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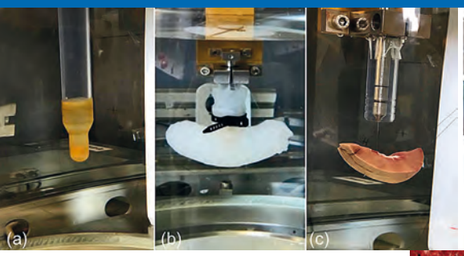
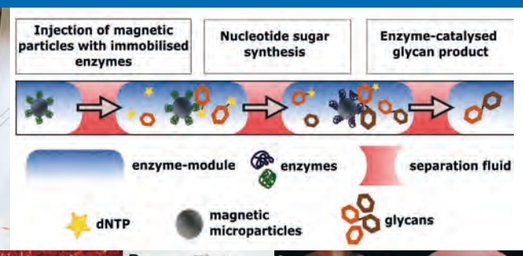
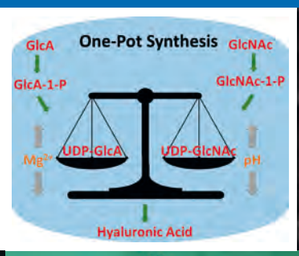
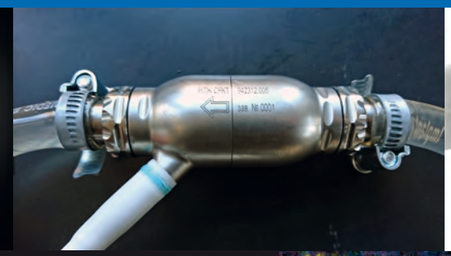
Helmholtz-Institute for Biomedical Engineering

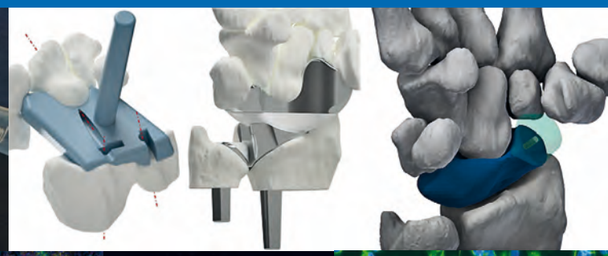
Annual Report 2019

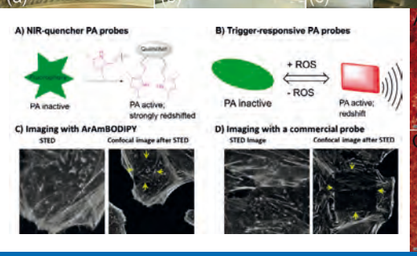


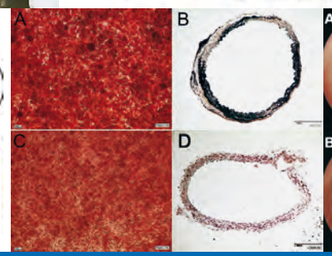


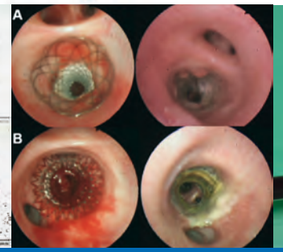


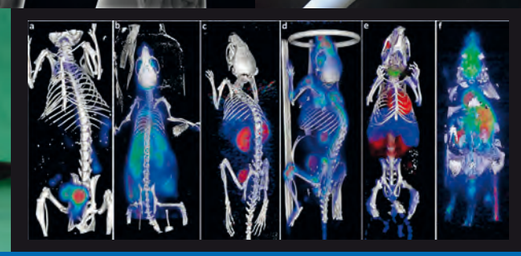


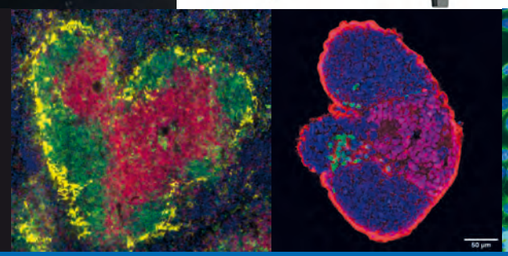


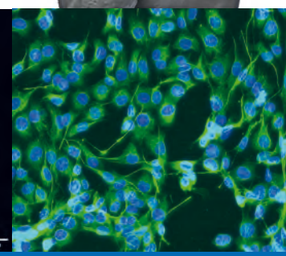












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Preface

The Helmholtz-Institute for Biomedical Engineering HIA represents a major hub for interdisciplinary basic research and development in biomedical engineering at RWTH Aachen University and beyond. In June, we hosted our biannual Helmholtz Symposium 2019 – on Biomedical Engineering and related fields. Invited talks covered the interdisciplinary spectrum of Biomedical Engineering at RWTH Aachen University. Most challenging for the presenters and entertaining for the audience was the poster session with one-minute teasers.

We contribute to Bachelor and Master courses of the Medical, Engineering and Natural Sciences faculties of RWTH Aachen University. Members of the Helmholtz-Institute coordinate master courses related to all fields of biomedical engineering. The practical education of students parallels their academic teaching. This comprehensive training has proved critical for successful national and international industries as well as the academic careers of our students and alumni. Biomedical Engineering, Medical Biology, and Biointerface Science are steadily gaining importance and have become important subjects in the study curricula of Biomedical and Engineering Master Courses. This development merely reflects the ever-evolving Biomedical and Health Industries, technological innovation and societal needs.

Research projects target improved health care. Continuous refinement of methods and technologies helps to achieve optimized diagnostic and therapeutic options for patients. Networking and cooperation within RWTH Aachen University as well as with national and international clinicians, academic and industry researchers are key to our work. Members of the Helmholtz-Institute for Biomedical Engineering have been instrumental in securing funding for both coordinated teaching and research. In 2019, external funding alone has reached well over 10 million euros.

This annual report is dedicated to our sponsors, partners, and friends for their support and cooperation and to all individuals that are interested in our institute. Enjoy reading our Annual Report 2019. We would be happy to provide further information on any of the topics reported herein and discuss future options of cooperation in the fascinating field of biomedical engineering.

Aachen, March 2020

The Board of Directors

In times of coronavirus disease 2019 (COVID-19)

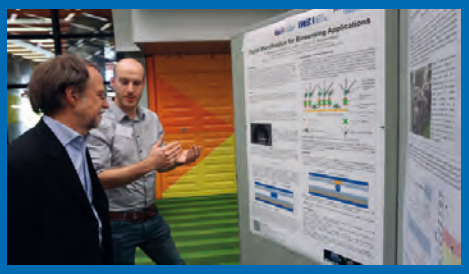
The HIA Board of Directors (from left to right): Steffen Leonhardt, Martin Zenke, Klaus Radermacher, Lothar Elling, Fabian Kiessling, Willi Jahnen-Dechent, Thomas Schmitz-Rode

HIA-Symposium 2019









Social Events – Christmas Party 2019








Gene Function in Cell Growth, Differentiation & Development

Director

Univ.-Prof. Dr. rer. nat. Martin Zenke

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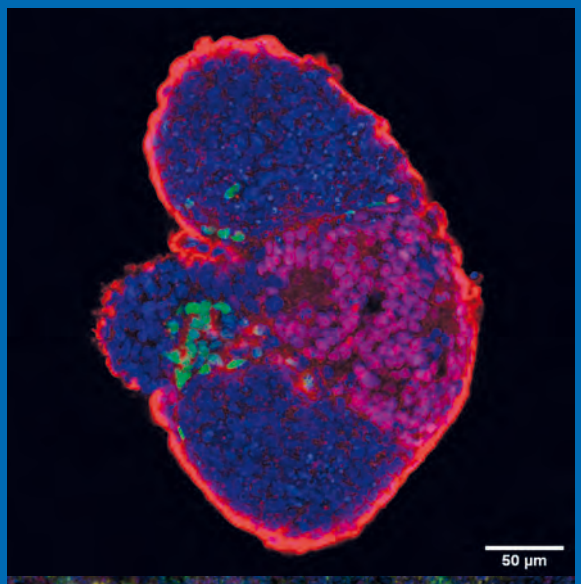

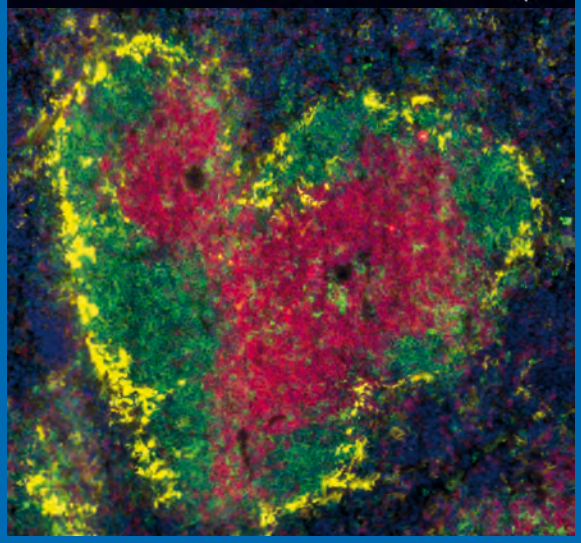

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Introduction

Elucidating cell functions and cell fate decisions has been the major focus of the institute during the year, which includes work on pluripotent and hematopoietic stem cells, cell adhesion and migration, cell tracking, DNA methylation and mechanobiology (Fig. 1). More specifically, induced pluripotent stem cells (iPS cells) were employed for disease modeling (leukemia, pain) and compound screening. Hematopoietic stem cells and their development in antigen presenting dendritic cells (DC) were studied.

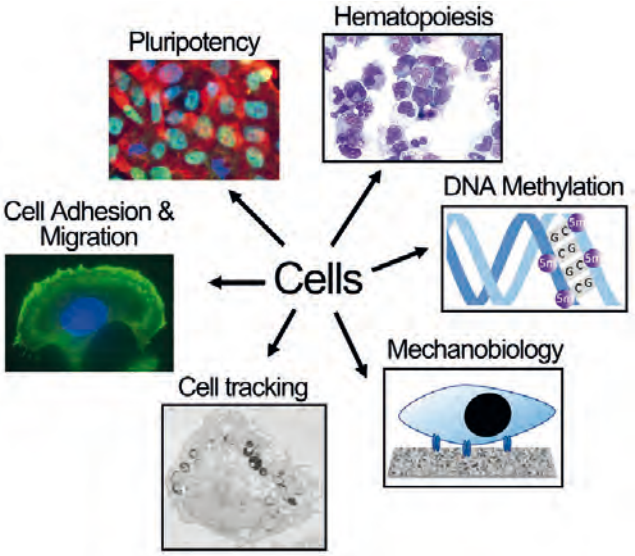

Fig. 1: Major research topics of the year 2019 are depicted.

We use genome editing with CRISPR/Cas as a particular versatile toolbox for precision genome engineering in pluripotent embryonic stem cells and adult somatic stem cells to generate cells with wanted properties. The Epi-BloodCount project aims at quantification of leukocytes in blood samples based on their DNA methylation signature.

KIT D816V iPS Cells for Precision Medicine

Patient specific iPS cells are engineered stem cells obtained from somatic cells of patients by reprogramming. iPS cells can differentiate into all cell types of our body and thus provide unique opportunities for disease modeling, drug development and regenerative medicine. We generated KIT D816V iPS cells from patients with aggressive systemic mastocytosis and mast cell leukemia to develop a disease model for mechanistic and drug discovery studies (Toledo et al., 2019; in collaboration with the Department of Hematology, Oncology, Hemostaseology and Stem Cell Transplantation, RWTH Aachen University Hospital; Fig. 2).

KIT D816V iPS cells differentiated into neoplastic hematopoietic progenitor cells and mast cells with patient-specific phenotypic features, which reflects the heterogeneity of the disease. The KIT D816V mutation was also introduced into human embryonic stem cells (ES cells) by CRISPR/Cas9n genome editing (Fig. 3). Such KIT D816V ES cells, when differentiated into hematopoietic cells, recapitulated the phenotype observed for KIT D816V iPS cells (Toledo et al., 2019).

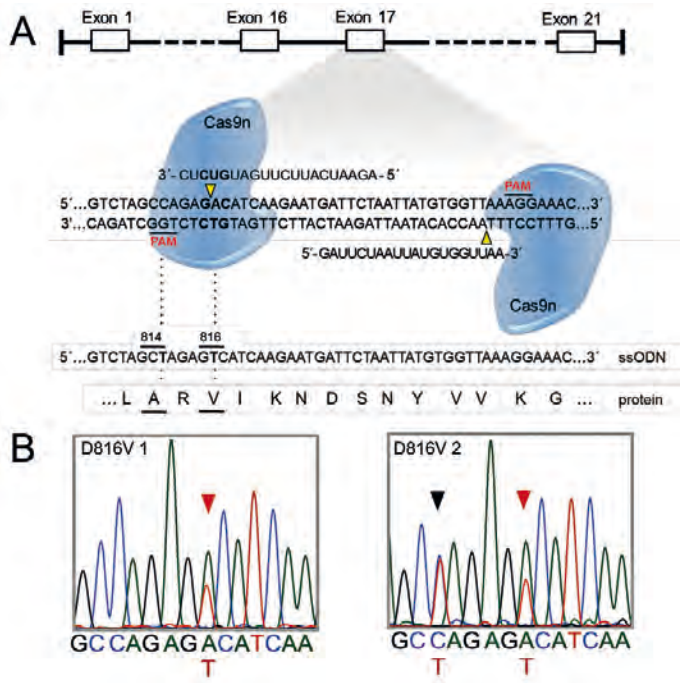

Fig. 3: Precision genome engineering of KIT D816V human ES cells by CRISPR/Cas9 nickase (Cas9n). (A) The A-T mutation and a silent C-T mutation in exon 17 of KIT gene were introduced by Cas9n and a synthetic oligonucleotide (ssODN). (B) DNA sequence of mutated KIT gene of (A) (Toledo et al., 2019).

KIT D816V causes constitutive activation of the KIT tyrosine kinase receptor and we exploited our KIT D816V iPS cells and ES cells to investigate new tyrosine kinase inhibitors targeting KIT D816V. Our study identified a new selective KIT D816V inhibitor and thus a new drug candidate for KIT D816V targeted therapy of advanced systemic mastocytosis and mast cell leukemia.

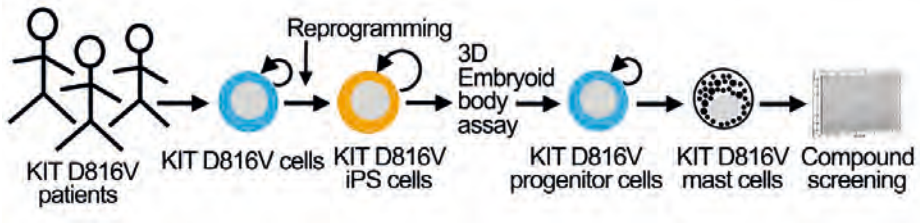

Fig. 2: Schematic representation of KIT D816V iPS cell generation from KIT D816V patients by reprogramming and of KIT D816V iPS cell differentiation into hematopoietic progenitor cells and mast cells for compound screening (Toledo et al., 2019).

Fig. 4: iPS cell production and differentiation in automatic cell production facility (iCellFactory).

In 2019 we also followed up on our efforts to further develop our automatic cell production facility for iPS cells, and of cells derived thereof, to meet the ever increasing need of these cells for various biomedical applications, such as compound screening (Fig. 4; see also above; in collaboration with Laboratory for Machine Tools and Production Engineering, WZL, RWTH Aachen University and Fraunhofer Institute for Production Technology, IPT, Aachen, Germany).

Patient-specific iPS cells for Studying Chronic Pain

Chronic pain represents a particularly devastating disease that requires intensive research on the underlying molecular mechanisms. To this end we generated iPS cells of inherited erythromelalgia (IEM) patients with chronic pain harboring a sodium channel Nav1.7 mutation (Meents* et al., 2019).

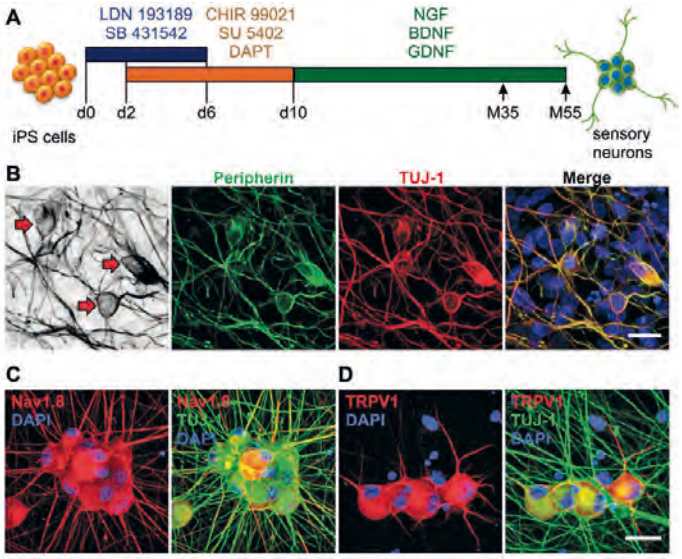

Fig. 5: Sensory neurons are obtained from IEM patient-specific iPS cells. (A) Schematic representation of iPS cell differentiation into sensory neurons. (B-D) IEM neurons express peripherin, TUJ-1, Nav1.8 and TRPV1 (Meents et al., 2019).*

These Nav1.7 mutation iPS cells were differentiated into sensory neurons (Fig. 5) and subjected to electrophysiology analysis. We found that the IEM mutation caused a hyperpolarizing shift of Nav1.7 activation (Meents* et al., 2019). Our model provides a new rational for Nav1.7 action and should be most valuable for developing more efficacious clinical analgesics.

TGF-β/BMP and HGF Receptors are Regulators of EMT and MET Programs in Dendritic Cell Development and Migration

DC are important regulators of adaptive immunity and act as sentinels in almost all peripheral tissues of our body. Accordingly, in the life cycle of DC, changes in the states of sedentariness and migration are closely related to their development. We propose the concept that genetic programs of mesenchymal-to-epithelial transition (MET) and epithelial-to-mesenchymal transition (EMT) regulate homing and migration of DC, respectively (Hieronymus et al., Semin. Cell Dev. Biol., 2015; Sagi and Hieronymus, Front. Immunol., 2018). We particularly focus on investigating signaling via TGF-β receptor and hepatocyte growth factor (HGF) receptor, which have a specific impact on regulating EMT and MET programs and thus act as relays during DC development, function and migration (Fig. 6).

DC develop from hematopoietic stem cells in bone marrow and migrate as precursors into peripheral tissues, such as skin (Fig. 6). Depending on TGF-β receptor signaling DC are functionally embedded there to act as guardians of the immune system. A differential and sequential role of BMP7 and TGF-β1 in differentiation of Langerhans cells, the contingent of DC in stratified squamous epithelia, was recently identified in collaboration with A.-H. Hovav from Hebrew University, Jerusalem, Israel (Capucha et al., J. Exp. Med., 2018).

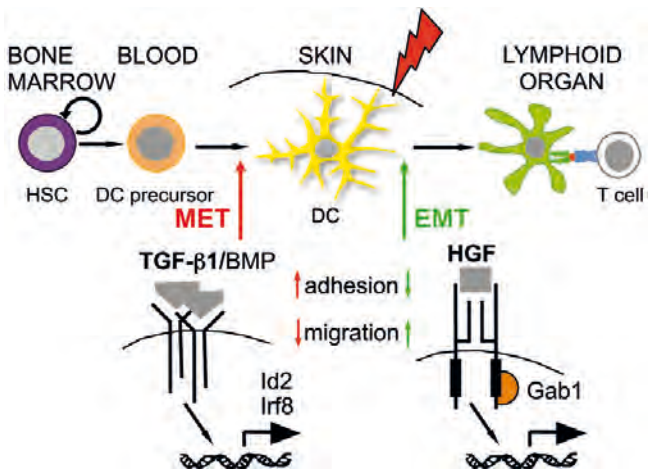

Fig. 6: DC development and migration are differentially regulated by TGF-β/BMP and HGF receptor signaling via MET and EMT programs, respectively.

The role of TGF-β/BMP-target genes Id2 and IRF8 in MET and thus in adhesion and migration regulation are further addressed. Following antigen uptake, DC are activated, leave the peripheral tissue and migrate via lymphatic vessels to lymphoid organs for antigen-specific T cell stimulation. We previously identified HGF receptor signaling in skin DC as essential in this EMT-like process. We now further study the underlining signaling process with a particular focus on the role of the adaptor protein Gab1.

Biotinylated and Near-Infrared Cellulose Nanocrystals for Cellular Labeling and Bioimaging

Cellulose nanocrystals (CNC) are a promising candidate for biomedical applications due to their special surface chemistry, low toxicological risk, negligible inflammatory response and the ability to penetrate cells. Higher tissue penetration, lower biological auto-fluorescence and reduced light scattering have greatly increased the interest of near-infrared fluorescent probes. Known limitations of these probes include dye aggregation, low solubility in water and undesired changes of photophysical properties.

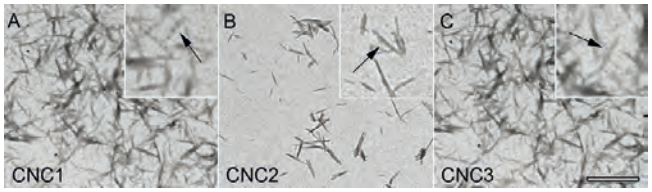

Fig. 7: Representative transmission electron microscopy images of CNC derivatives showing their typical needle-like structure (arrows in insets). CNC1: biotinylated CNC; CNC2: PDI-based NIR-CNC, CNC3: biotinylated and NIR-CNC. Scale bar: 500 nm.

To overcome these limitations, we are working on a joint project with Luiz H.C. Mattoso (LNNA, Embrapa Instrumentation, São Carlos, Brazil) centered on the development of near-infrared cellulose nanocrystals (NIR-CNC). We developed chemically modified CNC derivatives by covalent incorporation of PEGylated biotin, perylenediimide (PDI) based NIR organic dye or a combination of both (Fig. 7) and evaluated their suitability for labeling and imaging of different cell lines.

PDI-labeled CNC showed a superior photostability compared to similar commercially available dyes under long periods of constant and high intensity illumination. All CNC derivatives displayed excellent cytocompatibility towards all cell types. Moreover, CNC were effectively internalized and localized in the cytoplasm around perinuclear areas. Our findings demonstrate the suitability of these new CNC derivatives for labeling, imaging and long-time tracking of a variety of cell types.

Epi-Blood-Count: Quantification of Leukocytes Based on DNA Methylation

White blood cells (leukocytes) are vital components of our immune system and leukocyte numbers are indicative for many diseases. Traditionally, leukocytes are quantified in fresh blood samples based on their size and granularity or on specific proteins on their surface. We developed an innovative Epi-Blood-Count approach to quantify leukocytes in fresh as well as in frozen blood samples based on DNA methylation.

DNA methylation is a chemical modification of cytosine residues in the DNA molecule by which cells regulate their gene expression. Each cell type has a specific gene expression and thus specific methylation patterns in the DNA. For each major leukocyte type, we identified a single cytosine residue in the DNA whose methylation pattern discriminates it from all other leukocyte types. By measuring the DNA methylation level in blood at these cytosines (e.g. via pyrosequencing or digital droplet PCR) we can determine the number of leukocytes in any given sample. We have shown to perform relative (%) and absolute (cells/µl) cell counting for major leukocyte types, such as granulocytes, CD4+ T cells, CD8+ T cells, NK cells, B cells and monocytes (Frobel et al., Clin. Chemistry, 2018).

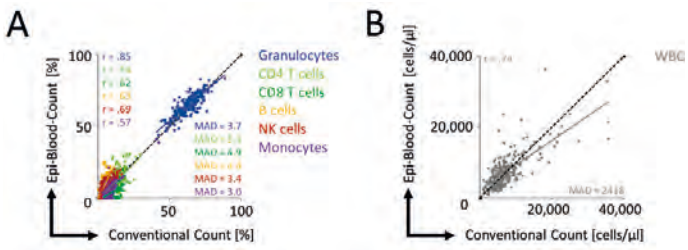

Fig. 8: Epi-Blood-Count for leukocyte quantification. (A) Epigenetic prediction for 6 blood cell types in comparison to conventional cell counts. (B) Epi-Blood-Counts for absolute cell numbers in comparison to conventional white blood cell (WBC) counts. Correlation coefficient r and mean absolute deviation (MAD) are given for each cell type.

By the end of 2019, we have collected and analyzed more than 900 blood samples from healthy donors and patients in collaboration with the Department of Hematology, Oncology, Hemostaseology and Stem Cell Transplantation and the Institute of Immunology, both at RWTH Aachen University Hospital. The correlation of relative Epi-Blood-Counts to conventional leukocyte counts is good as indicated by the coefficient of determination r and mean absolute deviation (MAD) (Fig. 8A). We can determine total leukocyte numbers by addition of a reference DNA molecule to each blood sample. The reference contains a human DNA sequence with an unmethylated cytosine residue whose counterpart in leukocytes is fully methylated. Consequently, the analysis of the DNA methylation level at this reference cytosine in blood (e.g. via pyrosequencing or digital droplet

PCR) provides the total leukocyte number for any given blood sample (Fig. 8B). In the future, we aim for further validation of the Epi-Blood-Count with pediatric and capillary blood samples and its application as *in vitro* diagnostic device.

Spatial Organization of Pluripotency Markers in Colonies and Aggregates of iPS cells

During development of tissues the stem cells progressively differentiate into multiple cell types. This process is tightly controlled by the preserved sequences and patterns of the differentiating tissues. The patterning is influenced by chemical gradients of morphogens and by mechanical stimuli. We are using iPS cells to model and study this phenomenon. We have shown that the shape of iPS cell colonies impact on the gradual expression of pluripotency factors (Abagnale et al., Stem Cell Reports, 2017).

The iPS cells are cultured on defined areas - using microcontact printing of adhesion proteins - and then the distribution of pluripotency factors (read-outs for pluripotency/differentiation pathways) is measured (Fig. 9). Also, 3D aggregates of iPS cells are used to study how they will be

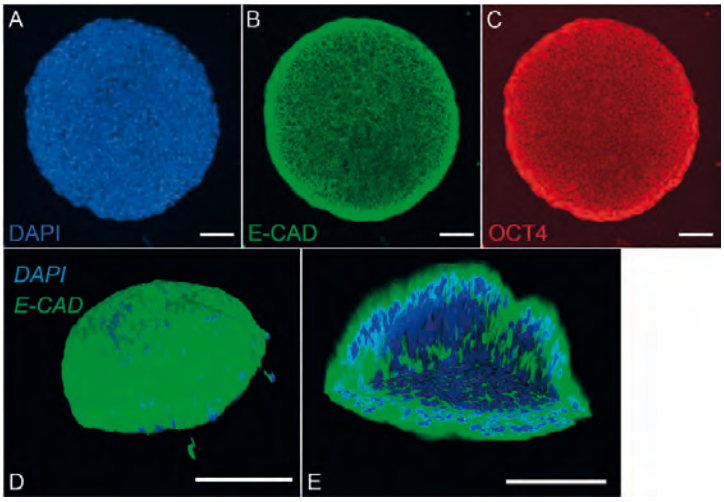

Fig. 9: (A-C) iPSC colony with circular shape showing high expression of pluripotency factors (OCT4/E-CAD) on rim region compared to its center. (D-E) 3D aggregate of iPSCs showing the same overexpression on the aggregate periphery.

patterned in 3D under similar conditions. The expression pattern of the pluripotency factors is closely related to the size of colony. Smaller colonies exhibited no patterning while the larger colonies showed constant width of the over-expression ring. We are currently evaluating the relationship between mechanical-related factor on the patterning process.

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- Donation by Vision4 Life Sciences
- StemCellFactory is co-funded by the European Union (European Regional Development Fund - Investing in your future) and the German Federal State North Rhine-Westphalia (NRW)

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Team

Lab retreat in Ghent, Belgium

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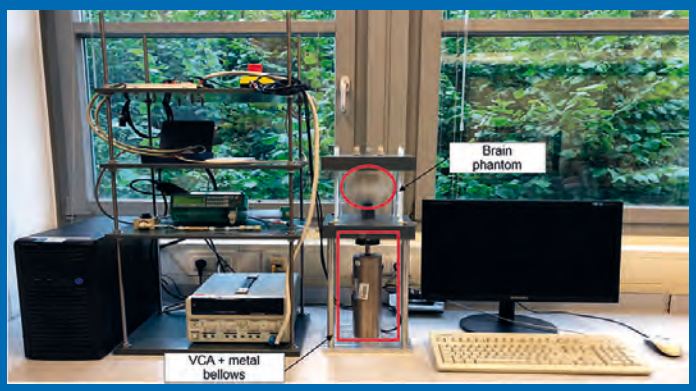
Medical Information Technology

Faculty of Electrical Engineering
and Information Technology

Smart Solutions for Advanced Healthcare



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Introduction

The Chair for Medical Information Technology is especially concerned with research problems in the **field of "Unobtrusive Measurement Technologies", "Personal Health Care",** and **"Automation and Control in Medicine".**
The topic *Personal Health Care* encompasses wearable medical devices, particularly diagnostic devices, designed for use at home. Current technological developments are in the fields of "Intelligent Textiles" and "Body Area Networks" (BAN), related basic research areas (e.g. signal processing and motion artifact rejection), and sensor fusion. Due to demographic trends, especially in developed nations, the laboratory also focuses on the needs of the elderly (e.g. enabling greater autonomy at home).
Automation and Control in Medicine is involved with the modeling of medical and physiological systems and the implementation of feedback controlled therapy techniques. Research topics include tools and methods for the modeling of disturbed physiological systems, sensor supported artificial respiration, active brain pressure regulation, and dialysis regulation and optimization.
Where necessary and sensible, sensors and measurement electronics are developed, for example, in the areas of non-contact sensing techniques (e.g. magnetic bioimpedance), bioimpedance spectroscopy and inductive plethysmography. Active research is currently conducted in biomechatronics.

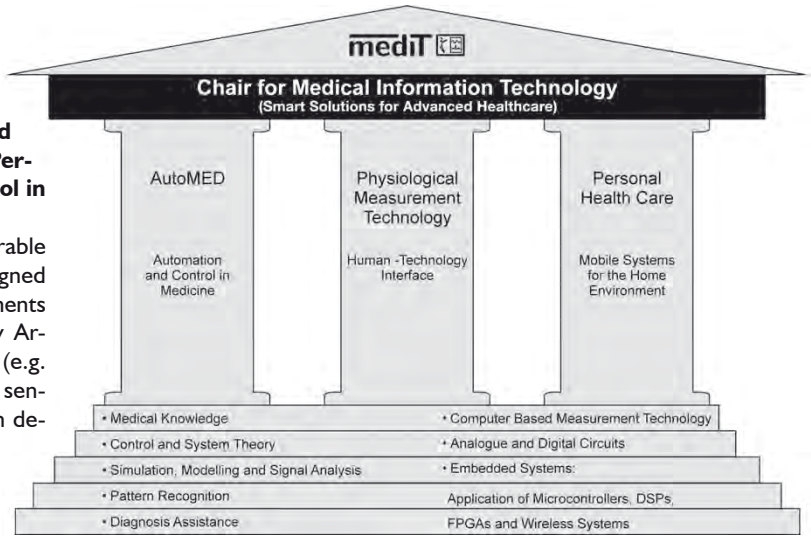

Fig. 1: *Research profile of MedIT.*

Ongoing Research – Selected Projects

Non-invasive Monitoring of the Peripheral Arteriovenous Oxygen Difference

Deficient oxygenation in tissues henceforth causes hypoxic cell damage, which is critical in vital organs such as heart and brain. Under normal physiological conditions, oxygen delivery and consumption relate to each other and are crucial for sustaining the fluctuating demands of cellular metabolism. To monitor regional oxygen distribution, the pulse oximeter can non-invasively be used and its working principle is to illuminate the skin with two specific wavelengths in order to distinguish absorbing property between oxygenated and deoxygenated hemoglobin, yielding peripheral oxygen saturation. Some microcirculatory dysfunctions such as diabetes mellitus and sepsis can alter the cohesion between oxygen supply and consumption. Thus, the determination of these factors is crucial for early diagnosis of tissue abnormality.
In blood circulation, blood flows to the organs via arteries and returns to the heart and lungs through veins. Therefore, oxygen consumption in the organs can be determined by the difference between its saturation in arteries and veins. In this project, we are developing a non-invasive monitoring system for the venous oxygen saturation in parallel with the arterial one. Our project partner (ELCAT GmbH, Munich), which specializes in cardiovascular diagnosis, is developing a hardware platform, while we design and implement the signal processing and algorithmic tasks. The novelty relies on the use of the venous muscle pump, which considers dorsal ankle extensions at a fixed frequency for generating easily identifiable venous blood volume variations, as shown in Figure 2. A reflective sensor placed on the foot detects these variations and obtains motion artifacts through accelerometers.

For signal processing, we implement different algorithms, which account for a variety of light-tissue interaction models in an anisotropic medium with multiple refraction layers. Simultaneously, the test of a wide range of filtering techniques is carried out for removing motion artifacts based on the data from the accelerometer. Besides, the analysis of the influential parameters such as the use of different wavelengths and sensor geometries entails another important aspect of the investigation. Monte Carlo simulations of the light interaction with a foot model will further validate our previous results.

Funded by: German Federal Ministry of Economic Affairs and Energy (BMWi)

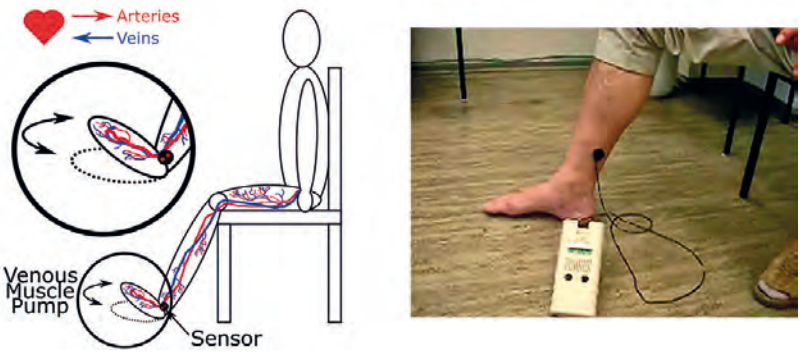

Fig. 2: *Monitoring concept of peripheral arteriovenous oxygen difference.*

Camera-based Early Detection of Sepsis in Newborns

In the neonatal intensive care unit (NICU), the occurrence of sepsis in newborns is one of the most common complications and poses a major threat to mortality and long-term morbidity due to the often-unspecific symptoms. Because of the rapid progression, the rate of mortality increases by 7.6 % every hour if antibiotic therapy is delayed. Therefore, sophisticated surveillance systems are crucial for an accurate early prediction when the condition is onset.
For monitoring purposes, various vital parameters are typically recorded using contact-based measurement techniques such as electrocardiography (ECG) and photoplethysmography (PPG). Some limitations such as the immature skin with the missing subcutis and the associated inefficient barrier to the environment of the neonate can

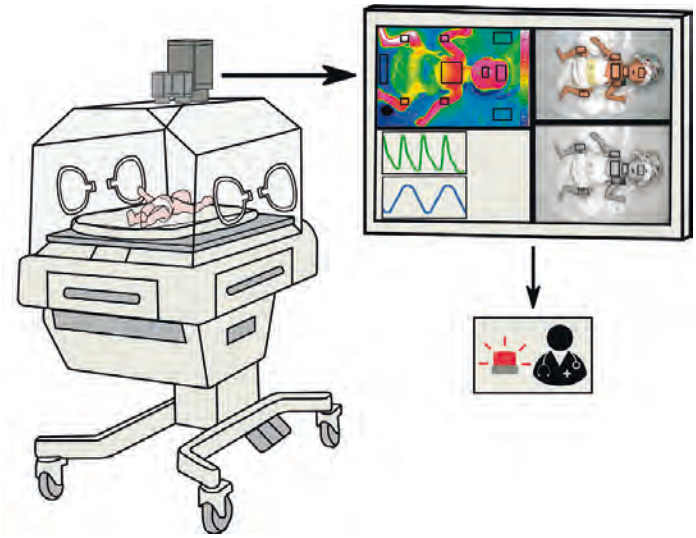

Fig. 3: *A camera-based surveillance system for blood poisoning detection in neonates.*

be the major issues in practice that the patient can be unintentionally injured or infected during the replacement of the adhesive electrodes. Therefore, the use of contactless measurement technologies should relieve the strain on the medical staff and the parents and enable infectious conditions to be continuously detected as early as possible.
The first signs of septic shock could be detected automatically using our proposed camera-based system based on the fusion of two unobtrusive measurement techniques, namely photoplethysmography imaging (PPGI) and infrared thermography. The PPGI enables the recording of heart rate and perfusion in the tissue and the quantification of microcirculation whilst infrared thermography presents the radiation of the patient's own heat. This allows local temperature distributions and central-peripheral gradients to be recorded and further analyzed. Furthermore, the system could enable the monitoring of respiration rates and physical activity. The early warning parameter should be derived and indicated directly at the incubator for triggering other therapeutic decisions in order to improve the survival rates of neonates in the future.

Funded by: German Research Foundation (DFG)

Breast Cancer Detection with the Aid of Electrical Impedance Tomography

Breast cancer is the most common life-threatening cancer affecting women around the world. Its survival rate can be significantly improved with early diagnosis and early treatment. There are different imaging modalities for breast cancer detection such as magnetic resonance imaging (MRI) screening, mammography with two x-ray beams at different angles, and sonography based on ultrasound-screening. The quality and performance of these techniques are still limited, for example, when dealing with dense breast tissue, facing the variability of personal experience and struggling with time-consuming issue. To overcome these disadvantages, a novel approach for the detection of breast cancer is developed in the project.

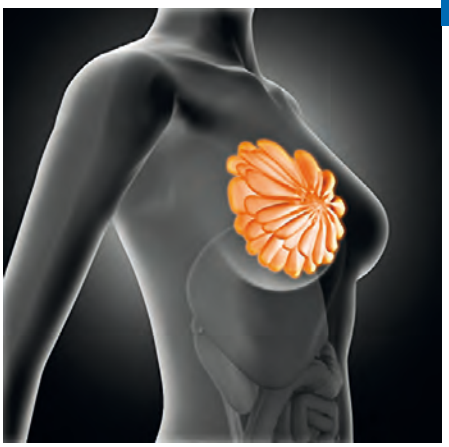

Fig. 4: *Schematic of a female breast.* [Source: Kjpargeter – Freepik.com]

The project aims to develop an imaging modality that allows for early detection of breast cancer and its therapy. Together with our project partners (Goethe University Frankfurt, Lisa Laser Products OHG, Dr. Sennewald Medizintechnik GmbH and Infeneon Technologies AG), we develop a system that combines imaging of breast cancer and minimally invasive therapy. For the therapy, a laser system will be developed by Lisa Laser Products OHG for the early treatment of breast cancer. The imaging will be realized with the help of electrical impedance tomography (EIT) and millimeter-wave-radar (mmW). Both EIT and mmW were individually considered in the past with mediocre success. Since EIT and mmW cover different parts of the electromagnetic spectrum, a combination of both techniques should be able to compensate for the drawbacks of each technology.
Although EIT has been well established in the two-dimensional domains, technology transfer to the three-dimensional domains is limited and becomes a challenging task. Hence, further research on optimal patterns of current injection and voltage measurement is required in order to reconstruct breast images effectively. Due to the lack of short-term impedance dynamics inside the breast, new reconstruction algorithms will be developed because time-difference EIT cannot be applied in a meaningful way. These challenges can be overcome by strong cooperation with all project partners.

Funded by: German Federal Ministry of Education and Research (BMBF)

Lower-Limb Exoskeleton for Gait Assistance with Compliant Actuators

A wearable lower-limb exoskeleton can be designed to assist the human gait by providing additional torques at the subject's joints using electric or other energy-based actuators, which can be applied for supporting age-related diseases and partial gait disorders, e.g., post-stroke hemiplegic patients. Therefore, it is crucial to achieving a safe interaction between a human and the machine. To address this challenge, we propose a tailored-made compliant actuator, composing of a mechanical-rotary variable impedance (MeRIA). The main idea behind this actuator is to transfer the generated motor torque via an adaptable elasticity to the human joint. The series elasticity is realized by two leaf springs and allows smooth interaction between the stiff motor and the compliant knee or hip joint of the patient. A unilateral exoskeleton is built using two compliant actuators (one at the hip joint and another at the knee joint, presented in Figure 5) to assist hemiplegic patients with additional torques and thus regain mobility and stability during walking. A power supply unit and a real-time controller are stationed on a walker. This walker is used not only for technical purposes such as measuring vital parameters i.e. electrocardiogram (ECG), but also for safety and stability reasons during rehabilitation training.

Fig. 5: *Realisation of the unilateral exoskeleton.*

Our goal is to achieve a patient-cooperative control that provides sufficient assistance torques for the patient as needed. Hence, a variety of sensors is used to detect the patient's states and movement intention, e.g., ground reaction force (GRF), angular positions, and surface electromyography (sEMG). These measurements are used to implement and validate different control strategies such as cascade, robust, and iterative learning approaches for position, impedance, and sensitivity control.

Funded by: German Research Foundation (DFG) and Stiftung Universitätsmedizin Aachen

Improving Hemolysis in Ventricular Assist Device Therapy using Physiological Control Strategies

Heart failure is one of the root causes of mortality in developed countries. Due to the imbalance between a restricted number of donor hearts and a huge number of patients, ventricular assist devices (VADs) are widely used as a bridge to transplantation or for destination therapy. In this project, we develop control strategies for such device, called Sputnik rotary blood pump (RBP), which was recently developed by our project partner from the "National Research University of Electronic Technology" in Moscow. It assists the heart in pumping blood from the left ventricle into the aorta.
Typically, RBPs operate either at a constant speed or at a constant flow, which may lead to risky situations i.e. overpumping or underpumping. To deal with changing demand in the cardiovascular system (CVS), advanced operating strategies using closed-loop physiological control are required to adapt blood flow. Its closed-loop configuration is provided in Figure 6.

Fig. 6: *Rotary blood pump (Sputnik RBP) used for a closed-loop physiological control.*

One of the main technical issues in building a VAD system is the minimization of hemolysis. Much work has been dedicated in the past to optimize the pump geometry in this respect. Within this research project, we want to investigate whether hemocompatibility can be improved by optimizing the dynamic control of the RBP. In order to achieve this, a model of hemolysis dependent on operating conditions has to be identified. Our hemolysis model will be based on the information from literature and the data from hemolysis experiments. Using this model, we will subsequently develop optimized physiological control strategies, which provide the required hemodynamics and minimize blood damage.
The optimized physiological control strategies will be evaluated using the operating principle of a preexisting hybrid mock circulatory loop to validate their performances in a wide range of dynamic load conditions. Different dynamic

load conditions include physiological as well as pathological conditions. For hemolysis assessment of our control strategies, the mock circulatory loop needs to be hemolysis optimized and porcine blood will be used.

Funded by: German Research Foundation (DFG)

Blood Glucose Control in the Intensive Care Unit

General patients in the intensive care unit (ICU) often face two main issues: stress hyperglycemia and high glycemic variability. Stress hyperglycemia can occur after an acute illness, surgery or disease. It is typically induced by a series of stress hormones, increasing insulin resistance. The detailed mechanisms are still unclear, and it is determined by extreme blood glucose (BG) level (> 140 mg/dl) whilst high glycemic variability is defined by the great swings of BG level throughout the day. Both stress hyperglycemia and high glycemic variability are associated with higher morbidity and mortality. To handle these issues, intensive insulin therapy is required to reduce the risk of hyperglycemia and simultaneously prevent excessive glycemic variability. Furthermore, it is crucial to prevent the life-threatening condition of hypoglycemia (BG level < 70 mg/dL). It is, therefore, a challenge to achieve these goals for life-saving.
A closed-loop system based on continuous BG measurement is proposed for insulin therapy by automatically injecting a proper amount of insulin at the right time. The system configuration is shown in Figure 7. The BG level is measured continuously in the venous blood. An expert system receives BG target range and patient data from a clinician. Within the expert system, a patient model incorporates the knowledge of glucose metabolism, the interaction between glucose and insulin, the pancreatic release of insulin, and preceding patient databases. Based on the dynamic input variables and the underlying patient model, a robust control technique is of interest for the development and evaluation of the overall system because its stable and robust performance is guaranteed for a large patient group.

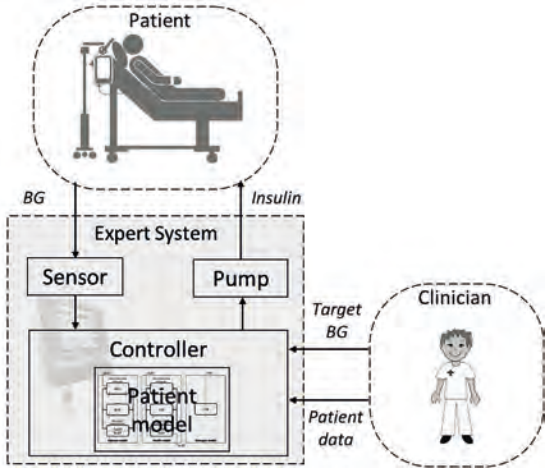

Fig. 7: Closed-loop control of blood glucose based on insulin therapy in the ICU.

Funded by: German Federal Ministry of Economic Affairs and Energy (BMWi)

Challenges of Unobtrusive ECG Monitoring

Capacitive electrocardiogram (cECG) electrodes can sense ECG signals through the clothing of a subject, by providing a capacitive coupling between the subject and analog instrumentation. cECG electrodes have been proposed and tested for a wide variety of applications by implementing the same principles of medical instrumentation in different scenarios. However, the suggested applications of cECG revolve around the out-of-hospital monitoring of vital parameters, where unobtrusiveness is aimed for at the expense of reduced signal quality, instead of becoming a tool for clinical diagnosis or an alternative for the gold standard ECG. The course of cECG is shaped by its inferiority to normal ECG in terms of signal quality, which can be attributed to several factors such as very high coupling impedance, triboelectric surface charges and high susceptibility to motion artifacts.
In cECG, the high impedance of the coupling between the human body and the analog instrumentation converts the existence of triboelectric surface charges into a dire problem by slowing down their discharge, thus, prolonging their influence. Moreover, even the smallest mismatches between the electrode impedances are reflected tremendously in the common-mode rejection of the analog instrumentation, as the impedance range of the electrodes becomes closer to the input impedance of the instrumentation. Aside from the electrode impedance mismatch, the variations in the coupling impedance were shown to cause motion artifacts.

***Fig. 9:** Multi-channel cECGs integrated in a car seat.*

These drawbacks of cECG lead to a low time-coverage in the signal availability, which is tried to overcome by monitoring with multi-channel cECGs to utilize signal fusion, as presented in Figure 8. Another way to make cECG a reliable tool is to understand all obstacles and solve the problems. Therefore, a significant amount of effort should be put into a better understanding of phenomena in cECG such as motion artifacts and triboelectricity.

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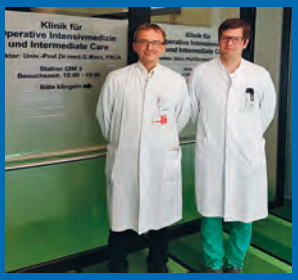
Prizes and Awards

- C. H. Antink received the Borchers-Plakette 2019, ProRWTH.
- L. Korn won 1st prize whilst S. Lyra and M. Paul won 2nd prize in the session of "Biomedical Engineering" at POSTER 2019, Prague.
- S. Leonhardt was giving guest lectures at the Massachusetts Institute of Technology (MIT).

People at MedIT



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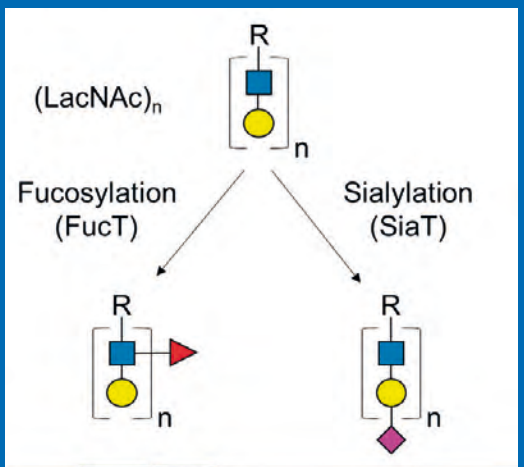

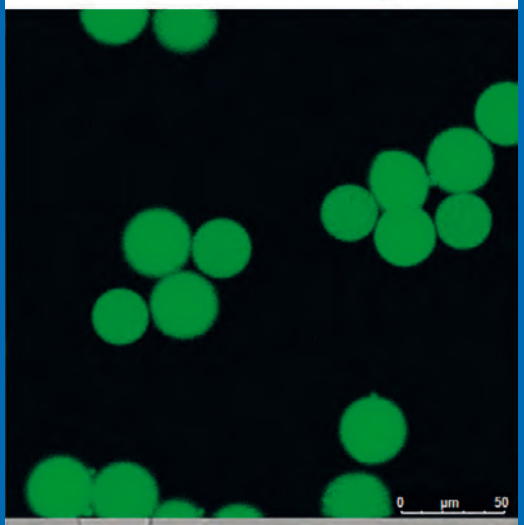

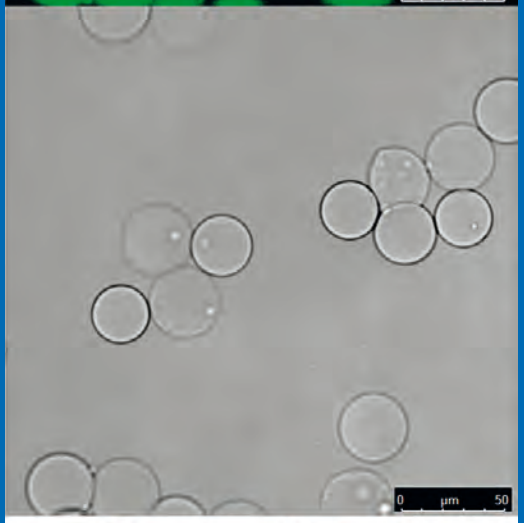

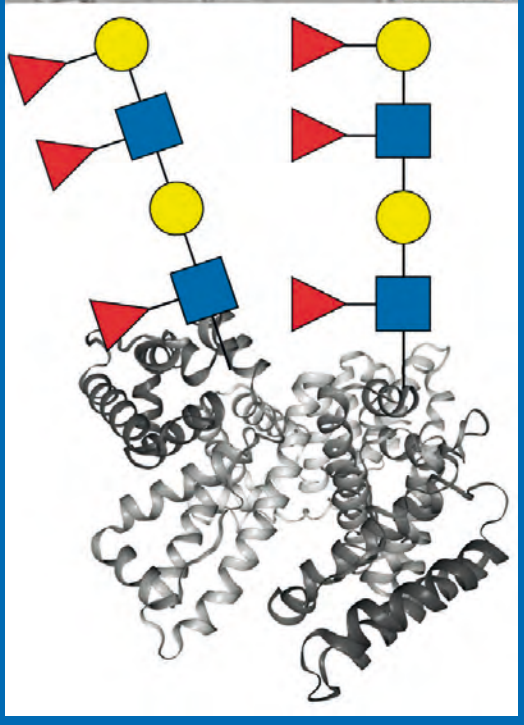

Introduction

Sugars (glycans) constitute the cell surface and the extracellular matrix (ECM) as parts of glycoconjugates such as glycoproteins, glycolipids, and proteoglycans. The complexity of glycans is a key factor for cell-cell and cell-ECM recognition, which is mediated by specific glycan-binding proteins, the lectins. Glycan structures are the "entry door" for pathogens and bacterial toxins. In disease-state, glycan structures are altered, triggering specific lectin interactions with subsequent cell responses. Furthermore, glycans of human milk are essential for infant nutrition and intestinal protection against pathogens. Sugars are also important for the bioactivity of natural products, such as anti-oxidants and are essential components of therapeutic and cosmetic products. With this background, sugar-based biomaterials are of special interest as diagnostic and therapeutic tools in biomedical research.
In 2019, we pursued our research studies for the synthesis and applications of glycoconjugates. We expanded our enzyme toolbox and developed novel enzyme cascades. High-throughput reaction analysis was key for fast enzyme reaction analysis. Multigram-scale synthesis of nucleotide sugar substrates for glycosyltransferases was accomplished, and automated enzymatic glycan synthesis in a microreactor was realized. Products are complex glycan structures, glyco- and biopolymers as well as neo-glycoproteins. Binding studies with human lectins and bacterial toxins revealed high-affinity glycoconjugates, e.g. glycan-based inhibitors for tumor-related galectins and glycopolymer toxin scavengers. This chapter summarizes the most recent results from our peer-reviewed publications in 2019.

Combinatorial Biocatalysis

a. The Golgi Glycan Factory (GGF)

The aim of our BMBF funded project "The Golgi Glycan Factory (GGF)" is the development and optimization of enzyme modules for the synthesis of nucleotide sugars and glycans. Nucleotide activated sugars are used by Leloir glycosyltransferases for the assembly of highly specific and defined oligosaccharides in the large-scale production. The main aspect of GGF is the assembly of enzyme modules in a one-pot or sequential mode to facilitate flexible glycan synthesis.

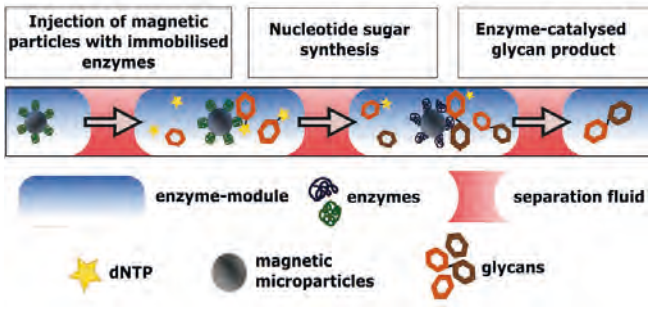

Fig. 1: Automated enzymatic glycan synthesis in a compartmented flow microreactor system.

With our cooperation partner, we realized an assembly line for glycans in an automated microreactor [1,2] (Fig. 1). Reaction compartments include enzyme-modules on magnetic beads and were assembled to synthesize a trisaccharide in 3.5 hours. Enlarging the production scale of oligosaccharides requires an adequate supply of costly nucleotide-sugars which can be produced by our repetitive batch mode technique, enabling us to produce those in multi-gram scales [2] (Fig. 2).

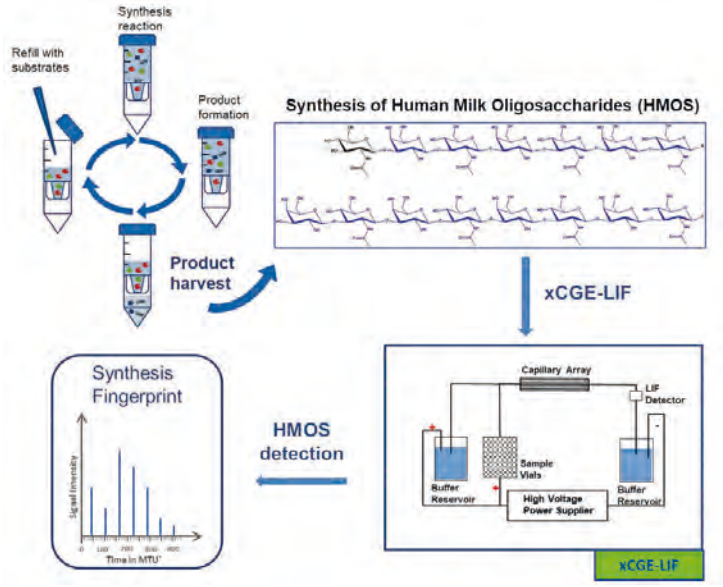

Fig. 2: Combination of repetitive batch-mode synthesis of nucleotide sugars with HMOS synthesis to create an analytical HMOS fingerprint database.

With the nucleotide-sugar production at hand, we focused on the synthesis of human milk oligosaccharides (HMOS) to develop new tools for the high-throughput analysis of human milk samples by our cooperation partner [3,4]. Especially large oligosaccharides of human milk were a long-time concern for the analytics. We produced stable isotope-labeled HMOS and established a system for the reliable quantification of those structures and to introduce an HMOS database for future analytical fingerprint analysis [5]. This provides a new tool for the deeper characterization of complex oligosaccharide mixtures for the whole variety of biofluids.

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Selected References

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[5] Fischöder, T., Cajic, S., Grote, V., Heinzler, R., Reichl, U., Franzreb, M., Rapp, E., and Elling, L. (2019) Enzymatic Cascades for Tailored $^{13}C_6$ and ^{15}N Enriched Human Milk Oligosaccharides, *Molecules 24*, 3482, doi:10.3390/molecules24193482.

Financial Support

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b. Enzymatic Synthesis of High-Molecular Weight Hyaluronic Acid

Hyaluronic acid (HA) is a nonbranched glycopolymer composed of glucuronic acid - *N*-acetylglucosamine disaccharide units. Due to the anionic character, HA is able to bind huge amounts of water, resulting in a viscoelastic gel. In humans, HA naturally occurs in the skin, joint fluid, and eye vitreous body. Because of its non-immunogenic and rheologic features, HA is used in many medical and cosmetic applications (Fig. 3). However, current industrial processes like extraction from rooster combs or bacterial fermentation bear difficulties to produce high-molecular-weight (HMW) HA with low dispersity, which makes these products less predictable for the use in the human body. To address this issue, we established an enzymatic strategy [1] (Fig. 4).

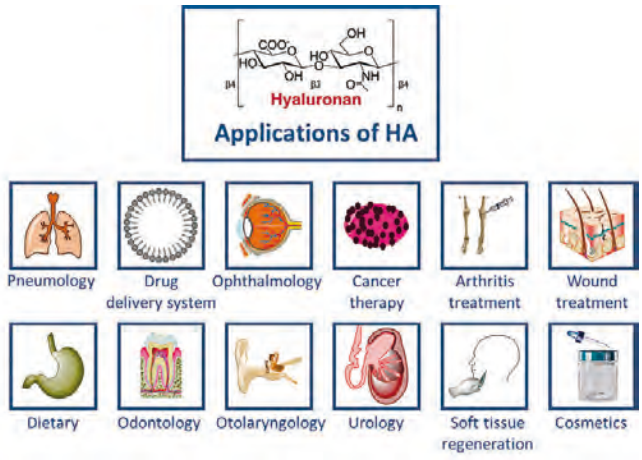

Fig. 3: Medical and cosmetic application of HA and its derivates. Modified from Fallcara et al. [3].

The one-pot synthesis consists of six enzymes from different organisms. Each enzyme has its own optima concerning temperature, cofactor, substrate, and pH value.
However, we optimized system parameters to tailor the size of HA with low dispersity and a high HA concentration. We previously discovered, that the ratio of UDP-GlcA/UDP-GlcNAc has a great influence on the activity of the hyaluronan synthase PmHAS [2].

We showed, that the synthesis of the UDP-sugars is directed by magnesium and pH value leading to distinct UDP-sugar ratios [1] and control of the HA molecular weight. We rationalize that UDP-sugar ratios vary PmHAS activity affecting *de novo* synthesis of HA chains. Fewer HA chains created at the beginning of the reaction lead in total to the production of longer HA chains. The highest HMW (1.54 MDa) was reached with 25 mM Mg^{2+} and pH 8, with a dispersity of 1.02 and a concentration of 1.4 g/L.

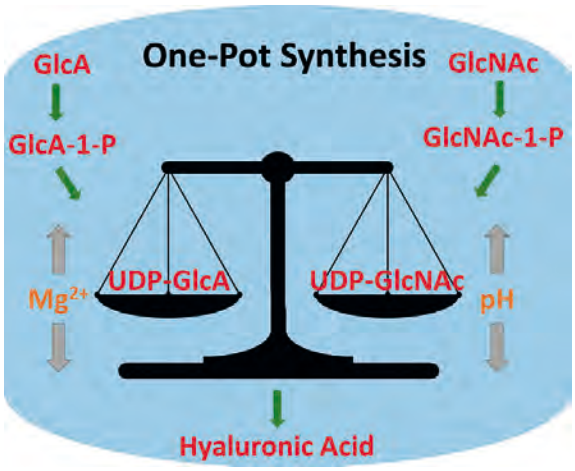

Fig. 4: One-pot synthesis of hyaluronic acid controlled by the key factors magnesium and pH value.

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Selected References

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Financial Support

Funding by the KMU-Innovative project 031B0104B from the German Federal Ministry of Education and Research (BMBF).

c. Hyperthermophilic Glycosidase for Glycoconjugate Synthesis (GlycoHype)

Thermophilic organisms love it warm: Their temperature optimum lies over 45°C. Hyperthermophilic organisms like it even hotter: Their temperature optimum is over 80°C! Hyperthermophilic organisms are mainly archaea and - more uncommon - eubacteria. They live for example in deep-sea hydrothermal vents or in hot springs. They are not only interesting for science because of the extreme biotope, but also their thermophilic enzymes are in focus for biotechnological/industrial applications. There are several advantages of hyperthermophilic enzymes: in addition to their catalytical optimum at high temperatures, they are often more stable and more tolerant towards acids and organic solvents. Therefore, they are attractive tools for reactions involving elevated temperatures, low water activity and substrates with poor water solubility. Furthermore, industrially important recombinant hyperthermophilic proteins are easy to purify by simple heating at high temperatures where other enzymes are denatured. Typical representatives are proteases or lipases in laundry detergents or thermostable DNA-polymerase in the polymerase chain reaction (PCR), the widely used method for DNA amplification.
We used a recombinant hyperthermophilic β-glycosidase from the organism *Pyrococcus woesei* (PwGly) for the synthesis of glycoconjugates at 85°C. The enzyme is able to perform the transglycosylation reaction meaning the transfer of a sugar unit from a disaccharide towards a hydroxyl group of an acceptor - in contrast to the normal hydrolysis reaction where the sugar is "transferred" to a hydroxyl group of water. Different substrates were tested as donor and acceptor substrates revealing a broad substrate spectrum of PwGly for diverse applications (Fig. 5).

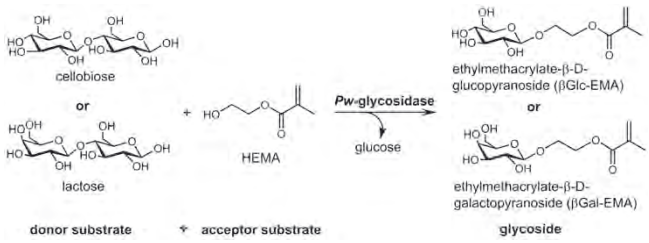

Fig. 5: Substrate spectrum of β-glycosidase from Pyrococcus woesei.

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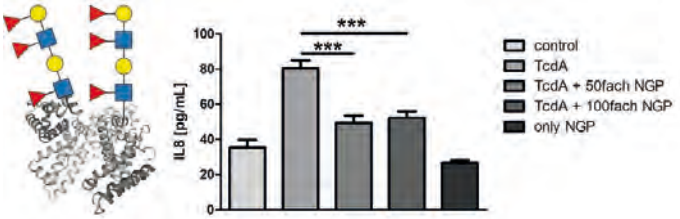

Fig. 6: Scavenging of TcdA by Le^y-Le^x-BSA (left) and the protective effect on human cells, determined via interleukin 8 (IL8) concentration (right). Controls (C) were compared to samples with TcdA and a 50x and 100x excess of neo-glycoprotein.

Financial Support

DFG International Research Training Group 1628, SeleCa (Selectivity in Chemo- and Biocatalysis), Bioeconomy Science Center (BioSc) seed fund project GlycoHype, supported by the Ministry of Innovation, Science and Research within the framework of the NRW Strategy Project BioSC.

The Glyco-BioInterface

a. Scavenging of Bacterial Toxins

Bacterial infections are interlinked with permanently increasing costs in our health care system. *Clostridium difficile* and *Vibrio cholerae* are two representatives that cause severe intestinal diseases. Those bacteria secrete toxins that damage and destroy the epithelial layer of the intestine of infected patients. Both toxins are known to bind to cell-surface glycans and induce signal transduction chains that lead to cell death. We developed different methods to scavenge the toxins and protect human cells. One ap-

proach is the production of neo-glycoproteins for multivalent glycan presentation [1] and proper binding of the glycans to the multiple carbohydrate recognition domains of the toxins. Screening a ligand library with the TcdA receptor domain, we found Le^y-Le^x to be a potent binder for TcdA. Twelve Le^y-Le^x epitopes were attached to one molecule bovine serum albumin (BSA) and applied in cell assays with TcdA, exhibiting a protective effect on the cells (decreased cytokine production) (Fig. 6). In the case of the cholera toxin (CT), a potent ligand – GM1a – is already known as a potent ligand and was applied in a second approach [2]. It was coupled to microgels (starPEG polymer networks) via reactive epoxy-groups and tested with the toxin in different assays. Fluorescently labeled CT (subunit B) binds specifically to GM1α-functionalized microgels (Fig. 7 A, B), while the complete toxin is scavenged from cell cultures via the microgels (Fig. 7 C), protecting the human cells. Non-functionalized microgels do not bind the toxin. We are now able to combine both approaches to reach the optimal scavenging efficacy of neo-glycoproteins and microgels and expand the systems to other bacterial toxins.

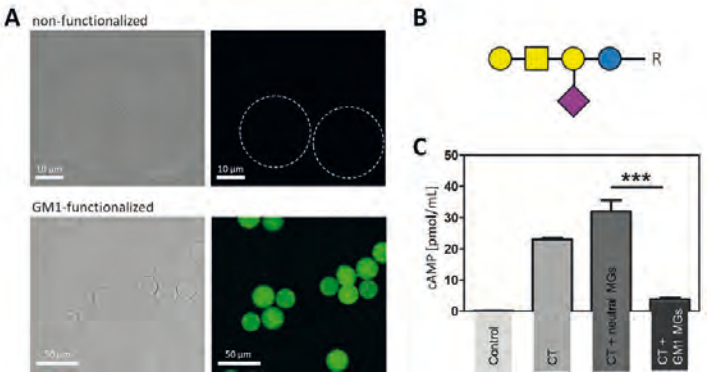

Fig. 7: Scavenging of CT by GM1a microgels (MGs). A) Specific binding of fluorescent CT subunit B to GM1a-functionalized microgels; B) GM1a; C) Protective effect of GM1a-functionalized microgels on human cells determined by cAMP concentration.

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Financial Support

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b. Inhibitors for the Tumor-related Lectin Galectin-3

Galectins are carbohydrate-binding proteins that specifically bind β-galactosyl residues [1]. They are structurally divided into three families. *In vivo*, galectins are involved in cell-cell or cell-matrix interactions and in cell-signaling processes (Fig. 8).

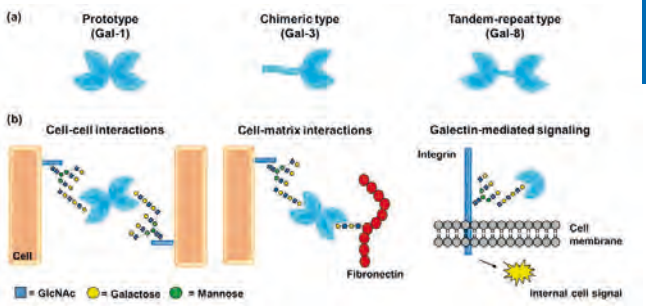

Fig. 8: Structural diversity of galectins (a) and cellular functions of galectins (b).

Galectin-3 (Gal-3) is a well-studied lectin that is of special interest due to its cancer-related functions. Interfering with the Gal-3 function by glycoconjugates is a promising strategy for cancer therapy. Using chemo-enzymatic enzyme cascades enables the tailor-made production of glycan ligands for Gal-3 like (poly)-*N*-acetyllactosamine type 2 (LacNAc).
By further enzymatic processing, such as sialylation or fucosylation, a high degree of structural diversity is reached (Fig. 9). In nature, high-affinity binding to glycan epitopes of the cell surface is achieved by multivalent glycan presentation. Thus, mimicking the natural conditions has become an established method to capture galectins. Various multivalent glycoconjugates based on chemical scaffolds were synthesized such as organic carriers. However, using chemical scaffolds is limited due to dense sugar packing that leads to low binding efficiencies. In biomedical applications, the focus is on applying glycan-decorated components from natural sources such as citrus pectin.
These biocompatible multivalent polysaccharides still require improvement due to non-specific galectin binding. Neo-glycoproteins are glycan tailored glycoconjugates. Hereby, serum albumin serves as a scaffold for the multivalent presentation of glycans. Our cooperation partner Laura Hartmann and co-workers recently reported the design of lactose-functionalized glyco-macromolecules

that were processed to glyco-functionalized liposomes in order to create a multiple multivalency glycostructure [2] (Fig. 9). We demonstrate inhibition of Gal-3 on different levels of multivalency and spacing. Gal-3 binding depended on the multivalency with inhibition constants in the nanomolar-range. In summary, galectin-binding glycoconjugates are efficient tools in biotechnology and in biomedical applications to gain insights into complex lectin-carbohydrate interactions.

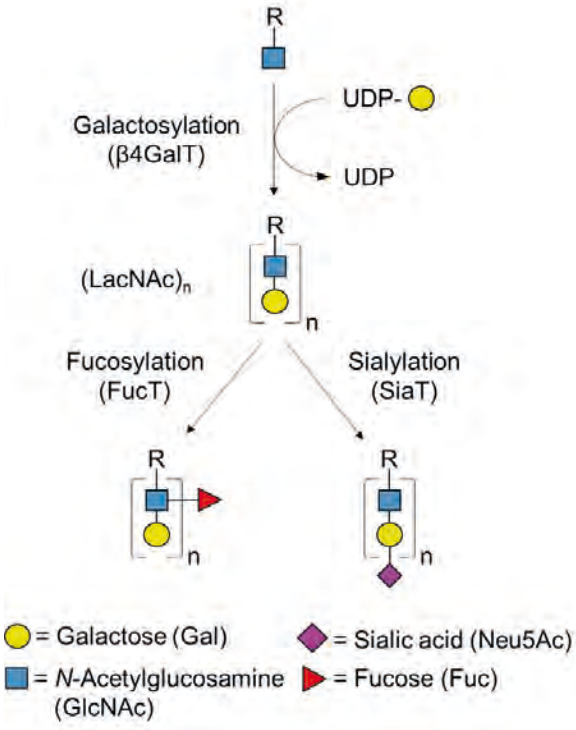

Fig. 9: Chemo-enzymatic synthesis of Gal-3 binding epitopes.

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Introduction

The mission of the Chair of Medical Engineering (mediTEC) of the RWTH Aachen University is to provide an active link between interdisciplinary basic sciences and application-oriented engineering research and development of innovative solutions for a better health care. Focus areas of our research are:

- Ultrasound & Shockwaves
- Biomechanical Modelling & Simulation
- Image & Model Guided Surgery
- Mechatronics & Robotics
- Integration, Usability & Risk Engineering

Apart from international publications and a practical transfer and implementation of scientific findings, the education of our students from different disciplines and specialties is a major objective. In addition to basic research grants, industrial cooperations represent an important complementary application-oriented pillar of our work for the transfer of our research and developments into clinical applications.
Based on the results of our research activities and technical developments of the last 10 years, we have been able to establish recognized expertise and a network of international partners from clinics, research and industry. Substantial industrial cooperation agreements have been contracted in each of our research focus areas. Furthermore, concerted actions such as the activities with our partners in the framework of the OR.NET initiative (www.ornet.org) resulted in a series of projects assuring the sustainability of our work on interoperability, usability and risk engineering of modular integrated medical work systems. New projects towards cooperative surgical robotics or on process automation for reprocessing of surgical instruments respectively as well as successful demonstrators of our approach towards cooperative emergency patient transport systems are further examples of our activities presented in this overview.

Selected Projects

In-vitro test bench for ESWL

A common practice to evaluate the efficiency of extracorporeal shock wave lithotripsy (ESWL) is to position a phantom stone in the focal area of the applied shock waves within a water tank. Thereby many factors are neglected, especially the impact of the surrounding tissue. Thus, we investigated the influence of different in-vitro setups on sound fields and stone comminution in order to evaluate transferability into clinical application. A kidney phantom, made of gel-wax and paraffin, with similar acoustic properties to kidney tissue was developed. It was analysed in a testing rig comprising a piezoelectric lithotripter and compared to a latex stone holder and porcine tissue. The influence on the sound field was investigated by pressure measurements, the amount and location of cavitation was determined and efficiency in stone comminution was analysed by fragmentation of gypsum stones.

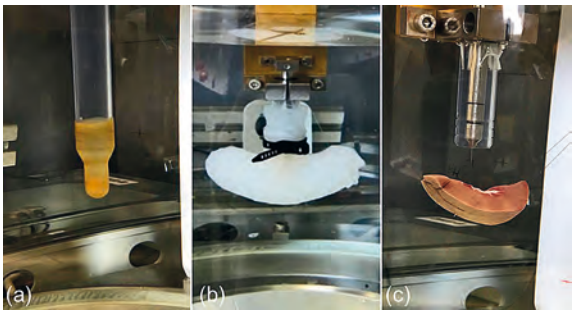

Fig. 1: Different in-vitro setups: latex holder (a), kidney phantom (b) and porcine kidney (c).

Sound field measurements behind phantom and tissue showed attenuation of the shock front as well as a reduced negative pressure in contrast to the latex holder. Cavitation amount and location differed for all setups. Stone fragmentation was less efficient in the kidney phantom than in the latex holder. Frequency-dependent material damping caused decreased peak pressures while negative pressure was absorbed by cavitation resulting in less efficient stone fragmentation behind tissue. Therefore, adapting in-vitro conditions closer to the in-vivo situation is necessary in order to analyse fracture mechanisms.

Image Processing for Diagnostic Ultrasound

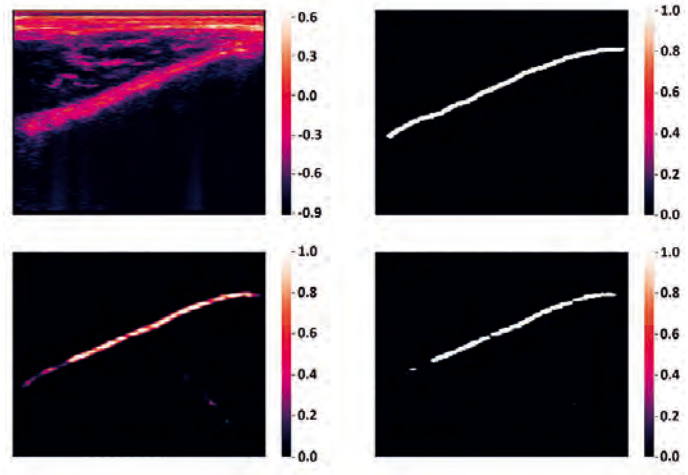

Fig. 2: Automatic segmentation of bone surface in an ultrasound image. Original image and ground truth on the left, and the raw confidence values as well as the thresholded prediction on the right.

Medical ultrasound is a widespread imaging modality utilized in a variety of different diagnostic tasks, ranging from echocardiography and mammography over prenatal screening to orthopedic applications like bone fracture detection. It offers real-time capabilities, which makes it especially useful for dynamic investigations. Yet, ultrasound requires skilled personal due to the low signal-to-noise ratio and other limitations. Therefore, we develop algorithms and tools based on image processing techniques that allow for an automatic processing of ultrasound images, easing the task of image interpretation for the sonographer. These tasks range from highlighting of relevant structures like bones to the full-au-

tomatic classification of injuries like a rupture of the anterior cruciate ligament. Furthermore, we develop a pipeline for full three-dimensional models of the knee and the wrist, reconstructed solely from ultrasound images, potentially replacing CT for preoperative planning in orthopedics. The reconstruction process is based on a-priori knowledge, statistical modelling as well as neural networks.

Preoperative Planning in Total Hip Arthroplasty

Preoperative planning is a mandatory step in total hip arthroplasty (THA). Usually, only the restauration of the osseous morphology derived from imaging data is considered in the planning process to determine the type, size and alignment of the implant components. However, other criteria such as the range of motion and implant loading are described in literature to reduce risk of implant failure due to edge-loading, accelerated wear, impingement and dislocation. We developed a preoperative planning tool incorporating multiple important criteria in a patient-specific target zone for both implant components. This includes individual postoperative functional parameters, such as the pelvic tilt, the range of motion or the resultant hip joint force. Our focus is on cost- and time-efficient methods that can be integrated into the common clinical routine.

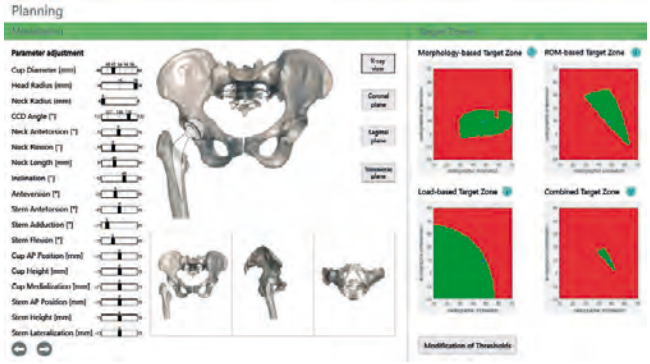

Fig. 3: Morpho-functional multiparameter optimization for preoperative planning of THA

Morpho-functional Analysis of the Knee

Total knee arthroplasty aims to restore function and to reduce pain. Despite decades of experience with this procedure, postoperative function is still limited and patient satisfaction is low in comparison to total hip arthroplasty. In order to address the described issues, implant design optimization is of major concern. Efforts are taken to better replicate the morphology of the native knee and thereby to better restore patient-specific kinematics and enable adequate functionality. In order to evaluate the population's knee morphology, we perform geometric parameter analysis on 3-dimensional surface data of the native knee's articulating surfaces. In addition, we perform statistical analysis to derive information on the main sources of shape variation. As an example, principal component analysis were conducted on the medial and lateral femoral J-Curve of 90 healthy knee joints (Figure 4). Furthermore, we compare the native knee's morphology and shape variation with those of modern implant designs. The results of the described analyses are relevant both for a better understanding of native knee morphology and kinematics as well as for implant design optimization.

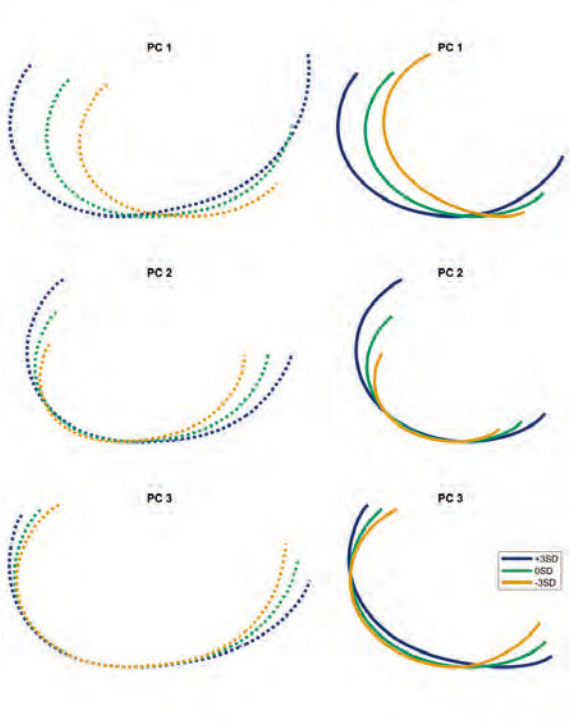

Fig. 4: Principal component analysis of the native femoral J-Curve based on surface geometry data of 90 healthy knees: Principal components 1-3 of (left) the lateral and (right) the medial femoral J-Curve.

Patient-Specific Wrist Implants

The wrist is one of the most complex joint systems of the musculoskeletal apparatus. It is prone to rheumatoid arthritis and is vulnerable to injuries due to its multi-layered ligament system. Due to the short lifetime, wrist implants are not a very common treatment option so far. Although wrist arthrodesis is substantially limiting the range of motion of the wrist, it is still the "gold standard" procedure to treat severe wrist joint degeneration. In this project, the current wrist implant designs are critically revisited and new patient-specific implant and spacer concepts are evaluated, taking the individual morphology and functional aspects into account. Furthermore, the use of additive manufacturing technologies for the production of the patient-specific implants is investigated.

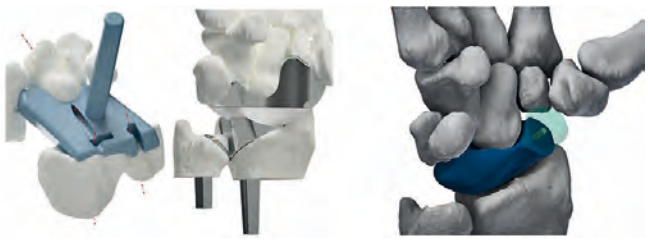

Fig. 5: A patient-specific instrumentation and wrist implant (left) and a patient-specific spacer (right)

Modular Design of Surgical Robots

There is a large variety of design approaches for surgical robotics. Robotic systems differ in e.g. functionality, size, kinematics and the degree of autonomy. An analysis of risks, requirements and context of use provides the basis for the definition of a generic reference structure of functions that can be modularized into universal and application-specific functions. Furthermore, systematic system design and risk management can be supported by a context specific catalogue of measures considering different design principles, rules or recommendations for further actions including usability evaluations and risk assessments. Module drivers, such as cost-efficiency, improved usability or simplified disassembly and reprocessing, are defined to optimize case-specific modularization.

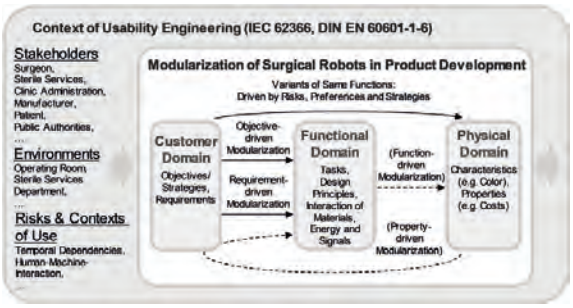

Fig. 6: Framework for integrated risk and usability engineering for modular surgical robotic system design

Cooperative Surgical Robotics

Cooperation is the natural human ability to work together in teams to reach a common goal, utilizing each team member's individual skills, knowledge, and judgement to generate synergistic effects. Cooperation, thereby, entails coordination and synchronization of individual actions and therefore requires communication and arbitration between team members. Especially within surgical teams, teamwork is of importance, as deficiencies are directly linked to adverse events.

While robots can improve surgical outcome with accurate execution of surgical plans, safe operation in highly unstructured environments is difficult due to limited perception and cognition. Cooperative surgical robotics combine the strengths of human and machine to collaborate successfully and improve the clinical outcome. In practice, different system implementations are developed which range from handheld robotic systems over collaborative hands-on robots to remote controlled master-slave systems. The latter, on one hand, offer the widest spectrum of cooperative functionalities, however, on the other hand, the surgeon is physically decoupled from the situs. To further investigate the impact of different modes of assistance, a cooperative surgical telemanipulator system is being developed. Thereby, planning-independent (PI) modulations such as scaling of movements or forces can be provided. Furthermore, the surgeon can be assisted by different patient-specific planning-based (PSPB) modulations, like haptic guidance on the master side. Additionally, forces on the surgical tool can be fed back to the surgeon. However, caution has to be taken when combining guidance and sensor feedback. The latter two can partly or fully cancel each other out resulting in the surgeon either not being able to differentiate the origins of the force information or not receiving any force information at all. The cooperative surgical telemanipulator will be used to evaluate different modes of interaction depending on particular surgical use scenarios to evaluate their effects on system usability.

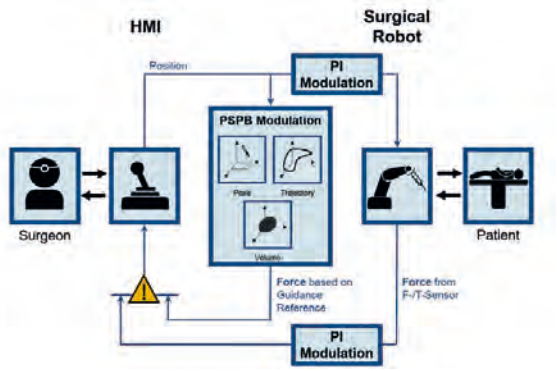

Fig. 7: Principle of Cooperative Bilateral Telemanipulation

Integrated Digital OR

Based on an initiative of the OR.NET association (www.or-net.org) founded in Aachen in 2016, the IEEE 11073-20701 SDC standard family has been approved at the beginning of 2019 by the international IEEE standards association. Thus, all three substandards of the SDC family (Service-Oriented Device Connectivity) are authorized by the IEEE and two substandards are already authorized by the international standardization organization (ISO).

Fig. 8: OR.NET demonstrator platform and integrated workstation on the DMEA exhibition 2019, Berlin

Under the direction of the OR.NET e.V. several research projects have been launched. The EFRE projects ZiMT (2016-2019) and PriMed (2019-2022) aim to develop, evaluate and synchronize basic concepts with safe and usable Human-Machine-Interfaces for surgical and anesthetic workstations as well as workstations for the OR management and the OR nursery. The projects ZiMT and PriMed have been represented at the DMEA 2019 and the Medica 2019 exhibitions at the NRW booth. Within the BMBF project MoVE different methods and testing procedures (conformity and interoperability tests), which support the approval and certification process (and therefore especially the risk management) of networked medical devices using

IEEE 11073 SDC, have been developed. For this, a simulation platform including test suite, test scenarios and device simulators has been developed, in order to provide future methods and tools for manufacturers, clinical operators and independent test institutions.
At mediTEC a central surgical workstation demonstrator with multimodal user interfaces has been developed. Numerous devices have been integrated (e.g. OR light, 3D X-ray C-arm, OR table, high-frequency cutting devices, endoscopic devices, ultrasound-cutting device, milling device, shaver, universal footswitch and hight-adjustable footboard).

Integrated Digital CSSD

Reprocessing of surgical instruments includes cleaning and sterilisation in the Central Sterile Services Department (CSSD) before they can be redeployed. Deficiencies in the process may be critical for the safety of the patient. OR personnel reports up to 30% of incorrectly assembled instrument-sets from the CSSD, leading to prolonged or postponed operations. In addition, more and more complex surgical systems, e.g. for robotic endoscopic surgery, demand high precision and focus from the CSSD staff. Reduction of associated workloads and infection risks are further motivations for the development of advanced concepts for process automation of integrated digital CSSDs.
Against this background, the integration of innovative concepts, based on multisensorfusion and cooperative robotics into the CSSD, are major objectives of the BMBF-project SteriROB. The goal is to standardize process steps and to decrease the workload of the employees. Multicenter field studies with in-depth work-flow and context analysis in the CSSD in cooperation with different clinics and major instrument manufacturers are conducted. On this basis use cases and concepts for integrated digital CSSDs will be developed and evaluated, including a cooperative robotic handling of surgical instruments and trays.

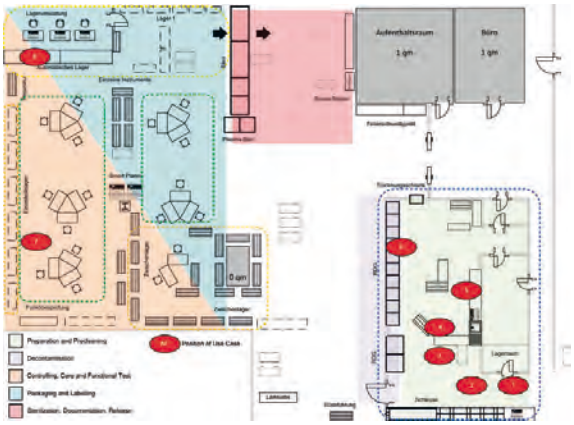

Fig. 9: Overview location of use cases in the CSSD Aachen.
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Patient Transport in Emergency Medical Services

Paramedics are not only responsible for execution of emergency medical services, but also for a safe and fast transport of the patient. Current active transport aids cannot offer universal assistance because of slow speeds and a big footprint, which leads to a limited range of use and a high rate of manual transports with critical loads on paramedics. A prototype for a novel transport aid was developed at mediTEC.
During patient transport paramedics need an intuitive control of the transport aid to be able to focus on the medical condition of the patient and the transport route. A specific self-balancing control strategy of the transport aid enables this, which allows for a synergistic cooperation with the paramedic without the need of user controls such as joysticks or buttons. However, the paramedic is not the only human in the loop and the patient has a significant influence on control, too. Therefore, the controller has to be optimized to be robust against uncooperative behavior of the patient, which occurs in 25 % of deployments as shown in our study. Based on these boundary conditions an advanced controller was designed and evaluated which simultaneously allows for a synergistic cooperation with the paramedic and robust characteristics against disturbances introduced by the patient. The evaluation with a control-prototype confirmed the good synergy and sufficient robustness for a stable and controlled behavior.
The combination with stair climbing kinematics provides a universal transport aid with the ability to efficiently overcome a wide range of obstacles. First results of initial usability studies show a reduced workload with healthy postures and acceptable loads in comparison to commercially available transport aids and emphasize the benefits of the new concept.

Fig. 10: Demonstration of the stair climbing prototype at the emergency medical services Düren district

To safely transport the patient in the ambulance vehicle, novel loading techniques as well as integration concepts are needed. Several concepts have been evaluated with respect to different vehicle categories used within the ambulance domain. Due to the integrated drives new compact loading solutions and innovative attachment options emerge. To evaluate the safety of the vehicle attachment a FEM analyses was conducted according to international standards.

Acknowledgements

We would like to thank all our clinical, technical and industrial partners for the fruitful cooperation*.
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- the German Federal Ministry of Education and Research (BMBF)
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- the German Research Foundation (DFG)

- German Academic Exchange Service (DAAD)
- the European Union, the European Regional Development Fund (EFRE), the Ministry of Innovation, Science, Research and Technology and the Ministry of Economic Affairs North-Rhine-Westphalia

* **Note:** In this report we can only provide a short overview of selected activities. For further information on the related projects, our cooperating partners, funding agencies and sponsors, please visit our website ***www.meditec.rwth-aachen.de*** or contact us directly.

Awards

- M. Asseln: CureMED Research and Travel Fellowship Laboratory for Orthopaedic Implant Design, NYU Langone Orthopedic Hospital, New York, USA
- M. Vossel et al., 2nd Best Technical Podium Award, 19th Annual Meeting of the International Society for Computer Assisted Orthopaedic Surgery - CAOS 2019, New York, USA7
- M. Asseln et.al.: 2nd Best Technical Poster Award, 19th Annual Meeting of the International Society for Computer Assisted Orthopaedic Surgery - CAOS 2019, New York, USA
- M. Fischer: Travel Award German Academic Exchange Service (DAAD) 25th Congress of the European Society of Biomechanics (ESB) in Vienna, Austria

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[3] M. Asseln, P. Meere, P. Walker & K. Radermacher: Relationship of the tibial tuberosity (TT) position, tibial tuberositytrochlear groove (TT-TG) distance, and internal and external rotation of the knee under weight-bearing conditions. In: P. Meere & F. Rodriguez Y Baena (ed.): CAOS 2019, pp. 26-30

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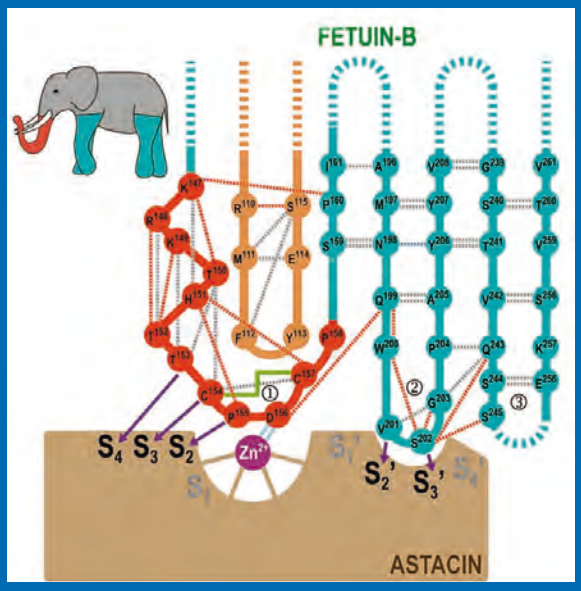
mediTEC-Team

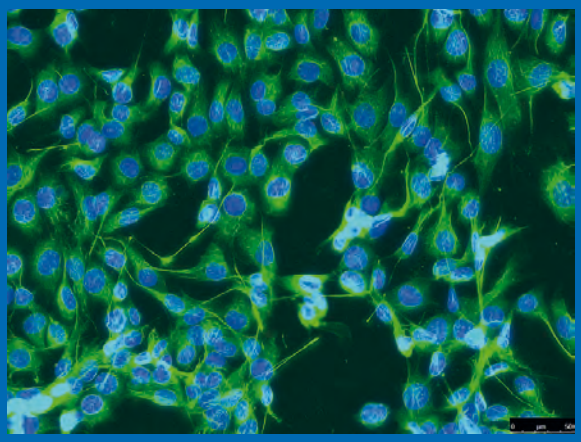
Biointerface Laboratory at Helmholtz-Institute for Biomedical Engineering

RWTH AACHEN UNIVERSITY

Faculty of Medicine

Cell-Material Interactions: Translating Basic Science Into Clinical Applications





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Cover Figures: Top, *mouse oocyte or "egg". **Center,** "raised-elephant-trunk" mechanism for astacin (light brown) inhibition by fetuin-B. The CPDCP amino acid motif in the linker region (red) of fetuin-B forms the raised trunk, while hairpin I and hairpin II of cystatin-like domain 2 (teal) form the front and back limbs of the elephant, respectively. **Bottom,** synthetic phenotype of vascular smooth muscle cells. Cytoskeleton myosin stained green and nuclei stained blue.*

Introduction

In the year 2019 we finally gained some insight into the "holy grail of protein science" of fetuin-B, a liver-derived blood protein involved in female fertility. As among the leading groups on fetuin researchers worldwide this constitutes a major collaborative achievement. With Xavier Gomis-Rüth's group from Barcelona in the lead, and Walter Stöcker's (Mainz) and Luca Jovine's groups (Stockholm) at our side, we co-published the three-dimensional structure of fetuin-B bound to its target proteinase, astacin. To a molecular biologist the three-dimensional structure and a mechanistic view to the detail of atom-atom interaction is as good as it gets in understanding how "nature works". Two post-Docs in the group, Carlo Schmitz and Julia Floehr, explain the structure of fetuin-B in the first topic of this research report. The second contribution by PhD students Andrea Büscher and Sina Köppert and Master student Aaron Morgan describe ongoing work on the role of protein-mineral complexes called calciprotein particles, an entity which we have first described in 2003. Aaron, an engineer by training adds a strong technical spin to this line of work by designing and fabricating 3D-printed microincubators hosting organs-on-a-chip. This kind of device enables complex interaction studies that go well beyond conventional single cell type culture, and complement our line of mouse experimentation. Finally, Sabine Neuss-Stein reports on progress made in her group towards cardiovascular and bone tissue engineering solutions. This highly interdisciplinary work improves biomaterials either by preventing adverse reactions, or by adding biological activity to direct cell behavior.

As a University-based researcher team we combine research and teaching to qualify young colleagues for their future jobs – on the job. It is therefore a great joy to see students successfully graduate at various levels of their academic careers. We congratulate Franziska Wahl for her BSc in Biology, Patrick Schmitz for his BSc in Chemistry, Hanna Malyaran for her MSc in Biomedical Engineering and Carlo Schmitz for his PhD in Natural Sciences. Sina Köppert received a 1000 $ Young Investigator Award at the International Conference on the Chemistry and Biology of Mineralized Tissues in Quebec, Canada. Congratulations to all of them!

Mouse Eggs and Elephant Trunks: the Structure of Mammalian Plasma Fetuin-B and its Inhibition Mechanism of Ovastacin

Carlo Schmitz

Julia Floehr

Mammalian fetuin-B is a circulating hepatic glycoprotein of the cystatin-superfamily of cysteine proteinase inhibitors. The cystatin superfamiliy is subgrouped into type I to III cystatins. Fetuin-B belongs to type III cystatins comprising glycosylated proteins with two or three cystatin-like repeats. Unlike the related single domain cystatins, fetuin-B is not a cysteine proteinase inhibitor. Instead, fetuin-B is a potent inhibitor of zinc-dependent metalloproteinases of the astacin family, which includes the oocyte-specific enzyme ovastacin in mammals. By inhibiting ovastacin activity in mouse eggs, fetuin-B prevents premature zona pellucida hardening and thus maintains female fertility.

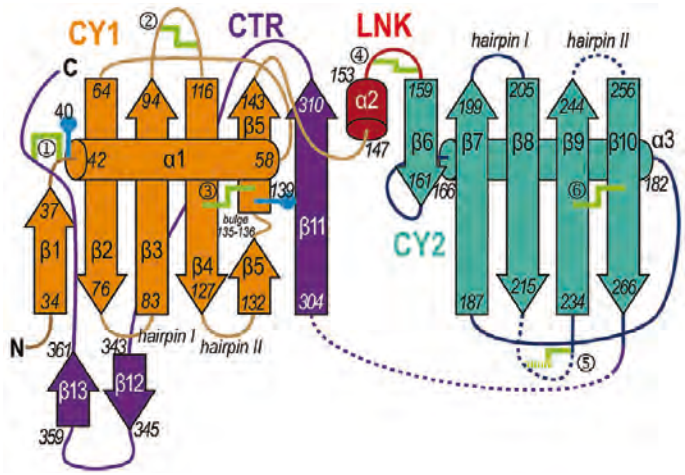

Fig. 1: Protein structure of fetuin-B.
Cartoon of murine fetuin-B. Fetuin-B consists of two cystatin-like domains (CY1, orange and CY2, teal) followed by the C-terminal region (CTR, purple). CY1 and CY2 are connected by an exposed linker (LNK, red), which mediates the inhibition of the proteinase astacin blocking access to the active center.

To understand this function at the molecular level, we solved the structure of mouse as well as human fetuin-B in complex with astacin that was used as a model for the closely related physiological target ovastacin [1,2] (Fig. 1). The 3D-structure revealed that fetuin-B consists of three domains, two N-terminal cystatin-like domains (CY1 andCY2, illustrated in orange and teal, respectively), followed by a proline-rich C-terminal region (CTR in purple). CY1 and CY2 adopt the typical cystatin folding and form the fundamental scaffold for the inhibitory potential of fetuin-B. We showed that the essential inhibitory segment is an exposed linker (LNK, depicted in red, Fig. 1) with a rigid, disulfide-linked CPDCP motif, located between CY1 and CY2. This linker region binds to the active site of astacin like a wedge into a cleft and thus blocks the catalytic activity of the proteinase. The mode of astacin inhibition by fetuin-B was termed 'raised-elephant-trunk' mechanism. The linker represents the raised trunk, while the hairpin structures I and II of CY2 form the front and the back limbs of the elephant, respectively (title figure, center).

To verify this structure-based mechanism we tested the inhibition of several fetuin-B mutants against astacin and ovastacin. It was striking that by a single point mutation at amino acid position 156 (D156A) the wildtype protein fetuin-B loses it inhibitory potential (Fig. 2). In comparison, the fetuin-B wildtype protein inhibited both astacin and ovastacin very potent with similar low K_i values (constants of inhibition) in the picomolar range. However, due to a point mutation affecting the CPDCP motif a distinct loss of inhibitory power, indicated by increased K_i values in the micromolar range, was observed. This result confirms the inhibitory mechanism that was proposed by solving the 3-D structure of the fetuin-B-astacin complex. The structural understanding of mouse and additional human fetuin-B shows that investigations using the mouse model can provide useful information for the study of female infertility.

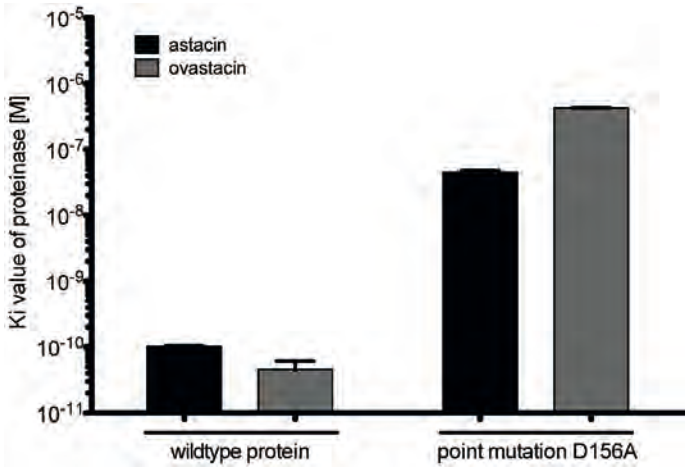

***Fig. 2:* In vitro *validation of the inhibitory mechanism*.** *Constants of inhibition (K_i values in M, logarithmic scale) of murine fetuin-B wildtype protein and fetuin-B point mutant D156A for both astacin (black) and ovastacin (gray), respectively.*

Calciprotein Particles CPP Regulate Calcification

Andrea Büscher

Sina Köppert

Aaron Morgan

Calcium and phosphate are indispensable for the cellular metabolism of all living beings. Both ions typically occur in millimolar concentrations in biological fluids. This causes a solubility and transport problem, because calcium phosphates precipitate easily from supersaturated solutions. Nature has found a way to handle water-insoluble minerals in circulation by forming colloids with proteins. This is highly reminiscent of cholesterol transport, which is mediated by lipoprotein particles, colloidal complexes of lipids and proteins. We proposed the concept of calciprotein particles (CPP) as carriers of otherwise insoluble calcium phosphates. These particles form with fetuin-A in supersaturated solutions. The particles start out as roundish, amorphous primary CPP. Primary CPP spontaneously convert into secondary CPP, which are larger, oblongate, more crystalline and less soluble. Thus, CPP mediate excess mineral transport and clearance from circulation.

We study CPP synthesis, metabolism and role in physiological mineralization and in pathological calcification. To this end we developed cell and tissue-based calcification assays. *In vitro*, vascular smooth muscle cell (vSMC)-based calcification assays showed calcification patterns deviating from *ex vivo* aortic ring cultures. vSMC were easily calcified by both calcium and phosphate, and CPP, while aortic rings only calcified with calcium and phosphate. The fact that CPP did not calcify aortic rings suggests that the endothelial cells (EC) formed a tight barrier against particles (Fig. 3).

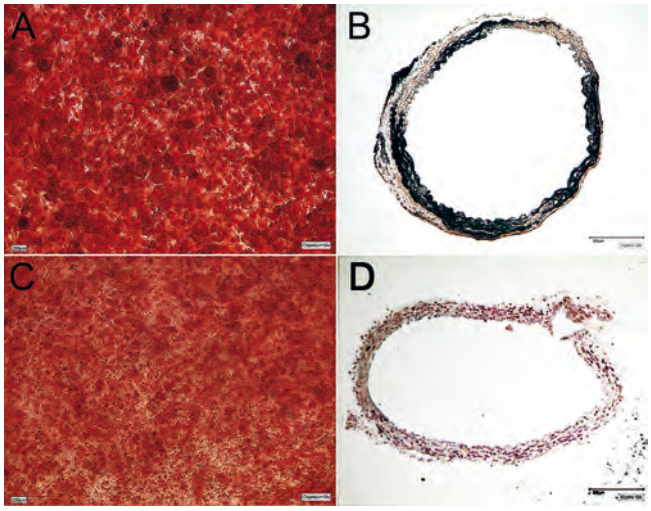

Fig. 3: Calcification assays of smooth muscle cells and aortic rings.
*Smooth muscle cells (**A, C**) and mouse aortic rings (**B, D**) were treated for four days with calcium and phosphate (final concentration 4.2 mM and 3.0 mM; **A, B**) or secondary calciprotein particles (sCPP; **C, D**) containing equal amounts of calcium and phosphate. Calcium was visualized by alizarin red (left) or van Kossa staining (right, both bars 200 µm). In SMC treated with calcium and phosphate or sCPP formation of calcium phosphate crystals on the cell-surface is observed. Mouse aortic rings treated with the same amount of calcium and phosphate showed media calcification in the calcium phosphate treated vessels, but not in the particle treated samples.*

We established a co-culture model of vSMC and EC using a microfluidic chip. The chip permits culture of both cell types in two opposing chambers separated by a porous membrane. The EC side is exposed to laminar flow of culture medium mimicking the blood stream (Fig. 4). The chip is produced in two parts, which are assembled with a cell-laden porous membrane in between. Computational fluid dynamics simulations show near laminar flow behavior with acceptable shear rates between 10-12 dyn/cm^2 in around 80% of the active test region (red square in Fig. 4C and Fig. 4G).

In summary, CPP stabilize and transport calcium phosphates. An intact endothelial layer prevents the transfer of CPP from the circulation into interstitial spaces. Endothelial damage, however, permits access of CPP to SMC and thus drives vascular media calcification.

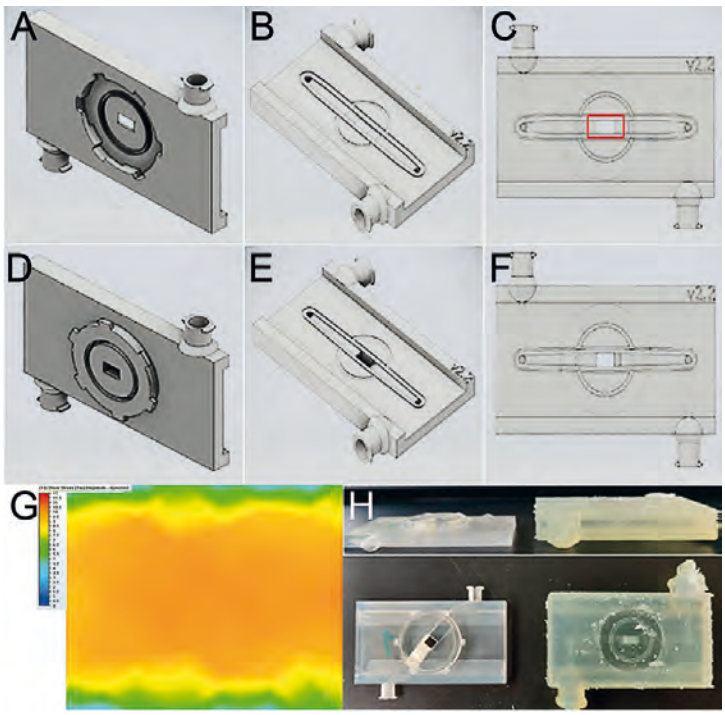

Fig. 4: 3D-printed microfluidic device for vessel-on-a-chip culture.
***(A)** Bottom view of endothelial cell side, **(B)**, top view of endothelial cell side, **(C)**, top view of endothelial cell side illustrating microfluidic flow, **(D)**, bottom view of smooth muscle cell side, **(E)**, top view of smooth muscle cell side, **(F)**, top view of smooth muscle cell side illustrating microfluidic flow **(G)**, computational fluid dynamics of active test region (area marked with red square in **(C)** at flow rate 10 ml/min. **(H)**, photographs of 3D-printed chip after (left) and before final cleaning (right).*

Stem Cells and Tissue Engineering

Sabine Neuß-Stein

In 2019, the group of Prof. Sabine Neuss-Stein on "Stem Cells and Tissue Engineering" further developed their research areas in bone and cardiovascular tissue engineering as well as in the biology of mesenchymal stem cells (MSC) and their use in tissue regeneration strategies. Over the last 15 years, an *in vivo* recruitment system was generated to guide endogenous MSC via a growth-factor loaded biomaterial towards a defect area and thus improve wound healing. We produced a tethered recom-

binant chemoattractant for MSC comprizing hepatocyte growth factor, HGF, which is readily released by protease activity present in wound fluid (Fig. 5).

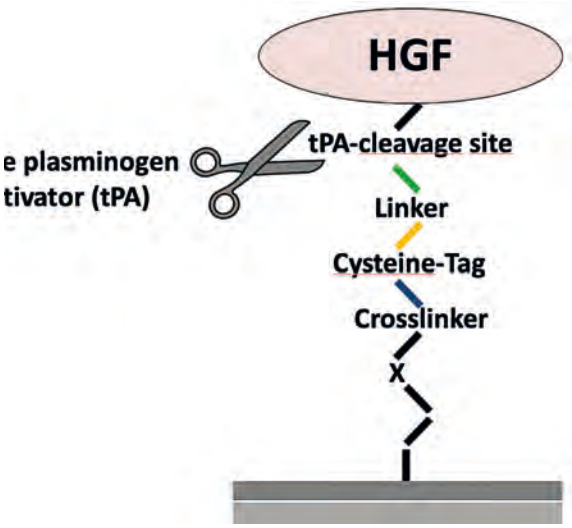

Fig. 5: Engineered hepatocyte growth factor with a cleavage site to be released from biomaterials in wound fluids.
We showed that modified HGF can be covalently bound to ceramic substrates and can be released by a specific serine protease. Released HGF is functionally active.

The project CeramActive with Prof. H. Fischer and Prof. M. Tingart (RWTH Aachen University Clinics) studies triggered release of HGF with future medical applications in mind.

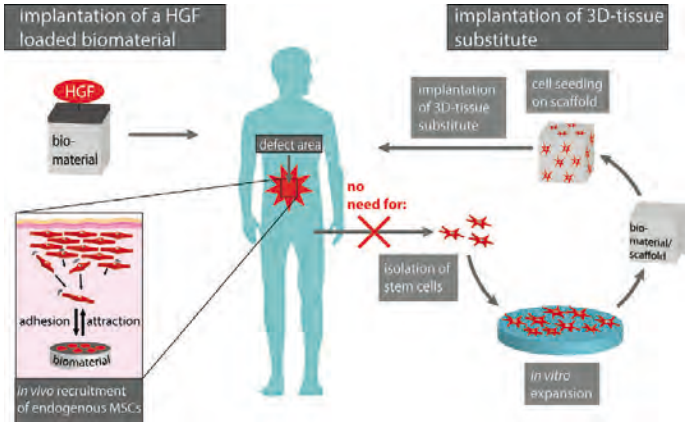

Fig. 6:* In vivo *recruitment system to guide endogenous MSC out of their niche towards a defect area for improved wound healing.

Regarding bone tissue engineering, we explored growth factor-loaded silk fibers[3] and graphene-based substrates as efficient supporting materials for the osteogenic differentiation of MSC. Fig. 7 shows scanning electron microscopy proof of osteoblastic differentiation of MSC. Alizarin red staining and transcriptome analyses together with Dr.-Ing. K. Schickle (Department of Ceramics and Refractory Materials, RWTH Aachen University) indicated more robust osteogenic induction and mineral formation of osteoblasts on graphene surfaces compared to plastic cell culture dishes.

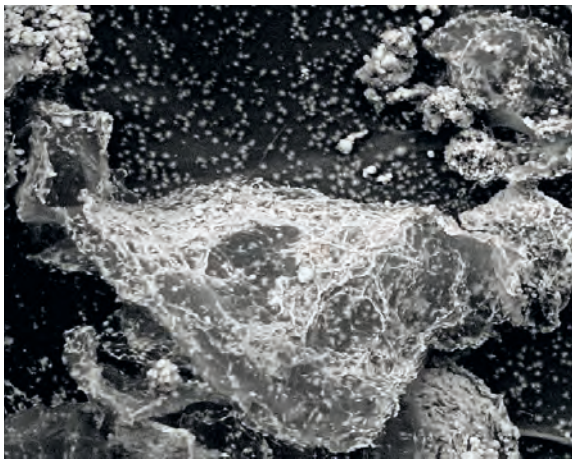

Fig. 7: MSC-derived osteoblasts on a graphene-based substrate.
Scanning electron microscopy after 21 days of incubation in osteogenic induction medium.

The group participates in the newly founded consortium "organ crosstalk" funded by "IZKF" the local Interdisciplinary Center for Clinical Research. The consortium will analyze the potential for alveolar bone regeneration of mesenchymal stem cells derived from the upper vs. lower jaws.

Regarding cardiovascular tissue engineering, we develop hemocompatible cardiovascular implants preventing restenosis and allowing for proper integration into the surrounding tissue as well endothelialization on the implant. Together with Prof. Andrij Pich (Institute of Textile and Macromolecular Chemistry, RWTH Aachen University) we evaluate fibrin-based hydrogels, which regulate cell differentiation. With Dr.-Ing. Karolina Schickle, we test ceramic nanoparticles for cardiovascular stent coating. A patent application was filed covering this work. Fig. 8 illustrates complex testing of hemocompatibility, hemolysis and thrombogenic activity under static and dynamic culture conditions [4].

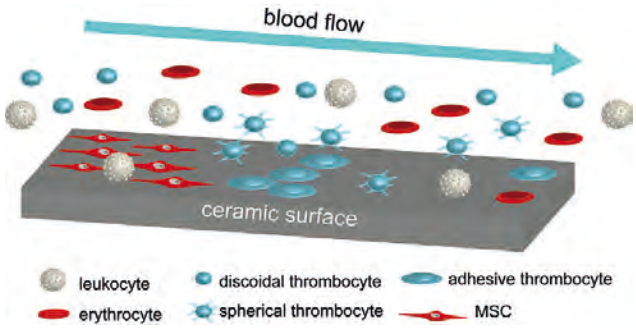

Fig. 8: Schematic representation of distribution and cell-activation during blood flow over an implant surface.

Fig. 9: UniStemDay 2019

As part of our public outreach we organized the first UniStemDay at RWTH Aachen. This meeting took place on 15th of March all over Europe. Scientists invited high school students to learn more about stem cell research and therapy. We hosted 70 high school students lecturing in the lecture hall and experimenting hands-on in stem cell laboratories.

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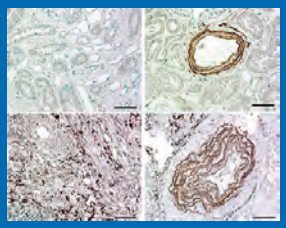
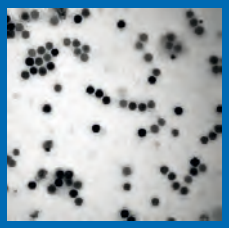
Team in February 2020

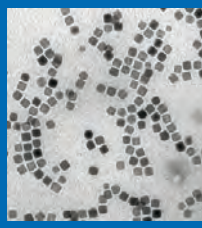
ExMI EXPERIMENTAL MOLECULAR IMAGING

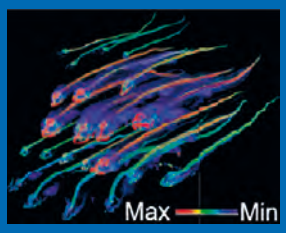
Chair of Experimental Molecular Imaging
Faculty of Medicine

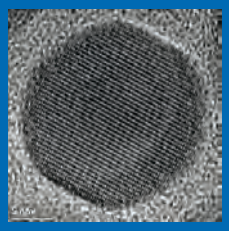
Improving therapy by integrated multiparametric imaging











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Introduction

Univ.-Prof. Dr. med. Fabian Kiessling

The Chair of Experimental Molecular Imaging (ExMI) focuses on the development and evaluation of novel imaging methods, contrast agents and theranostics to characterize and treat cancer, cardiovascular and inflammatory disorders. ExMI has a translational scope and many project are located at the interface between preclinical and clinical research. In this context, we often follow a multimodal approach, based on combinations of MRI, CT, ultrasound, optical and photoacoustic imaging, nuclear medicine techniques (in particular PET-MRI) and magnetic particle imaging (MPI). In order to develop image-guided therapies, we strongly interconnect our pathophysiological and pharmacological research with research in device engineering, image reconstruction, and data postprocessing. Basic research on the tissue microenvironment (including the barriers for drug delivery) provides us with new imaging biomarkers and new mechanistic insights that can be used to identify diagnostic biomarkers. Here, imaging features and omics data are considered in concert, evaluated using radiomic and radiogenomic approaches, and used to support mathematical disease models. As a second main focus area ExMI investigates materials and concepts to improve drug delivery to tumors. This includes the development and evaluation of novel biomaterials, including nanoparticles, polymeric carriers, liposomes, micelles and microbubbles as well as physical and biological treatments of the vasculature and the adjacent tumor stroma in order to improve drug accumulation and tumor penetration.
Research of ExMI gains increasing international visibility. As major achievements of 2019, F. Kiessling and T. Lammers were both awarded as highly Cited Researchers by Clarivate Analytics. Furthermore, in the ranking of the US rating agency Expertscape, F. Kiessling was ranked among the top 10 scientists worldwide in the categories Nanomedicine and in Molecular imaging and Twan Lammers in Nanomedicine and in Drug Delivery. Furthermore, Twan Lammers successfully applied for an prestigious ERC Consolidator grant.

Diagnostic and Therapeutic Ultrasound

Univ.-Prof. Dr. med. Fabian Kiessling

In 2018 we presented the first in vivo application of superresolution ultrasound imaging, i.e. motion model ultrasound localization microscopy. Currently, a larger clinical trial is running to assess chemotherapy effects on breast cancer by contrast enhanced ultrasound imaging and at the same time investigating whether the oscillation of disintegrating ultrasound microbubbles (contrast agent) enhances tumor perfusion and vessel permeability (clinicaltrials.gov: NCT03385200). In this context, we also aim to improve motion correction on superresolution ultrasound data, which is a severe limitation for its clinical implementation to date [1]. Furthermore, with a translational focus we continued evaluating our PBCA based microbubble platform [2] in order to improve batch stability, life time and storability [3]. We found that the microbubbles can be lyophilized and stored over longer periods without losing their acoustic properties. Besides microbubbles, superparamagnetic iron oxide nanoparticles play an important role in our research. These can be used to label cells, render microbubbles visible for MRI, and for labelling biohybrid vascular grafts [4,5]. Concerning the latter, we could show by PET that iron oxide nanoparticle labelling of biohybrid tissue engineered grafts dies not alter their biocompatibility but allows the exact determination of the position of the graft in the vessel.
In addition, in the DFG FOR 2591 we explored the impact of different imaging methods on animal welfare and study results. In this context, we evaluated the new PET radiotracer [68Ga] NODAGA-duramycin and showed that it sensitively depicts tissue damage during cytostatic therapy [6] – in some organs even more sensitive than clinical chemistry or behavioural parameters [7].
Besides this, basic research was performed on the identification of new targets for molecular imaging and on the mechanisms of therapeutics [8-10]. A new therapeutic mechanism of the multispecific tyrosine kinase inhibitor sorafenib was identified in hepatocellular carcinoma, which is not related to the inhibition of angiogenesis but pyroptosis of macrophages and activation of natural killer cells [9,10].

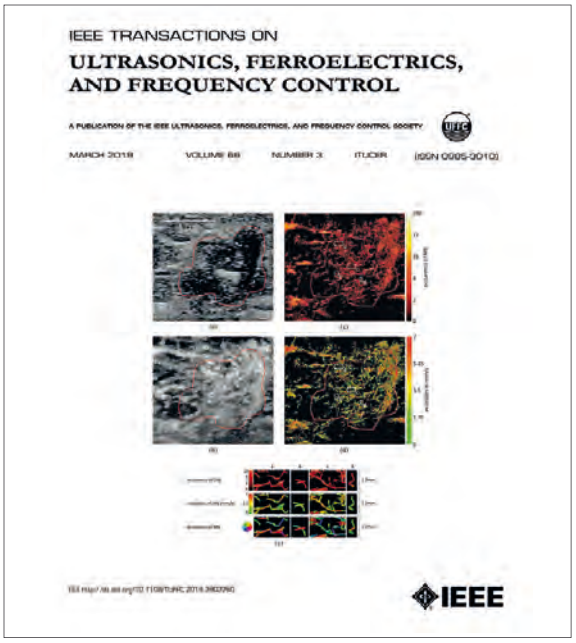

Fig. 1: Clinical superresolution ultrasound images of breast cancer presented at the cover of the journal IEEE Transactions on Ultrasonics, Ferroelectrics and Frequency Control [1].

Physics of Molecular Imaging Systems

Univ.-Prof. Dr.-Ing. Volkmar Schulz

In the last years, the PMI group jointly developed with Philips Research in Aachen the first fully-digital detector for simultaneous Positron Emission Tomography (PET) and Magnetic Resonance (MR) imaging. The team previously succeeded in integrating this new detector technology in a preclinical PET/MR insert for a human 3T MR system.

The group is currently applying its expertise acquired in the field of PET/MR in the EU Horizon 2020 HYPMED project, for which a clinical PET/MR insert for human breast cancer is developed.

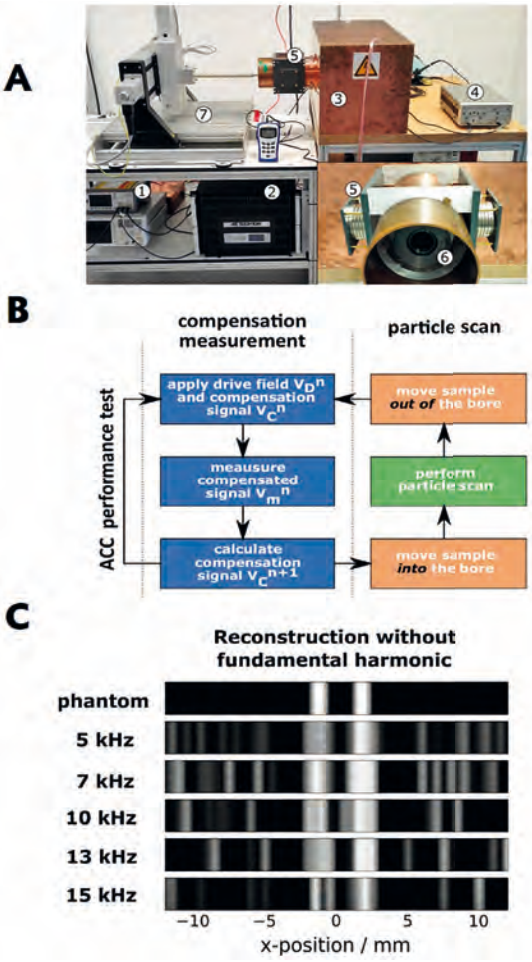

Fig. 2. A: Experimental setup for multifrequency magnetic particle imaging (mf-MPI): B: Flow chart of the active compensation control. C: Comparison of phantom image reconstruction with and without fundamental harmonic information. The applied drive field frequencies were 5, 7, 10, 13, and 15 kHz.

Gross-Weege et al. investigated the mutual influences of both imaging modalities. The gradient magnetic fields induce eddy currents in all conductive components of the PET insert. Eddy currents produce superimposing magnetic fields distorting the gradient magnetic field. A distorted gradient shape produces a distorted k-space trajectory which then results in a distorted image.
The dynamic performance of the gradient system has been characterized by measuring its gradient impulse response function (GIRF) using an own developed micro NMR coil. Based on the information of the NMR coil, we corrected the k-space trajectory and were able to correct for the eddy current induced distortion of the Hypmed breast PET-MRI device [11,12].
The PMI group also focuses it research on Magnetic Particle Imaging (MPI). MPI measures the magnetic fields generated by excited superparamagnetic nanoparticles that act as tracers. In 2019, the group successfully developed the first 1D multifrequency MPI (mf-MPI) scanner [13]. Broadband drive field feed-through cancellation was provided by a combined passive and active compensation approach. Thus, drive field frequency flexibility from 0.5 to 20 kHz was enabled. In total, a combined drive field feed-through suppression of up to −125 dB was achieved, which proved to be sufficient for image acquisitions. The technique further provides direct access to the fundamental frequency of the SPION signal. First images were acquired that demonstrate the feasibility of the presented mf-MPI. Excitation frequency dependent modulation of the system functions were observed. An SNR enhancement by 70% was shown when the fundamental harmonic was employed during image reconstruction. In future steps of this project, the presented scanner will be used to study the principle of multi-parameter estimation of the superparamagnetic nanoparticles.

Nanomedicines and Theranostics

Univ.-Prof. Dr. Dr. Twan Lammers

Nanomedicines are designed to improve the pharmacokinetics and biodistribution of systemically administered (chemo-) therapeutic drugs. By delivering drugs more specifically to pathological sites, and by preventing them from accumulating in healthy tissues, nanomedicines help to improve the balance between drug efficacy and toxicity.
In our department, we have a strong focus on cancer nanomedicine and on drug targeting to tumors. We recently proposed four strategic directions to improve cancer nanomedicine performance and translation [14]. These are patient stratification, rational drug election, integration in combination therapies, and nano-immunotherapy (Fig.2.A). Especially nano-immunotherapy seems to hold a lot of promise, as evidenced by a huge increase in the number of papers published on the use of nanoformulations to boost cancer immunotherapy [15,16]. In addition, a lot of recent attention has been dedicated to setting standards in translational nanomedicine research and bio-nano science [17], as well as to the use artificial intelligence in cancer nanomedicine and precision therapy [18].
In 2019, we formulated hypoxic cell radiosensitizers in temperature-sensitive liposomal nanomedicines, to improve radiochemotherapy [19]. In collaboration with colleagues from Internal Medicine III at the UKA, we also evaluated the targeting capabilities of prototypic drug delivery systems such as polymers, liposomes and microbubbles in mice suffering from liver fibrosis [20]. We furthermore analyzed the role of CCR2-positive macrophages in pathological liver tumor angiogenesis [21].
Important progress has also been made with regard to molecular imaging of kidney fibrosis. Translational drug development efforts in chronic kidney disease (CKD) suffer from the lack of available biomarkers to predict and monitor treatment outcome. Renal fibrosis is the common endpoint of CKD. Together with colleagues at Internal Medicine II, the Institute for Pathology and the Institute for Molecular Pathobiochemistry, Experimental Gene Therapy and Clinical Chemistry, we established probes for specific molecular imaging of the extracellular matrix components elastin and collagen, which are both highly overexpressed in fibrotic kidneys [22,23]. Using the elastin-specific probe ESMA, we demonstrated that molecular magnetic resonance imaging (MRI) can be employed for staging and treatment moni-

toring of kidney fibrosis (Fig.3b-c). Importantly, non-invasive imaging using molecular MRI outperformed routine clinical function tests, such a creatinine clearance, in terms of detecting residual fibrosis upon disease regression [9]. We are currently expanding these efforts by looking at other fibrosis targets and imaging probes, and by exploring the posibility of performing a small proof-of-concept clinical trial at UKA.

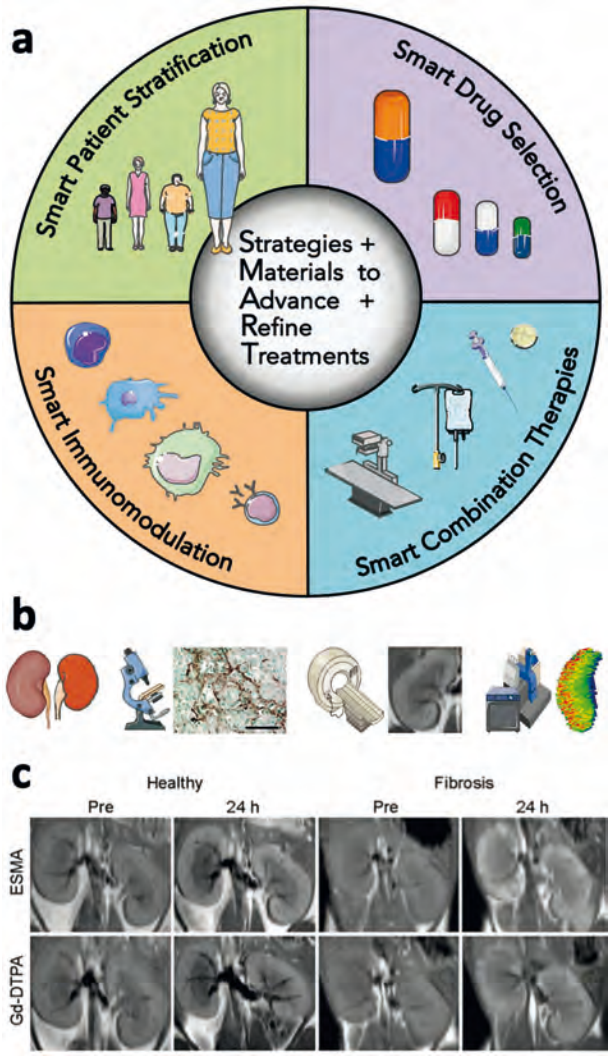

Fig. 3. A: Strategies to improve cancer nanomedicine performance. B-C: Comprehensive analysis of targeting elastin for molecular imaging of kidney fibrosis included microscopy validation of target expression in several different renal pathologies, MRI in multiple different mouse models with and without therapy, and validation of probe accumulation using LA-ICP-MS. Adapted from [14] and [22].

Mechanisms of tumor progression and metastasis

Dr. Wiltrud Lederle

The group "Mechanisms of Tumor Progression and Metastasis" uses innovative non-invasive imaging techniques and tools to investigate the influence of the microenvironment on tumor growth and progression and stroma remodeling during physiological tissue repair and inflammation [6].

Multi-scale methods including non-invasive imaging and histological analyses were applied in order to investigate liver regeneration after partial hepatectomy. CT-FMT with a novel fluorescent probe and immunohistochemical analyses revealed a transient increase in the density of CD68+ macrophages and an early induction of angiogenesis in the regenerating liver. Based on the non-invasive imaging and histological data, a model was established that describes the growth and interplay of different liver cell compartments during regeneration at the organ and tissue scale [24] (Fig. 4). Further research activities were directed towards modulating the tumor-associated immune response for an improved cancer therapy. Blockage of two immune checkpoint molecules exerted strong inhibitory effects on colon cancer progression, as obvious by stagnation of primary tumor growth and the absence of liver metastases. These therapy effects could be explained by the induction of anti-tumorigenic T cell responses and polarization of macrophages to the pro-inflammatory phenotype. In addition, a pronounced fibroblast activation was observed after dual immune checkpoint blockade, highlighting the link between immunomodulation and desmoplasia [25] (Fig. 4).

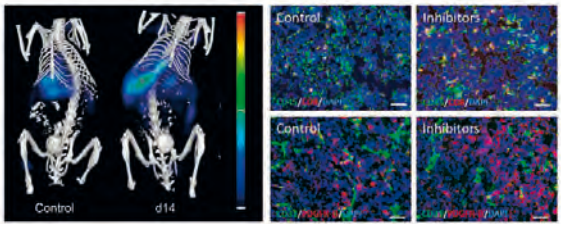

Fig. 4: Left: 3D Rendering of reconstructed CT-FMT data showing an enhanced fluorescent signal for CD68+ macrophages in the regenerating liver (day 14 after partial hepatectomy). Right: Immunofluorescent stainings showing higher numbers of CD8+ T cells (upper panels) and an increase in PDGFR-β+ fibroblasts (lower panels) in colon tumors after dual immune checkpoint inhibition (see also [24] and [25]).

Applied Medical Informatics

Dr. rer. medic. Dipl.-Inf. Felix Gremse

The group "Applied Medical Informatics" develops and applies software for reconstruction, segmentation, analysis and visualization of multimodal biomedical image data.

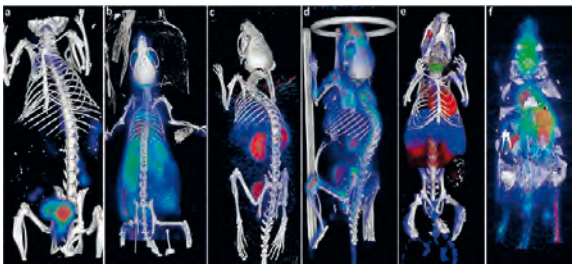

Fig. 5: Example files from multimodal imaging devices, curated with the novel file format [29].

Together with three hardware companies MILabs B.V. (Utrecht, The Netherlands), Molecubes (Ghent, Belgium) and Inviscan (Strasbourg, France), we developed and pub-

lished a well-defined file format to represent and curate 3D, 4D or 5D volume data [26]. This file format includes novel features such as parallel lossless compression, geometric information for image fusion, meta data and a cryptographic time stamp to facilitate provable protection from data manipulation and is meant to serve as interface between imaging devices and image analysis software.
Furthermore, we used our software for dental implant analysis [27], Organ segmentation [23], vascular grafts [28], μCT scans of Eels [29] and the evaluation of a lung-monitoring belt [30].

Probe design for molecular imaging

Dr. Srinivas Banala

This group develops organic chromophores [31] for diagnostic and theranostic applications. Our expertise in multi-step organic synthesis enabled the development of novel enabled the development of dyes for photoacoustic imaging (PAI) and superresolution microscopy/ naonoscopy (STED). For PAI, we developed new NIR quenchers by introducing pyrrol based moieties into formerly highly fluorescent species (e.g.Fig. 6A), and thereby also redshift the optical absorption and PAI emission [32]. Additionally, reactive oxygen species (ROS)-responsive PAI probes (Fig. 6B) were generated by using butylated hydroxy toluene (BHT). These probes switched in presence of ROS from a PAI deactivated state to a PAI activated state [33]. Studies concerning the in vivo application are ongoing [34].

In addition, we generated probes for super resolution STED nanoscopy. Here, we are particularly interested in the synthesis of highly stable, large Stokes shift exhibiting and bright dyes [35]. We have discovered an ArAmBODIPY core, that is many fold more photostable than commercial dyes using the 660 nm laser (Fig. 6C, 6D). We are currently fine-tuning the fluorophores properties and evaluate its applications.

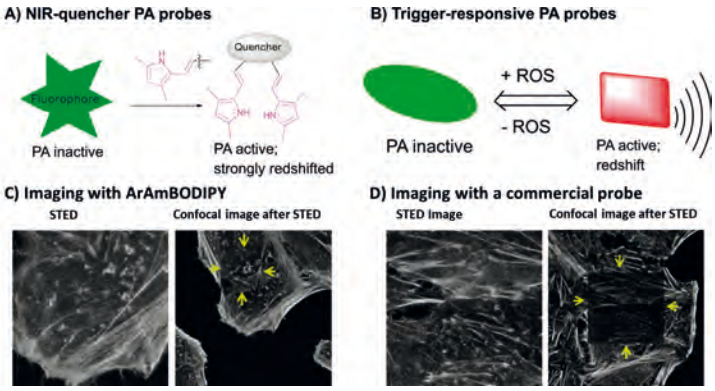

Fig. 6: Schematic depiction of A) quencher B) Trigger-responsive PA probes design concepts pursued in our group. STED imaging with C) ArAmBODIPY developed by our group, and D) a commerical probe at the same energy level for excitation and depletion, along with difference in photobleaching after actin filament imaging (area in yellow arrows), respectively.

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- Dr. R. Hetzel: IEEE MSS-MIC Trainee Grant
- F. Müller: IEEE NSS-MIC Trainee Grant
- Dr. D. Schug: IEEE NSS-MIC Trainee Grant
- L. Yin: IEEE NSS-MIC Trainee Grant
- F. De Lorenzi Best scientific talk: Category "Image-guided Therapy and Monitoring"
- M. Freese et al.: the Thünen-Research Award
- Univ.-Prof. Dr. med. F. Kiessling: Highly Cited Researcher 2019
- Univ.-Prof. Dr. Dr. T. Lammers: Highly Cited Researcher 2019
- Univ.-Prof. Dr. med. F. Kiessling: Awarded as "World Expert in Molecular Imaging" and in "Nandomedicine" by Expertscape
- Univ.-Prof. Dr. Dr. T. Lammers: Awarded as "World Expert in "Nanomedicine" and in "Drug Delivery Systems" by Expertscape
- B. C. Schüre et al.: MOBI , Münster: Poster Award
- J.-N. May et al.: Controlled Release Society, Annual Meeting and Exposition, Valencia , Spain: Poster Award
- K. Römhild et al.: Controlled Release Society, Annual Meeting and Exposition, Valencia , Spain: Poster Award
- K. Römhild et al.: Annual Meeting of the German Society of Pathology, Poster Award, Frankfurt
- O. Tatjana: the award of the Klee Foundation
- D. Möckel et al.: EMIM,Glasgow, England: Poster Award
- A. Rix et al.: European Symposium on Ultrasound Contrast Imaging, Rotterdam, NL: Poster Award
- Yang Shi: Europe Award, International Pharma Sciences Foundation/ Rottendorf Stiftung, 2019.

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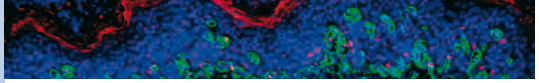

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Faculty of Medicine

Building Bridges, Creating Innovation


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Introduction

Univ.-Prof. Dr. med. Dipl.-Ing. Thomas Schmitz-Rode

Our Institute of Applied Medical Engineering (AME) is characterized by a consistent and comprehensive interdisciplinarity with which we pursue a biomedical engineering research profile. With our team of scientists and students from engineering, medicine, life sciences, physics and information science working closely together in multiple research and development projects, the AME represents a vital example for the often-quoted convergence of disciplines. The close interaction of highly innovative technologies of engineering sciences with the newest insights and methods of biosciences and medicine pervades all areas of activities and is characteristic of our undertakings and projects. National and international industrial and academic partners are among our cooperation partners. Arising from these collaborations are innovative diagnostic and therapeutic approaches, new momentum for teaching, and an extensive catalogue of jointly supervised engineering, natural science, and medical dissertations. The institute is located in the Helmholtz Institute's (HIA) building, the Medical Technology Center (MTZ) and the Center for Biohybrid Medical Engineering (CBMS), all of which are in close proximity to each other as well as to the University Hospital (UKA).

Fig. 1: AME Executive Team. Left to right: Thomas Schmitz-Rode, Robert Farkas, Martin Baumann, Catherine Disselhorst-Klug, Jutta Arens and Stefan Jockenhövel.

Biophysical & Education Engineering (BEE)

Prof. Dr. rer. nat. Dipl.-Ing. Martin Baumann, MME

Nanomagnetic Medical Engineering/NME, Dr. Ioana Slabu

Magnetic hyperthermia enables the controlled release of therapeutical heat using magnetic nanoparticles (MNP) as heating agents. The group NME develops hybrid implants made of polymer filaments with incorporated MNP allowing local hyperthermia treatment and, in this way, destroying the tumor tissue in close vicinity to the implant (Fig. 2). For this, the MNP are excited in an externally applied alternating magnetic field. The field excitation energy transforms into heat via magnetic relaxation of the MNP. This heat dissipates into the MNP immediate surroundings, e.g. tumours tissue, facilitating the therapy of organ-confined cancer. Tumour damage by hyperthermia occurs at temperatures of about 43 °C, for which healthy tissue remains unharmed. The implants, e.g. stents, can be used for the treatment of patients with endoluminal tumours (e.g. trachea carcinoma, oesophagus adenocarcinoma or bile duct Klatskin tumours). In such cases, the stent widens the occluded endoluminal site and destroys the tumours tissue by hyperthermia preventing a re-closure of the endoluminal organ. As adjuvant therapy, temperature-triggered local drug release is envisaged. Furthermore, due to the contrast agents abilities of MNP in magnetic resonance imaging (MRI) and magnetic particle imaging (MPI), non-invasive visualization of the stent after implantation is possible.

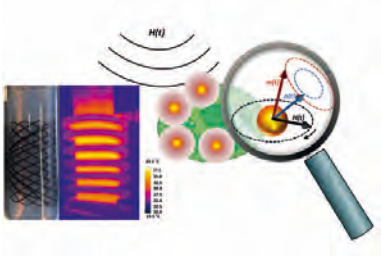

Fig. 2: Heatable stents (left) and magnetic nanoparticle relaxation processes (right) after excitation in an alternating magnetic field.

NRW Schwerpunktprofessur Biohybrid & Medical Textiles (BioTex)

Univ.-Prof. Dr. med. Stefan Jockenhövel

The *NRW-Schwerpunktprofessur* Biohybrid & Medical Textiles (BioTex) focuses on the development of viable biohybrid implants with the potential for remodelling, regeneration and self-repair. The mission statement of the *NRW-Schwerpunktprofessur* is "Innovation & Translation by Interdisciplinary Collaboration". Therefore, the department is organized as a bridging research group between the Aachen-Maastricht Institute for Biobased Materials (biomaterial research, Faculty of Science) via Textile Engineering (biomaterial processing and textile reinforcement, Faculty of Mechanical Engineering) towards the clinical application at the Institute for Applied Medical Engineering (biohybrid implant development and (pre-)clinical evaluation, Medical Faculty). In addition, Prof. Jockenhövel has also joined the scientific board of the DWI – Leibniz Institute for Interactive Materials as an associated scientist in 2019.

Regarding the translation into clinic, the biohybrid approach focuses on the optimal combination of a (i) (non-biodegradable) technical component to guarantee a high (re-)producibility with a (ii) cellular component to guarantee an optimal biological performance. Therefore, we have introduced the biomimetic textile-reinforcement in the field of regenerative medicine.

Selected research highlights in 2019:

- To support clinical translation of **tissue-engineered vascular grafts (TEVGs)**, our group has demonstrated the functionalization of textile scaffolds with ultra-small super-paramagnetic iron oxide (**USPIO**) nanoparticles for non-invasive monitoring of imageable TEVGs (**iTEVG**). Imaging was facilitated throughout the whole life cycle: from initial **quality control** to **longitudinal functional evaluation** in an ovine model for up to 8 weeks (Fig. 3; Wolf et al. in *Biomaterials*).

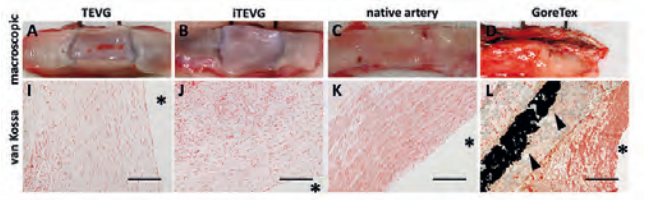

Fig. 3: Macroscopic view of explanted grafts showed neither thrombus formation nor calcification for TEVG and iTEVG, whereas GoreTex controls showed significant thrombus formation, occlusion and massive calcific depositions by van Kossa staining (arrows ahead). Asterisks indicate vessel lumen. Scale bar: 100 µm.

- **Small-caliber elastin-like vascular grafts** were sucessfully fabricated featuring an open macroporous structure as biohybrid cell-free implants for in situ tissue regeneration. The 3D architecture of the grafts favours cell ingrowth, while being endowed with the non-thrombogenicity and the elastic behaviour of the native elastin (Fig. 4). The textile components (i.e., warp-knitted and electrospun meshes) are designed to confer suture retention, long-term structural stability, burst strength, and compliance (Fernández-Colino et al. in *Frontiers in Bioengineering and Biotechnology*).

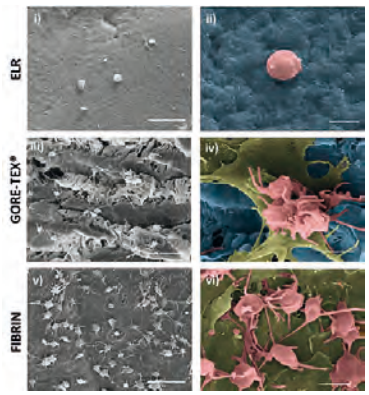

Fig. 4: Assessment of hemocompatibility by evaluation of adhered platelets based on SEM images. While elastin-like recombinamers (ELR) surfaces presented minimal platelet adhesion, activated (pink) and fully activated platelets (golden) were covering GoreTex and fibrin surfaces. Substrate surfaces are coloured in blue.

- **Complex tissue-engineered constructs** require **vascularization** for adequate supply with nutrients and oxygen. Our group has investigated the influence of **different cell types and cell sources** on pre-vascularization in fibrin and agarose-collagen gels, demonstrating the **high angiogenic potential** of co-culture of fibroblasts and adipose-derived mesenchymal stem cells (Fig. 5; Kniebs et al. in *Organogenesis*).

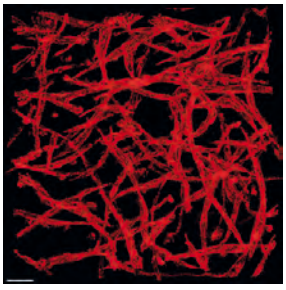

Fig. 5: Cross-sectional view of CD31-stained endothelial cells (HUVECs, red) co-cultured with fibroblasts (HNFs) in fibrin gels after 14 days of culture showing highly branched and elongated structures within the hydrogel. Scale bar: 50 µm.

- For the development of a **biohybrid lung** for chronic lung support in the **EndOxy** project, gas exchange membranes were seeded with **endothelial cells** and their **long-term stability** and **gas exchange performance** was evaluated. The study demonstrated the long-term stability of the endothelial layer for at least 33 days at a physiological flow rate and confirmed gas transfer across the cell-seeded membranes (Fig. 6; Klein et al. in *Annals of Biomedical Engineering*).

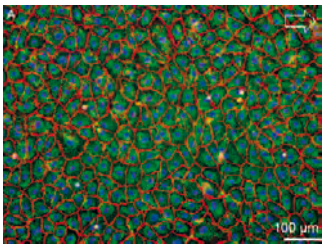

Fig. 6: Endothelial cells seeded on gas exchange membranes maintained an integral cell layer for at least 33 days of dynamic culture with a wall shear stress of 0.5 Pa. Cells stained positive for CD31 (red) and von Willebrand factor (green), confirming endothelial phenotype.

- Different **respiratory airway stents** for treatment of airway stenosis in lung cancer patients are available, but influence of mechanical performance on tissue response is not well understood. Two novel laser-cut and hand-braided nitinol stents were bench tested and implanted in sheep for 6 weeks. Our group has developed a mechanical and in vivo framework to compare the different stent designs in a large animal model, providing data, which may be employed to improve current stent designs and to achieve better treatment options for lung cancer patients (Fig. 7; Thiebes et al. in *Annals of Biomedical Engineering*).

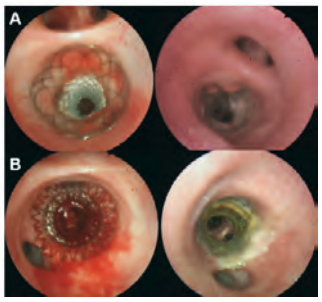

Fig. 7: Bronchoscopy images of braided stent (A) and laser-cut stent (B). Images were taken immediately after implantation (A and B left) and after 4 or 6 weeks (A and B right, respectively).

- Research group leaders Dr. Thiebes (Respiratory Tissue Engineering) and Dr. Fernández-Colino (Biomaterials) were awarded for their scientific work (*Fig.* 8).

Fig. 8: Awardees Dr. Thiebes (A, middle) at the Congress of the West German Respiratory Society (WDGP) in Düsseldorf and Dr. Fernández-Colino (B, left) at the Brightlands Rolduc Polymer Conference in Kerkrade, The Netherlands.

- **UniStem Day 2019**: BioTex opened its doors and welcomed pupils to its laboratory for the European Action Day on Stem Cell Research with the aim to arouse students' interest in stem cell research, to

deepen their knowledge of the subject and to provide insights into research.

- Prof. Jockenhövel was admitted to the **German Academy of Technical Sciences** (Deutsche Akademie der Technikwissenschaften, acatech).

Cardiovascular Engineering (CVE)

Univ.-Prof. Dr.-Ing. Ulrich Steinseifer, PD Dr.-Ing. Jutta Arens

In 2019, the Department of Cardiovascular Engineering underwent several changes in management. Professor Steinseifer returned to a full position as Head of Department from Monash University, Melbourne, Australia. His deputy, PD Dr. Jutta Arens, accepted a position as Professor and Chair of Engineering Organ Support Technologies at University Twente in Enschede, Netherlands. Former research associate Dr. Sebastian Jansen returned from industry as Chief Engineer and new Deputy Head of Department. Finally, Dr. Johanna Clauser took over the position of Chief Scientist after successful completion of her PhD with distinction. The research was restructured in three fields: Application & Therapies, Research & Validation and Modelling & Simulation. However, the mission stays firmly in place: engineering cardiopulmonary therapies for the benefit of patients.

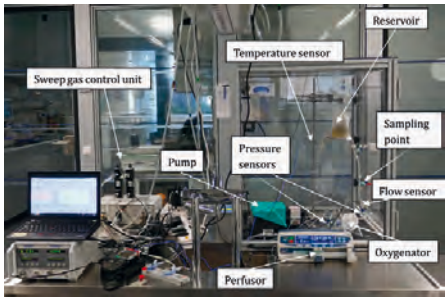

Fig. 9: Test bench for long-term oxygenator testing.

In the field of 'Research & Validation', various projects aimed at improving and standardizing in-vitro test methods for hemocompatibility testing. The OxyBench project (START funding) started to develop a test setup for long-term testing of protein adsorption on oxygenator membranes. Since protein deposits narrow the gas exchange performance and trigger coagulation, an in-vitro prediction would allow for a safer and more efficient oxygenator development. Multiple test series were performed over 10 days, detecting the loss of fibrinogen due to adsorption on the membranes (see Fig. 9).

For the analysis of platelet adhesion and activation on materials after blood testing, an automatized and standardisable analysis method was developed. Using image segmentation tools and a random forest machine learning algorithm, fluorescence images can be evaluated in terms of number and size of adherent platelets. Within the HOC-Surf project (EFRE funding) that ended by June 2019, an optimized test setup for blood pump testing according to the ASTM regulations was developed and validated. It allows for the use of one batch of donor blood for a comparative in-vitro test of two different pumps (see Fig. 10).

Fig. 10: Small-volume test loops for blood pump testing.

For a further improvement of blood pump testing, the Resistance Design Study developed a new resistance that regulates the flow and pressure values within the test circuit but at the same time does not affect the haemolysis like the standard resistances do (see Fig. 11).

Fig. 11: Non-haemolytic flow loop resistance.

The C-Arch Mockloop (Hirsch Foundation) is a test facility that presents the anatomy of the human heart and its surrounding. It fulfills all requirements to fit into a C-arch in an intervention lab in the clinic, like e.g. no metal inside, optical access and small size. The mockloop offers the possibility to clinicians to train the implantation of TAVI valves or stents under realistic conditions with the corresponding imaging.

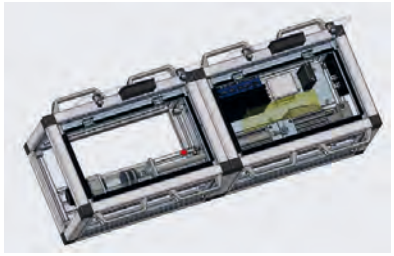

Fig. 12: CAD model of the C-Arch Mockloop.

Another training modality was developed in the EduDerm project (Deanery funding). A human skin model was built by means of foams and silicones with different elastic properties. Additionally, tubes with different elasticity and hardness mimic the vessels (see Fig. 13). The skin model allows for sewing and venipuncture training for clinicians and medical students.

Fig. 13: Skin model with different skin layers and vessels.

Within the PolyValve project (Interreg funding), the heart valve thrombogenicity tester was adapted to polymeric heart valves and the newly designed 'PolyValve' was tested in terms of thrombus formation and haemolysis. Furthermore, the calcification tendency of the material was evaluated with the CVE-developed calcification test bench. It mimics the physiological calcification which is one of the major problems with biological heart valve prostheses at the moment.
The Low-Flow project bundles the competences from 'Research & Validation' with those from 'Modelling & Simulation' as well as clinical expertise. Blood pumps are often run in the low-flow range which is below their standard operation point. Although this use is granted by the manufacturers, testing is only performed in the standard operation range. Within this project it

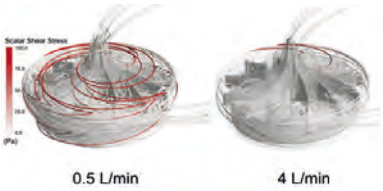

Fig. 14: Shear stress simulation in the 'Revolution 4' pump at low (left) and high (right) flow.

was shown that the low-flow range causes severely higher haemolysis due to higher shear stresses and longer contact times of blood and pump (see Fig. 14). First, numerical simulations evaluated critical contact times; afterwards in-vitro blood trials validated the results.
Numerical simulations were further used to determine the blood flow and washout in uni-ventricular hearts (funded by Kinderherzstiftung). Patient data was used to set up a moving heart model that allows for washout simulations. Using this model, different therapies and the effect on the washout can be evaluated numerically like e.g. increasing the blood volume.
The field "Therapies & Applications" focuses on research of innovative therapies or devices and their transfer into the clinic. Within the ReinHeart 2.0 project, a pulsatile total artificial heart (TAH) is developed in collaboration with the institute spin-off company ReinHeart TAH GmbH. In the course of the project, a fully automated mock circulation loop was developed that can apply different patient profiles to the ReinHeart TAH. This way, a physiological control that adjusts the performance of the artificial heart in accordance to the patients need can be extensively tested in vitro.

Fig. 15: Fully automated mock circulation loop for in-vitro tests of the ReinHeart TAH physiological control.

The ECCOR project (extra corporeal CO removal) will be funded by the EXIST program and is thus in the preliminary spin-off stage. It aims at the development of an emergency device (HBox) that is able to remove carbon-monoxide (CO) from the blood of an intoxicated person. The best therapy option to remove CO is by giving hyperbaric oxygen. In Germany, only few centers with over-pressure chambers exist, resulting in a long transportation duration for the patient. Since, time is crucial for the outcome, the ECCOR project develops a mobile device that pressurizes the patient's blood in a batch process. This way, a detoxification treatment in a hospital or even on location is possible.

Fig. 16: HBOX use scenario of an extra corporeal CO removal of an intoxicated patient by the emergency doctor.

At the beginning of 2018, the Department of Cardiovascular Engineering partly moved into the second level of new CBMS building (Center for Biohybrid Medical Systems) offering additional laboratories and offices. However, half of the group continues to work in the Helmholtz Institute. The CVE is an integral partner within the priority program "Towards an Artificial Lung" granted by the German Research Foundation and continues the scientific exchange with partners from all over the world (time wise starting in Melbourne, Australia, via Suzhou, China, Europe to Ann Arbor, MI, USA). Our general mission is the engineering of cardiopulmonary therapies for the benefit of the patients.

Rehabilitation and Prevention Engineering/RPE

Univ.-Prof. Dr. rer. nat. Catherine Disselhorst-Klug

The Department of Rehabilitation & Prevention Engineering (RPE) has over 30 years' expertise apropos the physio- and pathological function of the human musculoskeletal and neuromuscular systems. RPE continues to boost research and development by realizing methods, measurement systems and robotic-assistive systems that support the prevention, diagnosis and therapy of movement disorders.

Detection of spasticity
Spasticity causes involuntary muscle contractions and stiffness, which hampers normal movements. Research into spasticity emphasizes its detection, assessment and quantification. Fig. 17 shows a valuable relationship in spastic patients during voluntary elbow movement, namely that the change of muscular activation with movement velocity increases with greater spastic impairment.

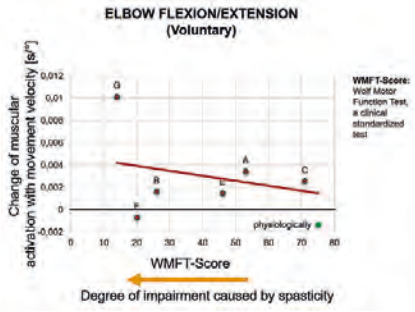

Fig. 17: Change of muscular activation with movement velocity vs. level of spastic impairment assessed according to the Wolf Motor Function Test.

Intelligent rehabilitation aids
SmartMove, a Mexico-Germany cooperation project addresses improving the movement capacity of spastic patients. This project aims to develop a smart orthosis that detects the onset of spastic contractures, hinders their progression and fosters functional movements. The relation shown in Fig. 17 can be used as a predictor for spasticity and is thus an important design parameter for a smart, adaptive orthosis (Fig. 18).

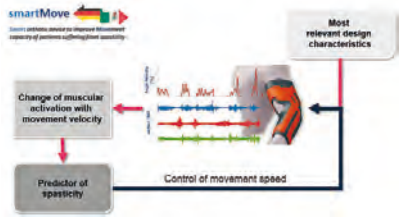

*Fig. 18: Flow diagram for the development of the smart, adaptive orthosis **smartMove**.*

Technically-complex arm/hand prostheses find limited use in developing countries due to the challenges posed by local environments, high purchase costs and limited technical support. **DeMaPro,** another bilateral project with Mexico, aims to develop new materials for the production and emergence of a prosthesis which satisfies the above challenges (Fig. 19).

*Fig. 19: Design of the **DeMaPro** prosthesis.*

inRehaRob (BMBF funded project) resulted in a robotic-assistive system that autonomously assists, monitors and provides feedback to both patient and therapist during therapy tasks. The system maximizes patients' attainable functionality and accelerates rehabilitation. When displayed at MEDICA 2019 it was extremely well received by rehabilitation professionals (Fig. 20). This bodes well for the future translation of the system from bench to bed.

*Fig. 20: Robotic-assistive system **inRehaRob** at MEDICA 2019.*

Growing instances for care among the aged raises the demands on caregivers. Especially for those in intensive care, physical demands often cause back injuries, which may shorten careers. The **PfleKoRo** project aims to reduce caregivers' physical burden by introducing a bedside robotic-assistance system (Fig. 21). The lightweight robot-based system, assists the caregiver with physically demanding holding and repositioning tasks during care.

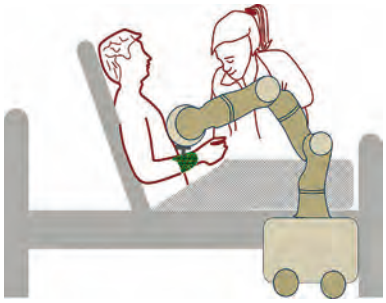

*Fig. 21: Conceptual design and proposed usage of a robot-assistive system in **PfleKoRo**.*

Science Management (SCM)

Dr. Robert Farkas (Head)

Translational Research aims at accelerating the process from invention to clinical application. Artificial Intelligence is considered one of the most promising levers to increase the pace of processes and significantly advance the health care system. Thus, clinical data of all different kinds could contibute to enhance the decision making in diagnosis and therapy. However, the required data integration is challenging due to isolation of re-positories, the lack of cross-linking or annotations, or missing standards, to name just a few given limitations.

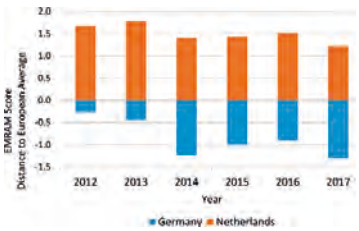

Fig. 22: Maturity level of digitisation of German and Dutch hospitals; distances of national EMRAM scores to European average. (Acknowledgement: HIMSS Europe GmbH (HIMSS Analytics)).

Under the roof of the CDCA (Comprehensive Diagnostic Center Aachen) the Science Management department led a consortium of local partners to analyse the status-quo of digitalisation at University Hospital Aachen and its potential to bolster future research and translation to clinical use compared to international developments. Two different use cases, i.e. breast cancer and heart failure, were assessed and jointly evaluated to conclude on neccesary decisions and measures to achieve a leading position in comprehensive diagnostic and perhaps in digitalisation of health care throughout. The frist steps to unlock the extraordinary potential in Aachen have been taken, but many more are ahead of us.

Acknowledgements

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- German Research Foundation (DFG)
- Excellence Initiative of the German federal and state governments
- European Regional Development Fund (EFRE)
- German Federal Ministry for Education and Research BMBF

Awards

- **Arens, Jutta**: Selected research personality of the year 2018 of the Annual Report of the RWTH Aachen University
- **Fernández-Colino, Alicia**: Winner of the Brightlands Rolduc Award 2019 for her work entitled "Biohybrid small caliber vascular grafts with tunable compliance and off-the shelf availability" at the Brightlands Rolduc Polymer Conference, Kerkrade, The Netherlands
- **Gesché, Valentine**: Recipient of the 2019 Innovation Prize of the State of North Rhine-Westphalia in the category "Young Talent"
- **Kaesler, Andreas**: Second prize of the Willem J. Kolff Best Abstract Awards for his work with the title "How a CFD Model Can Help to Predict Gas Transfer in Artificial Lungs Early During Development"
- **Menne, Mathias**: Poster award of the annual meeting of the Heart Valve Society for his poster "Influence of Paravulvar Leakage after TAVR on Left Ventricular Work and Coronary Flow. An In-vitro Study"
- **Steuer, Niklas**: Third prize of the American Society for Artificial Organs (ASAIO) Medical Device Entrepreneur's Forum on the topic "HBOX – An Extracorporeal Carbon Monoxide Removal Device"
- **Steuer, Niklas**: yESAO Exchange Award of the European Society for Artificial Organs (ESAO) congress 2019 in Hannover
- **Steuer, Niklas**: Young Investigator Award at the EuroELSO 2019 in Barcelona for his work on "Extracorporeal carbon monoxide removal as emergency therapy for CO-intoxications: Idea and first in-vitro-results"
- **Thiebes, Anja Lena**: Award of the Westdeutsche Gesellschaft für Pneumologie (WDGP) for her scientific work with the title "Comparison of Covered Laser-cut and Braided Respiratory Stents: From Bench to Pre-Clinical Testing"

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Team

Facts 2019

Third-party Funding

	Total Expense of Projects [EUR]
German Research Foundation (DFG)	3.080.379,00 EUR
German Federal Ministry of Education and Research (BMBF)	2.255.771,00 EUR
EU	1.243.453,00 EUR
Industry	1.605.682,00 EUR
Other	2.507.993,00 EUR
Sum	10.693.278,00 EUR

Theses

	Number
Student Mini-Thesis	
Bachelor	61
Diploma/Master	83
Doctoral	25
Habilitation	1
Sum	170

Staff

	Scientific	Non-Scientific
Total	218,20	45,00
Third party funded	166,45	9,50

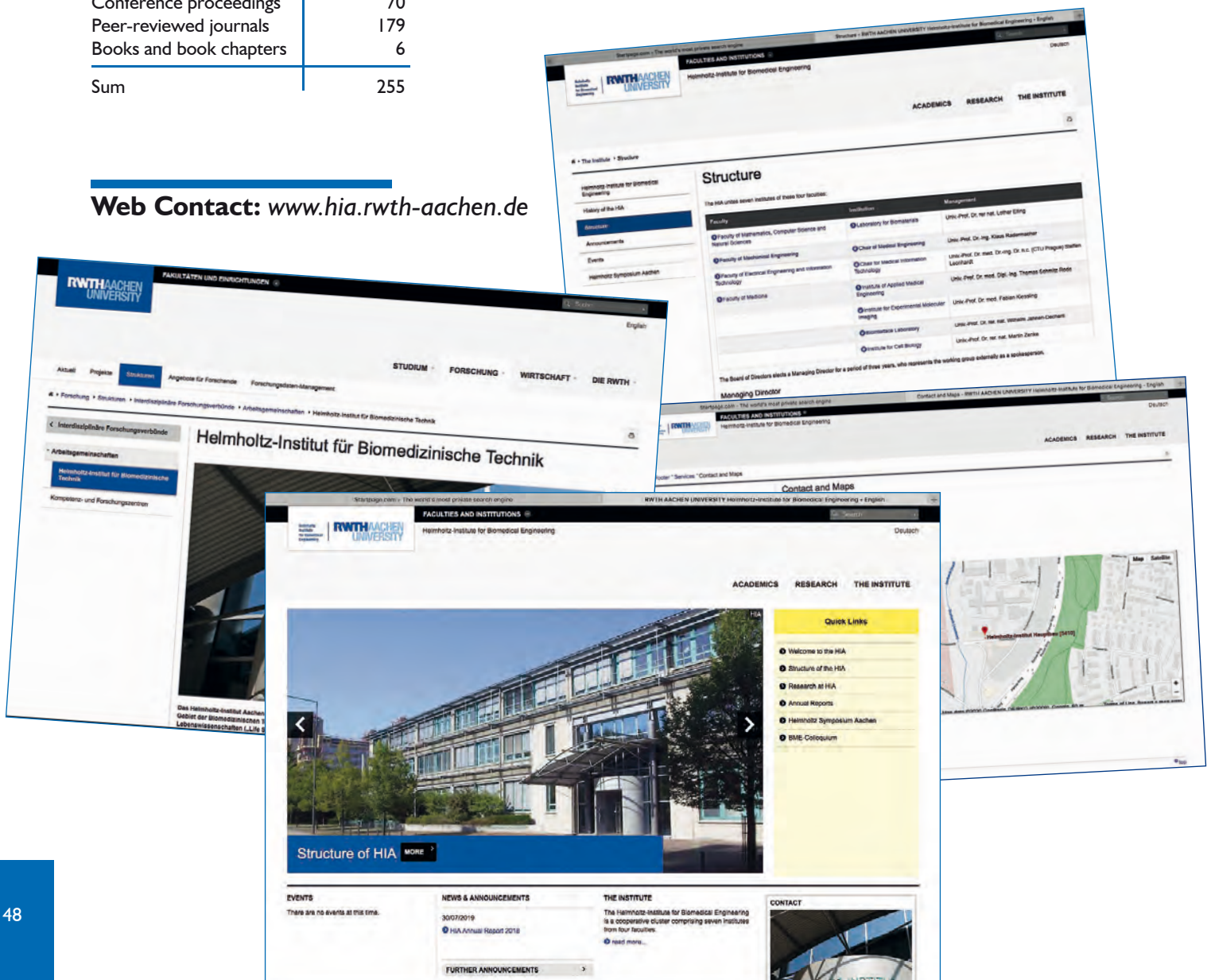
in full-time equivalent (FTE)

Publications

	Number
Conference proceedings	70
Peer-reviewed journals	179
Books and book chapters	6
Sum	255

Patents and patent applications: 13

Web Contact: *www.hia.rwth-aachen.de*



Content

Annual Report
2019
Helmholtz-Institute for Biomedical Engineering
RWTH Aachen University

How to reach us

Address

Helmholtz-Institute for Biomedical Engineering
Pauwelsstrasse 20
52074 Aachen
Germany

By car

- Follow the motorway from Cologne or Netherlands to Aachen (A4) and take the exit towards Laurensberg.
- Turn right into Kohlscheider Strasse and follow the signs Uniklinik.
- After approximately 750 m turn right on Toledoring/Pariser Ring, take the fifth exit (Uniklinik).
- In the roundabout take the exit towards RWTH Melaten and follow the Forckenbeckstrasse for 250 m.
- Opposite the restaurant Forckenbeck turn left into Pauwelsstrasse. After approximately 100 m the Helmholtz-Institute is on the right hand side.

By train/bus

Our Institute is well connected by public transport from the main train station, the train station 'Aachen West' or the main bus terminal in the city centre. Several bus lines lead to University Hospital (from the main train station line 3B; from the train station 'Aachen West' line 3A, 33, 73 from the bus terminal line 73, 33, 4, 5). Line 33, 73 and 3A stop directly at the Helmholtz-Institute, the other lines stop in front of the main entrance of the University Hospital. A short walk back over the bridge will take you straight to the Helmholtz-Institute.

By plane

Regular train service connects Aachen to major airports in Germany, Belgium and the Netherlands.

- From Düsseldorf airport the travel time by car is approximately 1.25 hours and 1.5 hours by train.
- From Cologne/Bonn airport travelling to Aachen takes about 1 hour by car and 1.25 hours by train.
- Travel time by fast train (ICE) from Frankfurt airport is approximately 2 hours.