in order to provide clinical health care at a distance. Telemedicine can be broken into three main categories: store-and-forward, remote monitoring and (real-time) interactive services. Real-time interactive service using the Adobe Connect Software is evaluated for routine outpatient care with great success. Trauma projects and telemedical cooperation with outpatient physicians are goals of further research work. We currently are evaluating a telomedical tool for pediatric surgical outpatient follow-up in a randomized, controlled study.

MULTIPHOTON MICROSCOPY (MPM)

Multiphoton Microscopy is investigated as an alternative to intraoperative frozen section biopsies for pediatric surgical oncology and Hirschsprung’s disease. Multiphoton Microscopy has been proposed as a real-time microscopic imaging modality that may be a useful adjunct for the surgeon in the operating room. We documented the ability to accurately determine the distribution of ganglion cells in mice with Hirschsprung’s disease. In pediatric surgical oncology three-dimensional real time imaging of tissue could provide immediate feedback to the surgeon on resection margins. We are currently evaluating its applicability for these indications.
FUTURE DIRECTIONS

Our future goal is the expansion of already initiated projects. For the design of subprojects, we are in communication with the IZKS (Interdisciplinary Centre for Clinical Trials). At the initiative of our clinic, an interdisciplinary telemedical working group was established at the University Medical Center Mainz. Together with the IZKS, we anticipate the implementation of further telemedical projects, and grant submission in this field. For multiphoton microscopy, we are currently creating a tissue bank covering a variety of childhood solid tumors and gastrointestinal pathology. In the long term tissue multiphoton microscopical examination at different stages of diseases and at different ages during childhood is planned. A longterm goal is the development of a laparoscopic MPM device to improve accurate determination of resection margins in Hirschsprung disease and a variety of pediatric neoplasias.

IMPORTANT PROJECTS // MAX. 5

- **MPM Examination of tissue of different origin in comparison to conventional histopathology in childhood**
  - **PROJECT MANAGER:** Prof. O. Muensterer, Dr. J. Gödeke
  - **FUNDING:** Else-Kröner-Fresenius Foundation
  - **PROJECT DURATION:** 2014 - 2019

- **Multiphoton Microscopy as an alternative to intraoperative frozen section biopsies for pediatric surgical oncologic diseases**
  - **PROJECT MANAGER:** Dr. J. Gödeke, Dr. S. Waldron
  - **FUNDING:** Else-Kröner-Fresenius Foundation
  - **FUNDING:** IPEG Research Fund
  - **PROJECT DURATION:** 2014 - 2019

- **Telemedicine in the diagnosis and treatment of pediatric surgical patients**
  - **PROJECT MANAGER:** Dr. J. Gödeke, Dr. M. Schwind
  - **FUNDING:** University Medical Center of Mainz
  - **SUM:** € 5,000
  - **PROJECT DURATION:** 2014 - 2019
In 2014, 200 in-patients were surgically treated at the Neurosurgical Department. In addition, over 6000 out-patient visits were managed. We employ the most advanced surgical tools, from intra-operative, frameless image-guidance to minimally invasive spinal or skull base equipment. We partner with industry leaders to ensure that we have access to and even influence the next generation of surgical technology. Specializing in a range of neurological disorders, the Neurosurgical Department focuses on patients with degenerative, traumatic or inflammatory diseases of the whole spine. We are providing a broad spectrum of minimally invasive techniques and modern instrumentation for spinal canal stenoses, disc herniations, spondylolisthesis, vertebral fractures or spondylodiscitis. Further, our department is specialised in awake craniotomies for primary and metastatic brain tumors, cerebrovascular diseases (e.g. aneurysms, AVMs) functional and stereotactic surgery for e.g. Parkinsons disease, movement disorders or epilepsy, and skull base surgery. Pituitary surgery for adenoma are routinely performed using 3D-guided endoscopy. Intracranial vascular diseases are evaluated by microvascular neurosurgeons and endovascular neuroradiologists in multidisciplinary conferences providing the patient both with option and the combined expertise of different therapeutic approaches.

One of the outstanding features of our Department is the possibility to perform minimally invasive robot-assisted surgery for brain and spine. Our multi-speciality Neurooncological Center is a highly developed facility were glioma as well as patients with brain metastases receive diagnostics, individualized tumor treatment including chemotherapy and psychooncological help.

**HIGHLIGHTS**

In addition, we strive for the highest quality of neurosurgical care by providing neurosurgical knowledge and practice through research and innovation. Scientifically the Neurosurgical Clinic focuses on neurooncological research, complex spine surgery as well as the development of innovative 3D planning, simulation techniques, intraoperative navigation and operation techniques. New patents are regularly applied for. In our translational neurooncological laboratory emphasis is put on the research of malignant glioma and brain metastases. Our particular interest aims at characterizing tumor stem cells.


**IMPORTANT PUBLICATIONS // MAX. 5**

**Fig. 1:** Intraoperative 3D navigation for transphenoidal approach to the sellar region.

**Fig. 2:** 3D-visualization of pathologies by fusion of different imaging techniques.

**IMPORTANT PROJECTS // MAX. 5**

Early lumbar drainage after aneurysmatic subarachnoidal bleeding: a randomized, clinical study (EARLYDRAIN)

**PROJECT MANAGER:** Dr. T Kerz
**PROJECT DURATION:** 2011 - 2015

Erythropoetin in SHT: a randomized placebo-controlled study in intensive care patients.

**PROJECT MANAGER:** Dr. T Kerz
**FUNDING:** The Australian & New Zealand Intensive Care Research Centre, Department of Epidemiology and Preventive Medicine, School of Public Health, Monash University, Melbourne, Australia
**SUM:** € 20,000
**PROJECT DURATION:** 2012 - 2015

Intraventricular hemorrhage trial

**PROJECT MANAGER:** Dr. T Kerz
**FUNDING:** National Institutes of Health (NIH) USA
**SUM:** € 100,000
**PROJECT DURATION:** 2011 - 2014

N-acetylcysteine, Methylprednisolone and Ventricular Irrigation in Subarachnoid Aneurysmal Hemorrhage (NAC-MEP-VI)

**PROJECT MANAGER:** Dr. T Kerz
**PROJECT DURATION:** 2014 - 2018

Therapeutic portenial of argon gas after subarachnoid hemorrhage in rats.

**PROJECT MANAGER:** Dr. N Keric
**FUNDING:** German Society of Neurosurgery (DGNC)
**SUM:** € 10,000
**PROJECT DURATION:** 2013 - 2015
Our Functional Diagnostic and BPH working group is concerned with the complete diagnostic, evaluation and therapy modalities relating to bladder dysfunction in both males and females. Within the framework of our Continence Center, there exists a close working cooperation with the Departments of Gynecology, Pediatrics and Neurology. We investigate various operative techniques in cases of benign prostatic hyperplasia, the predictive values of neurological diseases and the outcome of infravesical unobstruction.

The working group Uro-Oncology is concerned with basic scientific (under direction of Prof. Brenner) and clinical studies on prostate, bladder and renal cell carcinomas (RCC). The studies examine the mechanisms of new chemotherapeutics or "target therapy", largely in advanced and metastasized tumor stages. Furthermore, the molecular basis in pathogenesis and metastasis of RCC, in particular the signal transduction and resistance building, is analyzed. With regard to prostate carcinoma and bladder carcinoma, a patient-orientated therapy according to the "molecular biological fingerprint" is being investigated. The knowledge thus gained will assist in better selection of tumors according to their possible response to chemotherapy or hormonal therapy.

The working group Pediatrics/Reconstruction cooperates with CURE-Net, a network for congenital uro-rectal malformations that combines the modern principles of scientific basic research in the areas of genetic and molecular biology, with the purpose of identifying the reasons for congenital deformities of the urogenital tract. Through a multicenter transversal study including all age groups, this group evaluates the relevance of postoperative long-term complications to achieve an age and gender-suited algorithm for follow-up care, which will consider gender-specific needs and psychosocial aspects. Furthermore, as a member of the Johannes Gutenberg University BiomaTICS research group, the team is concerned with the establishment and optimizing of an in vitro generated pre-vascularized buccal mucosa for the reconstruction of the urethra. In this context, there exists a close cooperation with the Departments of Pathology, Otolaryngology, Head and Neck Surgery, Oral and Maxillo-Facial Surgery and the Max Planck Institute for Polymer Research.

As part of a working cooperation with an ESWL development team, the working group Renal and Bladder Stones (Nephrolithiasis) organizes annual international tutorials and workshops on the practical attributes of shock wave lithotripsy for kidney stone fragmentation. A key aspect of the working group, under the leadership of Dr. Neisius and in collaboration with Duke University in North Carolina, USA, is the further development of acoustic lens design for the next generation of electromagnetic lithotripters. The aim is ideal shockwave morphology at broadest focus possible. The first clinical studies on patients involving a new lithotripter are currently being initiated.


**FUTURE DIRECTIONS**

Our aim is to offer our patients optimal all-round care in accordance with the latest scientific findings. Our scientific projects will support basic research and the development of new therapeutic and diagnostic strategies in the many fields of Urology. For example, the objective of our uro-oncology research is to elucidate the molecular mechanisms of resistance to therapeutic agents in urological tumors in order to proceed towards personalized medicine. Furthermore, new strategies are being investigated to prevent metastases. In clinical trials, applications of new therapies are also being investigated for more successful health care.

**IMPORTANT PROJECTS**

**Detection of circulating tumor cells and -DNA (CTC, ctDNA) via the androgen receptor AR-V7 in mCRPC**

**PROJECT MANAGER:** PD Dr. C Thomas

**PROJECT DURATION:** 2014 - 2017

**Establishment and characterization of an in vitro-generated pre-vascularized mucosa equivalent based on collagen matrices**

**PROJECT MANAGER:** Prof. W Brenner, Prof. R Stein

**FUNDING:** MIC

**SUM:** € 28,000

**FUNDING:** MAIFOR

**SUM:** € 20,000

**FUNDING:** Geistlich Pharma Holding (Switzerland)

**SUM:** € 60,000

**FUNDING:** Fellowship of Rhineland-Palatinate

**SUM:** € 28,000

**PROJECT DURATION:** 2007 - 2018

**Improving the lens design and performance of a contemporary electromagnetic shock wave lithotripter**

**PROJECT MANAGER:** Dr. A Neisius

**FUNDING:** German Society of Urology

**SUM:** € 62,000

**PROJECT DURATION:** 2012 - 2016

**Role of E2EPF ubiquitin carrier protein in the pathogenesis of urological tumors**

**PROJECT MANAGER:** PD Dr. F Roos

**FUNDING:** MAIFOR

**SUM:** € 39,000

**PROJECT DURATION:** 2011 - 2019

**Role of Hedgehog signalling as predictor of the oncologic outcome in renal cell carcinoma**

**PROJECT MANAGER:** Dr. W Jäger, Prof. PC Black

**PROJECT DURATION:** 2013 - 2018

**FIG. 1:** Circulating tumor cells and -DNA as a prognostic marker are analyzed and correlated with patients outcome.

**FIG. 2:** Capillary-like structures in a tissue engineered buccal mucosa equivalent for urethra reconstruction
Both, basic and clinical research topics related to perioperative medicine reflect the core competence of anesthesiology. The state-of-the-art basic science research unit covers translational science on pulmonary and brain physiology as well as pathophysiology and cardiopulmonary resuscitation. The clinical research unit was inaugurated in cooperation with the IZKS Mainz, funded by the Federal Republic of Germany’s Ministry for Education and Research. This research unit realizes investigator-initiated trials, participation in international multicenter investigations, and studies initiated by pharmaceutical and/or medical equipment companies.

**OVERVIEW**

Both, basic and clinical research topics related to perioperative medicine reflect the core competence of anesthesiology. The state-of-the-art basic science research unit covers translational science on pulmonary and brain physiology as well as pathophysiology and cardiopulmonary resuscitation. The clinical research unit was inaugurated in cooperation with the IZKS Mainz, funded by the Federal Republic of Germany’s Ministry for Education and Research. This research unit realizes investigator-initiated trials, participation in international multicenter investigations, and studies initiated by pharmaceutical and/or medical equipment companies.

**HIGHLIGHTS**

**CLINICAL RESEARCH**

Neuromonitoring: During extreme Trendelenburg-position for robotic-assisted prostatic surgery cerebrovascular autoregulation was impaired over time, while cerebral oxygenation remained stable.

Airway management: A) The novel laryngeal mask LMA Supreme provided better handling and less injury than Ambu Gain. B) Topical anesthesia for awake fiberoptic intubation using the novel "Atomizer" set allowed faster awake intubation with less topical drug use and a higher patient comfort.

Fluid management/monitoring: New flow-related devices that are independent from an exact plethysmographic waveform were compared to standard monitoring.

MOPS: The Mainzer Outcome Predictor Study (>600 patients) revealed that pain after joint/back surgery persisted for up to 6 months with a need for analgesics/opioids. A predictor of postoperative pain is the occurrence of preoperative pain.

PROVHILLO: 60 patients from Mainz were included in this international multicenter trial. High levels of PEEP/recruitment maneuvers during open abdominal surgery did not protect against postoperative pulmonary complications.

RIPHeart: 116 patients from Mainz were included in this national multicenter trial which evaluated the effect of remote ischemic preconditioning for patients undergoing open heart surgery.

Emergency medicine: “Medical Task Force” Units (MTF) are deployed by the German federal government in order to deliver independent medical emergency service for up to 100 diseased/injured persons for up to 48 h. Using a full-scale human patient simulation a list of drugs for the MTF in due consideration of existing treatment guidelines and emergency medical practice in Germany was evaluated and defined.

**EXPERIMENTAL RESEARCH**

Traumatic Brain Injury: A) Propofol increases mortality and impairs neurological recovery/neuroregeneration after head trauma in rats. B) Pharmacological inhibition of HIF-1α by 2-methoxyestradiol (2ME2) mediates neuronal protection after brain trauma in mice.

Lung injury: A) Assisted spontaneous ventilation failed to improve pulmonary integrity in systemic sepsis-induced ARDS, although it was protective in ARDS caused by pulmonary lesions. B) The time dependency of cyclic alveolar recruitment was characterized by sophisticated real-time monitoring.

Cardiopulmonary-resuscitation: A) The calcium-sensitizer levosimendan improved cerebral oxygenation after cardiopulmonary resuscitation (rats/pigs). B) A MRI cerebral perfusion imaging setup was established that allows cardiopulmonary resuscitation in the MRI in pigs.

Rare diseases: L1 syndrome comprises rare neurodevelopmental disorders caused by mutations in the human L1CAM gene. In cell culture models molecules which play a role in the maturation and degradation of human pathological L1CAM proteins were identified.

CNS inflammation: In clinically relevant mouse models for diseases associated with neuroinflammation behavioral, cellular, and molecular changes were investigated.
**FUTURE DIRECTIONS**

Our ultimate goal is themed „zero preventable death“. Anesthesiology covers preclinical emergency medicine, perioperative anesthesia care, acute and chronic pain treatment, and critical care medicine. These objectives/tasks require charismatic basic and clinical research efforts, structured teaching, progressive caseload, and patient safety initiatives. Likewise, anesthesiology will only be accepted as a physician-based specialty as opposed to a service-provider, if important clinical questions are addressed applying principals of translational science.

The Department of Anesthesiology uses a multidimensional approach of linking basic and clinical science and the transfer of scientific evidence into clinical standards. As an example mechanical ventilation will be personalized according to the individual patient condition, based on pig MRI and dynamic CT research. Similarly, concepts of neuronal protection will be applied in patients with neuronal degeneration as evidenced by laboratory investigations. Clinical research related to preoperative mental status vs. postoperative surgical outcome and cutting edge airway management to eliminate asphyxia are other key goals of our scientific endeavor.

In defining a five year goal it is intended to further promote interdisciplinary networks of prevention and therapy including anesthesiology, surgery, neurology, and psychology (i.e. FTN, rmn²) in favor of personalized medicine as defined by Leopoldina National Academy of Science.
CLINICAL INSTITUTES AND DEPARTMENTS

Institute of Neuropathology
Institute of Human Genetics
Institute of Clinical Chemistry and Laboratory Medicine
Institute of Medical Biostatistics, Epidemiology and Informatics
Institute of Neurosurgical Pathophysiology
Institute of Neuroradiology
Institute of Pathology
Institute of Molecular Medicine
Department of Diagnostic and Interventional Radiology
Department of Nuclear Medicine
Department of Radiation Oncology and Radiation Therapy
Stroke is the second leading cause of death in industrial countries and is the greatest cause of disability. One focus of our research lies on testing neuroprotective and neuroregenerative therapeutic strategies in preclinical animal models of cerebral ischemia. During the last years, the hematopoietic growth factor G-CSF has become an interesting candidate due to its broad spectrum of effectiveness. Using a stroke model with G-CSF deficient mice, we could demonstrate that endogenous G-CSF obviously prevents the upregulation of excitotoxic AMPA receptors in adjacent and remote brain areas thus protecting the brain against ischemic injury (cooperative project with the Department of Neurology, University of Münster).

A second focus is on the antiphospholipid syndrome, an autoimmune disease characterized by high titers of auto-antibodies against phospholipids leading to thrombosis and consecutive infarcts. Many patients develop neurological symptoms in the absence of ischemia but the underlying mechanisms leading to these manifestations have not yet been identified. Using a mouse model of this disease we could identify a substantial loss of dendritic complexity in the hippocampus as structural basis for the cognitive deficits observed. This was a cooperative project with Prof. Chapman of the Department of Neurology (Sackler Faculty of Medicine), Tel Aviv University, Israel.

OVERVIEW

The Department of Neuropathology at the University Medical Center of the Johannes Gutenberg University in Mainz covers the complete spectrum of diagnostic services in neuropathology, not only applying histological techniques, enzyme histochemistry, immunohistochemistry and electron microscopy, but also adopting molecular methods for the diagnosis of biopsies concerning the central and peripheral nervous systems and skeletal muscle. Furthermore, our diagnostic spectrum includes cytological diagnosis of cerebrospinal fluid. Apart from biopsy examinations, we are also responsible for brain autopsies for Mainz University Medical Center and affiliated Academic Teaching Hospitals.

HIGHLIGHTS

Stroke: The narrow time window in the treatment of acute stroke is one major problem preventing successful translation into clinic up to now. In contrast, neurorestorative therapies have the attractive advantage of an extended time window to beneficially modulate brain regeneration after stroke. Future projects are planned to test the role and significance of enhanced dendritic plasticity in adjacent, remote and contralateral brain regions for an improved neurological outcome in preclinical stroke models.

Antiphospholipid syndrome: Future projects are designed to tackle two major issues. First, to detect ongoing intra-cerebral changes in the clinically silent period of the disease we will monitor the kinetics of disease progression between 4 to 16 weeks after immunization both at the behavioral and molecular level using a whole-genome transcriptome analysis. In addition, extensive quantitative and semi-quantitative assessment of the inflammatory and glial response will be done by immunohistochemistry and receptor autoradiography on multiple sections spanning representative regions of the whole brain to reliably detect also minor changes in the course of the disease. A grant application for this project has been submitted to the German-Israeli Foundation (GIF) together with Prof. Chapman of the Department of Neurology (Sackler Faculty of Medicine), Tel Aviv University, Israel.

FUTURE DIRECTIONS


**FIG. 1:** Areas of increased AMPA receptor ligand binding densities 24 hours after ischemic stroke in mice are labeled in red. This increase is prevented in G-CSF deficient mice suggesting a regulatory role of this growth factor eventually resulting in brain protection (Adapted from Paxinos and Franklin, 2001 with permission from Elsevier)

**FIG. 2:** Use of Methylation-Specific PCR has become a standard procedure in analysis of the MGMT-Promotor in malignant gliomas as one further small step towards personalized medicine.
Many functions of the healthy brain are regulated by local protein synthesis. Thus, the so-called synaptic plasticity representing the biology basis of learning and memory depends on the well-functioning and fine-tuned protein biosynthesis in the dendrites, axons and in particular the postsynaptic compartment. Deregulated local protein synthesis leads to diseases like Fragile X syndrome, Down syndrome and RETT syndrome. Similarly, deregulated local protein synthesis in neurons is critically involved in the pathogenesis of neurodegenerative diseases, especially HD. By studying patients with a rare genetic disease, the so called Opitz BBB/G syndrome, which is characterized by defects of the frontal midline and ID, we have identified a mechanism that regulates local protein synthesis in neurons. This mechanism is a promising and completely novel target for the development of specific therapies for HD, spinocerebellar ataxias, genetically caused ID and ASD. Based on these discoveries we are looking into the function of local protein synthesis in brain homeostasis and mental resilience and are studying the pathogenetic basis of the above-mentioned diseases. To establish an efficient therapy for late-onset neurodegenerative diseases, we are further very interested in understanding the molecular processes in particularly early phases of disease development in patients and animal models with monogenic forms of neurodegeneration. In addition, we have a well-established collaboration with one of the world-leading pharmaceutical companies to develop a causal therapy for HD and genetically caused ID. Another key research area represented by Prof. Ulrich Zechner focuses on epigenetic inheritance of behavior and experience. Transcriptomes and epigenetic marks of several brain regions are studied to determine the epigenetic impact of early life and social stress in mouse models. These research projects do not only address epigenetic signatures in the brain but also how they are inherited through the germline, in particular through sperm. This combines a research focus on the central nervous system with a research interest in reproductive medicine, where Prof. Zechner has a particular reputation. A third research team supervised by Dr. Jennifer Winter is interested in the molecular mechanisms of neurodevelopmental disorders presenting with ASD and/or ID. The functions of ASD causative genes recently identified by next generation sequencing studies are analyzed during brain development to understand the molecular mechanisms of ASD and provide a basis for future therapy development. In addition, Dr. Winter’s team studies how microRNAs control neuronal migration, which targets they regulate and if an ablation of these microRNAs rescues neuronal migration disorders.
**FUTURE DIRECTIONS**

We aim at understanding the pathological key events in the brain leading to genetically caused ID, ASD and/or epilepsy. We use biochemical pathways responsible for local protein synthesis as targets to establish molecules that can intervene with dysfunctional synaptic plasticity in the hope to utilize these as therapeutic strategies in patients with neurodevelopmental disorders presenting with ID, ASD and/or epilepsy as well as patients with monogenic forms of neurodegeneration such as HD. We are currently testing FDA approved molecules interfering with mTOR (mechanistic target of rapamycin) signaling for their ability to interfere with early phase disease progression in HD.

One further aim is to identify potential core epigenetic stress regulatory mechanisms in the mouse brain. Our studies will thus provide novel targets for subsequent in-depth analysis of the role of the identified genes and their epigenetic regulation in stress response, for the development of potential pharmacological interventions, and for epigenetic analysis in human cohorts.

In addition, we aim at understanding the brain-specific functions of newly identified ASD and/or ID causing genes. To study defective neuronal migration as one ASD- and/or ID-causative mechanism we further aim at determining which microRNAs are essential for neuronal migration and how we can target microRNA pathways to rescue neuronal migration defects. These studies will enable us to develop therapeutic strategies in the future.

**IMPORTANT PROJECTS** // MAX. 5

<table>
<thead>
<tr>
<th>Characterization of putative pluripotency-regulating genes and defining the role of germ cell-specific genes during reprogramming</th>
<th>Development of a novel therapy for Huntington’s Disease</th>
<th>Healing CAG-Repeat Disorder: Interference with the synthesis of aberrant protein in HD and SCA-modifier for disease progression and chances for therapy development</th>
<th>Molecular mechanisms of brain function in mTOR deficient intellectual disability syndromes</th>
<th>Spermatogonial stem cells and their potential</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROJECT MANAGER:</strong> Prof. U. Zechner</td>
<td><strong>PROJECT MANAGER:</strong> Prof. S. Schweiger</td>
<td><strong>PROJECT MANAGER:</strong> Prof. S. Schweiger</td>
<td><strong>PROJECT MANAGER:</strong> Prof. S. Schweiger</td>
<td><strong>PROJECT MANAGER:</strong> Prof. U. Zechner</td>
</tr>
<tr>
<td><strong>FUNDING:</strong> German Research Foundation (DFG)</td>
<td><strong>SUM:</strong> € 178,275</td>
<td><strong>SUM:</strong> € 2147-2158</td>
<td><strong>SUM:</strong> € 178,275</td>
<td><strong>FUNDING:</strong> German Research Foundation (DFG)</td>
</tr>
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<td><strong>PROJECT DURATION:</strong> 2011-2015</td>
<td><strong>PROJECT DURATION:</strong> 2011-2018</td>
<td><strong>PROJECT DURATION:</strong> 2013-2016</td>
<td><strong>PROJECT DURATION:</strong> 2013-2017</td>
<td><strong>PROJECT DURATION:</strong> 2011-2015</td>
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</tbody>
</table>
The research activities of the Institute are focused on the pathogenesis of arteriosclerosis and thrombosis and the development, application, and validation of novel diagnostic methods in laboratory medicine. The Institute is integrated in several research clusters of the University Medical Center, e.g. the Center for Thrombosis and Hemostasis (CTH), the Gutenberg Health Study (GHS), and the Center for Translational Vascular Biology (CTVB). Cooperation with the CTH has been further strengthened by the endowed professorship for Laboratory Medicine and Experimental Hemostasis which is supported by the German Society of Clinical Chemistry and Laboratory Medicine (DGKL). The professorship is held by Dr. Sven Danckwardt in the form of a joint appointment within the Institute and the CTH.

Research on the pathogenesis of arteriosclerosis has focused on the early development of the disease and the identification of biomarkers which identify persons at increased risk. We have analyzed the development of atherosclerosis in animal models with a focus on inflammatory mediators and antioxidant enzymes. The data from animal studies are associated with epidemiologic data obtained in humans. This permits a cross-validation of the two data sets, which strengthens the respective results. A very good example was the confirmation of human data identifying reduced glutathione peroxidase activity as a strong risk factor for myocardial infarction in a mouse model of glutathione peroxidase deficiency. Other research projects focus on the role of macrophage stimulation protein 1 (MSP-1) in atherogenesis and other inflammatory disorders.

Research on the pathogenesis of thrombotic events concentrates on the most common acquired thrombophilia, the antiphospholipid syndrome. While this autoimmune disease has been described more than 30 years ago the pathogenesis underlying the development of venous and arterial thrombosis is still not fully understood. Here we analyze the effects of human monoclonal antiphospholipid antibodies and immunoglobulin fractions isolated from patients with the antiphospholipid syndrome in in vitro and in vivo models. The human monoclonals are a unique resource which permits the unequivocal identification of signal transduction pathways involved in the antiphospholipid syndrome. Furthermore, the complementation of our in vitro data by in vivo thrombosis models available through the cooperation with the CTH provides additional insights into the pathogenesis. These experimental systems are completed by the investigation of clinical and epidemiologic cohorts, e.g. within the GHS.

Besides these basic research foci the Institute is involved in the development, improvement, validation, and quality control of clinical laboratory diagnostics which is a core competency of our specialty. The Institute is a reference laboratory for cerebrospinal fluid testing of the Reference Institute for Bioanalytics of the German Society of Clinical Chemistry and Laboratory Medicine. Development of laboratory diagnostics in the Institute applies to many different fields of laboratory medicine, but is focused again on cardiovascular diagnostics, haemostaseology, and molecular diagnostics. In particular in the latter area we have developed NGS based approaches to von Willebrand disease, hemoglobinopathies, and endocrine tumor syndromes. In particular, the latter area has grown as a joint effort with the endocrinology branch of the I. Dept. of Medicine and the Dept. of Surgery and several other institutions of the University Medical Center, which has become one of the largest centers in Germany caring for patients with endocrine tumors. Furthermore, the Institute supports clinical studies and also animal studies with the required laboratory tests.


Lackner KJ. Do we really need high-sensitive troponin immunoassays in the emergency department? Definitely, yes!. CLINICAL CHEMISTRY AND LABORATORY MEDICINE. 2014; 52 (2): 201-204.


**FUTURE DIRECTIONS**

In the coming years we will further strengthen the interaction between our basic research on arteriosclerosis and thrombosis with epidemiology and clinical research. The epidemiologic resources in Mainz provide a unique opportunity to validate our experimental data in humans which is a prerequisite for future translational projects. In particular, our research on the antiphospholipid syndrome will be expanded to epidemiologic analyses and clinical studies, some of which are already underway. Clinical studies will focus on the validation of promising novel diagnostic approaches derived from our experimental data to optimize the diagnosis of this complex and potentially devastating disorder.

A further focus will be the expansion of NGS approaches for diagnostics, in particular in hemostasology but also for the inherited tumor syndromes. The current status of the NGS platform for disorders in hemostasis will be further expanded as a technology platform within the Center for Thrombosis and Hemostasis (CTH). This implementation of novel state-of-the-art diagnostic methods which is not limited to NGS shall contribute substantially to further improve recognition of the CTH and the University Medical Center as a nationally recognized center for disorders of hemostasis.

**IMPORTANT PUBLICATIONS // MAX. 5**

**FIG. 1:** Effect of hydroxychloroquine on the translocation of TLR8 induced by RNA40.

**FIG. 2:** Detection of a causative mutation for multiple endocrine neoplasia type 2 in the RET protooncogene. RET, exon 11: c.1900T>C, Cys634Arg, het.

**IMPORTANT PROJECTS // MAX. 5**

**Functional analysis of regulated mRNA 3-end processing in the control of inflammatory processes, innate immunity and tumorigenesis**

**PROJECT MANAGER:** Prof. S Dandekarwad

**FUNDING:** German Research Foundation (DFG)

**PROJECT DURATION:** 2009 - 2016

**Genetic characterization of patients with inherited endocrine tumors**

**PROJECT MANAGER:** PD Dr. H Rossmann

**PROJECT DURATION:** 2011 - 2015

**In vivo model of thrombus induction in the antiphospholipid syndrome**

**PROJECT MANAGER:** Prof. K Lackner, Dr. D Manukyan

**PROJECT DURATION:** 2013 - 2015

**Pathogenesis of the Antiphospholipid Syndrom**

**PROJECT MANAGER:** Dr. N Müller-Calleja, Prof. K Lackner

**FUNDING:** Foundation for Pathobiocenomics and Molecular Diagnostics

**SUM:** € 77,400

**PROJECT DURATION:** 2002 - 2014

**The Gutenberg Health Study**

**PROJECT MANAGER:** Prof. T Münzel, Prof. S Blankenberg, Prof. K Lackner et al.

**FUNDING:** Academic Funding Institutions + Industrial Means

**PROJECT DURATION:** 2005 - 2016
The Institute for Medical Biostatistics, Epidemiology and Informatics (IMBEI) is supporting clinical research with methodological expertise and conducting methodological research and epidemiological studies. The IMBEI consists of the divisions: Biostatistics, Epidemiology, Informatics and Documentation, the German Childhood Cancer Registry and the Rhineland Palatinate Cancer Registry.

An interdisciplinary team of about 90 dedicated employees works at the IMBEI. The IMBEI is integrated into the training of students of medicine and is responsible for the courses “Biometry, Informatics and Epidemiology” and “Evidence-Based Medicine - How Knowledge is Generated”. In addition, the IMBEI offers a post-graduate and consecutive program leading to a master’s degree in epidemiology (M.Sc.).

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The Division “Biostatistics” is providing statistical support for research projects at the University Medical Center Mainz. The research of the division focusses on planning and evaluation of studies, in particular in the area of personalized medicine with high-dimensional molecular data. A further focus is on methods for the use of clinical registries and secondary data. We work closely together with clinical departments and the IZKS, and we offer a bioinformatics support interface via the Core Facility Bioinformatics (BIUM-MZ).

Epidemiologists at the IMBEI conduct population-based observational studies in the areas of radiation epidemiology, health services research and pediatric epidemiology. The focus for radiation epidemiology is on the health consequences of occupational and medical radiation exposure at low doses (such as workers in nuclear plant and patients with CT examinations). Cancer and cardiovascular disease are examined. The Division of Epidemiology and Health Services Research investigates the effects of diseases and health care on quality of life and mental health in patients with chronic diseases, the interplay of societal factors and health, and life course epidemiology. Other areas of interest are prevention of malignant diseases, occupational health risks, and evidence based medicine. The Division of Pediatric Epidemiology investigates health effects of transition from early childhood into school age and the impact of chronic diseases on school performance and academic achievement in children.

The Division of Medical Informatics is involved in three areas: “IT for collaborative research”, “IT innovation at the hospital” and “eHealth”. Under these headings are topics such as distributed systems, decentralized search algorithms for collaborative searching that maintain the data sovereignty of a centre, the use of mobile devices and Web 2.0 applications in patient-doctor interactions, the analysis and development of clinical documentation systems, establishing interoperability on the data and process levels, and empowering patients and citizens to actively take part in the data streams that affect them.

The nation-wide German Childhood Cancer Registry and the Rhineland Palatinate Cancer Registry are located at the IMBEI and built a rich resource for descriptive and analytic cancer epidemiology. With these data it is possible to determine incidence rates and changes in incidence over time as well as to identify regional clusters and calculate survival probabilities.
IMPORTANT PUBLICATIONS // MAX. 5


FUTURE DIRECTIONS

- Providing high quality statistical support for research projects
- Adapting statistical and bioinformatics methods for translational genomics
- Performing epidemiological research on causes of cancer, evaluation of prevention strategies and late effects after cancer
- Evaluation of changes in health care on national, regional level and local level (implementation of guidelines, guideline adherence, treatment adherence, stepped care models)
- Development of questionnaires to measure patient reported outcomes
- Establishing Pediatric Epidemiology as basis for improvements in Child Public Health and Health Services Research
- Developing concepts, methods and a generic IT architecture for the efficient and legally compliant operation of national medical research groups.
- Using data from cancer registries for descriptive and analytic epidemiological research

IMPORTANT PROJECTS // MAX. 5

Integrating clinical and molecular patient data into subgroup risk prediction models for enabling individualized therapy
PROJECT MANAGER: Prof. H Binder
PROJECT DURATION: 2014-2017

Need-based access to ambulatory psycho-social cancer counselling for men (BEZUG)
PROJECT MANAGER: Prof. S Singer
PROJECT DURATION: 2014-2016

PanCare projects (PanCareSurFup and PanCareLIFE): Pan-European studies on Childhood Cancer Survivor Care (Follow-up studies and studies on fertility, ototoxicity, and quality of life)
PROJECT MANAGER: PD Dr. P Kaatsch, Dr. D Grabow
FUNDING: European Union (EU)
PROJECT DURATION: 2011-2018

PASSOS: Personalized estimation of long-term outcomes after radiation exposure and orientations help for radiation help in medicine
PROJECT MANAGER: Prof. M Blettner, PD Dr. M Schmidt, Prof. H Schmidberger
PROJECT DURATION: 2013-2016

Projects of the German Cancer Consortium
PROJECT MANAGER: Prof. S Singer, Prof. F Ueckert
FUNDING: Federal Ministry of Education and Research (BMBF)
PROJECT DURATION: 2012-2015

FIG. 1
FIG. 2
FIG. 3

FIG. 2: Statistics in international context
FIG. 3: Members of the Institute
In 2014 the EU collaborative project ‘Neurocare’ entered its final state. Details can be found at http://neurocare-project.eu

Another important topic is the question how subdural hematomas induce secondary brain damage: below the hemorrhage an infarct-like zone develops which cannot be explained by the increase of intracranial pressure. We have confirmed that so far unidentified blood components trigger neuronal demise. Autologous blood and blood lysed by ultrasound damage the tissue, whereas a mediator function of plasma, red cells and thrombin could be excluded. Data indicate that a combination of increased intracranial pressure and blood components are responsible. The identification of the mediator mechanism would permit to find antagonists and hence to reduce the still high mortality of patients with acute subdural hematoma.

The institute is dedicated to cooperate with clinical partners to study current problems encountered in clinical practice. Main partners in 2014 were departments of neurosurgery, general surgery, and musculoskeletal surgery in Mainz and departments of neurosurgery in Heidelberg, Wiesbaden and Cologne. Our own dedicated research focusses on neurotraumatological pathophysiology as well as testing of monitoring systems for intensive care, electrode materials as well as new techniques of tumor detection. A BMBF grant was finally approved end of 2014 to establish a ‘blood-brain barrier on a chip’ in-vitro to test nanoparticles.

OVERVIEW

The institute was founded in 1990 with the aim to provide high quality research for clinical partners. It is equipped with operating rooms for small and large animals, labs for serial sections and immunohistochemistry, conventional and confocal microscopes, a cell culture lab etc. We focus on cooperation’s with clinical partners and have our own dedicated projects.

HIGHLIGHTS

In 2014 the EU collaborative project ‘Neurocare’ entered its final state. Details can be found at http://neurocare-project.eu

FUTURE DIRECTIONS


**Fig. 1:** Rat cortex stained for astrocytes (GFAP, red), microglia (IBA-1, pink), IL-1 (green) and nuclei (DAPI, blue). Result from EU-project

**Fig. 2:** Logo of the EU collaborative project 'Neurocare'

**Important Projects // Max. 5**

<table>
<thead>
<tr>
<th>Project</th>
<th>Project Manager</th>
<th>Funding</th>
<th>Sum</th>
<th>Project Duration</th>
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</thead>
<tbody>
<tr>
<td>Effects of the cerebral/ intracellular and the systemic thrombin system in the pathophysiology of intracerebral hemorrhage</td>
<td>Dr. B Alessandri, Prof. P Horn, Prof. S Danckwardt</td>
<td>European Union (EU)</td>
<td>€ 329,609</td>
<td>2013-2015</td>
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<tr>
<td>EU-project ‘Neurocare’</td>
<td>Prof. O Kempski</td>
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<td>Post-hemorrhagic hydrocephalus (PHH) after ‘germal matrix’-intraventricular hemorrhage (GM-IVH) in preterm infants</td>
<td>Dr. B Alessandri</td>
<td>The German Society of Neurosurgery (DGNC)</td>
<td>€ 10,000</td>
<td>2013-2015</td>
</tr>
<tr>
<td>Therapeutic portential of argon gas after subarachnoid hemorrhage in rats</td>
<td>Dr. N Keric</td>
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<td></td>
<td>PROJECT MANAGER: Dr. B Alessandri</td>
<td>FUNDING:</td>
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<td>PROJECT DURATION: 2013-2015</td>
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<td>PROJECT DURATION: 2013-2015</td>
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</table>
### OVERVIEW

In Rhineland-Palatine the Institute of Neuroradiology is the only university department that provides complete diagnostic and therapeutic neuroradiological assessment throughout the year (24/7/356).

In 2014 approximately 9,800 CT, 3,800 MRI (including fMRI, perfusion and spectroscopy) were performed as well as >450 angiographies, including interventional procedures. The latter comprise mainly coiling of aneurysms after life-threatening intracranial hemorrhages, mechanical thrombectomy in stroke patients, arterial embolisation of cerebral and spinal arteriovenous malformations and fistulae (AVMs/AVFs) or head and neck tumors. The focus of digital imaging contains beside fMRI the implementation of arterial spin labeling technique in special questions of brain perfusion (i.e. sick headache).

### HIGHLIGHTS

In cooperation with Prof. Kalisch, Director of the NeuroImaging Center (NIC) of the Focus Program Translational Neurosciences (FTN) investigations functional MRI is evaluated using optically presented memory paradigms, as well as diffusion-tensor-imaging (DTI) in patients with early stage Alzheimer disease. Additionally the database contains standard as well as DTI- and susceptibility-weighted images of healthy elder people in order to have a reference-collective for investigation of cerebral dysfunction in dementia patients.

A further study, performed together with the Clinic of Psychosomatic Medicine and Psychotherapy, investigates the impact of multimodal stationary acute therapy on the capacity of mentalisation using fMRI and is evaluated in patients with somatization dysfunction. We want to know if there is a difference in performance and functional neuroanatomy in mentalisation processes between the patients and a (concerning age, gender, and educational background) matched control group of healthy people. Additionally we wish to research whether or not a group multimodal psychotherapy over 8 to 12 weeks in stationary environment, focused on patients with somatization dysfunction, will lead to a better mentalisation capacity.

Together with other groups (i.e. ophthalmology, rheumatology, neurosurgery) we study a reliable biopsy planning in patients with giant cell arteritis. The basic data of high resolution imaging of the temporal artery are directly transmitted in a neuro navigation system.

In several clinical trials we evaluate the effectiveness of new medications in cases of multiple sclerosis and glioblastoma using standardized MR-protocols. In cooperation with the villa metabolica new investigations concerning arterial pathologies in patients with mucopolysaccharidosis are performed. Other clinical studies focus new clinical indication brain perfusion measurement with arterial spin labeling technique in special questions of cerebral blood flow (i.e. sick headache).

MR research on small animals is also carried out in conjunction with interdisciplinary groups e.g. anaesthesiology, nuclear medicine and neurosurgery.
**IMPORTANT PUBLICATIONS // MAX. 5**


**FUTURE DIRECTIONS**

**INTERVENTIONAL NEURORADIOLOGY:**
Implementation of new mechanical devices for different indications (stent retriever, stents for arterial stenosis/aneurysms)

**IMAGING:**
Upgrading of ASL (arterial spin labeling) methods and clinical indications

**CLINICAL STUDIES:**
1. in patients with metabolic accumulation diseases (i.e. mucopolysaccharidosis -MPS-) concerning arterial affection (in cooperation with villa metabolica of the UMM),
2. in the follow-up of infantile malign tumors with the focus on the development of cerebral cavernomas (in cooperation with the Department of Pediatrics of the UMM)

**IMPORTANT PROJECTS // MAX. 5**

- A multi-center double-blind parallel-group placebo-controlled study of the efficacy and safety of teriflunomide in patients with relapsing Multiple Sclerosis who are treated with interferon-beta.
  **PROJECT MANAGER:** Prof. F. Zipp, Dr. S. Schadmand-Fischer, PD Dr. AP Barreiros-Clara et al.
  **PROJECT DURATION:** 2011 - 2014

- A Radomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of ocrelizumab in comparison to interferon Beta-1a (Rebif) in patients with relapsing Multiple Sclerosis.
  **PROJECT MANAGER:** Prof. F. Zipp, Prof. W. Mueller-Forell
  **PROJECT DURATION:** 2012 - 2014

- Distribution and concentration of ferritin in cortical and subcortical brain parenchyma and its age- and gender correlation.
  **PROJECT MANAGER:** G. Vucorovic, Dr. J. Gawehn
  **PROJECT DURATION:** 2012 - 2014

- MR-based biomarker in diagnosis and follow-up of Niemann-Pick C-disease.
  **PROJECT MANAGER:** Prof. W. Mueller-Forell, Dr. F. Mengel, Y. Amarose et al.
  **PROJECT DURATION:** 2012 - 2015

- SAN FILIPPO (MPS III B)
  **PROJECT MANAGER:** Prof. W. Mueller-Forell, Dr. A. Arash
  **PROJECT DURATION:** 2012 - 2015

**FIG. 1:** Functional magnetic resonance (fMRI) of a patient with malignant brain tumor (glioblastoma), while moving the right hand, demonstrating the close vicinity of the tumor (light) to the motor function (red).

**FIG. 2:** Pyramidal tract tractography of the same glioblastoma patient.

**FIG. 3:** MR spectroscopy (CSI) of the same patient, showing the high choline (marker of proliferation) in the tumor.

**FIG. 4:** MR-spectroscopy (SV) of the tumor with low level of NAA (marker of loss of myelinated fibers).
INSTITUTE OF PATHOLOGY

Director:
Professor
Charles James Kirkpatrick

University Medical Center Mainz
Langenbeckstr. 1
D-55131 Mainz
phone: +49 (0) 6131 17-7305
kirkpatrick@uni-mainz.de
www.unimedizin-mainz.de/pathologie

OVERVIEW

The Institute of Pathology provide central service for histo-pathological, cytological, molecular-pathological and ultrastructural diagnosis for the University Medical Centre Mainz. Actually, in the Institute specimens of more than 60,000 patients are studied annually. Beneath the classical methods of histological, cytological, immunohistological and immunocytological analyses, which are all performed in an automated standardized manner, the Institute provide modern methods in molecular biological techniques including Laser Capture Microdissection. Furthermore, the Institute of Pathology provides the only complete electron microscopical laboratory at the clinic campus for both transmission and scanning electron microscopy with the possibility for ultrastructural tomography. In this context, in 2012 a new transmission electron microscope with a high-resolution digital camera was installed based on co-funding of the DFG and the state government. Since 2007, the Institute of Pathology in Mainz has been accredited. Thus, we ensure for all, our patients, our referring physicians and our research partners for high quality of diagnoses and analyses. By that we serve for collaboration in clinical and translational research with various national and international clinical partners. Actually, we established a Tissue-biobank based on a fully automated robotic system for tissue asservation at -196°C (Smartfreezer®) enriched with a dynamic monitoring system and automatic alert-system. Furthermore, we combined the biobank-data management system with other data bases such as the hospital information system, the management system of the laboratory chemistry and in near future with the clinical tumour documentation system to provide high quality, data rich specimens.

HIGHLIGHTS

The REPAIR-lab represents the research laboratory of the institute, which use life science approaches to study cell and tissue interaction with biomaterials. The REPAIR-Lab is one of the founding laboratories in the European Commission Network of Excellence EXPERTISSUES, now the European Institute of Excellence on Tissue Engineering & Regenerative Medicine. The German Federal Ministry of Education & Research (BMBF) awarded the REPAIR-lab funding for a German-Chinese Young Investigator Group in Regenerative Medicine for 5 years (2007-2012). The research team has also been part of two major Priority Programmes of the German Research Foundation (DFG), namely SPP1100: Interface between material and biosystem [2001-2007] and SPP1313: Biological responses to nanoscale particles: „Bio-Nano-Responses“ [2008-2013].

THE INSTITUTE IS FOCUSSED ON THE FOLLOWING:

• in vitro models of biomaterial vascularization

The REPAIR-lab has established quantifiable in vitro models to understand how various factors modulate this essential biological reaction, especially in the context of biomaterials and tissue engineering. We are using a number of human endothelial cell types, both primary and in the form of permanent cell lines, to investigate various biomaterial scaffolds for their suitability to support vascular growth. Endothelial function is studied using state-of-the-art cell and molecular biological methods.

• in vitro models for bone tissue engineering

It has become apparent that bone growth is dependent on adequate vascularization, which is a focus of our research. In our in vitro approach we investigate how osteoblasts interact with endothelial cells, with a view to better understanding of the regenerative process. Co-culture systems have been established and were used within the scope of two European projects (AUTOBONE & HIPPOCRATES).
**IMPORTANT PUBLICATIONS // MAX. 5**

Dohle E, Bischoff I, Boese T et al. Macrophage-mediated angiogenic activation of outgrowth endothelial cells in co-culture with primary osteoblasts. EUROPEAN CELLS & MATERIALS. 2014; 27: 149-165.


- in vitro studies on human adult stem cells
- in vitro models for NanoMedicine
- in vitro models for cartilage tissue engineering
- in vitro models for respiratory tract regeneration

The development of the field of NanoMedicine involves various concepts such as targeted drug- and gene delivery using engineered nanoparticles. Relevant portals of entry are the air-blood barrier (ABB) or the blood-brain-barrier (BBB). We have spent many years setting up functional co-culture systems using human cells to simulate these barriers. Also of relevance are environmental micro- and nanoparticles. Our in vitro models are being used to study nanotoxicity. Two EC projects, CellNanoTox (2006-2009) & NanoBioPharmaceutics (2006-2010), as well as a Priority Programme (SPP1313; 2008-2013) of the German Research Foundation (DFG) were concerned to these issues. Now beginning is a European integrated training network (ITN), called SNAL (Smart Nano-objects for Alteration of Lipid-bilayers), which will run from 2014 to 2017 and will be launched.

- in vitro models for reconstructive maxillofacial surgery
- in vitro studies on human adult stem cells
- in vitro models for respiratory tract regeneration

We are isolating endothelial progenitor cells (EPCs) from human peripheral blood with a view to unravelling the steps in lineage differentiation, their interactions with three-dimensional scaffolds and matrices for tissue engineering, as well as their possible integration into local microcirculation networks. More recently, in the scope of an EU project to tissue engineer an intervertebral disc (Disc Regeneration, 2008-2012) human mesenchymal stem cell cultures were set up.

**IMPORTANT PROJECTS // MAX. 5**

<table>
<thead>
<tr>
<th>Cell activity &amp; bone regeneration in biofunctionalized resorbable scaffolds made of polymer- &amp; Mg-toughened Ca phosphate-based nanocomposites</th>
<th>PROJECT MANAGER: Prof. CJ Kirkpatrick, Dr. R Unger</th>
<th>FUNDING: German-Israeli Foundation (GIF)</th>
<th>SUM: € 100,000</th>
<th>PROJECT DURATION: 2012-2014</th>
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<tbody>
<tr>
<td>Expression &amp; function of the non-neuronal cholinergic system in murine embryonic stem cells</td>
<td>PROJECT MANAGER: Prof. J Wessler</td>
<td>FUNDING: German Research Foundation (DFG)</td>
<td>SUM: € 80,000</td>
<td>PROJECT DURATION: 2010-2015</td>
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<tr>
<td>Resorbable multimodal hybrid materials for regenerative medicine, especially for reconstructive maxillofacial surgery</td>
<td>PROJECT MANAGER: Dr. E Dohle</td>
<td>FUNDING: German Research Foundation (DFG)</td>
<td>SUM: € 103,500</td>
<td>PROJECT DURATION: 2013-2014</td>
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<tr>
<td>Smart Nano-objects for Alteration of Lipid-bilayers (SNAL)</td>
<td>PROJECT MANAGER: Prof. Dr. S Ghanaati, Prof. CJ Kirkpatrick</td>
<td>FUNDING: European Union (EU)</td>
<td>SUM: € 444,138</td>
<td>PROJECT DURATION: 2014-2018</td>
</tr>
</tbody>
</table>
OVERVIEW

We focus on autoimmune diseases such as multiple sclerosis (MS) as well as other diseases that affect the gut, skin and heart. In addition to inflammatory/autoimmune diseases, our institute is also interested in basic mechanisms that control the function of the immune system, including signal transduction pathways, primary investigating molecules that control the activation of the nuclear factor kappa B (NFkB) transcription factors, in their involvement in malignant diseases.

Much of the research in the IMM involves genetically manipulated animals, using a technology termed conditional gene targeting. For example, we generated mice, which lack the gene coding for the IL-17 receptor, to study how the inability of these cells to respond to IL-17 influences autoimmunity.

HIGHLIGHTS

In November 2014 the 12th International Congress of Neuroimmunology was held in Mainz. Ari Waisman and Frauke Zipp (Neurology) were the Conference Chairs of this meeting that over 1000 people attended. http://www.isnicongress.org

The collaboration between the Institute for Molecular Medicine and the Cardiology, II. Medical Department, has been intensified and it was shown that Psoriasis and Cardiovascular Diseases are highly correlating. This was shown in two publications.

FUTURE DIRECTIONS

The main goal of the Institute for Molecular Medicine is to establish a new SFB in Mainz in the field of Inflammation Research.

OTHER SCIENTIFIC GOALS:

- To understand the molecular mechanisms governing the induction of autoimmune inflammatory diseases.
- To study the role of deubiquitinating enzymes in inflammation and B cell function.
- To study skin and lung immunity as dictated by dendritic cells and Langerhans’s cells.

FIG. 1: Analysis of the LC network in DC-Ecaddel and control mice. (A) Epidermal sheets of 18 weeks old DC-Ecaddel and control mice were stained for MHC-II and the LC network was analyzed by fluorescence microscopy. (B) Absolute LC numbers of DC-Ecaddel and control mice at different ages as determined by FACS analysis.


**IMPORTANT PROJECTS // MAX. 5**

**CRC-TR-128: Initiating/effector versus regulatory mechanisms in Multiple Sclerosis – progress towards tackling the disease**
**PROJECT MANAGER:** Prof. F. Zipp  
**FUNDING:** German Research Foundation (DFG)  
**SUM:** € 178,000  
**PROJECT DURATION:** 2012 - 2016

**G protein-mediated signaling in immune cells: implications for Neuroinflammation**
**PROJECT MANAGER:** Dr. F. Kurschus  
**FUNDING:** German Research Foundation (DFG)  
**SUM:** € 178,000  
**PROJECT DURATION:** 2012 - 2016

**Initial Training Network for Neurological disorders orchestrated by cytokines**
**PROJECT MANAGER:** Prof. A. Waisman  
**FUNDING:** European Union (EU)  
**SUM:** € 666,000  
**PROJECT DURATION:** 2013 - 2016

**Role and function of microglia cells in autoimmune CNS inflammation**
**PROJECT MANAGER:** Prof. A. Waisman  
**FUNDING:** German Research Foundation (DFG)  
**SUM:** € 592,800  
**PROJECT DURATION:** 2010 - 2016

**The role of the deubiquitinating enzymes Cyld and A20 in B cell lymphomagenesis**
**PROJECT MANAGER:** Dr. N. Hövelmeyer  
**FUNDING:** German Research Foundation (DFG)  
**SUM:** € 770,000  
**PROJECT DURATION:** 2010 - 2017

**FIG. 2:** T cell effector mechanisms in EAE. T cells enter the CNS via postcapillary venules and have to cross the blood brain barrier, composed of endothelial cells, the basement membrane, and the parenchymal basement membrane of the glia limitans. They often accumulate in the perivascular space between the two basement membranes. Penetration of the parenchymal basement membrane is facilitated by matrix metalloproteases (MMP2 and MMP9) secreted by T cells, macrophages, and neutrophils. T cells in the CNS are reactivated by macrophages, DCs, and B cells presenting myelin autoantigens and secrete, among others, the cytokines IL-17, IFN-γ, TNF and GM-CSF. IL-17 induces secondary cytokines, chemokines and MMPs, which help in the breakdown of BBB and in the attraction of monocytes and neutrophils. GM-CSF (together with G-CSF) has long-distance effects on neutrophil mobilization, but possibly also has direct influences on inflammatory monocytes and their capacity to polarize T helper cell differentiation. It probably works additionally by inhibiting Treg function via IL-6 induction in myeloid cells. Cytokines secreted by T cells also influence astrocytes and oligodendrocyte precursor cells (NG2 cells) in their differentiation and in their proliferation capacity. IFN-γ and TNF may have direct toxic effects on ODC, but most of all stimulate myeloid effector cells such as inflammatory monocytes, macrophages, and neutrophils. Stimulation of these cells leads to damage of myelin by the secreted reactive oxygen species followed by myelin attack and ingestion by macrophages. Macrophages are also activated by antibodies bound to myelin via FC receptors and by the complement products activated by these antibodies. Myelin-specific antibodies may be released from antibody-secreting plasma cells or plasma blasts originating from myelinspecific B cells activated by T cells in the CNS or in peripheral lymph nodes. Th17 cells damage axons also directly by secretion of glutamate, whereas cytotoxic CD8+ T cells secrete perforin, granzymes, and IFN-γ to directly attack ODCs. Abbreviations: E: Endothelial cell; P: Pericyte; T: T cell; B: B cell; PC: Plasma cell; Mc: Monocyte; Ac: Astrocyte; N: Neutrophil, MΦ: Macrophage; ODC: Myelin forming oligodendrocyte; DC: Dendritic cell; ROS: Reactive oxygen species.
OVERVIEW

Radiology is a medical specialty that employs the clinical and scientific use of imaging methods to both diagnose and treat disease.

Fields of activity of the clinic for diagnostic and interventional radiology:

Diagnostic methods
(all acquired image data are in digital format)
- Radiography (Conventional Radiology)
- Radioscopy (Fluoroscopy)
- Computed Tomography (256-slice CT)
- Magnetic Resonance Imaging (1.5 Tesla - 3.0 Tesla), Non-proton MRI (Helium-3, fluorinated gases)
- Digital Subtraction Angiography (DSA)
- Sonography
- Mammography

Therapy methods
(full spectrum of Interventional Radiology care):
- Balloon dilatation and stent implantation
- Occlusion of blood vessels
- Percutaneous tumor ablation
- Biliary tract interventions
- Biopsies and marking methods
- Percutaneous drainages

Patients treated with methods of interventional radiology which require in-patient monitoring are taken care in the ward of the Department of Radiology (which is used together with the Department of Radiooncology).

General responsibilities and specialties:
- Radiology Information System (Database since 1988)
- Picture-Archiving and Communication System (PACS) (Database since 1998)
- Teleradiology
- Clinical Trial Center Radiology
- Section of Medical Physics
- Section of Pediatric Radiology

HIGHLIGHTS

AREAS OF RESEARCH:
- Lung imaging using MRI and CT
- Interventional vascular and tumor therapy
- IT and image post-processing in radiology
- Innovative MRI techniques


Kloeckner R, Ruckes C, Kronfeld K et al. Selective internal radiotherapy (SIRT) versus transarterial chemoembolization (TACE) for the treatment of intrahepatic cholangiocellular carcinoma (CCC): study protocol for a randomized controlled trial. TRIALS. 2014; 15.


**Importantly Projects // Max. 5**

Assessment of Aortic Annulus Size at MD-CT: Influence of Heart Phase and Measurement Method in Patients before TAVI
PROJECT MANAGER: Prof. K Kreitner, Dr. Y Yang
PROJECT DURATION: 2014 - 2016

Cardiac magnetic resonance enables diagnosis in 90% of patients with acute chest pain, elevated biomarkers, and unobstructed coronary arteries
PROJECT MANAGER: Prof. K Kreitner
PROJECT DURATION: 2012 - 2015

Multichannel coils for MRI of the lung
PROJECT MANAGER: Prof. L Schreiber
FUNDING: Rhineland-Palatinate Foundation for Innovation.
SUM: € 230,096
PROJECT DURATION: 2011 - 2014

Pretherapeutic MR-imaging of pectus excavatum and pectus carinatum chest wall
PROJECT MANAGER: Prof. G Staatz
PROJECT DURATION: 2013 - 2014

Structured reporting in Radiology
PROJECT MANAGER: Prof. P Mildenberger
PROJECT DURATION: 2014 - 2018

**Important Publications // Max. 5**

**FIG. 1:** 64-channel cardiac phased array coil for 3T (left), four-chamber view at acceleration factor R= 5(middle), and shot-axis view at R=5 (left) in a male subject (Age=55 years, height=162cm, weight=103kg) using a bSSFP cine sequence (FA/Res/Slice = 57°/174x208/334x339mm/6mm)

**FIG. 2:** Hepatic angiography during a TACE procedure showing two hypervascular HCC nodules before selective chemoembolization

**FIG. 3:** Interventional therapy of infrarenal aortic aneurysm by stentgraft implantation

**FIG. 4:** Research efforts in the Section of Pediatric Radiology have contributed to an implementation of radiation-free pretherapeutic MR imaging of chest wall deformities instead of dose-intensive CT scans. The image shows a pectus excavatum deformity with accurately delineable osseous structures in a 14-year old girl (T1-VIBE sequence). Our results have been published in European Radiology (Lollert A, Funk J, Tietze N, et al. Morphologic assessment of thoracic deformities for the preoperative evaluation of pectus excavatum by magnetic resonance imaging. Eur Radiol 2015; 25:785-91, published online Oct 2014).
The current research projects of our neuro nuclear medicine group, which is part of the Focus Program Translational Neuroscience (FTN), are focused on two main aspects:

1. The functional relationship between the opioidergic neurotransmission and the dopaminergic reward system in experimental alcohol challenge and addiction.
2. The role of the endocannabinoid system in impulsivity using dedicated animal models and (subsequently) experimental challenges in healthy volunteers.

These interdisciplinary investigations are performed by means of PET-CT, animal PET and animal PET-MRI. The radiotracers used are synthesized in our radiochemical lab as well as in collaborating external laboratories.

For example, the clinical value of F-DOPA-PET-CT as an imaging screening modality for asymptomatic patients from family members with paraganglioma syndromes carrying an SDHx mutation was investigated. Preclinical research has a main focus on investigation of targeted internal therapy with alpha- and beta-emitting isotopes and their radiobiology in vivo and in vitro.
FUTURE DIRECTIONS

Based on the preclinical investigations on cannabinoid neurotransmission, in the next step our concept provides a translational approach to particular patient groups. We therefore plan to investigate patient collectives with disturbed impulse control (borderline personality disorder) as well as patients suffering from chronic complex regional pain syndrome (CRPS). The human PET experiments will be performed in close interdisciplinary collaboration with the Departments of Psychiatry and Neurology.

In Prostate Cancer a highly specific cell membrane protein called Prostate-Specific Membrane-Antigen (PSMA) will be used for improved diagnostic by Gallium-68-PSMA PET/CT and as target for experimental therapy with Lutetium-177-PSMA.

Unique physical properties of alpha-emitting nuclides promise clinical advantages in targeted therapies. In view of efficacy and possible side effects we plan to investigate molecular pathways following irradiation with alpha particles in normal blood cells and tumor cells.

FIG. 1: SPECT-CT der neuesten Generation

IMPORTANT PROJECTS // MAX. 5

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Project Manager</th>
<th>Funding</th>
<th>Sum</th>
<th>Project Duration</th>
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<tr>
<td>Changes in Cerebral Glucose Metabolism in Rats after THC-Administration by PET-CT</td>
<td>Prof. R. Urban</td>
<td>€ 2,000</td>
<td>2013 - 2015</td>
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<tr>
<td>Opioidergic modulation of alcohol action on the dopaminergic reward-system (DFG)</td>
<td>PD Dr. C. Fehr, Prof. M. Schreckenberger</td>
<td>€ 230,000</td>
<td>2011 - 2014</td>
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<tr>
<td>Quantitative PET imaging of the endocannabinoid system in behaviorally characterized animal models</td>
<td>Dr. I. Miederer</td>
<td></td>
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<tr>
<td>The endocannabinoid system and impulsivity: Investigations on the cerebral CB1-receptor status in normal and disturbed impulsivity</td>
<td>Prof. M. Schreckenberger, Dr. I. Miederer</td>
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<tr>
<td>Molekulare in vivo-Bildgebung zur Evaluierung nanodimensionaler Drug-Delivery-Systeme (SFB 1066 / Q3)</td>
<td>Dr. P. Bilümer, PD Dr. M. Miederer, Prof. F. Rösch</td>
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Important Publications


The radiation exposure during breast cancer radiotherapy was compared by means of biological dosimetry in patients who were treated either with three-dimensional conformal radiotherapy (3D-CRT) or with intensity modulated radiotherapy (IMRT). These differing techniques of radiotherapy are associated with varying distributions of dose in the normal tissue of the patient and thus different risks for radiation-induced stochastic late effects. To this end DNA damage was quantified as radiation-induced DNA double-strand breaks (γ-H2AX foci) and chromosomal aberrations in peripheral leukocytes after the first fraction of radiotherapy. Only the rate of γ-H2AX foci after 3D-CRT showed a linear correlation with the administered physical integral dose (Fig. 1 A and C). IMRT significantly increased the level of DNA damage compared to 3D-CRT in both assays with dependence on exposure time (Fig. 1 B and D). In conclusion, we show that different techniques of breast cancer radiotherapy cause significant variations in the biologically relevant radiation burden of patients. Compared to 3D-CRT, IMRT increased the integral radiation load of the patient by elevating the low-dose exposure of the normal tissue. Therefore, the potential risk for radiation-induced adverse late effects is presumably higher for IMRT than for 3D-CRT which should find consideration in the clinical practice of RT with regard to the increasing use of IMRT, specifically for the treatment of children and young adults.

**MULTICOLOR IMMUNE FLUORESCENCE IN TUMOR TISSUE**

The impact of the tumor microenvironment on radiation resistance, tumor invasiveness, metastasis and immune activation is evaluated in several retrospective studies. Progression free survival and local control of treated patients are correlated with biological factors in the original tissue slides. In situ analyses of protein expression patterns using multiplex immunofluorescence assays allow to generate data in human tumor tissue in a manner similar to flow cytometry. In contrast to the latter method, however, additional information on the spatial arrangement of cell populations can be obtained. This method enables us to characterize recurrent phenotypes (molecular tumor subtypes) using a combination of antigens and to carry out analyses specifically within the epithelial-neoplastic and/or the tumor stroma compartments. Currently analyses have been performed in brain tumors, cancers of the head and neck region and gynecologic tumors.

**PASSOS STUDY: RETROSPECTIVE ANALYSIS OF CARDIAC DOSE DURING RADIOTHERAPY AND LATER CARDIAC EVENTS**

400 survivors after breast cancer radiotherapy have been evaluated retrospectively. Doses to cardiac sub-structures have been identified by recalculation of old planning data. Cardiac events in later life are being identified through contacting the general practitioners of the patients.
**FUTURE DIRECTIONS**

The ISIMEP project will be followed by a new study called ISIBELA: Survivors of pediatric cancer will be asked to donate blood samples and fibroblasts. In these cells markers of individual radiosensitivity, pathways of DNA repair and risk factors for genetic instability will be analyzed. This project will be funded by the BMBF starting in September 2015. The investigations will be performed in cooperation with the IMBEI at the University Medical Center, The Dept. of Biology at the University of Darmstadt and the Dept. of Epidemiology at the University of Rostock.

The PREFERE study will recruit approximately 1000 patients per year in a multicenter setting of 100 participating centers. Half of the recruited patients will receive external beam radiotherapy or brachytherapy. Treatment plans of these patients are collected in the form of DICOM-RT files and analyzed at the Department of Radiotherapy in Mainz. The quality of treatment planning in this multicenter study will provide new data on patient care. At a later stage the dose distributions in individual patients will be compared with quality of life outcome within the study. The required technology for the exchange of radiotherapy data between different centers has been well established an will be used in further clinical trials.
INSTITUTES AND DEPARTMENTS OF DENTAL MEDICINE

Institute of Dental Materials Science and Technology
Department of Oral and Maxillofacial Surgery
Department of Dentofacial Orthopedics
Department of Prosthodontics
Department of Oral Surgery
Department of Operative Dentistry
OVERVIEW

At present the organization of courses, teaching and testing is primarily based on e-learning. By questionnaires our study in the field of dental propaedeutics evaluated the use and improvement possibilities of Internet-based e-learning as a multimedia tool of learning and teaching processes. Research activities of the Institute focus on scientific work referring to intolerance of patients against dental materials such as plastics and alloys. In case of partial dentures, the abutment kinematics and the pressure of the denture base are examined. Using a universal testing facility we determine the bond strength of the metal-ceramic compound and the metal-plastic compound. Contemporaneously the influence of denture adhesives on prosthetic stomatopathy is explored.
Evaluation of cytotoxicity of modified implant-capable titanium-surfaces on human cells
PROJECT MANAGER: Prof. B Al-Nawas, G Burgard
PROJECT DURATION: 2013 - 2015

Evaluation of the practical curriculum in pre-clinical section of the Clinic for Dental, Oral and Maxillofacial Diseases, University Medical Center Mainz
PROJECT MANAGER: Prof. J Kraft, Dr. V Büsser
PROJECT DURATION: 2012 - 2014

In vitro Analysis of the internal fit of CAD-CAM manufactured Zirkondioxidframework of fixed partial Dentures using different CAD-CAM-Systems.
PROJECT MANAGER: Prof. H Scheller, S Debatin
PROJECT DURATION: 2012 - 2014

Oral health- and oral hygiene situation of Old person and senior citizen’s home inhabitants in the space Mainz
PROJECT MANAGER: Prof. J Kraft, Dr. J Pistorius
PROJECT DURATION: 2012 - 2015

Retrospective study of root resorption after orthodontic treatment on panoramic radiographs
PROJECT MANAGER: Prof. H Wehrbein, Dr. A Schambberger
PROJECT DURATION: 2011 - 2014
The focus of research is: tumor biology, reconstructive surgery, implantology, and bone substitutes. Next to clinical research cell culture methods and animal research is used in close cooperation with the Institute of Physiology and Pathophysiology, the Max Planck Institute for Polymer Research and the Biomaterials, Tissues and Cells in Science group (BiomaTiCS).

**RESEARCH AREAS ARE:**

- OraIer lichen planus, orale lichenoid lesions, graft-versus-host reaction, and head and neck cancer: Quality of life
- Squamous cell cancer: Tumorbiology, therapy improvement (analyzed markers: PON-2, GSTM1, VEGF, p63, p73, lactat, ATP, glucose, pyruvat, GLUT1/3 and MCT1/4)
- Bisphosphonate-associated osteonecrosis and osteoradionecrosis: Pathology, treatment with in vitro and in vivo studies
- Bone substitutes: Evaluation and development of injectable hydrogel (2D and 3D cultures)
- Dental, enosseous implants: Material research (titanium alloys, circoncia, PEEK, surface modification with titanoxid, Ca-hydroxid or proteins) with in vitro and in vivo studies
- Alloplastic bone substitutes: Biocompatibility (gen and protein expression and SEM) with in vitro and in vivo studies
- Complex defect reconstruction: Development of 3D CAM/CAD solutions
- Deformity and orthognathic surgery: Evaluation of long-term success of procedures and adjuvant therapies

**FIG. 1:** Virtual planing of mandibular reconstruction with free microvascular fibula graft
FUTURE DIRECTIONS

The department is focusing the research according to the key research areas of the University Medical Center especially within BiomaTICS. In collaboration with material scientists of the University (JGU), Max Planck Institute for Polymer Research, University of Applied Science (Siegen) the following topics are addressed: 3D printing of bone substitutes, bone regeneration and vascularization, biomaterial related infections. The BiomaTICS platform offers a possibility for synergistic and successful research together with other surgical disciplines.

Translational aspects of head and neck oncology will be enforced in clinical studies and by evaluation of the local tissue bank. The research activities include prevention, early diagnosis, and individualized treatment for oral squamous cell cancer. Better understanding of pathophysiology of side effects of supportive therapy in cancer (bisphosphonate and osteoradionecrosis) will lead to more safety in oncologic therapy.

The structure of the local study center will seek a closer attachment to the IZKS to improve its quality and quantity and offers high-level back-up for medical device and oncologic studies.

In the future the new building of the dental school provides a modern environment which will lead to successful interdisciplinary research of the dental departments in collaboration with the medical disciplines.

IMPORTANT PUBLICATIONS // MAX. 5


OVERVIEW

FOCUS OF RESEARCH:

- Basic research on orthodontic tooth movement
- Cell metabolism during pharmacotherapy and orthodontic force application
- Interaction of Orthodontics and Periodontics
- Skeletal anchorage (miniscrews, palatal implants, bone anchors)
- Caries and Periodontal Prevention during orthodontic treatment
- Orthodontics after dental and maxillofacial Trauma
- Orthognathic Surgical Treatment
- Cleft lip and palate

HIGHLIGHTS

HIGHLIGHTS OF RESEARCH:

- Discovery of the interface between mechanical loading and the effects of bisphosphonates regarding the human periodontal ligament fibroblasts and osteoblasts.

- Evaluation of the oral hygiene status and quality of life of orthodontic patients before, during and after multibracket appliance treatment - a longterm study.

FUTURE DIRECTIONS

AIMS FOR COMING SCIENCE PROJECTS:

- The analysis of important for the bone remodeling during orthodontic tooth movement. This might help to improve the time of treatment and stability of the achieved result.


Jacobs C, Gebhardt PF, Jacobs V et al. Root resorption, treatment time and extraction rate during orthodontic treatment with self-ligating and conventional brackets. HEAD & FACE MEDICINE. 2014; 10.


Aesthetics and perception of different orthodontic appliances: A Cross-Sectional and Eyetracking Study
PROJECT MANAGER: Dr. M Försch, Dr. C Jacobs, L Krull
FUNDING: German Society for Lingual Orthodontics
SUM: € 7,000
PROJECT DURATION: 2014 - 2016

Influence of mechanical strain on periodontal fibroblasts and human osteoblasts
PROJECT MANAGER: Dr. C Jacobs, Prof. H Wehrbein
PROJECT DURATION: 2011-2016

Study evaluating the oral hygiene status and quality of life of the patient before, during and after the Aligner-Therapy (Invisalign®)
PROJECT MANAGER: Dr. C Erbe, Prof. H Wehrbein
FUNDING: Invisalign Research Award
SUM: € 21,167
PROJECT DURATION: 2014 - 2016

Study to assess the status of oral health before and in the first 6 months of an orthodontic treatment
PROJECT MANAGER: Dr. C Erbe
FUNDING: Intramural Funding
SUM: € 38,750
PROJECT DURATION: 2013 - 2016

The Effect of the Oral-B Triumph Professional Care/TM 9500 Toothbrush in Combination with 0.454% Stannous Fluoride Dentifrice and 0.07% Cetylpyridinium Chloride Mouthrinse on the Reduction of Plaque and Gingival Inflammation in Patients with Fixed Orthodontic Appliances.
PROJECT MANAGER: Dr. C Erbe, Prof. H Wehrbein
FUNDING: Braun GmbH, Kronberg im Taunus
SUM: € 108,000
PROJECT DURATION: 2008 - 2016
OVERVIEW

The Department of Prosthetic Dentistry is involved in clinical patient care, theoretical and practical education of dental students and clinical and in vitro research.

Within the reach of these work all prosthodontics are covered.

To fullfill these tasks, modern methods of diagnostic and therapy are used. The manufacture of dentures can be done in the department’s own laboratory. CAD/ CAM technique is used as well as the conventional methods.

Dental students are educated in clinical prosthetic dentistry treating patients by themselves as well as in the student’s dental laboratory. Students are also educated and involved in actual methods of treatment using CAD/CAM technology.

HIGHLIGHTS

Modern patient treatment assumes clinical and material based research. The department of prosthetic dentistry uses and proves digital technology for diagnostic and planning reasons, for example in 3D-based implantology. Radiological data from a digital volume tomography and model analysis are used to plan the position of dental implants as a “backward planning” before implantation.

Furthermore, clinical studies concerning the long-term survival rate of dentures and the biological compatibility are realised. Another focus in research ist the in vitro and in vivo evaluation of ceramic materials.

Computer aided methods in manufacturing are applied and examined concerning the precision and clinical outcome. Spectrophotometric colour analysis is utilized and the reproducibility of this method is proved during multiple studies in the department of prosthetic dentistry.

FUTURE DIRECTIONS

TOOTH COLOR:
Development of a new tooth color reference.

CAD/CAM SYSTEMS:
• Accuracy of different CAD/CAM-Systems.
• Hybrid Scan: tactile versus optical precision.

DENTAL IMPLANTS:
• effects of rinse fluids on the tightness of screw retained implant structures.
**IMPORTANT PUBLICATIONS** // MAX. 5


**FIG. 1:** Prosthetic 3D Diagnosis of implantpositions

**FIG. 2:** Digital Toothcolour Determination

**FIG. 3:** Digital Volume Tomography and diagnosis of the temporomandibular joint

**FIG. 4:** Adhesive bridgework of a CAD CAM fabricated framework and ceramic veneering material

**FIG. 5:** CAD Design of fixed ceramic restorations

**IMPORTANT PROJECTS** // MAX. 5

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Project Manager(s)</th>
<th>Project Duration</th>
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<tbody>
<tr>
<td>Influence of surface topography on the color of a ceramic CAD/CAM System</td>
<td>Dr. C Igiel, Prof. H Scheller</td>
<td>2012 - 2015</td>
</tr>
<tr>
<td>Research of reproducability and precision of dental 3D Scan Systems</td>
<td>Dr. K Lehmann, Dr. H Dietrich, Prof. H Scheller</td>
<td>2009 - 2014</td>
</tr>
<tr>
<td>Review and Optimization of the bond between CAD/CAM fabricated ceramic crowns and implantabutments using different adhesive systems</td>
<td>Dr. K Lehmann, Prof. H Scheller</td>
<td>2009 - 2014</td>
</tr>
<tr>
<td>Spectrophotometric analyses of surface modifications in a ceramic CAD/CAM material</td>
<td>Dr. C Igiel, PD Dr. K Lehmann, Dr. V Zinser et al.</td>
<td>2012 - 2014</td>
</tr>
<tr>
<td>The Influence of desinfectant rinse liquids concerning the interface of dental implants and abutments</td>
<td>Dr. S Wentaschek</td>
<td>2007 - 2014</td>
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</tbody>
</table>

**FUNDING:** BEGO Implant Systems

**SUM:** € 29,000

**PROJECT DURATION:** 2009 - 2015
OVERVIEW

The Dept. of Oral Surgery (and Oral Radiology) focuses on research in the following areas:

- Oral implantology
- Orofacial pain/orofacial anaesthesia
- Oral and Maxillofacial Radiology

Members of the Department are involved in international and national research collaborations and activities.

A key responsibility of the department is student training on diagnosis, patient oral surgical treatment, techniques of local anesthesia and dental radiology. The clinic also educates specialists in oral surgery (three-year post-graduate training).

For chronic facial pain treatment, diseases of the oral mucous membranes and implantological diagnosis, the clinic offers special consultations. Modern two- or three-dimensional x-ray techniques are available for pre-operative or pre-implantation diagnostics.


HIGHLIGHTS

Prof. R. Schulze is also editor of a leading international magazine (Dentomaxillofacial Radiology) and an expert member of various working committees for dental radiology (NADENT) at the German Institute for Standardization (DIN).

In 2014, Prof. Schulze was one of two international experts preparing the ratified policy statement „Radiation Safety in Dentistry“ (publication: FDI policy statement on radiation safety in dentistry. Int Dent J 64(6) pp 289–290, (2014)) of the World Dental Federation (FDI).

IMPORTANT PROJECTS // MAX. 5

<table>
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<th>Project Manager</th>
<th>Funding</th>
<th>Duration</th>
<th>Summary</th>
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<tr>
<td>A clinical evaluation of Nobel Procera implant bar overdentures in the mandible or maxilla on 4 NobelReplace CC implants</td>
<td>PD Dr. A Behneke, Prof. N Behneke</td>
<td>CAMLOG Foundation</td>
<td>2012 - 2017</td>
<td>€ 15,000</td>
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<td>Automated detection of (unintended) patient motion in dental Cone Beam CT (CBCT)</td>
<td>Prof. R Schulze</td>
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<td>2014 - 2015</td>
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<td>Differentiated comparison of the effect of articaine in pulp and soft tissue anesthesia depending on the concentration of the vasoconstrictor epinephrine using infraorbital nerve block</td>
<td>Prof. M Daubländer</td>
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<td>2013 - 2014</td>
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<td>Fourier-based automated detection of structures in radiographs</td>
<td>PD Dr. D Brüllmann</td>
<td></td>
<td>2012 - 2015</td>
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<td>Neurophysiological changes after implant placement</td>
<td>Prof. M Daubländer</td>
<td></td>
<td>2014 - 2015</td>
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INSTITUTES AND DEPARTMENTS OF DENTAL MEDICINE

DEPARTMENT OF OPERATIVE DENTISTRY

Director:
Professor
Brita Willershausen

University Medical Center Mainz
Augustusplatz 2
D-55131 Mainz
phone: +49 (0) 6131 17-7246
willersh@uni-mainz.de
www.unimedizin-mainz.de/
zahnerhaltungskunde

OVERVIEW

Structure, assignments and justification of the facility of the Department of Operative Dentistry (Poliklinik für Zahnerhaltung)

Key interests of our duties are the formation and training of dental students and to provide our ambulant patients, based in actual scientific knowledge, with modern dental restorations and materials. The students at the Department of Operative Dentistry are compelled to successfully complete three semesters at our facilitites. They learn actual theoretical and clinical knowledge of dental pain origin and elimination, root canal treatment and the usage of modern resin based materials, gold casting restorations, ceramic inlays and partial crowns. The students treat our patients under supervision of our clinical and scientific staff. Approximately 5500 out of our 6100 patients are treated solely by students. The three courses offered at our facilities have a capacity for 144 students and are held on a daily basis; occasionally they run parallel. Further specialties that are offered at the Department of Operative Dentistry are Paedodontics (children dentistry) and Periodontology. The final examinations, didactic and patient organisation for the proximate semeter have our main focus during the semester holidays. We possess 38 dental units, one of them is dedicated exclusively to treat patients with high medical risks and the other one for treament of children.

Our ambulant treatment modalities (aprox. 7000 cases a year) are:

- pain emergencies,
- traumata, crown fractures,
- individual and group prophylaxis for children and adults,
- operative dentistry (fillings),
- esthetic dentistry,
- endodontics and
- invasive and non-invasive periodontics.

HIGHLIGHTS

1. Biocompatibility of dental materials: Endodontic dental materials should fulfill the corresponding requirements. These type of materials are aimed to seal the root canal; thus, a direct contact between them and the periapical tissues can not be avoided. The biocompatibility of these materials has being constantly investigated by means of different methodologies at our laboratories. The results of the in vitro research methods facilitate a first sight evaluation of these materials; thus, facilitating the decision-making of a clinician upon their clinical employment. The research methodologies give information about the metabolism determination (proliferation, apoptosis, cytokine release among others) caused by these materials on different cell lines. The metabolism results are supported through visualization by means of fluorescence microscopy. A further special research interest of our investigations are the different formulations of zinc-oxide eugenol, calcium phosphate and epoxy resin based root canal sealers and their effect on the cell metabolism.

2. Morphology of the root canal system: Accurate knowledge of the root canal system morphology as well as precise root canal preparation and hermetical filing of the root canal system are decisive factors which play an important role in endodontic therapy success. The morphology of the root foramen and root canal system are being investigated by different methodologies such as microscopically, radiologically and by means of micro-tomography. The results of these investigations will be used to enhance a precise localization and preparation of the morphological entities of the root canal system. Furthermore, the results of different root canal preparation systems have been investigated and have shown that none of them are per se capable to completely eliminate the flora from the root canal; thus, the employment of irrigating solutions should be considered as a support to accomplish a complete disinfection of the root canal system.

FIG. 1: Photodynamic therapy (periodontal disease)
FIG. 2: Dental students (Phantomsaal)


3. Resin composite restorations, visible light curing, adhesive systems: Resin composites had been continuously developed further on over the last decades. Tremendous efforts had been undertaken to reduce shrinkage stress of those materials and to enhance physical properties as i.e. flexural strength. Both are crucial for longevity of dental restorations to avoid marginal gaps as well as cohesive type fractures of the material. In the department or operative dentistry, in vitro shrinkage stress investigations as well as clinical studies on low shrinkage resin composites and on bulk fill restoratives are the main focus of research. The clinical study on a low shrinkage, silorane-based material was prolonged to an observation period of a total of four years. A paper as already prepared and will be submitted soon. A clinical split mouth study on the bulk fill restorative Sonicfill is almost completed and will be published, too. Another focus is on the photocopolymerization of resin composite materials: In a clinical survey, more than 500 VLC-devices from more than 300 private dental offices were checked for their power output. With a questionnaire, the dentists’ protocol of the light curing procedure was evaluated. From both data sets, the clinical potential of the individual curing device was documented and - after a training - improved.

4. Periodontal diseases are the most common dental conditions in adults which require professional treatment. The main focus of this group was to study new materials and techniques in nonsurgical and regenerative periodontal therapy. In controlled clinical studies we evaluated the efficacy of antimicrobial therapy as an adjunct to nonsurgical periodontal treatment. Moreover, the effectiveness of different bone replacement grafts in regenerative periodontal therapy was evaluated in different randomized, controlled clinical trials. In vitro studies evaluated the influence of regenerative materials on cells of the periodontium. Moreover, we established different cell culture models to study the response of human gingival fibroblasts (proliferation, adhesion, migration) stimulated by different bone replacement grafts.
CENTRAL MEDICAL SUPPLIERS

Pharmacy
Transfusion Center
The aim of the Pharmacy’s research projects is to study the effective and safe use of medicinal products. The results of research are used to optimize the use of medicines and to improve the clinical and social outcomes of drug therapies. For this purpose, we analyze the pharmaceutical characteristics of ready-to-use drug preparations and investigate the influence of pharmaceutical care and pharmaceutical interventions on the clinical and social outcomes of patients.

**PHYSICOCHEMICAL COMPATIBILITY/STABILITY OF READY-TO-USE PARENTERAL PREPARATIONS**

Since many years, the Pharmacy of the University Medical Center has developed a database on the chemical and physical stability of ready-to-use cytotoxic preparations. The data documented in the database primarily represent the results of the experimental studies performed in the labs of the Pharmacy Department. In the case of newly approved antineoplastic drugs, physicochemical stability of the stock solutions and the ready-to-use injection or infusion solutions is investigated under defined conditions (solvent, vehicle solution, storage temperature, exposure to light) by various analytical techniques. The focus of the current studies is the stability of monoclonal antibodies licensed to be used in anticancer therapy, recently approved small molecules and epirubicin- or irinotecan-loaded beads for chemoembolization. The drug loaded beads are administered via a microcatheter after mixing with nonionic contrast media to guide the injection and facilitate the selective delivery to the targeted tumor. Mixing of loaded beads with non-ionic contrast media may rapidly decrease the loading efficiency. Therefore we investigated the compatibility of beads (different diameters) loaded with irinotecan or epirubicin and mixed with different volumes of seven different non-ionic contrast media. According to the results irinotecan-loaded beads should not be premixed with contrast media while epirubicin-loaded beads can be mixed in advance.
IMPORTANT PUBLICATIONS // MAX. 5


COMPATIBILITY AND AERODYNAMIC CHARACTERISTICS OF SIMULTANEOUSLY NEBULIZED INHALATION SOLUTIONS/SUSPENSIONS

Patients with cystic fibrosis and other pulmonary diseases have to inhale multiple medications several times daily using nebulizers. This time-consuming procedure is shortened for the patients by mixing the inhalation medications; however, the compatibility of the admixtures is mostly unknown. The safety and efficacy of the nebulizable admixtures of two, three or even four drugs is depending on the physicochemical compatibility of the components.

Compatibility is studied by different analytical methods, primarily HPLC assays. When compatibility is confirmed, the aerodynamic characteristics of the nebulized admixtures are experimentally studied using a second generation cascade impactor and impaction analysis. The research results are employed directly in clinical practice and used to educate patients in safe inhalation practice.

PHARMACOKINETIC STUDIES

In cooperation with the intensive care unit of the Department of Anesthesiology, the pharmacokinetics of selected antibiotics are studied in critically ill patients suffering from sepsis and acute renal failure demanding for continuous venovenous hemodialysis. HPLC methods were developed to measure the concentrations of piperacillin, ciprofloxacin, meropenem, and linezolide in the serum and dialysate under steady state conditions. The resulting concentration profiles show large inter-individual variations of the resulting serum levels. There is a high risk of underdosing. As a result, the standard dose of piperacillin/ tazobactam and ciprofloxacin was already increased. According to our preliminary results the risk of underdosing seems also to be the case when linezolide is used in standard doses. However, for meropenem standard doses seem to be effective and safe in this specific patient group.

EFFECTIVENESS OF PHARMACEUTICAL CARE

Little attention has been paid in Germany to date to the aspects of pharmaceutical care in general and the study of the impact of pharmaceutical care on the clinical, social and economic outcomes of treatment. The impact of ward pharmacists and pharmaceutical care services on the outcome of medication therapy in hospital patients is another topic of our research. The beneficial effects of pharmaceutical care have been demonstrated in several studies. A recent multicenter, open-label study has shown that there are fewer failures to take medication and better patient awareness if pharmaceutical care is provided in the case of discharge medicine. Currently we are running two studies to evaluate the clinical and social outcome of the use of written or electronic patient individual medication plans. The medication plans are prepared by hospital pharmacists when the patients are discharged from the hospital and updated over an observation period of 6 or 12 months by different health care professionals.

Studies of drug compliance in patients prior to organ transplantation and in patients with rheumatoid arthritis were initiated. Medication compliance was measured electronically with MEMS. Preliminary results show that especially in dialysis patients compliance enhancing patient education is necessary.

IMPORTANT PROJECTS // MAX. 5

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OVERVIEW

The Transfusion Center as one of the largest institutions of its kind in Germany, provides all services of current transfusion medicine. This includes blood components, laboratory testing and apheresis-therapy. In addition research deals with aspects of blood donor epidemiology, blood safety, hemovigilance, quality and use of blood components.

HIGHLIGHTS

VIRAL AND BACTERIAL RISK OF TRANSFUSION

Regularly new risks for transfusion arise from emerging pathogens or from well-known pathogens that become relevant because of epidemic expansion. Research is focussed on special aspects in transfusion medicine. Increasing viral and microbial safety of blood components is one of the predominant research focuses. Improving methods for detection of viral nucleic acids has the same importance as generating epidemiologic data for new emerging pathogens, such as West Nile Virus (WNV) and Hepatitis E Virus (HEV). On the basis of the data it is possible to evaluate the residual risk of transfusion-associated infectious complications.

QUALITY OF BLOOD COMPONENTS

The quality of blood components is influenced by the methods of production, handling and storage. Variation of methods affects the quality of plasma significantly. The methods are not standardized worldwide or even in Europe. Investigations about the stability of proteins active in coagulation lead to optimization of freezing and storage of Fresh Frozen Plasma (FFP).

EVALUATION AND VALIDATION OF NEW METHODS IN IMMUNOHEMATOLOGY

Automation of immunohematologic tests is still a diagnostic challenge. The detection of allo-antibodies and blood-group-antigens depends to a great extent on the methods used. Evaluation of new methods affords testing of different patient samples and comparison to molecular based methods such as PCR. Investigations are the basis for regulatory approval of methods.

FUTURE DIRECTIONS

TRANSFUSION MEDICINE AND IMMUNOHEMATOLOGIC AND TRANSPLANTATION IMMUNOLOGY LABORATORIES

A broad range of methods for immunohematological and transplantation-immunological testing is available to clarify routine and complex diagnostic and clinical aspects. Medical specialists are ready for consultation service in transfusion medicine.

PERIPHERAL BLOOD PROGENITOR CELL (PBSC) COLLECTION AND APERESIS THERAPY

Hemapheresis can be an efficient therapy in hematologic and immunologic disorders. The Apheresis Center with intermediate care provides all kinds of hemapheresis, such as therapeutic leucapheresis, therapeutic plasmapheresis and red blood cellapheresis.

PRODUCTION OF CELL PREPARATIONS FOR RESEARCH

Current research in cell therapy and immunology is often based on methods using human white blood cells. The Transfusion center provides leucapheresis products and about 4,000 human white blood cell preparations from whole blood for basic research.


FIG. 1: New Generation analyzer for fast high throughput blood donor Screening and patient testing for viral load

FIG. 2: Separation of blood components

Evaluation of the automated system DAYmate M for donor and patient blood grouping
PROJECT MANAGER: Dr. D Marandiuc, Prof. WE Hitzler, S Seifert-Hitzler
PROJECT DURATION: 2013 - 2014

Production of autologous serum eye drops
PROJECT MANAGER: Dr. D Marandiuc, Dr. R Conradi, Dr. S Runkel
PROJECT DURATION: 2013 - 2014

Stability of clotting factors in Fresh Frozen Plasma (FFP) produced and stored under different conditions
PROJECT MANAGER: Dr. S Runkel, Prof. W Hitzler
PROJECT DURATION: 2012 - 2014
FURTHER INFORMATION

Safeguarding of Good Scientific Practice
Contact Research Office | Further contacts
Department of the Chief Scientific Officer (Organization)
SAFEGUARDING OF GOOD SCIENTIFIC PRACTICE

1. PRELIMINARY REMARKS

As a result of the exposure of serious cases of scientific misconduct, the German Research Foundation, the Max Planck Society and the German Rectors’ Conference have drawn up complementary proposals with the aim of preventing the occurrence of such incidents. Rhineland-Palatinate’s Minister for Education, Science and Continuing Education has established a statewide task force that has put together proposals for methods of safeguarding good scientific practice. These proposals represent draft guidelines for the universities in Rhineland-Palatinate, and subject-specific aspects are to be inserted in and supplement these. For this reason, the University Medical Center of Johannes Gutenberg University has adopted the following recommendations. These are mainly based on a report of the committee ‘Responsibility in Research’ of the Medical Faculty of the Albert Ludwigs University of Freiburg. This committee has formulated exemplary recommendations for the field of medical science that have only had to be slightly adapted to local circumstances.

2. BASIC PRINCIPLES

In medical research, it is expected that the results of research will ultimately take on a concrete form as new diagnostic and therapeutic strategies that will benefit patients. This means that scientists and researchers bear major responsibilities. The welfare and lives of patients often directly or indirectly depend on the results of their work. There are thus consequences arising from such scientific research and the implementation of its results.

- Studies must always be conducted in conformity with the latest scientific information. Awareness of recent publications and appropriate methodology is therefore imperative.
- The methods used and the results must be documented. A fundamental characteristic of scientific research is that it is repeatable, which is only possible if methodologies and results are accurately documented.
- Another fundamental characteristic of scientific research is the aspect of uncertainty. Results of scientific research and their interpretation should continually be assessed until the most plausible explanation for these is identified. This requires, among other things, the proper use of statistical methods.
- Scientific results are communicated in the form of publications. These represent the public announcement of the insight obtained. Thus, they are, like the scientific observation or experiment itself, a product of the work of the scientists acting as authors.

3. RECOMMENDATIONS FOR THE FORMATION OF WORK GROUPS

In medicine, several people usually contribute to a specific research project. The individuals who form a work group are thus usually responsible for defining the hypothesis, testing it, interpreting the results, and preparing the report for the scientific community. A responsible approach to research of this type can be facilitated by observing a few simple rules.
SIZE OF WORK GROUPS

Work groups should not exceed a certain size. A typical work group might have the following composition:

- A group leader with a postdoctoral lecturing qualification or the equivalent
- One to three researchers with doctoral degrees
- One to three doctoral/diploma candidates
- One or two technical assistants

The size of groups may vary according to the specific field in which they are working. In larger institutions (e.g., university hospitals), there will usually be several work groups active at any one time.

RESPONSIBILITIES OF THE DIRECTOR OF THE ACADEMIC INSTITUTION

- The director coordinates the individual work groups and represents the institution externally.
- The director also implements the overall responsibility that they have for the institution as a whole by delegating responsibility for specific areas to the work group leaders.
- The overall responsibility the director has for the institution does not extend to the individual studies and publications of the various work groups, unless the director is one of the authors (see below).

TASKS OF THE WORK GROUP LEADER

Definition of the research priorities of the group
- Specification of work processes and their monitoring
- Preparation of work programs for doctoral/diploma candidates and guidance with regard to scientific research
- Organization of weekly laboratory meetings, with laboratory reports by research associates, doctoral and diploma candidates
- Release of results for publication

The disclosure of methods and results by research and technical associates, doctoral and diploma candidates is permitted only with the explicit approval of the work group leader and, where appropriate, the institution’s director.
- Positive cooperation with other colleagues and internal conflict resolution with employees and superiors.

TASKS OF DIPLOMA AND DOCTORAL CANDIDATES AND POSTDOCTORAL RESEARCHERS

- When they commence their dissertations, diploma and doctoral candidates undertake scientific research. At this time, it is important not only to provide them with the necessary technical skills, but also to ensure that they are familiar with the ethical aspects of research, of the treatment of results and collaboration with other researchers.
- Through their participation, diploma and doctoral candidates and postdoctoral researchers play a decisive role in determining the research project. They are entitled to regular academic supervision, guidance and support by the group leader. They themselves are required to work responsibly and to collaborate with others.
- They are required to report regularly on the progress of their research, to participate in internal seminars and, to a limited extent, undertake routine tasks within the work group.
- When it comes to specifying research aims, the publication and evaluation of research results, they are subject to the instructions of the work group and institution directors.
- Like all other research and technical members of a work group, diploma and doctoral candidates and postdoctoral researchers are required to document their research accurately and in detail. These records must be archived for at least 10 years.
4. RECOMMENDATIONS FOR CONFLICT RESOLUTION AND COURSES OF ACTION IN CASES OF SUSPECTED MALPRACTICE

The leader of the work group is initially responsible for the resolution of conflicts within the work group. He is obligated to inform his institutional directors about internal conflicts and consult with these when necessary. Should conflicts arise, doctoral candidates should make use of the opportunity to consult with the representative for doctoral candidates of the faculty.

In addition, the Senate of Johannes Gutenberg University has appointed an ombudsman to represent the interests of doctoral and diploma candidates and research associates. The deputy ombudsman works in the field of medicine. If suspicion arises that academic misconduct has occurred (e.g. invention and falsification of data, plagiarism, breach of trust as an expert or supervisor), the guidelines specified above that apply to universities in Rhineland-Palatinate should be followed.

5. RECOMMENDATIONS FOR QUALITY ASSURANCE IN THE LABORATORY AND DATA DOCUMENTATION

- Quality assurance of studies employing standardized operating procedures must be provided for. It is recommended that quality management systems are put in place at different organizational levels. At the departmental level, the objectives and structure of the department’s quality management system are to be formulated and responsibilities defined.
- If a quality assurance representative for a work group in the laboratory is appointed, the responsibility for implementation of quality management guidelines is delegated to the work group itself. The quality assurance measures for each work group should be summarized in manuals.
- All research projects undertaken by a work group are to be fully documented. These records are legal documents, and are, in accordance to legal regulations, to be archived for at least 10 years.
- Other documents, such as data printouts and films, should be labeled accurately and, for example, filed chronologically. These documents should also be archived for at least 10 years.
- Appropriate measures are to be put in place for the quality assurance of the transfer of data to disks for computerized processing (e.g. duplicate and plausibility checks).
- Electronic data discs with data on which publications are based must be archived in unmodifiable form (e.g., WORM, CD) for at least 10 years.
- Prior to the publication of results, the proposed manuscript must always be submitted to all members of the work group. It is also advisable to present the results to members of other work groups (e.g. at the weekly meetings). The methodology employed and findings should be discussed in detail. The authors will benefit because timely criticism of the methodology or interpretation of the findings can be incorporated into the manuscript. The manuscript should be read critically by members of the work group in question and also by other groups (for authorship, see below).
- In the case of projects that involve a statistical analysis of research results, it is advisable prior to commencement to consult with the Institute of Biomedical Statistics and Documentation or a similar institution regarding the proposed experimental design and statistical procedures to be used.
- With regard to the ethical aspects of research projects of the department or work group, institutional directors and subordinate research associates are subject to the instructions and recommendations of the local ethics committee and the animal protection committee. In addition, researchers are to ensure that to the best of their knowledge and belief, they are able to comply with the relevant laws and regulations of the competent authorities and institutions.
6. AUTHORSHIP OF SCIENTIFIC PUBLICATIONS

DESIGN OF SCIENTIFIC PUBLICATIONS

- Original publications are used to communicate new observations or experimental results, including conclusions. Hence the repeated publication of the same results is not a permissible practice.
- Scientific research must be verifiable. Hence publications must contain an accurate description of the methodology employed and the results obtained.
- Findings which do not support the hypothesis of the authors must also be published.
- The fragmentation of projects so that separate publications can be produced is to be avoided.
- Findings and ideas of other researchers as well as relevant publications of other authors must be properly cited.

CRITERIA FOR AUTHORSHIP OF SCIENTIFIC PUBLICATIONS

To be considered the author of a research report of a work group and thus also responsible for the report, a researcher must have contributed significantly

1) to the project in the form of participation in the formulation of the research hypothesis, formulation of the research plan, evaluation of results,
2) interpretation of results and the drafting or critical review of the manuscript.

Both requirements must be met. Those who provide financial support to the project, manage the institution in which the research was conducted or read the manuscript are not entitled to be considered authors.

- In reports that are authored by several work groups, the contribution of each group should be identified.
- A form permitting the release of a manuscript for publication should be signed by all authors and the contributions of individual authors are to be identified (see form in the appendix).
- If unpublished observations of other persons are cited in the manuscript, findings of other institutions are used, or other persons thanked, their written consent must be obtained.
- Diploma and doctoral candidates whose results are included in the publication are to be cited as co-authors. If these have not yet completed their diploma/doctoral dissertation, it should be noted in the acknowledgment that the publication contains data from the dissertation of the person(s) concerned.
CONTACT RESEARCH OFFICE

DEPARTMENT OF RESEARCH AND TEACHING
RESEARCH OFFICE

HEAD OF RESEARCH OFFICE
DR. M. SCHWABE
phone: +49 6131 17-9704
matthias.schwabe@uni-mainz.de

RESEARCH CONSULTANT
DR. A. CLEMENT
phone: +49 6131 17-9948
angela.clement@uni-mainz.de

PROGRAMS/REPORTING
M. SKIADA
phone: +49 6131 17-9709
marina.skiada@uni-mainz.de

RESEARCH CONSULTANT, EPO
DR. S. TSCHAUDER
phone: +49 6131 17-9695
silvia.tschauder@uni-mainz.de

RESEARCH CONSULTANT
DR. U. VEITH
phone: +49 6131 17-9717
uta.veith@uni-mainz.de
FURTHER CONTACTS

VICE CHIEF SCIENTIFIC OFFICER AND VICE DEAN FOR RESEARCH
PROFESSOR M. BEUTEL
+49 6131 17-2841
ursula.nischwitz@unimedizin-mainz.de

GUIDING COUNSELLOR OF THE GERMAN RESEARCH FOUNDATION (DFG)
PROFESSOR B. KAINA
Department of Toxikology
phone: +49 6131 17-9217
kaina@uni-mainz.de

OMBUDSMAN
PROFESSOR J. KNOP
phone: +49 6131 17-5902
knop@uni-mainz.de

CHAIRMAN OF THE COMMITTEE ON
PROMOTION OF YOUNG RESEARCHERS (AWN)
PROFESSOR O. KEMPSKI
Neurosurgical Pathophysiology
phone: +49 6131 17-3636
oliver.kempski@uni-mainz.de

CHAIRWOMAN OF THE COMMITTEE ON EQUAL OPPORTUNITIES
PROFESSOR L. PRÜLL
Department of History, Theory and Ethics of Medicine
phone: +49 6131 17-9539
pruell@uni-mainz.de
PUBLISHER
Professor U. Förstermann
Chief Scientific Officer (CSO)
University Medical Center of the Johannes Gutenberg University Mainz

EDITING
M. Skiada, M. Sadowksi, A. Russell
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