We have gone to great length to ensure that all information in the report is correct and actual. All content, pictures and images used in this report are based on the information provided in good faith by each entity itself.

Throughout the report, gender-specific terms may be used in order to ease the text flow. Whenever a gender-specific term is used, it should be understood as referring to both genders.

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For more information, please visit our website at www.um-mainz.de
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First, I would like to express my gratitude to all our researchers, research partners, collaborators and funders. Thanks to your joint efforts and contributions we continued publishing highly appreciated scientific work and bolstering the scientific profile of the University Medical Center of the Johannes Gutenberg University Mainz (UMC-Mainz). It is my pleasure to share with you my reflections about our scientific accomplishments in 2017.

UMC-Mainz’s successful profiling, especially visible in the continuous development of its research foci in vascular biology, neurosciences and immunotherapy under the roof of the Research Center Translational Medicine, and further development of the relatively new Focus Research Area Biomaterials, Tissues and Cells in Science (BiomaTiCS), was positively recognized by the German Council of Science and Humanities (Wissenschaftsrat). We will continue on this path and yet provide the necessary support for innovative research ideas outside our research foci.

In its evaluation report, the German Council of Science and Humanities further highlighted the UMC-Mainz’s strategy to improve its research infrastructure. An essential part of UMC-Mainz’s infrastructural improvement in 2017 was the completion of the new Paul Klein Center for Immune Intervention (PKZI), a state-of-the-art building accommodating around 200 theoretical and clinical immunologists in 4,300 m² of laboratory space. The PKZI also harvests all core facilities of the Research Center for Immunotherapy (FZI), which have been equipped with new instruments thanks to numerous grants awarded by the German Research Foundation (DFG; to the sum of 2.2 million euro). The new building provides optimal conditions for application-oriented immunological researchers who develop innovative strategies in immunotherapy as shown by several publications in Nature journals (cf. FZI).

Immunological research at UMC-Mainz was further strengthened by the formation of the new Helmholtz Institute HI-TRON, a collaborative effort between UMC-Mainz, Translational Oncology at UMC-Mainz (TRON) - and the German Cancer Research Center (DKFZ) in Heidelberg, aimed at spurring the development of individualized immunotherapy concepts. After an initial start-up phase, the Helmholtz Association will support HI-TRON with annual funding of more than 5 million euros. Additionally, the state of Rhineland-Palatinate and the DKFZ will provide significant financial resources. We expect these research structures to prove beneficial also for new cross-disciplinary research projects. Several of our publications in 2017 showed that malfunctions of the immune system influence the function of other organs, thus also becoming of growing interest for other research areas. For example, certain T-cell subpopulations are an important factor in the pathogenesis of thrombosis (cf. CTH) and multiple sclerosis (cf. Institute of Molecular Medicine).

Other interdisciplinary research endeavors are flourishing as well. In the neurosciences, the German Resilience Center, founded in 2014, developed into a leading European center for resilience research, and was positively evaluated by the Joint Science Conference (GWK) in 2017, a fundamental step towards being recognized as a Leibniz Institute by the Leibniz Association and the GWK (scheduled for 2019). The new DFG-funded priority program “Computational Connectomics” (spokesperson Prof. Triesch, Frankfurt; participation of Prof. Rumpel, Institute of Physiology, UMC-Mainz) started its work in 2017. It adds interesting topics to the research questions addressed by the neuroscientists of the Rhine-Main Neuroscience Network (rmn²) in several DFG-funded Collaborative Research Centers (CRCs) geared towards a better understanding of the principles governing brain functions. In November 2017, the DFG approved the CRC 1292 “Targeting convergent mechanisms of inefficient immunity in tumors and chronic infections” for funding. Under the leadership of Professor Hansjörg Schild, the central aim of the CRC is to perform an unprecedented comparative analysis of the various immune evasion mechanisms in cancer and in chronic infections in order to obtain a detailed map of common and disease-specific immune escape checkpoints. In addition, the DFG renewed funding for the CRC 1066
"Nanodimensional polymer therapeutics for tumor therapy" for a period of four years and a budget of 13 million euros. Co-Spokesperson Medicine is Professor Stephan Grabbe, Department of Dermatology.

In 2017, the Gutenberg Health Study (GHS) celebrated its 10th anniversary. During these last ten years, the GHS was able to compile a substantial nationally and internationally renowned database of large-scale prospective and population-based data. With more than 15,000 participants, this study is one of the biggest interdisciplinary studies in its field and is therefore invaluable for the development of new preventive measures and therapies here in Mainz.

Last year, UMC-Mainz attracted funding from various funding schemes for numerous research areas, some of which are exemplarily mentioned here: In total, 3.8 million euros were provided by the Federal Joint Committee (G-BA) for the development of innovative forms of healthcare. Two projects granted in 2017 by the G-BA are coordinated at UMC-Mainz: GenHE, which aims to build up an e-health based, multi-sectoral geriatric network, and POSOP, which will transfer an Australian psychological self-help online program for oncological patients to Germany. Furthermore, UMC-Mainz is partner in three additional projects since 2017: ZSE-DUO to improve diagnosis of patients with unexplained rare diseases, PART-CHILD to innovate treatment of children with chronic diseases, and DAVOS to help geriatric patients with depressions.

As already stated in our research report 2016, UMC-Mainz is a partner in the MIRACUM consortium (Medical Informatics for Research and Care in University Medicine). A 9-month concept phase, which started in August 2016, was successfully completed in 2017. Starting in 2018, MIRACUM will be funded for four years with 32 million euros from the Federal Ministry of Education and Research (BMBF). Seven other university hospitals, two universities, and a partner from the healthcare industry are participating in the project, which aims to unite different data islands from health care and research into data integration centers.

Furthermore, the DFG awarded an Emmy Noether Junior Research Group grant to Dr. Michael Kuehn, Department of Internal Medicine III, with a budget of 1.8 million euros. The Emmy Noether Junior Research Group investigates the role of epigenetic changes in leukemia.

Successful funding was also attracted at the international level. One of the most important international funding schemes is Horizon 2020, the biggest EU Research and Innovation program from which UMC-Mainz was awarded funding totaling 2.2 million euros. Professor Kalisch, German Resilience Center (DRZ), serves as coordinator for the project “Dynamic Modelling of Resilience” (DynaMORE) funded under the call “Personalised Medicine.” Researchers from DynaMORE will develop a personalized computer model to measure and enhance the individual psychological resilience. UMC-Mainz is partner in the project MEDIRAD “Implications of Medical Low Dose Radiation Exposure”, which aims to enhance the understanding of low dose radiation risks. Professor Werner E. G. Müller, Institute of Physiological Chemistry, was awarded a third European Research Council (ERC) Proof-of-Concept Grant called “ArthroDUR: Bifunctional and regeneratively active biomaterial: Towards an ultimate solution for osteoarthritis treatment”. The goal of this project is to develop an innovative therapeutic concept for the treatment of arthrosis.

Additionally, in 2017 UMC-Mainz became a partner in two projects funded under the “Work Programme "Nanotechnologies, Advanced Materials, Biotechnology and Production" (NMBP): "Multimodal nanoparticles for structural and functional tracking of stem cell therapy on muscle Regeneration" (nTRACK) and "Innovative materials and techniques for the conservation of 20th century concrete-based cultural heritage" (InnovaConcrete). UMC-Mainz was also successful in the European Innovative Medicines Initiative 2 Joint Undertaking (IMI) calls. Two projects received funding: “European Quality In Preclinical Data (EQIPD)” and “Liver investigation: Testing Marker Utility in Steatohepatitis” (LITMUS). The Interreg project “Patient-as-Partner” (APPS), in which all four Grant Region countries are involved, was granted about 340,000 euros in funding. Within the context of this project, researchers aim to evaluate the patient’s potential to become partner in their own care and to develop solutions for the implementation of APPS.

The awarded funding is a recognition of the successful work of all grant recipients in the past and allows our researchers to remain actively involved in pioneering research on contemporary questions.

Looking into the future, we are working extensively to secure the long-term financial stability of our University Medical Center and to advance discoveries at the cutting edge of biomedicine and their impact on human health. On a more personal note, I would like to thank all UMC-Mainz’s scientists for their enthusiasm and diligent work which made the manifold discoveries presented to you in this research report possible and which provided the basis for all funding proposals.

With best regards,

Ulrich Foerstermann
Mainz, October 2018
MILESTONES

Professor Jakob von Engelhardt
NAMED DIRECTOR OF THE INSTITUTE OF PATHOPHYSIOLOGY

Professor Jakob von Engelhardt commences his work as the new Director of the Institute of Pathophysiology. Professor von Engelhardt’s research focuses on the molecular and physiological basis of neuronal communication in the brain as well as on the pathophysiological processes of neurodegenerative brain disorders. Further, in his research he also investigates the causes of rare genetic brain diseases.

Grant Agreement Signed for New Marie Skłodowska Curie Individual Fellowship

Professor Berninger, Institute of Physiological Chemistry, is supervising a new Individual Fellowship under the Horizon 2020 Framework Program. The project “Repro_Organoid: Direct reprogramming of human astrocytes into functional neurons in cerebral organoids derived from genome edited hiPSCs” will allow post-doctoral fellow Dr. Andrea Gamir to address the fundamental biological question of whether human glia can be reprogrammed within a human tissue setting, and if so, whether this depends on their state of maturation.

Helmholtz Institute HI-TRON Established

The new Helmholtz Institute HI-TRON is a collaboration between TRON – Translational Oncology at UMC-Mainz - and the German Cancer Research Center (DKFZ) in Heidelberg. The aim of HI-TRON is to promote development of individualized cancer immunotherapies by merging the strengths of both partners and to create optimum conditions for rapid clinical entry and testing of innovative diagnostic and therapeutic concepts. The state of Rhineland-Palatinate, the DKFZ and the Helmholtz Association are providing significant funding for this new think tank, which will be located on the UMC campus in a new laboratory building.

UMC-Mainz Publishes New Findings About T-Cells and Their Therapeutical Use in the Treatment of Thrombosis

Researchers of the Center of Thrombosis and Hemostasis gained new knowledge about the role of memory cells of the immune system in the dissolving of blood clots. The findings, published in “Innate Effector-Memory T-Cell Activation Regulates Post-Thrombotic Vein Wall Inflammation and Thrombus Resolution” (Journal: Circulation Research), can help to understand the mechanisms of clot dissolution more clearly and to develop better therapies.

UMC Participates in “EndoERN” and “MetabERN”

UMC-Mainz is partner in two new European Reference Networks (ERN) approved by the European Commission: EndoERN, which aims to improve the diagnostics and treatment of endocrine rare diseases in children and adolescents, and MetabERN, which focusses on enhancing treatment for patients with inherent metabolic disease.
EDITH HEISCHKEL-MENTORING PROGRAM ENTERS TENTH ROUND

The Edith Heischkel-Mentoring Program starts its tenth round of mentoring. The program supports 16 highly qualified female physicians, dentists, natural scientists, and humanities scholars. The goal of the program is to provide mentoring for female academics whose aim it is to reach managerial positions in their field. As part of the program, mentees are paired up with an established academic who will serve as their mentor for one year and offer advice on such subjects as the habilitation process and career development.

PAUL KLEIN CENTER FOR IMMUNE INTERVENTION OPENS

The official inauguration ceremony of the new building complex of the Paul Klein Center for Immune Intervention (PKZI) marks an important milestone in UMC’s efforts to improve research conditions at the UMC campus. Around 200 researchers from the Research Center of Immunology (FZI) will be able to conduct innovative and cutting-edge research, as well as applied immunological basic research in the new state-of-the-art facilities of the PKZI.

APRIL

IMI FUNDS PROJECT “EUROPEAN QUALITY IN PRECLINICAL DATA (EQIPD)”

UMC-Mainz is a partner in the project “European Quality In Preclinical Data (EQIPD)”, which is funded by the European Innovative Medicines Initiative 2 Joint Undertaking (IMI). The project receives an overall funding of about 4.5 million euros to create simple and sustainable solutions that facilitate data quality without impairing innovation and freedom of research.

GERMAN RESILIENCE CENTER RECEIVES 6 MILLION EUROS

The Boehringer Ingelheim Foundation provides 6 million euros for the development of the German Resilience Center (DRZ) of the UMC-Mainz. Professor Beat Lutz, Director of the Institute of Physiological Chemistry, and Professor Klaus Lieb, Director of the Department of Psychiatry and Psychotherapy, started the initiative and serve as Directors of the DRZ.
PROFESSOR TANJA GERMEROTT APPOINTED DIRECTOR OF THE INSTITUTE OF LEGAL MEDICINE

Professor Tanja Germerott is named Director of the Institute of Legal Medicine. It is the first time in the history of the institute that a female director is appointed. Professor Germerott’s research addresses postmortem imaging and forensic physics, the analysis of physical processes in connection with acts of violence.

FUNDING PERIOD EXTENDED FOR CRC 1066

The Collaborative Research Center (CRC) 1066 “Nanodimensional polymer therapeutics for tumor therapy” receives funding in the sum of 13 million euros for a second four-year interval. Professor Stephan Grabbe, Director of the Department of Dermatology, serves on behalf of UMC-Mainz as Co-Spokesperson. Also involved in the CRC are the Faculty 08 - Physics, Mathematics and Computer Science, the Faculty 09 - Chemistry, Pharmaceutical Sciences and Geosciences of the Johannes Gutenberg University Mainz and the Max Planck Institute for Polymer Research (MPI-P).

ELSE-KRÖNER-FRESENIUS STIFTUNG FUNDS RESEARCH GROUP

The Else-Kröner-Fresenius Stiftung provides about 1 million euros for a research group on the subject “Functional clustering of T cell and other immune cell sub-phenotypes across plasticity and individualities of immune-mediated diseases”. Professor Bopp, Institute of Immunology, is involved along with researchers from Marburg, Würzburg and Berlin.

HORIZON 2020: "nTrack" AND "InnovaConcrete"

The EU Framework Programme for Research and Innovation (Horizon 2020) funds two projects in which UMC-Mainz serves as partner, namely "nTRACK: Multimodal nanoparticles for structural and functional tracking of stem cell therapy on muscle Regeneration" (UMC-Mainz: Professor Volker Mailänder, Department of Dermatology), and "InnovaConcrete: Innovative materials and techniques for the conservation of 20th century concrete-based cultural heritage" (UMC-Mainz: Professors Werner E. G. Müller and Xiaohong Wang, Institute of Physiological Chemistry). nTrack researchers investigate how stem-cell therapy can be used for the regeneration of muscles. The consortium of InnovaConcrete aims at preserving concrete-based monuments by e.g. exploring a biotechnology based approach, specifically enzyme-assisted self-healing of damaged surfaces.

SECOND PHASE OF THE GUTENBERG HEALTH STUDY STARTS

Ten years after its start, the Gutenberg Health Study (GHS) successfully completed the first phase in April 2017. The Second phase has commenced and will run for another ten years. Boehringer Ingelheim International GmbH provides 3.4 million euros for the survey phase 2017 to 2022. Under the coordination of Professor Philipp Wild, Center of Thrombosis and Hemostasis (CTH), this interdisciplinary health study investigates the general health and in particular the cardiovascular and vascular health state of the residents of Mainz and the district of Mainz-Bingen.

UMC-Mainz is involved in the project “CARE for CAYA”, which is funded by the Innovationsfonds of the Federal Joint Committee (G-BA). “CARE for CAYA” is a preventive program for patients, who overcome a cancerous disease in childhood, youth or young adulthood. The aim is to improve aftercare and thus reduce and prevent secondary diseases.
BMBF FUNDS MIRACUM CONSORTIUM

The German Federal Ministry of Education and Research (BMBF) funds the consortium MIRACUM (Medical Informatics for Research and Care in University Medicine) with 32 million euros, to foster IT innovations for healthcare research and medical care. The overall goal is to foster IT innovations for healthcare research and medical care by taking advantage of digitalization in medicine to link data and generate medical knowledge, as well as to develop and apply innovative IT solutions for a better, data-based healthcare delivery system. UMC-Mainz is a partner in the consortium spread out over five German states and made up of eight universities with their respective university hospitals, two universities of applied sciences and one industrial partner. The spotlight in the consortium is on the data integration centers that will be embedded in the hospital's IT-infrastructure and will facilitate the collection and exchange of data within the consortium.

JULY

GERMAN COUNCIL OF SCIENCE AND HUMANITIES CERTIFIES POSITIVE DEVELOPMENT

UMC-Mainz’s positive development is praised by the German Council of Science and Humanities (Wissenschaftsrat). Especially highlighted is the research conducted in the focus areas vascular biology, neurosciences, and immunotherapy under the roof of the Research Center Translational Medicine, and the relatively new Focus Research Area Biomaterials, Tissues and Cells in Science (BiomaTiCS).

LATEST ADVANCES IN CANCER IMMUNOTHERAPY HIGHLIGHTED IN NATURE

Professor Ugur Sahin from the Institute of Immunology is first author of “Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer,” published in Nature (Journal Impact Factor: 41,6). Dr. Carmen Loquai from the Department of Dermatology is shared senior author of this publication, which based on results from a phase 1 clinical trial provides evidence that personalized RNA-based vaccines might be a successful approach to treat cancer. Additionally, further researchers from UMC-Mainz are among the authors of this publication. The publication is accompanied by a News and Views article in Nature highlighting the significance of these encouraging findings.

IN VIVO INVESTIGATION OF NEURONAL APOPTOSIS SHOWS THAT BRAIN MATURATION IS REGULATED BY ELECTRICAL ACTIVITY

Research shows that programmed cell death accompanies the development of the vertebrate brain. Professor Heiko Luhmann (Institute of Physiology) and his team describe in “Electrical activity controls area-specific expression of neuronal apoptosis in the mouse developing cerebral cortex” (published in Elife) that not neuronal identity, but rather electrical activity patterns regulate brain maturation in a region-dependent manner.

AUGUST

HORIZON 2020 FUNDS “DynaMORE”

EU Horizon 2020 funds the project “Dynamic Modelling of Resilience” (DynaMORE) under the coordination of Professor Kalisch, German Resilience Center (DRZ) of UMC-Mainz. Dyna-More researchers will develop a personalized computer model to measure and enhance individual psychological resilience. Partners in this project are the universities of Berlin, Freiburg, Löwen, Nimwegen, Tel Aviv, Warschau, and Zürich, as well as the Belgian-Dutch research center IMEC.
UMC-MAINZ RECEIVES 3.8 MILLION EUROS FROM INNOVATIONSFONDS (G-BA)

UMC-Mainz once again attracts funding from the Federal Joint Committee (G-BA) for the development of innovative forms of healthcare. UMC-Mainz is the coordinator of two projects and is involved as partner in three additional projects. Professor Roland Hardt, Department of General Medicine and Geriatrics, is coordinator for GenNE, which aims to set up an e-health based, multi-sectoral geriatric network. Dr. Rüdiger Zwerenz from the Department of Psychosomatic Medicine and Psychotherapy is coordinating POSOP, representing UMC-Mainz in the project together with Professor Beutel, Director of the Department of Psychosomatic Medicine and Psychotherapy. Collectively with their partners, they will transfer an Australian psychological self-help online program for oncological patients to Germany. Furthermore, UMC-Mainz is a partner in the projects ZSE-DUO (Dual structural guides for the evaluation of uncertain diagnosis in Centers for Rare Diseases), PART-CHILD (Improvement of the quality of treatment for children with chronic diseases and disabilities) and DAVOS (Retirement home depression: Improvement of the treatment through a staggered collaborative supply model).

RESEARCH REPORT 2017

SEPTEMBER

GERMAN RESILIENCE CENTER: RECOMMENDATION FOR LEIBNIZ-ASSOCIATION

After the German Resilience Center (DRZ) became a medical business unit in July 2016, the Joint Science Conference (Gemeinsame Wissenschaftskonferenz, GWK) recommends the DRZ for admission to the Leibniz Association in September 2017.

OCTOBER

PROFESSOR FOERSTERMANN RECEIVES ARIENS AWARD

The Chief Scientific Officer and Dean of the UMC-Mainz and former Director of the Institute of Pharmacology, Professor Ulrich Foerstermann, receives the Ariens Award from the Dutch Pharmacological Society for his work in the area of vascular function regulation. His research has contributed to a better understanding of the regulatory mechanisms of the vascular function.

ERC PoC “ArthroDur” COMMENCES

“ArthroDUR: Bifunctional and regeneratively active biomaterial: Towards an ultimate solution for osteoarthritis treatment” is the third European Research Council Proof of Concept (PoC) Grant awarded to Professor Werner E. G. Müller, Institute of Physiological Chemistry. The project will run for 18 months, through February 2019. Professor Müller seeks to develop an innovative therapeutic concept for the treatment of arthrosis.

Consecutive regions of shin. The joint cartilage can be produced by 3D-print-casting process.
Photo: Professor W.E.G. Müller (UMC-Mainz)

REORGANIZATION OF THE DEPARTMENTS AND INSTITUTES OF DENTAL MEDICINE

Following the retirements of two directors and the advice of an expert review commission, the number of departments and institutes of Dental Medicine was reduced from six to four through internal merging. The former Institute of Dental Material Sciences and Technology and the Department of Prosthodontics merged to form the Department of Prosthodontics and Dental Material Sciences, while the Department of Oral Surgery (and Oral Radiology) joined the Department of Oral and Maxillofacial Surgery – Plastic Surgery. The Department of Orthodontics and Dentofacial Orthopedics and the Department of Restorative Dentistry round out Dental Medicine at UMC-Mainz.
The German Research Foundation (DFG) approved funding for the Collaborative Research Center (CRC) 1292 “Targeting convergent mechanisms of inefficient immunity in tumors and chronic infections,” coordinated by Professor Hansjoerg Schild, Director of the Institute of Immunology. Also involved in CRC 1292 is TRON - Translational Oncology at UMC-Mainz. Further partners are the Goethe University Frankfurt, the University of Cologne, the Paul-Ehrlich-Institut Langen, the Charité Berlin, and the Institute for Tumor Biology and Experimental Therapy of the Georg Speyer Haus. A budget of approximately 11.7 million euros is provided for the development of new immunotherapies against cancer and chronic infections.

The DFG awarded an Emmy Noether Junior Research Group grant to Dr. Michael Kuehn, Department of Internal Medicine III. The grant includes 1.8 million euros in funding for the investigation of the role of epigenetic changes in leukemia. Dr. Kuehn’s overarching goal is to develop a targeted, more gentle, less toxic therapy for the treatment of leukemia.

After the reorganization of the institutes and departments of Dental Medicine led to the consolidation of the Department of Oral Surgery into the Department of Oral and Maxillofacial Surgery – Plastic Surgery, Professor Bilal Al-Nawas is selected as its first director. Professor Al-Nawas is an internationally renowned expert in the fields of implantology and reconstructive plastic surgery. In addition, his research also focuses on 3D-printing in medicine.

The European Innovative Medicines Initiative 2 Joint Undertaking (IMI) approves funding for the project “Liver investigation: Testing Marker Utility in Steatohepatitis” (LITMUS) in which UMC-Mainz is a partner. LITMUS researchers will investigate new technologies to improve the diagnosis of non-alcoholic fatty liver disease (NAFLD). Overall, 34 million euros are provided for this research, of which UMC-Mainz receives around 1 million euros. 47 international research institutions, pharmaceutical companies and biotech companies are participating in the project.

As of 1st December 2017, Professor Alexander Schuster is holder of the Endowment Professorship of Healthcare Research in Ophthalmology funded by the Stiftung Auge of the DOG (Deutsche Ophthalmologische Gesellschaft). The new professorship at UMC-Mainz will contribute to the development of better health care strategies by systematically collecting data regarding ophthalmological care.

Dr. Michael Kuehn
Photo: Barbara Hof-Barocke
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Professor Alexander Schuster
Photo: Peter Pulkowski (UMC-Mainz)
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Photo: UMC-Mainz
NEW CRC 1292 GRANTED BY GERMAN RESEARCH FOUNDATION
The German Research Foundation (DFG) approved funding for the Collaborative Research Center (CRC) 1292 “Targeting convergent mechanisms of inefficient immunity in tumors and chronic infections,” coordinated by Professor Hansjoerg Schild, Director of the Institute of Immunology. Also involved in CRC 1292 is TRON - Translational Oncology at UMC-Mainz. Further partners are the Goethe University Frankfurt, the University of Cologne, the Paul-Ehrlich-Institut Langen, the Charité Berlin, and the Institute for Tumor Biology and Experimental Therapy of the Georg Speyer Haus. A budget of approximately 11.7 million euros is provided for the development of new immunotherapies against cancer and chronic infections.

Dr. Michael Kuehn
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The DFG awarded an Emmy Noether Junior Research Group grant to Dr. Michael Kuehn, Department of Internal Medicine III. The grant includes 1.8 million euros in funding for the investigation of the role of epigenetic changes in leukemia. Dr. Kuehn’s overarching goal is to develop a targeted, more gentle, less toxic therapy for the treatment of leukemia.

Photo: Markus Schmidt (UMC-Mainz)
Formal handover of directorship of the Department of Oral and Maxillofacial Surgery – Plastic Surgery to Professor Bilal Al-Nawas (third from the left).

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Photo: UMC-Mainz
DECEMBER
MICHAEL KUEHN AWARDED AN EMMY NOETHER JUNIOR RESEARCH GROUP GRANT
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UMC-MAINZ SUCCESSFUL IN IMI CALLS
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Photo: UMC-Mainz
PROFESSOR BILAL AL-NAWAS NAMED NEW DIRECTOR OF THE DEPARTMENT OF ORAL AND MAXILLOFACIAL SURGERY – PLASTIC SURGERY
After the reorganization of the institutes and departments of Dental Medicine led to the consolidation of the Department of Oral Surgery into the Department of Oral and Maxillofacial Surgery – Plastic Surgery, Professor Bilal Al-Nawas is selected as its first director. Professor Al-Nawas is an internationally renowned expert in the fields of implantology and reconstructive plastic surgery. In addition, his research also focuses on 3D-printing in medicine.

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Photo: UMC-Mainz
ALEXANDER SCHUSTER APPOINTED TO ENDOWMENT PROFESSORSHIP OF OPHTHALMOLOGY
As of 1st December 2017, Professor Alexander Schuster is holder of the Endowment Professorship of Healthcare Research in Ophthalmology funded by the Stiftung Auge of the DOG (Deutsche Ophthalmologische Gesellschaft). The new professorship at UMC-Mainz will contribute to the development of better health care strategies by systematically collecting data regarding ophthalmological care.
This section provides you with the most important Key Performance Indicators (KPIs) for all research activities conducted at UMC-Mainz. An in-depth analysis of the UMC-Mainz’s current standing is provided for the following five categories: bibliometrics, third-party funding, technology transfer, promotion of young researchers, and gender distribution.

(October 2018)

I. BIBLIOMETRICS

One of UMC-Mainz’s chief KPIs is the number of publications with Impact Factor Points (Figure 1). In 2017, a record 1,175 UMC-Mainz publications had Impact Factor Points, an increase of 11% in the last five years. This increase reflects the growing interest of the scientific community in the research results of our scientists and furthers UMC-Mainz’s national and international standing among fellow university medical centers.

![Number of Publications with Impact Factor](image1)

**Figure 1:** Number of Publications with Impact Factor

**Figure 2** shows the total of all Journal Impact Factor Points (5,562) for all UMC-Mainz publications in 2017. The Journal Impact Factor reflects the influence of a scientific journal. Compared to the previous year (2016: 5,163) the total number of Impact Factor Points rose by 7.7%. Moreover, in the last five years, the total number of Impact Factor Points increased significantly by nearly 20%, highlighting UMC-Mainz’s continuously growing contribution to medical research.

![Total Journal Impact Factor Points for all Publications](image2)

**Figure 2:** Total Journal Impact Factor Points for all Publications
In addition to the Journal Impact Factor Points, individualized Cumulative Impact Factors (CIF) are used to evaluate the overall performance of all scientists, highlighting the individual contribution of UMC-Mainz scientists to a publication. The CIF is calculated by dividing a publication’s impact factor into three parts, with one third each allocated to the first author and the senior author, and the last third divided equally between all co-authors.

The Impact Factor Points of all 2017 publications from the clinical fields at UMC-Mainz were accumulated in order to show the CIF achieved by UMC-Mainz scientists and are presented in Figure 3. Internal, performance-based funding is allocated based on the Cumulative Impact Factors of the individual institutes.

As shown in Figure 3, the Clinical Institutes saw the highest CIF increase, with an impressive growth of 29.5 % in 2017 over the previous year. Together with CIF increases of 15.2 % in Surgery, 9.5 % in the Dental Clinics, 9.9 % in the Conservative Medicine fields, and 9.1 % in the Multidisciplinary Units, UMC-Mainz records a growth in CIF of 6.6 % in 2017, despite CIF decreases experienced by the Clinical Theoretical Institute and the Pre-Clinical units. In all, UMC-Mainz registers a noteworthy total CIF increase of 32 % in the last five years.
UMC-Mainz and the Johannes Gutenberg University (JGU) Mainz have adopted an Open Access policy that promotes the publication of research data in an Open Access format. To this purpose, both institutions continue to supplement the Open Access Publication fund supported by the German Research Foundation (DFG) with internal funding, increasing the funds to 158,000 € in 2017.

**Figure 4** shows the development of Open Access publications at UMC-Mainz from 2013 to 2017. The number of Open Access publications nearly doubled from 137 in 2013 (7.4 % of all publications of the UMC-Mainz), to 270 in 2017 (14.7 % of all publications). By increasing the Open Access output, UMC-Mainz is contributing to the open exchange of information among scientists and in doing so is making its research more readily available to the public as well.

**Figure 5** shows the numbers of publishing staff in each clinical field. Although several fields registered either a decrease or little change in their number of publishing staff, the clinical fields Surgery, Dental Clinics and Multidisciplinary Units experienced significant growth. This led to an increase in the overall number of publishing staff from 1,320 in 2016 to 1,329 in 2017. Currently two-thirds of UMC-Mainz’s scientific staff publish their research results in scientific journals.
Of the total number of publishing scientific staff at UMC-Mainz in 2017, there were 15 scientists with a person-related Cumulative Impact Factor (CIF) higher than 15 (Figure 6). These scientists represent 1 % of UMC-Mainz’s publishing scientific staff and were together responsible for 308 CIF points, (which translates to 15 % of all CIF points). The remaining 99 % of publishing researchers accounted for a combined total of 1.766 CIF points.
II. THIRD-PARTY FUNDING

Because of the different nature of the clinical fields at UMC-Mainz, each receives varying levels of third-party funding. These differences result for instance from unequal conditions in the number of funding programs available for the different clinical fields, as well as from their internal focus on research and clinical work.

Figure 7 shows third-party funding expenditures from 2013 to 2017. Compared to the previous year, funding expenditures in 2017 decreased by about 2.7 % to 52 million euros. The Clinical Theoretical Institutes, the Clinical Institutes, Conservative Medicine and the Dental Clinics saw only marginal differences, while the Pre-Clinical Unit experienced a drop in third-party funding of approximately 18.5 %. On the other hand, Surgery saw a large increase of nearly 24 %.
Figure 8 shows third-party funding by funding source. Funding from foundations increased steadily, in line with the last five years. Also positive is the growth in corporate funding (e.g. industrial project partners). Public funding (e.g. EU funding and funding from the German Research Foundation, DFG) and funding from private sources such as patient donations decreased slightly.

Figure 9 shows the amount of funding attained from the DFG in 2017 for individual and collaborative projects. Scientists at UMC-Mainz successfully attained approximately 5.3 million euros in funding for individual projects. In this same period, the amount granted for collaborative research projects was approximately 7 million euros. Compared to the previous year, this is an increase of around 0.6 million euros (4.8 %), resulting from collaborative projects.
In 2017, the DFG funded a total of 146 UMC-Mainz projects (Figure 10). More than half of the projects funded were Research Grants (Sachbeihilfe, 47.3 %) and Temporary Positions for Principal Investigators (Sachbeihilfe - Eigene Stelle, 4.1 %). With a share of 37.7 %, Collaborative Research Centers / Transregios also make up a large portion of the projects funded. The remaining 16 projects were funded under various other DFG programs, including the Priority Programme, International Scientific Events, the Emmy Noether Programme, the Heisenberg Programme and Research Training Groups.

![Pie chart showing the distribution of DFG projects funded at UMC-Mainz by funding opportunity.]

### III. TECHNOLOGY TRANSFER

Technology transfer, e.g. transferability of research results into medical practice, is an important topic at UMC.

The number of disclosed inventions increased from 10 in 2016, to 26 in 2017. Three invention disclosures were transferred to enterprises.

The Know-how of UMC scientists contributed to the success of two new startup companies. LIME medical (collaboration with surgeon Dr. Eric Hanke) was awarded the highly renowned Start-Up Prize of the “Wirtschaftswoche”, which is endowed with 300,000 euros. The Start-up NovoScreen (collaboration with gynecologists Professor Marcus Schmidt, Dr. Roxana Schwab) was one of ten winners of the Venture Cup of the Science4Life business plan competition.
IV. PROMOTION OF YOUNG RESEARCHERS

The promotion of young researchers is one of UMC-Mainz's central tasks. In 2017, UMC-Mainz conferred 303 doctoral degrees. Of these, 228 were awarded in human medicine, 65 in dentistry and 10 in the physiological sciences. Four outstanding candidates achieved "summa cum laude" distinction. Additionally, 16 scientists successfully completed their habilitation.

FIG. 11: Number of New and Transferred Invention Disclosures

FIG. 12: Doctoral and Habilitation Degrees awarded by Type of Degree
V. GENDER DISTRIBUTION

Figure 13 shows the gender distribution at different career levels of UMC-Mainz for the year 2017. While more doctoral degrees are awarded to female than to male researchers (62.4 % to 37.6%), the proportion of scientific staff with this qualification-level at UMC-Mainz was nearly equal for both genders. The gender ratio for the number of completed habilitations takes a turn in the other direction: there are significantly more male graduates (87.5 %) than female (12.5 %). In the last three years, the percentage of female graduates fluctuated between 12.5 % and 28 %. The significantly lower number of woman completing a habilitation affects the number of female professors. In 2017, 84 % of the professorships at UMC-Mainz were filled by male researchers and 16 % by female researchers. Moreover, female researchers occupy only one in eight medical business unit directorships at UMC Mainz. Thus, gender equality issues remain on the agenda of UMC’s board and together with the Committee on Equal Opportunities measures to promote female researchers will be further intensified in order to achieve gender equality on all career levels.

FIG. 13: Gender distribution at different career levels
HABILITATIONS

DR. MAXIMILIAN ACKERMANN
INSTITUTE OF FUNCTIONAL AND CLINICAL ANATOMY
SUBJECT: Anatomy
THESIS: Sprouting and intussusceptive angiogenesis in tissue regeneration, inflammation, and carcinogenesis

DR. FRANK GERHARD DETTE
DEPARTMENT OF ANESTHESIOLOGY
SUBJECT: Anesthesiology
THESIS: Sleep and breathing in a perioperative setting

DR. THOMAS HÖFNER
DEPARTMENT OF UROLOGY AND PEDIATRIC UROLOGY
SUBJECT: Urology
THESIS: Techniques and benefits of the ex vivo expansion of primary adult prostate stem cells

DR. CAREN HELANI JAYASINGHE ARACHCHIGE DON
JOINT PRACTICE “PATHOLOGY DR. WISPLINGHOFF” KÖLN
SUBJECT: Pathology
THESIS: Functional significance of the VEGF ligands and their receptors regarding the metastatic behaviour of colon carcinomas

DR. ROLF MATTHIAS HEIKO KAISER
BOEHRINGER INGELHEIM
SUBJECT: Clinical Pharmacology
THESIS: Pharmacogenetics of serotonergic and dopaminergic systems

DR. ROMAN TRUTZ KLÖCKNER
DEPARTMENT OF RADIOLOGY
SUBJECT: Radiology
THESIS: Radiologic diagnosis and therapy of hepatocellular carcinoma
DR. OLIVER PETER KÖTH
KLINIKUM WORMS GMBH
SUBJECT: Internal Medicine
THESIS: Current use and clinical benefit of a guideline-recommended therapy in high-risk patients with ST-elevation myocardial infarction in clinical practice

DR. NIELS ARNE WILHELM LEMMERMANN
INSTITUTE OF VIROLOGY
SUBJECT: Molecular Medicine
THESIS: Murine cytomegalovirus host adaptation - characterization of viral and cellular parameters

DR. FELIX EMANUEL LÜSSI
DEPARTMENT OF NEUROLOGY
SUBJECT: Neurology
THESIS: The modulation of antigen-presenting cells in the treatment of multiple sclerosis

PROF. DR. HELMUT E. M. NEUMANN
DEPARTMENT OF INTERNAL MEDICINE I
SUBJECT: Internal Medicine
THESIS: Innovate techniques for enhanced diagnosis of gastrointestinal diseases

DR. MARKUS PASCHOLD
DEPARTMENT OF GENERAL, VISCERAL AND TRANSPLANTATION SURGERY
SUBJECT: Surgery
THESIS: Evaluation of virtual-reality laparoscopic simulation in training and further education

DR. ANNA KATHARINA PONTO
DEPARTMENT OF OPHTHALMOLOGY
SUBJECT: Ophthalmology
THESIS: Immonologic, psychosocial, and health economic aspects of thyroid associated orbitopathy
DR. VERENA PROKOSCH-WILLING  
DEPARTMENT OF OPHTHALMOLOGY  
SUBJECT: Ophthalmology  
THESIS: Pathophysiology of glaucomatous optic neuropathy in experimental models and therapeutical approaches for neuroprotection and neuroregeneration

DR. BERND ROLAND ROSSBACH  
INSTITUTE OF OCCUPATIONAL, SOCIAL AND ENVIRONMENTAL MEDICINE  
SUBJECT: Public Health  
THESIS: Studies on biomonitoring-based risk assessment using permethrin-treated workwear as an example

PROF. DR. MIRKO H. H. SCHMIDT  
INSTITUTE OF MICROSCOPIC ANATOMY AND NEUROBIOLOGY  
SUBJECT: Biological Chemistry  
THESIS: Regulation of the Cbl Interactome

PROF. DR. SEBASTIAN STRIETH  
DEPARTMENT OF OTO-RHINO-LARYNGOLOGY, HEAD AND NECK SURGERY  
SUBJECT: Oto-Rhino-Laryngology  
THESIS: Experimental evaluation of an innovative antivascular tumor therapy using liposomal paclitaxel (EndoTAG-1)

DR. THOMAS THOMAIDIS  
DEPARTMENT OF INTERNAL MEDICINE I  
SUBJECT: Internal Medicine  
THESIS: Gastrointestinal tumours - From diagnostics to targeted therapy

DR. JOHANNES ANDREAS VOGT  
INSTITUTE OF MICROSCOPIC ANATOMY AND NEUROBIOLOGY  
SUBJECT: Anatomy  
THESIS: Mechanisms of neuronal circuit formation and maintenance in the hippocampus
DR. JOACHIM WOLF
DIACKONISSEKRAINENHAUS MANNHEIM
SUBJECT: Neurology
THESIS: Epidemiology of amyotrophic lateral sclerosis in Germany - data from the population-based prospective ALS-registry Rhineland-Palatinate

DR. THOMAS GERHARD WOLF
DEPARTMENT OF OPERATIVE DENTISTRY
SUBJECT: Dental, Oral and Maxillary Medicine
THESIS: Root canal morphology and configuration of maxillary and mandibular molars using a micro-computer tomographic analysis - with clinical reference

DR. CHRISTIAN WOLFRAM
DEPARTMENT OF OPHTHALMOLOGY
SUBJECT: Ophthalmology
THESIS: Population and ophthalmology - opportunities and perspectives for outcomes research in eye medicine

PROF. DR. CHRISTIAN WÜSTER
HORMONE AND METABOLISM CENTER PROFESSOR WÜSTER, MAINZ
SUBJECT: Internal Medicine
THESIS: Osteoporosis due to Calcitonin or Growth Hormone Deficiency - Investigations using bone cell cultures, animal models and osteodensitometry
NEW FACULTY

PROFESSOR BILAL AL-NAWAS
DEPARTMENT OF ORAL AND MAXILLOFACIAL SURGERY - PLASTIC SURGERY
Full Professorship (W3) for Oral and Maxillofacial Surgery - Plastic Surgery
FORMER AFFILIATION: Martin Luther University Halle-Wittenberg

PROFESSOR JAKOB VON ENGELHARDT
INSTITUTE OF PATHOPHYSIOLOGY
Full Professorship (W3) for Pathophysiology
FORMER AFFILIATION: Heidelberg University

PROFESSOR TANJA GERMEROTT
INSTITUTE OF LEGAL MEDICINE
Full Professorship (W3) for Legal Medicine
FORMER AFFILIATION: Hannover Medical School

PROFESSOR FLORIAN RINGEL
DEPARTMENT OF NEUROSURGERY
Full Professorship (W3) for Neurosurgery
FORMER AFFILIATION: University Medical Center of the Johannes Gutenberg University Mainz
PROFESSOR ESTHER MARIA HOFFMANN
DEPARTMENT OF OPHTHALMOLOGY
Full Professorship (W2) for Glaucoma
FORMER AFFILIATION: University Medical Center of the Johannes Gutenberg University Mainz

PROFESSOR WERNER KNEIST
DEPARTMENT OF GENERAL, VISCERAL AND TRANSPLANTATION SURGERY
Full Professorship (W2) for Oncological Colorectal Surgery / Minimally Invasive Surgery and Robotics
FORMER AFFILIATION: University Medical Center of the Johannes Gutenberg University Mainz

PROFESSOR ALEXANDER SCHUSTER
DEPARTMENT OF OPHTHALMOLOGY
Endowed Professorship (W2) for Ophthalmological Healthcare Research
FORMER AFFILIATION: University Medical Center of the Johannes Gutenberg University Mainz
SPECIAL AWARDS

PD DR. MAXIMILIAN ACKERMANN  
INSTITUTE OF FUNCTIONAL AND CLINICAL ANATOMY  
Young Investigator Award of the Anatomische Gesellschaft

DR. JONAS ECKRICH  
DEPARTMENT OF OTO-RHINO-LARYNGOLOGY, HEAD AND NECK SURGERY  
Stiftung Tumorforschung Kopf-Hals Award  
Sum: € 15,000

DR. NIHAIL ELNAHRAWY  
DEPARTMENT OF PSYCHIATRY AND PSYCHOTHERAPY  
Fulbright Alumni Development Grant  
Sum: € 2,500

DR. JÖRG FAHRER  
INSTITUTE OF TOXICOLOGY  
Boehringer Ingelheim Award  
Sum: € 15,000

DR. URS VON HENNING  
DEPARTMENT OF CARDIOLOGY  
Dissertation Prize of the Margarete Waitz Foundation  
Sum: € 3,000

DR. LUKAS HOBOHM  
CENTER OF THROMBOSIS AND HEMOSTASIS (CTH)  
Young Investigator Award ‘Pulmonary Embolism’ of the 3rd European Spring School on Venous Thromboembolism

PROF. DR. STAVROS KONSTANTINIDES  
CENTER OF THROMBOSIS AND HEMOSTASIS (CTH)  
Jaap de Graeff Medal of the University of Leiden

PROF. DR. STAVROS KONSTANTINIDES  
CENTER OF THROMBOSIS AND HEMOSTASIS (CTH)  
Theodor Naegeli Prize of the Theodor Naegeli Foundation  
Sum: CHF 60,000

DR. MAXIMILIAN KRÜGER  
DEPARTMENT OF ORAL AND MAXILLOFACIAL SURGERY – PLASTIC SURGERY  
Dissertation Prize of the Professor Dr. Lothar Diethelm Memorial Foundation  
Sum: € 2,000

PD DR. SEBASTIAN KUHN  
DEPARTMENT OF ORTHOPAEDICS AND TRAUMATOLOGY  
Teaching Award of the Johannes Gutenberg-University Mainz  
Sum: € 1,000

DR. VINAY V. KUMAR  
DEPARTMENT OF ORAL AND MAXILLOFACIAL SURGERY – PLASTIC SURGERY  
André Schröder Research Prize 2017  
Sum: CHF 10,000

PROF. DR. BERNHARD LÄMMLE  
CENTER OF THROMBOSIS AND HEMOSTASIS (CTH)  
BACH Distinguished Career Award, ISTH

DR. CHRISTIAN LANG  
DEPARTMENT OF INTERNAL MEDICINE I  
Rehabilitation Research Award of the Promotion of Economic Development Bad Kreuznach  
Sum: € 5,000

DR. MICHAL LEVIN  
CENTER OF THROMBOSIS AND HEMOSTASIS (CTH)  
Dagmar-Eißner-Award  
Sum: € 3,000

DR. ANDRÉ LOLLERT  
Department of Radiology  
Publication Award of the Society for Pediatric Radiology, Germany

PD DR. CARMEN LOQUAI  
Department of Dermatology  
German Skin Cancer Award 2017 of the German Skin Cancer Foundation  
Sum: € 10,000

DR. JULIANE MATLACH  
DEPARTMENT OF OPHTHALMOLOGY  
EYEnovative Prize Novartis  
Sum: € 25,000

DR. KAI W. MÜLLER  
DEPARTMENT OF PSYCHOSOMATIC MEDICINE AND PSYCHOTHERAPY  
Research Award of the North German Addiction Research Network e.V.  
Sum: € 1,000

PD DR. KATHARINA PONTO  
DEPARTMENT OF OPHTHALMOLOGY  
Boehringer Ingelheim Award  
Sum: € 15,000

PROF. DR. DIRK-MATTHIAS ROSE  
INSTITUTE OF OCCUPATIONAL, SOCIAL AND ENVIRONMENTAL MEDICINE  
Joseph Rutenfranz Medal 2017
DR. DANIEL SASCA
DEPARTMENT OF INTERNAL MEDICINE III
Postdoctoral Fellowship of the Dr. Mildred Scheel Foundation

PROF. DR. ERIK SCHULTE
INSTITUTE OF FUNCTIONAL AND CLINICAL ANATOMY
Teaching Award of the Johannes Gutenberg University Mainz
Sum: € 1,000

PROF. DR. SUSANNE SINGER
INSTITUTE OF MEDICAL BIOSTATISTICS, EPIDEMIOLOGY
AND INFORMATICS
Helmut Wölte Prize for Psycho-Oncology 2017
Sum: € 2,500

DR. DANIEL TURNER
DEPARTMENT OF PSYCHIATRY AND PSYCHOTHERAPY
Hedwig Wallis Dissertation Prize for Psychosocial Medicine
Sum: € 1,250

DR. STEFAN WENTASCHEK
DEPARTMENT OF PROSTHODONTICS AND DENTAL MATERIAL SCIENCES
Teaching Award of the Johannes Gutenberg University Mainz
Sum: € 1,000

TILL WENZ
DEPARTMENT OF INTERNAL MEDICINE I
Promotional Prize of the Gastroenterological Association of Rhineland-Palatinate/Saarland
Sum: € 1,000

PROF. DR. PHILIP WENZEL
CENTER OF THROMBOSIS AND HEMOSTASIS (CTH)
Robert Müller-Science Award 2017
Sum: € 5,000

PROF. DR. PHILIPP WILD
CENTER OF THROMBOSIS AND HEMOSTASIS (CTH)
Robert Müller-Science Award 2017
Sum: € 5,000
RESEARCH CENTER OF TRANSLATIONAL MEDICINE

Center for Translational Vascular Biology (CTVB)
Focus Program Translational Neurosciences (FTN)
Research Center for Immunotherapy (FZI)
RESEARCH REPORT 2017

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). This 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 UMC-Mainz.

HIGHLIGHTS

Central research aim of the CTVB is the investigation of the dynamic adaptation of the cardiovascular system. These adaptation processes to ageing processes, environmental and societal factors, metabolic, inflammatory and immunologic changes contribute substantially to the maintenance of organ function and thereby physical and mental health. The working program requires an interdisciplinary collaboration of different research fields. The research program is continuously further expanded within the overall strategy by innovative cooperation projects and a structural development in the area of multidimensional phenotyping, especially of blood and vascular cells.

The fundament for the programmatic development in last years, are nationally and internationally established large-scale projects with unique character for the research center Mainz. Important basic structures are the CTH (Center of Thrombosis and Hemostasis) and the DZHK (German Center for Cardiovascular Research), which are thematically interdisciplinary. The Gutenberg-Health Study (GHS) is an interdisciplinary large-scale project with an established highly complex biodatabase for translational population-based clinical research.

GHS is one of the largest single center epidemiological population-based cohort studies world-wide and offers interfaces to other research areas, especially research in ageing and maladaptation of human health.

The second 10-year study phase of the GHS-study center started in 2017. In addition to an extensive research program, biobanking has also been expanded (e.g. by samples of the intestinal microbiome), and the age range was extended. The BMBF-funded CTH, an integrated research and treatment center addresses translational science 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.

The UMC-Mainz contributes with these unique facilities as member to the BMBF-funded DZHK. The translational research program of the DZHK-Center RhineMain covers the exploration of the interaction between myocardium and vasculature. With around 3,200 study participants, the MyoVasc cohort study is the largest single-center cohort in the DZHK.

Within the framework of its research network, the CTVB has various junior research funding instruments of the CTH, DZHK and GHS available. For a sustainable development, several scholarships for Master students, MDs and postdoctoral fellowships were awarded to support excellent projects.

In 2017, a W2-professorship for „Interventional Heart Valve Therapy“ (Prof. E. Schulz) has been implemented to strengthen the scientific profile of the Center. With the „Children’s Health Academy“ of the Center for Cardiology and the Foundation Stiftung Mainzer Herz, the CTVB continues its prevention program and public outreach.
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 for future sustainability
• To strengthen the visibility of the research within the CTVB on a national and international level
OVERVIEW

The FTN has developed into one of the most visible places for Neuroscience research in Germany. A specific strength is the alliance within the Rhine Main Neuroscience Network (rmn²). The focus of the FTN on network homeostasis in the Central Nervous System and the neuronal homeostasis under challenges presented by the immune system was expanded by work on molecular mechanisms underlying mental resilience. The two existing CRCs (CRC 1080, CRC/TRR 128) were successfully prolonged to a second funding period and a third CRC (CRC 1193, molecular mechanisms of resilience) was established. The German Center for Resilience (DRZ, Deutsches Resilienz Zentrum) was further developed and successfully separated from the FTN.

HIGHLIGHTS

Since 2016 the German Resilience Center exists as a medical business unit (Medizinische Betriebseinheit MBE) of the University Medical Center Mainz providing administrative and organizational structures for the establishment of the DRZ as an independent institute.

In 2017, the Ministry of Science of the State of Rhineland-Palatinate (MWWK) made major financial contributions to the FTN which all group leaders of the DRZ are associated to. In order to further support resilience research in the DRZ, a grant application was submitted to the Boehringer Ingelheim Foundation (BIF) in February 2017 with a positive decision received in March 2017. The scientific projects started in May 2017.

In September 2017, the MWWK submitted an application to the Gemeinsame Wissenschaftskonferenz (GWK) to establish the DRZ as a member institute of the Leibniz Association. The positive vote by the GWK on 26th September 2017 allowed the DRZ to enter into the evaluation procedures by the Leibniz Association.

In 2017, the FTN has further developed its strategic planning in clearly separating from the DRZ by further strengthening its focus on the combination of basic and clinical neuroscience. Pathology and disease as a challenge to stability and flexibility of the nervous system and neuronal dysfunction as a model are used to understand homeostatic and allostatic mechanisms of the CNS.

The Center for Rare Diseases (Zentrum für selten Erkrankungen ZSEN) plays a major role in the translational efforts of the FTN. An application to the Innovation funds of the G-BA of health insurances (Gemeinsamer Bundesausschuss) was successful, generating substantial structural support for the ZSEN.
## FUTURE DIRECTIONS

The FTN will further expand its successful topics on network homeostasis, chronic dysregulation of immune/nervous system crosstalk, and molecular mechanisms and therapeutic options in rare diseases into translational strategies of understanding development and defense of neural network dysfunction. It will establish a disease centered structure complementary to the DRZ. Special emphasis will be put into the translation of knowledge from model organisms into patients and back by using established advanced imaging (human, small animals) and microscopy technology. A set of model organisms to study gene function and their implication on brain development and function throughout evolution will be established and expanded. These will include C-elegans, drosophila and, with Soojin Ryu, zebrafish as well as man and mouse. A central core unit for stem cell research and organoids will substantially strengthen these attempts and a bioinformatic hub will be established to allow advanced data analysis of big data. The FTN has started a close cooperation with the Center for computational sciences of the Johannes Gutenberg University to establish a new, cross-functional research group „computational Neurosciences“. The FTN is participating in a number of research initiatives within the Johannes Gutenberg University and in joint efforts together with numerous national and international research institutes.

### IMPORTANT PUBLICATIONS

<table>
<thead>
<tr>
<th>Authors</th>
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<td>Bicker F, Vasic V, Horta G et al.</td>
<td>Neurovascular EGFL7 regulates adult neurogenesis in the subventricular zone and thereby affects olfactory perception.</td>
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<td>2017</td>
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<td>784-790</td>
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Research Center for Immunotherapy (FZI)

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OVERVIEW

The Research Center for Immunotherapy (Forschungszentrum für Immuntherapie; FZI) aims to perform groundbreaking research in the area of immunology with a strong translational perspective. It was founded in 2008 as one of five research centers of the Johannes Gutenberg University, Mainz. It is a joint effort of scientists of the Faculties of Medicine, Biology and Chemistry of the Johannes Gutenberg University in the field of immunology providing a close connection between clinical and basic sciences. The FZI is founded on the conviction that a better understanding of basic immunobiology and immunological diseases will lead to new therapeutical options for the treatment of infections, autoimmune diseases, allergies and cancer.

Research in the FZI is focusing on a better understanding of the molecular and cellular bases of uncontrolled innate and adaptive immunity against environmental or “self” antigens and how this leads to the development of allergies, inflammatory diseases and autoimmune diseases. On the other hand, innate and adaptive immune system deficiencies lead to an increased susceptibility against infections and an increased incidence of tumors. The complex molecular mechanisms of inflammation, tumorigenesis and host-pathogen interaction are an unsolved task for basic and clinical immunologists. Therefore, it is the main aim of the FZI research groups to better understand the calibration of immunological circuits to prevent autoimmune, inflammatory and allergic diseases but also to harness the power of the immune system for the immunotherapy of tumors.

HIGHLIGHTS

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. The FZI provides 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 and cell sorting and mass spectrometry, are available to researchers of the University Medical Center and the Johannes Gutenberg University.

Our activities are supported by the collaborative research center CRC 1066 „Nanodimensional polymer therapeutics for tumor therapy” (Coordinators: Rudolf Zentel and Stephan Grabbe) that started in 2017 into the second funding period with ten projects coordinated by scientists of the FZI. The transregional research projects CRC/TRR 156 „The skin as sensor and effector organ orchestrating local and systemic immune responses” (Coordinator: Alexander Enk, Heidelberg) and CRC/TRR 128 „Initiating/effecter versus regulatory mechanisms in Multiple Sclerosis – Progress towards unraveling and treating the disease” (Coordinator: Heinz Wiendl, Founding-Coordinator: Frauke Zipp) are connecting FZI-members with other leading research groups all over the country. In 2017 the CRC 1292 „Targeting convergent mechanisms of inefficient immunity in tumors and chronic infections” (Coordinators: Hansjörg Schild and Tobias Bopp) has been granted by the DFG and will start in 2018.
FUTURE DIRECTIONS

The Paul-Klein-Center for Immune Intervention (PKZI) has been inaugurated on April 6, 2017. About 200 scientists from four different institutes of the FZI will move to the new research building. In addition all FZI core facilities will operate centralized at the PKZI.

The hyper-reactivity of the immune system can lead to allergic reactions. The immunology research at the FZI has a long history in this topic. In cooperation with the Max Planck Institute for Polymer Research (MPI-P), the FZI plans to propose a DFG funded Graduate School with the focus on Allergy and Nanoparticles. That consortium will complete the already established research on therapeutically aspects on Nanoparticles of the CRC 1066 and was already supported by the innovations fund of the President of the JGU.

Several immunologists of the FZI are very successfully investigating on T-cells and above all regulatory T-cells. In addition, the research focus group “T-cells” of the German Immunological Society (DGfI) is coordinated by the Spokesperson of the FZI Tobias Bopp. As a consequence, the FZI is planning to propose for a new DFG funded CRC (coordinated by Ari Waisman) focused on T-cells.

While the classical roles of the cardiovascular system are already very well investigated, so far only little is known about non-traditional roles of such systems. Members of the FZI will contribute to the CRC initiative with the working title „The non-traditional roles of vascular protective systems centered around our strength in extravascular coagulation and cell signaling of the hemostatic system and translational approaches“, coordinated by Wolfram Ruf.
FOCUS RESEARCH AREA

Biomaterials, Tissues, and Cells in Science (BiomaTiCS)
**OVERVIEW**

The use of artificial materials is state-of-the-art in almost every surgical discipline for the functional replacement of lost tissue after injury, diseases or just as consequence of natural degeneration processes. The translational and interdisciplinary research priority of „BiomaTiCS, Biomaterials, Tissues and Cells in Science“ is a network of surgeons and materials scientists, who are interested in understanding and modulating the complex interactions between biological systems and artificial as well as biogenic materials. Therefore, the transfer of surgical expertise from medical applications and difficult clinical situations in regenerative medicine to basic research of material science is one of the main aims of BiomaTiCS.

**HIGHLIGHTS**

In 2017, BiomaTiCS continued its established collaboration projects in the area of „vascularization and biomaterial integration“, nanomaterials and 3D printing in medicine. Together with its partners Max Planck Institute for Polymer Research and the Department of Chemistry, BiomaTiCS published over 100 publications and submitted several patents. 5 representative publications are listed below:

Important milestones have been the 2nd International Conference on 3D Printing in Medicine that took place on 19th and 20th of May 2017 at the Electoral Palace of Mainz. Furthermore, two scientific initiatives of BiomaTiCS, namely for the postgraduate Course (Graduiertenkolleg) „Determinants at bio-material interfaces and their potential for improvements in surgery“ headed by Prof. Strieth (ENT) and for the clinical research group (Klinische Forschergruppe) Vaskularisation, headed by Prof. Brieger (ENT) have successfully acquired funding by the Impulsfond Rhineland-Palatinate. BiomaTiCS participated again at the 5th MedTech Rhineland-Palatinate on 17th of May 2017 and supported 8 interdisciplinary cooperation projects in the context of biomaterial integration and angiogenesis together with the Center of Thrombosis and Hemostasis (CTH). Finally, in October 2017 BiomaTiCS started a seminar in the context of the postgraduate Course Initiative.

**FUTURE DIRECTIONS**

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.


Schiegnitz E, Kaemmerer PW, Sagheb K et al. Impact of maxillary sinus augmentation on oral health-related quality of life. INTERNATIONAL JOURNAL OF IMPLANT DENTISTRY. 2017; 3.


FIG. 1: Microvasculary integration of a 3D printed polycaprolactone scaffold (PCL) (white area) that was modified with anorganic poly phosphate. The PCL scaffold was placed on top of the chondrio-allantoic membrane (CAM) of chicken embryos. [Dr. Martin Heller, Department of Obstetrics and Gynecology, Prof. Jürgen Brieger, Department of Oto-Rhino-Laryngology, Head and Neck Surgery; Prof. Werner E. G. Müller, Institute of Physiological Chemistry]

FIG. 2: Nanoparticle uptake by a mesenchymal stem cell. A stem cell membrane marker is visualized in blue. The nanocarriers which were taken up by the cell are shown in red, the cytoskeleton is stained in green. [Prof. Volker Mailänder, Department of Dermatology and Max Planck Institute for Polymer Research]

FIG. 3: Microscopic analysis of different cell types seeded on collagen coated 3D-printed polylactide-discs. A: human primary osteoblasts; B: normal human dermal fibroblasts; C: human umbilical vein endothelial cells and D: osteosarcoma cells [Dr. Ulrike Ritz, Department of Orthopedics and Traumatology]

FIG. 4: Aorta 3D-model of transparent plastics with thoracic and abdominal aortic aneurysm. In both aneurysms a stent prosthesis (thoracic tubular prosthesis and abdominal bifurcational prosthesis) has been implanted. [Prof. Dr. Bernhard Dorweiler, Department of Cardiothoracic and Vascular Surgery]
COLLABORATIVE RESEARCH PROJECTS

CRC 1066 Nanodimensional polymer therapeutics for tumor therapy
CRC 1080 Molecular and Cellular Mechanisms of Neural Homeostasis
CRC 1193 Neurobiology of resilience
CRC/TRR 128 Initiating/effector versus regulatory mechanisms in Multiple Sclerosis
CRC 1066  
Nanodimensional Polymer Therapeutics for Tumor Therapy

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OVERVIEW

The CRC 1066 “Nanodimensional polymer therapeutics for tumor therapy” addresses the development of a nanoparticle-based tumor immune therapy. The organizational structure of the Collaborative Research Center 1066 reflects the manifold scientific disciplines and the different participating scientific institutions. In addition to UMC-Mainz, the following scientific institutions take part in the CRC: Faculty 08 (Physics, Mathematics and Computer Science) and Faculty 09 (Chemistry, Pharmaceutical Sciences and Geoscience) of the Johannes Gutenberg University Mainz and the Max-Planck-Institute for Polymer Research Mainz.

HIGHLIGHTS

The examination of a second funding period took place in January 2017 (January 31st – February 1st 2017). Funding for the CRC 1066 has been extended by the senate of the DFG another four years (July 1st 2017 until June 30th 2021).

FUTURE DIRECTIONS

Within a highly interdisciplinary course, the CRC 1066 aims at combining (i) innovative therapy approaches arising from immunology and oncology with (ii) the synthesis of a variety of functionalized nanoparticles and (iii) novel characterization methods for complex nanomaterials within biologically relevant media. The expertise of the Johannes Gutenberg University Mainz (JGU) and the Max Planck Institute for Polymer Research (MPI-P), which together are leading entities for polymer science in Germany, are combined with the CRC 1066 as an excellent research structure in the field of tumor immunotherapy. Therefore, scientists from biology, medicine, chemistry, and physics work hand in hand to develop nano-sized therapeutics, which enable the combination of vaccination and abolishment of immune tolerance as well as induction of localized inflammation. Whereas in the first four years, the primary focus was set on identifying promising nanoparticle-based carrier systems, the main aim of the second funding period is to further evaluate suitable systems in relevant melanoma models especially with a view towards clinical translation in a potential third funding period. As a consequence of the already well-established collaboration between chemists and immunologists, individual projects are jointly run by polymer chemists and immunologists.


CRC 1080
Molecular and Cellular Mechanisms of Neural Homeostasis

Spokesperson:
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Heiko Luhmann

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OVERVIEW

In recent years, research into homeostasis in the nervous system has gathered significant momentum. What is more, with its move to the center 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 ever-changing 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.

During the first project term from 2013 to 2016, important insights on neuronal homeostatic mechanisms and their limits in pathophysiological brain states as well as improved methods how to study homeostatic with cellular and subcellular resolution have been published by members of the consortium. These include for example the role of GRIP/14-3-3 pathway in dendrite development and homeostasis, the function of PRG-mediated lipid signaling in synaptic homeostasis and the failed homeostatic in vivo firing rate control via impaired potassium channel function in dopamine neurons in Parkinson Disease.

HIGHLIGHTS

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

PARTICIPATING INSTITUTES:
- Goethe University Frankfurt
- Max Planck Institute for Biophysics
- Max Planck Institute for Brain Research
- Institute of Molecular Biology Mainz (IMB)
IMPORTANT PUBLICATIONS // MAX. 5


PROJECTS:

A01 Activity-Dependent Regulation of Apoptosis in Developing Rodent Cerebral Cortex: Heiko J. Luhmann; Anne Sinning
A03 EGFL7 and progranulin (PRGN) in neurogenesis: a notch above as a duo in neural Homeostasis: Mirko H.H. Schmidt; Stephan Schwarzacher; Irmgard Tegeder
A05 Deciphering the molecular adaptions underlying network homeostasis when facing the challenge of new neuron integration: Benedikt Berninger; Albrecht Stroh; Vijay Tiwari
A06 Gadd45a as a regulator of memory consolidation by post-transcriptional control Mechanisms: Beat Lutz; Christof Niehrs
A11 (B07) Interaction of homeostatic challenges in activity control for dopamine substantia nigra neurons by alpha-synuclein pathology, aging and cell loss: Jochen Roeper
B01 Coordination of Protein Synthesis and Degradation in Neurons: Erin M. Schuman
B02 Optogenetic and Ultrastructural Analysis of Synaptic Vesicle Homeostasis at Hyperstimulated Synapses in Caenorhabditis elegans: Alexander Gottschalk
B03 Molecular mechanisms of homeostatic neuronal adaptations after denervation: Thomas Deller; Andreas Vlachos
B04 Molecular mechanisms of dendritic development and maintenance: Amparo Acker-Palmer
B05 Role of bioactive lipid signaling in homeostatic control of excitatory transmission: Jisen Huai, Ph.D.; Robert Nitsch; Johannes Vogt
B09 (A08) The role of the protein receptor-mediated endocytosis B (RME8) in neuronal Homeostasis: Christian Behl; Albrecht Clement
B10* Homeostatic regulation of mTOR dependent synaptic function: Heiko J. Luhmann; Susann Schweiger
B11# Activity-dependent regulation of AMPA receptor function by auxiliary subunits in the dentate gyrus: Jakob von Engelhardt
C01 (B06) Immune Cytokines in the Regulation of Neuronal Homeostasis: Jonathan Kipnis; Frauke Zipp
C02 (A07) Adaptive cellular mechanisms of functional reorganization and recovery after traumatic brain injury (TBI): Thomas Mittmann
C03* Activity driven homeostatic regulation of connectivity to optimize information content: Tatjana Tchumatchenko
C04* Homeostatic regulation of REM-SWS balance in sleep: Gilles Laurent
C05* Homeostatic maintenance of neuronal function in a dynamic network: Yonatan Loewenstein; Simon Rumpel
CRC 1193
Neurobiology of Resilience

Spokesperson:
Professor
Beat Lutz

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OVERVIEW

CRC 1193 represents an integrative approach developed by neuroscientists, psychologists and clinicians from Mainz and Frankfurt in order to advance mental health research in the field of stress-related mental dysfunctions. We aim to investigate protective mechanisms in the brain supporting the maintenance of mental health during and after adversity. CRC 1193 was established in July 2016 with a funding volume of 12.1 Mio € for 4 years and has 3 program areas:

A: Molecular and cellular resilience mechanisms
B: Neural-network and systems mechanisms
C: Neural basis of cognitive and behavioral resilience mechanisms

Focusing on resilience rather than on pathophysiology represents a paradigm shift in mental health research with great potential for the development of new prevention strategies.

FUTURE DIRECTIONS

CRC 1193 HAS DEFINED THREE GOALS:

- Develop an unified theory of neurobiological resilience mechanisms
- Identify and understand neurobiological resilience mechanisms
- Improve prevention of stress-related mental dysfunctions

Goal 1 starts with the assumption that flexible short- and long-term regulation of stress responses is key in minimizing resource depletion and allostatic costs caused by stress. On this basis, researchers will focus on regulation of neural excitability and neural-network activity during and after stress, and on neurobiological underpinnings of stress-regulatory appraisal (emotional evaluation) processes.

Both frameworks will be evaluated and refined with the ultimate goal to consolidate the results into a unified theory of neurobiological resilience mechanisms. Goal 1 and Goal 2 require an interdisciplinary and integrative research strategy combining molecular-cellular and neural network-based with behavioral and cognitive analyses. All subprojects are designed to include at least two of these levels of analysis. The projects are focused on fine-grained mechanistic studies in animal and human models, and results obtained will be incorporated into theory development. Wherever possible, the projects perform causal manipulations of the neural mechanisms that they investigate. These manipulations will be the basis for proof-of-principle intervention studies to achieve Goal 3.
Haaker J, Lonsdorf TB, Schuemann D et al. Where There is Smoke There is Fear-Impaired Contextual Inhibition of Conditioned Fear in Smokers. NEUROPSYCHOPHARMACOLOGY 2017; 42(8):1640-1646


HIGHLIGHTS

PARTICIPATING INSTITUTES
- University Medical Center Mainz
- Johannes Gutenberg University Mainz
- Institute of Molecular Biology Mainz (IMB)
- Goethe-University Frankfurt
- Max Planck Institute for Brain Research, Frankfurt

PROJECTS
A01 Active resilience mechanisms of dopamine midbrain neurons: Jochen Roeper/Susann Schweiger
A02 Unraveling the relation between adult-born hippocampal neuron’s connectivity and resilience: Benedikt Berninger/Beat Lutz
A03 Neuronal actin dynamics shaping resilience: the role of the novel actin-interacting protein ‘downregulated in renal cancer’: Amparo Acker-Palmer/Marianne Müller
A04 Developing a zebrafish model to identify novel mediators of resilience mechanisms: Sookyin Ryu/Erin M. Schuman
A05 Deciphering the epigenetic basis of resilience: Vijay Tiwari/Ulrich Zechner
B01 Finding the good in the bad: fear extinction reconceptualized as an appetitive learning process: Sevil Duvardi/Raffael Kalisch
B02 Cortical mechanisms of adaptive fear extinction underlying stress resilience: Johannes Letzkus
B03 Fear network interactions underlying resilience to stress: Torfi Sigurdsson
B04 Lipid signaling by anandamide and the bliss of resilience: genetic models at cellular and neural-network levels: Heiko Luhmann/Beat Lutz
B05 Regulation of neural excitability and neural-network function in resilience - a multimodal and (back-) translational approach: Sergiu Gropoa/Robert Nitsch/Albrecht Stroh
C01 Making extinction last: role of spontaneous activity in a mesoprefrontal circuitry in long-term extinction memory consolidation: Raffael Kalisch/Albrecht Stroh
C02 The functional contributions of prefrontal dopamine and norepinephrine projections to cognitive and social resilience: Sevil Duvardi
C03 Psychological flexibility as active resilience mechanism: neurocognitive mechanisms and dopaminergic mediation: Christian Fiebach/Mathias Schreckenberger
C04 Goal pursuit despite emotional distraction: Neural network mechanisms of emotional interference inhibition and their role for resilience: Oliver Tüscher/Michael Wibral
C05 Cognitive emotion regulation in the face of stress: Michèle Wessa
C06 Seeing the good more than the bad: Neural mechanisms of positivity biases in information processing and their role for resilience: Ulrike Basten/Christian Fiebach
C07 Neural correlates of instrumental control: immunization as potential resilience mechanism: Andreas Reif/Michèle Wessa
Z02 Modelling individual differences in response to stress in mice: an approach to identify neurobiological mechanisms underlying resilience: Beat Lutz/Marianne Müller/Konstantin Radyushkin
Z03 Longitudinal determination of resilience in humans to identify mechanisms of resilience to modern-life stressors: Klaus Liebl/Andreas Reif

FIG. 1: General study scheme for resilience research in CRC T193. Trajectory of mental health changes from before (T1) to after (T2) stressor exposure and relation to resilience study designs. Main panel: Three prototypical trajectories (arrows) of mental health changes as a consequence of stressor exposure are shown. ΣD expresses summed mental dysfunctions. These can increase (mental health deterioration), not change, or also decrease (mental health gain, psychological growth or maturation) from T1 to T2. Individuals exhibit the more resilience (outcome R on right side), the less mental dysfunctions are increased by stressor exposure.
OVERVIEW

Multiple sclerosis (MS) is the most common chronic inflammatory disease of the central nervous system (CNS) 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 repair capacities 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 co-spokesperson, as well as the principal investigators Prof. Ari Waisman (Institute of Molecular Medicine), Prof. Tobias Bopp (Institute of Immunology), Prof. Helmut Jonuleit (Department of Dermatology), Prof. Stefan Bittner (Department of Neurology), Prof. Sergiu Groppa (Department of Neurology), Prof. Detlef Schuppan (Institute of Translational Immunology), Juniorprof. Albrecht Stroh (Institute of Microscopic Anatomy and Neurobiology), and Jacqueline Trotter (Focus Program Translational Neurosciences) being based here.

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.
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.

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

**IMPORTANT PROJECTS // MAX. 5**

**CRC-TR-128 Project B04: T helper cell balance in chronic neuroinflammation - influence by antigen-presenting cells**
- **PROJECT MANAGER:** Prof. T Bopp, Prof. F Zipp
- **FUNDING:** German Research Foundation (DFG)
- **PROJECT DURATION:** 2016 - 2020

**CRC-TR-128 Project B05: Identifying distinct functional and structural connectivity patterns of network compensation and repair in early autoimmune neuroinflammation**
- **PROJECT MANAGER:** Prof. S Groppa, Prof. F Zipp
- **FUNDING:** German Research Foundation (DFG)
- **PROJECT DURATION:** 2016 - 2020

**CRC-TR-128 Project B09: Mechanisms underlying immune-mediated neuronal damage: neuronal hyperexcitability as starting point for neurodegeneration in Multiple Sclerosis**
- **PROJECT MANAGER:** A Stroh, Prof. F Zipp
- **FUNDING:** German Research Foundation (DFG)
- **PROJECT DURATION:** 2016 - 2020

**CRC-TR-128: Initiating/Effecter Versus Regulatory Mechanisms in Multiple Sclerosis - Progress Towards Tackling the Disease**
- **PROJECT MANAGER:** Prof. F Zipp
- **FUNDING:** German Research Foundation (DFG)
- **PROJECT DURATION:** 2016 - 2020
OVERVIEW

Starting with the evolutionary oldest still extant animals, the siliceous sponges, we succeeded to elucidate the formation of their biosilica skeleton, the first biomineralization process that has been understood from the gene level up to the hierarchically organized 3D biomineral structures. The discovery that biosilica formation, as well as the formation of biocalcite (calcareaous sponges) and calcium phosphate/hydroxyapatite is controlled by enzymes, one of the main achievements of this project, resulted in a paradigm change in the understanding of human bone formation. The identification of these enzymes and the development of new routes allowing a bioinspired biomineral synthesis have opened new avenues in the field of tissue engineering scaffold biomaterials for human therapy.

HIGHLIGHTS

BIOSILICA – FROM SPONGE SKELETON TO HUMAN BONE FORMATION
The elucidation of the enzymatic basis of biomineral formation, first for biosilica in sponges and later for hydroxyapatite (HA) in bone, allowed us to develop new concepts for the therapy of human bone disorders. We discovered that HA deposition proceeds via the formation of amorphous Ca-carbonate (ACC) bioseeds, mediated by a carbonic anhydrase, and their subsequent transformation into HA using phosphate delivered by enzymatic cleavage of the physiological polymer inorganic polyphosphate (polyP) by alkaline phosphatase (ALP).

POLYPHOSPHATE, A SECOND INORGANIC BIO MEDICAL BIOPOLYMER
We demonstrated that besides biosilica and ACC, amorphous calcium polyP (Ca-polyP) nanoparticles cause a strong stimulatory effect on bone formation both in vitro and in vivo. These materials are the first that are morphogenetically active: they elicit the expression of genes that are crucial for cell proliferation and differentiation.

SOURCE FOR EXTRACELLULAR ENERGY
Polyp has another unexpected feature: this polymer acts as an extracellular energy store and supply. We found that extracellular ATP is formed from polyp via an interaction of the enzymes ALP and adenylate kinase. This makes polyp interesting when used in bradytrophic tissues like cartilage.

MORPHOGENETICALLY ACTIVE MATRIX FOR CARTILAGE REPAIR
The biological (cytokine induction) and physical (hardness, stiffness) properties of the polyp nanoparticles depend on the divalent counterion (Ca, Mg, or Sr). Using magnesium instead of calcium, we obtained nanoparticles that preferentially enhance cartilage regeneration. The Mg-polyP particles are morphogenetically active: upregulation of SOX9, a transcription factor that regulates chondrocyte differentiation/proliferation, as well as collagen 3A1 and aggrecan.

STIMULATION OF MICROVASCULARIZATION
We discovered that polyp, in the presence of calcium, accelerates tube formation of human endothelial cells (HUVEC), allowing the development of novel strategies to stimulate angiogenesis/microvascularization. This effect is abolished by apyrase which degrades ATP.

ARTIFICIAL BLOOD VESSELS
With biosilica/polyP, we were also able to develop a novel material for artificial blood vessels. The material is extruded into a hardening solution under formation of small diameter vessels, whose mechanical properties can be adapted by the concentration of calcium ions.

FURTHER APPLICATIONS: FROM WOUND HEALING TO CARIES PROPHYLAXIS
In addition, with biosilica/Ca-polyP, novel strategies for wound treatment and caries prophylaxis could be developed. The topical application of the morphogenetically active nanoparticles improved wound healing in normal and diabetic mice. Also, the development of a bifunctional toothpaste was possible: Ca-polyP, like biosilica, is an effective regenerative active sealant. In addition, polyP has antibacterial activity against the cariogenic bacterium Streptococcus mutans.
The novel biomimetic materials based on biosilica, ACC and polyP, developed in this project revealed unexpected properties with new applications in biomedicine. These materials enable, for the first time, the design of scaffolds that are morphogenetically active, attract stem cells and induce cell differentiation/proliferation in situ, without growth factor/cytokine supplementation. These materials can be applied in 3D-printing/bio-printing for the development of patient-specific implants. The proof-of-concept has been provided or is currently going on in three ERC-PoC projects, Si-Bone-PoC (focus: bone implants; already completed), MorphoVES-PoC (artificial blood vessels; completed) and ArthroDUR (cartilage repair; ongoing). In addition, the self-healing property of biosilica can be utilized to engineer novel hybrid materials, with silicatein as a functional template, which are more resistant towards physical stress and fracture. Based on this knowledge we even developed a new concept for self-healing of technical concrete. Moreover, in sponges biosilica spicules are involved in light-transmission functioning as a nerve-like system. Similar constructs together with polyP, used as sheets for human nerve cells, could contribute to the treatment of neuronal disorders like Alzheimer disease. And last but not least, the discovery that polyP functions as an energy store/supplier in the extracellular space waits for further applications which could go far beyond this ERC project.
ERC Advanced Grant LiPsyD

Grant Awardee:
Professor Robert Nitsch

Project-Coordinator:
PD Dr. Johannes Vogt

Overview

Accurate synaptic transmission is fundamental for normal brain function, and alterations of excitatory transmission affect cortical network function as described in psychiatric disorders. We have recently shown that bioactive phospholipids like lysophosphatidic acid (LPA) critically affect synaptic transmission by activating LPA2-receptors and increasing presynaptic release probability. Moreover, we have shown that synaptic LPA-signaling is regulated by an LPA-interacting molecule named Plasticity-Related Gene 1 (PRG-1), which is located at the postsynaptic density (Trimbuch et al., 2009). Within this project, Robert Nitsch and Johannes Vogt have analyzed the molecular mechanisms of synaptic LPA-signaling and have unraveled its role in psychiatric disorders in animal models and in humans.

Highlights

PRG-1/Lipid Signaling in Cortical Network

Loss of PRG-1 leads to hyperexcitability altering cortical excitation/inhibition (E/I)-balance. A recently reported SNP in prg-1 (R345T/mutPRG-1) affects ~5 million European and US citizens in a monoallelic variant. Our studies show that this mutation leads to a loss-of-PRG-1-function at the synapse due to its inability to control LPA levels via a cellular uptake mechanism. PRG-1+/R345T transgenic mice show an altered cortical network function and an altered resilience against psychiatric disorders (Fig. 1). This could be reversed by modulation of phospholipid signaling via inhibition of the LPA-synthesizing molecule autotaxin. In line, EEG-recordings in a human population-based cohort revealed an E/I balance shift in monoallelic mutPRG-1 carriers and an impaired sensory gating, which is an endophenotype of stress related mental disorders. Intervention into bioactive lipid signaling is thus a promising strategy to interfere with glutamate-dependent symptoms in psychiatric diseases.

PRG-1 Acts as a Lipidoporin

Transfer of molecules across the cytoplasmic membrane is a fundamental cellular function, and specific transporters or porins have been characterized for various types of molecules. However, a mechanism how cells can support rapid transmembrane transport of bioactive lipids has remained enigmatic. Our discovery of rapid LPA-uptake mediated by LPPR-4/PRG-1 is the first example for the existence of lipidoporins allowing for transmembrane transport of a polar bioactive phospholipid in the body (Fig. 2).

PRG-1 Mediates Spine Development via PP2A/Integrin S1 Activation

Dendritic spines are essential for neuronal information processing, and decrease in spine density is the morphological basis of altered memory function. We have identified PRG-1 as a critical mediator of spine formation acting via protein phosphatase 2A (PP2A)/β1-integrin activation. Deletion of PRG-1 reduces the number of dendritic spines and...
Recent data show that lysophosphatidic acid (LPA) is a synaptic modulator regulating cortical excitation-inhibition balance and controlling sensory information processing in mice and man. Since we found that the LPA-synthesizing enzyme autotaxin (ATX) is expressed in the astrocytic compartment of the tripartite synapse we are now able to understand bioactive synaptic signaling in terms of molecular signaling and of synaptic kinetics. Our preliminary data show that astrocytic ATX-activity is dynamically regulated via astrocytic glutamate receptors. Since ATX-inhibition is able to rescue hyperexcitability syndromes in different animal models of schizophrenia, our studies aim at targeting ATX as a versatile strategy for a novel drug therapy of psychiatric disorders.

**CHARACTERIZATION OF BIOACTIVE PHOSPHOLIPID SIGNALING AS A NEW TARGET FOR TREATING PSYCHIATRIC DISORDERS**

Recent data show that lysophosphatidic acid (LPA) is a synaptic modulator regulating cortical excitation-inhibition balance and controlling sensory information processing in mice and man. Since we found that the LPA-synthesizing enzyme autotaxin (ATX) is expressed in the astrocytic compartment of the tripartite synapse we are now able to understand bioactive synaptic signaling in terms of molecular signaling and of synaptic kinetics. Our preliminary data show that astrocytic ATX-activity is dynamically regulated via astrocytic glutamate receptors. Since ATX-inhibition is able to rescue hyperexcitability syndromes in different animal models of schizophrenia, our studies aim at targeting ATX as a versatile strategy for a novel drug therapy of psychiatric disorders.

**CHARACTERIZATION OF LPPR-4/PRG-1 AS A NEURONAL LIPIDPORIN**

Using live-imaging and confocal microscopic analyses at the spine level as well as electrophysiological measurements, we could demonstrate that the membrane protein LPPR-4/PRG-1 may act as a lipidporin in neurons. In order to understand the role of PRG-1 as a lipidporin, we aim to structurally characterize this protein which contains unique structural components shared by LPPR/PRG family members and which may enable this group of proteins for transmembrane transport of a polar bioactive phospholipid.
OVERVIEW

Liver cirrhosis is the most relevant predictor of mortality in chronic liver diseases (CLD). The project focuses on quantitative imaging of liver fibrosis and fibrogenesis, a much needed toll for antifibrotic drug development and therapy control of patients with CLD. We have synthesized and tested a large variety of constructs for near infrared (NIR) and radioactive imaging, applicable to rodents and patients based on peptide and non-peptide ligands. The biological targets are fibrillar collagen type I, the main extracellular matrix protein in fibrotic tissue, the αvβ6-integrin, which is uniquely expressed on fibrogenic biliary cells, and the PDGF-β receptor and fibroblast activation protein (FAP) that are expressed on activated hepatic stellate cells and myofibroblasts.

HIGHLIGHTS

NEW LIGANDS FOR MOLECULAR IMAGING

Collagen type I for fibrosis imaging. 4 different peptides with high affinity to the triple helical collagen-I have been derivatized. The new constructs were validated and structurally optimized. One construct showed promising binding affinities and preliminary promising in vivo behavior (Fig.1). These peptides are currently optimized for stability and affinity, using cyclized variants.

αvβ6-integrin for fibrogenesis imaging. Several radio- and fluorescent-labeled ligands have been developed, including trimeric and bimodal constructs. The lead peptidomimetic EMD 527040 proved challenging in terms of optimal coupling without loss of affinity, and a very fast on/off kinetic. Further ligands based on the peptide motif RTDLXXL have been developed and improved towards site-specific labelling, multivalency and spacer/linker design. Based on a new binding motif a high affinity cyclic peptide has been designed which showed the expected specificity and 3-7 fold increased uptake in fibrotic vs normal liver between 6 and 12 h after injection and which is currently further optimized (Fig.2 and 3).

PDGF-β receptor for fibrogenesis imaging. New stabilized dimers of a high affinity cyclic peptide have been synthesized and are currently under biological evaluation.

FAP for fibrogenesis imaging. Apart from the originally suggested above targets, a small molecule binding FAP has been investigated. The first constructs revealed molecular instability. New approaches focusing on stabilized lead structures are ongoing.

Multimodality. Different new molecular structures have been designed to enable bimodal (NIR and nuclear imaging with a single construct). These constructs, when proven useful in rodents via NIR and radioactive imaging, can be immediately tested in patients. One of them, a high affinity cyclic peptide for the αvβ6-integrin (see above) has already been successfully developed. Furthermore, a new chelator design (DOTA-PYR) allows multimodal imaging just by exchange of the central trivalent metallic atom.

Trimerization. We established the TRAP chelating system for our targeting vectors. A new, highly selective and very mild coupling method based on squaric acid was established for the first time in radioligand development.
**FUTURE DIRECTIONS**

**LIGAND DEVELOPMENT**

Several most promising ligand developments are under intense investigation to identify the best candidates for liver fibrosis imaging and therapy monitoring. Currently, we have begun mouse studies where we treat liver fibrotic mice with antifibrotic agents. Validation of the fibrosis and fibrogenesis imaging constructs will be done before during and after effective antifibrotic treatment, as assessed by collagen quantification and fibrogenesis readouts in the livers. This scenario mimics antifibrotic treatment trials in humans. We expect to have at least 4 candidates in the next 6 months that promise to qualify for liver fibrosis and fibrogenesis imaging in patients. Notably, the low quantities needed for radioactive imaging in patients (<100mcg) fall below normal toxicity levels and correspond to the micro dosing concept. In addition, all radioligands can be produced in full GMP-compliant processes. Therefore, requirements for a fast translation into humans are fulfilled. We plan to apply for follow-up funding via the ERC Translational Funding call (ERC-PoC) to allow first in-man studies. The ethics protocol for these studies which will be accompanied by the best available invasive (liver biopsy and histology) and noninvasive measures (Fibroscan, serology, MR imaging) of fibrosis and fibrogenesis has already been formulated and will be submitted for approval once the first optimized constructs are fully validated in mice.

**FIG. 1:** Molecular structure of the collagen-I binding radioligand (68Ga)NODAGA-HEG-RLDGNEIKR; (B) results of in vitro studies using collagen type I coated microwells; (C) in vivo µPET imaging in Mdr2KO and wildtype mice.

**FIG. 2:** Bifunctional αvβ6-integrin construct for validation in mice using near infrared (NIR) imaging and immediate translation to man using PET imaging (Ellenbogen, Kim et al, unpublished).

**FIG. 3:** Quantitative in vivo imaging of αvβ6 integrin expressing fibrogenic cholangiocytes. Mdr2KO mice, age 8 weeks, that spontaneously develop a biliary fibrosis with a 3-fold increased liver collagen content were i.v.-injected with a bimodal peptide based on a 9-mer αvβ6 integrin-binding linked to the NIR-dye Sulfo-Cy5.5 and the radiochelator NODAGA. 5-7 fold higher signal in fibrotic vs normal livers 6 h after injection of the imaging construct (Kim YO et al, unpublished).
OVERVIEW

The last decade has witnessed an explosion of research into the molecular networks ensuring homeostasis at barrier 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 or inflammation-induced intestinal cancer. Much has been learned about how the microbiota contributes to intestinal homeostasis. In contrast to the role of the microbiota, the role of nutrients in such processes has largely been a matter of speculation. Given the broad role of nutrients in metabolic diseases, 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

ROLE OF THE DNA DAMAGE RESPONSE FOR THE INSTRUCTION OF POLYPLOID MACROPHAGE FATE.
In recent years, significant progress has been made in defining the molecular programs controlling the development of tissue resident macrophages. However, in chronic inflammation, macrophage subsets arise that differ in their ontogeny and in their developmental programs from those existing in tissues at homeostasis. The mechanisms controlling their differentiation remain to be addressed. Granulomatous diseases of infectious (e.g., mycobacterial disease), autoinflammatory (e.g., vasculitis, inflammatory bowel disease, sarcoidosis), allergic and malignant etiologies affect millions of people worldwide. Their common hallmark is the formation of a granuloma, a compact and often highly ordered aggregate of immune cells that forms in response to a persisting inflammatory stimulus. In its core, the granuloma consists of different macrophage subsets displaying a range of morphologies, such as epithelioid macrophages, foam cells (i.e., macrophages containing lipid droplets), multinucleated macrophages and multinucleated giant cells (i.e., Langhans cells). The molecular programs that control the differentiation of such macrophage populations in response to a chronic stimulus are likely critical for the outcome of disease. For example in tuberculosis, a pandemic infectious disease, distinct spectra of macrophage differentiation determine disease outcome. On the one end of the spectrum, microbicidal macrophages (producing reactive nitrogen species) kill intracellular bacteria while permissive macrophages provide them with a replicative niche.

Expression of pro-inflammatory cytokines by macrophage subsets promotes disease control while expression of inflammation-resolving lipid mediators promotes bacterial replication. Thus, the mechanisms controlling macrophage differentiation in granulomas are key to identifying novel strategies to promote host resistance.

Within the scope of understanding macrophage cell fate decisions in granulomas, an important and unresolved question relates to the issue of macrophage polyploidization. It is generally believed that the formation of polyploid giant cells can be explained by cell-to-cell fusion. While this has been well documented for RANKL-induced osteoclasts in vitro, direct evidence for cell-to-cell fusion for the genesis of the various polyploid macrophage subsets found in granulomatous diseases is lacking. Further, the fact that macrophages in granulomas carry various copies of their genomic information poses a series of basic questions that have not been addressed to date. How do polyploid macrophages deal with the genomic instability associated with carrying multiple copies of their genomic information? What is the role of the DNA damage response in macrophage differentiation into polyploid subsets? Do polyploid macrophages constitute a distinct fate that contributes to the pathogenesis of granulomatous diseases? Using an array of robust techniques and combining in vitro and in vivo granuloma models, we delineate a new macrophage differentiation pathway.
Sensing of bacterial lipoproteins control differentiation of proliferating macrophage precursors into polyplid macrophages expressing distinct metabolic and extracellular matrix-remodeling gene signatures. Toll-like receptor (TLR)2 signaling promoted macrophage genome duplications by modified cell divisions and mitotic defects but not by cell-to-cell fusion. TLR2-induced polyploid macrophages grew by re-entering the cell cycle and by overcoming p53-dependent barriers to their proliferation. TLR2 signaling promoted macrophage polyplid and alleviated genomic instability, inherent in a polyplid cell fate, by regulating Myc and the DNA damage response (DDR). Thus, we have unlocked a previously unknown and unique role of growth and DDR signals in determining macrophage differentiation in the presence of chronically persisting inflammatory stimuli.
GERMAN CENTERS OF HEALTH RESEARCH

German Cancer Research Center (DKTK)
German Center for Cardiovascular Research (DZHK)
OVERVIEW

The German Cancer Consortium (Deutsches Konsortium für Translationale Krebsforschung, DKTK) encompasses eight partner sites in Germany including the University Cancer Center Mainz (UCT Mainz), together with our partners in Frankfurt (UCT Frankfurt). The main task of the DKTK is translating innovations from basic research to clinical practice (bench-to-bedside) and vice versa (bedside-to-bench). With currently 10 Faculty members and 77 DIs (DKTK investigators), the UCT Mainz contributes strongly to several research programs within the DKTK, namely „Cancer Immunotherapy”, „Molecularly targeted Therapy” and „Exploitation of Oncogenic Mechanisms” plus a strong commitment to the program „Molecular Diagnostics, Early Detection and Biomarker Development”, „Radiation Oncology” and the Clinical Communication platform.

HIGHLIGHTS

In addition to the funding of the Junior Group led by Dr. Borhane Guezguez („Engineering Tumor Antigen-specific T cells from pluripotent stem cells as novel source for cancer immunotherapy applications”), specific projects funded by the DKTK in Mainz / with participation of researchers from Mainz include the development of comprehensive biomarker panels in cancer immunotherapy (Wölfel/Echchannaoui/Kindler/Theobald), glioblastoma research (Schmidt), mutant immunogenic epitopes for T cell therapy of cancer (Wölfel/Theobald) and CAR-NK cells (Theobald/Wels (FFM)). Mainz actively participates in the NCT MASTER (Molecularly Aided Stratification for Tumor Eradication Research) program, which aims at identifying individual, targeted treatment approaches for cancer patients applying whole-exome- and RNA-sequencing approaches. Prof. Düber from the Department of Radiology participated in the Joint Funding Initiative „IT infrastructure for Imaging” with his project „DKTK Joint Imaging Platform: Distributed IT Infrastructure for Multilateral Imaging Cohort Analysis” and Prof. Lang and PD Dr. Stefan Heinrich contributed to the JF initiative „Surgery” with their project „Surgical Oncology in the era of precision medicine: Identification of predictive markers for individualized surgical treatment of gastrointestinal tumors”. Additionally, researchers from Mainz actively participated in the DKTK program retreat in Heidelberg in October 2017.

FUTURE DIRECTIONS

Several collaborative scientific DKTK projects have been defined in which Mainz will contribute in a visible manner, such as:

- DKTK Imaging Network (Düber)
- Immune monitoring of combinational immunotherapy in patients with various cancers (Grabbe)
- Cross entity dissection of oncogenic RAS signaling networks for precision oncology (Kindler)
- Mutanome-encoded neoepitopes as tumor-specific target antigens for T cell therapy of solid cancers (Theobald/Wölfel)
- Novel approaches to screening and early detection in the high risk group of people with a family history of colorectal cancer (Roth)
- Personalized clinical vaccination trials against cancer (Sahin/Wölfel)
- Individualized surgical treatment of gastrointestinal tumors (Lang/Heinrich)

The Faber/Paret group will - together with Frankfurt- participate in the Joint Funding Project „Exploiting the methylome of circulating DNA for the early detection of pediatric brain Tumors” starting in 2018. Moreover, we have recently increased the number of our School of Oncology fellows from one to three plus three more applications pending. Additionally, we have a high number of motivated and enthusiastic young DIs who are eager to productively contribute to the different programs and platforms of the DKTK in 2018, helping to increase our visibility and impact within the consortium.
**IMPORTANT PUBLICATIONS // MAX. 5**


**IMPORTANT PROJECTS // MAX. 5**

- Impact of mutational pathways on immune environment, neoantigens and tumor rejection for the development of comprehensive biomarker panels in cancer immunotherapy
  - PROJECT MANAGER: Prof. M. Theobald, Dr. H. Echchannaoui, Prof. T. Wölfel, PD Dr. T. Kindler et al.
  - FUNDING: German Cancer Consortium (DKTK)
  - SUM: 999,900 €
  - PROJECT DURATION: 2017-2019

- Chimeric antigen receptor-engineered natural killer cells as a universal cellular therapeutic for adoptive cancer immunotherapy
  - PROJECT MANAGER: Prof. M. Theobald et al.
  - FUNDING: German Cancer Consortium (DKTK)
  - SUM: 999,900 €
  - PROJECT DURATION: 2017-2019

- Junior Group of the German Cancer Consortium: Emergence of Leukemia Cells in Bone Marrow.
  - PROJECT MANAGER/HEAD: Dr. Borhane Gueguez (Prof. M. Theobald)
  - FUNDING: German Cancer Consortium (DKTK)
  - SUM: 1,750,000 €
  - PROJECT DURATION: 2017-2022

- Aberrant EGFR signaling in malignant glioma
  - PROJECT MANAGER: Prof. MHH Schmidt, Dr. M. Teodorczyk
  - FUNDING: German Cancer Consortium (DKTK)
  - PROJECT DURATION: 2013-2018

**FIG. 1:** DKTK Program Retreat in Heidelberg in October 2017.
**FIG. 2:** In cell culture models with cancer cell lines or primary tumor cells, scientists validate novel therapeutic strategies.
**FIG. 3:** Dr. Borhane Gueguez, principle investigator of the new DKTK young investigator group for cancer immunotherapy.
The „German Center for Cardiovascular Research (DZHK)“ is one of the six German centers of health research (Deutsche Zentren der Gesundheitsforschung, DZGs) established by the German Federal Ministry of Education and Research (BMBF). The University Medical Center of the Johannes Gutenberg-University Mainz (UMC-Mainz) is part of the Center Rhine-Main of the DZHK. The translational research of UMC-Mainz concentrates primarily on identifying markers and mechanisms relevant for cardiac and vascular disease development and progression. A special focus is put on the entities heart failure and acute coronary syndrome, the interaction of structure and function of blood vessels and myocardial tissue, and the investigation of thrombosis mechanisms and platelet function.

STRUCTURE
In 2017, DZHK researchers at the UMC-Mainz comprise working groups from 6 principal investigators (PIs) and 10 DZHK researchers headed by the speaker and scientific coordinator, Prof. P. Wild. The Young DZHK supports the personal and professional development of currently 34 young scientists on their way to becoming independent, successful clinical scientists in cardiovascular research. A Clinical Study Group with dedicated staff implements and conducts clinical trials within the DZHK network. Nine clinical trials have been initiated or were ongoing in 2017. In the DZHK-internal ranking of study centers UMC-Mainz developed very positively. The DZHK W3-Professorship „Vascular and Myocardial Interaction“ (Prof. T. Gori) started in mid-2016 integrated in the Department of Cardiology. The local research program was successfully reviewed by an external review panel and is funded by the BMBF until 12/2018. The funding for the next program period was approved until 2020.

SCIENTIFIC WORKING PROGRAM
Cardiac dysfunction appears in varying clinical phenotypes ranging from subclinical changes to terminal heart failure and sudden cardiac death. The vascular system is central player and mediator of the development and course of myocardial disease. The MyoVasc-Cohort Study focuses on the transition from the asymptomatic to the symptomatic heart failure syndrome. This cohort includes a yearly follow-up of individuals with a deep phenotyping by a highly standardized 5-hour investigation in the study center including biobanking every two years. A 4-year follow-up (telephone interview and study center visit) of study participants was initiated in early 2017. By end of 2017, the cohort included over 3,000 individuals. A prospective cohort study for the evaluation of diagnostic and therapeutic strategies in the Chest Pain Unit (ProsPECTUS-Study) with comprehensive biobanking and detailed, structured follow-up investigations started in June 2014. More than 2,100 subjects have been recruited by end of 2017. The existing CPU cohort was expanded by individuals with elective cardiac catheterization. The biodatabase will be investigated by DZHK researchers from the UMC-Mainz. The research questions include topics like „Investigation of coronary pathophysiology and influence of new therapeutic approaches“, „Vascular phenotype and clinical outcome in CAD“, „Assessment of vascular-myocardial interactions in heart failure“ as well as „Peripheral endothelial and vascular function“. Within the professorship a translational and patient-oriented research approach is applied to improve diagnostics, therapy and prognosis of cardiovascular disease. The program focusses on the macro- and microcirculation of coronary arteries and is also making use of the generated biodatabases. In 2017, 8 projects were conducted by the UMC-Mainz within the funding program „Shared Expertise“. This program supports collaborations within the German network by sharing scientific competences, data and methods.
**FUTURE DIRECTIONS**

**SCIENTIFIC AIMS**
- To investigate the interaction of myocardial and vascular disease by especially focusing on molecular mechanism and cells,
- 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,
- To analyze mechanisms involved in thrombosis, and in-stent thrombosis, and
- To investigate at a molecular, functional and structural level myocardial infarction in low-risk individuals.

**STRUCTURAL AIMS**
- To foster young researchers in a career in cardiovascular science
- To extend the scientific collaboration within the DZHK network
- To strengthen the cardiovascular research program for a visible and sustainable participation of the UMC-Mainz within the DZHK
- To develop cooperations with industrial partners
- To develop a common regional concept for cardiovascular science with the Johann Wolfgang Goethe University Frankfurt for future sustainability.

*FIG. 1: Prof. Gori, DZHK W3 Professorship for Myocardial and Vascular Interaction. His focus of research is intracoronary imaging, coronary physiology and endothelial function.*

*FIG. 2: Echocardiographic 3D-analysis of cardiac function.*

*FIG. 3: Echocardiographic 3D-analysis of cardiac function.*
PROFILE CENTERS

Comprehensive Cancer Center: University Center for Tumor Diseases (UCT)
Integrated Research and Treatment Center: Center of Thrombosis and Hemostasis (CTH)
Center for Rare Diseases of the Nervous System (ZSEN)
**OVERVIEW**

The University Cancer Center (UCT) Mainz, selected as one of 13 centers of excellence in Germany in 2016 by the German Cancer Aid (DKH), provides a framework for diagnosis, treatment and psychosocial care for cancer patients at the University Medical Center Mainz. By organizing Tumor Boards for all cancer entities it offers a nexus for interdisciplinary diagnostic and therapeutic decisions. Four core research areas employ an increasing number of outstanding clinician and medical scientists in clinical, translational and basic research as well as outreach projects. With its Clinical Cancer Registry, state-of-the-art core facilities and growing liquid and solid biobank to support translational research, the UCT Mainz attracts interest of researchers from all over Germany and Europe.

**HIGHLIGHTS**

Following the distinction of the UCT as a CCC (Comprehensive Cancer Center) by the DKH, a major aim in 2017 was to establish necessary structures to strengthen our outreach program and our research profile. Positions for a Medical and a Scientific Coordinator were created, with additional support in quality management and administration. Increasing man power enabled us to coordinate the application for a comprehensive career center for Medical and Clinician Scientists published by the DKH. Together with already established investigators but also new researchers within the UCT the first step was successfully accomplished and a full grant version is currently prepared. The final decision is expected in Mid-2018. Additionally, the initiative for a new CRC, led by FZI, TRON and UCT scientists, was finally rewarded with the new CRC 1292 “Targeting Convergent Mechanisms of Inefficient Immunity in Tumors and Chronic Infections” in fall 2017. Moreover, funding for another CRC with UCT participation, CRC 1066 (Nanodimensional Polymer Therapeutics for Tumor Therapy), was extended for four more years in June 2017. The new DKTK (German Cancer Consortium) Young Investigator group led by Dr. Borhane Guezguez from the Department of Internal Medicine III was awarded a prestigious Emmy-Noether Fellowship by the DFG to build up his own group. Prof. Igor Tsaur and Dr. Hendrik Borgmann from the Department of Urology and Pediatric Urology received awards from the German Urology Society for their work on new biomarkers and treatments for prostate cancer. In May, Jonas Eckrich from the Department of Oto-Rhino-Laryngology, Head and Neck Surgery was awarded a research grant from the “Tumor Research in Head and Neck Foundation” for his work on the blood brain barrier and magnetic fields and in June, Dr. Jörg Fahrer from the Institute of Toxicology received the prestigious Boehringer Ingelheim Award for his work on PhIP, a newly discovered carcinogen. Epidemiologist Prof. Susanne Singer received the Helmut-Wölte Award for her work on improvement of psychological care for chemotherapy patients. Additionally, a team led by Prof. Manfred Beutel and Dr. Rüdiger Zwerenz received substantial funding for their psychoncological online self-help project from the G-BA (Gemeinsamer Bundesausschuss) Innovation Fonds. The Department of Urology and Pediatric Urology was certified by the DKG as prostate cancer center and the Breast and Gynaecological Cancer Center was re-certified for their Quality Management in an audit in August. Certifications by the DKG were also achieved for the Head and Neck Cancer Center as well as for the Visceral Oncological Cancer Center. Finally, the Oncology Center of Mainz was re-certified in November 2017. In September, the 27th German Skin Cancer Congress took place at the UCT/UMC-Mainz, organized by Prof. Grabbe and Dr. Loquai, bringing together national experts in the field.
Major aims for 2018 are the re-certification of the comprehensive Oncology Center as well as the implementation of a Pediatric Oncological Center. The establishment of a Molecular Tumor Board, will be completed, as well as the availability and expansion of the UCT biobank technology. The UCT partner network will be expanded, resulting in better treatment options for the patients’ benefit and increased participation in innovative clinical trials. Another focus will be on scientific interaction and acquisition of group funding tools at the UCT. We aim to strengthen our UCT TransMed Clinician Scientist program to bring more Clinicians into research and to provide an interface for intense collaborations with Medical Scientists on the development of new therapeutic options.

A comprehensive lecture series will be initiated whereby we hope to bring speakers from all fields of Cancer Research to Mainz to instigate national and international collaborations. Additionally, for the first time, a UCT Science Day will be organized on the 6th of September 2018 to serve as a think tank and hub for the scientists to share ideas. Integrated into the Science Day will be the Mildred Scheel Lectureship, which we are honored to organize in 2018, with a lecture given by Prof. Margaret Shipp, (Dana Farber Cancer Center, Boston, USA), a renowned expert in Lymphoma Research and Cancer Immunology. The Science Day will be followed by the 1st UCT Clinical Research Day on Sep, 7th.
Modern research in thrombosis and hemostasis is often characterized by the integration of basic science, clinical expertise, and the latest technologies. The Integrated Research and Treatment Center: Center of Thrombosis and Hemostasis (CTH) is a unique interdisciplinary environment that brings together scientists, clinicians, and technologists to advance our understanding of these complex biological processes.

**OVERVIEW**

The CTH serves as an Integrated Research and Treatment Center (IFB) and its associated clinical departments provide a unique interdisciplinary environment for basic research, the development of new diagnostic approaches and clinical evaluation of therapies. Research activities include investigations of molecular mechanisms in thrombosis and hemostasis, analysis of complex cellular interactions in vascular biology and thrombo-inflammation, translational experimental and clinical studies, and investigator-initiated, international multicenter studies. In 2017, the platform infrastructure was expanded by addition of new experimental models, a new intravital confocal spinning disk microscopy work station and a successful application for a new DFG-funded high resolution ultrasound device.

**HIGHLIGHTS**

**CAREER DEVELOPMENT PROGRAM**

The CTH supports young Clinician Scientists by offering protected time for research and biomedical researchers by funding career advancing independent projects. In 2017, the CTH Fellows participated in 26 CTH-affiliated publications and 3 of our fellows, Dr. S. Steven, Dr. S. Kossman, and Dr. C. Graf, secured new DFG funding.

**RESEARCH HIGHLIGHTS**

Major translationally important findings were published by CTH investigators in 2017. Virchow Fellow Dr. S. Kossman in the group of Prof. P. Wenzel described a novel mechanism that connects the hemostatic system with vascular inflammation and hypertension. They delineated that platelets orchestrate a factor XI feedback loop that amplifies leukocyte infiltration of the vessel wall relevant for the chronic complications of hypertension. Dr. S. Jäckel working with Jun.-Prof. C. Reinhardt uncovered a new connection between gut microbiota and thrombosis. Using germ-free mouse technologies established at the CTH, they described a role for the innate immune receptor TLR2 in influencing the production of the prothrombotic von Willebrand Factor in the liver. This study sheds new light on how nutrition can contribute to the tendency for developing thrombosis. The study of Dr. S. Subramaniam working with Prof. W. Ruf delineated unexpected interactions of the anti-microbial complement system and thrombosis. Complement influences both, the activation of blood platelets and the coagulation system. Because complement inhibitors are already used in patients with hematological disorders, these results indicate new therapeutic modalities for treating thrombosis in inflammatory disorders. Virchow Fellow Dr. M. Bochenek and colleagues characterized the cellular and structural composition of lung tissue from CTEPH patients and defined the different stages of thrombus organization towards fibrosis. The immune cell composition and expression profile suggest that hypoxia plays a role in the pathophysiology of the disease. Junior group leader Dr. J. Prochaska determined age-dependent changes in inflammatory blood markers and their value in assessing thrombosis risk. These epidemiological studies provided new insight into connections between inflammation and thrombosis. The multi-center PEITHO trial of Prof. Konstantinides revealed that long-term thrombolytic treatment does not affect long-term mortality rates and residual pulmonary hypertension or right ventricular dysfunction in patients with intermediate-risk pulmonary embolism.
IMPORTANT PUBLICATIONS // MAX. 5


EVENTS 2017

Prof. Konstantinides and his team organized the 3rd European Spring School on VTE in Greece with international experts discussing state-of-the-art treatment and understanding of the disease. With 16 oral and 3 invited presentations, the CTH was well represented at the Berlin Congress of the International Society on Thrombosis and Haemostasis that was held for the first time in Germany. Prof. Lämmlle received the BACH Distinguished Career Award for his long-standing research on TTP.

FUTURE DIRECTIONS

PATIENT CARE

The major goals for the upcoming years are to create a sustainable translational center and develop the (inter)national profile of the CTH as reference center for integrated multidisciplinary patient care and translational research. In 2017, the integration of the outpatient clinics for thrombophilia (previously located in the CTH), and bleeding disorders (previously located in the Department of Internal Medicine III) was implemented. Now, physicians of the CTH and the Med III treat all patients in the joint outpatient clinic for hemostaseology.

SUPPORT OF YOUNG SCIENTISTS

The external scientific advisory board (ESAB) approved the applications of six new Virchow Fellows who will start their projects beginning of 2018. A cornerstone of the CTH career program is to support the career development beyond the post-doctoral training. Three Physician Scientist were appointed to junior group leader positions beginning in 2018. Dr. S. Barco will initiate a research program on Clinical and translational research in VTE, Dr. C. Graf will investigate Coagulation factors in immunity, and Dr. S. Karbach will focus her research on Systemic inflammation and vascular disease.

IMPORTANT PROJECTS // MAX. 5

Cardiac and vascular late sequelae in long-term survivors of childhood cancer-study (CVSS-study)

PROJECT MANAGER:
Prof. P Wild, Prof. J Faber, Dr. H Merzenich
FUNDING: German Research Foundation (DFG)
SUM: € 1,142,680
PROJECT DURATION: 2013 - 2017

Cross-talks between oxidative and ER stress influencing metabolic regulation

PROJECT MANAGER:
Prof. W Ruf
FUNDING: Boehringer Ingelheim International GmbH
SUM: € 504,000
PROJECT DURATION: 2017 - 2019

Extracellular histones in acute lung injury and fibrosis

PROJECT MANAGER:
PD Dr. M Bosmann
FUNDING: German Research Foundation (DFG)
SUM: € 248,356
PROJECT DURATION: 2017 - 2020

HoT-PE: Home Treatment of Patients with Low-Risk Pulmonary Embolism with the Oral Factor Xa Inhibitor Rivaroxaban: Prospective Management Trial

PROJECT MANAGER:
Prof. S Konstantinides
FUNDING: Bayer AG
SUM: € 1,700,000
PROJECT DURATION: 2017 - 2019

Microbiota-induced morphogenetic adaptation of the small intestine

PROJECT MANAGER:
Junior Prof. C Reinhardt
FUNDING: German Research Foundation (DFG)
SUM: € 231,800
PROJECT DURATION: 2017 - 2019

RESEARCH REPORT 2017

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OVERVIEW

The Center for Rare Diseases of the Nervous System (ZSEN) was founded in 2014 as the central translational backbone of the Focus Program Translational Neurosciences (FTN). The aim of this center is to strengthen the care of patients with rare diseases in the areas of diagnostics, treatment and patient management through an interdisciplinary approach. ZSEN is thus closely interlinked with the strong basic research conducted at the FTN and within the Rhine Main Neuroscience Network (rmn²) in order to stimulate the development of innovative therapies. To this end, the close interlinking of ZSEN with other national and international centers for rare diseases is also of decisive importance.

HIGHLIGHTS

A monthly interdisciplinary meeting has been established, in which extraordinary cases and research strategies are discussed. Additionally, various interdisciplinary consultation hours established, such as for Genetic Movement Disorders/Huntington’s (Department of Neurology, sect. for Movement Disorders and Neurostimulation, Department of Psychiatry and Psychotherapy, and the Institute of Human Genetics) and for Children with Rare Diseases with Behavioral Problems (Department of Child and Adolescent Psychiatry and Psychotherapy, and the Institute of Human Genetics).

Several national and international structures and connections have been established since the founding of ZSEN. In particular, the support of the medical information consortium MIRACUM should be mentioned here. Within the scope of this partnership, a data integration center is to be established in Mainz with the aim of collecting relevant patient information in one database, thereby contributing to the improvement of the diagnostics and therapy for patients with rare diseases. In addition, a proposal has been developed with the aim of improving the psychosomatic and psychiatric care of patients at the ZSEN within the framework of the BMBF’s innovation fund.

The B-center Neurometabolic Diseases was successfully established within the framework of the European Network MetabERN (see below). ZSEN is also involved in the Deciphering Developmental Disorders (DDD) study of the British Genome Center (Sanger Center) and is a member of the European Huntington’s Disease Network (EHDN).

Furthermore, ZSEN was granted a participant slot in the international observation study Enroll-HD and also participates in the international consortium for the investigation of the ATP1A3 diseases, as well as in the national initiative for the diagnosis of Niemann-Pick Type C disease. Research infrastructures within the framework of the FTN (Mouse Behavioral Unit [MBU], the Mainz Animal Imaging Center [MAIC], the Neuroimaging Center [NIC] and the Clinical Investigation Center [CIC]) were strengthened; all while also linking them to the ZSEN. A stem cell laboratory with an iPS (induced pluripotent stem cells) cell pipeline was established for the creation of patient- and tissue-specific cell models. Innovative treatments with small molecules and new enzyme replacement therapies were started in phase 1, 2 and 3 trials for various rare lysosomal diseases.

INNOVATION FUND

In 2017, an application of the ZSEN together with 10 other German centers for rare diseases to the Innovation Fund for a network to improve diagnosis of patients with unexplained rare diseases (“ZSE-DUO”) was positively assessed. Aim of the network is to improve and to fasten diagnosis in patients with or suspected to have a rare disease, as well as of those with an unclear, complex pattern of symptoms to improve efficacy of diagnostics and to early transfer patients to standard care.
Established structures are to now be used to develop novel therapies. In the Huntington Research and Treatment Center, patients are examined at the prodromal stage to define parameters for clinical trials. The next step, to be carried out in cooperation with the EHDN, is to test substances which have proven to be promising in mouse models on patients. Similar approaches can also be found in studies of genetic autism and of the genetic reduction of intelligence. For rare lysosomal diseases, treatment of brain disease in progressive neurodegenerative disorders, e.g. for Niemann-Pick disease type C, Gaucher disease type 3, are in development.

**IMPORTANT PUBLICATIONS // MAX. 5**


Mengel E, Pineda M, Hendriksz CJ et al. Differences in Niemann-Pick disease Type C symptomatology observed in patients of different ages. MOLECULAR GENETICS AND METABOLISM. 2017; 120 (3): 180-189.


**EUROPEAN NETWORK FOR RARE DISEASES**

The establishment of European reference networks serves the exchange of knowledge, the expansion of joint studies and the improvement of health care in the EU. The European network for rare congenital metabolic diseases, MetabERN was established by the EU in 2016. At the request of the Villa Metabolica, ZSEN is a member of MetabERN and is responsible for lysosomal storage disorders as well as diseases of the amino acid and neurotransmitter metabolism. ZSEN’s participation in MetabERN strengthens its external impact.

MetabERN seeks to network the expertise of metabolic centers within Europe, standardize the collection of data within all participating European metabolic centers and to establish uniform procedures for prevention, diagnostics and treatment of these disorders and diseases. Moreover, the aim is to develop and establish European guidelines, as well as cross-national joint research projects on the subject, and to further new innovative therapeutic developments and to develop and expand the education and training opportunities currently available in this area.

**FUTURE DIRECTIONS**

Established structures are to now be used to develop novel therapies. In the Huntington Research and Treatment Center, patients are examined at the prodromal stage to define parameters for clinical trials. The next step, to be carried out in cooperation with the EHDN, is to test substances which have proven to be promising in mouse models on patients. Similar approaches can also be found in studies of genetic autism and of the genetic reduction of intelligence. For rare lysosomal diseases, treatment of brain disease in progressive neurodegenerative disorders, e.g. for Niemann-Pick disease type C, Gaucher disease type 3, are in development.
RESEARCH PLATFORMS

Interdisciplinary Center of Clinical Studies (IZKS)
Neuroimaging Center (NIC)
Translational Animal Research Center (TARC)
Biomaterials in Medicine (BioAPP)
OVERVIEW

The Interdisciplinary Center for Clinical Trials (IZKS) is an academic coordination center for clinical trials. As a central facility of the University Medical Center Mainz (UMC-Mainz), IZKS closely cooperates with all clinical departments, institutes and divisions of UMC-Mainz. Furthermore, IZKS supports all clinical departments of UMC-Mainz in patient-oriented research by improving qualification of clinical trial personnel. IZKS collaborates with academic and non-academic partners in medicine and translational research and conducts numerous scientific projects with partners in Germany and Europe. Because of the widespread portfolio of its employees, IZKS is able to cover every aspect of clinical trials, such as planning, coordination, implementation and publication.

HIGHLIGHTS

- In 2017, IZKS conducted more than 40 trials. The broad study spectrum of the IZKS ranges from public to industrially funded trials including a very wide range of indications (more than 20 disease entities), confirming the clear trend towards large multicenter and multinational projects.
- About 40 trained and experienced medical, scientific, and technical employees at IZKS contributed to planning, coordination, evaluation, and publication of clinical trials. The employees are organized in matrix-oriented specialized teams: Study Coordination, Clinical Monitoring, Safety Management, Regulatory Affairs, Statistics, Data Management, and Study Systems and Processes.
- IZKS supported over 15 funding proposals of different public institutions such as BMBF, DFG and EU.
- 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.
- IZKS is certified by the Independent Certification Board of ECRIN (European Clinical Research Infrastructures Network) as high-quality data centre until 2020. The ECRIN Data Centre Certification programme identifies non-commercial clinical trial units in Europe demonstrating that they can provide safe, secure, compliant and efficient management of clinical research data. The program tests units for compliance with ECRIN data standards in various areas (IT, general, data management) through on-site audits. ECRIN strongly recommends the use of certified data centres for the multinational trials it supports (see www.ecrin.org).
- Furthermore, IZKS has continued with its focus on translational research as well as health care research. For example, IZKS provides key services in a translational project which receives funding by the Federal Joint Committee (Gemeinsamer Bundesausschuss - G-BA) in order to develop new forms of health care. Therefore, IZKS has expanded its randomisation and registry tool to a flexible project management software that can be adapted according to customers’ needs.
FUTURE DIRECTIONS

• To provide full and high quality service according to the requirements of clinical trials at the UMC-Mainz including all aspects of clinical research.
• To fulfill the ICH-GCP guidelines with focus on conception, planning, organization, monitoring and analysis of innovative clinical trials by investigating drugs, medical devices, or other interventions.
• To successfully prepare the implementation of the new EU regulation 536/2014.
• To successfully prepare the implementation of the new amended version of the international guidelines for GCP: ICH GCP E6 (R2)
• To further improve the quality, quantity, and efficacy of clinical trials with emphasis on prospective, randomized, controlled clinical trials, translational research, health care research, registries, and EU-research projects.
• To increase the number and qualification of study personnel at the UMC-Mainz and implement new GCP and investigator training courses,
• 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), German Cancer Aid (DKH), European Commission, and pharmaceutical and medical device industry.
• To further establish close collaborations with other University Hospitals and Biomedical Research Institutions in Germany.
• To expand national and international trial networks in Europe.

IMPORTANT PROJECTS // MAX. 5

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 - 2018

NeoVita: A prospective, multicenter, double blind, placebo-controlled, two-arm parallel group phase 3 trial to evaluate the effect of early postnatal additional high dose oral vitamin A supplementation of 5000 IU/kg/d versus placebo for 28 days for preventing bronchopulmonary dysplasia (BPD) or death in extremely low birth weight (ELBW) infants.
PROJECT MANAGER: Prof. S. Meyer; Dr. A. Ehrlich
FUNDING: German Research Foundation (DFG)
SUM: € 1,200,000
PROJECT DURATION: 2012 - 2018

PAD-ON: Peg-interferon AddEd to an Ongoing Nucleos(t)ide based treatment in patients with chronic hepatitis B to induce decrease of HBs antigen
PROJECT MANAGER: Prof. P. Galle, Dr. A. Grambihler, PD Dr. M. Springl
FUNDING: Roche Pharma AG
SUM: € 1,200,000
PROJECT DURATION: 2012 - 2017

PEITHO-2: Safety and efficiency of low molecular weight heparin for at least 72 hours followed by dabigatran for the treatment of acute intermediate-risk pulmonary embolism (Pulmonary Embolism International Trial)
PROJECT MANAGER: Prof. S. Konstantinides
FUNDING: Boehringer Ingelheim
SUM: € 4,200,000
PROJECT DURATION: 2014 - 2018

The GOAL trial: Rescue treatment with the monoclonal anti CD20-antibody Obinutuzumab (GA101) in combination with Ptxane for the treatment of patients with relapsed aggressive B-cell Lymphoma
PROJECT MANAGER: Prof. G. Heß
FUNDING: Roche Pharma AG
SUM: € 976,700
FUNDING: CTI
SUM: € 250,000
PROJECT DURATION: 2015 - 2022
OVERVIEW

The Neuroimaging Center (NIC) is a core research platform of the University Medical Center Mainz. The NIC provides assistance with neuroimaging and behavioral research in humans to all interested parties at the University Medical Center Mainz as well as to cooperation partners within the Focus Program Translational Neuroscience (FTN) in Mainz. Regular users include the departments of Neurology, Psychiatry and Psychotherapy, Psychosomatic Medicine and Psychotherapy, Microscopic Anatomy and Neurobiology (all University Medical Center), and Clinical Psychology and Neuropsychology (Institute of Psychology).

HIGHLIGHTS

SERVICES

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 annual courses in design and analysis of functional MRI experiments, in magnetic resonance spectroscopy (MRS), and courses in Matlab programming 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 resilience, 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 PROJECTS // MAX. 5**

<table>
<thead>
<tr>
<th>Project Name</th>
<th>Project Manager</th>
<th>Funding</th>
<th>Sum</th>
<th>Project Duration</th>
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<tbody>
<tr>
<td>CRC 1193: Neurobiology of Resilience to stress-related mental dysfunction (Project C01)</td>
<td>Prof. R Kalisch, Dr. S Duvarci</td>
<td>German Research Foundation (DFG)</td>
<td>€ 477,200</td>
<td>2016 - 2020</td>
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<tr>
<td>CRC 1193: Neurobiology of Resilience to stress-related mental dysfunction (Projekt B01)</td>
<td>Prof. R Kalisch, Dr. S Duvarci</td>
<td>German Research Foundation (DFG)</td>
<td>€ 396,800</td>
<td>2016 - 2020</td>
</tr>
<tr>
<td>Mainz Resilience Project (MARP)</td>
<td>Prof. R Kalisch, Dr. A Schick</td>
<td>Ministry of Science, Rhineland-Palatinate</td>
<td>€ 888,700</td>
<td>since 2013</td>
</tr>
</tbody>
</table>
OVERVIEW

The Translational Animal Research Center (TARC) is responsible for all aspects of housing and breeding of laboratory animals. Our veterinarians and scientists specialized for laboratory animal science and animal welfare take care of all belongings of the facility. The protection of the hygiene and the import and export of laboratory animals are part of our services as is the counseling of scientists regarding the planning and implementation of animal experiments. Our biotechnology unit provides a full range of state-of-the-art services, from cryopreservation and IVF to the generation of genetically modified mice and also supports research projects. Another central area is our training program for scientists, where we offer a steadily growing number of training courses for the work with laboratory animals.

HIGHLIGHTS

We provide a variety of services, such as:

- breeding and housing of laboratory animals
- protection of the hygiene and health monitoring
- import and export of laboratory animals
- education courses for scientists (for all required qualifications for the work with laboratory animals)
- education program for veterinary and scientist to become a specialist for laboratory animal sciences
- generation of genetically modified mice
- support of research projects
- counseling of scientists regarding animal experiments

RESEARCH

The main focus of our research is on the 3Rs (Replace, Reduce and Refine). The 3Rs 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 one of our primary concerns. 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, were implemented. 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 and experimental conditions. 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. Therefore we introduced clicker training as a specific handling program, which has already been shown to be beneficial in other captive animals. Other projects aim to develop replacement models, which help to at least reduce the number of animals used for education and research. 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:** Rat handling.
**FIG. 2:** Animal facility.
**FIG. 3:** Advanced education course.
**FIG. 4:** Clicker training: mouse following a target stick.
Biomaterials in Medicine (BioAPP)

Head:
Professor Bilal Al-Nawas

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 Mainz) and the interdisciplinary network of material scientists at the Johannes Gutenberg University Mainz with specialized analytical methods not available in the standard laboratory equipment. The structural and chemical composition analysis by means 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), X-ray microtomography (μCT) and 3D-Printing technologies.

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 collagen membranes
- Treated and untreated metallic implants
- Characterization of the polymeric coating of implants by means of XPS
- Characterization of new ceramic implants
- 3D-Printing Technology: Development of 3D-printed bone graft materials
- In-vitro and in-vivo characterization of biocompatibility and biomechanical properties of a new acellular collagen matrix
- Opacification of hydrophilic acrylic intraocular lens attributable to calcification
- Soft-tissue imaging of mouse embryos by micro-CT
RESEARCH PLATFORMS

RESEARCH REPORT 2017

IMPORTANT PUBLICATIONS // MAX. 5


FUTURE DIRECTIONS

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)
- Electronphotospectroscopy 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. W.Tremel)
- FT-Raman, FT-IR, IR-Microscopy (Group of Prof. E Rentschler)
- Thin section cutting technology, 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)

IMPORTANT PROJECTS // MAX. 5

Accuracy of magnetic resonance imaging in monitoring neovascularization after guided bone regeneration - a preliminary study
PROJECT MANAGER: Prof. B Al-Nawas, Dr. L Righesso
PROJECT DURATION: 2016 - 2019

Analysis of posthemorrhagic vasospasm in the mouse model of subarachnoid hemorrhage
PROJECT MANAGER: Prof. F Ringel, Dr. A Neulen
PROJECT DURATION: 2016 - 2019

Bone Substitutes Developed from 3D-Prints of PLA
PROJECT MANAGER: Dr. U Ritz, Prof. PM Rommens, h.c.
PROJECT DURATION: 2017 - 2019

Evaluation of bone sialoprotein in bone regeneration
PROJECT MANAGER: Dr. U Ritz, Dr. A Branowski
PROJECT DURATION: 2016 - 2020

Soft-tissue imaging of mouse embryos by micro-CT
PROJECT MANAGER: Prof. C Niehrs, Dr. S Ritz, H Götz
PROJECT DURATION: 2016 - 2019
PROGRAMS FOR EARLY STAGE RESEARCHERS

RTG 2015 Life Sciences - Life Writing
Mainz Research School of Translational Biomedicine (TransMed)
Participation in further Graduate and Postdoc Programs
OVERVIEW

The Research Training Group (RTG) converges the areas of life sciences and life writing 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 RTG started in April 2014. Since then, we managed to publish numerous 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. Novel neurobiological and psychiatric approaches to resilience are a major focus of our group. In close collaboration with the German Resilience Center (ORZ), Mainz, we are currently exploring boundaries between the fostering of resilience and more or less subtle forms of neurocognitive enhancement. Our goal is to stimulate an ethical discourse on the ethical and social dimensions of resilience research and derived applications which are based on a deep epistemological understanding of the explanatory reach of both, neurobiological and behavioral concepts of resilience.

2. Historical findings are effectuated to unveil culturally contingent practices of organ harvesting. We joined an international group of scientists from the US, Canada und Germany addressing unethical practices of organ harvesting in China. Numerous publications were prepared and submitted. We are currently investigating the role of international agencies in banning organ harvesting in prisoners and continue to publish in this field.

3. 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 cooperation with the Institute of Pharmacology at the University Medical Center of the Johannes Gutenberg University we are working on transcultural and ethical aspects of biopiracy and of xenobiotics in the framework of eco-criticism.

Our work in clinical ethics resulted in a closer scientific cooperation with our Neonatal Intensive Care Unit (NICU). Especially the impact of language and the framework of decision making and prognosis was explored. First results were published in 2016.

In 2016 and 2017, Prof. Ilhan Ilkilic, M.A., Professor for History and Ethics of Medicine at Istanbul University and member of the German National Ethics Council (Deutscher Ethikrat), joined the program as a DFG Mercator Fellow.
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. In this regard we are currently extending our research regarding posttraumatic stress disorder (PTSD) into more fundamental questions of resilience (together with Prof. Klaus Lieb, Mainz, and Prof. Frank Stahnisch, Calgary). Furthermore we are preparing grants at the interface of narrative knowledge and neurosciences.
Mainz Research School of Translational Biomedicine (TransMed)

Program Director:
PD Dr. Julia Weinmann-Menke

Program Coordinator:
Dr. Petra M. Schwarz

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Head of the Office for Doctoral Affairs
phone: +49 (0) 6131 17-9149
petra.schwarz@uni-mainz.de

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 2017, additional TransMed Fellows have been selected through a competitive application procedure. Two TransMed Fellowships were awarded to natural scientists performing a PhD; two further fellowships were awarded to clinician scientists. One of the new appointed clinician scientists works in the field of clinical oncology and cancer research (UCT / TransMed Fellow).

The TransMed Fellow community now consists of 89 scientists, twelve of them are clinician scientists. The support by TransMed allows the clinician scientists — in parallel to their specialist training — protected time to perform their research project for half of the duration of the fellowship. The other 77 fellows are natural scientists performing a PhD or Dr. rer. nat. thesis. As medical scientists 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 2017, seven doctoral candidates successfully completed their theses and were awarded a PhD in Translational Biomedicine (six of them) and a Dr. rer. nat. in Chemistry (one), respectively.

Within the structured training program, TransMed offers a wide range of transferable skills courses in the fields of academic performance, management competences, and career planning. TransMed also hosts several training elements offered by the research foci „Immunotherapy“, „Translational Neurosciences“, „Translational Vascular Biology“, and „BiomaTiCS“. For medical students performing experimental thesis projects, TransMed offers basic „how to…“ training elements.

In September 2017, the fourth TransMed Science Day brought together more than 150 participants (doctoral students, postdoctoral fellows and senior scientists) working in translational medicine. Doctoral students gave short talks on their project and their respective mentors evaluated the progress of the students and provided guidance towards future goals. The participants discussed about scientific publications and „bench-to-bedside“ approaches with the pharmaceutical industry. An internationally renowned speaker gave a perspective talk about translational research. Special meet-the-speaker sessions facilitated the informal exchange.
FUTURE DIRECTIONS

- Final preparations for a Graduate School for Medical Thesis Students (MAInz-DOC; start in 2019) within the scope of an improved basic scientific training for medical students
- Opening of the clinician scientist program for junior clinician scientists (in the first two years of residency)
- Further development of the training for (advanced) clinician scientists and medical scientists

FIG. 1: Part of the TransMed Fellow community with the TransMed Program Director PD Dr. med. Julia Weinmann-Menke (first from right) and the TransMed Program Coordinator Dr. rer. nat. Petra Schwarz (second from right).
PARTICIPATION IN FURTHER GRADUATE AND POSTDOC PROGRAMS

MAX PLANCK GRADUATE CENTER (MPGC)

The Max Planck Graduate Center (MPGC) is a virtual department across two Max Planck Institutes and four faculties of the Johannes Gutenberg University in Mainz, one of which is the University Medical Center. The MPGC offers an advanced PhD program characterized by excellence and interdisciplinarity, with integrative projects in the fields of biology, chemistry, physics, and medicine. PhD students receive support in the form of a work contract during their enrollment in the program. Three PhD students affiliated with the University Medical Center were enrolled in the MPGC program in 2017; one of them graduated during the year.

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MARI CURIE TRAINING NETWORKS

[NeuroKine - Initial Training Network for Neurological disorders orchestrated by cytoKines, funded by EU FP7] The Marie Curie Initial Training Network’s aim is to train young and ambitious researchers in Neuroimmunology. The project is coordinated at UMC-Mainz and supervised by Professor Dr. Ari Waisman. NeuroKine combines prominent academia and industry laboratories in Mainz, Zurich, Vienna, Rotterdam, and Berlin, among others, to study the communication networks between immune and CNS-resident cells. From a total of 15 participating young researchers in 2017, one postdoctoral and two PhD researchers were trained at the University Medical Center.

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[LISTEN - Liaison in Scientific Training for European auditory Neuroscience, funded by EU Horizon2020] The Marie Skłodowska-Curie Innovative Training Network will train 10 early stage researchers during its project duration, with one PhD student being trained at the University Medical Center Mainz. The individual PhD-projects conducted in Rotterdam, Leicester, Goettingen, Paris, Salamance, London, and Mainz focus on neural coding of sounds from the cochlea to neocortex in both normal hearing and following hearing loss, and in cellular mechanisms of tinnitus. Professor Dr. Simon Rumpel supervises the training at the University Medical Center Mainz.

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INTERNATIONAL PHD PROGRAMME (IPP)

The International PhD Programme coordinated by the Institute of Molecular Biology (IMB) and funded by the Boehringer Ingelheim Foundation offers PhD students the possibility to conduct research at the cutting edge of modern life sciences. A wide range of topics are covered within the program: the overarching theme of Gene Regulation, Epigenetics and Genome Stability, includes expertise in biochemistry, genetics, cell and developmental biology, bioinformatics, systems biology and applied physics. The University Medical Center hosts 16 research groups involved in IPP. In 2017, the University Medical Center oversaw the training of 25 students; two of them graduated during the year.

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INTEGRATED RESEARCH TRAINING GROUPS WITHIN CRCs

[CRC 1066 - Nanodimensional polymer therapeutics for tumor therapy] The Collaborative Research Center 1066 „Nanodimensional polymer therapeutics for tumor therapy“ offers an Integrated Research Training Group introducing young researchers to a wide variety of scientific topics in order to foster a lively exchange between researchers from different disciplines, such as chemistry, pharmacy, physics and biomedicine. Amongst the many benefits this training group offers PhD students are the organization of lecture series, tutorials, student seminars, and summer schools. In 2017, researchers from the University Medical Center supervised 11 of the CRC’s 38 PhD students.

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zentel@uni-mainz.de
www.crc1066.uni-mainz.de/graduate-school

[CRC 1080 - Molecular and Cellular Mechanisms of Neural Homoeostasis] The Collaborative Research Center CRC 1080 „Molecular and Cellular Mechanisms of Neural Homoeostasis“ provides an interdisciplinary training program offering support to five PhD students during their doctoral studies at UMC in 2017. The CRC’s guiding principles are to explore the fundamental molecular and cellular processes that enable the nervous system’s acquisition and retention of a homeostatic state during development, achievement of homeostasis during adult life, and, in response to adversity, adjustment to new set-points.

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PRE-CLINICAL INSTITUTES

Institute of Functional and Clinical Anatomy
Institute of Microscopic Anatomy and Neurobiology
Institute of Pathobiochemistry
Institute of Pathophysiology
Institute of Physiological Chemistry
Institute of Physiology
Institute of Functional and Clinical Anatomy

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Director:
Professor
Erik Schulte

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.

HIGHLIGHTS

MAIN FOCUS OF RESEARCH

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 and molecular-biological techniques.

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. The focus of our laboratory are processes fundamental to normal tissue repair and regeneration; the perturbation of these processes is a major contributor to lung disease and lung cancer. The Ackermann research group also further investigated the effects of angiogenesis in inflammatory processes and tumors. 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 (as the „Theatrum anatomicum et chirurgicum“).
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.

RESEARCH GROUP ACKERMANN

The accumulation of excess connective tissue after injury and repair leads to scarring and organ fibrosis. A cell-type common to all forms of fibrotic disease is the myofibroblast. Our recent single-cell gene expression data has suggested that the myofibroblast is the pivotal „regenerative cell“ during compensatory lung growth. Our central hypothesis of this application is that the common pattern of fibrosis in different organ systems is a reflection of the tissue migration of blood-borne myofibroblasts. We will characterize the single-cell transcriptional activity of myofibroblasts isolated from the evolving lung fibrosis. The long-term goal of our research program is to identify control points in normal wound healing and potential therapeutic targets in human fibrotic disease.

IMPORTANT PROJECTS // MAX. 5

<table>
<thead>
<tr>
<th>Project</th>
<th>Title</th>
<th>Project Manager(s)</th>
<th>Funding</th>
<th>Duration</th>
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<td>Adult tissue morphogenesis: Functional regulation of intussceptive angiogenesis</td>
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<td>PD Dr. M Ackermann</td>
<td>National Institutes of Health (NIH) USA</td>
<td>2009 - 2018</td>
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<td>Exploring the niche for lung stem cell replacement</td>
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<td>National Institutes of Health (NIH) USA</td>
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<tr>
<td>Morphogenetically active matrix for cartilage repair</td>
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<td>PD Dr. M Ackermann</td>
<td>National Institutes of Health (NIH) USA</td>
<td>2017 - 2018</td>
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<tr>
<td>The circadian system in diabetic retinopathy</td>
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<td>Prof. R Spessert, P Vancura</td>
<td>National Institutes of Health (NIH) USA</td>
<td>2015 - 2018</td>
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<tr>
<td>The role of the gene Clock in diabetic retinopathy</td>
<td></td>
<td>Prof. R Spessert, Dr. T Wolloscheck</td>
<td>National Institutes of Health (NIH) USA</td>
<td>2015 - 2018</td>
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IMPORTANT PUBLICATIONS // MAX. 5

Acknowledgments: We acknowledge the financial support of the National Institutes of Health (NIH) USA (Grant Number: T32HL007247) for the study of circulating myofibroblasts in lung fibrosis.

**FIG. 1:** Retina of wild-type mice - fluorescence microscope image - AG Spessert.
**FIG. 2:** Synchronous radiation tomographic microscopy reconstructions of microvascular corrosion casts of liver fibrosis illustrate the vascular alterations in hepatic microvasculature - AG Ackermann.
**FIG. 3:** Scanning electron micrograph of cerebral microvasculature shows various altered microaneurysms in mice with Alzheimer's disease - AG Ackermann.
**FIG. 4:** The alterations of microvascular architecture of pulmonary fibrosis in the bleomycin mouse model, (SEM, top, SRXTM, below).
HIGHLIGHTS

The „Molecular Signal Transduction” labs of MHH 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 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, including their implications in resilience disorders. II) It is studied how malignant brain tumors, e.g., glioma are formed and how they can be treated beyond conservative medicine. These studies have the goal to offer new and unexplored alternatives for the cure of brain neoplasms. III) The molecular causes of neurovascular diseases, such as stroke, are explored and it is studied how these diseases can be prevented, cured or at 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 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.

Albrecht Stroh’s group combined spatio-temporally precise optical Ca2+ recordings with blood oxygenation level-dependent (BOLD) fMRI and optogenetics. Correlating localized and spiking-specific Ca2+ recordings with offMRI, both the specificity of offMRI and the scope of optogenetic network recruitment could be assessed. In the context of slow oscillations, we developed an amplitude and duration-based algorithm capturing slow-oscillation-associated Up-Down state transitions in the Ca2+ traces. Using this vector as a regressor for the fMRI data, we discovered a spatially confined correlation between spontaneous slow oscillatory activity and the BOLD signal, the entire cortical network oscillates in synchrony to the locally optically recorded slow oscillations.

Johannes Vogt’s group studies have shown that a recently reported SNP in prg-1 (R345T/mutPRG-1) affecting 5 million European and US citizens resulted into a loss-of-PRG-1-function at the synapse due to its inability to control LPA levels via a cellular uptake mechanism. Using EEG-recordings in a human population-based cohort we found an E/I balance shift in mutPRG-1 carriers and an impaired sensory gating which is regarded as an endophenotype of psychiatric diseases. Furthermore, it was shown that PRG-2 is crucial for thalamo-cortical axon guidance. Loss of PRG-2 resulted in a misrouting of these fibers and relied on lost axonal sensitivity towards lysophosphatidic acid (LPA), which failed to repel PRG-2-deficient fibers and resulted in sensory discrimination deficits in PRG-2/- animals.
FUTURE DIRECTIONS

MHH Schmidt’s research work aims at understanding the CNS and its pathologies in order to develop novel therapies; observing and illustrating neural processes in vivo as well as exploring the basis of brain development and function. Albrecht Stroh’s research work aims at causally investigating an oscillatory neuronal population activity highly relevant to maintaining cognitive function, i.e., the slow oscillation. Just recently, a link between the level of cortical excitability, slow oscillations, normal network function, and behavior was suggested. Slow oscillations can hence be characterized as cortical on/off states constituting an important mechanism for long-range cortical and subcortical coherence. 

Johannes Vogt’s research work aims at developing specific therapies for psychiatric and neurological disorders relying on altered cortical hyperexcitability syndromes. These include disorders like schizophrenia as well as hyperexcitable cortical states as present after stroke. They are also working on the role of metabolic changes in altering cortical function and aim at analyzing the role of cross-modal plasticity in therapy for individuals with sensory deficits as present after stroke.

FIG. 1: Analysis of current neuroscientific issues.
FIG. 2: PRG-1 in human cortex.
FIG. 3: Thalamocortical fibers in transgenic animals.
FIG. 4: Setup for simultaneous optical recordings and optogenetic stimulation during BOLD fMRI, adapted from Schmid et al, JCBFM 2016. a: Scheme of experimental setup. b, c: Confocal images from fixed sections of rat brain injected with ChR2-mCherry AAV in somatosensory cortex. b: mCherry expression in cortical layers II/III, V and VI becomes evident. scale bar = 100 µm. c: High-resolution imaging reveals membrane-bound localization of ChR2-mCherry fusion protein; scale bar = 50 µm. d, e: Photomicrographs of rat brain injected with Ca2+ indicator OGB-1. d: Whole rat brain, overlay of transmitted light image with green fluorescence channel; scale bar = 2 mm. e: Coronal brain slice at the level of the somatosensory cortex of OGB-1 fluorescence; scale bar = 1.5 mm.

IMPORTANT PUBLICATIONS // MAX. 5

Keller S, Schmidt MHH. EGFR and EGFRvIII Promote Angiogenesis and Cell Invasion in Glioblastoma: Combination Therapies for an Effective Treatment. INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES. 2017; 18 (6).

IMPORTANT PROJECTS // MAX. 5

CRC 1193: Neurobiology of Resilience to stress-related mental dysfunction (Project C01)
PROJECT MANAGER: Prof. R Kalisch, Prof. A Stroh
FUNDING: German Research Foundation (DFG)
PROJECT DURATION: 2016 - 2020

CRC 1080/2; A03: EGFL7 and progranulin (PGRN) as dual regulators of notch-mediated adult neurogenesis
PROJECT MANAGER: Prof. MHH Schmidt
PROJECT DURATION: 2016 - 2020

CRC 1080/805 Role of the signal transduction of bioactive lipids in the homeostatic control of the excitatory transmission
PROJECT MANAGER: PD Dr. J Vogt
FUNDING: German Research Foundation (DFG)
PROJECT DURATION: 2017 - 2020

CRC 1292/1, 09: Mechanisms of immune evasion by malignant glioma
PROJECT MANAGER: Prof. MHH Schmidt, Prof. F Zipp
FUNDING: German Research Foundation (DFG)
PROJECT DURATION: 2017 - 2021

Endothelial-derived factors in blood vessel homeostasis during stroke
PROJECT MANAGER: Prof. MHH Schmidt
PROJECT DURATION: 2016 - 2020

CRC 1080/2016-2020

OVERVIEW

The research of the Institute of Pathobiochemistry is dedicated to the investigation of the molecular mechanisms underlying neurodegenerative disorders and aging. Employing different experimental strategies, the three research groups within the institute pursue the common goal to create a full picture of the addressed human diseases leading to novel strategies for prevention and therapy.

Since protein homeostasis is disturbed in a number of age-associated neurodegenerative disorders, the Behl group (Biochemistry of Neurodegeneration and Aging) aims to decipher the role of proteostasis in neuronal function and dysfunction especially concentrating on the process of autophagy. The focus of the Pietrzik group (Molecular Neurodegeneration) is on various pathomechanisms particularly relevant in Alzheimer’s disease (AD), notably the molecular function of the blood brain barrier and the functional role of the protein LRP1 in the CNS. The Moosmann group (Evolutionary Biochemistry and Redox Medicine) studies the natural evolution of longevity, to identify adaptations and mechanisms that could one day be harnessed to increase the human healthspan and to prevent degenerative diseases, particularly those affecting the brain.

HIGHLIGHTS

Based on its seminal finding that long-lived animals including humans strictly avoid the 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. As these very unusual radicals cannot be trapped by any of the traditional, well-known antioxidants, the group currently tries to develop novel thiyl radical scavengers by studying thiyl detoxification in vivo. Selenoproteins seem to play a special role in this respect. Intriguingly, thiyl radical toxicity appears to corrupt primarily protein homeostasis, which has long been known to be at the heart of tissue repair and longevity.

Dysfunction of the blood brain barrier (BBB) results in inadequate supply of nutrients to the brain and reduced clearance of processed material from the brain. Clearance mechanisms across the blood brain barrier are thought to be disturbed during numerous neurodegenerative disorders.

Recently the Pietrzik group has generated a novel mouse model for lipoprotein receptor-mediated transport across the blood brain barrier. Using this mouse model they were able to demonstrate the importance of clearance mechanisms for the pathology of Alzheimer’s Disease.

With respect to novel modulators of autophagy, the Behl group succeeded to identify that the RAB GTPase RAB18 is a positive modulator of autophagy and is relevant for the maintenance of cellular proteostasis. RAB18 activity is dependent on RAB3GAP1 and RAB3GAP2 previously described by us to affect autophagy as well. Mutations in the genes for RAB3GAP1/2 and RAB18 are causally linked to the human Warburg Micro (WARBM) syndrome, a neurodevelopmental disorder, suggesting an important pathogenetic role of autophagy in neuronal disorders.
**FUTURE DIRECTIONS**

The Behl group as part of the Collaborative Research Center on Selective Autophagy (CRC 1177; GU Frankfurt, speaker: Ivan Dikic, vice-speaker: Christian Behl) is investigating the molecular mechanism of BAG3-mediated selective macroautophagy dealing with disease-associated protein aggregates. Moreover, scientists in the Behl lab are exploring in depth the function of Rab18 and Rab GTPase activating proteins as well as the protein RME-8 in macroautophagy and disease. Studies on the molecular consequences of brain hypoperfusion as a permanent shortage of glucose and oxygen and the consequences for metabolism and mitochondria are driven by Panvana Hajieva in the framework of her foundation-funded professorship. The Pietrzik group will further explore novel pathways to restore transport across the blood brain barrier to develop strategies for improved clearance of debris out of the brain. Additionally we will focus on the role of the metalloprotease meprin β in neurodegenerative diseases. The Moosmann group is currently investigating the mechanisms by which thyl radicals are induced in vivo and how they lead to premature aging and tissue dysfunction. Since exogenous factors and food components specifically induce thyl radicals and may thus accelerate the aging process, these studies could result in future interventions to extend the human healthspan.

**IMPORTANT PROJECTS**

- **The role of the protein receptor-mediated endocytosis β (RME8) in neuronal homeostasis** (SP B09) - CRC 1080/2 „Molecular and Cellular Mechanisms of Neural Homeostasis“  
  **PROJECT MANAGER:** Prof. C Behl, Dr. AM Clement  
  **FUNDING:** German Research Foundation (DFG)  
  **PROJECT DURATION:** 2017 - 2020

- **BAG3-mediated selective macroautophagy and its modulation (TP A03) - CRC 1177/1 „Molecular and Functional Characterization of Selective Autophagy“**  
  **PROJECT MANAGER:** Prof. C Behl  
  **FUNDING:** German Research Foundation (DFG)  
  **PROJECT DURATION:** 2016 - 2019

- **Exocytotic receptor antagonists in Alzheimer’s disease**  
  **PROJECT MANAGER:** Prof. B Moosmann  
  **FUNDING:** Corona-Foundation  
  **PROJECT DURATION:** 2013 - 2017

- **Hyoperfusion and neuronal adaptation**  
  **PROJECT MANAGER:** Prof. C Behl  
  **FUNDING:** Corona-Foundation  
  **PROJECT DURATION:** 2014 - 2018

- **The role of the blood brain barrier in Alzheimer’s disease: analysis of the functional interaction of LRP1 and ABC transporter proteins**  
  **PROJECT MANAGER:** Prof. CU Pietrzik  
  **FUNDING:** German Research Foundation (DFG)  
  **PROJECT DURATION:** 2014 - 2017
OVERVIEW

As of January 2017, Jakob von Engelhardt is the new head of the Institute of Pathophysiology, which consists of three research units. The group of Prof. Jakob von Engelhardt studies the role of synaptic molecules in the healthy and diseased brain. The group of Jun.-Prof. Maik C. Stüttgen is interested in the cognitive and neural mechanisms underlying adaptive behavior. The group of Prof. Wolfgang Müller-Klieser / PD Stefan Walenta focuses on tumor pathophysiology with a special emphasis on tumor metabolism and its impact on therapy resistance and development of metastases. Members of the Institute are involved in curricular teaching activities for medical students at the pre-clinical level, as well as for students of pharmacy and biomedical science.

HIGHLIGHTS

RESEARCH GROUP VON ENGELHARDT

We investigate the molecular basis of neuronal communication in the central nervous system. We are particularly interested in what role different glutamate receptors and glutamate receptor-interacting proteins play in physiological and pathophysiological processes. We aim to understand how AMPA-interacting proteins (Fig. 1) modulate channel function. A second goal is to better understand the role of different NMDA receptors in neuronal function in the healthy and diseased brain. NMDA receptors are important for synaptic plasticity. In addition, excessive activation of NMDA receptors is detrimental for neurons and contributes to the pathophysiology of brain diseases such as stroke and neurodegenerative diseases. Finally, we search for the genetic causes of rare familial movement disorders by next-generation sequencing (NGS).

RESEARCH GROUP STÜTTGEN

The brain’s arguably most challenging task is to orchestrate behavior in the face of ever-changing environments. The main research interests of the lab are the psychological and neural mechanisms underlying such adaptive learning processes. To that end, we subject animals to behavioral tasks requiring the simultaneous consideration of several sources of information, such as sensory evidence, and the probabilities of reinforcement and punishment for specific actions. Employing in-vivo multi-electrode recordings in sensory and association cortices in freely moving animals, intracerebral drug infusions, and cognitive modeling methods, we seek to elucidate the hidden variables enabling animals to adapt rapidly (and frequently optimally) to a world full of uncertainty (Fig. 2).

RESEARCH GROUP WALENTA/MÜLLER-KLIESER

De-regulation of the carbohydrate metabolism is an early and potentially causal event during the development of cancer. The metabolic status of human tumors is characterized by increased glucose uptake, elevated glycolytic flux, and increased lactate efflux, eventually followed by accumulation of lactate in the tumor tissue. The increase in cellular glucose uptake can be exploited for tumor diagnosis and treatment follow-up using positron emission tomography (PET) to measure the uptake of 2-fluoro-deoxy-glucose (FDG). Our group showed that accumulation of high levels of lactate in the primary tumor lesions are associated with a high risk of metastasis formation and reduced patient survival.

FUTURE DIRECTIONS

RESEARCH GROUP VON ENGELHARDT

To investigate how AMPA receptor interacting proteins modulate information processing in the brain, we use in vitro and in vivo electrophysiology as well as genetics to modulate protein expression in mice. Moreover, we will elucidate the role of NMDA receptors in the pathophysiology of Alzheimer’s and Huntington’s disease. Finally, we will investigate how the function of proteins is compromised by mutations that we identified by NGS in families with rare neurodegenerative diseases. This may lead to a better understanding of the proteins or pathways that play a role in disease pathophysiology.
FIG. 1: Overview on the functional diversity of AMPAR-interacting proteins. AMPAR complex constituents influence AMPARs on several levels (a – c). They regulate (a) AMPAR gating, (b) surface localization and (c) receptor translation and trafficking to the cell surface. From: E. Jacobi & J. von Engelhardt. Diversity in AMPA receptor complexes in the brain. adapted from: Curr Opin Neurobiol. 2017

FIG. 2: Results from a behavioral experiment with rat subjects. A) Rat in a Skinner box performing a single-interval forced choice task in which nose pokes to the center port lead to presentation of one of two auditory stimuli (S1 and S2). Following S1, the rat should move to the right nose port to retrieve reward, following S2, the rat should move to the left nose port. B) Signal detection theoretical model of task performance. Each stimulus yields a noisy neuronal representation, equal to drawing a random value from a normal distribution. A variable decision criterion (dotted line) specifies whether a given value of the decision variable leads to an “S1” or an “S2” response. C) Behavioral data (blue) from an example session in which reward probabilities for S1 and S2 responses were changed several times (vertical lines). Within a few dozen trials, the performance of the rat approaches the optimal value for a given condition (horizontal dotted lines). The behavioral data were well fit by an income-based learning model (red; Behav Processes 96: 59).
OVERVIEW

The Institute of Physiological Chemistry consists of three research groups: „Molecular Mechanisms of Behavior“ (Lutz), „Adult Neurogenesis and Cellular Reprogramming“ (Berninger), „Applied Molecular Biology“ (Müller/Schröder/Wang).

In teaching, we represent the subject „Biochemistry/Molecular Biology“ for medical and dental students. In preparation for the first period of the medical exams („Physikum“), a broad knowledge in biochemistry and molecular/cellular biology is conveyed by lectures, practical courses and seminars.

We also educate young academics from the Faculties of Biology, Chemistry and Medicine, and are interested in highly motivated bachelor, master and doctoral students. We often host foreign Ph.D. students and scientists for further education in our laboratories.

HIGHLIGHTS

Communication processes between neurons in the brain as well as the mutual interaction between the brain and peripheral system are necessary for proper organism’s functioning. The lipid signaling system of endocannabinoids in interaction with other systems holds central places in these control mechanisms and are involved in emergence of pathological states. For example, we found that adipocyte cannabinoid CB1 receptor regulates energy homeostasis (Ruiz de Azua et al, 2017), allowing new views of therapies of obesity. We also investigated endocannabinoid signalling in specific neuronal populations regarding fear extinction (Remmers et al. 2017).

In the adult mammalian brain, neurogenesis is restricted to very few niches such as the ventricular/subventricular zone of the lateral ventricle. Understanding the microenvironment that constitutes the neurogenic niches may help to instruct the generation of new neurons in other brain regions lacking neurogenesis. Work spearheaded by our group in collaboration with the Leibniz Institute for New Materials could demonstrate that mechano-adhesive properties of the microenvironment have prominent effects on neurogenesis both from embryonic and adult neural progenitor cells (Farrukh et al 2017).

Moreover, in collaboration with the University of Lyon, we could show that, by administration of small molecules in vivo, it is possible to promote the specific generation of neurons and oligodendrocytes from neural stem cells in both the postnatal and adult brain, as well as in regenerative contexts after lesion.

The elucidation of the decisive function of the inorganic bio-polymer polyphosphate (polyP) in bone mineral formation allowed the Müller/Schröder/Wang group to develop new approaches in osteoarticular therapy. Using a bioinspired route we succeeded to synthesize polyP nanoparticles that are smart and able to induce a directed differentiation of stem cells into the osteogenic or chondrogenic lineages. These particles, along with 3D printing techniques, enabled the 3D fabrication of scaffolds of adaptable hardness for personalized tissue repair. Surprisingly, polyP acts as an extracellular energy store and ATP supply. This unexpected property of polyP could be exploited for bradytrophic tissue (cartilage) repair and acceleration of microvascularization and wound healing. The proof-of-concept of these results of the ERC Advanced grant „BIOSILICA“ (Müller) has been provided in three ERC-PoC projects. In addition, we started a new H2020 project („InnovaConcrete“) on self-healing materials.
In the context of the newly established CRC 1193, the Lutz group aims at investigating how the endocannabinoid system is involved in stress resilience and vulnerability. By using state-of-the-art genetic tools in combination with behavioral, transcriptomic, epigenetic, biochemical and cellular analyses, mechanisms underlying the behavioral outcome of stress resilience will be explored. We will also address peripheral-brain interactions, and the involvement of the immune system in stress resilience.

In parallel to our current approaches, the Berninger group is developing new experimental models for studying the lineage conversion of human glia into induced neurons. Towards this, we have established the cerebral organoid model of human neurogenesis in which both neurons and glia are generated. We hypothesize that human cerebral organoids can serve as a model system that mimics a more complex in vivo-like environment than classical 2D cultures.

The biomimetic materials developed by the Müller/Schröder/Wang group show biological effects not found in other materials used in regenerative medicine. The bio-polymer polyP can be prepared as smart amorphous nanoparticles for specific biomedical applications. In addition, we are able to combine polyP with hydrogel-forming polymers to produce hardenable bio-inks for 3D printing and 3D cell bioprinting procedures. Our aim is the fabrication of regenerative active patient-specific tissue implants.

**Deciphering the molecular adaptions underlying network homeostasis when facing the challenge of new neuron integration (CRC 1080, TP A05)**

**PROJECT MANAGER:** Prof. B Berninger  
**FUNDING:** German Research Foundation (DFG)  
**SUM:** € 366,400  
**PROJECT DURATION:** 2017 - 2020

**ERC Advanced Grant BIOSILICA: From gene to biomimeral: Biosynthesis and application of sponge biosilica**

**PROJECT MANAGER:** Prof. WEG Müller  
**FUNDING:** European Union (EU)  
**SUM:** € 2,183,600  
**PROJECT DURATION:** 2011 - 2017

**ERC Proof of Concept Grant ArthroDUR: Bifunctional and regeneratively active biomaterial: Towards an ultimate solution for osteoarthritis treatment**

**PROJECT MANAGER:** Prof. WEG Müller  
**FUNDING:** European Union (EU)  
**SUM:** € 150,000  
**PROJECT DURATION:** 2017 - 2019

**Lipid signaling by anandamide and the bliss of resilience: genetic models at cellular and neural-network levels (CRC 1193, TP B04)**

**PROJECT MANAGER:** Prof. B Lutz, Prof. H Luhmann  
**FUNDING:** German Research Foundation (DFG)  
**SUM:** € 254,000  
**PROJECT DURATION:** 2016 - 2020

**Unraveling the relation between adult-born hippocampal neuron’s connectivity and resilience (CRC 1193, TP A02)**

**PROJECT MANAGER:** Prof. B Lutz, Prof. B Berninger  
**FUNDING:** German Research Foundation (DFG)  
**SUM:** € 564,000  
**PROJECT DURATION:** 2016 - 2020
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 group of Prof. Rumpel focuses on sounds and neocortex. The subgroup of PD Dr. Kilb is studying the development of GABAergic inhibition, network interactions and the role of developmental disorders in the generation of neuronal pathologies. The subgroup of PD Dr. Kirischuk has a focus on neuron-glia interactions in the cerebral cortex and on chloride-transporters in neurons and in glial cells. 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. Finally they revealed, that inhibitory neocortical neurons convey tactile sensory information with higher efficacy and less redundancy.

The group of Prof. Mittmann studies the adaptive homeostatic mechanisms of neuronal GABAergic inhibition in the somatosensory cortex of mice following a traumatic brain injury in order to better understand the functional recovery from a damage in the central nervous system. Moreover, the group is interested in the neuromodulatory role of oligodendrocyte precursor cells in the neocortex.

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.

It is becoming increasingly clear how dynamic the structure of cortical circuits is - even during adulthood and without explicit behaviorally relevant experiences. Combining in vivo two-photon imaging of dendritic spines in transgenic mice and theoretical modeling, Yonatan Loewenstein from the Hebrew University Jerusalem and Simon Rumpel developed a model based on the dynamics of synaptic connections in the brain that allows future connectivity states (Loewenstein et al., 2015, J. Neurosci.).

The group of Werner Kilb demonstrated that methylxanthines like caffeine and theophylline provoke epileptiform activity and reduce hippocampal synaptic transmission at supraclinical doses. In addition, they identified a fraction of subplate neurons, a neuronal cell type that is considered as crucial but transient element of developing neocortical circuits, escape apoptosis and populate layer 6b.

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. 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.
Important Publications // Max. 5

**Activity-Dependent Regulation of Apoptosis in Developing Rodent Cerebral Cortex** (CRC 1080/2, TP A01)

- **Project Manager:** Dr. A. Sinning, Prof. H. Luhmann
- **Funding:** German Research Foundation (DFG)
- **Sum:** € 565,592
- **Project Duration:** 2017 - 2020

**Homeostatic regulation of mTOR dependent synaptic function** (CRC 1080/2, TP B10)

- **Project Manager:** Prof. H. Luhmann, Prof. S. Schweiger
- **Funding:** German Research Foundation (DFG)
- **Sum:** € 586,088
- **Project Duration:** 2017 - 2020

**Adaptive cellular mechanisms of functional reorganization and recovery after traumatic brain injury (TBI)** (CRC 1080/2, TP C02)

- **Project Manager:** Prof. T. Mittmann
- **Funding:** German Research Foundation (DFG)
- **Sum:** € 594,872
- **Project Duration:** 2017 - 2020

**Homeostatic stabilization of neural function in a dynamic network** (CRC 1080/2, TP C05)

- **Project Manager:** Prof. Y. Loewenstein, Prof. S. Rumpel
- **Funding:** German Research Foundation (DFG)
- **Sum:** € 782,996
- **Project Duration:** 2017 - 2020

**Lipid signaling by anandamide and the bliss of resilience:** genetic models at cellular and neural network levels (CRC 1193, TP C04)

- **Project Manager:** Prof. B. Lutz, Prof. H. Luhmann
- **Funding:** German Research Foundation (DFG)
- **Sum:** € 12,100,000
- **Project Duration:** 2016 - 2020

**Important Projects // Max. 5**


**FIG. 1:** Prof. Dr. Luhmann at setup

**FIG. 2:** Cross section of the auditory cortex of a transgenic mouse used for in vivo spine imaging. A single neuron is highlighted by green fluorescent protein. The dendritic processes are decorated with spines, the morphological correlate of excitatory synapses. Counterstaining for synaptic marker proteins ErbB4 (cyan) and Synapsin1 (magenta).

**FIG. 3:** Inhibitory neocortical neurons contain more information about tactile stimuli than excitatory neurons. A: Schematic illustration of experimental setup for selective mechanical stimulation of single whiskers and simultaneous VSD imaging or multi-electrode recordings in four barrel-related columns. The right scheme illustrates the 8x16 channels probe showing shank and site spacing, position of the barrels C0 to D3, and the location of the cortical layers relative to the electrode sites. B: Influence of network size on ensemble-based mutual information about stimulus location. Three different traces are presented for networks containing only excitatory (red triangles, n= 66), only inhibitory (blue circles, n=8), or both classes of neurons (grey line, n= 74). Note that the 8 inhibitory neurons convey as much information as an ensemble consisting from more than 50 excitatory neurons. C-E: Summary diagram of the encoding schemes for three different stimulus modalities. Symbols illustrate the inhibitory (blue circles) and excitatory (red triangles) neurons inside the principal column of the stimulated whisker. Size of the symbols indicates the amount of stimulus location information carried by the corresponding neuronal groups. Lines connecting the neurons mark the level of the stimulus-independent noise correlations, where lighter tones of gray relate to lower values. From Reyes-Puerta et al. (2015) PLoS Comput Biol. 11(6):e1004121.
DEPARTMENTS AND INSTITUTES OF CLINICAL AND THEORETICAL MEDICINE

Department of Medical Microbiology and Hygiene
German Resilience Center (DRZ)
Institute of History, Philosophy and Ethics of Medicine
Institute of Immunology
Institute of Legal Medicine
Institute of Occupational, Social and Environmental Medicine
Institute of Pharmacology
Institute of Toxicology
Institute of Translational Immunology
Institute of Virology
OVERVIEW

Basic research conducted at the Institute of Medical Microbiology and Hygiene (IMMH) covers a rather broad range of subjects in the biomedical sciences. Besides addressing genuinely microbiological problems like central mechanisms of host-pathogen interactions relevant to bacteria and viruses, the IMMH continued throughout 2017 to support work in the field of cellular biology and to host coworkers of principal investigators previously affiliated with the IMMH and focusing on themes in cellular Immunology. Our Department of Hygiene and Environmental Medicine contributed research in the area of applied sciences. The work of investigators of the IMMH is documented by a number of publications in well regarded Journals.

HIGHLIGHTS

Tetraspanins have been identified as essential cellular membrane proteins during infections by most types of pathogens. The Florin laboratory made fundamental contributions in understanding the role of tetraspanins in viral infections and in cellular processes such as membrane organization and intracellular trafficking. One review recently published by the group highlights data on the role of tetraspanin CD151, CD81, and CD63 and their interaction partners in host cell entry by human cytomegalo- and human papillomaviruses, and provides a model on how tetraspanin interactions may organize viral infection factors into tetraspanin trafficking platforms.

The Husmann laboratory investigates membrane repair as an archaic, innate defense program protecting target cells against bacterial pore forming toxins (PFT), the largest group of bacterial protein toxins. In a paper by von Hoven et al. (MBio 2017), the group uncovered how some of these toxins are able to subvert membrane repair. In joint projects with N. Hellmann (Mainz) and C. Osorio (Santiago, Spain), respectively, the role of P2X-receptors for PFT-dependent membrane damage was critically reassessed, and new bacterial virulence factors of an emerging marine pathogen were identified.

The von Loewenich laboratory works on Anaplasma phagocytophilum, a tick-transmitted obligate bacterium that replicates exclusively in neutrophils. In mice, the control of A. phagocytophilum in the early phase of infection depends on NK cell-derived IFN-γ. In contrast, its elimination requires CD4+ T-cells. To investigate if neutrophils serve only as host or also as killers to A. phagocytophilum, in vitro generated murine neutrophils were used. When stimulated with IFN-γ, bacterial growth was impaired, indicating that neutrophils may contribute to the control of infection. They are currently investigating whether interaction between T-cells and neutrophils is required for final bacterial elimination.

Infections with the Hepatitis B virus (HBV), an enveloped pararentrovirus, cause about one million deaths per year, as therapies currently available rarely achieve a cure. Understanding the HBV life cycle and concomitant host cell interactions are instrumental to developing new antiviral concepts. Current investigations of the Prange group led to the identification of the cell autophagy pathway as a proviral machinery. Autophagy is an essential defense mechanism of the cell to confront viral invasion, but HBV subverts autophagic pathway functions along with cellular Rab GTPases to benefit its own replication. Interfering with the HBV/autophagy cross-talk may be a tool for virus control.
FUTURE DIRECTIONS

The overriding goal of investigators at the IMMH is to gain truly novel and significant insights into basic processes that are relevant to the development of and bodily defense against infectious diseases. Researchers of the IMMH are thus committed to traditional academic science; their efforts intend to contribute to a solid foundation of knowledge, thus enabling translational scientists to uncover novel preventative, diagnostic and therapeutic approaches. The continuous development of projects over sufficient periods of time and the sustained promotion of talented and motivated scientists are thereby perceived to be of paramount importance. Last but not least, science at the IMMH shall benefit academic teaching by helping lecturers to keep up with – and to convincingly convey - the ever-changing picture of medical microbiology.

FIG. 1: Immunofluorescence microscopy images of human epidermal cells (HaCaT), transfected with Gasdermin D (GSDMD) and treated (left), or not (right), with pore forming S. aureus alpha-toxin. GSDMD was stained with a specific antibody and Alexa488 conjugate, nuclei were stained with DAPI. Note signs of pyroptosis in toxin-treated cells. Membrane attack by bacterial toxins from the exterior milieu may lead to secondary perforation by cellular proteins, e.g. GSDMD, attacking from the cytosolic side of the plasma membrane. Because secondary effects co-determine consequences and outcome of an attack they have become a focus of our current research.

FIG. 2: Inferred structure of phobalysin, a new pore forming toxin recently characterized by researchers of the IMMH. Although a member of the small beta-barrel PFT family of toxins it forms an unusual, highly conductive membrane channel. Studies using this toxin led to novel insights into scope and limitations of cellular membrane repair.
The German Resilience Center (Deutsches Resilienz Zentrum, DRZ) is a Medical Business Unit of the University Medical Center Mainz (UMC-Mainz) since 2016. Its mission is to improve our understanding of the neurobiological, psychological, and social mechanisms of stress resilience, the individual’s ability to adapt to stress or adversity, thereby preventing the emergence of stress-related neuropsychiatric disorders. The DRZ hosts research groups and platforms of the UMC-Mainz as well as the JGU Mainz, covering basic and clinical neurosciences, and social sciences to uniquely address a central public health challenge of modern, knowledge-based societies. The DRZ is a unique research institution in Europe, bundling efforts to tackle these challenges and to advance our understanding on resilience.

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HIGHLIGHTS

In 09/2017, the Ministry of Science of the State of Rhineland-Palatinate (MWKK), with support of the IGU and the UMC-Mainz, filed an application to the Gemeinsame Wissenschaftskommission (GWK) for admittance of the DRZ in the Leibniz Association. The positive vote by the GWK allowed the DRZ to enter the evaluation procedures by the Leibniz Association, which will take place in 2018 with final decision of the GWK in 2019. Additionally, a grant application was submitted to the Boehringer Ingelheim Foundation in 02/2017, with a positive decision in 03/2017, and the start of the projects in 05/2017. This grant supports 11 individual projects and 3 research sections, focusing on basic resilience research in animals and humans. On the basis of the DRZ’s scientific excellence and importance for Rhineland-Palatinate and in order to strengthen applied resilience research in humans as well as the infrastructure and administration of the DRZ, the MWKK furthermore supported the DRZ in the process of establishing the structure of a later Leibniz Institute.

In 03/2017, an international consortium under the leadership of the DRZ, applied for funding by the European Commission under the Horizon 2020 framework. The project called DynaMORE („Dynamic MOdelling of REsilience“) was approved in 07/2017 and will start in 04/2018. The focus is on the integrative analysis of multidimensional longitudinal human cohort data from various sites and the development of a mathematically formalized model of resilience. Another major grant „Coping Practices“ was approved in 2017 by the Leibniz Association. In this research alliance of the Römisch Germanisches Zentralmuseum Mainz, the DRZ and other Institutes in the Rhine-Main area coping practices across mankind are studied. In 2017, the participating groups of the DRZ significantly contributed to the promotion of resilience research. Two review papers on resilience (Kalisch et al., 2017 Nat Hum Behav; Chmitorz et al., 2018 Clin Psych Rev) are of particular note, as they provide basic conceptual, theoretical and...
methodological foundations for resilience research in animal as well as human studies. Furthermore, several original papers on mechanistic aspects of resilience, stress response, and network activities were published. DRZ groups are also involved in the CRC 1193 „Neurobiology of resilience to stress-related mental dysfunction: from understanding mechanisms to promoting prevention“ since 2016. The granted funding from 07/2016 to 06/2020 involves several DRZ groups. A further highlight was the 3rd International Resilience Symposium in Mainz in 09/2017. It is emerging as a highly recognized event in the scientific community and has strengthened the international reputation of the DRZ. These activities were complemented by the further establishment of the International Resilience Alliance (intresa; https://intresa.org/) as well as by many activities for knowledge transfer and public outreach at national and local levels.

The DRZ pursues three main goals while shifting the research paradigm from being disease oriented towards being health oriented by:

- Understanding neurobiological resilience mechanisms: The DRZ aims to identify neurobiological and psychological mechanisms that will help to explain and understand resilience during and after challenging endogenous or exogenous stressors. In addition, we plan to contribute to population-based research studies of resilience.
- Exploiting these mechanistic insights for the development of new and improved health education strategies and translating these new strategies into validated and practicable health programs: The DRZ aims to develop and implement innovative prevention strategies based on the latest insights from neuroscientific research, analyses from the state-of-the-art literature and analyses of current living conditions both at work and in private life.
- Acting in society in order to improve the effective implementation, application and availability of new forms of sustaining public mental health: The DRZ analyses the impact of lifestyle factors and social frameworks and constraints on the prevention, implementation and societal impact of specific preventive measures. Based on this, we will attempt to influence relevant decision-making processes, including knowledge dissemination and advising decision-makers throughout society, especially in politics, the health system, and industry.
DEPARTMENTS AND INSTITUTES OF CLINICAL AND THEORETICAL MEDICINE

Institute of History, Philosophy and Ethics of Medicine

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OVERVIEW

The Institute of History, Philosophy and Ethics of Medicine researches and teaches at the intersection of theoretical and clinical medicine on theoretical principles, historical developments and ethical implications of medical practices.

We focus on and address socially relevant and currently debated topics of health care, aiming at the application of research results on problems of daily clinical routine. A high level of practical relevance is assured by Prof. Norbert Paul’s chairmanship of the Clinical Ethics Committee and by his active role in advisory rounds and counselling.

The research library of the Institute is equipped with a non-circulation collection of more than 75,000 volumes.

HIGHLIGHTS

RTG 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 has given rise to the differentiation of the sciences into the natural sciences and humanities, nowadays the life sciences and the social and cultural sciences. In biomedicine, which explains and sustains human life through the use of empirical methodologies and frameworks, the search for rational foundations for decision-making and clinical intervention have resulted in the dominance of natural scientific models as the prime perspective on man as such. 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 novel tools and explanations 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 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. The German-French graduate college with Université de Strasbourg 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.
IMPORTANT PUBLICATIONS // MAX. 5


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“ triggered projects for a reassessment of the methodology of clinical ethics based on narrative practices.

NEUROETHICS
In cooperation with the German Resilience Center we are currently establishing a neural ethics working group to explore the descriptive, evaluative and prescriptive dimensions of concepts of cognitive enhancement and resilience. Our goal is to develop ethical standards for a socially and scientifically responsible layout of research in the area of cognitive enhancement and resilience. A number of grand applications is pending.

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

DIGITALISATION
Innovations in handling knowledge, data transform care and medical treatment. We are investigating new emerging questions of responsibility using interdisciplinary approaches.

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.

IMPORTANT PROJECTS // MAX. 5

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 Banjeee
PROJECT DURATION:
2014 - 2018

Master Degree Program in Medical Ethics
PROJECT MANAGER:
Prof. NW Paul,
Dr. J Inthorn
PROJECT DURATION:
2016 - 2019

Narrative Practices in Medicine. Historical, Sociological, Philosophical and Ethical Discourses
PROJECT MANAGER:
Prof. NW Paul,
Dr. T Hainz,
C Buir
FUNDING:
Franco-German University
SUM: € 203,000
PROJECT DURATION:
2015 - 2017
OVERVIEW

The Institute of Immunology is one of the basic research institutes of the University Medical Center Mainz. We conduct immunological research, transfer research results in the preclinical phase and interact closely with clinical partners for the translation of these findings into innovative therapies. Preclinical disease models play a central role in this process. In this regard, several preclinical infection, tumor and asthma models have been established. Using these models, therapeutic strategies towards the treatment of allergic asthma, autoimmunity and cancer have been developed. To support this research, a modern Flow Cytometry and a state-of-the-art Next-Generation-Sequencing (NGS) unit as well as Mass Spectrometry and Microscopy units have been established.

HIGHLIGHTS

The research activities realized at the Institute of 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. Of special interest are the consequences of tissue-specific interactions of these cells, for example in the skin, with members of the adaptive immune system, e.g. T cells. These studies are paralleled on one hand by research activities addressing the role of different populations of dendritic cells in the skin and in peripheral lymphoid organs where tolerance and induction of antigen-specific immunity is established. On the other hand, we are interested in the role of different cytokines in the differentiation of T cells and the function of regulatory T cells. The analysis of T cell differentiation is focused on transcriptional regulation of the development and function of different T helper cell populations, such as Th2, Th9 and Th17 cells. Furthermore, we study the function of regulatory T cells which play an essential role in maintaining the immunological tolerance in the periphery. Of special interest is the influence of this subpopulation on the activity of dendritic cells and also CD4 and CD8 positive T cells. Malfunctions of regulatory T cells are therefore associated with the development of allergic and autoaggressive diseases as well as tumors and chronic infections. For this reason, studies on the understanding of the inhibitory mechanisms of regulatory T cells including surface molecules and molecular pathways play a central role. In addition, we perform studies leading to a better understanding of antigen processing and presentation of MHC Class I ligands in tumors and virus-infected cells as well as the induction of antigen-specific 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. In November 2017, the DFG approved the CRC 1292 "Targeting convergent mechanisms of inefficient immunity in tumors and chronic infections" under the leadership of Professor Hansjörg Schild for funding. The central aim of the CRC is to perform an unprecedented comparative analysis of the various immune evasion mechanisms in cancers and in chronic infections to obtain a detailed map of common and disease-specific immune escape checkpoints.

FUTURE DIRECTIONS

Research at the Institute of 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 trials will be planned and initiated with the help of clinical partners. All of this would not be possible without continuous improvement of the Institute’s 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 of Immunology provides immunological teaching programs within the studies of Biomedicine, Biomedical Chemistry, Medicine and Pharmacy.
**IMPORTANT PUBLICATIONS // MAX. 5**

Carrascosa LC, Klein M, Kitagawa Y et al. Reciprocal regulation of the IL9 locus by counteracting activities of transcription factors IRF1 and IRF4. NATURE COMMUNICATIONS. 2017; 8.


Schmitt E, Bopp T. Discovery and initial characterization of Th9 cells: the early years. SEMINARS IN IMMUNOPATHOLOGY. 2017; 39 (1): 5-10.


**FIG. 1:** Macrophages (CD68+ cells) in melanoma metastasis.

**FIG. 2:** In mass spectrometric experiments ion-mobility separation adds an additional dimension of separation and allows to resolve overlapping features.

**FIG. 3:** Work from the Molecular Signaling Unit (MSU) revealed that Cdc42 is ubiquitinated at lysine 166 which could impair the interaction with its effector PAK6. Model analysis was performed by Dr. Akutsu, Goethe University, Frankfurt.

**FIG. 4:** Human lung cancer cells grown on 2D matrices were decorated with Phalloidin to stain the polymerised F-actin the nuclei in blue.

**IMPORTANT PROJECTS // MAX. 6**

1. **Functional analysis of skin subsets of dendritic cells in T cell priming and tolerance using inducible transgenic mice that allow subset specific antigen expression (TRR156, B02)**
   - **PROJECT MANAGER:** Prof. T Bopp
   - **FUNDING:** Else Kröner-Fresenius-Foundation
   - **PROJECT DURATION:** 2017 - 2020

2. **Functional clustering of T cell and other immune cell sub-phenotypes across plasticity and individualities of immune-mediated diseases**
   - **PROJECT MANAGER:** Prof. K Rajalingam
   - **FUNDING:** German Research Foundation (DFG)
   - **PROJECT DURATION:** 2014 - 2019

3. **Heisenberg (DFG)**
   - **PROJECT MANAGER:** Prof. K Rajalingam
   - **FUNDING:** German Research Foundation (DFG)
   - **PROJECT DURATION:** 2014 - 2019

4. **Multifunctional nanoscale peptide/glycopeptide conjugates as synthetic vaccines for anti-tumor immunotherapy**
   - **PROJECT MANAGER:** Prof. E Schmitt, Prof. P Besenius
   - **FUNDING:** German Research Foundation (DFG)
   - **PROJECT DURATION:** 2017 - 2021

5. **Transcutaneous immunization: Mechanisms of intracellular networks of the skin (TRR156, A05)**
   - **PROJECT MANAGER:** Prof. M Radsak, PD Dr. M Stassen
   - **FUNDING:** German Research Foundation (DFG)
   - **PROJECT DURATION:** 2015 - 2019

6. **Thiol switches controlled by the glutathione-S-transferase GDAP1**
   - **PROJECT MANAGER:** Prof. S Tenzer
   - **FUNDING:** German Research Foundation (DFG)
   - **PROJECT DURATION:** 2017-2020
HIGHLIGHTS

The Forensic Physics in the service of the Department of Institute for Forensic Medicine of the University Medical Center of the Johannes Gutenberg University Mainz, engages in regards to regulations of hazardous potentials, including the appraisal of the mechanical impact on the structures of the human body and thus contributes to the responds of questions in the sector of Justice.

The assignment spectrum of Forensic Physics includes sharp and blunt force and classifies it in sectors of case-related work, of research activity and doctrines.

Assigned to the area of case-related works, is the reconstruction of action and accident process under the observation of the laws of physics and will be put into practice by means of experimental research including physical calculations. This allows, amongst others, the appropriateness of energy, which are necessary for the corresponding case, in order to determine the severity, that where inflicted on the victims, recreate injuries, and to disclose valid information on the potential of hazards with the respective energy of impact, as well as insights of the sequence of the course of action on criminal actions. The case-related work ends with the generation of the Court of Justice expertise report and supports the Justice Department in order to assess the degree of penalty.

The research activity service the acquisition of knowledge and dedicates itself to the investigation of mechanism, which plays a relevant role in the generation of physical injuries and serves the purpose to linking influential energy and force in regards to the extent dimension and the type of arising injury pattern. Furthermore this results in the determination of the maximum permissible value for capacities of structures of the human body.

In these cases forensic experiments will be executed, in order to implement them, special devices, for each case of operational purpose will be developed and designed; therefore equipment is required, such as the Forensic Drop-tower. Once the research operation has been completed, it results in the publishing of the corresponding publication of literature.

One of the higher-level targets in research operation, are the findings of principals of laws and the establishing of their mathematical description. Case-related works go hand-in-hand with research activities. The case-activities show, were research-demands are necessary; the gained research-insights support the increase of high-grade quality of expertise reports. Aside of conveying expertise knowledge, the doctrines in the area of Forensic Physics, also serve the interdisciplinary exchange of various technical disciplines.
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:

- Set-up of medical care for victims of crime throughout Rhineland-Palatinate,
- Epidemiology of child maltreatment and sexual abuse to develop prevention strategies,
- Installation of Postmortem Computed Tomography (PMCT) und CT-Angiography (PMCTA),
- 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.

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.

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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</thead>
<tbody>
<tr>
<td>Detection of New Synthetic Drugs and Polar Metabolites by Liquid Chromatography-Tandem Mass Spectrometry.</td>
<td>PD Dr. J. Röhrich</td>
<td>Association for the clinical examination of violence victims and general legal research in Rhineland-Palatinate</td>
<td>€ 5,000</td>
<td>2014 - 2017</td>
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<tr>
<td>Cerebral glucose metabolic changes after THC-administration in rats</td>
<td>Prof. M. Schreckenberger, Dr. I. Miederer, Prof. R. Urban</td>
<td>B. A. D. S.</td>
<td>€ 2,000</td>
<td>2013 - 2018</td>
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**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 of 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**

**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 and Social Psychology**

Occupational health of nurses: In this area, two projects on working conditions and occupational health of more than 1,500 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.

**Teachers’ Health**

The Institute of Teachers’ Health as a part of the Institute of Occupational, Social and Environmental Medicine 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-over study on occupational strain and stress of staff working at classrooms with inappropriate acoustic conditions. The aim of this study is to analyze and to compare the interaction of noise and reverberation in classrooms with adequate and inappropriate acoustic conditions. Results will lead to eligible structural and behavioral preventive measures. The annual report on the health status of teachers and educational staff in Rhineland-Palatinate for the school year 2016/2017 is currently in press.
FUTURE DIRECTIONS

Current and future developments and changes in work and society such as 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).

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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<tbody>
<tr>
<td>Occupational factors influencing cardiovascular diseases - longitudinal analysis of the Gutenberg health study</td>
<td>Prof. S. Letzel</td>
<td>Federal Institute for Occupational Safety and Health (BAuA)</td>
<td>€ 1,064,600</td>
<td>2014 - 2018</td>
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<tr>
<td>Female Refugee Study – Representative Study on Refugee Women in different Federal States in Germany</td>
<td>U. Zier, Dr. R. Kimbel, Prof. S. Letzel</td>
<td>Federal Government Commissioner for Migration, Refugees and Integration</td>
<td>€ 74,644</td>
<td>2016 - 2017</td>
</tr>
<tr>
<td>Handling of non-cytostatic drugs in nursing care: nationwide survey on occupational exposure, acute effects of exposure and information requirements concerning occupational safety (working title: „ABBI“)</td>
<td>Dr. B. Rollbach, Dr. R. Kimbel, Prof. S. Letzel</td>
<td>BGW</td>
<td>€ 80,000</td>
<td>2016 - 2017</td>
</tr>
<tr>
<td>Improvement and validation of the employee survey as part of the occupational health management (OHM) in the area of responsibility of the Federal Ministry of Defence, taking into account the challenges of a nationwide implementation of the OHM</td>
<td>Prof. O. Rose</td>
<td>Federal Office of Bundeswehr Equipment, Information Technology and In-Service Support (BAAINBw)</td>
<td>€ 570,700</td>
<td>2017 - 2021</td>
</tr>
<tr>
<td>Work situation and health of nurses in palliative care in Germany</td>
<td>PD Dr. LC Escobar Pinzon</td>
<td>BGW</td>
<td>€ 199,450</td>
<td>2016 - 2018</td>
</tr>
</tbody>
</table>

IMPORANT PUBLICATIONS // MAX. 5


Dudenhoeffer S, Claus M, Schoene K et al. Sickness presenteeism of German teachers: prevalence and influencing factors. TEACHERS AND TEACHING. 2017; 23 (2): 141-152.


**OVERVIEW**

The Institute’s mission is to enhance the international stature of the University Medical Center Mainz by internationally recognized research and high quality teaching. Research in the Institute focuses on Molecular Cardiovascular Pharmacology, Cell and Redox Signaling, Immunopharmacology, Clinical Pharmacology and Pharmacogenetics, Solute transport through biological membranes, and Gender-specific Medicine. Research in the Institute is carried out using up to date techniques (analytical/biochemical methods, cell- and molecular biology techniques, genetically modified animals, and in-vitro organ experiments). The Institute provides state-of-the-art teaching to medical students, dental students and PhD-students in General Pharmacology and Toxicology, as well as Clinical Pharmacology and Pharmacotherapy.

**HIGHLIGHTS**

**VASCULAR PHARMACOLOGY**

We are currently analyzing the following mechanisms regulating vascular function: (i) developmental origins of cardiovascular disease (fetal programming) and pharmacological re-programming as a potential prevention strategy; (ii) the role of perivascular adipose tissue (PVAT) in vascular physiology and pathophysiology; (iii) the role of B lymphocytes in maintaining vascular function and hemostasis as well as the molecular mechanisms of B cells dysregulation in obesity.

**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. The current research is centered on the PON2-mediated modulation of ROS production important for interaction of vascular cells and hematoipoiesis.

**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. Current work focuses on the regulation of human iNOS expression and the importance of the RNA-binding protein KSRP in innate and adaptive immune responses.

**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 IIIB 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.
FUTURE DIRECTIONS

A major research focus of Vascular Pharmacology is regulation of vascular function: We investigate the role of nitric oxide from the endothelium and from the perivascular adipose tissue, B lymphocytes, and vascular oxidative stress (Huige Li, Ning Xia, 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 Kleinert, Andrea Pautz, and collaborators).

The Clinical Pharmacology and Pharmacogenetics Group 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 and collaborators). Projects in Gender-specific Medicine analyze the gender-specific regulation of pro- and anti-inflammatory genes in mouse models of chronic inflammation (Andrea Pautz and collaborators).

IMPORTANT PUBLICATIONS // MAX. 5


Werner A, Koschke M, Leuchtner N et al. Reconstitution of T Cell Proliferation under Arginine Limitation: Activated Human T Cells Take Up Citrulline via L-Type Amino Acid Transporter 1 and Use It to Regenerate Arginine after Induction of Arginosuccinate Synthase Expression. FRONTIERS IN IMMUNOLOGY. 2017; 8.


FIG. 4: Cardiovascular risk factors induce vascular oxidative stress and reduce endothelial nitric oxide (NO) production. From: Forstermann U, Xia N, Li H. Roles of Vascular Oxidative Stress and Nitric Oxide in the Pathogenesis of Atherosclerosis. Circ Res. 2017; 120:713-735
OVERVIEW

The Institute of Toxicology in Mainz focuses on DNA damaging agents, DNA damage and repair, damage-triggered signaling, genomic instability, chromosomal changes, malignant transformation and mechanisms of cell death. The genotoxicity of alkylating compounds, including food and tobacco-borne carcinogens, and the cellular mechanisms protecting against them, notably DNA repair, are being investigated intensely. Furthermore, the response of immune competent cells to genotoxicants, including chemical ROS and ionizing radiation, is also under study. Since alkylating drugs are widely used in cancer therapy, the different responses of cancer cells to therapeutics, including DNA damage processing, apoptosis, autophagy, senescence and its relation to drug resistance, are being explored.

HIGHLIGHTS

REGULATION OF DNA REPAIR FOLLOWING DNA DAMAGE
Central to our interest is the question of how cells react to treatment with genotoxic agents and whether this treatment activates specific DNA repair systems. We showed that exposure to non-toxic concentrations of the environmental carcinogen benzo(a)pyrene provokes transcriptional activation of the p53-regulated repair genes DDB2 and XPC, enhancing the DNA repair capacity and inducing an adaptive response, protecting cells from a subsequent high-challenge dose of this carcinogen. Moreover, polymerase eta (POLH), which acts as the main polymerase during translesion synthesis, was also induced, leading to a reduced frequency of apoptosis at the expense of an enhanced mutation frequency.

FOOD-BORNE CARCINOGENS AND COLORECTAL CARCINOGENESIS
In this project, we elucidated cellular defense mechanisms in human colonic epithelial cells against the heterocyclic aromatic amine PhIP, which is an abundant dietary carcinogen found in cooked meat and fish. Our studies showed that PhIP-induced DNA adducts trigger replication stress to the detriment of the cell. We further demonstrated that the DNA damage response regulated by the kinase ATR is crucial for curtailing replication stress and chromosomal instability, both hallmarks of the pathogenesis of colorectal cancer.

ROLE OF HISTONE DEACETYLASES IN CANCER CELL SURVIVAL
Here, we demonstrated that HDACi can regulate the crosstalk between the transcription factors p53 and NF-κB p65 in cells following chemotherapy-induced replicative stress. We revealed that the vitamin A derivative ATRA protects leukemic cells from apoptotic cell death and DNA damage induction by class I HDACi. Moreover, we showed that HDAC1 and HDAC2 regulate mutant p53 through the transcription factor c-MYC.

HISTONE DEACETYLASES AND DNA REPAIR
We further demonstrated that enhanced histone deacetylase activity found in some tumors is related to upregulation of the DNA repair proteins RAD51 and FANCD2, causing drug resistance. Furthermore, we showed that novel pharmacological inhibitors of RAD51 and MRE11 sensitize cancer cells to alkylating drugs. In addition, we showed that integrins have an impact on DNA repair with downregulation of αVβ3, which is accompanied by reduced RAD51-mediated homologous recombination. These findings open up new avenues for therapeutic interventions.

EPIGENETIC REGULATION OF DNA REPAIR
We showed that the DNA repair genes MGMT and XAF1 are strongly regulated by epigenetic mechanisms. Both genes correlate in their expression with glioblastoma cell resistance. The expression level can be determined by promoter methylation analysis. A new and sensitive assay for promoter methylation (by HRM) was established.
FUTURE DIRECTIONS

We wish to gain a better understanding of the mechanisms protecting against environmental, food-borne and endogenously formed carcinogens. Further, we wish to extend our knowledge of the molecular mechanisms of genotoxic anticancer drugs and their interaction with novel therapeutics, notably inhibitors of DNA damage-triggered signaling, for improving cancer chemotherapy. Mechanisms of apoptosis, DNA damage-induced repair, autophagy and senescence as well as adaptive responses to genotoxic carcinogens will also remain in focus. The DNA-damaging mechanisms of diet-induced colorectal cancer, in particular, heme iron from red meat, will further be addressed in our studies. Findings on DNA repair factors obtained from experimental studies will be translated to human cancers in close co-operation with our clinical partners.

IMPORTANT PROJECTS // MAX. 5

Alkylation-induced DNA damage response and role of DNA repair in colon carcinogenesis (DFG KA 724/29-1)
PROJECT MANAGER: Prof. B. Kaina
FUNDING: German Research Foundation (DFG)
SUM: € 216,028
PROJECT DURATION: 2014 - 2017

HDAC dependent regulation and functional characterization of WT1 upon replicative stress (DFG KR 2291/5-1)
PROJECT MANAGER: Prof. O. Krämer
FUNDING: German Research Foundation (DFG)
SUM: € 214,150
PROJECT DURATION: 2016 - 2018

Influence of DNA double-strand break repair in the sensitivity of cancer cells to chloroethylating drugs (DFG AZ NI 1319/1-2)
PROJECT MANAGER: Dr. T. Nikolova
FUNDING: German Research Foundation (DFG)
SUM: € 291,600
PROJECT DURATION: 2014 - 2017

Influence of IAPs and DNA double strand break repair on the resistance of tumor cells against alkylation and TopoI inhibiting anticancer drugs (DKH No. 111404)
PROJECT MANAGER: PD Dr. M. Tomicic-Christmann, Prof. M. Christmann
FUNDING: Dr. Mildred Scheel Foundation (DKH)
SUM: € 250,100
PROJECT DURATION: 2014 - 2017

Role of DNA-repair and DNA-damage response in maintaining endothelial function upon genotoxic stress (KA 724/28-1)
PROJECT MANAGER: Prof. B. Kaina
FUNDING: German Research Foundation (DFG)
SUM: € 184,000
PROJECT DURATION: 2014 - 2017
OVERVIEW

The Institute of Translational Immunology (TIM) has been founded with the appointment of Prof. D. Schuppan from Harvard University. It brings diagnostic and therapeutic developments from bench to bedside. Unique clinical activities are focused on intestinal inflammatory diseases, including celiac disease, inflammatory bowel disease, food allergies and novel food intolerances, and the interaction of the gut, its immune system and the microbiota with peripheral organs in health and disease. Other areas include non-alcoholic fatty liver disease, fibrosis of liver and skin, and liver, colon, lung and skin cancer. The TIM is active in lecturing in (translational) medicine and basic research and clinical practice, guiding, promoting and mentoring Master, MD and PhD students in Translational Immunology and Medicine.

HIGHLIGHTS

Focus on mechanisms of chronic inflammation, especially of liver, gut, skin and its resolution, with a special focus also on fibrosis and cancer. Characterization and validation of anti-inflammatory, antifibrotic and anti-cancer therapies. IT studies in patients with these diseases.

1. LIVER

Studies of experimental biliary and lobular fibrosis, fibrosis reversal, of non-alcoholic steatohepatitis (NASH) and liver cancer. Development of novel transgenic mice, e.g. to inducibly delete ECM or immune genes. In vitro studies with effector cells in inflammation, fibrosis and cancer. Modulation of hepatic progenitor cells and macrophages to induce fibrosis reversal and cancer regression. Liver and cell specific nanoparticles for effective delivery of therapeutic small molecules and siRNA. Extension of studies to skin, pulmonary and kidney inflammation, fibrosis and cancer.

2. INTESTINAL DISEASES

Pathogenesis/immunology of celiac disease, wheat sensitivity, inflammatory bowel disease non-classical food allergies as main cause of irritable bowel syndrome (IBS). Identification of the celiac disease autoantigen, tissue transglutaminase (TG2), amylase-trypsin inhibitors (ATI) as cause of nonceliac wheat sensitivity and of IgE-negative food allergies as major cause of IBS. Clinical codevelopment of a TG2 inhibitor as novel treatment for celiac disease. Use of (humanized) celiac disease mouse models. Prime clinical and research center for celiac and small intestinal diseases. Several IIT studies on ATI sensitivity, including multiple sclerosis, primary sclerosing cholangitis and nonalcoholic steatohepatitis.

Studies within the Mainz project on Chemical Allergology (MPCA) on environmental modulators of airway and nutritional inflammation and allergies.

3. THE IMMUNE SYSTEM IN CANCER

Projects investigating and targeting macrophages, dendritic and myeloid suppressor cells in cancers, including metastatic melanoma, primary liver and non small cell lung cancer.

4. THE ROLE OF MACRONUTRIENTS AND THE MICROBIOTA IN INTESTINAL AND EXTRAINTESTINAL INFLAMMATORY DISEASES

The role of ATIs and specific lipids, their interaction with the intestinal microbiota and the immune system. Diseases addressed are inflammatory bowel disease, IBS, cancers, various autoimmune diseases, CNS inflammation, NASH/type 2 diabetes.

5. IDENTIFICATION, ASSAY ESTABLISHMENT AND VALIDATION OF NOVEL BIOMARKERS OF INFLAMMATORY AND NEOPLASTIC DISEASE AS TOOLS FOR A BETTER DIAGNOSIS, PROGNOSIS AND ESPECIALLY THERAPY CONTROL

Development of non-invasive techniques to monitor (liver) fibrogenesis and fibrolysis (serum markers) and of quantitative imaging agents (PET and MR) to quantitate tissue fibrosis and fibrogenesis. Other projects develop proteomic, lipidomic and microparticle based serum biomarkers for the diagnosis and activity assessment of celiac disease, atypical food allergy, inflammatory bowel and autoimmune diseases, and several cancers.
IMPOR TANT PUBLICATIONS // MAX. 5


Karsdal MA, Nielsen SH, Leeming DJ et al. The good and the bad collagens of fibrosis - Their role in signaling and organ function. ADVANCED DRUG DELIVERY REVIEWS. 2017; 121: 43-56.


Zevallos VF, Raker V, Tenzer S et al. Nutritional Wheat Amylase-Trypsin Inhibitors Promote Intestinal Inflammation via Activation of Myeloid Cells. GASTROENTEROLOGY. 2017; 152 (5): 1100-+

FUTURE DIRECTIONS

To further develop the research and clinical areas highlighted above. Currently, several proposals for EU and DFG/CRC projects are being prepared, many in collaboration with research and clinical centers in Germany and abroad. Projects are based on published and preliminary data from prior research. Many of the research projects below are relevant for other disciplines, making participation of the TIM in larger initiatives attractive. Currently, several patents on biomarkers, quantitative imaging but also therapeutics are being filed.

FIG. 1: Therapy of cancer, cancer metastatic and fibrosis by addressing tolerance inducing and profibrotic M2-macrophages with therapeutic nanoparticles and small molecules.

FIG. 2: Pathogenesis and innovative therapies for non-alcoholic steatohepatitis and liver fibrosis.

FIG. 3: The role of wheat amylase trypsin inhibitors (ATIs) and modified fatty acids as modulators of chronic inflammation, allergies and cancer.

IMPORTANT PROJECTS // MAX. 5

CI3 Cluster for Individualized Immune Intervention: „Clinical Development of Transglutaminase-Inhibitors for the Treatment of Celiac Disease“ (phase 2)
PROJECT MANAGER: Prof. D Schuppan
FUNDING: Federal Ministry of Education and Research (BMBF)
SUM: € 524,160
PROJECT DURATION: 2015 - 2017

CRC 1066/2: Nanodimensional polymer therapeutics for tumor therapy, „Therapy of metastatic melanoma by addressing tolerance inducing M2-macrophages with therapeutic nanoparticles“
PROJECT MANAGER: Prof. D Schuppan, PD Dr. A Tüttenberg
FUNDING: German Research Foundation (DFG)
SUM: € 329,292
PROJECT DURATION: 2016 - 2019

Modulation of allergen-induced lung and gut inflammation by nutritional wheat amylase trypsin inhibitors (ATIs), activators of the innate immune system
PROJECT MANAGER: Prof. D Schuppan, PD Dr. I Bellinghausen
FUNDING: German Research Foundation (DFG)
SUM: € 444,600
PROJECT DURATION: 2017 - 2020

„Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS)“
PROJECT MANAGER: Prof. D Schuppan, PD Dr. J Schattenberg
FUNDING: European Union (EU)
SUM: € 1,106,250
PROJECT DURATION: 2017 - 2022
Institute of Virology

Director:
Professor
Matthias J. Reddehase

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OVERVIEW

Research at the Institute of Virology flanks the focus areas of the medical service by specialization 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 giving high priority 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

Key features of CMV infection are immune control in the immunocompetent host that prevents disease and terminates productive infection, leading to a state of latency defined by the presence of viral genome in absence of virus production. Clinical problems arise when latent viral genomes reactivate to productive infection under conditions of a weakened immune system. The Institute of Virology is internationally renowned for preclinical models of CMV infection in the context of HCT as well as for translational research aimed at developing a CMV vaccine based on recombinant subviral particles. The Institute of Virology is part of the Research Center for Immunotherapy and of the priority research field „Immunology“ of the University Medical Center Mainz.

SPECIFIC RESEARCH TOPICS:

Topic 1: Pre-clinical evaluation of a subviral particle vaccine for the prevention of CMV associated complications following allogeneic HCT.

Human CMV (HCMV) infection is a serious complication of HCT. We have developed a vaccine candidate based on subviral dense bodies (DBs) for the application in this clinical setting. The project addresses the question of how DBs alter cell homeostasis and influence antigen presentation pathways in professional antigen presenting cells.

Topic 2: Analysis of the protein interaction networks that orchestrate tegument assembly and envelopment of HCMV virions and DBs.

The morphogenesis of HCMV particles is a complicated process that requires multiple interactions of viral proteins to assemble capsids, to attach the tegument layer, and to perform final envelopment in the cytoplasm. This project focusses on elucidating the protein networks required for the formation of HCMV virions and DBs.

Topic 3: Role of mast cells (MC) in the control of CMV infection.

We showed that CMV triggers two pathways of MC degranulation, of which the first depends on TLR3/TRIF signaling, whereas the second is TLR3/TRIF independent and involves productive infection of the MC. Release of chemokine CCL5 by infected MC attracts CD8 T cells to the lungs and thereby limits infection of pulmonary epithelial cells.

Topic 4: Immunomodulation of cytomegalovirus latency and reactivation by regulatory T cells and dendritic cells.

CMV infections are efficiently controlled by CD8 T cells but they do not succeed in eliminating the virus. We showed that CD8 Tregs significantly increase after mCMV infection and suppress T-cell proliferation in vitro. This could explain the failure of the antiviral CD8 T cells in eliminating the virus.
**Important Publications** // Max. 5


Lemmermann NAW, Reddehase MJ. TLR3-independent activation of mast cells by cytomegalovirus contributes to control of pulmonary infection. CELLULAR & MOLECULAR IMMUNOLOGY. 2017; 14 (6): 479-481.

Popovic B, Golemac M, Podlек J et al. IL-33/ST2 pathway drives regulatory T cell dependent suppression of liver damage upon cytomegalovirus infection. PLOS PATHOGENS. 2017; 13 (4).


**Future Directions**

**AIM 1**
Improvement of immunotherapy of CMV disease after HCT by evaluating the function of human CD8 T cells in HLA-transgenic mouse models (FIG).

**AIM 2**
Evaluation of the impact of an HCMV subviral particle vaccine on cell homeostasis.

**AIM 3**
Definition of the protein interaction networks that orchestrate tegument assembly and envelopment of HCMV virions and dense bodies.

**AIM 4**
Development of vaccine strategies to prevent CMV-related complications in solid-organ and hematopoietic cell transplantation.

**AIM 5**
Identification of CMV genes that trigger mast cell degranulation by modulation of intracellular Ca2+ levels.

**AIM 6**
Identification of the role of type-I interferon-signaling to promoters of viral immune evasion genes in CMV evasion of natural killer cells.

**AIM 7**
Interactom analysis of the mCMV immune evasion protein m06/gp48 to identify new immune evasion functions.

**AIM 8**
Immunomodulation of cytomegalovirus latency and reactivation by regulatory T cells and dendritic cells.

**AIM 9**
Pathophysiological contribution of CMV infection to allergic airway disease.

**Important Projects** // Max. 5

Analysis of the protein interaction networks that orchestrate tegument assembly and envelopment of human cytomegalovirus virions and dense bodies

**Project Manager:** Prof. B Plachter

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

**SUM:** € 327,150

**Project Duration:** 2016 - 2019

Preclinical evaluation of a cytomegalovirus vaccine for the prevention of complications of allogeneic hematopoietic stem cell transplantation

**Project Manager:** Prof. B Plachter

**Project Duration:** 2017 - 2019

**Topic 5: Pathophysiological interaction between chronic CMV infection and allergic airway disease.**

Applying an Ovalbumin (OVA)-based model for allergic airway disease, we showed CMV promotes disease by licensing migratory dendritic cells for efficient antigen cross-presentation. Thereby, CMV increases the allergic potential of an otherwise poorly allergenic environmental antigen.
DEPARTMENTS OF CONSERVATIVE MEDICINE

Department of Cardiology
Department of Child and Adolescent Psychiatry and Psychotherapy
Department of Dermatology
Department of General Medicine and Geriatrics
Department of Internal Medicine I
Department of Internal Medicine III
Department of Neurology
Department of Pediatrics
Department of Psychiatry and Psychotherapy
Department of Psychosomatic Medicine and Psychotherapy
Department of Cardiology

OVERVIEW

The Center for Cardiology is the leading cardiology center in Rhineland-Palatinate and the metropolitan Rhine-Main area. This includes an intensive/intermediate care, a Chest Pain Unit and Atrial Fibrillation Unit. Main focuses are the treatment of patients with acute coronary syndromes and chronic coronary artery disease, interventional heart valve therapy, interventional treatment of peripheral artery disease. We also perform diagnostic and interventional electrophysiology including ablation of paroxysmal and persistent atrial fibrillation and complex ventricular tachycardia and are a focus clinic for adults with congenital heart disease. We established the Gutenberg Health Study, the Center of Thrombosis and Hemostasis and are part of the German Center for Cardiovascular Research (DZHK).

HIGHLIGHTS

STRUCTURE

In 2017, the center treated about 10,500 inpatients and 27,000 outpatients. The clinic has 6 cardiac catheterization laboratories in which per year > 5,000 diagnostic cardiac catheterizations and percutaneous coronary interventions in patients with stable coronary heart disease, acute myocardial infarction, heart failure, peripheral artery disease, valvular disease and complex arrhythmias (about 1,000 atrial fibrillation ablations) are performed. Furthermore, we implant approx. 500 pacemakers and 250 defibrillators with or without resynchronization. Our Chest Pain Unit treats more than 5,000 patients per year, approx. 800 with an acute coronary syndrome. Recently we introduced a so called „manager check“ unit. We have an excellent network with cardiologists and clinics within Rhineland-Palatinate. In 2017 our clinical study center was involved in more than 50 clinical trials. 500 patients were enrolled in ongoing clinical trials and 500 patients could be included in new clinical trials.

SCIENTIFIC WORKING PROGRAM

Key research areas are the identification of causes leading to vascular dysfunction. In preclinical and clinical studies we investigate the influence of genes and traditional but also novel environmental risk factors, and the diagnostic value of biomarkers with respect to cardiovascular disease. Furthermore, we focus on the mechanisms of improving 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 enrolled 15,010 participants and finished the 5 year follow-up investigation of all participants in April 2017. The study will continue until 2023. The Center is part of the Center of Thrombosis and Hemostasis (CTH) and of the German Center for Cardiovascular Research (DZHK), with a research group focusing on the interaction between myocardial and vascular disease. In 2017 we obtained funding from the Boehringer Ingelheim Foundation for the project: „Novel and neglected cardiovascular risk factors: molecular mechanisms and therapeutic implications“.

Research in 2018 will include new antidiabetics such as the gliptins (DPP-4) inhibitors which are 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. Our group is also focused on the role of AMPK and PGC-1alpha in the regulation of vascular homeostasis. A 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. Currently, about 10 projects are supported by the German Research Foundation (DFG).
IMPORTANT PUBLICATIONS // MAX. 5


FUTURE DIRECTIONS

SCIENTIFIC AIMS
To further expand the translational research combining techniques of sleep research and vascular function studies trying to figure out, why people living close to airports and railways are suffering from cardiovascular disease, arterial hypertension, myocardial infarction and stroke. We will also study the effects of e-cigarette smoke on vascular function in translational preclinical and clinical studies.

STRUCTURAL AIMS
To further expand interventional valve therapy in the Center of Cardiology with new treatment options and devices. We will introduce the nationwide first Heart Valve Unit in Germany to further optimize diagnostic and treatment of patients with complex heart valve disease. We will also continue to offer preventive cardiology and „manager checks” and will expand the offer to include more disciplines in a preventive medicine program.

IMPORTANT PROJECTS // MAX. 5

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

Interleukin-6 (IL-6) and the interaction between IL-6 and Interleukin-17 (IL-17) on the development of vessel inflammation in vascular dysfunction (DFG KA 4035/1-1) PROJECT MANAGER: Dr. S Karbach FUNDING: German Research Foundation (DFG) SUM: € 202,790 PROJECT DURATION: 2014 - 2017

Myocardial Texture Analysis in healthy volunteers and cardiomyopathies PROJECT MANAGER: Dr. T Emrich PROJECT DURATION: 2017 - 2019

Resolution of Left Atrial-Appendage thrombus - Effects of Dabigatran in patients with AF (RE-LATED AF) PROJECT MANAGER: Prof. T Münzel, Prof. T Rostock FUNDING: Boehringer Ingelheim GmbH & Co. KG SUM: € 650,000 PROJECT DURATION: 2013 - 2018


FIG.: Performing Mitral Valve Repair.
OVERVIEW

The Department of Child and Adolescent Psychiatry and Psychotherapy is a science and teaching orientated institution. Main research interests of the department in the field of child and adolescent psychiatry are eating disorders, ADHD and pediatric depression.

We are the first University Medical Center in Germany to offer a compulsive teaching model in child and adolescent psychiatry in medicine.

In cooperation with the Rheinhessen-Fachklinik Mainz, Child and Adolescent Psychiatry, Psychotherapy and Psychosomatic, also headed by Prof. Michael Huss, clinical research is conducted and treatment is provided for 2,500 outpatients and 350 inpatients per year.

HIGHLIGHTS

EATING DISORDERS

Smartphone-Enhanced Low-Threshold Intervention for Adolescents with Anorexia Nervosa (SELTIAN): In the SELTIAN study, the influence of an innovative real-life and smartphone-based assessment tool on the weight course and psychopathology of female adolescents with anorexia nervosa is investigated. SELTIAN is conducted in cooperation with the Johanniter-Zentrum Neuwied and the University Medicine Charité Berlin. The study is supported by an intramural research grant of the Johannes Gutenberg-University Mainz. In the ActivAN study, we examine if physical activity in anorexia nervosa is used as a dysfunctional emotion regulation strategy. Data collection in cooperation with the Schön-Klinik Roseneck in Prien is still ongoing. Since 2009, the MaiStep-project (Mainz School Training for Eating Disorders Prevention), was continuously further developed and implemented in a large number of schools in Rhineland-Palatinate. The project is conducted in cooperation with the insurance group KKH (Kaufmännische Krankenkasse), the Ministry of Social Affairs, Labour, Health and Demography (MSAGD), the Ministry of Education (MB), the Ministry of Science, Further Education and Culture (MWWK) and the Association for Facilitating Feminist Social Work for Girls (FEMMA). In an international cooperation with Universidad del Norte, Barranquilla, Colombia, cultural differences in body image and related constructs such as drive for thinness/muscularity or disordered eating are investigated. In this joint project, we collected data from more than 2,500 participants both in Germany and Colombia.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

The PAD-study (Polyunsaturated Fatty Acids) was conducted to assess the efficacy of Omega-3-supplements (e.g. fish oil) in the treatment of ADHD. In addition, effects of stepped care in the treatment of ADHD were assessed in the multi-center ESCA school study.

MAJOR DEPRESSION

The efficacy of a promising pharmaceutical drug for children and adolescents with major depression is currently tested in an international multicenter RCT study in our outpatient center.

STRESS PREVENTION

In cooperation with the insurance company Unfallkasse Rheinland-Pfalz, we initiated the „startklar“ project, a mindfulness based stress prevention program for student teachers. Data collection was completed in 2017.

CBT SELF-EXPERIENCE IN CLINICAL TRAINING

The efficacy of a CBT-based self-experience training for psychology students is tested in an innovative teaching project (Therapie unter der Lupe - therapy in focus).
**FUTURE DIRECTIONS**

A main future research goal of the Department of Child and Adolescent Psychiatry and Psychotherapy is the translation of cutting-edge clinical research into standard treatment processes, especially in the field of eating disorders. In 2018, we want to implement a specialized work group focusing on modern digital approaches to assessment, experimental testing and treatment in child and adolescent psychiatry. Hereby we aim to focus our research experience in ecological momentary assessment and digital mental health. In addition, the concept of self-compassion will be validated in a juvenile population and its efficacy for the treatment of eating disorders will be investigated.

**IMPORTANT PUBLICATIONS // MAX. 5**


**IMPORTANT PROJECTS // MAX. 5**

**Body Image Study - Impact of the internalization of the beauty ideal on the body image of women and men**
- PROJECT MANAGER: F Hammerle
- PROJECT DURATION: 2016 - 2018
- FUNDING: German Research Foundation (DFG)
- SUM: € 61,788
- FUNDING: Else-Kröner-Fresenius-Foundation
- SUM: € 52,102

**Clinical register for congenital malformations**
- PROJECT MANAGER: Dr. E Jenetzky
- FUNDING: German Research Foundation (DFG)
- SUM: € 14,984

**Innovative teaching project: therapy in focus**
- PROJECT MANAGER: H Preuss, F Hammerle
- FUNDING: Gutenberg Teaching Council, JGU Mainz
- SUM: € 40,000

**SELTIAN: Smartphone-Enhanced Low-Threshold Intervention for adolescents with Anorexia Nervosa**
- PROJECT MANAGER: D Kolar
- FUNDING: University Medical Center Mainz
- SUM: € 260,709

**startklar – mindfulness-based stress prevention in student teachers**
- PROJECT MANAGER: F Hammerle, S Kuhlmann
- FUNDING: Unfallkasse RLP
- SUM: € 120,709

**PROJECT DURATION:**
- 2015 - 2018
OVERVIEW

Five professors, eight senior physicians and fifteen specialists and junior doctors ensure medical diagnostics and therapy on the highest level. We offer state-of-the-art diagnosis and therapy in all areas of dermatology. In addition to skin specialists, the Department employs 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. In addition, the Department hosts a basic research laboratory with >50 researchers, and we also conduct >50 clinical trials on innovative therapies in dermatology.

HIGHLIGHTS

Our goal is to investigate immunobiological causes of skin diseases and autoimmunity and allergy. Research on the development of allergic diseases is the focus of Prof. 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. Steinbrink and Prof. von Stebut-Borschitz. The focus of the working group of Dr. Jonuleit and Prof. Tüttenberg is the study of the regulatory T cells, immune cells that prevent autoaggressive immune responses including graft-versus-host disease. The molecular characterization of T cell function and dysfunction in autoimmune and allergic diseases and the development of biologicals that modify this function is the focus in the research group of PD Dr. Becker. Another important focus of our basic research is melanoma (Prof. Grabbe). The development of new, multifunctional polymers for the improved treatment of melanoma patients are at the center of the research of Prof. Mailänder. The Department of Dermatology currently participates in two DFG-funded collaborative research centers (CRC). Seven PIs from our Department participate in the CRC 1066 „Nanodimensional polymer therapeutics for tumor therapy“, where our immunologists closely collaborate with clinical colleagues, chemists and the Max Planck Institute for Polymer Research to develop multifunctional nanoparticles for immunotherapeutic treatment of melanoma. The activities in this field have led to the inauguration of the Center for Translational Nanomedicine – CTN. The CTN acts as platform for the interaction of all the groups concerned with nanomaterials and their use in biomedical applications. In a collaborative research center, the CRC TR156 „The skin as sensor and effector organ orchestrating local and systemic immune responses“, four PIs from the Department investigate the interplay between the skin and the systemic immune system. In addition, the GO-Bio Project „GP120-activated Tregs for Tolerance“ was established by Dr. Jonuleit and PD Dr. Tüttenberg with the support of the BMBF. The aim is to bring a cell therapy to suppress the graft-versus-host disease after blood stem cell transplantation into the clinical application.
**IMPORTANT PUBLICATIONS // MAX. 5**

- Sahin U, Derhovanessian E, Miller M et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. NATURE. 2017; 547 (7662): 222-+

**FUTURE DIRECTIONS**

- Analysis of the skin immune system (all researchers of the Department)
- Molecular and cellular processes triggering and control the induction of type I allergy (Prof. Saloga, PD Dr. Bellinghausen, Prof. Steinbrink)
- Functional and molecular characterization of T lymphocytes and regulatory T cells (Dr. Jonuleit, Prof. Tüttenberg, PD Dr. Becker, Prof. Steinbrink)
- Investigation of dendritic cells as modulators of tolerance and immunity (Prof. Grabbe, Prof. Steinbrink, Dr. Jonuleit)
- New multifunctional polymers for immunotherapeutic treatment of melanoma (Prof. Grabbe, Prof. Steinbrink, Dr. Jonuleit, Prof. Tüttenberg, PD Dr. Becker, Prof. Mailänder)
- The role of dendritic cells and Langerhans cells in the development of protective immune responses against cutaneous leishmaniasis

**IMPORTANT PROJECTS // MAX. 5**

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Project Manager</th>
<th>Funding Agency</th>
<th>Summary</th>
<th>Project Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP120-activated Tregs for Tolerance</td>
<td>Prof. A Tüttenberg, Dr. H Jonuleit</td>
<td>Federal Ministry of Education and Research (BMBF)</td>
<td>€ 3,300,000</td>
<td>2016 - 2019</td>
</tr>
<tr>
<td>Nanodimensional polymeric therapeutics for tumor therapy (TP 89, CRC 1066)</td>
<td>Prof. S Grabbe, PD Dr. M Bros, Prof. K Steinbrink et al.</td>
<td>German Research Foundation (DFG)</td>
<td>€ 3,213,514</td>
<td>2016 - 2017</td>
</tr>
<tr>
<td>CRC 1066: Nanodimensional polymer therapeutics for tumor therapy</td>
<td>Prof. S Grabbe, PD Dr. M Bros, Prof. K Steinbrink et al.</td>
<td>German Research Foundation (DFG)</td>
<td>€ 3,213,514</td>
<td>2017 - 2021</td>
</tr>
<tr>
<td>CRC Transregio 156: The skin as sensor and effector organ, orchestrating local and systemic immunity</td>
<td>Prof. S Grabbe, PD Dr. M Bros, Prof. K Steinbrink et al.</td>
<td>German Research Foundation (DFG)</td>
<td>€ 1,472,750</td>
<td>2015 - 2019</td>
</tr>
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</table>
OVERVIEW

The Department of General Medicine and Geriatrics (ZAG) was founded in November 2015 and comprises of teaching, research and didactical research. Refounding the Department allows greater scientific engagement in General Medicine at the University Medical Center of the Johannes Gutenberg-University Mainz. The research focuses on the provision of medical care and other health services. Aiming to establish the Department as the link between licensed general practitioners and the University hospitals, the Department’s research addresses issues and needs of general practitioners. The transfer and application of research conducted at the Department of General Medicine benefits from a large network of local teaching practices and physicians.

HIGHLIGHTS

Research activities at the Department of General Medicine and Geriatrics currently focuses on 6 areas:

1. DEMENTIA PATIENTS IN GENERAL PRACTICES
   The Department of General Medicine and Geriatrics is closely working together with experts in geriatric psychiatry to improve the screening, diagnostics, and treatment of patients with dementia. Through several studies, qualitative interviews and (online) surveys are being combined to develop vocational training courses tailored to the needs of general practitioners and their medical staff.

2. LIVER DISEASES IN GENERAL PRACTICES
   The Department of General Medicine is part of the SEAL study (Structured Early Assessment for Asymptomatic Liver Cirrhosis), funded by the innovation fund of the German Joint Government Committee (G-BA). Current approaches to screen for liver diseases and which strategies are employed to clarify abnormal liver function test results are being investigated. Also, potential education and training needs are identified and addressed.

3. IMPACT OF eHEALTH AND mHEALTH ON MEDICAL PROFESSIONALS
   To assess benefits of internet- and telemedicine-based health care services, as well as derive implications and recommendations for general practitioners, the Department of General Medicine and Geriatrics is pursuing several studies. In particular, the Department investigates the impact of websites for patients to rate their physician on general practitioners and surveys users of medical counselling websites as well as health-apps.

4. INTERNET-ASSOCIATED HEALTH ANXIETY IN EVERYDAY PRACTICE
   In certain cases, exaggerated Internet research may provoke fears of a patient’s health that can become entrenched in the long term (‘cyberchondria’). The ZAG does research on Internet-related health anxiety and develops application-oriented intervention approaches for primary care physicians.

5. RESEARCH ON EDUCATION
   The Department of General Medicine and Geriatrics is constantly striving to improve the education in general medicine. Research projects on education are focusing on how to improve the student – general practitioner interactions during practicums and the long-term patient care during the course of study of medical students. To improve diagnostic competence and raise interest for general medicine amongst students, the Department of General Medicine and Geriatrics is developing several e-learning platforms and teaching videos.

6. PRIMARY HEALTH CARE FOR ASYLUM SEEKERS THROUGH GENERAL PRACTITIONERS
   The Department of General Medicine and Geriatrics is also investigating the needs of Arabic speaking asylum seekers. Somatoform disorders (e.g. posttraumatic stress disorder, sleep disorders) can be challenging to diagnose and address for general practitioners due to language and cultural barriers. Additionally, the Department investigates the hepatitis C prevalence among asylum seekers.
The Department of General Medicine is moving toward the following goals:

**GOAL 1**
Expansion of research on primary care dementia diagnostics and patient care, including the design of application-oriented further education programs

**GOAL 2**
In-depth research on the influence of internet- and telemedicine-based health care services on the work of general practitioners and primary patient care; exploration of the importance of Internet-related health anxiety (‘cyberchondria’) in general practice

**GOAL 3**
Expansion of research on education to improve innovative teaching concepts and increase student interest in becoming a general practitioner

**GOAL 4**
Implementation of a center of excellence for continuing education in general medicine, including the development of teaching concepts, a mentoring program, and participation in a nationwide network

**IMPORTANT PROJECTS // MAX. 5**

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Project Manager</th>
<th>Funding Source</th>
<th>Budget</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Dementia Diagnosis in General Practices</td>
<td>Prof. M. Jansky</td>
<td>Stiftung Perspektive Haushalt</td>
<td>€ 45,000</td>
<td>2016 - 2019</td>
</tr>
<tr>
<td>Mainz General Medicine - Practical Guidance and Support (MA-BS)</td>
<td>Prof. M. Jansky</td>
<td>Federal Ministry of Education and Research (BMBF)</td>
<td>€ 36,000</td>
<td>2016 - 2019</td>
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<tr>
<td>Structured Early Assessment for Asymptomatic Liver Cirrhosis (SEAL)</td>
<td>Prof. M. Jansky</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The Significance of eHealth and mHealth for General Medicine</td>
<td>Prof. M. Jansky</td>
<td></td>
<td></td>
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</tbody>
</table>

**FIG. 1:** MA-BS, Teaching modules for smartphones.
**FIG. 2:** Cardiac examination in family practice.


**OVERVIEW**

The biomedical research of the Department of Internal Medicine I 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 focus of our Gastroenterology/Gastrointestinal (GI) Oncology section is the molecular pathogenesis and treatment of inflammatory bowel diseases as well as GI tumors with a particular interest in gastric and liver cancer. Clinical research involves systemic therapies including new biological agents and targeted therapies. Innovative immunotherapeutic approaches including oncolytic virus therapy are pursued. Our Interdisciplinary endoscopy (Head: Prof. Helmut Neumann) offers the full spectrum of endoscopic diagnostic and therapeutic procedures, including different ESD and EST techniques and endoscopic full thickness resection. Moreover, radiofrequency ablation is offered to our patients with Barrett’s esophagus and GAVE. ERCP, cholangioscopy, capsule endoscopy and EUS guided interventions are completing the armamentarium. Our translational research activities focus on the application of functional and molecular imaging.

Our research in Hepatology/Infectiology is aimed at understanding the pathogenesis and treatment of a large spectrum of chronic liver diseases including 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.

All patients with end-stage liver diseases and associated major complications are treated in our interdisciplinary Cirrhosis Center Mainz (CCM). We aim at improving awareness and early recognition of chronic liver disease. The SEAL project, funded by the innovation fund provided by the federal government, examines a new algorithm of care with the goal of improving early diagnosis of liver fibrosis and cirrhosis by implementing a liver screening program in approximately 18,000 individuals. The Imaging Core Facility supports laboratories within and beyond the Department of Internal Medicine I 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. The Rheuma-VOR project (funded by the innovation fund provided by the federal government) from the department of Rheumatology was designed to connect partners across different sectors involved in the diagnosis and treatment of inflammatory rheumatic diseases. The overall aim is to enhance the quality of rheumatology care by coordinating treatment in a trans-sectoral network in Rhineland-Palatinate, Lower-Saxony and Saarland.

The research in the Endocrinology area is directed at endocrine tumors and immune mediated thyroid disorders. Work on islet cell transplantation offers a promising strategy for the treatment of diabetes in the future.
FUTURE DIRECTIONS

Translational research in the field of gastrointestinal and hepatobiliary tumorigenesis will be significantly expanded with the overall goal to identify clinically relevant molecular subtypes of patients by next-generation technologies that qualify for individualized treatment strategies. This precision medicine approach includes the identification of predictive and prognostic molecular profiles, and of actionable mutations, which is the focus of Lichtenberg Research Group awarded to Jun. Prof. Jens U. Marquardt by the Volkswagen Foundation. Another professorship on Molecular Hepatology (Prof. Susanne Strand), supported by the "Professorinnenprogramm" 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. Another major focus will be the application and modeling of immunotherapies in GI and hepatobiliary cancers. These investigations will include the establishment and rigorous characterization of novel pre-clinical models that closely mimic the human disease. Clinical research in the field of Hepatology will be advanced by further expansion of the CCM (SEAL-Project), the implementation of LITMUS (Liver Investigation: Testing Marker Utility in Steatohepatitis) and complemented by clinical databases from the Clinical Registry Unit (CRU).

FIG. 1: Confocal laser scanning image of a dividing human liver cancer cell (chromosomes are depicted in blue, microtubuli in green, an epigenetic modifier associated with chromatin in red).

FIG. 2: 3D rendering of a confocal laser scanning images showing the bile canalicular network of the liver (nuclei in blue, bile canaliculi in green).

IMPORTANT PUBLICATIONS // MAX. 5

Castven D, Fischer M, Becker D et al. Adverse genomic alterations and stemness features are induced by field cancerization in the microenvironment of hepatocellular carcinomas. ONCOTARGET. 2017; 8 (30): 48688-48700.

FIG. 1

FIG. 2
OVERVIEW

The Department of Internal Medicine III (Hematology, Oncology, and 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 diseases. It is part of the University Cancer Center Mainz (UCT Mainz), of the Center of Thrombosis and Hemostasis and of the Center for Allergy Rhineland-Palatinate. The major scientific effort of the department is the immediate transfer of innovative basic science findings into novel therapies. Therefore the clinic maintains ten basic research groups and is member of several joint initiatives and institutions, such as the German Cancer Consortium and the Research Center for Immunotherapy.

HIGHLIGHTS

The following outstanding developments in 2017 should be highlighted:

PATIENT CARE

Our specialized outpatient clinic for patients with Myelodysplastic Syndrome (MDS) (PI: M. Radsak) was awarded the title „Center of Excellence“ by the Myelodysplastic Syndrome Foundation (MDSF) in recognition of extensive experiences in the treatment of MDS patients as well as in oncological basic and clinical research. At our certified center of transplantation (PI: E. Wagner-Drouet) the number of stem cell transplantations in patients with hematological diseases has nearly doubled within the past ten years (2017: 162 transplantations).

CLINICAL RESEARCH

The certified clinical trial unit on hematology, oncology, infectious diseases, hemostaseology, and palliative care (PI: G. Heß) with its separate phase I unit as well as the pneumology study section (PIs: R. Buhl, S. Korn) provide the basis for early, first-in-man- to late-stage clinical investigations. The clinical trial unit on hematology and oncology is leading member of the UCT working group clinical trials (Arbeitskreis Klinische Studien, AKKS; spokesman G. Heß). Consistent with the distinction of the UCT Mainz as Comprehensive Cancer Center by the German Cancer Aid, major aim of the AKKS in 2017 has been to develop a comprehensive clinical trial program for all oncologic entities in harmonized structures of the AKKS network. Until now (1) a uniform web portal for clinical trials, (2) a joint document and quality management system and (3) a central study database have been established. Importantly, a number of joint cross-entity early phase study projects have been initiated with a special focus on early precision medicine trials based on molecular profiling. At the pneumology study section in 2017 more than 200 patients have been treated with innovative therapy strategies within clinical trials. Additionally, several research projects in the field of airway diseases have been conducted.

BASIC RESEARCH

The foci of basic research within the clinic range from tumor immunology (PIs: H. Echchannaoui, U. Hartwig, B. Hauptrock, M. Munder, M. Radsak, M. Theobald, T. Wölfel), immunobiology of stem cell transplantation (PI: E. Wagner-Drouet) to molecular mechanisms of malignant hematologic transformations (PI: T. Kindler). In 2017 the new young investigator group of the German Cancer Consortium (PI: B. Guezguez) has taken up work, and a novel research group has been initiated (PI: D. Sasca). Moreover M. Kühn, the principal investigator of a newly founded research group focusing on epigenetic alterations in leukemogenic gene expression, was accepted into the DFG’s prestigious Emmy Noether Program. Also, three research groups of our clinic have been involved in the newly granted Collaborative Research Center 1292 (PIs: M. Munder, M. Theobald) or in the extended Collaborative Research Center 1066 (PI: T. Wölfel). All in all, more than 65 articles in high-ranking peer-reviewed journals have been published in 2017.
FUTURE DIRECTIONS

The Department of Hematology, Oncology, and Pneumology is in a continuous process of improving its high clinical and scientific standards. In 2018, the main focus of our interest will be on three important aims: First, the principal investigators of our research groups will help to meet all requirements for successful applications for collaborative research consortia, such as CRC or Transregio, in the field of our main research areas. A second significant objective will be the increase of the proportion of investigator initiated trials (IITs) emerging from our clinical trial units. Here cross-entity early precision medicine projects with special focus on molecular profiling, like „umbrella” or „basket” trials, are of particular interest. Third, our clinical trial unit will proceed the process of optimizing clinical oncology research by harmonizing common structures within all UCT clinical trial units. And finally, as in 2017, improved educational opportunities in basic and translational cancer research will be offered to young physicians from our clinic in 2018. The achievement of these aims will be essential for the improvement of cancer therapy and for a functioning as backbone for translational and basic research according to the quality standards of a comprehensive cancer center.

IMPORTANT PROJECTS  //  MAX. 5

<table>
<thead>
<tr>
<th>Project Title</th>
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<th>Funding</th>
<th>Sum (€)</th>
<th>Project Duration</th>
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</thead>
<tbody>
<tr>
<td>Chimeric antigen receptor-engineered natural killer cells as a universal cellular therapeutic for adoptive cancer immunotherapy (collaborative research project within translational immunotherapy program)</td>
<td>Prof. W Weis, Prof. M Theobald, Prof. M Bachmann et al.</td>
<td>German Cancer Consortium (DKTK)</td>
<td>999,900</td>
<td>2017 - 2019</td>
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<tr>
<td>Epigenetic control of leukemic gene expression by menin and wildtype MLL1 complex members</td>
<td>Dr. M Kühn</td>
<td>German Research Foundation (DFG)</td>
<td>1,588,971</td>
<td>2017 - 2022</td>
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<tr>
<td>Junior Group of the German Cancer Consortium</td>
<td>Dr. B Guezguez, Prof. M Theobald</td>
<td>German Cancer Consortium (DKTK)</td>
<td>1,750,000</td>
<td>2017 - 2022</td>
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<tr>
<td>Transcutaneous immunization: Mechanisms of intracellular networks of the skin (TRR156, A05)</td>
<td>Prof. M Radsak, PD Dr. M Stassen</td>
<td>German Research Foundation (DFG)</td>
<td>453,100</td>
<td>2015 - 2019</td>
</tr>
<tr>
<td>Transfection of tumor-reactive T cells with RNA-loaded nanocapsules (TP B9, SFB 1066 „Nano-dimensional polymeric therapeutics for tumor therapy”)</td>
<td>Prof. T Wölfel, Prof. V Mailänder</td>
<td>German Research Foundation (DFG)</td>
<td>324,600</td>
<td>2013 - 2017</td>
</tr>
</tbody>
</table>

IMPORTANT PUBLICATIONS  //  MAX. 5

- Werner A, Koschke M, Leuchtner N et al. Reconstitution of T Cell Proliferation under Arginine Limitation: Activated Human T Cells Take Up Citrulline via L-Type Amino Acid Transporter 1 and Use It to Regenerate Arginine after Induction of Argininosuccinate Synthase Expression. FRONT. IMMUNOL. 2017; 8.
Overview

Each year, the Department of Neurology cares for approximately 3,000 inpatients in its 66 beds including a nationally certified Stroke Unit, as well as 6,000 outpatients in nationally renowned specialized outpatient clinics, especially in the areas of multiple sclerosis and other inflammatory diseases, pain, epilepsy, neuromuscular diseases, neuro-oncology and movement disorders. In addition to providing medical care, the Department also conducts state-of-the-art and internationally recognized research into neuroimmunology, neuroimaging, signaling pathways, pain and neurovascular diseases. Translational studies are performed so that patients can benefit from new research findings as quickly and efficiently as possible.

Highlights

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) and Research Center for Immunotherapy (FZI), 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.
**IMPORTANT PUBLICATIONS** // MAX. 5

Cerina M, Narayanan V, Goebel K et al. The quality of cortical network function recovery depends on localization and degree of axonal demyelination. BRAIN BEHAVIOR AND IMMUNITY. 2017; 59: 103-117.


**IMPORTANT PROJECTS** // MAX. 5

**Competence Network Multiple Sclerosis (KKNMS): MSNetworks (Project B3.2)**
- **PROJECT MANAGER:** Prof. F Zipp, Prof. S Groppa, Dr. F Lüssi
- **FUNDING:** Federal Ministry of Education and Research (BMBF)
- **PROJECT DURATION:** 2016 - 2018

**CRC 1080 Project C01: Immune Cytokines in the Regulation of Neuronal Homeostasis**
- **PROJECT MANAGER:** Prof. F Zipp, J Kipnis
- **FUNDING:** German Research Foundation (DFG)
- **PROJECT DURATION:** 2017 - 2020

**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)
- **PROJECT DURATION:** 2016 - 2020

**Non-coding RNAs in neurogenic and neuropathic pain mechanisms and their application for risk assessment, patient stratification and personalised pain medicine**
- **PROJECT MANAGER:** Prof. F Birklein
- **FUNDING:** European Union (EU)
- **SUM:** € 396,000
- **PROJECT DURATION:** 2013 - 2017
Department of Pediatrics

Director:
Professor Fred Zepp

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OVERVIEW

The Department of Pediatrics at the University Medical Center Mainz serves as a hospital for supra-maximum medical care and is the single 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: A prospective evaluation of adverse events related to intubations in neonates aims to identify potential factors related to an improved safety of this procedure. A collaborative project aims to demonstrate the usefulness of a novel analytic approach to neonatal EEG. Two further studies investigate the incidence of viral nosocomial infections in newborns and the causes of nonimmune hydrops fetalis.

Oncology: The interdisciplinary „Cardiac and vascular late sequelae in long-term survivors of childhood cancer (CVSS-) study“ investigates the current health status of 1,000 former pediatric oncology patients and genome and expression analysis-based projects aim to identify novel therapeutic strategies for a pediatric malignant high-grade neuroepithelial tumor of the central nervous system with BCOR gene alteration (CNS HGNET-BCOR).

Metabolism (Villa Metabolica): Research focuses on the investigation of the pathogenesis, clinical presentation and new treatment options in patients with lysosomal storage diseases. Phase 1, 2 and 3 trials with small molecules and new enzyme replacement therapies for various lysosomal storage diseases were started. Furthermore, the Villa Metabolica has become member of the MetabERN, the European reference network for rare inherited metabolic diseases.

Pediatric Infectious Disease: Our research focuses on epidemiologic studies targeting respiratory diseases, Malaria, Dengue and other arboviral infections. In addition, we work on the development of novel nanocarrier-based vaccines for neonates and children.

Microbiome Research: Chronic Inflammatory Bowel Diseases in children were shown to be correlated to gut microbial patterns. History of antibiotic medication may impact the pediatric microbiome. Effects of probiotic supplementation on gut microbiota development of late preterm newborns are tested using metagenomic and 16S-rRNA characterization with next generation sequencing.

Pediatric Immunology: We study the biology of IL-27 as a highly expressed Th1 cytokine in newborn immunity, partly replacing IL-12, weakly secreted by neonatal dendritic cells. We explore this cytokine as a new marker for early onset neonatal sepsis.

Pediatric Rheumatology: Phenotypical differentiation of T and B cells and the expression of pro- and anti-inflammatory cytokines on mRNA and protein levels is tested.

The Molecular Pediatrics research group investigates the genetic and epigenetic mechanisms responsible for rare pediatric disorders, pediatric tumors and endocrine defects. The group is a founding member and representative of the EU Endocrine-reference network (Endo-ERN) and the EU-COST action BM1208.
FUTURE DIRECTIONS

Neonatology: Interdisciplinary multicenter studies on relevant clinical issues in neonatology. Oncology: Investigation of clinical, epidemiological and genetic aspects of cardiovascular late sequelae in long-term survivors of childhood cancer, new approaches for targeted therapies in Phase 1/2 studies and evaluation of physical activity for childhood cancer patients. Metabolism: One focus lies on clinical trials to treat brain disease in so far progressive neurodegenerative disorders as for Niemann-Pick disease type C and Gaucher disease type 3. One further focus is the establishment of new treatments for yet untreatable lysosomal storage diseases. Pediatric Infectious Disease: Development of a respiratory array-based detection platform. Enhancing epidemiological awareness and future aspects of norovirus and arboviral spread. Investigation of polymeric nanocarriers as a novel vaccine platform. Pediatric Immunology: Role of IL-27 in neonatal sepsis. Relevance of IL-27 in the gut barrier function of the neonatal system will be explored. IL-27 and its relevance in vaccine response. Microbiome Research: Microbiome data of neonates will be related to clinical development and risks for early onset sepsis. Molecular Pediatrics: The group aims to improve and standardize diagnostics and patient care for rare and complex disorders such as the Beckwith-Wiedemann syndrome (BWS) or endocrine defects associated with early childhood growth disturbances and tumor development.

IMPORTANCE PROJECTS // MAX. 5

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

Fabry disease under chaperone therapy with Migalastat-HCl
PROJECT MANAGER: Prof. J. B. Heinemann, Dr. I. Arash-Kaps
PROJECT DURATION: 2017 - 2018

Imprinting defects – clinical spectrum and pathogenic mechanisms, TP3b (molecular characterization of 11p15.5 associated imprinting defects (SRS, BWIS))
PROJECT MANAGER: Prof. D. Prawitt
FUNDING: Federal Ministry of Education and Research (BMBF)
SUM: € 143,545
PROJECT DURATION: 2015 - 2018

PRIMAL - The role of the microbiota for the development of the immune system at the beginning of life
PROJECT MANAGER: Prof. S. Gehring, Dr. C. Meyer
FUNDING: Federal Ministry of Education and Research (BMBF)
PROJECT DURATION: 2017 - 2021

Prospective evaluation of adverse events during neonatal endotracheal intubation
PROJECT MANAGER: Dr. A. Kidszun, Dr. S. Tippmann, Prof. E. Mildenberger, Dr. J. Köng, M. Gießen-Scheideler et al.
PROJECT DURATION: 2017 - 2021
OVERVIEW

The Department of Psychiatry and Psychotherapy is the main mental health institution for the city of Mainz providing basic and specialized mental health services for more than 200,000 people locally 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 prevention and treatment of psychiatric diseases and to strengthen resilience.

HIGHLIGHTS

The Department of Psychiatry and Psychotherapy is a highly active and productive research institution. It is also a well-evaluated education and training center for undergraduate, graduate and advanced medical training. It closely collaborates with other departments of the University Medical Center and is a member of the Focus Program Translational Neuroscience (FTN), the rmn2 network and the German Resilience Center (Deutsches Resilienz Zentrum, DRZ). Methodological expertise ranges from molecular biology, biochemistry (RG Endres, Lüddens) via mouse models (RG Müller, Endres), and neurophysiological and behavioral assessments in humans (RG Fellgiebel, Retz, Tüscher) to pharmacology and psychotherapy as well as systematic reviews (RG Lieb).

Research focuses are:

RESILIENCE TO STRESS
Resilience Research complements transdiagnostic yet disorder-related research in our Department. See Aims section below.

DISORDERS RELATED TO STRESS AND AFFECT DYSREGULATION
A major research focus of our Department is the study of disorders related to stress and affect dysregulation. By following a transdiagnostic approach to the study of psychiatric disorders, we try to overcome major problems in identifying underlying mechanisms and in developing innovative treatment approaches for affect dysregulation in disorders such as Attention Deficit Hyperactivity Disorder, Borderline Personality Disorder, Major Depressive and Bipolar Disorders. We also follow a translational approach by interdisciplinary work of basic and clinical neuroscientists, e.g. in the understanding of emotion regulation, impulse control or therapy response prediction (see figure).

HEALTHY AGING AND NEURODEGENERATION
Another major research focus of our Department is the study of healthy aging and neurodegeneration. In a translational approach, basic and clinical neuroscientists are working together to understand mechanisms of healthy aging to develop strategies to prevent dementia and to discover new avenues to successfully treat Alzheimer’s dementia.

FORENSIC PSYCHIATRY AND PSYCHOTHERAPY
Forensic psychiatry and psychotherapy is a major research topic of our department. It offers ambulatory clinical care and focus on diagnosis and treatment of Attention Deficit Hyperactivity Disorder (ADHD) both in psychiatry in general as well as forensic psychiatry and psychotherapy in particular. Forensic Psychiatry investigates the neurobiology of disorders often found to be associated with disruptive behaviors like ADHD in close collaboration with other groups of the department.

CONFLICTS OF INTEREST IN CLINICAL MEDICINE AND RESEARCH
Conflicts of interest (COI), e.g. by financial ties of researchers or clinicians to pharmaceutical companies, increase the risk of undue influences on professional decision-making and may have far-reaching consequences in healthcare. Therefore, our research group investigates financial and non-financial COI in clinical medicine and research and collaborates with other researchers in the field.
IMPOR TANT PUBLICATIONS // MAX. 5


FUTURE DIRECTIONS

RESILIENCE RESEARCH

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 active mechanisms of resilience and developing measures to secure and promote optimal functioning of these mechanisms is a necessary paradigm shift away from but complementing classical disorder-related research and is being performed in close collaboration with the German Resilience Center (Deutsches Resilienz Zentrum, DRZ, Managing Directors of DRZ: Prof. Lutz and Lieb).

Within the Resilience Health Care Center of DRZ, an approach is pursued, which combines basic neuroscience, clinical neuroscience, social science and public health outreach. Research within the DRZ is funded by the DFG-Collaborative Research Center 1193 „Neurobiology of resilience“, the Boehringer Ingelheim Foundation (BIF) and the State of Rhineland-Palatinate.

A major aim and focus has been and will further be the development of the DRZ into an independent, nationwide acting, interdisciplinary research center.

IMPORTANT PROJECTS // MAX. 5

**Consequences of COI regulations in medicine**

**PROJECT MANAGER:** Prof. K Lieb
**FUNDING:** Volkswagen Foundation
**PROJECT DURATION:** 2017 - 2019

**Epigenetic Changes in Longevity gene loci in Aging**

**PROJECT MANAGER:** PD Dr. K Endres
**FUNDING:** NMFZ
**PROJECT DURATION:** 2017 - 2018

**Home-based support program for patient with dementia and their primary informal caregiver administered by professionalized nursing staff (DYADEM)**

**PROJECT MANAGER:** Prof. A Fellgiebel
**FUNDING:** Ministry of Social Affairs, Labor, Health and Demography (Rhineland Palatinate)
**PROJECT DURATION:** 2017 - 2019

**CRC 1193 „Neurobiology of resilience to stress-related mental dysfunction: from understanding mechanisms to promoting preventions“**

**PROJECT MANAGER:** Prof. K Lieb, Prof. M Müller, Prof. O Tüscher
**FUNDING:** German Research Foundation (DFG)
**PROJECT DURATION:** 2016 - 2020

**Single cell-based microbiome analysis for prediction of cognitive decline in Alzheimer’s disease**

**PROJECT MANAGER:** PD Dr. K Endres
**FUNDING:** Impulse Fond Mainz
**PROJECT DURATION:** 2017 - 2018
Department of Psychosomatic Medicine and Psychotherapy

Director:
Professor Manfred E. Beutel

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 and prevention of sexual offenses by pedophiles. Consultation-liaison services are provided to all patients of the UMC-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 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, social integration, mental disorders, cognitive function, health behavior and cardiovascular disease. Specific psychosomatic treatments have been developed and tested for patients with cardiovascular disease.

TRANSLATIONAL NEUROSCIENCE

In EEG studies 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 disorders. In a number of studies with patients and with the general population we have investigated the relationship between childhood adversity and resilience.

PSYCHOONCOLOGY

The department of psychosomatic medicine provides psychooncological treatment in the University Cancer Center (UCT) and performs psychooncological research.

PSYCHOTHERAPY RESEARCH

Aiming at the improvement of psychotherapeutic care we have been conducting all phases of psychotherapy research, from feasibility trials to application of new treatments in clinical practice which we have tested rigorously in RCTs. We have been developing psychodynamic short-term treatments for various anxiety disorders and depression in mental and in somatically ill outpatients (e.g. cancer, cardiological patients). Special expertise refers to quality assurance (competence and adherence ratings of video recordings of sessions, process research) and to manualized psychodynamic treatments. Our postgraduate psychotherapy training program aims at establishing practice-research networks. In the DFG funded Research Training Group Life Sciences- Life Writing we study patients’ narratives undergoing psychotherapy.

ATTACHMENT RESEARCH

In multidisciplinary studies we determine interactions between childhood trauma, attachment patterns, mentalization, emotion regulation, life events (child birth, bone fractures) and biological markers (gene toxicity, oxytocine).
**Future Directions**

Psychosomatic medicine and psychotherapy endorses a holistic and interdisciplinary model of patient care. Medical Psychology and Sociology focuses on 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 Medical Center Mainz.

**Our Goals Are:**

- To determine the impact of coping with adversity (childhood, life events, chronic disease), social integration and support, health behavior and biological processes on health and disease outcomes
- To translate basic science and clinical research into innovative and integrative patient care fostering resilience to adversity
- To advance evidence-based prevention and psychotherapeutical treatment in mental and psychosomatic disorders
- To disseminate new findings in teaching, psychotherapy training and prevention
- To develop methods for excellent medical education: improving knowledge and communication skills

**Important Publications // max. 5**


Hartung TJ, Friedrich M, Johansen C et al. The Hospital Anxiety and Depression Scale (HADS) and the 9-item Patient Health Questionnaire (PHQ-9) as screening instruments for depression in patients with cancer. CANCER. 2017; 123 (21): 4236-4243.


**E Mental Health and Rehabilitation Research Group**

A junior research group has dedicated itself to the development of e-mental-health. We are conducting a new trial implementing a validated psychodynamic online intervention on vocational reintegration. We are currently testing novel online approaches on preparing patients for psychotherapy and supplementing self-guided online support to inpatient psychotherapy as a blended care model.

**Sabine M. Grüsser-Sinopoli Outpatient Clinic for Behavioral Addiction**

The clinic has been active defining standards for research, diagnosis, care and prevention in the evolving field of behavioral addictions consulting state and federal commissions. We offer the whole range of medical care for behavioral addictions: an anonymous and free hotline, assessment, consultation, innovative cognitive-behavioral treatments, day hospital and inpatient care, outpatient rehabilitation and aftercare. The clinic is dedicated to international epidemiological, neurobiological studies, conducting the first international RCT on treatment efficacy for computer gaming and online addictions. We have successfully initiated a cohort study with students. The third mission refers to the development, implementation and evaluation of effective preventive measures.

**Important Projects // max. 5**

A register based, longitudinal study on long-term effects of childhood cancer on psycho-social, health behavior and prevention measures among long-term cancer survivors

**Project Manager:** Prof. M. Beutel, Dr. J. Burghardt
**Project Duration:** 2016 - 2019

Development and evaluation of a multimodal internet-based intervention as preparation for inpatient psychosomatic rehabilitation (BMBF)

**Project Manager:** R. Zwerenz, Prof. M. Beutel
**Funding:** German pension insurance
**SUM:** € 322,288
**Project Duration:** 2014 - 2017

Explaining gender differences in Internet-related disorders: A comparison of female and male treatment-seekers (IBSfemme)

**Project Manager:** Dr. K.W. Müller
**Project Duration:** 2017 - 2019

GENDER-SENSITIVE ANALYSES OF MENTAL HEALTH TRAJECTORIES AND IMPLICATIONS FOR PREVENTION: A MULTI-COHORT CONSORTIUM

**Project Manager:** Prof. M. Beutel
**Funding:** Federal Ministry of Education and Research (BMBF)
**SUM:** € 469,734
**Project Duration:** 2017 - 2020

Online assessment of medical students’ communication skills – digitoHOLE

**Project Manager:** Dr. S. Fischbeck
**Funding:** Federal Ministry of Education and Research (BMBF)
**SUM:** € 416,210
**Project Duration:** 2017 - 2019
DEPARTMENTS OF SURGERY

Department of Anaesthesiology
Department of Cardiothoracic and Vascular Surgery
Department of General, Visceral and Transplantation Surgery
Department of Neurosurgery
Department of Obstetrics and Gynecology
Department of Ophthalmology
Department of Orthopaedics and Traumatology
Department of Oto-Rhino-Laryngology, Head and Neck Surgery
Department of Pediatric Surgery
Department of Urology and Pediatric Urology
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 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

Functional imaging of the lung: A prospective clinical trial in patients after open upper-abdominal surgery revealed that electrical impedance tomography (EIT) is able to detect patients early after surgery who will later develop postoperative pulmonary complications.

Airway management: For airway management the LMA® Supreme™ was superior in terms of first-pass success, insertion time and airway morbidity compared to Ambu®AuraGain™ in 364 adult patients undergoing general anesthesia for routine surgery.

Fluid management and monitoring: Pulse Wave Transit Time (PWTT), a noninvasive hemodynamic monitoring parameter derived from ECG and pulse oximetry, might be a valuable predictor of intraoperative fluid responsiveness.

Patient blood management in children: A prospective diagnostic study revealed that noninvasive hemoglobin measurement and Hemocue® measurement method of capillary blood can be safely applied in term and preterm infants. However, as they did not agree sufficiently with the reference method they cannot be recommended for clinical decisions.

Mainzer Outcome Predictor Study: A significant percentage of patients undergoing procedures in joint or back surgery still need pain medication up to 6 months postoperatively due to ongoing pain symptoms.

EXPERIMENTAL RESEARCH

Experimental Intensive Care Medicine and Organoprotection:
- Non-invasive end-expiratory lung volume measurement reliably predicts changes in pulmonary ventilation/perfusion distribution.
- Ultra-low tidal volume ventilation is a novel approach for lung as well as for cerebral protection during experimental cardiopulmonary resuscitation.
- Rosuvastatin mitigates cerebral inflammatory response and oxidative stress in experimental lung failure.
- Controlled hypotension following successful cardiopulmonary resuscitation enhances cerebral perfusion and may limit reperfusion injury.

Experimental Traumatic Brain Injury:
- Dimethylfumarate treatment after traumatic brain injury is neuroprotective.
- Genetic inhibition of the autophagic pathway delays but does not prevent secondary brain damage after traumatic brain injury.
- Traumatic brain injury causes long-term behavioral changes related to region-specific increases of cerebral blood flow.
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.

**IMPORTANT PUBLICATIONS** // MAX. 5


**IMPORTANT PROJECTS** // MAX. 5

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Project Manager</th>
<th>Project Duration</th>
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<tbody>
<tr>
<td>Posttraumatic anesthetic neurotoxicity</td>
<td>PD Dr. S Thal, Dr. A Sebastiani</td>
<td>2014 - 2017</td>
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<tr>
<td>Therapeutic Potential of Progranulin in Traumatic Brain Injury</td>
<td>Prof. M Schäfer</td>
<td>2017 - 2020</td>
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<tr>
<td>Therapeutic Strategies for Preclinical Treatment of L1 Syndrome</td>
<td>Prof. M Schäfer</td>
<td>2017 - 2020</td>
</tr>
<tr>
<td>Validation of non-invasive bedside measurement of hemoglobin concentration in premature and mature babies (Hb for Babies)</td>
<td>Dr. E Wittenmeier, Dr. I Schmeh, Prof. E Mildenberger</td>
<td>2016 - 2017</td>
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**FIG.** Traumatic brain injury causes dramatic structural and cellular changes. (A) T2-weighted MR image demonstrating structural damage (black asterisk). (B) Low power magnification showing the lesion core and the perilesional area in the cerebral cortex after traumatic brain injury. Immunohistochemistry using antibodies specific to CD45 (red) or Iba-1 (green) indicates the presence of double-immunolabelled microglia/macrophages and leukocytes immunolabelled by anti-CD45 only. The boxed region is shown in higher magnification (C). Arrows depict CD45+/Iba-1-leukocytes at perilesional sites.
The Department of Cardiothoracic and Vascular Surgery offers the complete spectrum of modern and innovative cardiothoracic and vascular surgery. The center specializes in aortic surgery, including open and endovascular procedures of the complete aortic tree, and belongs to the most experienced European centers for aortic arch surgery. Important interdisciplinary projects include minimal invasive treatment of cardiac valvular diseases (together with the Department of Cardiology) and the treatment of patients with diabetes and peripheral arterial disease in conjunction with the Division of Endocrinology. The center is certified to treat aortic diseases, Peripheral Arterial Occlusive Disease (PAOD) and diseases of the carotid artery. More than 3,000 surgeries were performed in 2017.

RESEARCH
The central foci of the clinical research conducted at the department are: 1.) aortic surgery, 2.) peripheral vascular disease and 3.) minimal invasive valve repair. Within the activities of basic Cardiothoracic and Vascular research we distinguish „function, tissue and material“.

In the context of the aortic register, nationwide-innovative tracks are processed scientifically at the department, making Mainz a national reference center.

Under the subpriority „function,“ the process of intra- and intercellular signaling in particular is systematically explored. The Department of Cardiothoracic and Vascular Surgery is in a special, prototypical position here in that it offers methods under various model conditions for the measurement of intracellular calcium, pH and sodium on vital, human heart muscle specimens.

Different projects are conducted under a model of „skinned fiber“ of the heart muscle. Currently pathophysiological effects of near-infrasound signals on multicellular biological tissue formation are analyzed in detail. Gaining an understanding of the arterial vessel wall is becoming more and more important in our increasingly aging society. In our lab, we succeeded in establishing a method for the determination of isometric force and dynamic stiffness on vital human strip preparations of the internal mammary artery using the force clamping technique.

The results suggest that patients with coronary heart disease may need to be differentiated in subpopulations that could benefit to varying extents from using different medication meant to reduce pre- and postoperative stiffness.

An innovative, highly respected and prize-winning group from the field of 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-sponsored grant). This represents an essential step on the pathway to biological implants. In addition, a basic research project funded by the German Research Foundation directed towards assessing the role of proteases in endothelial cell apoptosis. Similar work is being undertaken in cardiac surgery in the context of the optimization of biological prosthesis. An important and fledgling research area is that of obesity research. From the standpoint of cardiac and vascular surgery, this area is of particular interest because it offers both clinical and scientific perspectives.

Within the „Forschungsschwerpunkt Medienkonvergenz“ (Research on media-convergence), the night lecture series continues to enjoy great popularity. This lecture series is considered the largest and most sustainable media-supported prevention project in the region.
FUTURE DIRECTIONS

A new Department of Thoracic Surgery will open in 2018 as part of the department. Research at the new department will focus on the development of minimal invasive strategies of cancer therapy. In addition, a Department for Pediatric Cardiac Surgery will also be established in 2018. Solutions for important infrastructural aspects could be encountered.

The department is part of the EMAH Center at the University Medical Center Mainz. Research projects at the cardiac experimental laboratory are focused on the examination of the contractile functions of human myocardium in diabetic and obese patients and in patients with intracellular storage diseases (mucopolysaccharidosis), as well as on the pathophysiology of infrasound in biological multicellular tissue.

Furthermore, under an ERC Proof-of-Concept Grant successfully obtained by Prof. W.E.G. Müller (Institute of Physiological Chemistry) with Prof. Dorweiler serving as collaborator, the focus is on the future development of tissue-engineered, small-caliber blood vessels based on novel marine-based biodegradable polymers.

IMPORTANT PROJECTS // MAX. 5

<table>
<thead>
<tr>
<th>Project Name</th>
<th>Project Manager(s)</th>
<th>Funding</th>
<th>Project Duration</th>
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<tbody>
<tr>
<td>Aortic remodeling after aortic dissection</td>
<td>Dr. D Dohle, Dr. H El Beyrouti</td>
<td></td>
<td>2017 - 2020</td>
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<tr>
<td>Development and evaluation of 3D-printed models</td>
<td>Prof. B Dorweiler, Dr. A Ghazy</td>
<td></td>
<td>2016 - 2019</td>
</tr>
<tr>
<td>Ice-Free Valve Preservation</td>
<td>Prof. A Beiras Fernandez</td>
<td></td>
<td>2014 - 2017</td>
</tr>
<tr>
<td>Night lectures as instrument for media-supported</td>
<td>Prof. C Vahl, Dr. L Emrich</td>
<td>German Research Foundation</td>
<td>2004 – 2020</td>
</tr>
<tr>
<td>Production of biofunctional vascular prostheses</td>
<td>Prof. A Beiras-Fernandez</td>
<td></td>
<td>2015 - 2019</td>
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</table>

IMP O RTANT PUBLICATIONS // MAX. 5

Chaban R, Kombberger A, Branski N et al. In-vitro examination of the positive inotropic effect of caffeine and taurine, the two most frequent active ingredients of energy drinks. BMC CARDIOVASCULAR DISORDERS. 2017; 17.  
Department of General, Visceral and Transplantation Surgery

Director:
Professor
Hauke Lang

OVERVIEW

In 2017 the Department of General-, Visceral- and Transplantation Surgery performed more than 2,900 surgeries including 52 liver transplantations. In addition, more than 5,000 cases were treated in our outpatient clinic.

In particular, close interdisciplinary care in cooperation with the Departments of Internal Medicine I (Department of Gastroenterology and Hepatology), Anesthesiology, Diagnostic and Interventional Radiology, Radiation Oncology and Radiation Therapy, among others, ensures high quality treatment for our patients before, during and after surgery.

The presence of interdisciplinary tumor boards guarantee optimal treatment based on current guidelines and help screen for patients eligibility for innovative treatment concepts or inclusion in clinical trials.

HIGHLIGHTS

Our highlight for the year 2017 was the 12th International Congress of the European-African Hepato-Pancreato-Biliary Association (E-AHPBA) hosted in Mainz from 23rd until 26th of May, 2017 at the Rheingoldhalle, under the scientific organization of Prof. H. Lang and PD Dr. S. Heinrich.

During the pre-congress day, a separate 1-day symposium dedicated to the 10th anniversary of the ALPPS procedure was held along with a postgraduate course for pancreas surgery conducted in accordance with the training program of the E-AHPBA. The congress attracted more than 1,000 experts in the field of HPB surgery from Europe and abroad and covered the entire scientific field of HPB diseases through key note, special and invited lectures as well as through scientific and poster presentations. Moreover, intensive scientific discussions took place during get-together events and meeting breaks. The congress included symposia for allied healthcare professionals and offered young researchers travel support, which was funded by the Boehringer Ingelheim Foundation.

FUTURE DIRECTIONS

The main focus of the Department of General, Visceral and Transplantation Surgery is hepatobiliary pancreatic surgery, oncologic surgery, minimal invasive surgery, endocrine surgery and visceral organ transplantation. In oncologic surgery, efforts will be directed towards developing more gentle surgical approaches, in particular minimal invasive or robotic surgery as well personalized tumor therapy. In hepatobiliary surgery, new diagnostic tools, such as improved visualization via 3D reconstruction, 3D printing as well as fluorescence guidance will increase surgical precision and minimize the operative trauma. These techniques will also be increasingly used for partial liver transplantation. Living donation of both kidneys and liver crafts will provide one solution against organ shortage. Surgical research is dedicated towards minimizing donor morbidity, again through better surgical planning and the use of more minimal invasive techniques.

The analysis of differential protein and gene expression in endocrine and neuroendocrine tumors is a main focus of the area of endocrine surgery at the department. All encompassing studies are performed in close cooperation with Department of Pathology, the Section of Endocrinology, and the Center for Immune therapy. In the near future, the emanations will also include neuroendocrine neoplasia’s of the small intestine and pancreas, aiming at the identification of specific expression patterns that are associated with certain tumor entities as well as of the progression rate of these tumors.
**IMPORTANT PUBLICATIONS** // MAX. 5

- Grimminger PP, Fuchs HF. Minimally invasive and robotic-assisted surgical management of upper gastrointestinal cancer. CHIRURG. 2017; 88 (12): 1017-1023.

**IMPORTANT PROJECTS** // MAX. 5

- **A prospective randomized controlled trial to evaluate computer-assisted 3D-navigation in liver resections (NaLiS)**
  - **PROJECT MANAGER:** Prof. H Lang, Dr. T Huber
  - **FUNDING:** University Medical Center of Mainz
  - **SUM:** € 15,000
  - **PROJECT DURATION:** 2015 - 2018

- **Development of a virtual-reality simulation system for liver surgery**
  - **PROJECT MANAGER:** Prof. H Lang, Dr. M Paschold
  - **FUNDING:** University Medical Center of Mainz
  - **SUM:** € 39,000
  - **PROJECT DURATION:** 2016 - 2018

- **Eurocrine® (European Surgical Registry for Rare Endocrine Tumours)**
  - **PROJECT MANAGER:** Prof. TJ Musholt, F Angeletti, Dr. A Gohrbandt et al.
  - **FUNDING:**
    - European Union (EU)
    - CAEK/DGAV
    - Region Skane
  - **PROJECT DURATION:** 2015 - 2020

- **Influence of transarterial chemoembolization (TACE) treatment of patients with HCC on the expression and regulation of insulin-like growth factor molecules and their receptors**
  - **PROJECT MANAGER:** Dr. A Lautem
  - **PROJECT DURATION:** 2015 - 2017

- **Joint research project: Interactive Microimplants - INTAKT -; partial project: experimental examinations to establish interactive microimplants as therapeutic option for disturbed motility in the intestinal tract**
  - **PROJECT MANAGER:** Prof. W Kneist
  - **FUNDING:** Federal Ministry of Education and Research (BMBF)
  - **SUM:** € 835,900
  - **PROJECT DURATION:** 2016 - 2021

**FIG. 1:** Congress poster of E-AHPBA in Mainz.
**FIG. 2:** The congress at the Rheingoldhalle.
**FIG. 3:** Travel Grant recipients.
OVERVIEW

The Department of Neurosurgery utilizes a full-range of neurosurgical technologies to provide the most up-to-date and effective treatment for the entire spectrum neurooncology, neurovascular diseases, spinal pathologies, peripheral nerve diseases and functional neurosurgery. In 2017 we performed more than 2,200 neurosurgical procedures for primary or secondary brain tumors, neurovascular diseases, skull base lesions, neurotrauma and spinal pathologies. 2,600 patients received inpatient treatment; 5,300 patients have been seen in our outpatient center. We are actively engaged in scientific studies not only in clinical research, but as well in basic science investigations, which is funded by several international and national programs.

HIGHLIGHTS

CLINICAL RESEARCH
Clinical research at the Department of Neurosurgery covers different areas of relevance. It spreads from quality of life assessment and supportive care evaluation in neurooncology to new technical approaches in the treatment of intracranial hemorrhages, minimally invasive surgical approaches to the pituitary and upper cervical spine as well as spinal image guidance and robotics.

New techniques for the management of neurovascular problems are assessed in close collaboration with innovative industrial partners. Overall, we closely partner with industrial leaders to ensure that we have access to and even influence the next generation of surgical technology related to complex spine surgery as well as spinal image guidance and robotics. A dedicated group strives to facilitate new approaches to the spine as well as for surgical simulation and to improve resident training.

BASIC RESEARCH
Research of the Neurosurgical Department aims to identify mechanisms of glioma resistance to genotoxic therapy in a dedicated laboratory for neurooncology. In a translational approach results of this laboratory aim to develop individualized pharmacological therapies for primary brain tumors, which since 2016 is funded by the BMBF (“ERA-NET Euro TransBio-10”). The project uses next generation sequencing to identify individual tumor signatures and to identify individualized anticancer drug treatment.

A further basic research group aims to contribute to the elucidation of mechanisms underlying vasospasm following subarachnoid hemorrhage (SAH), funded by a university-based research support. The group employs experimental models of SAH making use of modern techniques for evaluation of immunological aspects of vascular constriction. These projects are run in close collaboration with the Department of Anesthesiology and Neuroradiology.

Another research group explores new techniques for lysis of intracerebral blood clots using experimental models operated in partnership with the Institute of Neurosurgical Pathophysiology, funded by the DGNI.
FUTURE DIRECTIONS

Our expertise goes beyond that of delivering best medical care. Research is an integral part of our mission. We are actively engaged in scientific studies not only in clinical research, but as well in basic science investigations, which is funded by several international and national programs.

IMPORTANT PROJECTS // MAX. 5

**Evaluation of genome-wide transcriptome analysis for individualized treatment of malignant brain tumours in children.**
*PROJECT MANAGER:* Dr. C Paret, Prof. A Faber, PD Dr. E Kim et al.
*FUNDING:* University Medical Center of Mainz
*SUM:* € 40,000
*PROJECT DURATION:* 2015 - 2017

**Omics-based integral approach for prediction of therapeutic success in treatment of human glioblastoma.**
*Euro Trans Bio Call 2015 *
*PROJECT MANAGER:* Dr. C Paret, Prof. A Faber, PD Dr. E Kim et al.
*FUNDING:* European Union (EU)
*SUM:* € 1,120,000
*PROJECT DURATION:* 2016 - 2018

**IVH volume or mGRAEB-score in patients with intraventricular hemorrhage: What should treatment decisions be based on? Results from the CLEAR III study.**
*PROJECT MANAGER:* Dr. T Kerz, Prof. F Ringel
*PROJECT DURATION:* 2017 - 2018

**MISTIE III A phase III, randomized, open-label, 500-subject clinical trial of minimally invasive surgery plus rt-PA in the treatment of intracerebral hemorrhage.**
*PROJECT MANAGER:* Dr. T Kerz
*FUNDING:* NINDS
*SUM:* € 60,000
*PROJECT DURATION:* 2014 - 2017

**Swiss trial of decompressive craniectomy versus best medical treatment of spontaneous supratentorial intracerebral hemorrhage (SWITCH): a randomized controlled trial**
*PROJECT MANAGER:* Prof. F Ringel
*PROJECT DURATION:* 2016 - 2018

**Keric N, Masomi-Bornwasser J, Mueller-Werkmeister H et al. Optimization of Catheter Based rtPA Thrombolysis in a Novel In Vitro Clot Model for Intracerebral Hemorrhage.**
*BIOMED RESEARCH INTERNATIONAL. 2017; .*

*CLINICAL SPINE SURGERY. 2017; 30 (7): E1000-E1009.*

**Neulen A, Pantel T, Kosterhon M et al. A segmentation-based volumetric approach to localize and quantify cerebral vasospasm based on tomographic imaging data.**
*PLOS ONE. 2017; 12 (2).*

*FRONTIERS IN NEUROLOGY. 2017; 8.*

**Ringel F, Ryang YM, Kirschke JS et al. Radiolucent Carbon Fiber Reinforced Pedicle Screws for Treatment of Spinal Tumors: Advantages for Radiation Planning and Follow-Up Imaging.**
*WORLD NEUROSURGERY. 2017; 105: 294-301.*

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

**FIG. 2:** Cell culture overlay. Glioblastoma cell line 1095 under differentiation conditions (x20); Nestin (green), GFAP (red).
OVERVIEW

The Department of Obstetrics and Gynecology, chaired by Prof. Annette Hasenburg, covers all clinical aspects and research in this field. Prof. Hasenburg provides the opportunity for young physicians to complete a half-yearly rotation in the research lab. The gynecological clinic is an integral part of the University Center for Tumor Diseases (UCT) of the University Medical Center Mainz. We have a proven expertise in gynecological oncology (including senology), uro-gynecology, obstetrics and gynecological endocrinology. Our Tissue Engineering projects are tied to the research network BiomaTiCS. With our wide range of specialized knowledge we aim to cover the field of obstetrics and gynecology.

HIGHLIGHTS

The research field of our clinic includes clinical studies as well as basic science. The wide range of patient's care is reflected in the topics of our research. A main focus is the investigation of prognostic and predictive factors in breast and ovarian cancer. We describe the prognostic and predictive influence of tumor-infiltrating B-lymphocytes and especially plasma cells in breast cancer. In NGS analyses, performed in collaboration with the Institute of Translational Oncology (TRON), Mainz, we characterize the genetic background of breast cancer. In cooperation with Prof. Schild, Institute of Immunology, we investigate the impact of a special MUC variant in breast cancer. In parallel we analyze various projects in molecular and cell biology, like the manipulation of tumor metabolism or the adhesion and invasion behavior of ovarian cancer and endometriosis cells in the context of cell spreading in the peritoneum.

In addition to the participation in numerous international multicenter studies, main topics are predictive gene-expression signatures and psychoeducative intervention to support patient’s competence. In addition, we have launched the multinational Mutanome Engineered RNA Immuno-Therapy (MERIT) trial breast cancer (phase I). In the first-in-human-study MERIT, a novel individual RNA vaccination targeting the mutanome of triple-negative early breast cancer patients will be utilized.

In our Tissue Engineering research field a pre-vascularized buccal mucosa equivalent has been developed. Commercial materials for wound covering have the disadvantage of insufficient vascularization in reasonable time. Together with the Department of Urology and Pediatric Urology and the research network BiomaTiCS of the University Medical Center Mainz we demonstrated a significant benefit in pre-vascularizing the in vitro scaffolds. Currently we explore opportunities for using patient’s-derived cells for future applications.

The fertility research group analyzes human granulosa cells gained during follicular puncture. We are measuring receptors for growth factors, steroids, proteohormons and Follistatin as a function of stimulation protocol and patient population. We evaluate the impact of anti-Müllerian hormone (AMH), which has a regulative function in the activation of folliculogenesis and which is considered a marker for the ovarian reserve. Furthermore, we examine the background of the ovarian hyperstimulation syndrome, a frequent complication during in vitro fertilization.

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. The aim is to predict implantation and thus the possibility to achieve pregnancy by a single transfer, which will lead to a decrease in multiple births.
FUTURE DIRECTIONS

Our future aim is a close interaction between patient care and research, so that patients will be treated according to the latest scientific insights. One focus will represent individualized vaccination strategies in breast cancer. The immunogenic antigens usable as immunotherapeutic targets and the specificity of tumor-infiltrating plasma cells will be characterized in cooperation with TRON. The analyses of the impact of B lymphocytes in breast cancer will be extended both to other entities as well as to breast cancer patients treated with adjuvant therapy. In the area of ovarian cancer and endometriosis the research will be extended by analyzing molecular backgrounds of disease progression.

In the course of Tissue Engineering, the development of a pre-vascularized mucosa using autologous cells will be forwarded. Within the research network BiomaTICS and in cooperation with the Center of Thrombosis and Hemostasis Mainz (CTH), the molecular background of co-cultures is an important question.

IMPORTANT PUBLICATIONS


Analysis of antibody responses against tumor-derived neo-antigens in triple-negative breast cancer (TNBC)

Characterization of lymphocytic infiltrates as prognostic and predictive markers in breast cancer

Development and characterization of an in vitro generated pre-vascularized mucosa equivalent

Energy metabolism in ovarian cancer

Impact of the tissue factor in the integration of a pre-vascularized in vitro mucosa equivalent
Department of Ophthalmology

Director:
Professor Norbert Pfeiffer

OVERVIEW

The Department of Ophthalmology entertains a great variety of research activities in ocular disease, including but not limited to glaucoma, age-related macular degeneration, ophthalmological characterisation of storage disease and dry eye disease. The large research facilities, the associated Clinical Trial Site, scientific and medical staff contribute to a better understanding of ocular pathogenesis and aim at optimizing diagnostic and therapy for ocular diseases. 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, biochemical, and epidemiological data on ocular diseases.

HIGHLIGHTS

GERMAN PEDIATRIC-GLAUCOMA CENTER
In glaucoma therapy, the University Eye Clinic is one of the leading German centers with well over 1,400 procedures a year - also in the treatment of children. In 2017, the first German Pediatric-Glaucoma Center was founded in Mainz under the leadership of Prof. Esther Hoffmann.

GUTENBERG HEALTH STUDY
The ophthalmic branch of the large-scale GHS aims at determining the frequency of eye diseases and their risk factors in the population. An additional focus is the interdisciplinary evaluation of vascular morphology including retinal and choroidal vasculature. Vision-related quality of life and psychiatric comorbidities in eye diseases are investigated to estimate the burden of eye diseases.

OPHTHALMIC HEALTHCARE RESEARCH
The center of ophthalmic epidemiology and healthcare research analyzed the healthcare utilization of ophthalmologists in Germany using survey data from the Robert-Koch Institute. Prevalence of pediatric eye diseases such as strabismus and myopia were investigated for Germany using secondary data. The center aims to further investigate the German healthcare system using primary and healthcare claim data in the recent future with a particular focus on ophthalmology.

CLINICAL TRIAL SITE
The Clinical Trial Site currently performs and monitors about 35 clinical trials (Phase I-IV AMG and MPG; Non Interventional studies). Amongst others, the Trial Site coordinates the multi-national FP7-Project „STRONG“ which is funded by the EU Commission and investigates the prevention of neovascular glaucoma following ischemic central retinal vein occlusion and potential biomarkers and risk factors for central retinal vein occlusion. Within the CAPTAIN Study patients with neovascular age-related macular degeneration and healthy subjects were enrolled to analyze antibody profiles in cooperation with the Experimental and Translational Ophthalmology. A phase II study investigates an innovative oral medication for Diabetic Macular Edema instead of intravitreal injections. A trial for glaucoma patients evaluates a biodegradable implant with IOP-lowering medication.

EXPERIMENTAL AND TRANSLATIONAL OPHTHALMOLOGY
One of the research highlights is the investigation of autoimmunity and neurodegeneration/regeneration in glaucoma. Utilizing different glaucoma animal models, we aim to identify molecular biomarkers for glaucoma diagnosis and to investigate possible neuroprotective effects and treatment options. Cauterization of episcleral veins results in long-term continuously elevated intraocular pressure. The effect of the administration of possible protective molecules can then be monitored and evaluated.

CORNEA BANK
The Cornea Bank of Rhineland-Palatinate, operated by the Department of Ophthalmology, is among the 3 largest facilities of its kind in Germany. In 2017, it was possible to obtain 707 corneas, 402 were used as corneal transplants.
The „Experimental and Translational Ophthalmology“ will pursue clinic-related basic research utilizing the large proteomics unit with mass spectrometric and antigen-microarray techniques, as well as cell culture and retinal organ culture, and animal models. A special highlight are ophthalmological proteomic analyses in small volumes, like tear fluid, for non-invasive diagnostics. The objective is to elucidate the functional relevance of molecular biomarkers in glaucoma, dry eye disease, AMD and others. The overall goal of the research projects is to gain a better understanding of pathogenesis and characteristics of ocular diseases and to develop new diagnostic and therapeutic options.

The „Ophthalmological Epidemiology“ will cooperate with the GHS to investigate prevalence and incidences of ophthalmological risk factors and diseases. The ongoing and future research projects include the distribution and associated factors of tear fluid quantity in the general population, the association of autoantibody levels with different stages of age-related macular degeneration (AMD), the vision-related quality of life in relation to visual acuity in both eyes, anterior segment morphology and axial length in relation to self-reported birth weight in the GHS, or the relationship between autoantibodies and glaucoma.

For 2018, several AMG and MPG studies are in preparation at the Clinical Trial Site of the Department of Ophthalmology.
Department of Orthopedics and Traumatology

Director:
Professor Pol Maria Rommens

Vice-Director:
Professor Philipp Drees

OVERVIEW

The Department of Orthopedics and Traumatology focuses on interdisciplinary network projects in the field of regenerative medicine. In a modern cell- and molecular biology laboratory we perform studies on interaction between cells and materials with focus on bone tissue engineering, development of implants, muscle injuries including modern imaging and molecular biology as well as 3D printing. Biomechanical studies focus on problematic fracture types of extremities and spine. Various prototypes have been developed for implants that are used worldwide, such as the distal tibial nail (DTN, Mizuho) and the expert tibia nail (ETN, DePuySynthes). The PROMISE project funded by Innovationsfonds aims to establish a Best-Practise-Guideline for treatment of joint diseases.

HIGHLIGHTS

The research activities of the Department of Orthopedics and Traumatology continue to focus on three main directions in the field of reconstructive surgery – biomechanical research (i), fracture healing & biomaterials (ii) and muscle injuries and lesions (iii). 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 PD 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, 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 Dr. Ritz and Prof. Rommens, assisted by Dr. Baranowski and Dr. Mattyasovszky, finished and published the first studies on polysaccharide hydrogels as biomaterials in tissue engineering, composite materials of 3D-printed polylactide modified with collagen and cytokines, influence of bone sialoprotein on bone regeneration and impact of IL-4, TGF-B and PDGF on myofibroblasts and joint contractures. Polysaccharide hydrogels could be identified as a biomaterial with all necessary prerequisites as carrier for cells or cytokines and as a fundament for various applications in tissue engineering as well as for development of novel cellular or growth factor-based approaches in the field of regenerative medicine. 3D-printing offer broad possibilities for establishing new (bio)materials for medical applications. Bone sialoprotein, when coupled to titanium or calciumphosphate scaffolds, demonstrated an inducing effect on osteogenesis. Joint contractures are a significant problem after surgery and our team could demonstrate an inhibition of the contractile function in human joint capsule myofibroblasts by targeting the TGF-beta 1 and PDGF pathways. Parallel to the in vitro analyses, the group successfully established animal models for future research projects, which allows for a precise analysis of the described effects in vivo. The PROMISE-project under the leadership of Prof. Drees aims to establish a Best-Practise-Guideline for treatment of joint diseases. In this project various institutes of the University Medical Center Mainz work together with regional clinics from Wiesbaden, Rüsselsheim, Bad Kreuznach and Mainz as well as with a health insurance company.
FUTURE DIRECTIONS

The upcoming projects of the „biomaterials“ group will focus on investigations of biomaterials for tissue engineering and one new focus will be on 3D printing to establish new composite materials. The established in vivo models will be applied and results obtained by x-ray, µCt and histology. Concerning muscle injuries and atrophy the group will determine the mechanisms behind muscle atrophy by analyzing miRNAs that could be responsible. 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 study within the next year. A new radiation-free analysis system of the human gait and spine (DIERS) was established 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. PROMISE-project aims to establish a Best-Practise-Guideline for treatment of joint diseases.

IMPORTANT PROJECTS // MAX. 5

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Project Manager(s)</th>
<th>Funding</th>
<th>Project Duration</th>
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<tbody>
<tr>
<td>Bone Substitutes Developed from 3D-Prints of PLA modified with collagen</td>
<td>Dr. U Ritz, Prof. PM Rommens</td>
<td>University Medical Center Mainz</td>
<td>2017 - 2019</td>
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<tr>
<td>Defining miRNA as cause for muscle atrophy</td>
<td>Dr. U Ritz, Prof. S Mattyasovszky</td>
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<td>2017 - 2017</td>
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<tr>
<td>Evaluation of bone sialoprotein in bone regeneration</td>
<td>Dr. U Ritz, Prof. PM Rommens</td>
<td></td>
<td>2017 - 2020</td>
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<tr>
<td>PROMISE - Process optimization by interdisciplinary and cross-sectoral care</td>
<td>Prof. P Drees, Dr. U Betz</td>
<td></td>
<td>2017 - 2020</td>
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<tr>
<td>The Distal Tibia Nail - A new implant for distal tibia fractures</td>
<td>PD Dr. S Kuhn, Prof. PM Rommens</td>
<td></td>
<td>2016 - 2018</td>
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Rommens PM, Wagner D, Hofmann A. Fragility Fractures of the Pelvis. JBJS REVIEWS. 2017; 5 (3).


FIG. 1: The Distal Tibia Nail - A new concept for distal tibia fractures.
FIG. 2: 3D-printed polylactide discs and cages, modified with Collagen I and SDF-I are biocompatible and induce cell proliferation of various cell types.
FIG. 3: Scanning electron microscopy (SEM) showing the morphology of the pores and the surfaces in b-TCP- and CDHA ceramics.
DEPARTMENTS OF SURGERY

Department of Oto-Rhino-Laryngology, Head and Neck Surgery

Director:
Professor Christoph Matthias

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OVERVIEW

In order to guarantee an optimal and innovative patient care now and in the future, ENT typical diseases as well as translational treatment strategies are explored trans-disciplinary. Microsurgical operations, minimally invasive laser surgical procedures, and open surgical procedures are investigated and continuously improved. Surgically, the entire field of ear, nose, and throat medicine is covered. Another clinical research focus are novel strategies for hearing preservation, employing latest cochlear implants (CI) in children and adults. Key research areas are oncology of the head and neck and ENT-related allergies, as a continuous translational process from molecular-based treatment- and prevention methods to clinical practice, including translational nanobiomedicine.

HIGHLIGHTS

ONCOLOGY AND NANOBIMEDICINE
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, as well as for cancer patients in general, as part of the UCT/CCC. Cellular mechanisms regulating survival, metastases, and therapy resistance are key for tumor development and progression. As such, these molecular regulations significantly impact also response to therapy, quality of life and overall survival of cancer patients. Hence, we specialize on the identification of mechanisms contributing to irradiation- and/or chemo-resistance of tumors, protease pathobiology, tumor angiogenesis as well as on the development of nanomedical- and chemical interference strategies, including the exploitation of natural products as potential drugs. Research is performed in close collaboration with UMC’s main research areas together with „Chemical- and Nano-Biomedicine“ research nets. Besides key publications in leading journals, the success of our work is underlined by the implementation of extramural funded projects, supported by the DFG, EU, Carl-Zeiss-Foundation, BMBF, and several other foundations. To evaluate and further promote the clinical transfer of our knowledge, we are interacting with the IZKS and UCT/CCC in order to optimally design and execute clinical trials. The generated knowledge will improve our understanding of basic processes at the molecular level for a better prevention and therapy of cancer patients.

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 research cluster, we work on the development and improvements of implants, also aiming at the education of Clinician Scientists.

RHINOLOGY
Allergies are continuously increasing and have a major socio-economic and clinical impact. Our (pre)clinical 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 fungal spores, nanoparticles as well as pollen are investigated.
FUTURE DIRECTIONS

OTOLOGY AND COMMUNICATION DISORDERS
Aiming at the improvement of hearing impairments we focus on analyzing molecular causes and optimize treatment strategies by introducing novel therapies in daily clinical practice. Increasingly, the body’s own molecular protection mechanisms, such as the cytoprotective proteins combined with NO-treatments, will be investigated for the potential (clinical) prevention and treatment of hearing loss. The findings from basic research will ultimately be the key for innovative otologic therapy principles. Latest hearing improving operations and innovative cochlear implants (CiS) will be complemented by drug-mediated modulation of regulatory and regenerative cellular circuits.

ONCOLOGY AND NANOBIO MEDICINE
Owing to their unique nanoscale physical and chemical properties combined with their potential for multiple surface functionalization, the emerging repertoire of nanomaterials (NMs) has raised high expectations for the early detection and treatments of diseases, including tumors. We seek to develop and apply multifunctional NMs as „smart” diagnostic tools and multifunctional drug-carriers in oncology, allergy research, and otology. Future research is based on the trans-disciplinary pillars of „Chemical- and Nano-Biomedicine”, targeting protease-driven pathomechanism and angiogenesis.

IMPORTANT PROJECTS // MAX. 5

<table>
<thead>
<tr>
<th>Basic research and applied science of salivary gland tissue &amp; Basic research and applied science of immortalized olfactory receptor cells</th>
<th>Chemical BioMedicine (ChemBioMed)</th>
<th>Development of the HINT-language test in German</th>
<th>DFG (OtoProtect): Mechanisms of Otoprotection: Impact of Survivin-NO-Signaling for Microcirculation and Otoprotection for Cochlea-Implantation</th>
<th>INTERREG V Ober-Rhein- NanoTransMed: Nanomedicine from Diagnostics to Implants</th>
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<tr>
<td>PROJECT MANAGER: PD Dr. S Becker, Prof. S Strieth</td>
<td>PROJECT MANAGER: Prof. R Stauber</td>
<td>PROJECT MANAGER: Dr. T Rader</td>
<td>PROJECT MANAGER: Prof. R Stauber, Prof. S Strieth</td>
<td>PROJECT MANAGER: Prof. R Stauber</td>
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<tr>
<td>FUNDING: Federal Ministry of Education and Research (BMBF)</td>
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<td>FIG.: Small meets smaller - Fungal spores decorated with nanoparticles as potential disease modulators in ENT.</td>
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OVERVIEW

We are the only academic pediatric surgery center in Rhineland-Palatinate and committed to research in a wide spectrum of pediatric surgical disease. In the last year, we built up a dedicated pediatric surgical laboratory. Our research team comprises a PhD in biology and a dedicated research fellow, along with a number of graduate students.

Clinically, we are part of several research consortiums on congenital malformations. We also perform research on telemedicine, care of refugee children, infertility after childhood operations, and short bowel syndrome.

Our lab focuses on Multiphoton Microscopy of Hirschsprung disease and pediatric solid tumors, as well as esophageal lengthening for congenital esophageal atresia.

HIGHLIGHTS

MULTIPHOTON MICROSCOPY (MPM)

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 previously proved the ability to accurately determine the distribution of ganglion cells in mice with Hirschsprung’s disease, and are currently working on translation of the method to human application. In pediatric surgical oncology three-dimensional real time imaging of tissue may provide immediate feedback to the surgeon on resection margins. Recently, we published our first results on characterizing pediatric solid tumors using MPM. The next step is to document sensitivity, specificity, and interobserver congruence compared to conventional histology.

SINGLE-INCISION PEDIATRIC ENDOSURGERY (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 new research projects is to establish this method for minimal invasive tumor surgery in comparison to standard laparoscopy, and to expand indications in combination with other innovative techniques.

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. Future goals are the evaluation of telemedical consultation as second opinion for rare diseases in childhood like esophageal atresia.

ESOPHAGEAL GROWTH INDUCTION

Management of congenital long-gap esophageal atresia is one of the greatest challenges in pediatric surgery. While several esophageal lengthening procedures have been described and are currently used in our department clinically, the mechanisms behind esophageal growth induction through traction are yet poorly understood. We are evaluating the physical, histologic and molecular effects of esophageal traction in the porcine and human model.

CONGENITAL CHEST WALL MALFORMATION

Recently minimal invasive surgical technics have been introduced in correction of congenital chest wall deformities. Therefore new concepts and materials have to be developed and tested before put into practice. In cooperation with the Institute of Functional and Clinical Anatomy (UMC-Mainz) biomechanical testing is carried out to improve and evaluate new materials and surgical approaches.
Future Directions

Our future goal is to establish the intraoperative use of MPM to map the aganglionic segment in children with Hirschsprung disease in real-time, and to determine resection margins of pediatric solid tumors during surgery. Also, we would like to expand our telemedicine initiative to include other centers and indications, studying both potential economic and ecologic effects, as well as the benefits on patient care and interdisciplinary collaboration.

Concerning esophageal lengthening, we recently completed a study evaluating the effect of traction on the esophagus in a porcine model, particularly focusing on how traction induces growth and the relationship between anastomotic tension and later stenosis.

In terms of clinical research, we are currently reviewing the largest patient series of thoracoscopic sympathectomy for the treatment of hyperhidrosis and its impact on patient quality of life. A further project is testing the availability of a YouTube video as a supplemental source of information for the parents in the consent process when children are scheduled for inguinal hernia repair. Two projects investigate how childhood operations impact on later fertility. And finally, we are evaluating the effect of sleep deprivation, interruptions, and alcohol intoxication on the workflow and performance of robotic surgery in a simulator model.

Important Projects

### Congenital chest wall malformation
**Project Manager:**
S Rohleder, Prof. O Muensterer, Dr. M Ackermann
**Funding:** MedXpert GmbH
**Project Duration:**
2017 - 2019

### Induction of esophageal growth by traction
**Project Manager:**
Prof. O Muensterer, Dr. C Oetzmann von Soochaczewski, A Lindner
**Funding:** Else-Kröner-Fresenius Foundation
**Project Duration:**
2017 - 2022

### Multiphoton Microscopy as an alternative to intraoperative frozen section biopsies for pediatric surgical oncologic diseases and comparison to conventional histopathology in childhood
**Project Manager:**
Dr. J Gödeke, Prof. O Muensterer, F Simon et al.
**Funding:** Else-Kröner-Fresenius Foundation
**Project Duration:**
2014 - 2019

### Telemedicine in the diagnosis and treatment of pediatric surgical patients
**Project Manager:**
Dr. J Gödeke, S Rohleder, Prof. O Muensterer
**Funding:** University Medical Center Mainz
**Sum:** € 5,000
**Project Duration:**
2014 - 2019

### The MIMIC dv-trainer - a robotic simulator to improve the surgical performance of residents and experienced surgeons
**Project Manager:**
Prof. O Muensterer, Dr. J Gödeke
**Funding:** Sterntaler e.V.
**Sum:** € 2,500
**Project Duration:**
2016 - 2020

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**FIG. 1:** The pediatric surgical team.
**FIG. 2:** Multiphoton microscopy imaging of Wilms tumor.
**FIG. 3:** Thoracoscopic esophageal elongation procedure showing the lower esophageal pouch in traction towards the thoracic inlet, where it later will be anastomosed to the upper esophagus.
**FIG. 4:** Telemedical follow up with one of our international patients after pectus excavatum surgery.
**FIG. 5:** Biomechanical analysis for minimal-invasive Pectus carinatum repair.
Department of Urology and Pediatric Urology

Director:
Professor
Axel Haferkamp

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OVERVIEW

The Department of Urology and Pediatric Urology provides the complete armamentarium of urological diagnostics and treatment. We cover the entire spectrum of surgical techniques and medical treatment available for all malignant urogenital tumors. Minimal invasive interventions, such as robotic-assisted radical prostatectomy, rank among our standard procedures. Our Interdisciplinary Continence Center and Stone Center complete the range of services available. Since 2016, the Urogenital Core Center has been established as an integral part of the University Comprehensive Cancer Center (CCC).

Our scientific lab offers a broad spectrum of functional and molecular approaches, thus providing excellent basic and translational research on clinically highly relevant uro-oncologic questions.

HIGHLIGHTS

The Uro-Oncology group performs basic and translational research (Ass. Prof. Jüngel) and clinical studies on prostate, bladder and renal cell carcinomas.

THERAPY RESISTANCE AND NOVEL TREATMENT OPTIONS

One key problem in the treatment of advanced urologic cancers is therapy resistance. Thus, a main objective is to examine the mechanisms underlying therapy resistance in prostate, bladder and renal cell carcinomas. In our scientific lab we investigate molecular and functional alterations of therapy resistant urologic tumor cells regarding tumor cell growth, de-differentiation, metastatic spread and tumor-immune-escape mechanism. Moreover, we combine conventional therapies and novel therapeutics with the intention of reversing or preventing resistance development. A further focal point is the establishment of novel anti-tumor therapeutics in general. Several compounds are under investigation regarding their anti-tumor potency on the progressive behavior of urologic tumors in vitro and in vivo. The use of alternative medicine is very popular, but evidence-based benefit from natural based compounds is often lacking. Thus, our research studies also include promising alternative compounds. Concurrently, clinical trials are performed to investigate the application of new therapies for improved health care.

BIOMARKERS

A further focus is the analysis of the molecular basis of pathogenesis and metastasis of urologic tumors, especially in advanced and metastasized tumor stages. To identify predictive and prognostic biomarkers, we evaluate the functional relevance of deregulated structures in tumors (e.g. miRNAs and proteins) and their impact on several pivotal signaling pathways. Moreover, we correlate immunohistochemical expression levels of promising biomarkers with survival of RCC patients undergoing surgery. For prediction of treatment outcome in the metastatic state of prostate and bladder carcinoma, the role of new biomarkers is determined. Biomarkers will assist in a better selection of tumor patients, enabling a more effective therapy response, proceeding towards personalized medicine.
We are committed to offering our patients optimal urological care and treatment according to latest scientific findings. Our scientific projects will continue to support basic research and the development of new therapeutic and diagnostic strategies in urology. In particular, the understanding of the complex mechanisms that contribute to tumor progression and therapy resistance are a high priority interest to us in proceeding towards personalized medicine. New strategies are under investigation to avoid tumor progression and prevent or reverse therapy resistance (in vitro, in vivo, in clinical trials).

**IMP O RTANT PROJECTS // MAX. 5**

<table>
<thead>
<tr>
<th>Project Description</th>
<th>Project Manager(s)</th>
<th>Funding</th>
<th>Project Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A multicenter, randomized, double-blind, placebo-controlled, phase III study of ARN-509 in men with non-metastatic (M0) castration-resistant prostate cancer (SPARTAN)</td>
<td>Prof. C Thomas, Prof. G Bartsch, Prof. I Tsaur et al.</td>
<td>Project Manager: Prof. C Thomas, Prof. I Tsaur, PD Dr. W Jäger et al.</td>
<td>2014 - 2020</td>
</tr>
<tr>
<td>A multinational, randomized, double-blind, placebo-controlled, phase III efficacy and safety study of BAY1841788 (ODM-201) in men with high-risk non-metastatic castration-resistant prostate cancer (ARAMIS)</td>
<td>Project Manager: Prof. C Thomas, Prof. I Tsaur, PD Dr. W Jäger et al.</td>
<td>Project Manager: PD Dr. E. Jüngel</td>
<td>2016 - 2020</td>
</tr>
<tr>
<td>Preclinical studies on therapy resistant renal cell carcinomas on the effectiveness of substances found in traditional Chinese medicine</td>
<td>Project Manager: PD Dr. E. Jüngel</td>
<td>Funding: Prof. Dr. Karl and Gerhard Schiller-Foundation</td>
<td>2017 - 2018</td>
</tr>
<tr>
<td>Primary xenograft tumor lines generated from patient tumors as a preclinical model for the development of new targeted therapies for urothelial carcinoma of the urinary bladder</td>
<td>Project Manager: Dr. W Jäger, Prof. PC Black</td>
<td>Project Manager: University Medical Center Mainz</td>
<td>2012 - 2017</td>
</tr>
<tr>
<td>The significance of STAT5 on the growth and invasion of docetaxel-resistant prostate carcinomas</td>
<td>Project Manager: PD Dr. E. Jüngel</td>
<td>Funding: University Medical Center Mainz</td>
<td>2017 - 2018</td>
</tr>
</tbody>
</table>
CLINICAL DEPARTMENTS AND INSTITUTES

Department of Nuclear Medicine
Department of Radiation Oncology and Radiation Therapy
Department of Radiology
Institute of Clinical Chemistry and Laboratory Medicine
Institute of Human Genetics
Institute of Medical Biostatistics, Epidemiology and Informatics
Institute of Molecular Medicine
Institute of Neuropathology
Institute of Neuroradiology
Institute of Neurosurgical Pathophysiology
Institute of Pathology
OVERVIEW

The Department of Nuclear Medicine provides all available diagnostic and therapeutic applications with radiopharmaceuticals. One main clinical focus is the diagnosis and treatment of benign and malignant thyroid diseases (radioiodine treatment), whereas a second focus is the radioligand therapy of neuroendocrine tumors. The required follow-up examinations are also done by our clinic. Coordination and discussion of complex, interdisciplinary treatment concepts are taking place in a regularly scheduled tumor board in cooperation with specialists from various areas of expertise.

HIGHLIGHTS

Isotope therapies with a variety of radiopharmaceuticals are performed in our specialized therapy ward with a total of eight beds. Approximately 600 patients per year are admitted to the ward with a mean duration of stay of 3.6 days. About 30% of these patients undergo special (non-radioiodine) therapies with complex radiopharmaceuticals.

THE FOCUSES HERE ARE THE FOLLOWING APPLICATIONS:

- Peptide radioreceptor therapy in metastatic neuroendocrine tumors (NET),
- Selective Internal Radiation Therapy (SIRT) for malignant diseases of the liver,
- MIBG therapy in neuroblastoma and metastatic pheochromocytoma,
- Xofigo® therapy in metastatic prostate cancer.

FUTURE DIRECTIONS

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.

In the field of oncology a main focus of clinical research is the evaluation of efficacy and toxicity of Lutetium-177-DOTATATE therapy (PRRT) in neuroendocrine tumors. The clinic is participating in an international multicenter trial (Netter1) and a German registry network. Additionally, retrospective analyses from patients treated at the ENETS Center Mainz are conducted.

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 its radiobiology in vivo and in vitro.
Cerebral glucose metabolic changes after THC-administration in rats
PROJECT MANAGER:
Prof. M Schreckenberger,
Dr. I Miederer,
Prof. R Urban
FUNDING: B. A. D. S.
SUM: € 2,000
PROJECT DURATION: 2013 - 2018

Characterization and preclinical evaluation of the CB1-ligand [18F] MK-9470
PROJECT MANAGER:
Dr. I Miederer,
Prof. M Schreckenberger
PROJECT DURATION:
2017 - 2020

Molecular Imaging for evaluation of particle based drug delivery
PROJECT MANAGER:
PD Dr. M Miederer
FUNDING: German Research Foundation (DFG)
SUM: € 230,000
PROJECT DURATION:
2015 - 2018

Performance comparison of the positron emitting isotopes Sc-44 and Ga-68 using preclinical PET systems
PROJECT MANAGER:
Dr. H Buchholz,
F Rosar
PROJECT DURATION:
2017 - 2018

Psychological Flexibility as Active Resilience Mechanism: Neurocognitive Mechanisms and Dopaminergic Mediation
PROJECT MANAGER:
Prof. M Schreckenberger,
Dr. I Miederer
FUNDING: German Research Foundation (DFG)
SUM: € 451,000
PROJECT DURATION: 2016 - 2020
HIGHLIGHTS

INTRINSIC RADIATION SENSITIVITY: IDENTIFICATION, BIOLOGICAL AND EPIDEMIOLOGICAL LONG-TERM EFFECTS (ISIBELa)
Childhood malignancies might be attributed to genetic and epigenetic alterations of genomic maintenance mechanisms and cell cycle regulation. The treatment of pediatric cancer by chemotherapy and radiotherapy has been associated with a 4-6-fold elevated risk for second primary malignancies in later life. To this end, the BMBF-funded ISIBELa study (Grant 02NUK042A) investigates genetic predispositions and radiation sensitivity in fibroblasts from donors with no malignancies (n=260), a primary malignancy in childhood (n=195) or a second malignancy after the treatment of a primary malignancy during childhood (n=65). So far, skin biopsies were successfully collected from 140 donors. An inter-institutional network will provide data on Next Generation Sequencing, gene-expression, epigenetics as well as cellular and chromosomal radiation sensitivity to reveal mechanistic insights into intrinsic radiation sensitivity and carcinogenesis. First results obtained from cohorts of a pilot study did not reveal any difference in cellular or chromosomal radiosensitivity between the study populations whereas intrinsic spontaneous genomic instability was observed in donors with second primary malignancies (Fig. 1).

MULTICHANNEL IMMUNOFLUORESCENCE IN TUMOR TISSUE
The impact of the tumor microenvironment on radiation resistance, tumor invasiveness, metastasis and immune activation is evaluated in several retrospective studies. Response to therapy, progression free survival, overall 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 allows 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, gynecologic tumors and melanomas.

These preliminary results indicate that only very mild alterations in genomic maintenance and associated cell cycle checkpoint pathways by genetic polymorphisms or epigenetic changes might underlie a cancer prone or radiosensitive phenotype.

OVERVIEW

The research topics in the Department of Radiation Oncology and Radiation Therapy can be divided in two segments, which are interacting.

1. Tumor biology and identification of targets for novel therapies.
2. Radiation protection, late effects of radiotherapy and cancer survivorship

The research in both segments is pursued in clinical studies and in laboratory research.

ISIBELa-Study: Intrinsic radiation sensitivity: identification, biological and epidemiological long-term effects.
PASSOS-Study: Retrospective study on cardiac dose in survivors of breast cancer.
PREFERE Study: Randomized (IIT) trial on four different treatment modalities for low risk prostate cancer.
Impact of treatment on quality of life.
Multichannel immunofluorescence in tumor tissue: retrospective evaluation of risk factors.
Within the ISIBELa project a large biobank of primary human fibroblasts from 600-700 individuals will be established and serve as a valuable resource for future genetic and molecular studies. Detailed analyses of the study populations might identify low-penetrance or hypomorphic mutations and epigenetic changes relevant to the etiology of childhood cancer and the risk of second primary cancer. These findings might help to personalize oncologic treatments to reduce the risk for second primary malignancies and to unravel new pathways for targeted cancer therapies.

**IMPORTANT PUBLICATIONS // MAX. 5**


**FUTURE DIRECTIONS**

**FIG. 1:** Radiation sensitivity assessed as (A) clonogenic survival or (B) chromosome aberrations in fibroblasts. Cytogenetic analysis of metaphase spreads of a donor with a second primary malignancy after the successful treatment of a primary malignancy during childhood showing (C) a normal diploid metaphase and (D) a metaphase with a high frequency of spontaneous numerical and structural aberrations indicated by arrows.

**FIG. 2:** Heterogeneity of the tumor micro-environment. 5-plex staining of a squamous cell carcinoma of the head and neck region. Analysis of co-expression of: receptor tyrosine kinase expression (orange), blood vessels (magenta), activity of the mTOR system (red), and tumor hypoxia (green). This method enables the analysis of co-expression patterns of antigens on a single-cell basis within tissue sections: „cytometry in tissue“.

**IMPORTANT PROJECTS // MAX. 5**

- **Combined radiotherapy and anti-CTLA-4 antibodies for brain metastases of malignant melanoma**
  PROJECT MANAGER: Prof. H Schmidberger
  PROJECT DURATION: 2015 - 2017

- **ISIBELa: Intrinsic radiation sensitivity: identification of biological and epidemiological long term sequelae**
  PROJECT MANAGER: Prof. M Blettner, Prof. H Binder, Prof. H Schmidberger et al.
  PROJECT DURATION: 2015 - 2018

- **Quality Assurance of radiotherapy within the mulectenter PREFERE study on low risk prostate cancer**
  PROJECT MANAGER: Prof. H Schmidberger, Dr. M Stockinger
  FUNDING: German Cancer Aid, Federal Association of Health Insurance
  SUM: € 130,000
  PROJECT DURATION: 2012 - 2017
OVERVIEW

DIAGNOSTIC METHODS:
• Radiography
• Radioscopy
• Computed Tomography
• Magnetic Resonance Imaging
• Digital Subtraction Angiography
• Sonography
• Mammography

THERAPEUTIC METHODS:
• Balloon dilatation and stent implantation
• Occlusion of blood vessels and tumor embolization
• Percutaneous tumor ablation
• Biliary tract interventions
• Biopsies and implantation of markers for targeted therapies
• Percutaneous drainages

GENERAL SERVICES AND SPECIALTIES:
• Radiology Information System
• Picture-Archiving and Communication System (PACS)
• Teleradiology
• Clinical Trial Center Radiology
• Section of Medical Physics
• Section of Pediatric Radiology

HIGHLIGHTS

MAIN AREAS OF RESEARCH:
• Liver and cardiovascular imaging using MRI and CT
• Interventional vascular and tumor therapy
• IT and image post-processing in radiology
• Innovative MRI techniques
**IMPORTANT PUBLICATIONS** // MAX. 5


**MAIN PROJECTS** // MAX. 5

**Irreversible electroporation:**

**Correlation of necrosis in MRI and ultrasound using an animal model**

**PROJECT MANAGER:**
Dr. S Schotten, Dr. F Jungmann, Prof. MB Pitton

**PROJECT DURATION:**
2016 - 2019

**MaiCo-MR**

**PROJECT MANAGER:**
Dr. T Emrich

**PROJECT DURATION:**
2017 - 2025

**Mapping of myocardial T1- an T2-relaxation times in 3 Tesla-MRI**

**PROJECT MANAGER:**
Prof. K Kreitner, Dr. T Emrich

**PROJECT DURATION:**
2015 - 2017

**MEDIRAD**

**PROJECT MANAGER:**
Prof. P Mildenerger

**FUNDING:**
European Union (EU)

**SUM:**
€ 194,953

**PROJECT DURATION:**
2017 - 2021

**Predictive scoring systems for patients with hepatocellular carcinoma**

**PROJECT MANAGER:**
PD Dr. R Kloeckner

**PROJECT DURATION:**
2016 - 2019

FIG. 1: HE stain, 400x. Temporal pattern of tissue damage. 1h after ablation hepatocytes appear almost unremarkable. There is sinusoidal congestion. 3h after ablation hepatocytes shows signs of cellular death with shrinkage of nuclei and eosinophilic cytoplasm. 24 h after ablation there is clear cellular death with pyknotic nuclei.

FIG. 2: Artificial neural network for the prediction of overall survival after the first transarterial chemoembolisation in patients with hepatocellular carcinoma.

FIG. 3: Left Ventricular Strain Imaging in a healthy volunteer.

FIG. 4: The multi-disciplinary consortium combines the expertise of 33 partners from 14 European countries. It includes major universities and research institutes as well as clinical partners.
Institute of Clinical Chemistry and Laboratory Medicine

Director:
Professor Karl J. Lackner

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OVERVIEW

Research of the Institute of Clinical Chemistry and Laboratory Medicine is 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 Mainz, e.g. the Center of 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 was implemented with the support of 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.

HIGHLIGHTS

Research on the pathogenesis of arteriosclerosis has its focus on the early development of the disease and identification of biomarkers which identify persons at increased risk. 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.

Research on the pathogenesis of thrombotic events concentrates on the most common acquired thrombophilia, the antiphospholipid syndrome. We use in vitro and in vivo models including mouse thrombosis models, which have been established in cooperation with the CTH to shed more light on the pathogenesis of this disease. Of particular importance are human monoclonal antiphospholipid antibodies cloned from patients. These are a unique resource, which permits the unequivocal identification of signal transduction pathways involved in the antiphospholipid syndrome. Data, we generated over the past 5 years, has shown that the current concept of the pathogenesis of the antiphospholipid syndrome has to be revised.

The research group of Sven Danckwardt actively develops tools for genome wide discovery of disease eliciting perturbances of RNA-protein interactomes. One such tool is sCLIP which permits genome wide mapping of ‘footprints’ of RNA-binding proteins in single nucleotide resolution. These projects have already revealed unexpected insights into genome regulation with implications for major disease entities, e.g. neurodegenerative disorders and cancer. Combined with a bioinformatic pipeline sCLIP thus fosters the illumination of RNA-protein interaction landscapes and provides novel insights into disease mechanisms.

Besides these basic research foci, the Institute is involved in the development, improvement, validation, and quality control of clinical laboratory diagnostics. 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 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 Department of Internal Medicine I and the Departments 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. These efforts are now complemented by the development of methods to analyzed cell free (cf) DNA.
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.

FUTURE DIRECTIONS

A further focus will be the expansion of NGS approaches for diagnostics, in particular in hemostaseology but also for the inherited tumor syndromes. The current status of the NGS platform for disorders in hemostasis has been further expanded as a technology platform within the Center of 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.

FIG. 1: All-trans-retinoic acid (ATRA) induced differentiation of neuroblastoma cells which is associated with massive changes of mRNA 3’-UTRs (AG Prof. Danckwardt).

FIG. 2: Quality controls for laboratory tests.

Adapting conCLIP to illuminate the role of RNA-binding proteins (RBPs) in pathophysiologic processes

**PROJECT MANAGER:** Prof. S Danckwardt

**FUNDING:** Foundation for Pathobiochemistry and Molecular Diagnostics (SPMD)

**SUM:** € 52,000

**PROJECT DURATION:** 2016 - 2017

Advanced diagnostics

**PROJECT MANAGER:** PD Dr. H Rossmann, Prof. S Danckwardt

**FUNDING:** Federal Ministry of Education and Research (BMBF)

**SUM:** € 435,000

**PROJECT DURATION:** 2014 - 2020

Gutenberg Health Study (GHS)

**PROJECT MANAGER:** Prof. P Wild; Prof. M Beutel; Prof. K Lackner et al.

**FUNDING:** Boehringer Ingelheim International GmbH

**SUM:** € 103,000

**PROJECT DURATION:** 2013 - 2019

In vivo model of thrombus induction in the antiphospholipid syndrome

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

**FUNDING:** Pathobiochemistry and Molecular Diagnostics

**SUM:** € 135,000

**PROJECT DURATION:** 2015 - 2017

Pathogenesis of the Antiphospholipid Syndrome

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

**FUNDING:** Federal Ministry of Education and Research (BMBF)

**SUM:** € 135,000

**PROJECT DURATION:** 2015 - 2017
Institute of Human Genetics

Director:  
Professor  
Susann Schweiger

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phone: +49 (0) 6131 17-5790  
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OVERVIEW

The Institute of Human Genetics is the leading institution of that kind in Rhineland-Palatinate and the metropolitan Rhine-Main area. We are responsible for the counselling, diagnostics and management of patients with a large variety of genetic disorders and are specialized in patients with developmental delay and intellectual disability (ID), behavioural problems including autism spectrum disorder (ASD), epilepsy, hearing loss, retinal degeneration, movement disorders and other entities affecting the nervous system. We have built up a Huntington’s Disease research and treatment center for the care of patients with Huntington’s Disease (HD) and a Center for Rare Diseases of the Nervous System for the care of patients with orphan diseases.

HIGHLIGHTS

Many functions of the healthy brain are regulated by local protein synthesis. Thus, the so-called synaptic plasticity 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. Based on these discoveries we are looking into the function of local protein synthesis in brain homeostasis and mental resilience and are studying the pathogenic basis of the above-mentioned diseases.

To establish an efficient therapy, we are particularly interested in understanding the molecular processes in the early phases of disease development in patients and animal models with monogenic forms of neurodevelopmental and neurodegenerative disorders. We will then use our gained knowledge with the aim to develop therapeutic strategies that start very early in disease development and progression. In close interaction with this research focus, a research team supervised by Dr. Jennifer Winter is particularly interested in the molecular and developmental 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. 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. Research represented by Dr. Matthias Linke focuses on the epigenetic imprint of behavior and experience. The research projects do not only address epigenetic signatures in the brain but also how they are inherited through the germline, in particular through sperm. The research within the Institute of Human Genetics is embedded into the research center for translational neuroscience in Mainz and the Rhine-Main Neuroscience Network (rmn²). A grant application to analyse homeostatic regulation in mTORopathies has been successfully brought into the CRC1080 („Molecular and Cellular Mechanisms of Neural Homeostasis“). Interdisciplinary research collaborations with several groups within the FTN and the rmn² are a central core of the work. PIs of the Institute are involved in the German Resilience Center (Deutsches Resilienz Zentrum, DRZ). Two projects are funded by the CRC 1193 („Neurobiology of Resilience“). Central focus here is the question why, while most individuals carrying substantial risk factors (e.g. highly penetrant gene mutations) develop disease symptoms with time, some individuals stay healthy.
FUTURE DIRECTIONS

We aim at understanding the pathological key events in the brain in early phases of monogenic forms of neurodevelopmental and neurodegenerative disorders. 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. We are also looking at 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. This will generate novel paths for therapeutic intervention. Furthermore we are analysing epigenetic stress regulatory mechanisms in the mouse brain. Our studies will 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.

IMPORTANT PROJECTS // MAX. 5

<table>
<thead>
<tr>
<th>Project Title</th>
<th>Manager(s)</th>
<th>Duration</th>
<th>Funding</th>
<th>SUM</th>
</tr>
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<tbody>
<tr>
<td>Brain functions and neurocognitive phenotypes of heterozygous and homozygous Kcnk9 knockout mice</td>
<td>Prof. U Zechner, Dr. M Linke, A Cooper</td>
<td>2013 - 2017</td>
<td>University Medical Center Mainz</td>
<td>€ 48,325</td>
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<td>Development of a novel therapy for Huntington’s Disease</td>
<td>Prof. S Schweiger</td>
<td>2011 - 2018</td>
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<tr>
<td>The functions of the imprinted miR379-410 cluster during neuronal migration in the developing telencephalon</td>
<td>Dr. J Winter</td>
<td>2015 - 2018</td>
<td>German Research Foundation (DFG)</td>
<td>€ 214,550</td>
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<tr>
<td>Molecular mechanisms of brain function in mTOR deficient intellectual disability syndromes</td>
<td>Prof. S Schweiger</td>
<td>2013 - 2017</td>
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OVERVIEW

The Institute of 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 and Bioinformatics, Epidemiology, Medical Informatics, Documentation, the German Childhood Cancer Registry and is associated with the Cancer Registry Rhineland-Palatinate.

An interdisciplinary team of about 80 dedicated employees works at the IMBEI. The IMBEI is responsible for the courses „Biostatistics, 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.).

HIGHLIGHTS

The IMBEI’s goal is to contribute to sustaining and improving the health of the general public and patients through its expertise in the areas of biostatistics, epidemiology, informatics and documentation. Our main objective is to support medical research with our diverse methodical expertise. The Division Biostatistics and Bioinformatics is providing statistical support for all kind of research projects at the UMC-Mainz. The research of the division focusses on planning and evaluation. A further focus is on methods for the use of clinical registries and secondary data. We work closely together with different clinical departments and the IZKS, and we offer a bioinformatics support interface via the Core Facility Bioinformatics.

Epidemiologists at the IMBEI conduct population-based observational studies in radiation epidemiology, health services research, and pediatric epidemiology. One focus is on the health consequences, mainly secondary cancer and cardiovascular diseases of occupational and medical radiation exposure. 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, life course epidemiology, as well as the prevention of malignant diseases.

The Division of Pediatric Epidemiology investigates health indicators at the time of school enrollment, transition from early childhood into school age, the impact of chronic medical conditions on school performance, and the needs and utilization of special pediatric health care services, social and educational support in children with chronic medical conditions. The Division also supports national and international clinical and health services research in neonatology, pediatrics, and sleep medicine with methodological and statistical expertise.

The Division of Medical Informatics realized system and data integration at the UMC-Mainz through a message broker. It is involved in new topics like a data warehouse, big data techniques and a decentralized search. We care for the semantics of data integrated from several sources. Pseudonymization of personal data and identity management in research scenarios is another working field. Furthermore, we develop and run a telemedicine solution according to data protection rules, which transmits medical pictures and statements via internet.

The nation-wide German Childhood Cancer Registry is located at the IMBEI and builds a rich resource for descriptive and analytic cancer epidemiology. Incidence rates and changes in incidence over time as well as regional clusters and survival probabilities are reported regularly. This registry is the base to investigate therapy-related late effects after cancer in collaboration with the Pediatric Oncology Department and several partners in the EU.
FUTURE DIRECTIONS

- Providing high quality methodological 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 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 future improvements in Child Public Health and Pediatric 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

Epidemiologic study on late cardiac effects and second primary neoplasms after radiotherapy for breast cancer (EsKaRa)
PROJECT MANAGER:
Dr. D Wollschläger, Dr. H Merzenich
PROJECT DURATION:
2017 - 2021

KiDSafe - Improving the care of children and adolescents with medicines through enhanced medication safety
PROJECT MANAGER:
PD Dr. A Neubert, Prof. MS Urschitz
PROJECT DURATION:
2017 - 2020

Late Toxicity and Long-term Quality of Life in Head and Neck Cancer Survivors
PROJECT MANAGER:
Prof. S Singer, Prof. V Gregoire
FUNDING: European Organisation for Research and Treatment of Cancer (EORTC)
PROJECT DURATION:
2017 - 2020

PanCareLIFE: PanCare Studies in Fertility and Ototoxicity to improve Quality of Life after cancer during childhood and adolescence
PROJECT MANAGER:
PD Dr. P Kaatsch
PROJECT DURATION:
2013 - 2018

Software support of the organizational process for telemedicine doctor consultations
PROJECT MANAGER:
L Hadidi, Dr. J Gödeke, Dr. T Panholzer
PROJECT DURATION:
2017

IMPORTANT PUBLICATIONS // MAX. 5


Merzenich H, Bartkowiak D, Schmidberger H et al. 3D conformal radiotherapy is not associated with the long-term cardiac mortality in breast cancer patients: a retrospective cohort study in Germany (PASSOS-Heart Study). BREAST CANCER RESEARCH AND TREATMENT. 2017; 161 (1): 143-152.


Institute of Molecular Medicine

Director:
Professor
Ari Waisman

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OVERVIEW

The Institute of Molecular Medicine (IMM) focuses on autoimmune diseases such as multiple sclerosis (MS) as well as other diseases that affect the gut, skin and heart.

Members of the institute are interested in basic mechanisms that control the function of the immune system, including signal transduction pathways, and primary investigating molecules that control the activation of the nuclear factor kappa B (NF-kB) transcription factors in their involvement in malignant diseases.

HIGHLIGHTS

The work of the different groups of the institute involves genetically manipulated animals, using a technology termed conditional gene targeting. For example, the Waisman group generated mice, which lack the gene coding for the IL-17 receptor, to study the inability of these cells to respond to IL-17 influences autoimmunity.

The Clausen group is using similar techniques to interrogate the role of dendritic cells (DCs) in inflammatory diseases affecting the skin, lung and the intestine. Pathways of interest include β-catenin, IL-10 and TGF-β signaling to govern DCs as well as the unexplored contribution of ‘a disintegrin and metalloproteinase’ (ADAM) family of ectodomain-shedding proteases to fine-tune DC function in vivo.

The research in the Hövelmeyer group is focused on studying molecular alterations, mainly of the NF-kB pathway, driving the development of lymphoma/leukemia as well as B-cell subset differentiation using loss and gain of function approaches in the mouse.

The Kurschus group focused on understanding the interplay between the immune cells and cells of the target tissues, including the central nervous system and the skin.

Finally, Dr. Khalad Karram is focused on coordinating and helping students achieve their goals in the M.Sc. Biomedicine at the University Medical Center of the Johannes Gutenberg University Mainz. The program has been running now well for 6 years. The graduates have furthered their education by starting a PhD or have started working at well know companies developing and advancing technology in the field of Biomedicine.

Dr. Khalad Karram in conjunction with Dr. Hövelmeyer are in the process of implementing a new International Master of Biomedicine with the Université de Strasbourg and University of Luxembourg. The program offers excellent training for Master students in the field of Biomedicine, linking the gap between medicine and research. It is characterized by a very rigorous and fixed program that encompasses specific fields, like clinical medicine, bioinformatics, neurosciences, and immunology. Future graduates will have an excellent concept of Biomedicine strengthened by adapted training in fundamental sciences, integrative knowledge in cardiovascular and metabolic diseases, and neurosciences and immunology.
The main goal of the Institute of Molecular Medicine is to establish a new collaborative research center (CRC) in the field of regulatory T cells.

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.

**IMPORTANT PUBLICATIONS // MAX. 5**

Heink S, Yogev N, Garbers C et al. Trans-presentation of IL-6 by dendritic cells is required for the priming of pathogenic T(H)17 cells. NATURE IMMUNOLOGY. 2017; 18 (1): 74-85.


Mufazalov IA, Schelmbauer C, Regen T et al. IL-1 signaling is critical for expansion but not generation of autoreactive GM-CSF+ Th17 cells. EMBO JOURNAL. 2017; 36 (1): 102-115.

Reissig S, Tang Y, Nikolaev A et al. Elevated levels of Bcl-3 inhibits Treg development and function resulting in spontaneous colitis. NATURE COMMUNICATIONS. 2017; 8.


**FUTURE DIRECTIONS**

Deciphering the tubulin code of dendritic cell homeostasis and function

PROJECT MANAGER: Prof. B Clausen
FUNDING: German Research Foundation (DFG)
SUM: € 489,010
PROJECT DURATION: 2017 - 2020

The role of E-cadherin and β-catenin signaling in myeloid antigen presenting cells in the maintenance of immune homeostasis at epithelial interfaces

PROJECT MANAGER: Prof. B Clausen
FUNDING: German Research Foundation (DFG)
SUM: € 240,050
PROJECT DURATION: 2016 - 2019

The role of IL-1 signaling in the regulation of microglia development and function

PROJECT MANAGER: Prof. A Waisman
FUNDING: German Research Foundation (DFG)
SUM: € 346,150
PROJECT DURATION: 2016 - 2020

The role of the deubiquitinating enzymes Cyld and A20 in B cell lymphoma genesis

PROJECT MANAGER: Dr. N Hövelmeyer
FUNDING: German Research Foundation (DFG)
SUM: € 391,030
PROJECT DURATION: 2014 - 2017

TRR128/2, A03: A novel IL-6 signaling modality in the direct interaction of immune cells

PROJECT MANAGER: Prof. A Waisman
FUNDING: German Research Foundation (DFG)
SUM: € 471,700
PROJECT DURATION: 2016 - 2020
HIGHLIGHTS

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 in cooperative projects. During the last years, the hematopoietic growth factor G-CSF has become an interesting candidate due to its broad spectrum of effectiveness. Using various stroke models in rodents the neuroprotective and neuroregenerative potential of this growth factor has been demonstrated. Nevertheless, translation into the clinic was not successful yet. To further increase post-stroke regeneration, the combination of different therapeutic therapies seems to be a promising approach. The current state and the unresolved problems of such combination strategies have recently been discussed in an invited review in Stroke (Sommer and Schäbitz, 2017; c.f. Fig. 1).

A second focus is 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 number of subtle structural alterations in the brain of diseased mice, which may represent the biological basis for the cognitive changes observed. Very recently, we could demonstrate that eAPS in mice is associated with decreased hippocampal cell proliferation, which may represent an additional neuropathological substrate of eAPS psychopathology (c.f. Fig. 2). This was a cooperative project with Prof. Chapman (Department of Neurology, Chaim Sheba Medical Center, Robert und Martha Harden Chair in Mental and Neurological Diseases, Sackler Faculty of Medicine, Tel Aviv University, Tel Hashomer, Israel).
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.

The role of inflammatory cells in acute ischemic stroke is currently a hot topic in stroke research. It has become clear that post-stroke inflammation is a complex and dynamic process which may also induce beneficial events. However, knowledge about the temporo-spatial distribution of the various inflammatory cells in human stroke is sparse. In a cooperative project we will analyse the spatial distribution of inflammatory processes in whole-brain sections of human brains.

FIG. 1

A simplified scheme of possible post-stroke combination therapies to enhance functional recovery.

Any of the priming treatments can theoretically be combined with respective consolidation treatments. Some combination paradigms have already been tested in humans (colored boxes) partially with beneficial outcome (thick lines). Other combinations have been tested in experimental stroke models only (thin lines) or are promising combination candidates (dashed thin lines). Within the priming or consolidation treatment groups various paradigms may again be combined with each other. Concerning neuromodulators/neuroenhancers they may be beneficial both for priming and consolidation treatment. Similarly, enriched environment has also been proven effective both in the priming and consolidation phase (from Sommer CJ and Schäbitz W-R, Fostering post-stroke recovery: towards combination treatments, Stroke (2017) 48:1112-1119).

FIG. 2

Experimental eAPS and white matter changes.

Using electron microscopy of myelinated axons in the corpus callosum revealed a shift towards larger axon diameters compared to control mice. However, overall axon and fiber size as well as g-ratio did not significantly differ. Representative images of callosal fibers from control (left) and eAPS mouse (right) (bar corresponds to 1 μm).
OVERVIEW

The Institute of Neuroradiology is the only university department in Rhineland-Palatinate providing complete diagnostic and therapeutic neuroradiological assessment 24/7 throughout the year.

In 2017, approximately 11,867 CTs, 4,953 MRI (including fMRI, perfusion and spectroscopy) were performed as well as >1,240 angiographies, including interventional procedures. The latter comprise mainly coiling of aneurysms after life-threatening intracranial hemorrhages, mechanical thrombectomy in acute stroke patients, arterial embolisation of cerebral and spinal arteriovenous malformations and fistulae (AVMs/AVFs) or head and neck tumors. Beside fMRI, the implementation of arterial spin labeling technique in special questions of brain perfusion (i.e. sick headache) is explored as part of the focus on digital imaging.

HIGHLIGHTS

In cooperation with Prof. Kalisch, Director of the NeurolImaging Center (NIC) of the Focus Program Translational Neurosciences (FTN), our focus is functional MRI 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 elderly people in order to have a reference-collective for the investigation of cerebral dysfunction in dementia patients.

A further study, performed together with the Department 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 a stationary environment, focused on patients with somatization dysfunction, will lead to a better mentalisation capacity.

Together with other groups (i.e. from ophthalmology, rheumatology, neurosurgery) we study reliable biopsy planning in patients with giant cell arteritis. The basic data of this 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 MRprotocols. In cooperation with the villa metabolica, we are conducting new investigations concerning arterial pathologies in patients with mucopolysaccharidosis. Other clinical studies focus on new clinical indication brain perfusion measurement with arterial spin labeling (ASL), i.e. in patients with acute headache/migraine or follow-up control in patients, who underwent combined (operation, chemotherapy and radio-) therapy after suffering from medulloblastoma (in cooperation with the Department of Pediatrics of the University Medical Center Mainz).

MR research on small animals is also carried out in conjunction with interdisciplinary groups including from anesthesiology, nuclear medicine and neurosurgery.
RESEARCH REPORT 2017
CLINICAL DEPARTMENTS AND INSTITUTES

IMPORTANT PUBLICATIONS // MAX. 5


FUTURE DIRECTIONS

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

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

CLINICAL STUDIES:
1. on patients with metabolic accumulation diseases (i.e. mucopolysaccharidosis (MPS)) concerning arterial affection (in cooperation with the villa metabolica of the UMC),
2. on 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 UMC)

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).

IMPORTANT PROJECTS // MAX. 5

MeVa-Study (Medulloblastoma analysis of cerebro-vascular subsequent damage following radio-chemo-therapy).

PROJECT MANAGER:
Prof. J Faber

PROJECT DURATION:
2015 - 2017
Institute of Neurosurgical Pathophysiology

Director:
Professor
Oliver Kempski

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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
PROJECT: GLIOMA DETECTION BY SPECTROSCOPY
In cooperation with the department of neurosurgery Köln-Merheim and Siemens AG we evaluate new optic methods to differentiate tumor from healthy brain in rats using the C6 glioma model.
**IMPORTANT PUBLICATIONS // MAX. 5**


**IMPORTANT PROJECTS // MAX. 5**

**Glioma detection by spectroscopy**

*PROJECT MANAGER:* Dr. A Heimann

*PROJECT DURATION:* 2014 - 2017
Institute of Pathology

Director:
Professor
Wilfried Roth

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OVERVIEW

The Institute of Pathology provides central services for histo-pathological, immunohistochemical, cytological, molecular-pathological and ultrastructural diagnosis for the University Medical Center Mainz. Currently, specimens of more than 60,000 patients are studied annually in the Institute. Since 2007, the Institute of Pathology in Mainz has been accredited. In addition to the classical methods of histological, cytological, and immunohistological analyses, the Institute provides modern methods in molecular diagnostics including a Next Generation Sequencing Facility. Furthermore, the Institute of Pathology operates a state-of-the-art Tissue Biobank, a virtual microscopy platform with digital image analysis as well as a complete electron microscopical laboratory.

HIGHLIGHTS

HIGHLIGHT #1: CYCLIN K AS NOVEL THERAPEUTIC TARGET AND BIOMARKER FOR PROSTATE CANCER

Resistance towards therapeutic drugs and a lack of clinically relevant biomarkers are key challenges in the treatment of prostate cancer. We found that inhibition of Cyclin K expression in prostate cancer cells represents a promising strategy to induce cell death and proliferation arrest in tumor cells by activation of mitotic catastrophe (Figure 1). By analysis of Cyclin K expression in tissue from 91 prostate cancer patients, we further identified Cyclin K as putative biomarker for therapy response (Schecher et al., 2017, International Journal of Cancer).

HIGHLIGHT #2: ANDROGEN RECEPTOR IS AN INDEPENDENT PROGNOSTIC FACTOR FOR RENAL CELL CARCINOMA

Five year survival rate is only 12% in patients with advanced renal cell carcinoma. There is an urgent demand for new biomarkers to provide information for patient risk stratification and molecular guided targeted therapy. Digital image analysis (Figure 2) of >900 renal cell carcinoma specimen revealed that high expression levels of androgen receptor are associated with low tumor extent, absence of distant metastasis and increased cancer-specific survival rates. In addition, androgen receptor status is a potential predictive marker to guide therapeutic use of androgen receptor pharmaceuticals in patients with renal cell carcinoma. (Foersch et al., 2017, Oncotarget).

HIGHLIGHT #3: REGULATION OF CELLULAR MIGRATION IN COLORECTAL CARCINOMA

The molecular mechanisms underlying the varying degree of invasiveness of colorectal carcinoma are largely unknown. We found that overexpression of the multifunctional phosphoprotein PEA-15 decreased migration of colorectal cancer cells in a phosphorylation-dependent manner (Figure 3). Immunohistochemical staining of patient derived tumor tissue further provided evidence for a differential expression of PEA-15 and its phosphorylated forms in colorectal carcinoma. This implicates that phospho-PEA-15 might represent an interesting candidate both as a potential diagnostic marker and therapeutic target.
IMPORTANT PUBLICATIONS // MAX. 5


IMPORTANT PROJECTS // MAX. 5

A randomized, 2x2 biomarker prevention trial of low-dose aspirin and metformin in colon cancer patients
PROJECT MANAGER: Prof. W Roth
FUNDING: Federal Ministry of Education and Research (BMBF)
SUM: € 340,800
PROJECT DURATION: 2016 - 2019

Lipid droplets and associated proteins in chronic liver diseases and hepatocarcinogenesis
PROJECT MANAGER: Prof. B Straub
FUNDING: German Research Foundation (DFG)
SUM: € 180,200
PROJECT DURATION: 2015 - 2018

Mechanisms of invasiveness and metastasis in colorectal carcinomas: functional relevance of the PEA-15 protein
PROJECT MANAGER: Dr. K Tagscherer
FUNDING: Wilhelm-Sander-Foundation
SUM: € 96,000
PROJECT DURATION: 2016 - 2018

Mechanisms of therapy resistance in colorectal carcinomas: apoptosis regulation by microRNA mediated oxidative-metabolic effects
PROJECT MANAGER: Prof. W Roth
FUNDING: German Research Foundation (DFG)
SUM: € 218,000
PROJECT DURATION: 2013 - 2017

Systematic histomorphologic analysis of senescence-associated markers in colorectal carcinoma
PROJECT MANAGER: Dr. S Försch
FUNDING: University Medical Center Mainz
SUM: € 37,200
PROJECT DURATION: 2016 - 2017

FUTURE DIRECTIONS

The research groups of the Institute will consequently advance molecular diagnostics, digital pathology, and biomarker development for immunoncology. Promising prognostic and predictive biomarkers will be evaluated in order to develop robust tests for clinical diagnostics. Next generation sequencing techniques will play an important role in the identification of molecular biomarkers. Moreover, the Institute will expedite the development of novel ex vivo 3D tumor models to obtain reliable and less artificial models for studying tumor biology. Specifically, human tumor tissue models to directly evaluate drug response and resistance will be developed. These tissue-based model systems will contribute to personalized response prediction and individualized tumor therapy. Additionally, improved ex vivo tumor models will substantially promote the precise characterization of crucial hallmarks of cancer, such as heterogeneity and resistance. Another focus of the Institute will be the development of digital image analysis algorithms for tumor immunology.

FIG. 1: Prostate cancer cells undergoing mitotic catastrophe upon downregulation of Cyclin K.
FIG. 2: Digital image analysis of androgen receptor expression in papillary renal cell carcinoma.
FIG. 3: Effects of PEA-15 overexpression on cellular migration.
DEPARTMENTS AND INSTITUTES OF DENTAL MEDICINE

Department of Orthodontics and Dentofacial Orthopedics
Department of Restorative Dentistry
Department of Oral and Maxillofacial Surgery - Plastic Surgery
Department of Prosthodontics and Dental Material Sciences
OVERVIEW

RESEARCH FOCI

- Basic research on orthodontic tooth movement
- Cell metabolism during pharmacotherapy and orthodontic force application
- Interaction of Orthodontics and Periodontics
- Skeletal anchorage (cortical miniscrews and palatal implants; in cooperation with the Department of Oral and Maxillofacial Surgery, Mainz)
- Caries and Periodontal Prevention during orthodontic treatment
- Orthodontics after dental and maxillofacial trauma
- Orthognatic Surgical Treatment
- Cleft lip and palate

HIGHLIGHTS

RESEARCH HIGHLIGHTS

- 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 FUTURE SCIENCE PROJECTS

- The analysis of importance for bone remodeling during orthodontic tooth movement. This might help to improve the time of treatment and stability of the results achieved.
Aesthetics and perception of different orthodontic appliances: A Cross-Sectional and Eyetracking Study

PROJECT MANAGER:
Dr. M Försch, Dr. Dr. C Jacobs, L Krull

FUNDING: German Society of Lingual Orthodontics
SUM: € 7,000
PROJECT DURATION: 2014 - 2018

Biofilm characterization from people with different mechanical Plaque removal profile

PROJECT MANAGER:
Dr. C Erbe, Prof. H Wehrbein

FUNDING: The Procter and Gamble Company, Mason, Ohio, USA
SUM: € 55,145
PROJECT DURATION: 2015 - 2019

Comparison of aligner therapy versus Herbst treatment in an adolescent population

PROJECT MANAGER:
Dr. C Erbe, Prof. H Wehrbein

FUNDING: Invisalign Research Award
SUM: € 25,000
PROJECT DURATION: 2016 - 2020

Staining Potential of two Marketed Fluoride Rinses

PROJECT MANAGER:
Dr. C Erbe, Prof. H Wehrbein

FUNDING: The Procter and Gamble Company, Mason, Ohio, USA
SUM: € 81,261
PROJECT DURATION: 2011 - 2020
Department of Restorative Dentistry

Director:
Professor
Brita Willershausen

OVERVIEW

Central to our operation at the Department of Restorative Dentistry are the formation and training of dental students and the provision of modern dental restorations and materials. Students at the department are compelled to successfully complete three semesters at our facilities in which they are expected to learn theoretical and clinical knowledge of dental pain origin and elimination, root canal treatment, modern resin based materials, gold casting restorations, ceramic and partial crown inlays.

HIGHLIGHTS

1. BIOCOMPATIBILITY OF DENTAL MATERIALS
Endodontic dental materials should fulfill the corresponding requirements. These type of materials are used to seal the root canal; thus, direct contact between them and the periapical tissues can not be avoided. The biocompatibility of these materials is being constantly investigated at our laboratories using different methodologies. The results obtained through in vitro research methods facilitate first-sight evaluation of these materials. This aids clinicians in the decision-making process on how to use these materials. Such research methodologies give information about the metabolism determination (for example on proliferation, apoptosis, cytokine release) caused by these materials on different cell lines.

2. MORPHOLOGY OF THE ROOT CANAL SYSTEM
The morphology of the root foramen and root canal system are being investigated through different methodologies including microscopy, radiology 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.

3. RESIN COMPOSITE RESTORATIONS, VISIBLE LIGHT CURING, ADHESIVE SYSTEMS
Resin composites have been continuously further developed over the last several decades. Tremendous efforts have been undertaken to reduce the shrinkage stress of these materials and to enhance their physical properties including for example their flexural strength. Both are crucial to the longevity of dental restorations, in particular to avoid marginal gaps and cohesion-type fractures of the material. 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 conducted at the Department of Restorative Dentistry. The clinical study on a low shrinkage, silorane-based material was prolonged to an observation period of a total of four years. A paper is 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 shortly thereafter.

4. PERIODONTAL DISEASES ARE THE MOST COMMON DENTAL CONDITIONS IN ADULTS WHICH REQUIRE PROFESSIONAL TREATMENT
The main focus of this group is to study new materials and techniques in nonsurgical and regenerative periodontal therapy.
FUTURE DIRECTIONS

THE AIMS OF OUR DEPARTMENT ARE BASED ON THREE MAIN COLUMNS

First, we care for our patients: Therefore our highest goal is the proper treatment of our patients at the highest level available including all therapy options, modern restorative dentistry can offer. In particular, this encompasses a wide range of restorative dentistry practices based on minimal invasive dentistry-approaches including direct and indirect restorations, endodontic treatment, periodontology, pediatric dentistry as well as fixed partial dentures. Our staff includes specialists in each field. Their knowledge is then transferred to the students at our department. In relation to this, our second aim is to offer our students a state-of-the-art education based on a modern restorative dentistry. To ensure an educational program, strengthened by continuous scientific research our third aim is to encourage all members of our team to conduct their own research, assist in existing projects and to publish research results in the form of overview-papers and case-reports.

IMPORTANT PROJECTS // MAX. 5

Comparison of two surgical techniques using connective tissue to treat Miller class I and II: a randomized controlled trial
PROJECT MANAGER: Dr. A Azariipour, Prof. B Willershausen
PROJECT DURATION: 2014 - 2020

Evaluation of the biocompatibility of dental materials
PROJECT MANAGER: Dr. I Willershausen, Prof. B Briseño Marroquin, Prof. B Willershausen
PROJECT DURATION: 2010 - 2019

In vitro and in vivo tests of tooth-colored dental restoratives
PROJECT MANAGER: Dr. V Ehlers, Dr. A Callaway, M Patyna et al.
FUNDING: Heraeus Kulzer, VOCO, 3M ESPE, Ivoclar Vivadent
SUM: € 135,000
PROJECT DURATION: 2014 - 2019

Influence of rehydration on the physico-chemical properties of a new resorbable 3D-collagen matrix
PROJECT MANAGER: PD Dr. A Kasaj, Dr. A Pabst, Prof. B Willershausen
PROJECT DURATION: 2012 - 2019

Root canal system morphology, configuration and dimensions of maxillary and mandibular molars by means of micro-CT
PROJECT MANAGER: Dr. T Wolf, Prof. B Briseño, Prof. B Willershausen
PROJECT DURATION: 2014 - 2020


DEPARTMENTS AND INSTITUTES OF DENTAL MEDICINE

Department of Oral and Maxillofacial Surgery - Plastic Surgery

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Director:
Professor
Bilal Al-Nawas

OVERVIEW

After restructuring in 2017, the Department of Oral and Maxillofacial Surgery and Plastic Surgery continues focusing research activities on the fields of biomaterials and oncology. Work on bone regeneration and reconstruction finds a place at the department, as does the regeneration of soft tissues and the interaction with neovascularization of biomaterials. In the clinical context, the subject of implantology is very important. In oncology, the areas of early clinical and preclinical diagnosis as well as clinical studies on tumor prognosis are currently being studied. This includes questions of reconstruction, in which, for example, 3D printing technology is used.

HIGHLIGHTS

The former Department of Oral Surgery (and Oral Radiology) joined the Department of Oral and Maxillofacial Surgery – Plastic Surgery. The scientific focus of the newly formed clinic and polyclinic will be based on the previous ones and mainly cover the fields of biomaterials and oncology. A close connection to the Clinical Focus BiomaTiCS is therefore important and will continue to be actively pursued. The focus of this research includes: tumor biology, reconstructive surgery, implantology, and bone substitutes. Next to clinical research, cell culture methods and animal research are also explored.

RESEARCH AREAS:

Oral Surgery:
- Oral lichen planus, orale lichenoid lesions, graft-versus-host reaction, and head and neck cancer: Quality of life
- Neurologic changes after Dental Surgery
- 3D imaging in Dental Radiology

Bone Biology:
- Bisphosphonates- and RANK-Ligand-associated osteonecrosis and osteoradionecrosis: Pathology, treatment with in vitro and in vivo studies

Biomaterials and Implants:
- Bone substitutes: Evaluation and development of injectable hydrogel (2D and 3D cultures)
- Dental, enosseous implants: Material research (titanium alloys, circonia, 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

Oncology and Reconstruction:
- Squamous cell cancer: Tumorbiology, therapy improvement (analyzed markers: PON-2, VEGF, p63, p73, lactat, ATP, glucose, pyruvat, GLUT1/3 and MCT1/4)
- Complex defect reconstruction: Development of 3D CAD/CAM solutions (Deformities, cleft patients, trauma, cancer)
- Deformity and orthognathic surgery: Evaluation of long-term success of procedures and adjuvant therapies

Neurophysiology in the maxillo-facial region
- Somatosensory profiling of patients with nerve damage
- characterization of patients with chronic orofacial pain
- differentiated local anesthesia
RESEARCH REPORT 2017
DEPARTMENTS AND INSTITUTES OF DENTAL MEDICINE

FUTURE DIRECTIONS

The department is focusing its research according to the key research areas of the University Medical Center Mainz, especially within BiomaTiCS by focusing on the following topics: 3D printing of bone substitutes, bone regeneration and vascularization, and on biomaterial-related infections. The BiomaTiCS platform offers the possibility for synergistic and successful research to be conducted together with other surgical disciplines.

RESEARCH AIMS:
- Further development of dental implantology on an internationally recognized level
- Improving the possibilities of bone regeneration
- Establishment of 3D printing methods in applied surgery
- Improvement of algorithms of 3D image processing
- Early diagnosis of precursor lesions and small carcinoma
- Better understanding of the physiological processes in use of antiresorptive at the emergence of bone necrosis

IMPORTANT PUBLICATIONS // MAX. 5


Kaemmerer PW, Schneider D, Palarie V et al. Comparison of anesthetic efficacy of 2 and 4 % articaine in inferior alveolar nerve block for tooth extraction-a double-blind randomized clinical trial. CLINICAL ORAL INVESTIGATIONS. 2017; 21 (1): 397-403.


IMPORTANT PROJECTS // MAX. 5

Accuracy of magnetic resonance imaging in monitoring neovascularization after guided bone regeneration – a preliminary study
PROJECT MANAGER: Prof. B Al-Nawas, Dr. L Righesso
PROJECT DURATION: 2016 - 2019

An open, prospective, single cohort, multi-centre study evaluating the NobelReplace Conical Connection implants supported single-unit crowns in the maxilla
PROJECT MANAGER: PD Dr. A Behnke, Prof. N Behnke
FUNDING: Nobel Biocare Services AG, Switzerland
SUM: € 35,000
PROJECT DURATION: 2011 - 2019

Efficacy of postoperative adjuvant radiotherapy in patients with squamous cell carcinoma of the oral cavity or oro-pharynx with histologically confirmed ipsilateral solitary cervical lymph node metastasis (pN1)
PROJECT MANAGER: Prof. B Al-Nawas, Dr. M Moergel, Prof. W Wagner
FUNDING: German Cancer Aid
SUM: € 1,142,880
PROJECT DURATION: 2009 - 2017

Determination of sensory norm values in the innervation area of the alveolar inferior nerve by means of extra- and intraoral quantitative sensory testing
PROJECT MANAGER: Prof. M Daublaender, Dr. C Welte-Jzyk
PROJECT DURATION: 2015 - 2017

Kephalos: Low radiation 3D-reconstruction of the facial skull surface from multimodal input data
PROJECT MANAGER: Prof. R Schulze
PROJECT DURATION: 2015 - 2018
HIGHLIGHTS

Modern patient treatment assumes clinical and material based research. The Department of Prosthodontics and Dental Material Sciences 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 is 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 Prosthodontics and Dental Material Sciences. In our dental laboratory, students are educated in the use of Computer Aided Manufacturing of fixed and removeable dentures.

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.
- Advantage of CAD CAM produced bite splints
- Immediately produced implant retained fixed dental crowns
- Digital workflow in dentistry

DENTAL IMPLANTS:
- Effects of rinse fluids on the tightness of screw retained implant structures.

OVERVIEW

The Department of Prosthodontics and Dental Material Sciences 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 fulfill 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 using CAD/CAM technology.
**IMPORTANT PUBLICATIONS // MAX. 5**


**IMPORTANT PROJECTS // MAX. 5**

A clinical evaluation of Nobel Procera implant bar overdentures in the mandible or maxilla on 4 NobelReplace CC implants

**PROJECT MANAGER:**
PD Dr. A Behneke, Prof. N Behneke

**PROJECT DURATION:**
2012 - 2018

An open, prospective, single cohort, multi-centre study evaluating the NobelReplace Conical Connection implants supported single-unit crowns in the maxilla.

**PROJECT MANAGER:**
PD Dr. A Behneke, Prof. N Behneke

**FUNDING:** Nobel Biocare Services AG, Switzerland

**SUM:** € 35,000

**PROJECT DURATION:**
2011 - 2019

Evaluation of cytotoxicity of modified implant-capable titanium-surfaces on human cells

**PROJECT MANAGER:**
Prof. B Al-Nawas, G Burgard

**PROJECT DURATION:**
2013 - 2018

In-vivo-analysis of the bleaching efficacy of the external tooth-whitening agent VOCO Perfect Bleach 16 %®

**PROJECT MANAGER:**
Prof. H Scheller, Dr. C Igiel, A Herzog

**PROJECT DURATION:**
2015 - 2017

The randomized shortened dental arch study

**PROJECT MANAGER:**
Dr. S Hartmann, Prof. H Scheller

**PROJECT DURATION:**
2008 - 2018

**FIG. 1:** Prosthetic 3D Diagnosis of implant positions.

**FIG. 2:** Digital Volume Tomography and diagnosis of the temporo mandibular joint.

**FIG. 3:** Adhesive bridgework of a CAD CAM fabricated framework and ceramic veneering material.

**FIG. 4:** Zirkondioxid milled bridgework.

**FIG. 5:** Computer Aided Designed of dental ceramic crowns.
CENTRAL MEDICAL SUPPLY UNITS

Pharmacy
Transfusion Center
OVERVIEW

The Department of Pharmacy performs

PHARMACEUTICAL LOGISTICS, i.e. management and supply of medicinal products and medical devices for in- and outpatients.

PHARMACEUTICAL PRODUCTION, which encompasses manufacturing of all different kinds of dosage forms, especially ready-to-administer aseptic preparations for pediatric, intensive care and oncology patients.

PHARMACEUTICAL SERVICES, where the key issues are the development of treatment guidelines, drug-use-evaluation, drug-use reviews and formulary management. Ward pharmacists perform patient-individual drug monitoring and are responsible for taking patient drug history at admission and counselling on discharge medication.

RESEARCH, i.e. collaborating on various clinical trials regarding drug preparation and other tasks.

HIGHLIGHTS

PARENTERAL PREPARATIONS
The focus of the current studies is the chemical and physical stability of ready-to-use cytotoxic preparations of recently approved small molecules (e.g. oxaliplatin, plerixafor, carfilzomib) and epirubicin- or irinotecan-loaded beads for chemoembolization. We investigated the compatibility of beads (different diameters) loaded with irinotecan or epirubicin mixed with different volumes of 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.

COMPATIBILITY AND AERODYNAMIC CHARACTERISTICS OF SIMULTANEOUSLY NEBULIZED INHALATION SOLUTIONS/SUSPENSIONS
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.

MEDICATION ADHERENCE
Medication adherence (compliance) of patients plays a major role in the outcome of various diseases. Previously, we investigated the compliance in organ transplant patients (pre-, posttransplant) as well as in patients suffering from rheumatoid arthritis. By educating the patients, we were able to improve medication adherence. Therefore medication adherence was measured by different methods (e.g. drug serum levels, self-reports, pharmacy refill, pill count or electronic monitoring with MEMS). Currently, we are studying the adherence of patients suffering from systemic lupus erythematoses (SLE) regarding their immunosuppressive therapy and patients suffering from lung cancer regarding oral anticancer therapy.

EFFECTIVENESS OF PHARMACEUTICAL CARE
Little attention has been paid in Germany to date to the study of the impact of pharmaceutical care on the clinical, social and economic outcomes of treatment. In a recent multicenter, open label study we showed that there are fewer failures in taking medication, if pharmaceutical care is provided in the case of discharge medicine. Currently we are running studies to evaluate the clinical and social outcome of the use of written or electronic patient individual medication plans. The medication plans are prepared...
Compatibility and aerodynamic characteristics of simultaneous nebulized inhalation admixtures

**PROJECT MANAGER:**
Prof. I Krämer, Prof. W Kamin, G Seifert

**PROJECT DURATION:**
2016 - 2018

Medication adherence and health related quality of life in patients suffering from systemic lupus erythematoses

**PROJECT MANAGER:**
Prof. I Krämer, Prof. A Schwarting, J Boventer

**PROJECT DURATION:**
2016 - 2018

Medication adherence with oral anticancer therapy in lung cancer patients

**PROJECT MANAGER:**
Prof. I Krämer, Prof. M Theobald, J Krause

**PROJECT DURATION:**
2015 - 2018

Stability and compatibility of ready-to-aminister drug preparations for cancer patients

**PROJECT MANAGER:**
Prof. I Krämer, I Sarakbi, SH Kim et al.

**PROJECT DURATION:**
2013 - 2017

**IMPORTANT PUBLICATIONS // MAX. 5**

Collins C, Krämer I. Evaluation of a Process Monitoring Method for Compounding Parenteral Nutrition with the Baxter EM2400 in a Hospital Pharmacy Department. PHARMACEUTICAL TECHNOLOGY IN HOSPITAL PHARMACY. 2017; online: online.


**FUTURE DIRECTIONS**

The aim of the Pharmacy’s research projects is to study the effective and safe use of medicinal products. The results of research are utilized 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.

**TOPICS OF RESEARCH:**

- Stability of ready-to-use preparations
- Medication Compliance
- Electronic medication plan

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. About 600 patients were recruited in five study centers in Rhineland-Palatinate. Feasibility and usefulness of the nationwide medication plan in an electronic and printed version were demonstrated. Patients especially appreciated information about the indication and how to use the medication. Physicians and pharmacists appreciated the availability of current and accurate information about patients’ medication.
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 focused on special aspects in transfusion medicine. Increasing viral and microbial safety of blood components is one of the predominant research foci. 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 IM IMMUNOHEMATOLOGY

Automation of immunohematologic tests is still a diagnostic challenge. The detection of allo-antibodies and blood-group-antigens depends to a great extend 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 APHERESIS 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.

INCREASING SAFETY BY DONOR SCREENING ON HEPATITIS E VIRUS

Since November 2016, all blood donors are screened for HEV-RNA, although this is not mandatory in Germany. This increases safety of blood transfusion. This is beneficial especially for immunocompromised patients.
**IMPORTANT PUBLICATIONS // MAX. 5**


Hellstern P, Hitzler WE. PROFESSOR CLAUS MAURER, MD 1929-2017. CLINICAL LABORATORY. 2017; 63 (5-6).

Werner A, Koschke M, Leuchtner N et al. Reconstitution of T Cell Proliferation under Arginine Limitation: Activated Human T Cells Take Up Citrulline via L-Type Amino Acid Transporter 1 and Use It to Regenerate Arginine after Induction of Argininosuccinate Synthase Expression. FRONTIERS IN IMMUNOLOGY. 2017; 8.

**FIG. 1:** New Generation analyzer for fast high throughput blood donor screening and patient testing for viral load.

**FIG. 2:** Separation of blood components.

**IMPORTANT PROJECTS // MAX. 5**

<table>
<thead>
<tr>
<th>Project</th>
<th>Description</th>
<th>Project Manager</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet function in pooled and apheresis platelet concentrates</td>
<td></td>
<td>Prof. WE Hitzler, K Blath</td>
<td>2015 - 2017</td>
</tr>
<tr>
<td>Prevalence of Hepatitis E among Blood Donors</td>
<td></td>
<td>Dr. S Runkel, Prof. WE Hitzler</td>
<td>2015 - 2017</td>
</tr>
</tbody>
</table>
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 on good scientific practice 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, which are to be supplemented with university-based subject-specific aspects. For this reason, the University Medical Center of the Johannes Gutenberg University Mainz 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 slightly adapted to meet 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 attained 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. The 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 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 from 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, with the handling of results and with how to collaborate 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 from 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 evaluation and the publication 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 faculty representative for doctoral candidates. 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 to consult with the Institute of Medical Biostatistics, Epidemiology and Informatics or a similar institution regarding the proposed experimental design and statistical procedures to be used prior to commencing work.
- 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.
- The 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 the 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, the formulation of the research plan and in the evaluation of results,
2) to the 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 at which the research was conducted or read the manuscript of results are not entitled to be considered authors.

- In reports 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.
- 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 coauthors. 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.

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We have gone to great length to ensure that all information in the report is correct and actual. All content, pictures and images used in this report are based on the information provided in good faith by each entity itself. Throughout the report, gender-specific terms may be used in order to ease the text flow. Whenever a gender-specific term is used, it should be understood as referring to both genders.

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