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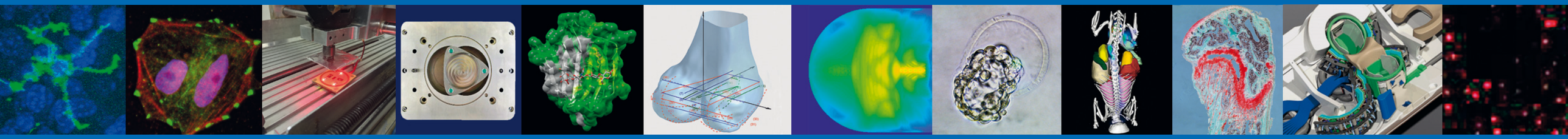
Helmholtz-Institute for Biomedical Engineering

Annual Report 2017



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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. Our Biannual Helmholtz Symposium has become a prime meeting place fostering collaborations with partners from within and outside our University.
We contribute to Bachelor and Master courses of the Medical, Engineering and Natural Sciences faculties of RWTH Aachen University. HIA members coordinate master courses related to the field of biomedical engineering. Practical education of students parallels their academic teaching. This comprehensive training has proved critical for successful national and international industrial as well as academic careers of our students and alumni.
Research projects target better 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 outside clinicians, academic and industry researchers on the national and international level are key to our work.
This past year saw the completion of a new building, the Centre for Biohybrid Medical Systems CBMS. The building will be home for the Departments of Biohybrid & Medical Textiles and Cardiovascular Engineering of the Institute of Applied Medical Engineering AME and for the Institute for Experimental Molecular Imaging ExMI including its Departments of Nanomedicines and Theranostics and Physics of Medical Imaging Systems. Significant building space will be dedicated to collaborative projects with partners from nearby research institutions. The CBMS also hosts units for small animal imaging, polymer textile scaffold production, and automated cell and tissue culture. Thus, the CBMS serves as a beacon of Biomedical Engineering at RWTH Aachen University.

The new Center for Biohybrid Systems CBMS building as seen from the nearby Helmholtz Insitute for Biomedical Engineering. ExMi, AME-BioTex and the OXY group of AME-CVE moved to the new CBMS building in December 2017. The official opening ceremony will be in June 2018.

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. We wish you a pleasant reading and would be happy to provide further information on any of the topics reported herein - as well as to discuss future options of cooperation in the fascinating field of biomedical engineering.

Aachen, January 2018

The Board of Directors

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

Events 2017

The **2017 Helmholtz Symposium** was well attended by guest from RWTH Aachen University and abroad …





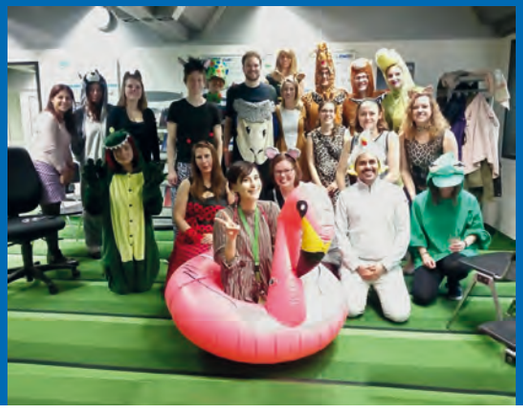

Congratulations to Professor Leonhardt who received an honorary Doctorate degree (Dr. h. c.) from the Technical University of Prague. The award ceremony was attended by Rectors of major Czech Universities, representatives of RWTH Aachen University, and the German Ambassador to the Czech Republic.



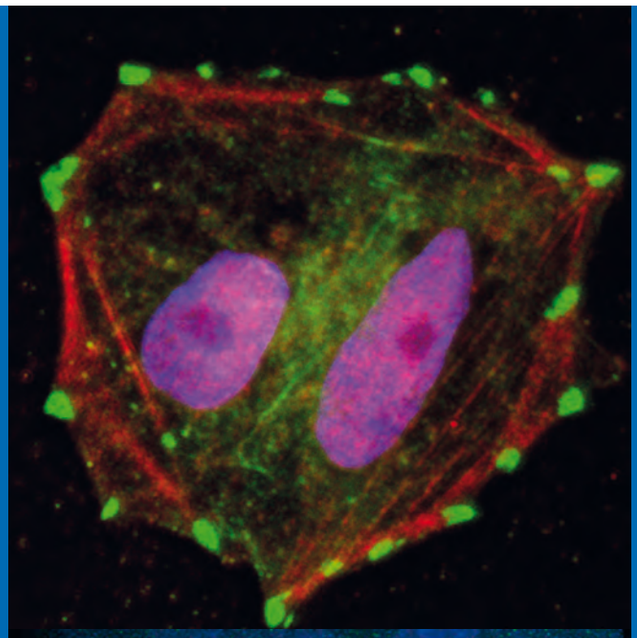

Team building Events 2017

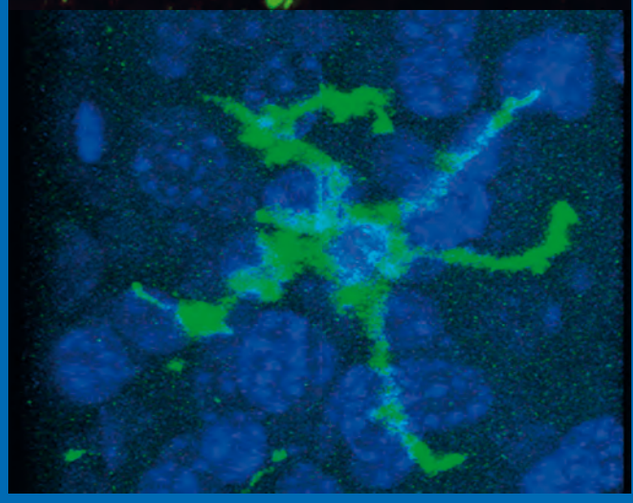





Gene Function in Cell Growth, Differentiation & Development





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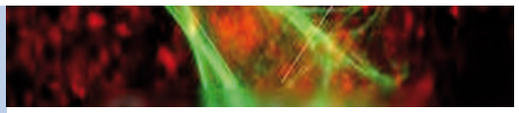


Introduction

Precision medicine (also referred to as personalised medicine) aims at tailoring medical therapy to the specific disease and needs of the individual patient. Stem cells are particularly well suited for precision medicine both for diagnosis and cell based therapy.

The institute studies various stem cell types and their differentiated progeny. A particular focus is on pluripotent stem cells, hematopoietic stem cells and mesenchymal stem cells. Additionally, engineered pluripotent stem cells are generated from normal body cells by reprogramming, referred to as induced pluripotent stem cells (iPS cells). Further to this we use precision genome editing by CRISPR/Cas technology for generating iPS cells with wanted properties for e.g. disease modelling.

Hematopoietic stem cells give raise to all cells of blood and we study blood cell composition based on DNA methylation signatures. Dendritic cells (DC) represent a highly specialized blood cell type required for immunity and immune tolerance. We investigate molecular mechanism of DC development from hematopoietic stem cells and DC migration. These studies also extend to general mechanism of cell-biomaterial interaction and their impact on cell motility and adhesion.

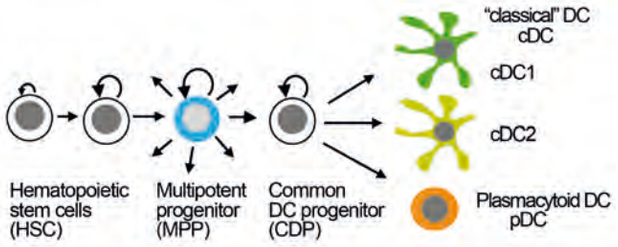


Fig 1: *Hematopoietic stem cells develop into specific DC subsets cDC1, cDC2 and pDC by successive steps of lineage commitment and differentiation.*

Finally, computational approaches are being widely used to study gene expression, chromatin architecture and gene networks in both normal physiological and pathological states. We would like to congratulate our computational expert Ivan Costa for accepting the position as Professor and founding head of the Institute for Computational Genomics, Joint Research Center for Computational Biomedicine, RWTH Aachen University, Aachen, Germany.

iPS Cells for Disease Modelling in vitro

Patient specific cells for studying human diseases are limited or not available. Here iPS cell technology provides a solution: iPS cells represent an inexhaustible cell source and can differentiate into cells of all three germ layers and thus a large array of cell types are readily obtained for disease modelling in vitro (Zenke, 2017; Zenke et al., 2017).

Our focus is on immunodeficiency and hematopoietic malignancies, such as leukemia. We have generated iPS cells deficient in the transcription factor IRF8 by CRIPSR/Cas (Sontag et al., 2017a; 2017b; Sontag and Zenke, 2017; Fig. 2) and patient specific iPS cells harbouring leukemia causing and/or associated mutations, such as those in Jak2, Kit,

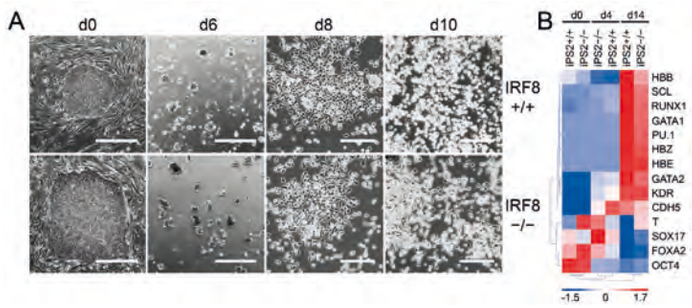


Fig. 2: *iPS cells deficient for IRF8 and controls (IRF8-/- and IRF8+/+, respectively) are differentiated into hematopoietic progenitors in embryoid body assays (A) and analysed for specific changes in gene expression by qRT-PCR (depicted in heat map format in B; red, high gene expression; blue, low gene expression; Sontag et al., 2017a).*

Tet2, NFE2 and Asxl1 (in collaboration with Department of Hematology, Oncology, Hemostaseology and Stem Cell Transplantation, RWTH Aachen University Hospital, Aachen, Germany and Department of Medicine I and Ludwig Boltzman Cluster Oncology, Medical University, Vienna, Austria). Patient specific iPS cells are differentiated into leukemic cells and used for molecular studies and compound screening (in collaboration with Department of Organic Chemistry, RWTH Aachen University, Aachen, Germany).

To study large scale production of patient specific iPS cells a new cell production facility is being set up (iCellFactory, Fig. 3; in collaboration with Laboratory for Machine Tools and Production Engineering, WZL, RWTH Aachen University (mechanical design, automation and control software) and Fraunhofer Institute for Production Technology, IPT (microscopy), Aachen, Germany).

Fig. 3: *New robotic system for automatic iPS cell production under construction.*

EMT Regulators as Switches in DC Development

DC originate from hematopoietic stem cells in bone marrow (Fig. 1) and exit the bone marrow niche as precursors to immigrate into peripheral tissues, such as skin (Fig. 4). Here DC become sessile and functionally embed to act as sentinels of the immune surveillance system. Following antigen uptake DC are activated, emigrate the peripheral tissue and travel via lymphatic vessels to lymphoid organs where they encounter T cells to present processed antigens (Fig. 4). We investigate signaling via TGF-β1 receptor and hepatocyte growth factor (HGF) receptor (also known as MET) in DC development, function and migration. We propose that mechanisms of mesenchymal-to-epithelial transition (MET) and epithelial-to-mesenchymal transition (EMT) are important for generating sessile and migratory DC, respectively (Hieronymus et al., Semin. Cell Dev. Biol., 2015; Sagi and Hieronymus, 2017, in press). In addition, a study in collaboration with Hovav et al., Hebrew University, Jerusalem, Israel revealed a differential and sequential role of BMP7 and TGF-β1 in differentiation of Langerhans cells (LC), the contingent of DC in the stratified squamous epithelia (Capucha et al., 2017). Hence, we propose the concept that EMT and MET programs are regulated in DC/LC development by Met, and TGF-β1 and/or BMP7 signaling, respectively (Fig. 4).

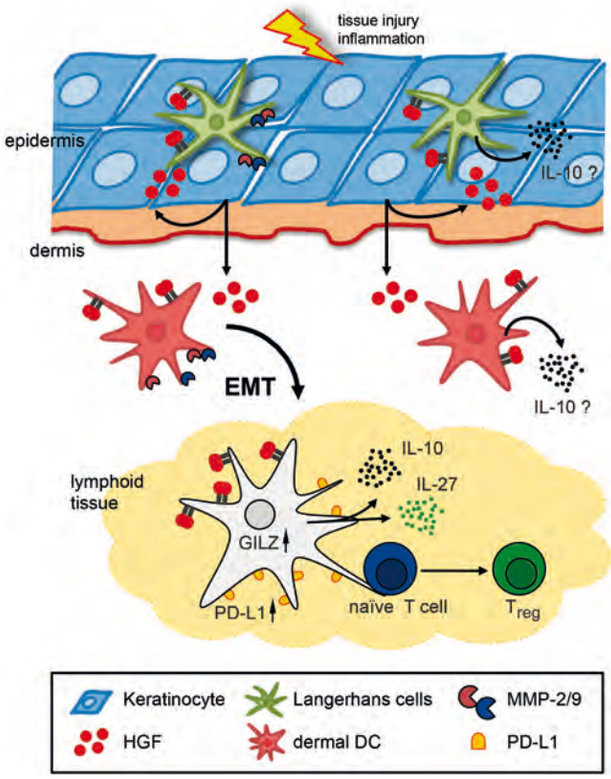


Fig. 4: HGF/Met signaling induces LC and dermal DC emigration from skin in an EMT-like process, including matrix metalloproteinase (MMP) activation to facilitate arrival in lymph nodes and antigen presentation to naive T cells. In addition, HGF induces tolerogenic phenotypes by IL-10 and IL-27 secretion which results in enhanced numbers of regulatory T cells (Tregs).

Epi-Blood-Count: DNAm Based Leukocyte Subset Quantification

Analysis of the cellular composition of blood is a routinely requested laboratory test in hematological diagnostics. So far such measurements done with fresh blood samples and immunophenotypic analysis are labour intensive. Here we established an alternative approach based on DNA methylation (DNAm) measurements at individual CG dinucleotides (CpGs) that reflect the relative composition of leukocytes. The DNAm measurements, referred as "Epi-Blood-Count" show nearly the same precision as conventional hematocytological methods and are applicable also to frozen blood samples (in collaboration with Department of Hematology, Oncology, Hemostaseology and Stem Cell Transplantation and Institute for Immunology, RWTH Aachen University Hospital, Aachen, Germany).

Predicted blood counts for granulocytes, lymphocytes and monocytes – based on our "Epi-Blood-Count" – correlate well with measurements on a hematology analyzer (Fig. 3A). In analogy, the method is also applicable to other leukocyte subsets, such as CD4 T cells, CD8 T cells, B cells and NK cells. Additionally, the calculated absolute cell numbers based on DNAm correlate nicely with absolute cell counts (Fig. 3B). Our Epi-Blood-Count approach allows determining white blood cell composition in frozen blood samples, improves the cost effectiveness and advances the standardization of white blood cell counts (Frobel et al., in press).

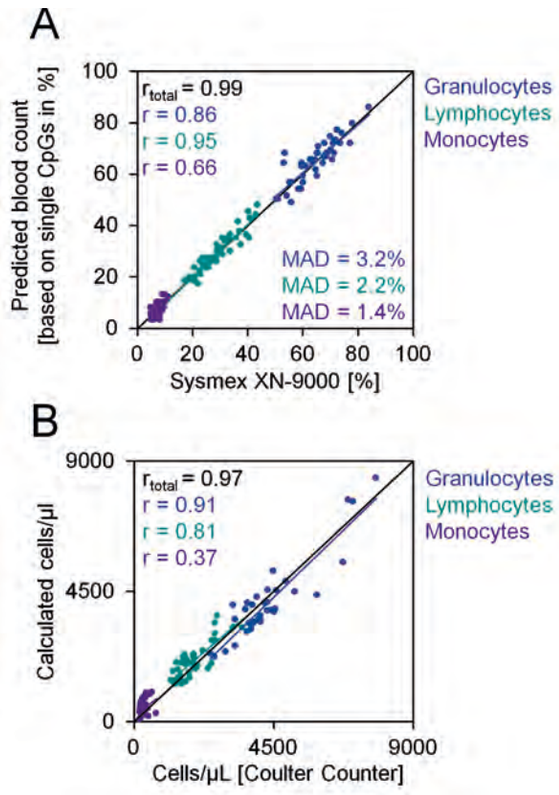
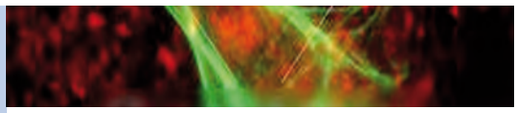


Fig. 5: Leukocyte subset Epi-Blood-Count and absolute quantification of cells based on DNA methylation (Frobel et al., in press).



Solution Blow Spinning Fibres for the Analysis of Cell Motility and Adhesion

New technologies have made possible the development of polymeric biomaterials with controlled geometry and physico-chemical properties. Solution blow spinning technique has the advantage of ease of use allowing the production of nano or microfibres and the direct fibre deposition on any surface in situ. Yet, very little is known about the influence of such fibres on biological functions such as immune response and cell migration. We engineered polymeric fibres composed of either pure poly(lactic acid) (PLA) or blends of PLA and polyethylene glycol (PEG) by solution blow spinning (SBS) and determined their impact on DC and on cell adhesion and motility (Paschoalin et al., 2017).

Cells readily interacted with fibres resulting in an intimate contact characterised by polymerisation of actin and the accumulation of focal adhesion components at sites of cell-fibre interactions (Fig. 6). Remarkably, fibres did not elicit any sizeable increase of activation markers and inflammatory cytokines in DC, which remained in their immature (inactive) state (Paschoalin et al., 2017). These findings will allow the development of new biomaterials for tissue engineering and regenerative medicine.

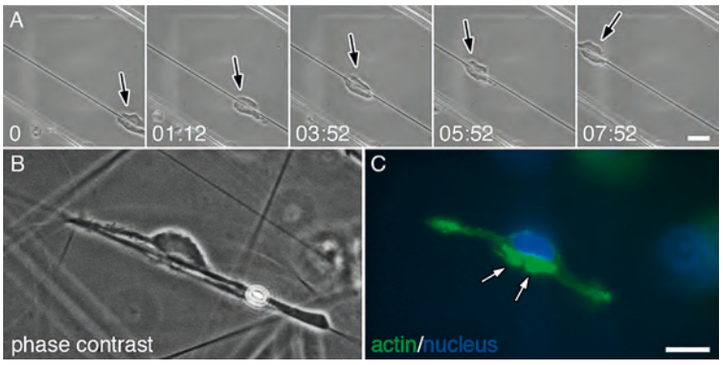


Fig. 6: *Motility of mouse DC along SBS fibres. DC were seeded on fibres for 24 hours before being imaged at 37°C, 5% CO2. The arrow points to a DC moving in a high directional way along one SBS fibre. Numbers indicate elapsed time in minute and seconds. Immunofluorescence microscopy of mouse DC seeded on SBS fibres (B, C). Note the accumulation of actin filaments at cellular regions in contact with SBS fibres (white arrow in C). Cell nucleus stained with DAPI (blue); actin filaments stained with Alexa 488-phalloidin (green). Scale bars: 20 µm (for A), 10 µm (for B, C) (Paschoalin et al., 2017).*

Computational Approaches for Personalized Medicine in Type II Diabetes

Type 2 diabetes (T2D) is a disease with an increasing prevalence in industrialized countries. T2D is currently treated with a combination of lifestyle changes and pharmacological therapies. However, there are no specific guidelines for how to use available anti-diabetic drugs to target the underlying genetic traits. In a collaborative work with Anders Rosengren (University of Gothenburg, Sweden), we have analysed genome-wide data from T2D patients to find novel biomarkers and evaluate therapeutic approaches targeting these genes.

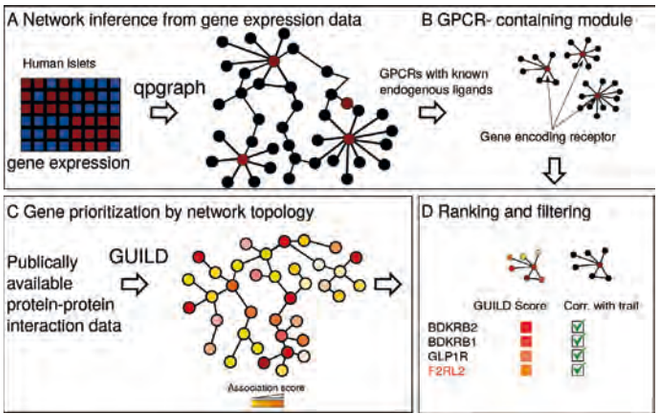


Fig. 7: *Workflow of the computational strategy to find modules of receptor genes dysregulated in T2D patients.*

In a first study, we propose a methodology to identify receptor modules dysregulated in T2D patients using co-expression networks (Fig. 7). We demonstrate that the receptor PAR3 is associated with increase in insulin secretion. Moreover, antibodies blocking PAR3 counteracted the insulin secretion of pancreatic beta cells (Hänzelmann et al., 2016). Next, we performed an integrative analysis of gene expression and open chromatin data on T2D patients. We observed binding of the Sox5 transcription factor in genes, which are down regulated in T2D patients and are associated to open chromatin in precursors of islet cells. This indicates an association of Sox5 with islet cell maturation. Importantly, treatment of T2D diabetic mice with inhibitors of a chromatin remodelling factor rescued Sox5 expression and restore normal insulin secretion (Axelsson et al., 2017).

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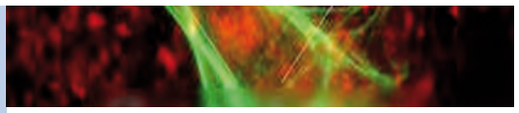
[2] Verfahren zur Bestimmung der Zellzahl von eukaryotischen Zellen; 2017; Az: 10 2017 004 108.3 (Wagner W, Bozic T)



Team

On the Left: Poster Award to Kristin Seré, PhD at Medical Sciences Day 2017, Medical Faculty, RWTH Aachen University

Figure below: Lab Retreat in Antwerp, Belgium

Visiting the opencast coal mining area Weisweiler in the vinicity of Aachen, Germany

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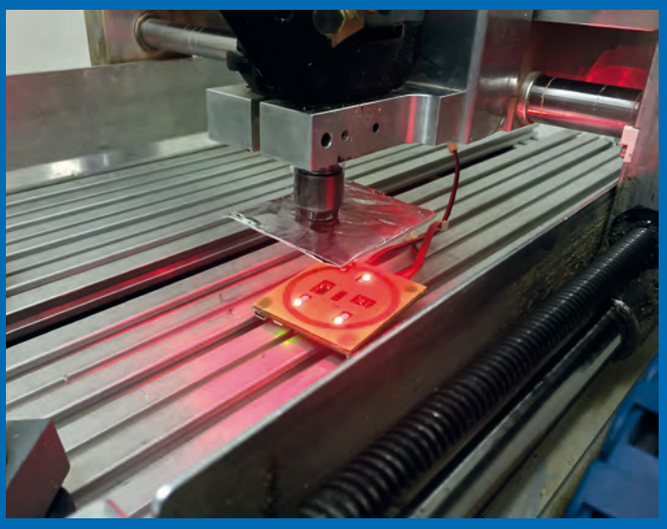
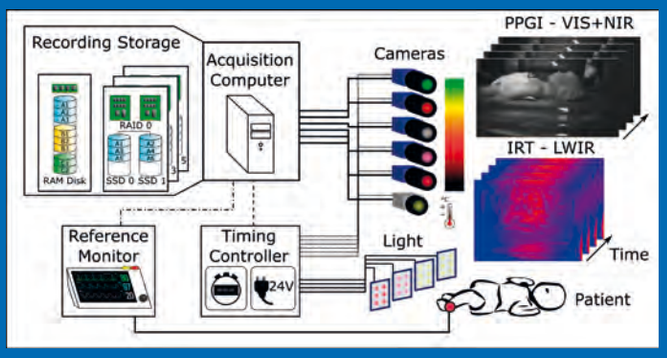
Medical Information Technology

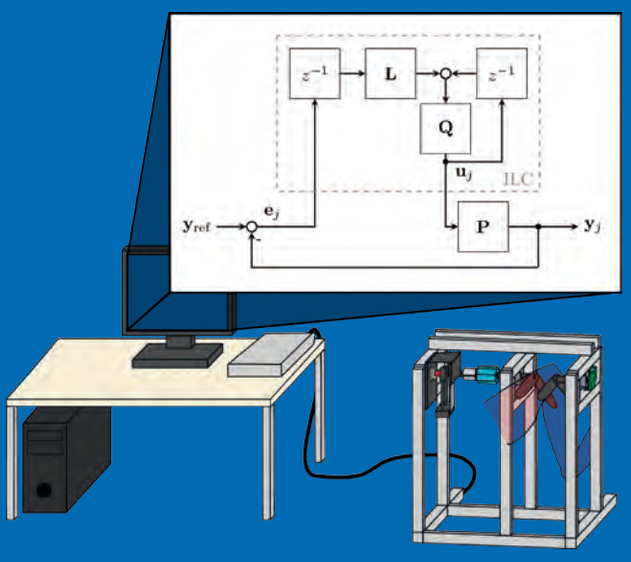
Faculty of Electrical Engineering
and Information Technology

RWTH AACHEN UNIVERSITY

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.

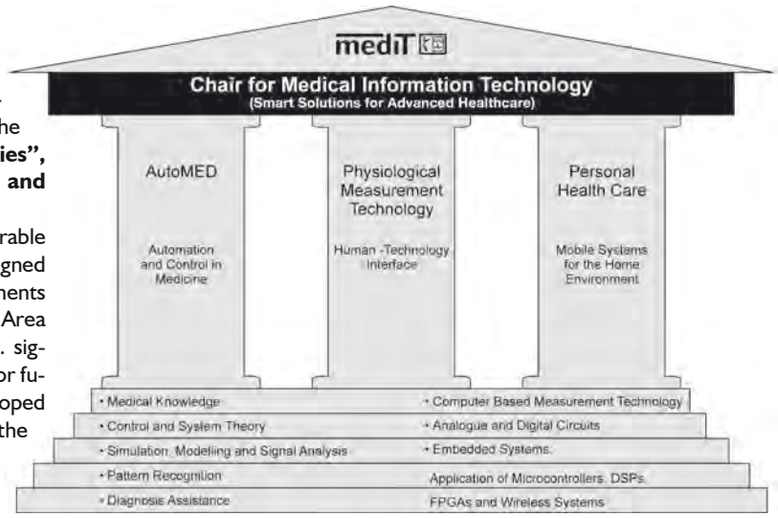

Fig. 1: *Research profile of MedIT.*

Ongoing Research – Selected Projects

Regional Lung Perfusion by Electrical Impedance Tomography

In intensive care unit, gas exchange in the lung of patients with acute respiratory distress syndrome (ARDS) is often severely impaired. For these patients, a careful guidance of ventilation therapy is essential for survival. Regional lung ventilation (V) and regional lung perfusion (Q) are the critical variables for ventilation care. Due to the fact that gas exchange only takes place in lung regions of both adequate ventilation and perfusion, it would be highly beneficial to also measure and quantify regional lung perfusion. Electrical impedance tomography (EIT) can be applied to monitor regional lung perfusion in real-time at bedside, which is a noninvasive and radiation-free imaging modality. The principle of EIT is based on the injection of small current into electrode pairs in a successive order of a belt (usually 16 or 32 electrodes) that is placed around the thorax of the patient. This yields different voltages across the thorax from which tomographic images of

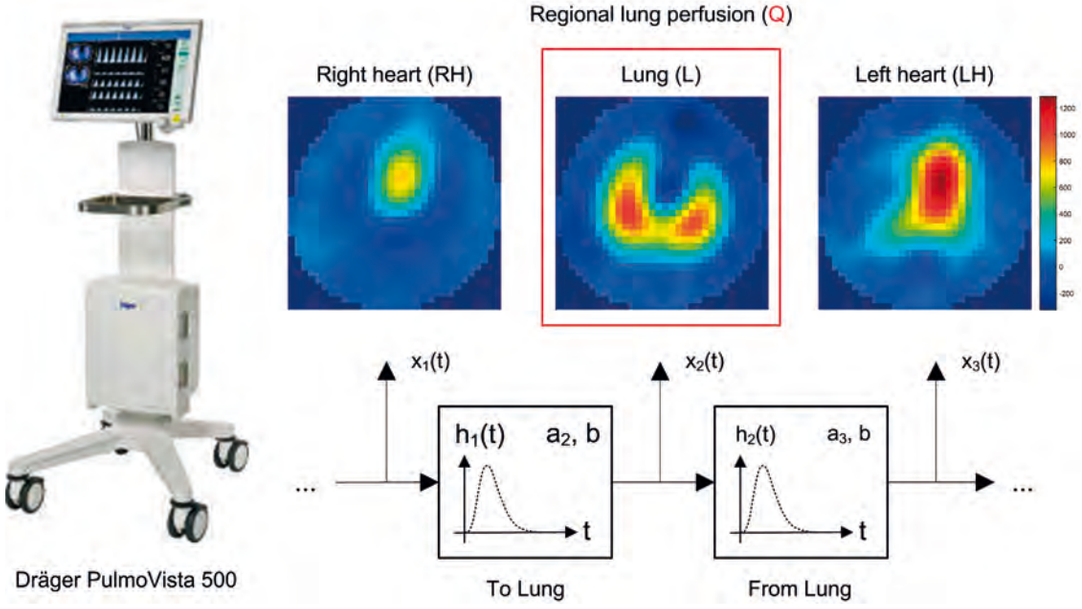

Fig. 2: *Monitoring of regional lung perfusion based on electrical impedance tomography.*

tissue impedance can be reconstructed. Tissue impedance strongly varies with lung air content and it yields the ventilation-related signal (VRS) from which regional lung ventilation is obtained. Regional lung perfusion can be determined either from the cardiac-related signal (CRS) or the indicator-based signal (IBS). While the CRS describes impedance changes in the lung region resulting from pulsatile activity of the heart, the IBS can be obtained by electrically conductive contrast agents, such as hypertonic saline. The focus of this project is to monitor regional lung perfusion based on the IBS. The work covers model-based algorithms and signal processing to separate right-heart (RH), lung (L) and left-heart (LH) phases of the IBS. Furthermore, it involves finite element simulation (FEM) and in-vivo validation of contrast agents in order to advance clinical applicability. The overall motivation is to derive regional ventilation to perfusion ratio (V/Q) by EIT to achieve patient individual, lung protective guidance in ventilation therapy.

Funded by: German Research Foundation (DFG)

Parkinson's Disease Monitoring

Parkinson's disease (PD) is the most common neurodegenerative disease and its predominance is growing in population ageing. It is associated with a series of neurological movement disorders. These include the main symptoms of the well-known Parkinsonian triad, which is defined in terms of rigidity (stiffness of the extremities and cogwheel effect), tremors, and akinesis / bradykinesis (movement deprivation / deceleration). Most of these syndromes are directly connected to the movement. For the diagnosis of Parkinson's disease, the occurrence of one of these symptoms can be used among other symptoms such as freezing of gait (FoG), postural instability, and orthostatic dysregulation, which appear individually.

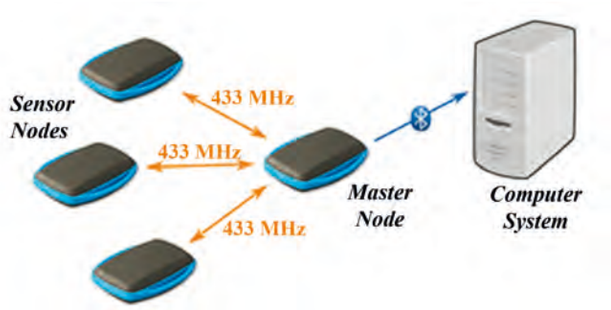

Fig. 3: System configuration of body sensor network (BSN) with the application to Parkinson's disease monitoring.

The focus of this project is to develop a body sensor network (BSN) distributed over the body (i.e. wrists, joints, ankles), which is able to accurately classify and quantify the various Parkinsonian symptoms by using different sensor modalities for real-time monitoring. To this end, biomechanical and physiological models are designed in order to identify appropriate parameters for assessing the patient's constitution by fusion of the collected sensor data and the classification of movement type is of particular interest, which can be used not only for Parkinsonian symptom but also for the fall prediction.

Video Camera-based Functional Imaging of Vital Signs

Contactless monitoring of vital signs is advantageous for patient comfort. Compared with conventional sensors such as photoplethysmography (PPG) or temperature probes, camera-based sensing does not require cabling or skin contact and it does not carry the risk of medical adhesive-related skin injuries (MARSI). These modalities can be therefore used for patients with sensitive skin like neonates. Videos carry spatially resolved information of vital signs.
In thermal imaging, temperature values can directly be extracted from the video sequence. In light-based video cameras, signal processing can be used to extract the PPG signal from skin pixels. Here, each pixel is used as a remote PPG probe. Consequently, a variety of vital signs can not only be extracted from a single point but also from the whole body regions. Thus, spatial differences can be made visible and allow for enhanced diagnostics. Similar to imaging modalities such as computer tomography (CT) and magnetic resonance imaging (MRI), a functional assessment becomes feasible. Currently, processing power is insufficient for real-time computing of imaging applications. However, this allows remote monitoring of heart rate and breathing rate as classical one dimensional (1D) vital signs.

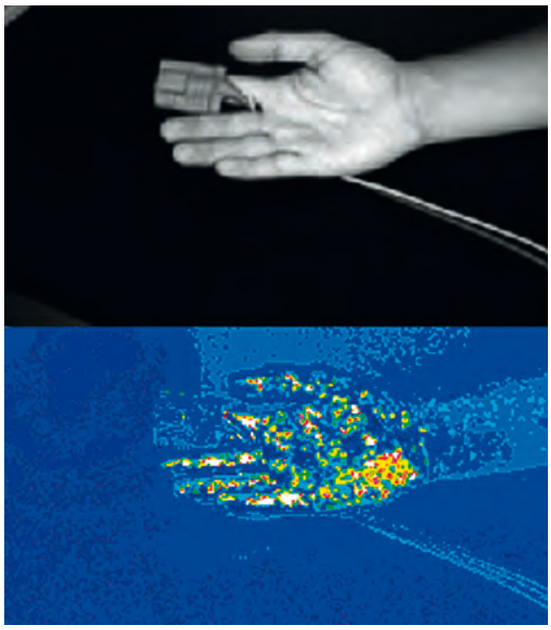

Fig. 4: Functional imaging of vital signs.

To demonstrate the imaging approach, the first illustration in Fig. 4 shows a single preprocessed image of a video sequence of a hand. Here, pixels are grouped together which results in a blurry and blocky representation. The second illustration shows the mapping of the signal strength of alternating AC components in relation to slow varying DC components extracted from the video sequence. Strong variation can be observed in the palm of the hand, where blood volume clouds move over time. In comparison, there is less variation visible at the forearm. Further research will focus on the robustness of the sensing modalities and their potential for medical applications.

Vital Signs Monitoring with Seat Integrated Sensors for Driver State Estimation

Due to the progression of autonomous and semi-autonomous driving, research in driver state estimation has become a topic of increasing interest. Nevertheless, the driver state can be used to improve road safety in all stages of the development towards autonomous cars. For example, in non-autonomous cars, if inattention is detected, warning signals can be played via speakers. For semi-autonomous cars, an emergency maneuver can be initiated, if the driver does not respond to first warning signals. The information can also be used to make a safer transition between autonomous and human controlled driving with improved human-machine interaction (HMI). If the driver is incapable of driving, i.e. falling asleep or fainting, vital signs allow detecting, whether the driver needs medical attention and an ambulance should be informed.

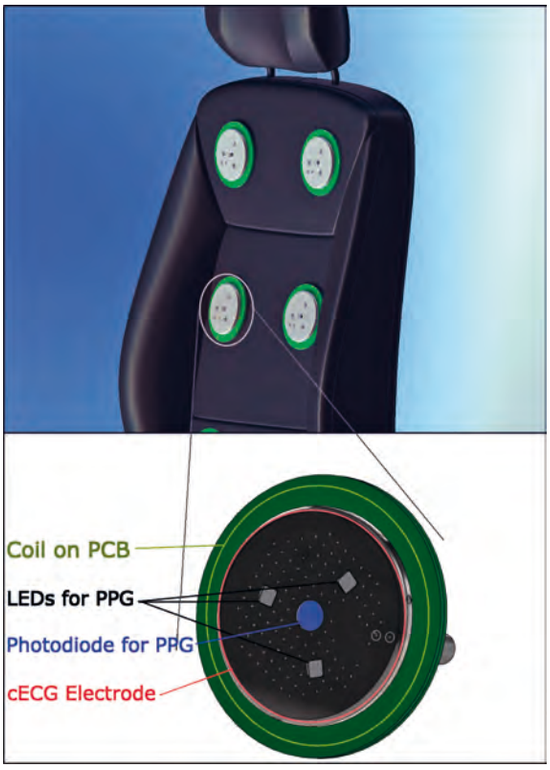

Fig. 5: Car seat integrated with multi-sensors for driver state estimation.

To preserve the convenience of today's driving, our research is focused on unobtrusive measurement techniques for driver state estimation. These sensors have inferior signal quality and are more prone to movement artifacts compared to attached counterparts. In this project, a seat integrated multimodal solution is evaluated. The history of driver state monitoring at MedIT started with the capacitive ECG (cECG) integrated into the driver seat. In subsequent studies, sensors have been evaluated in multiple studies. There have been, for example, studies with cameras, cECG and magnetic induction measurement (MIM). A new multimodal sensor, which combines the measurement of cECG, MIM and PPG through the fabric in a single unit, is developed and evaluated in the car. The goal of the sensor is to robustly extract heart rate (HR) and respiratory rate (RR) with high coverage rate in automotive environments. Therefore, data from multiple sensors, each combining the three mentioned measurement modalities, will be fused to estimate the parameters. Further signal features will be extracted and data-driven algorithms will be developed to detect driver states.

Funded by: European Union's Horizon 2020 research and innovation programme

A New Centre for Gerontotechnology

Non-contact and unobtrusive vital signs monitoring has nowadays become one of the most important research topics. To this extent, we bring our existing non-contact measurement technologies into a new area of Geriatrics that focuses on personal health care of elderly people for individual needs. A patient room laboratory and a motion laboratory have newly set up in Franziskushospital Aachen, which is part of the new Department of Geriatrics at RWTH Aachen University that we cooperated with. In the patient room laboratory, various non-contact sensors have been installed, for example, photoplethysmography-imaging (PPGi), infrared thermography, capacitive ECG sensor integrated in bed and further advanced signal processing algorithms are developed in order to unobtrusively extract vital signs such as heart rate and respiratory rate.

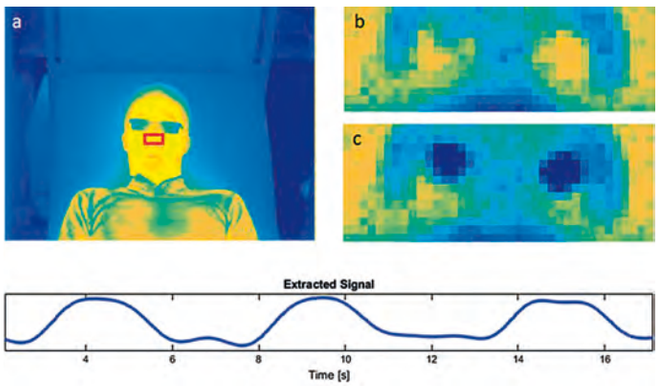

Fig. 6: Measurement of respiratory rate using infrared thermography. a: thermal image. b: area around the nose during expiration (warm). c: area around the nose during expiration (cold). Bottom: extracted respiration signal.

Due to the fact that non-contact monitoring techniques are more sensitive to patient's movement than conventional measurement modalities, we also use multiple sensors and sensor fusion technologies to enhance robustness and the strength of the signals.

In the motion laboratory, we develop and test personal healthcare devices and also perform gait analysis since accurate examination of the locomotor system is of importance in rehabilitation, gerontology and sports medicine. Different technologies can be used for the gait analysis, for example, body-supported inertial sensor nodes, multi-camera system and stationary pressure/force measuring devices. In our new facility, the development of gait training and gait therapy concepts can be realizable with the application to patient-oriented rehabilitation robotics. A wide range of researches has been conducted in terms of human biomechanical models of muscular activity towards electromyography (EMG), testing rehabilitation robotic prototypes under clinically approved conditions and its safety concern, and the specific mobility limitations of the patient target group.

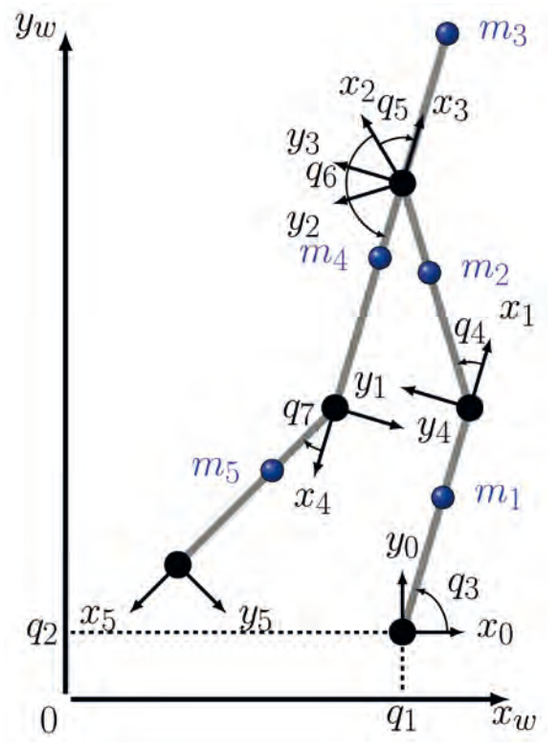

Fig. 7: *Model of the human lower extremity.*

For instance, a musculoskeletal model of the human lower extremity is shown in Fig. 7 in order to simulate musculotendon function and muscle coordination during movement. The model incorporates the salient features of muscle and tendon, specifies the musculoskeletal geometry and musculotendon actuators. This includes the active isometric moment of these actuators about the hip, knee, and ankle joints.

Fig. 8: *Motion laboratory located at Franziskushospital Aachen.*

The new established cooperation has been made with kinesiologists from the team of Prof. Dr.med. Bollheimer from the Department of Geriatrics at RWTH Aachen University Hospital. Future research questions can therefore be addressed.

Funded by: Robert Bosch Foundation

Blood Glucose Modelling and Control for Diabetes Patients

The number of people with diabetes mellitus was around 415 million worldwide in 2015 and is predicted to increase to 642 million by 2040. Approximately 10% of them have diabetes mellitus Type 1, which means they always need exogenous insulin injection to regulate their blood glucose. Improper control of their blood glucose concentration can lead, on the one hand, to hyperglycemia and induced secondary complications, on the other hand, to hypoglycemia, which may be caused by over-delivery of insulin and is life-threatening. Proper control of patients' blood glucose concentration is therefore essential to improve health and quality of life. To achieve this goal, the combination of theoretic and clinical research is carried out to facilitate the development of innovative control strategies and to enhance the understanding of the glucose metabolism. Specifically, animal trials on Göttingen MiniPigs were conducted for mathematical modelling of the glucose metabolism, which is crucial for model predictive control design and for in silico studies.

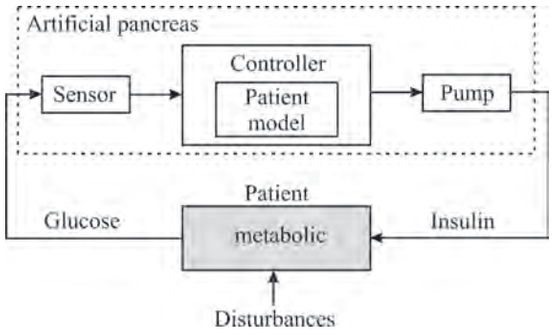

Fig. 9: *Schematic of blood glucose management with an artificial pancreas.*

Theoretical work focuses on state observers and controllers that are capable of controlling of glucose for a broad spectrum of patients. This is an essential field of research because inter-patient and intrapatient variations are relatively high. Recent work merged machine learning methods with model predictive control for personalized control in personal health care. With this new approach, the controller is able to intensively learn and intelligently change patient-specific parameters during closed-loop control and incorporate the predicted future parameter changes in the control decision. Our expertise in the field of glucose modelling and control is enlarged with a newly started cooperation. As part of the Karman Fellowship program, bilateral guest visits with Harvard University have initiated this new cooperation in 2017. From the RWTH Aachen, Dr. Berno Misgeld and Lukas Ortmann have visited Harvard University, Cambridge, MA, USA.

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Prizes and Awards

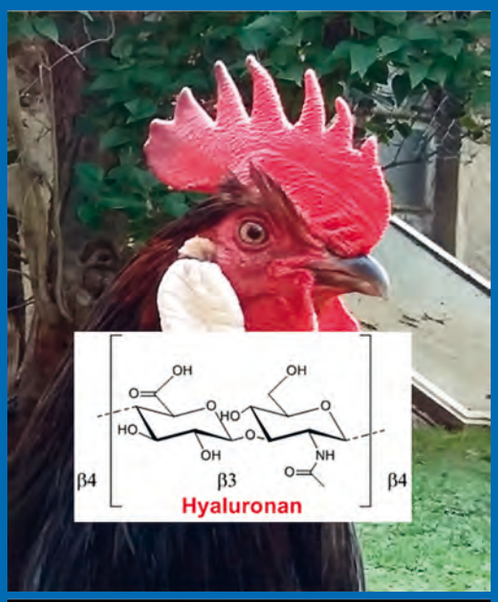
- B. Misgeld: RWTH ERS fund at Harvard John A. Paulson School of Engineering and Applied Sciences, Cambridge, MA, USA.
- C. Hoog Antink and B. Penzlin won 1st Prize awards in session "Biomedical Engineering", D. Rüschen won 3rd Prize award in session "Electronics and Instrumentation", and D. Umutcan Uguz received an undergraduate prize at the 21st International Student Conference on Electrical Engineering (Poster 2017), Prague, Czech Republic.
- V. Blazek: Medal award in the garden of the senate of the Czech Republic.
- D. Rüschen: 2nd Prize at the Young Investigators Competition at the European Medical and Biological Engineering Conference (EMBEC), Tampere, Finland
- C. Castelar: 2nd Prize at The 9th Meeting of the International Society for Hydrocephalus and Cerebrospinal Fluid Disorder, Kobe, Japan

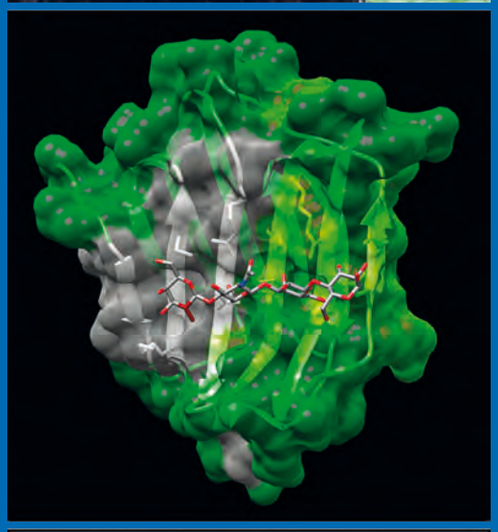
People at MedIT

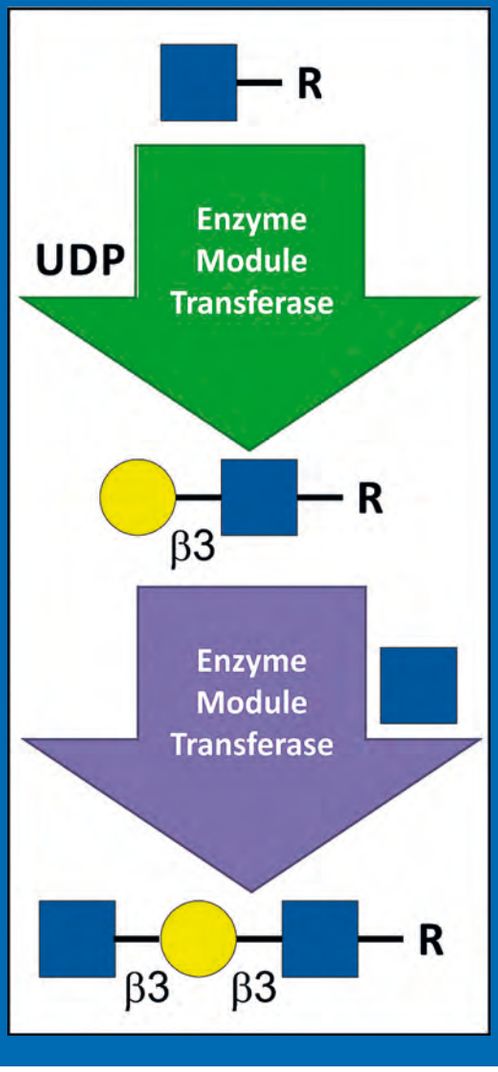
Laboratory for Biomaterials

Faculty of Mathematics,
Computer Science and
Natural Sciences

From Genes to Glyco-conjugates







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Introduction

Glycoconjugates is a class of biomolecules carrying biofunctional sugar moieties. The mammalian cell surface and its microenvironment are 'sweet'. Glycoproteins, glycolipids, and proteoglycans present sugars on the cell surface and in the extra-cellular matrix (ECM). Their complex oligosaccharides (glycans) serve as 'multifunctional information carriers' and play a vital active role in intercellular communication events and for the contact of cells with the ECM. Sugars are also important for the bioactivity of natural products, such as antibiotics and anti-tumor compounds, and for the detoxification of xenobiotics.

Novel glycan-based biomaterials are of special interest as diagnostic and therapeutic tools. Also in 2017, we pursued our research studies for the synthesis and applications of glycoconjugates. The basis is our enzyme toolbox to develop and optimize synthetic enzyme cascades. High-throughput analysis is essential for fast screening of reaction parameters. In this way, our combinatorial approach leads to the synthesis of complex glycan structures and biopolymers such as hyaluronic acid. In cooperation with our partners, we incorporate glycans as biofunctional units into polymeric microgels. Binding studies with lectins, the 'sugar-reading' proteins, are another important focus of our research studies. Multivalent glycan presentation is the key to identify high-affinity glycoconjugates. In our studies, we work on glycan-based inhibitors for tumor-related galectins and glycopolymer toxin scavengers. This chapter compiles our most recent results from ten peer-reviewed publications in 2017.

The scope of our BMBF funded project 'The Golgi Glycan Factory' is the development and establishment of novel multi-enzyme modules for the synthesis of nucleotide sugars and glycans (Fig. 1).

Novel synthesis modules for e.g. UDP-α-D-galactose (UDP-Gal) were established and straightforwardly developed to high space-time yields utilizing an analytical multiplexed capillary electrophoresis system (MP-CE) as high-throughput screening system for parameter optimization.

By the use of well available and affordable substrates, the salvage pathway-like synthesis routes provide the essential nucleotide sugar for the *Leloir*-glycosyltransferases mediated glycan synthesis. In combination with novel transferase modules we synthesized novel (poly-)*N*-acetyllactosamine type I glycan structures for binding studies of tumor associated galectins revealing novel insights into binding specificities of Gal-3 and Gal-3Δ.

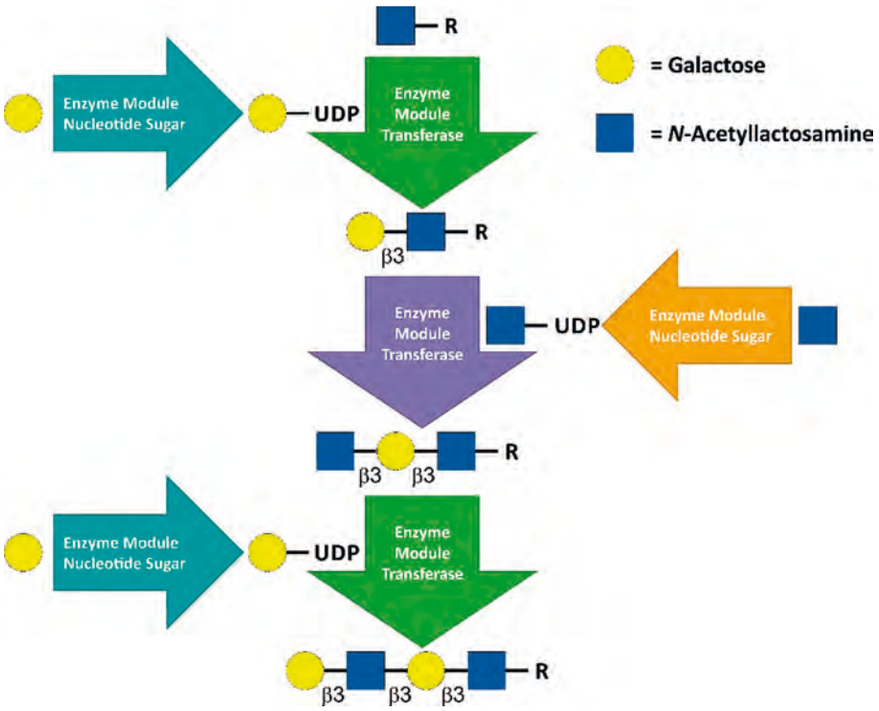

Fig. 1: *Reaction scheme of a multi-enzyme cascade reaction for the glycan synthesis.*

Combinatorial Biocatalysis

a. The Golgi Glycan Factory (GGF)

Leloir-glycosyltransferases utilize nucleotide-activated sugars for the formation of several glycan structures (Fig. 1). Due to an excellent stereo- and regioselectivity, they are the way of choice for the synthesis of complex glycan structures. Further development of synthesis strategies is an important future task to provide novel structures in the required quantities to nutrient, pharmacological or biomedical research and industry, which have shown a rising interest in this field in the last decades. Modularization is a characteristic quality of modern production lines and factories. The major benefit is that it enables an efficient way to set up flexible assembly lines.

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Financial Support

Financial support by the BMBF, funding the projects "The Golgi Glycan Factory" and "The Golgi Glycan Factory 2.0" (AZ: -31P7317 and AZ: 031A557A) in the BMBF program Biotechnology 2020+ - Basic Technologies, is gratefully acknowledged.

b. Optimization of Enzyme Cascades for the *in vitro* Synthesis of Hyaluronic Acid

Hyaluronan (HA) is a linear glycosaminoglycan composed of β1,4-glucuronic acid (GlcA) and β1,3-*N*-acetylglucosamine (GlcNAc) with a molecular weight (MW) of up to 10^7 MDa. As poly-anion, HA binds huge amounts of water resulting in visco-elastic gel properties. These features make the non-immunogenic HA useful for medical and cosmetic applications (Fig. 2). Current industrial production is based on extraction from rooster combs or biotechnological production with *Streptococcus*. Contaminations with proteins or viruses could cause allergic reactions or infectious diseases. These processes are time-, cost- and labour-intensive. A challenging task is still to obtain HA with a high molecular weight (>2 MDa) with low polydispersity.

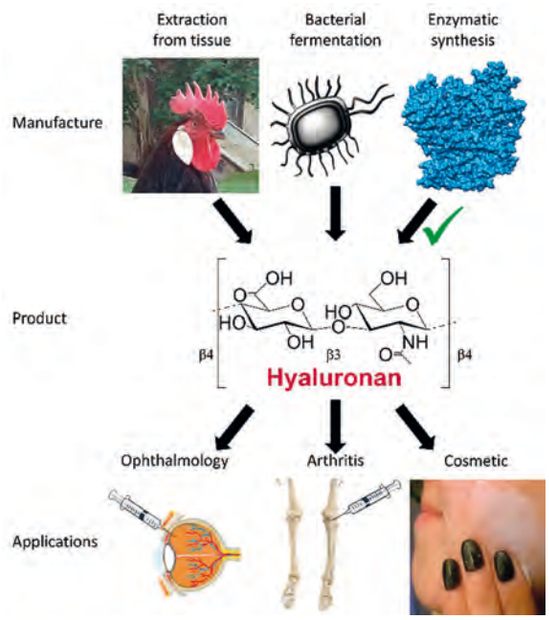

Fig. 2: Production and applications of hyaluronic acid. In contrast to enzymatic synthesis, the extraction from rooster combs and bacterial fermentation has disadvantages such as contaminations and varying product quality. A highly defined product is very important for medical and cosmetic application.

We aim at a cell-free process for optimal production of monodisperse HA with a molar mass of >2 MDa. Starting from the monosaccharides GlcA and GlcNAc, we develop enzyme cascades for UDP-GlcA and UDP-GlcNAc syntheses. Both modules are combined with the hyaluronan synthase (HAS) module to produce HA in one reaction step.
To guarantee efficient combination of all three enzyme modules for one-pot HA synthesis, reaction conditions are optimized and analyzed by multiplexed capillary electrophoresis (MP-CE) (Fig. 3).

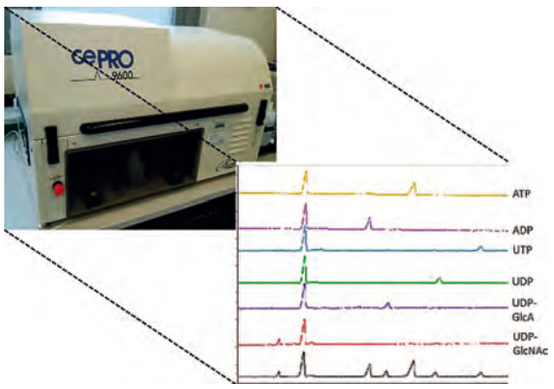

Fig. 3: Electropherogram of nucleotides and nucleotide sugars separated by multiplexed CE. The MP-CE analyzes reaction parameters in high-throughput.

The final goal of our project is the development of a multi-enzyme membrane reactor. Together with our project partners from RWTH Aachen University and our industrial partner, we work on efficient enzyme production and enzyme immobilization. Based on our collective results a membrane reactor with immobilized enzymes shall be constructed for continuous and efficient production of HA.

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Financial Support

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c. Synthesis of Guanosine 5´-diphospho-β-L-galactose

Nucleotide sugars are activated monosaccharides that serve as donor substrates in glycan synthesis catalyzed by *Leloir*-glycosyltransferases (GTs). Guanosine 5'-diphospho-β-L-galactose (GDP-L-Gal) is a nucleotide sugar, which occurs in plants and algae as an intermediate in the synthesis of L-ascorbic acid. Although being of high interest for the *in vitro* synthesis of glycoconjugates and the characterization of novel GTs, this particular substrate is not commercially available. One reason for this is the low yield in the chemical synthesis of this compound. Likewise, the enzymatic synthesis approaches starting from GDP-D-Man so far were hampered by the formation of the by-product GDP-L-gulose, which led to a lower yield and a more complex purification approach.

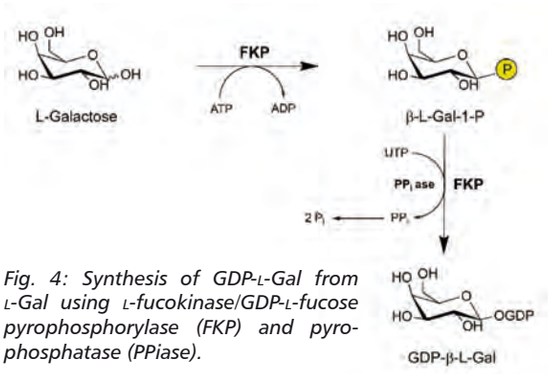

Fig. 4: Synthesis of GDP-L-Gal from L-Gal using L-fucokinase/GDP-L-fucose pyrophosphorylase (FKP) and pyrophosphatase (PPiase).

In our approach, we utilized the enzyme L-fucokinase/GDP-L-fucose pyrophosphorylase (FKP) from *Bacillus fragilis* (Fig. 4). The one-pot synthesis of GDP-L-Gal starting from L-galactose is combined with a simple purification of the product. Furthermore, analysis of the reaction is monitored via high-throughput multiplexed capillary electrophoresis (MP-CE).
We used FKP previously for the synthesis of GDP-β-L-Fuc from L-Fuc, a structural analogue of L-Gal. Due to the enzyme's broad substrate spectrum, L-Gal is also accepted as a substrate, thereby enabling the synthesis of GDP-L-Gal. The overall yield of 92 % is the best achieved so far. Product isolation was accomplished by salting-out with organic solvents and subsequent ion exchange chromatography. GDP-L-Gal can be used as a substrate for the characterization of novel glycosyltransferases or as a building block of glycoconjugates.

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doi:10.1002/adsc.201700901

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The Glyco-BioInterface

a. Development of a glycan library and production of glycan-functionalized microgels to scavenge *Clostridium difficile* toxins.

Bacterial toxins are known to bind to cell-surface glycans, induce cellular processes and damage their targets in human bodies. One bacterial representative is *Clostridium difficile*, which colonizes the human colon and destroys the cell layer via production of the toxins TcdA and B. These inhibit Rho-dependent GTPases and therefore cytoskeletal processes and shatter the epithelial cell layer. Fig. 5 shows the structure of TcdA with its four domains, especially the lectin domain, which binds to glycans.

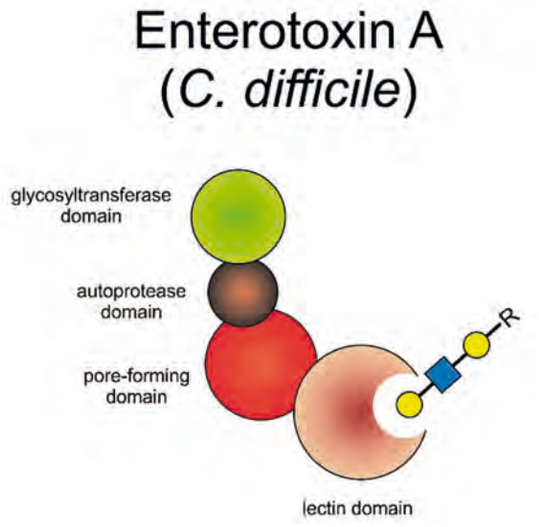

Fig. 5: *Structure of TcdA with its four domains.*

Human glycan structures to which TcdA and TcdB bind are still unknown. However, the non-human Galili epitope (Fig. 6) has been identified as a promising ligand for TcdA. The epitope consists of the trisaccharide Galα1,3Galβ1,4GlcNAc and is the starting point for glycan ligand screening in our group.

Bovine serum albumin (BSA) serves as protein scaffold for multivalent glycan presentation. Glycan epitopes based on *N*-acetyllactosamine type I (Galβ1,3GlcNAc) and type II (Galβ1,4GlcNAc) are combined in different manners to present fucosyl- and sialyl-residues. Binding studies finally reveal high affinity glycan epitopes for TcdA.

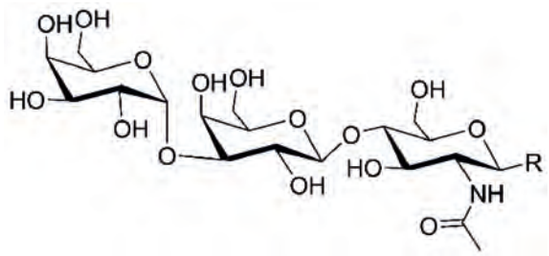

Fig. 6: *Galili epitope. The trisaccharide consists of a N-acetyllactosamine and a terminal α3-linked galactose.*

In our interdisciplinary project in the SFB 985, we aim at the synthesis of glyco-functionalized microgels together with our partners from the DWI-Leibniz-Institute for Interactive Materials and the Clinic of Gastroenterology (RWTH University Hospital Aachen). These microgels (Fig. 7) shall carry the best binders for TcdA and TcdB. *In vivo* studies will verify the scavenging capacity of our gels in infected mice.

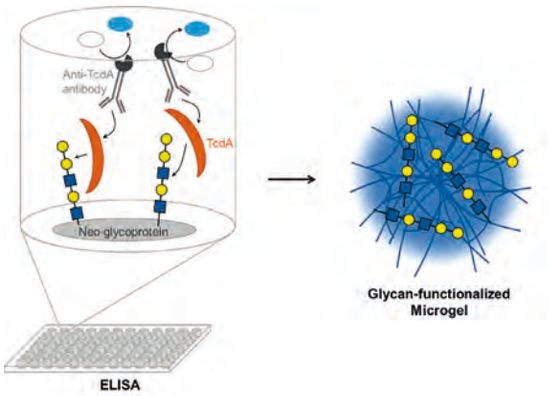

Fig. 7: *Screening of different glycans with BSA as protein scaffold and application of the best binding glycans to polyethylene-microgels for scavenging of toxins in infected mice and humans.*

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Financial Support

DFG in the framework of the SFB 985.

b. Expansion, Evaluation and Application of a Galectin-3 Binding Ligand Library

Galectins belong to a subgroup of carbohydrate-binding proteins, which depict high specificity for *N*-acetyllactosamine (LacNAc). This β-galactoside providing molecule is indeed a precursor molecule for more advanced glycosylation patterns but represents the major interaction partner of galectins. Interestingly, also parasitic glycosylation epitopes, e.g. *N',N''*-diacetyllactosamine (LacdiNAc), are confirmed galectin binders. Galectins are ubiquitously abundant in fungi, invertebrates and vertebrates and are of crucial importance for cellular homeostasis by influencing cellular communication processes. Prototype galectin-1 (Gal-1) and chimera-type galectin-3 (Gal-3) are two of the most thoroughly studied galectins because of their involvement in tumor progression, escape and spreading.
We generate high-affinity carbohydrate ligands for the specific entrapment and detection of galectins. The focus is on the combination of selected sugar-transferring enzymes for the *in vitro* assembly of tailored galectin ligands. After cultivation of recombinant host organisms (e.g. *Escherichia coli*), purification and characterization of the biological catalysts, an efficient chemo-enzymatic production of a (poly-)

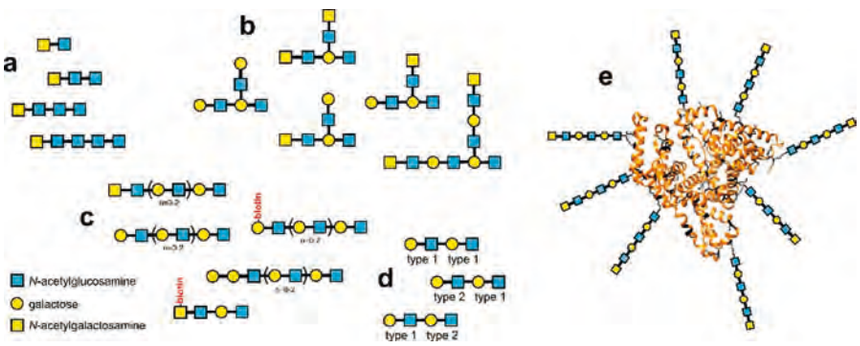

Fig. 8 (left): *Galectin ligand library based on monovalent and multivalent (poly-)LacNAc glycans. Chitooligomers (a), branched Lac(di)NAc structures (b), extended poly-LacNAc with different terminal glycan epitopes (c) and hybrids of LacNAc type 1 and type 2 (d) are generated by sequential or one-pot enzymatic syntheses. Conjugation to non-glycosylated protein carriers yields multivalent neo-glycoconjugates (e).*

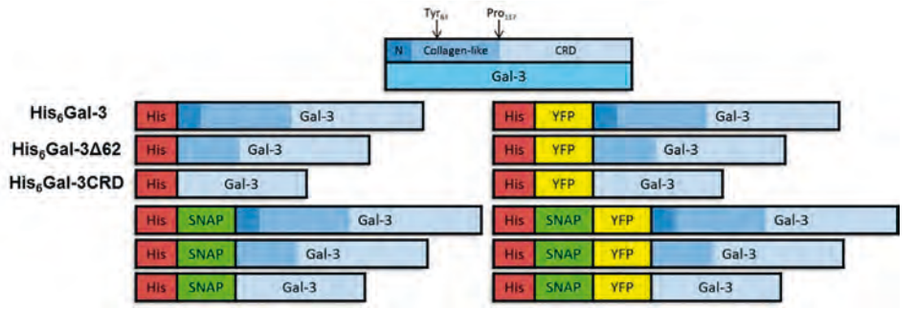

Fig. 9: *Twelve individual modified Gal-3 constructs by N-terminal truncation and/or fusion of SNAP-tag and yellow fluorescent protein (YFP) for immobilization and imaging purposes. The binding behavior is analyzed in solid-phase binding assays.*

LacNAc glycan library follows. The enzymatic toolbox comprises β-*N*-acetylhexosaminidase from the filamentous fungi *Talaromyces flavus* and glycosyltransferases from pro- and eukaryotic hosts. The obtained structures are depicted in Fig. 8.

On the way towards tailored biomaterials, the produced glycans are conjugated to bovine serum albumin as non-glycosylated protein carrier to obtain multivalent neoglycoconjugates, which are essential for the design of more natural ligands and an enhancement of the total galectin binding strength. Both the monovalent and multivalent compounds were evaluated in galectin binding assays such as enzyme-linked lectin assay (ELLA) or surface plasmon resonance (SPR). The multivalent structures raised the galectin binding strength many times due to multivalence effects. Besides naturally occurring Gal-1 and Gal-3, also biotechnologically modified and/or truncated derivatives were developed and analyzed in order to gain novel insights into the binding mechanisms and pursuing application (Fig. 9). The ligand library enables the identification of selective high-affinity ligands for Gal-3 and its truncated variants, e.g. Gal-3Δ, which lacks a part of its *N*-terminus.

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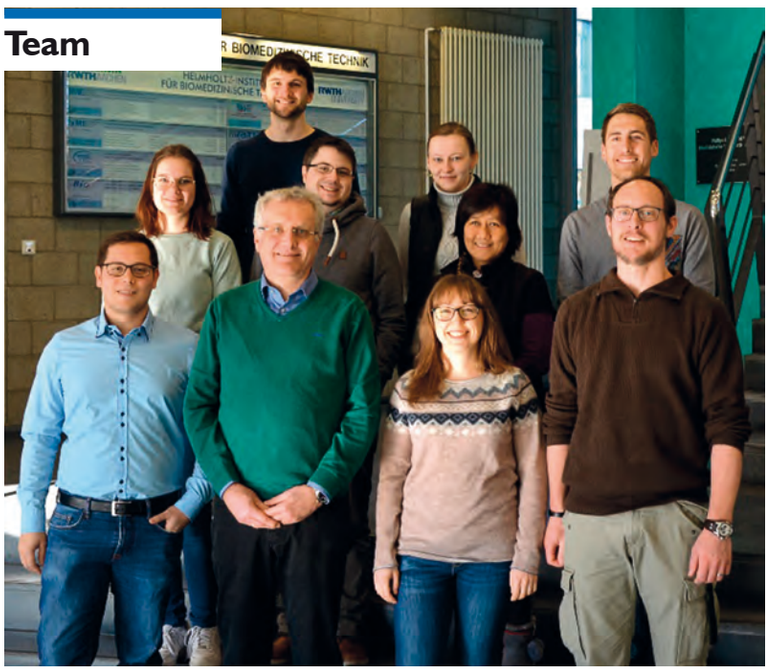

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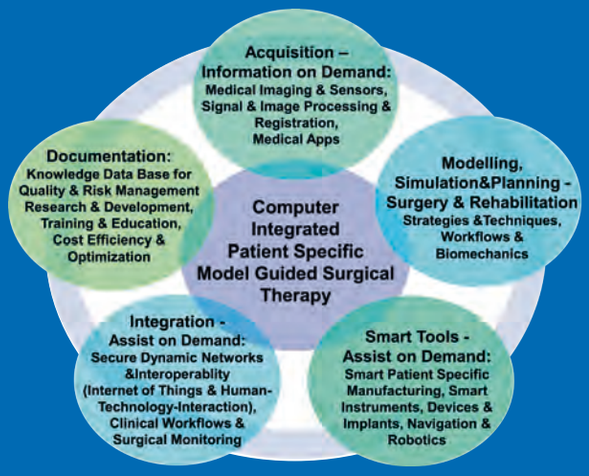

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Introduction

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. 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. As a complementary partner of clinicians and industry, our aim is to analyse the issues in health care systematically using engineering methodology and to identify, develop, implement and evaluate most appropriate solutions based on and beyond the state of the art of science and technology. Therefore interdisciplinary cooperation is crucial:

- With clinical experts – for the identification and analysis of the clinical challenges and boundary conditions, the need-oriented development and the evaluation of the cost-to-benefit ratio of technical developmental products and methods.
- With industrial partners – for the development of innovative lab-types and its efficient transfer into clinically as well as commercially attractive products. This can be implemented in cooperation with established industrial partners and/or industrial spin-offs of our chair.

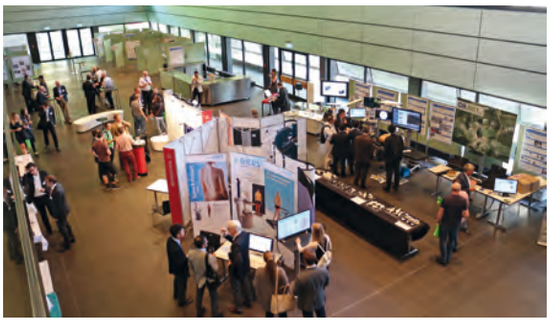

Fig.1: *Impressions from CAOS2017*

In 2017, various projects related to basic research issues (e.g. funded by the German Research Foundation (DFG)) as well as industrial co-operations in different focus areas have been continued or started by our team. The continuous success of the BMBF flagship project OR.NET coordinated by mediTEC in the years 2012-2016 (18,5 M €; more than 90 partners) is one outstanding example. Based on the achievements of the OR.NET project, the new standard IEEE 11073-10207 for "Domain Information & Service Model for Service-Oriented Point-of-Care Medical Device Communication" has been approved by the international IEEE standards association. Moreover, the concerted activities with our partners in the framework of the OR.NET association (www.ornet.org) resulted in new projects assuring the sustainability of our work. As president of the International Society for Computer Assisted Orthopaedic Surgery 2016/17, Prof. Radermacher coordinated the CAOS2017 Annual Meeting in Aachen (Fig. 1). During 4 days more than 300 international researchers from clinics, industry and research presented and discussed latest developments in the field. International co-operations, publications of our research, the market applications of products originally developed in our lab as well as international patent applications continuously confirm our general concept of combining basic as well as problem oriented medical engineering research and application development. Last but not least, this also provides a sound basis for the education of our students.

Selected Projects

In-vitro simulation of cranial arteriovenous blood flow affecting CSF dynamics

Age-related changes of viscoelastic properties of arteries affect the intracranial pressure (ICP) as well as the cere brospinal fluid (CSF) dynamics and might lead to neurological disorders like normal pressure hydrocephalus. For the in-vitro simulation of related effects we designed a cam disk driven piston pump, which is connected to an in-vitro model of the cranio-spinal system. It enables an easy simulation of different physiologic as well as pathologic arteriovenous flow characteristics and the influence of the cerebral blood vessel pulsation on the CSF dynamics. The setup includes a drive, piston and cylinder unit (Fig. 2). The core piece of the unit is the cam disk which is driven by a stepping motor. Due to its outline, the cam disk forces an arteriovenous flow on the system. By adapting and exchanging the disk, various changes of the blood dynamics can be investigated. We established an integrated digital workflow for the automatic generation of 3D-printed cam disks from clinical flow profiles. The piston pump is a cost efficient alternative to using a voice coil.

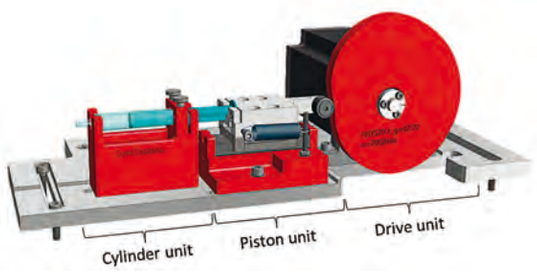

Fig.2: *CAD model of the cam plate driven piston pump.*

Patient Specific Target Zone for Implant Placement in Total Hip Arthroplasty

During total hip arthroplasty planning, suitable parameters for implant placement (position and orientation) are determined based on certain criteria such as good fit to the bony anatomy and leg length equality. More complex criteria such as a sufficient range of motion and adequate resulting hip forces are not systematically planned and are only considered based on the surgeons experience. During surgery, the parameters might need to be adapted due to intra-operative findings which might have an effect on the overall result. We developed a framework and algorithm to automatically calculate optimized set of parameters for a specific patient based on all relevant criteria derived from literature and to provide an intraoperative decision support system for the analysis of effects if certain parameters are changed

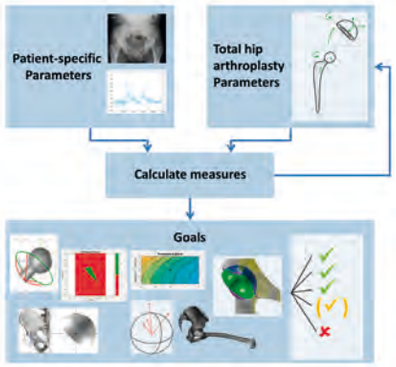

Fig. 3: Framework and clinical workflow for the optimization of patient-specific total hip arthroplasty.

The loading of the implant during activities of daily living is among the most important factors for the lifetime of the prosthesis. Since morphology and motions patterns are inter-individually different, the alignment of the prosthesis should be planned patient-specifically to avoid adverse loading conditions during activities of daily living. Within a clinical workflow the simulation time has to be minimized and the number of required input parameters should be reduced to avoid additional time-consuming and expensive data acquisition. Therefore, the development and validation of integrated morpho-functional models that can be efficiently personalized for each patient on the basis of standard clinical information is one major objective of our work.

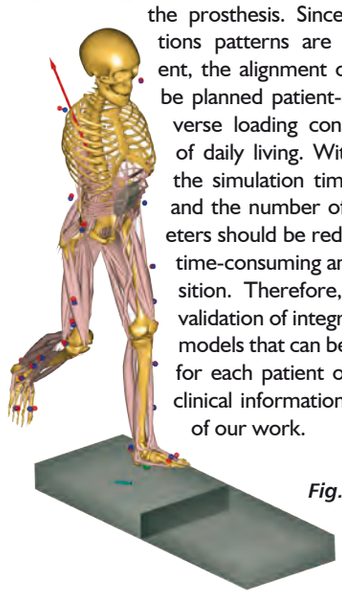

Fig. 4: A patient-specific adapted model for the approximation of the hip joint force during level walking.

Biomechanical Investigation of the Shoulder Joint

Understanding of shoulder joint biomechanics is of major importance for surgery as well as for shoulder arthroplasty design. We developed an ex-vivo shoulder simulator with an innovative "teach-in" function. This allows us to investigate the behaviour of the shoulder in any assigned free spatial movement without the need of any external or pre-set input. The experiment can be conducted using both cadaver and the artificial joint. With the use of additive manufacturing (3D printing), various shoulder joint geometries can be designed and tested, enabling us to conduct parameter studies and perform biomechanical evaluation of different shoulder implant designs. Furthermore, the experimental results are also useful for the verification of multi-body in-silico simulations.

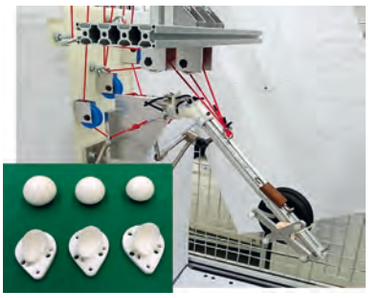

***Fig. 5:** In-vitro analysis of the impact of a variation of different implant design parameters using the Aachen shoulder simulator*

Morphological analysis of the native knee

In total knee replacement, the clinical outcome is significantly influenced by the implant design. Different concepts of gender-, race- or patient-specific designs have been developed. This is based on reported anatomical differences in the knee shape (morphology), as reported in literature. However, little is known whether these differences originate from phenotypic differences between men and women or different ethnicities, or e.g. overall body size, and thus can be eliminated by a simple scaling. Therefore, we develop parametric models to quantify the knee morphology. This includes fully automatic methods for landmark recognition and feature extraction. Subsequently, we use statistical, correlation, and cluster analysis to investigate the knee morphology for patient specific implant design.

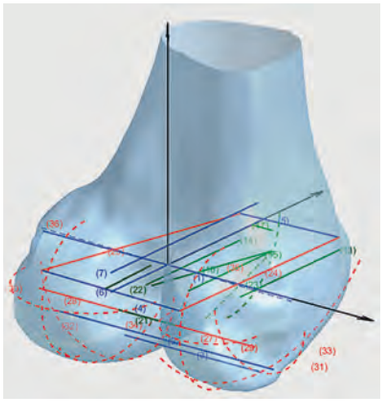

***Fig. 6:** Morphological analysis of the native knee.*

Reconstruction of knee joint bones from multiple ultrasound images

A crucial factor for success in total knee arthroplasty (TKA) is the exact fit of the prosthesis on the involved bones. Under- or overhang may cause irritation of the surrounding ligaments or tendons as well as expose the spongy bone to abrasion particles. Further consequences include postoperative pain, osteophytes growth and inflammation. To ensure a tight fit, patient-specific implants may be planned and manufactured on the basis of CT- or MRI-based images. However these imaging modalities suffer from ionizing radiation or high costs. Therefore 3D ultrasound is investigated as an alternative. It is widely available, cheap and non-invasive. Yet it suffers from restrictions such as a limited field-of-view, acoustic shadowing and a low signal-to-noise ratio. This induces the

need for a simultaneous segmentation of the bone surface in the image as well as a registration of the partial views. We developed an algorithm capable of both, the Interleaved Partitioned Active Shape Model Search (IPASM). Whereas our initial approach was based on 3D-US-Volumes, the actual algorithm is using conventional 2D B-Mode images while maintaining the precision of the reconstruction.

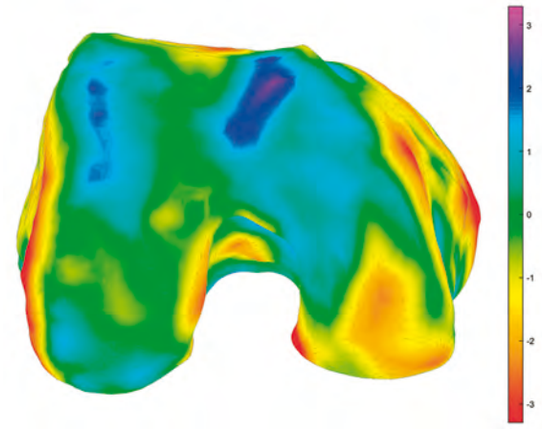

Fig. 7: *Surface error compared to a CT-based ground truth of a distal femur reconstruction with the IPASM.*

Simulative evaluation of stone fragmentation during shockwave lithotripsy

The commonly used treatment for patients suffering from kidney stones is the extracorporeal shockwave lithotripsy (ESWL), where shockwaves are used in order to destroy the stones non-invasively. When the wave hits the stone, reflection and refraction arise due to impedance changes. Therefore, the pressure and the stresses inside the stone increase and cause fine cracks. Under the load of multiple shockwaves, these cracks lead to fractures. Since the fracture mechanisms of the stones are not completely understood we investigate the effects of various acoustic fields on artificial kidney stones in silico and evaluate their fracture efficiency.

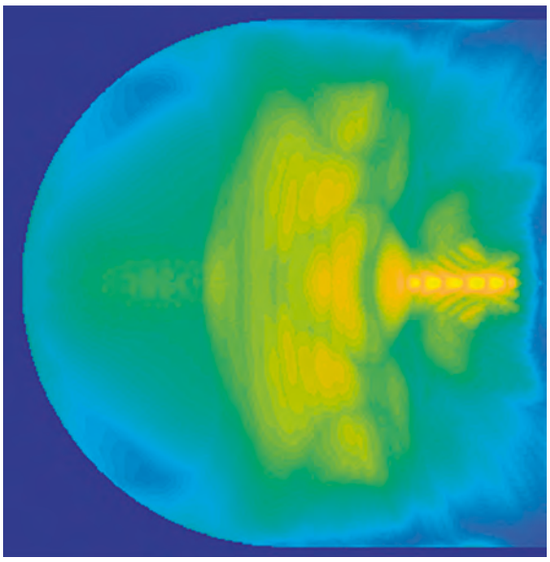

Fig. 8: *Stress distribution inside an artificial kidney stone during shockwave lithotripsy.*

The simulation comprises wave propagation in water and gypsum as well as calculations of stresses and strains inside the stone. By application of e.g. the Tuler Butcher fracture criterion on the calculated stresses the approximate location and extent of fracture is determined. Moreover, our experimental shockwave test system for in-vitro analysis is used for verification.

ALLEGRO: Artificially intelligent robotic device for improved orthopaedic surgical care

ALLEGRO aims to bring to the market the first device of a new generation of intelligent and cost-efficient medical systems that will help surgeons significantly improve the usability (effectiveness, efficiency, learnability and user satisfaction) of surgical robot systems for orthopaedic surgery. The product suite combines a computer-assisted navigation system incorporating a real-time tracking device and a robotic surgical cutting tool associated with a smart stabilization support unit.

Fig. 9: *Manipulator with milling tool for active path control in UKA and optional holding arm.*

Interoperability, risk management, usability engineering and approval of medical devices based on open communication standard

Based on the achievements of the OR.NET project (a flagship project of the Federal Ministry for Education and Research (BMBF) coordinated by our chair (2012-2016); 18,5 M €; more than 90 partners from industry, research, clinics and associations), the new standard IEEE 11073-10207 for "Domain Information & Service Model for Service-Oriented Point-of-Care Medical Device Communication" has been approved by the international IEEE standards association. Initiated by Prof. Radermacher, partners of the consortium founded the non-profit organization OR.NET e.V. in order to ensure sustainability of the project work and continued active cooperation. Apart from joint presentations of the OR.NET demonstrator e.g. on the exhibitions and international conferences (Fig.10a), further research projects (such as the EFRE project ZiMT on certifiable and integrated medical devices on the basis of IEEE 11073 and BMBF project MoVE on a modular validation environment for medical device networks) issued from these concerted activities. These projects enabled us to continue our research regarding the open integration of medical technology and corresponding approval strategies, methods and tools for the risk management and usability engineering as well as innovative human-machine-interfaces. Our team developed a surgical workstation with a touch-based graphical user interface including numerous device panels (e.g. OR light, 3D X-ray C-arm, OR-table, high-frequency cutting devices, endoscopic devices and ultrasound-cutting device) and a process-specific function group view (Fig. 10b) as well as a possibility for gesture control for the surgeon and OR nurse and a universal

footswitch in combination with a vertically (and automatically) adjustable footboard for the surgeon. Moreover, the integrated system enables access to clinical information and PACS systems. The alarm concept (technical and patient related) and the workflow-supporting strategy provide the OR team with valuable information during the intraoperative process.

Fig. 10 (a): OR.NET demonstrator on the conhIT exhibition 2017, Berlin; ***(b)*** *Process-specific function group view*

Field studies and development for improved patient transport aids

Patient transport is a demanding task for emergency rescue personnel worldwide. According to several studies paramedics have the highest work related injury rates compared to all other industries. This is mainly caused by high physical loads during patient transport in association with unphysiological postures, which leads to musculoskeletal problems, especially lower back pain.

One approach may be the use of improved technical transport aids. The development of such a rescue and transport aid is the objective of the SEBARES-project. However, detailed information about the status quo in patient transport is essential but not yet available in literature, especially regarding the quantitative occurrence of obstacles. Therefore an objective survey at a local emergency medical service provider was conducted and 400 deployments could be quantitatively analyzed showing severe bottlenecks and very high workloads for the paramedics.

Fig. 11: Local medical service provider.

These studies are one major basis for the development of the novel SEBARES transportation system to improve the situation for paramedics by reducing the physical load during patient transport, while maintaining high maneuverability throughout the transportation process including stairs. To evaluate the ergonomics of the system in an early state and to get a first notion of the situational improvement for paramedics, a primary user study was conducted with a labtype (Fig. 12). The system was evaluated regarding different body sizes, terrains and slopes, while the postures of the different subjects and their applied forces and torques were recorded.

Fig. 12: Evaluation of the first SEBARES laptype

Acknowledgements

We would like to thank all our clinical, technical and industrial partners for the fruitful cooperation*.
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- the German Research Foundation (DFG)
- the START program of the Medical Faculty of the RWTH Aachen University
- 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.med-itec.rwth-aachen.de** or contact us directly.

Selected Publications

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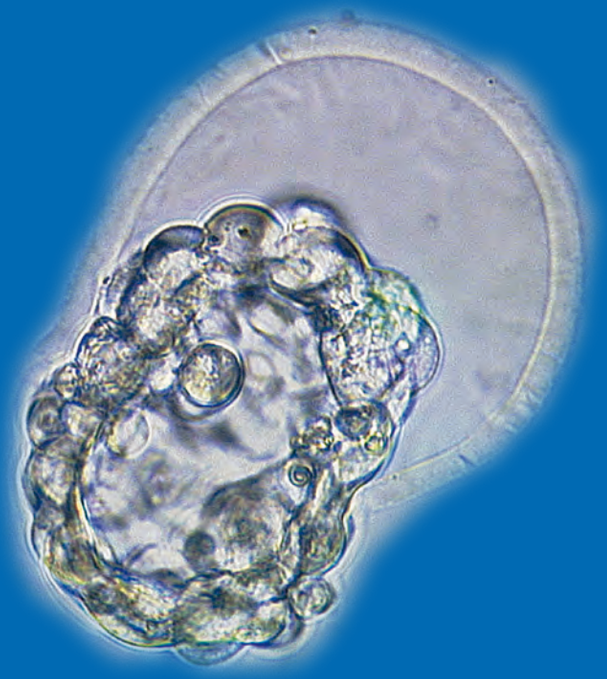
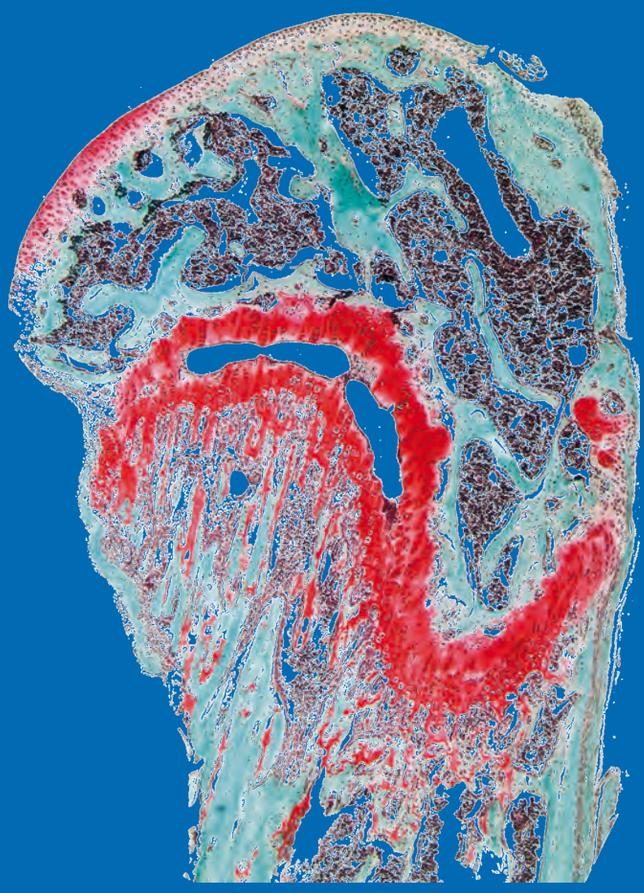
Biointerface Laboratory at Helmholtz-Institute for Biomedical Engineering

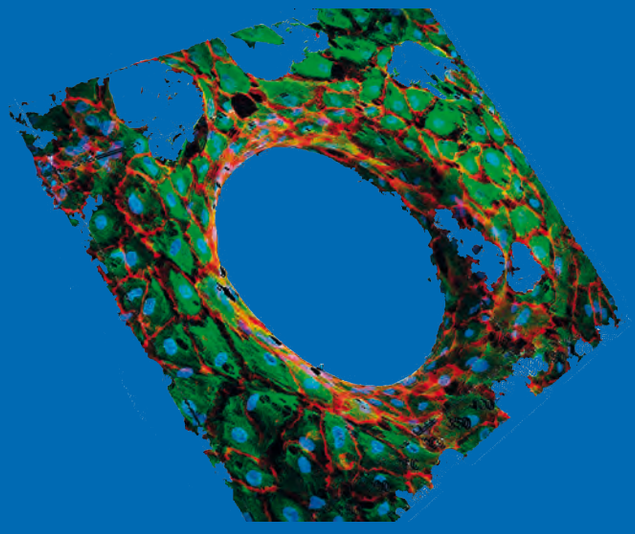
RWTH AACHEN UNIVERSITY

Faculty of Medicine

Cell-Material Interactions: Translating Basic Science Into Clinical Applications







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Cover Figures: *Top, hatching blastocyst penetrating the zona pellucida; Center, breaking bone - epiphyseal lysis in a genetic mouse model deficient in fetuin-A protein; Bottom, making bone – co-culture of bone stromal cells with endothelial cells on a porous scaffold creates highly organized bone-like tissue.*

Introduction

These past year collaborative projects with partners were finally published. We contributed to the discovery by an international team of researchers that the scavenger receptor MARCO, which is expressed in several subsets of naive tissue-resident macrophages mediates in sensing adenoviral infections thus triggering an immune response [4]. Thus, MARCO may influence antiviral innate responses in a virus type-specific manner, which may determine the delivery route of adenoviral gene delivery in live animals and humans.

Together with engineers from RWTH Aachen we applied electrical impedance spectroscopy of single cells in hydrodynamic traps, a versatile method, which is used to study cell integrity, but never before in single mouse oocytes [5]. Ultimately this method may be employed to judge the quality of oocytes destined for *in vitro* fertilization.

Laura Brylka published the results of her PhD work, which she performed in close collaboration with researchers from Hamburg and Cologne [13].

Sabine Neuss-Stein has published in »Angewandte« collaborative work with Andrij Pich's lab on nanogel coatings for taylored biointerfaces [7].

The EU International Network for Training on Risks of Vascular Intimal Calcification and roads to Regression of Cardiovascular Disease (INTRICARE) had its kickoff in March 2017 and most early stage researchers, i.e. PhD students funded by this project have started their work. We also secured a grant within a new Transregional Collaborative Research Center of the German Research Foundation (DFG) addressing reno-cardiovascular interactions underlying enhanced cardiovascular risks in patients with chronic kidney disease (CKD). Our work will focus on circulating high molecular weight protein-mineral complexes triggering soft tissue calcification.

Laura Brylka has left the group after a 7 year stint, first as student aid, next as master student, then as a PhD student, to join as a post-Doc the Hamburg lab of Thorsten Schinke. We wish her well and will stay in touch!

Sarah Peglow returned to Fachhochschule Bonn-Siegen to complete her MSc course work.

Stephan Reinhold completed his MSc and started PhD work as an early stage researcher of the INTRICARE consortium at University of Maastricht.

Electrical Impedance Spectroscopy as Indicator for Oocyte Quality

MSc Carlo Schmitz
Dr. Julia Floehr

Oocyte *in vitro* fertilization (IVF) is an established procedure in human and animal assisted reproduction techniques (ART). IVF critically depends on the quality of oocytes, especially on the state of the *zona pellucida* (ZP), a gelatinous outer layer of extracellular matrix that spontaneously hardens and becomes impenetrable to sperm during oocyte isolation and culture. Oocyte quality is typically judged microscopically by an experienced observer. Optical inspection methods are however observer-biased and thus subjective, time consuming, and they require specialized equipment. Thus, observer-independent characterization methods are highly desirable.

With respect to miniaturization, integration and portability, increased focus has been devoted to electrochemical biosensors with particular interest to electrical impedance spectroscopy (EIS). In cooperation with the group of Prof. Uwe Schnakenberg a novel microfluidic chip for trapping and EIS characterization of single mouse oocytes was developed [5]. Figure 1 shows the top-view of the chip, which mainly consists of a microfluidic channel with four embedded trapping sites defining the detection regions of the device. The trap structures are arranged along the main inlet microchannel and featuring a narrow cross connection region to the outlet channel (hydrodynamic trap). Four microelectrodes (12 μm * 22 μm) are located inside one trap. The four black bars in the pictures correspond to the interconnection lines for the four electrodes. Two electrodes for impedance measurement are pinpointed on the bottom and two on the side walls of the trap, respectively.

In our study, we analyzed the influence of the ZP on the electrical impedance response. Zona-intact oocytes had an overall smaller increase in impedance compared to the zona-free oocytes with respect to empty traps, as depicted in figure 2. The smaller impedance change is induced by the high conductivity of the ZP. The frequency of highest sensitivity was determined to be around 100 - 200 kHz. The results show that EIS is highly sensitive to the ZP structural

changes, suggesting impedance as a novel, non-destructive criterion to judge the quality of oocytes meant for IVF. For further experiments, the device will be improved by an optimized layout.

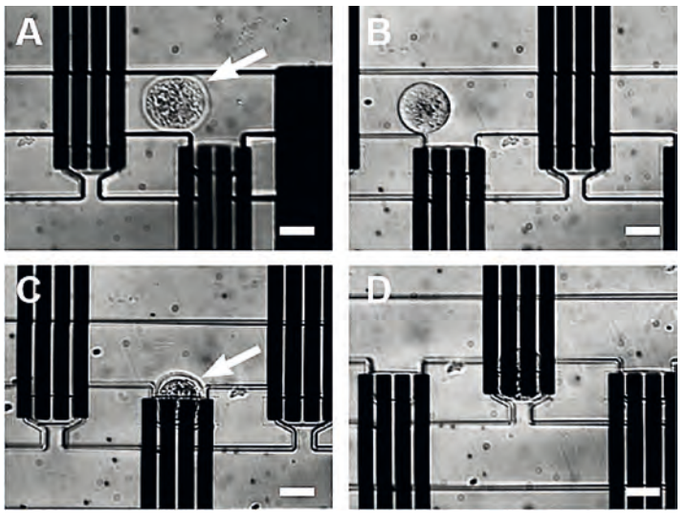

Fig. 1: Single mouse oocytes trapping in the microfluidic device. *(A) Oocytes with surrounding ZP within the microchannel before trapping. (B) Zona-free oocyte in the microchannel before trapping. (C) Successfully trapped zona-intact oocyte. (D) Trapped zona-free oocyte, according [5]. Scale bars are 50 µm.*

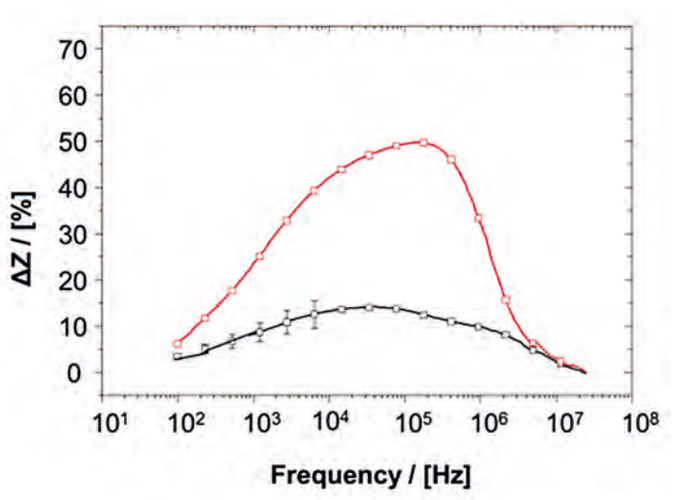

Fig. 2: Normalized impedance change *of ZP-free (red top curve) and ZP-intact (black bottom curve) mouse oocytes with respect to empty traps, according [5].*

Stem Cells and Tissue Engineering

Prof. Dr. Sabine Neuß-Stein

In the working group "Stem Cells and Tissue Engineering" the main issues being addressed are (i) the choice of promising cell types and (ii) the choice of suitable biomaterials for specific tissue engineering applications, as well as (iii) vascularization of three-dimensional biomaterial scaffolds and (iv) mineralization efficiency for bone tissue engineering.

In the past, mesenchymal stem cells (MSC) were used from different species (human, murine, ovine) and origins (bone marrow, umbilical cords, adipose tissue) and in 2017 we fully characterized MSC from an additional and ontogenetically early origin, the chorionic villi of placenta [16]. Compared to MSC from other sources, chorionic villi-derived MSC possess an extended life span due to a delay in replicative senescence and aging as a result of improved telomere length maintenance. This makes chorionic villi-derived MSC an attractive cell type for Regenerative Medicine.

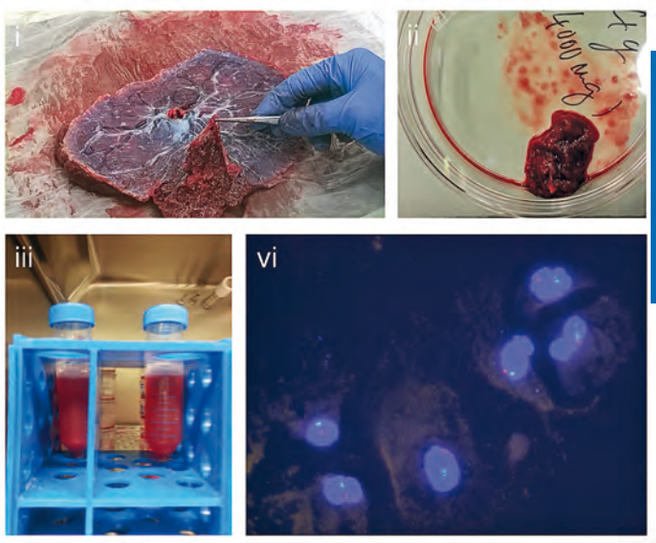

Fig. 3: Isolation of human chorionic villi-derived mesenchymal stem cells (CV-MSC) from human placenta. *i) Removal of the amnion to access the chorionic plate, ii) pieces of chorionic villi dissected from human placenta, iii) collagenase digestion of chorionic villi; iv) interphase FISH analysis using a X/Y dual color probe to identify male cells in male/female mixed placenta tissue. X chromosome fluorescence is green while Y chromosome fluorescence is orange. Scale = 50 µm [16].*

Besides comprehensive analyses on cell characteristics [16] the group optimized a biomaterial-based stem cell recruitment system with hepatocyte growth factor (HGF) being released from silk membranes by cleavage of a tPA restriction side via serine proteases in wounded areas. After a successful proof-of-concept where endogenous MSC are guided to wounds in a mouse model [1], the group is currently adopting the protocols for the human system and could already produce (in mammalian cells) and purify the secreted HGF with first successful pilot experiments on its functionality.

In addition, the group gained more experience in novel biomaterials, e.g. in polymers for drug delivery systems [14], polymers for implant coatings allowing for both, cell adherence and microbe repellence [7] and in high strength ceramics and polymers for bone tissue engineering [9, 15, 17]. For larger three-dimensional, tissue engineered bone constructs, co-cultures are needed, providing bone building cells (e.g. MSC) and endothelial cells (e.g. human umbilical vein endothelial cells, HUVEC) for capillary-formation for future warranty of nutrient supply. Both cell types have to be in proper cross-talk and we could already optimize culture conditions in a way that MSC show increased mineralization, while HUVEC form capillary-like structures.

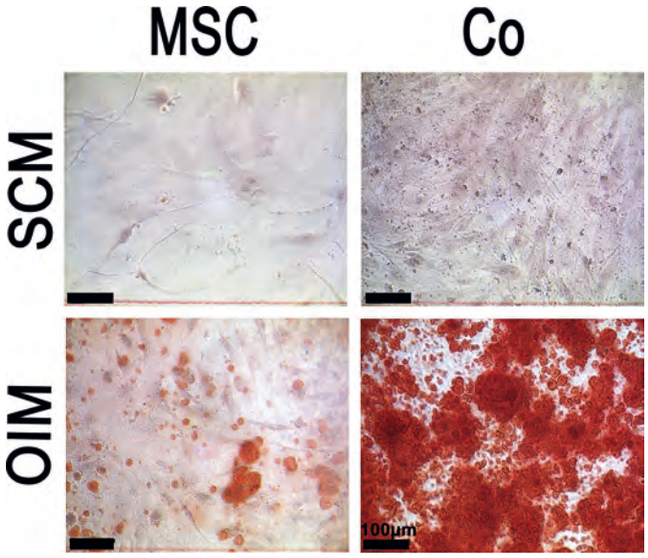

Fig. 4: Enhanced osteogenic differentiation of MSC after co-culture with endothelial cells. *Human MSC were cultured in mono- (MSC) or co-culture (Co) either in stem cell expansion medium (SCM) or osteogenic induction medium (OIM). Success of differentiation/presence of calcium accumulations was visualized via Alizarin red stainings. A co-culture with endothelial cells enhanced osteogenic differentiation of MSC compared to monoculture conditions. Scale = 100 µm.*

Growth Factor-functionalized Silk Membranes Support Wound Healing In Vitro

MSc Michaela Bienert

Chronic wounds represent a serious problem in daily medical routine requiring improved wound care. Silk of the domesticated silkworm *(Bombyx mori)* has been used to form a variety of biomaterials for medical applications. *B. mori* was genetically engineered to produce silk functionalized with growth factors. In this study EGF-, FGF-, KGF-, PDGF- or VEGF functionalized silk membranes were compared to native *B. mori* silk membranes without growth factors for their ability to support wound healing *in vitro*.

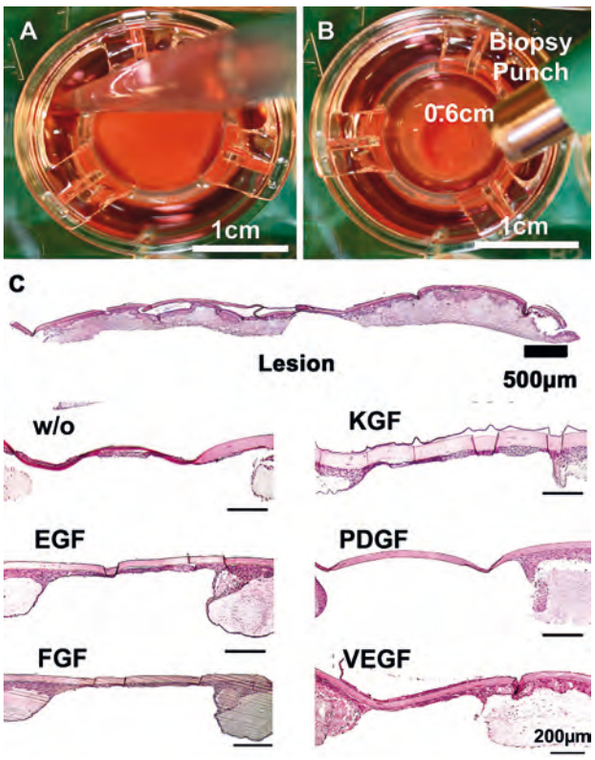

Fig. 5: Growth factor-functionalized silk membranes in dermal equivalents (DE) in vitro. *(A) Dermal fibroblasts in collagen gels covered by keratinocytes are exposed to the air by removing the medium from the top compartment of the transwell system. (B) Biopsy-punch lesion with a diameter of 0.6 cm and an area of 1.13 cm2. Lesions were covered with silk membranes functionalized with FGF, EGF, KGF, PDGF, VEGF or without growth factors. (C) 17 days after setting the lesion, gels were embedded in paraffin, sliced longitudinally and stained with HE. Keratinocytes (dark pink) grow underneath the silk layer/on top of the collagen embedded fibroblasts (light blue); scale bar 500 µm. HE staining of silk covered DE with growth factors EGF, FGF, KGF, PDGF, VEGF or without growth factors; scale bar 200 µm.*

Our *in vitro* wound healing studies showed as a trend that EGF-, FGF- and VEGF-functionalized silk enhanced wound closure compared to silk without growth factors.

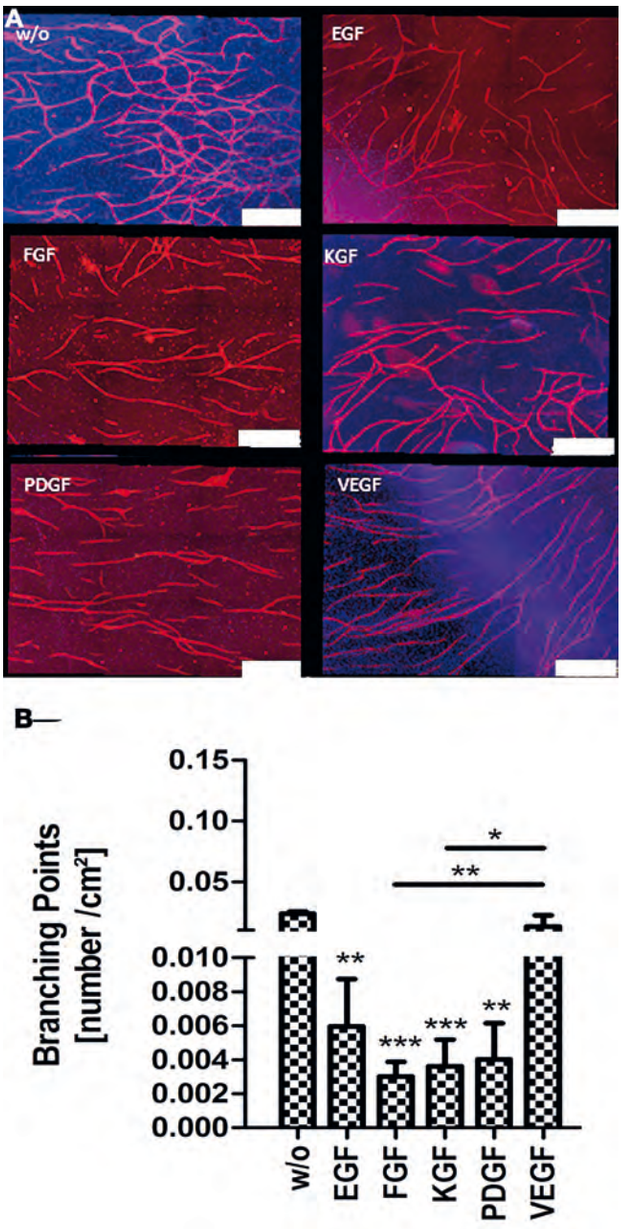

Fig.6: Angiogenic capacity of growth factor-functionalized silk membranes. *(A) Capillary-like structure formation on silk membranes without growth factors or functionalized with FGF, EGF, KGF, PDGF, VEGF. or silk without growth factors. HUVEC stained with anti-CD31 (red) and counterstained with DAPI (blue). Scale bar indicates 500 µm. (B) Quantification of branching. All values are normalized to relative cell numbers, error bars represent the standard deviation n=3, t-test, p=0.05.*

In angiogenesis studies, VEGF-functionalized silk membranes and native silk membranes significantly outperformed the other growth factor-functionalized silk membranes by producing longer and more branched capillary-like structures.

Murine macrophages on all silk membranes secreted cytokines and chemokines promoting neutrophil infiltration (CXCL1) and macrophage infiltration (MCP-1) whereas the proinflammatory cytokines IFN-γ, IL-6 or TNF-α could not be detected (figure 7).

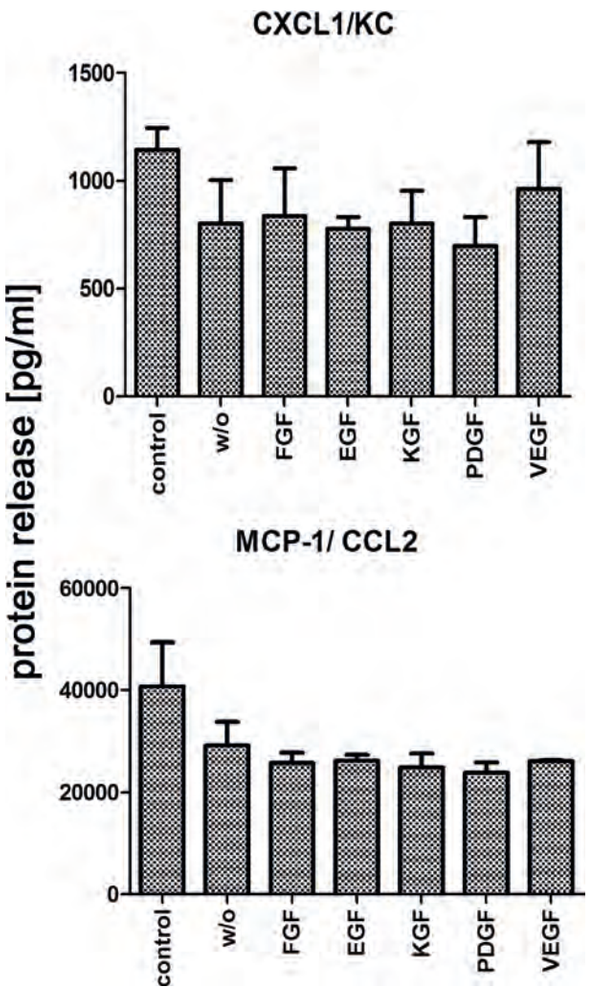

Fig. 7: Macrophage cytokine and chemokine secretion on different silk membranes. *Silk functionalized with growth factors FGF, EGF, KGF, PDGF, VEGF and silk without growth factor were incubated with macrophages for 1 day. Macrophages on cell culture plastic served as a control. CXCL1/KC, MCP-1/CCL2 chemokines were quantified by flow cytometry using FlowCytomix®. Error bars represent the standard deviation n =3, t-test, p = 0.05.*

Thus, we here introduce *Bombix mori* derived, growth factor-functionalized silk membranes as promising biomaterials for wound healing therapies.

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Team in 2017

ExMI EXPERIMENTAL MOLECULAR IMAGING

Chair of Experimental Molecular Imaging
Faculty of Medicine

Improving therapy by integrated multiparametric imaging

Director

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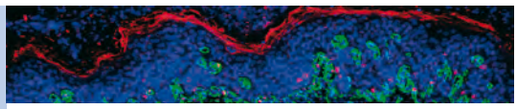


Introduction

Univ.-Prof. Dr. med. Fabian Kiessling

The Chair of Experimental Molecular Imaging (ExMI) at the Helmholtz-Institute for Biomedical Engineering (HIA) 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.
Currently, the institute consists of 2 departments and 4 research groups working on the biological mechanisms of tumor progression, on novel imaging agents, on medical informatics, on nanomedicines and theranostics, diagnostic and therapeutic ultrasound imaging, and on the development of novel tools for MR-PET hybrid imaging and MPI.

Diagnostic and Therapeutic Ultrasound

Univ.-Prof. Dr. med. Fabian Kiessling

Ultrasound imaging is still limited by its user dependence and moderate reproducibility. Thus, there is a need for automation of imaging and image-analysis [1,2]. In this context, Theek et al. developed a software that is capable of assessing the reliability of color-coded parametric maps using systematic voxel binning. In detail, perfusion values should be identical if the mean of all voxels is determined or if the total area is analysed at once. Thus, by varying the degree of binning a resolution can automatically be determined that displays a reliable parametric map then allowing the extraction of structural and functional image features, which may be the basis for further radiomics analyses. Multiparametric ultrasound imaging may not only provide structural and functional features but also molecular imaging data [3]. In this context, Curaj et al. completed a large preclinical study where JAM-A was evaluated as a target of early vascular dysfunction. Using molecularly targeted microbubbles we could show in carotid arteries of mice that acute changes in blood flow and sheer stress induce the presentation of JAM-A at the luminal side of the endothelium, which rapidly normalizes under physiological conditions but remains enhanced in case of atherosclerotic plaque development [4].

[1] Kiessling, Radiology (2017)
[2] Theek et al., Contrast Media Mol Imaging (2017)
[3] Guevener et al., Methods (2017)
[4] Curaj et al., Arterioscler Thromb Vasc Biol (2018)

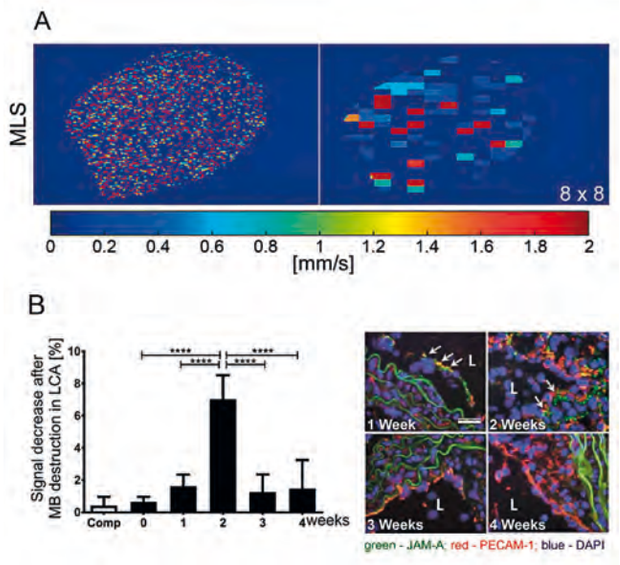


Fig. 1: A: In the original parametric perfusion map (left) of a MLS ovarian cancer xenograft regional differences in tumor perfusion are hardly detectable. However, by applying systematic voxel binning an image resolution can be determined that provides reliable voxel values. In the optimized parametric map high and low vascularized tumor regions can faithfully be localized (image adapted from [2]).
B: JAM-A expression in a partially ligated carotid artery assessed by molecular ultrasound imaging (left) and the corresponding immunohistological images (right). The acute change in flow induced a temporary high increase in luminal JAM-A expression. Over time JAM-A expression decreases but remains higher than the baseline level indicating atherosclerotic remodeling of the vessel wall (image adapted from [4]).

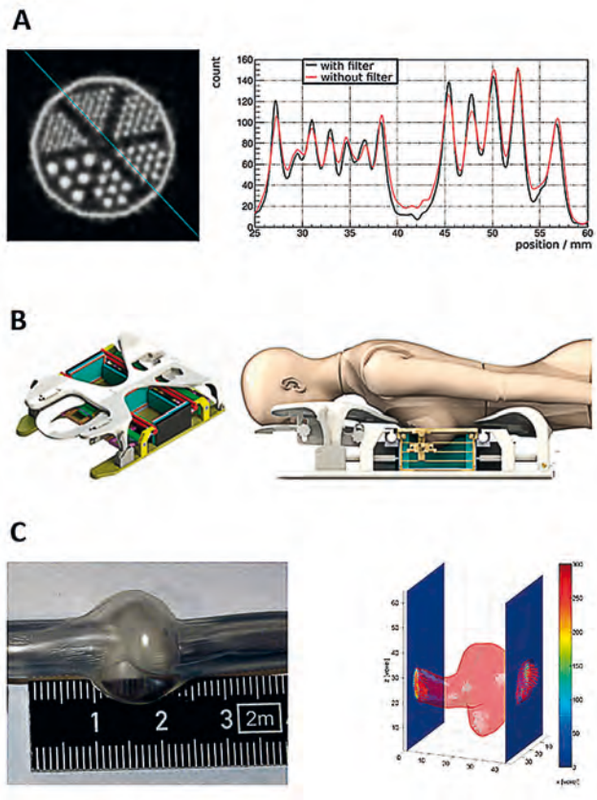
Physics of Molecular Imaging Systems

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

In the last years, the PMI group and Philips Research Aachen have jointly developed the first fully digital detector concept 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.

Continuous efforts are put into boosting the detector performance: Schug et al. showed that the timing resolution is improved by adding a refined crystal delay calibration and a time walk correction as a post processing steps, resulting in coincidence resolving times as low as 208/240 ps on system level for the preclinical/clinical scintillator configuration [5]. Ritzer et al. equally improved the detectors' spatial resolution by rejecting multi-scatter events [6], cf. Fig. 2 (A).
Our group is currently applying its expertise acquired in the field of PET/MR in the EU Horizon 2020 HYPMED project, for which we are developing a clinical PET/MR insert for human breast cancer, cf. Fig. 2 (B). In this context, Gross-Weege et al. proposed a characterization method for different shielding materials using an in-house developed MR field probe. Efficient RF shielding is crucial for minimizing MR perturbations on the PET electronics.
Besides research on PET/MR, the PMI group also focuses on Magnetic Particle Imaging (MPI). MPI measures the magnetic fields generated by excited superparamagnetic nanoparticles that act as tracers. To enhance the signal-to-background ratio of our Philips preclinical MPI device, Straub et al. developed a joint reconstruction method that simultaneously reconstructs the tracer distribution and the scanner's background noise from two consecutive image acquisitions, thereby minimizing the contributions of the background to the reconstructed image [8].

[5] Schug et al., IEEE TRPMS (2017)
[6] Ritzer et al., IEEE TRPMS (2017)
[7] Berker et al., IEEE TRPMS (2017)
[8] Franke et al., IJMPI (2017)



Nanomedicines and Theranostics

Univ.-Prof. Dr. Dr. Twan Lammers

Nanomedicines are carrier materials, which are designed to improve the 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.
We have a strong focus on passive drug targeting to tumors, which is based on the Enhanced Permeability and Retention (EPR) effect. The EPR effect, however, is highly variable, both in animal models and in patients. Together with other working groups at ExMI, we are exploring pharmacological and physical strategies to modulate EPR-mediated tumor targeting [9, 10]. As part of an ERC Starting Grant, which ended in 2017, we evaluated multiple different approaches to induce vascular normalization (Fig. 3A), e.g. via polarizing tumor-associated macrophages towards a more M1-like phenotype, via overexpression of the histidine-rich glycoprotein, contributing to improved drug delivery to and into tumors [11]. Iron oxide-based nanoparticles are clinically relevant formulations that can help to polarize macrophages towards an M1-like phenotype, and we are currently exploring means to employ them to prime the tumor microenvironment for enhanced drug delivery [12]. As a physical means to enhance tumor targeting, we employ sonoporation. Sonoporation is based on the combined use of ultrasound (US) and microbubbles (MB). As depicted in Fig. 3B, MB can besides for functional and molecular US imaging also be applied to open up compressed blood vessels and endothelial junctions in tumors, thereby improving drug delivery [13]. We recently extensively characterized the shell composition of PBCA-based polymeric MB, developed differently sized PBCA-MB, and showed that they can be easily co-loaded with different types of model drugs molecules [14] (Fig. 3C-D).
Other projects completed in 2017 include studies in which we established PEGylated and folate-targeted nanogels, to improve in vivo performance and overcome multi-drug resistance [15,16]. In addition, imaging and drug targeting methods have been explored for the diagnosis and treatment of (liver) fibrosis [17, 18, 19]. Furthermore, we provided proof-of-concept for the use of fluorine-containing polymers for theranostic tissue engineering [20]. And finally, we have contributed to the initiation of a first-in-man phase I clinical trial at UK Aachen [21], in which Prof. Bruemmendorf and colleagues are evaluating the potential of liposomal dexamethasone in patients suffering from multiple myeloma.

Fig. 2: A (left): Improvement of PET detector spatial resolution by incorporating multi-scatter rejection [6]: Hot rod phantom reconstructed with multi-scatter rejection (left). Line profiles along blue line show improved peak-to-valley ratios when incorporating multi-scatter rejection into image reconstruction (right). B: Prototype sketch of the HYPMED breast PET/MR insert. C: Measurement of an MPI stenosis phantom (left), corresponding velocity field in mm/s as measured at the in- and outlet plane (right) [8].

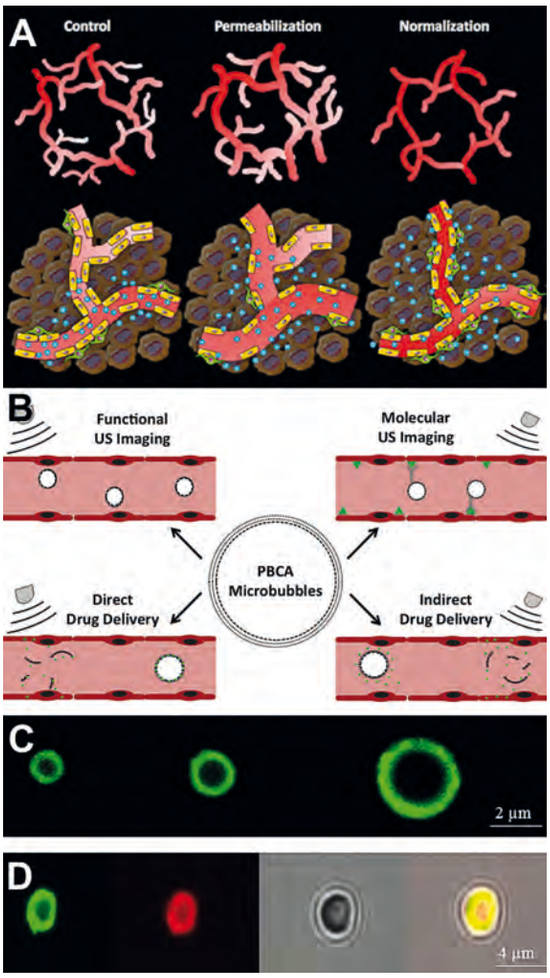


Fig. 3: A: Vessel modulation strategies to improve EPR-mediated tumor targeting. B: Diagnostic and therapeutic applications of polymeric. C-D: Differently sized PBCA microbubbles can be co-loaded with multiple model drug molecules (rhodamine in red, coumarin in green). Adapted from refs [9] and [12].

[9] Ojha et al., Adv Drug Deliv Rev (2017)
[10] Sun et al., Biomacromolecules (2017)
[11] Theek, Baues et al., J Control Release (in press)
[12] Crielaard et al., Nat Rev Drug Discov (2017)
[13] Koczera, Appold et al., J Control Release (2017)
[14] Appold et al., Macromol Biosci (2017)
[15] Chen et al., Macromol Biosci (2017)
[16] Chen, Tezcan et al., Nanoscale (2017)
[17] Lammers et al., Chem Mater (2017)
[18] Baues et al., Adv Drug Deliv Rev (2017)
[19] Bartneck et al., ACS Nano (2017)
[20] Bangen et al., Hepatology (2017)
[21] Clinicaltrials.gov, NCT03033316 (2017)

Mechanisms of tumor progression and metastasis

Dr. Wiltrud Lederle

The group "Mechanisms of Tumor Progression and Metastasis" focusses on the influence of the microenvironment on tumor growth and progression. Non-invasive imaging techniques are combined with ex vivo and in vitro analyses in order to investigate tumor stroma interactions and the effects of anti-cancer drugs. In addition, novel diagnostic and theranostic probes are evaluated in vitro and in tumor models in vivo.

Molecular ultrasound imaging with clinically used VEGFR2-targeted microbubbles was applied to assess the effects of PDGFR and VEGFR inhibition in orthotopic breast cancer xenografts. A multi-tyrosine kinase inhibitor impaired vessel maturation by blocking PDGFR signaling but enhanced tumor angiogenesis leading to higher tumor volumes. By contrast, vessel formation was inhibited in vitro. Further analyses revealed an increased VEGF expression by the tumor cells in response to the drug, thus providing an explanation for the enhanced tumor angiogenesis observed in vivo (Fig. 4, [22]).

In collaboration with Dr. Alexander Kühne, novel conjugated polymer nanoparticles were evaluated for optical imaging of macrophages. The nanoparticles were degraded by reactive oxygen species upon macrophage activation suggesting that they are well suited for diagnostic or theranostic approaches targeting activated macrophages [23].

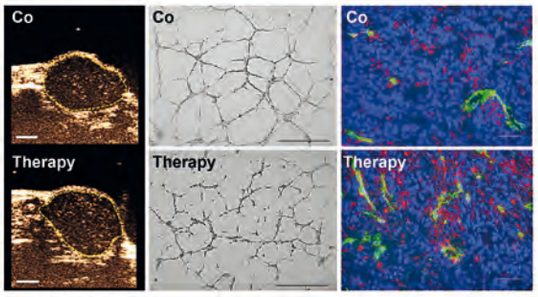


Fig. 4: Left: Molecular ultrasound imaging shows higher signal intensities of bound VEGFR2-targeted microbubbles in the treated tumor (tumors encircled in yellow). Middle: The multi-tyrosine kinase inhibitor blocks endothelial tube formation in vitro. Right: Immunostainings show enhanced VEGF expression in the treated tumor (VEGF: red, CD31: green, nuclei: blue); Figure modified from [22].

[22] Zafarnia et al., Neoplasia (2017)
[23] Repenko et al., Nat Commun (2017)

Applied Medical Informatics

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

The main objective of the group "*Applied Medical Informatics*" is the development, improvement and evaluation of software tools for preclinical and clinical imaging studies. This includes quantitative reconstruction algorithms, image fusion for multimodal studies, efficient tools for interactive image analysis, and automated segmentation algorithms for different imaging technologies such as CT, FMT, PET, SPECT, MRI, and ultrasound. A focus of our group is the combination of two or more imaging modalities to join their mutual strengths regarding specificity, resolution, sensitivity and anatomic contrast. Using the combination of fluorescence-mediated tomography (FMT) with computed tomography (CT) we noninvasively assessed elimination routes and retention sites [24] and established a novel kinetic whole-body model for robust extraction of physiological parameters (Fig. 5).

Together with the pharma company Roche, we evaluated the accuracy of μCT-FMT against an established method: MR-PET and showed high congruency for the biodistribution of antibodies and antibody fragments [25]. The increasing interest in the μCT-FMT technology triggered an intense cooperation with an industrial partner (MILabs) to finally develop a fully integrated μCT-FMT. Furthermore, we successfully applied our software tools in interdisciplinary studies about bone repair in rabbit models [26, 27], a synthetic tissue glue [28], and tumor-targeting nanoparticles [29].

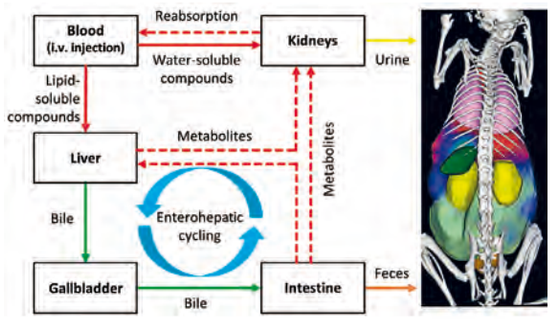


Fig. 5: Simplified kinetic model derives physiological parameters from the organ curves determined from longitudinal μCT-FMT images. Figure content from [29].

[24] Al Rawashdeh et al., Theranostics (2017)
[25] Hage et al., J Nucl Med (2018)
[26] Kamal et al., J Transl Med (2017)
[27] Kamal et al., J Transl Med (2017)
[28] Srinivasan et al., World J Hepatol (2017)
[29] Tsvetkova et al., Nano Lett (2017)

Probe design for molecular imaging

Dr. Srinivas Banala

The research in probe design group is focused on development of novel diagnostic and theranostic agents. Our expertise is in multi-step organic synthesis, and in particular development of novel chromophores for photoacoustic (PA) imaging, optical applications. We have designed and synthesized probes especially based on porphyrins and BODIPYs, which can work as stand-alone and trigger-responsive PA probes. Peripheral conjugation of BODIPY with heterocylic units having different number of methyl groups generated a highly bathochromic shifted PAI probes (Fig. 6). Moreover, these probes in cremophore EL-H_2O solution gave over 4 times intense PA signal than current 'gold standard' indocyanine green.

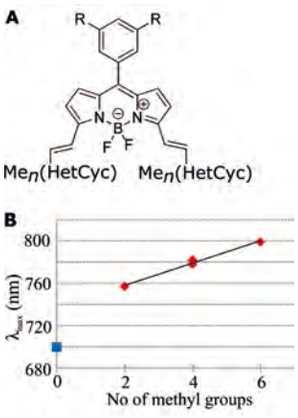


Fig. 6: A: Schematic presentation of the heterocyclics conjugated BODIPY; B: Overview of methyl group effect on the absorption maxima.

In trigger-responsive probes, which increase PA signal along with a shift in the PA maximum in response to chemical and biochemical triggers, we have designed and synthesized reactive oxygen species (ROS) reactive BODIPY dyes. These dyes trap short-lived ROS and increase PA signal accompanied by red-shift in PA maxima than the respective non-reactive chromophore (Fig. 7). These dyes might be interesting to probe pathological ROS generation, e.g. early diagnosis of inflammatory diseases by PA imaging.

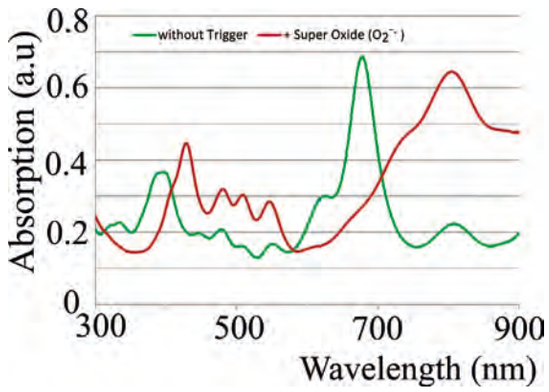


Fig. 7: Change in absorption spectra of a ROS-reactive BODIPY.

In the development of optical probes for super resolution imaging, we have developed BODIPY based low-bleaching fluorescent dye. This probe withstood for hundreds of irradiation cycles in 2-photon laser, thus can be useful as alternative for cyanine dyes. Similarly, we are exploring its applications in STED super-resolution microscopy.

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Awards

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- Jan Grahe: IEEE NSS-MIC Trainee Grant
- Florian Müller: IEEE NSS-MIC Trainee Grant
- Dr. David Schug: IEEE NSS-MIC Trainee Grant
- Laiyin Yin: IEEE NSS-MIC Trainee Grant
- Federica De Lorenzi: Best scientific talk: Category "Image-guided Therapy and Monitoring"
- J.-N. May, Immuno-imaging and molecular therapy Workshop, Poster Award
- A. Dadfar, 12th EMIM, Poster Award
- T. Opacic, FUJIFILM VisualSonics Inc, Vevo Travel Award-Oncology track
- A. Dasgupta, RWTH Research Ambassador-Stipendium

Selected publications

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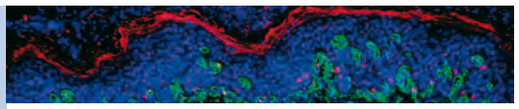

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Team

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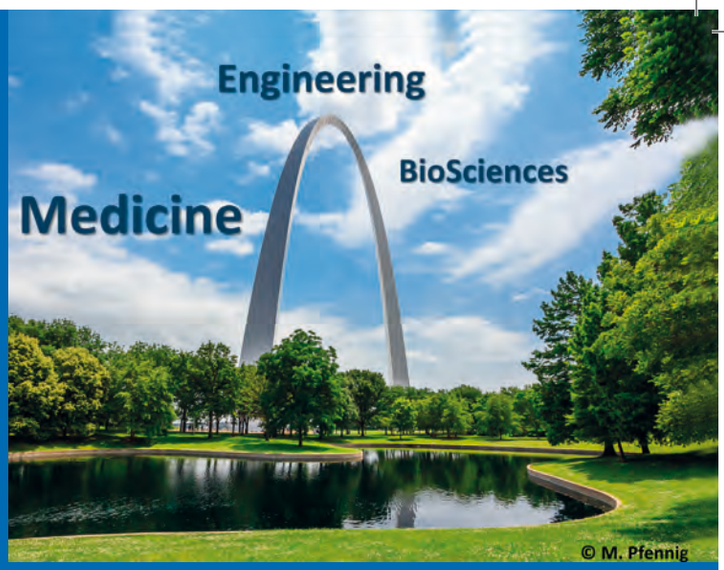
Institute of Applied Medical Engineering

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 pursues a biomedical engineering research profile, which is characterized by consistent and comprehensive interdisciplinarity. Therefore, AME represents a vital example for the often-quoted convergence of disciplines.
The close interaction of the highly innovative technology offers of the 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.

Our team consists of scientists and students from engineering, medicine, physics, information science and chemistry, working closely together in multiple research and development projects. Our cooperations include a great variety of national and international industrial and academic 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 building "Helmholtz Institute" close to the University Hospital, in the Medical Technology Center MTZ across the street, and since December 2017 as well in our new research building CBMS, the Center for Biohybrid Medical Engineering at Forckenbeckstraße 100 m away.

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

Cardiovascular Engineering/CVE

Univ.-Prof. Dr.-Ing. Ulrich Steinseifer

In 2017, the Department of Cardiovascular Engineering continuously strengthened its research activities in the fields of mechanical circulatory support, artificial lung and valve & interventional technologies, with a strong focus on the development of new methods and technologies incorporating hemocompatibility and blood experiments and computational as well as experimental cardiovascular modeling:
The group **Valve and Interventional Technologies** is supporting the startup company Protembis with the development of a polyurethane-based cerebral protection device (funded by the Federal Ministry of Education and Research). Figure 2 gives an overview of some of the work conducted within VIT. Further device developments include a patient-specific left atrial appendage (LAA) occluder (funded by the VDI) and further development of a tissue engineered endobranchial stent, the PulmoStent (funded by the VDI/VDE and PTJ). Research on novel *in-vitro* test methods is performed to enable the development and regulatory approval of new medical devices.

These methods include biomechanical testing of LAA occluders, hydrodynamic and fatigue testing of transcatheter heart valves and calcification testing on animal tissue. Additionally, employees of the CVE are involved in standardization committees regarding heart valve testing within ISO and DIN.

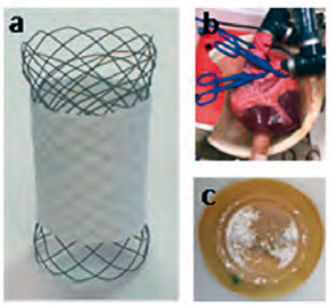

Fig. 2: *a) PulmoStent prototype, b) Heart simulator for testing of catheter devices, c) bovine pericardial patch after calcification testing*

In the field of **Hemocompatibility and Blood Experiments** the HOC Surf, Ghost Cell and von-Willebrand project are still ongoing. The HOC Surf project aims at the improvement of the hemocompatibility of Ventricular Assist Devices by means of ceramization. Therefore, new staining protocols were adapted and test routines established (Figure 3 (left)).
In order to improve Particle Image Velocimetry (PIV) techniques for flow visualization in cardiovascular devices, the DFG-funded Ghost Cell Project contains the batch

production of large amounts (>450 ml) of ghost cells (see Figure 3 (right)). Ghost cells loaded with a fluorescence marker will be used for a spatially resolved hemolysis detection via PIV.
For additionally implementing coagulation properties into PIV, a plasma-based PIV fluid was developed which has the non-Newtonian rheology of native blood and is able to clot in case of a trigger like stasis or foreign surfaces. A first feasibility study with intracranial aneurysm models including flow diverters was conducted showing a severe impact of the non-Newtonian rheology on flow fields using PIV-plasma.

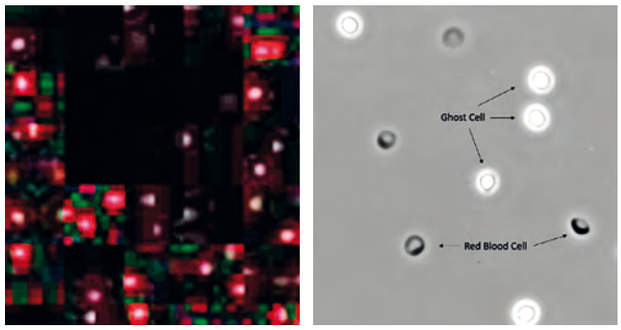

***Fig. 3**, left: Platelet P-Selectin staining on ceramized titanium; right: Microscope image of red blood cells and ghost cells*

Further experimental methods were developed aiming at the research of the interaction between biological and technical systems. A custom-made ELISA for porcine von-Willebrand testing was set up to improve in-vitro blood pump testing. Within an inter-laboratory round robin study, comparability of static in-vitro hemocompatibility test protocols were evaluated aiming at a standardized, valid test routine. Within the new START-funded project "Microstructures" the impact of microstructures on hemocompatibility and platelet behavior on polyurethane surfaces will be investigated.
The focus of the working group **Experimental Cardiovascular Modelling** lies on the development of new experimental methods to optimize blood pumps, heart valve prostheses and artificial lungs.
Using experimental methods like Mock Circulatory Loops (Figure 4) the group supports ongoing projects e.g. the ReinHeart TAH by evaluating different concepts of the right-left flow balance as part of a physiological control and pump curve characteristics under various circulatory conditions.
To obtain sufficient information about durability and wear within an acceptable time period, TAH components are tested under physiological conditions or accelerated examinations. For evaluating long time durability a modular system tester was developed (Figure 5).

***Fig. 4:** Active Mock Loop, Durability Tester*

***Fig. 5:** TAH System*

In addition, a durability test laboratory infrastructure including an automated central data acquisition was implemented. Therefore, we developed hydrodynamic and accelerated wear testing systems and methods, which address the complexities of innovative mitral and tricuspid prostheses.

In the field of **Computational Cardiovascular Modeling**, numerical simulation are employed as a tool to support and drive the development and optimization of blood pumps, stents, heart valve prostheses and artificial lungs. The development of numerical evaluation and experimental validation methods are driven by the objective to quantitatively assess the device performance with regard to efficiency and hemocompatibility. In this regard, blood modelling and numerical blood damage prediction play an important role. New approaches are explored to allow reliable blood damage prediction even in complicated flow conditions such as in a rotary blood pump, see Figure 6.

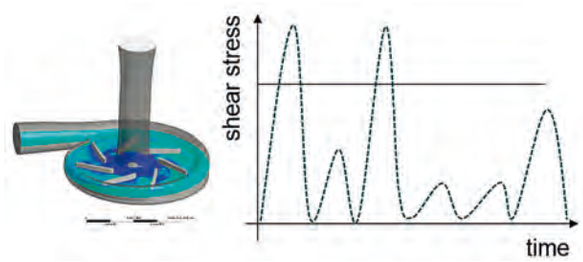

***Fig. 6:** Dynamic shear stress exposure of blood cells travelling through a rotary blood pump*

Further numerical studies cover lumped parameter modeling of the circulatory system, the flow and washout behavior of blood immersed medical devices (TAHs, oxygenators, heart valves) as well as the fluid structure interaction of the blood flow with anatomical structures (vessel walls, heart valves, etc.).
Preliminary work lead to two applications with the Kinderherzstiftung and BMBF project with Berlin Heart, which were granted for 2018. Furthermore, mass transfer and exchange simulations are becoming more and more important, especially for the design of oxygenators, see Figure 7. Adequate gas exchange models and quantifiable predictions are explored in the project OxySim.

***Fig. 7:** The simulation of oxygen saturation of blood passing through an arrangement of fiber bundles of an oxygenator for gas exchange.*

The working group **Mechanical Circulatory Support**, is researching, developing and testing innovative blood pump concepts. The current developments of the workgroup focus on miniaturized heart support pumps for minimally invasive implantation and on heart replacement.
In the research project Scarabaeusherz, a total artificial heart is being developed based on the rotary piston principle. In 2017, the first functional prototype, see Figure 8, with a sealless drive was brought to completion. This proof-of-concept is a breakthrough in the development and forms the basis for the clinical application of rotary piston blood pumps.

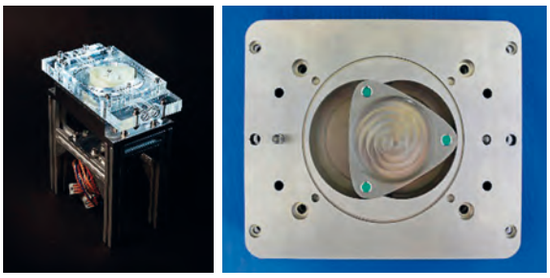

Fig. 8: The total artificial heart concept Scarabaeus

The development of the minimal invasive right ventricular assist device MIRVAD was supported in 2017 with the RWTH Innovationsfond, ERS Boost Fund and Hirsch-Stiftung. With its foldable rotor, MIRVAD allows for placement in the pulmonary artery at an earlier state than common RVADs. Furthermore, the integration of flexible materials lower shear stress exposures and allow for minimal invasive surgery and application within transcatheter implantation procedures.
In the field of **Artificial Lung Technologies**, the development project MobiLung for a wearable ECMO system for better mobilization of bridge-to-lung-transplant patients was successfully finished in July. The EndOxy project stands for an endothelialized oxygenator membrane, developed in close cooperation with the Biohybrid & Medical Textiles department. In order to better understand the internal processes of gas exchange, flow distribution and hemocompatibility during pulsatile and non-pulsatile blood flows in oxygenators, the research projects PulsOxy and OxySim with funding from the German Research Foundation DFG are still ongoing. Within the DFG priority programme (#2014), starting from July on, the projects ConnLA and ConnExAL research novel cannulation methods for either peripheral or central longterm-connection between patient and extracorporeal equipment, both in cooperation with different clinics of the UKA, whereas 3D-ECMO focusses on the development of a 3D printed membrane with improved geometry for ECMO application.

Rehabilitation and Prevention Engineering/RPE

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

Coordinated movement is the key to the world. Movement disorders and restrictions cause pain, disable and make daily activities more difficult to perform. The motivation of the Department of Rehabilitation & Prevention Engineering (RPE) has been the development and realization of adaptive systems and methods which support the prevention, diagnosis and therapy of movement disorders.
To be successful RPE has gathered extensive knowledge about the physiological and pathological function of the human musculoskeletal- and neuromuscular systems. Technical expertise is combined with aspects of the biomechanics of movement in particular muscle biomechanics and movement coordination via the central nervous system. Early consideration of clinical stipulations such as the requirements of therapists and patients boosts the acceptance of new devices and systems and supports the rapid translation in usage.

Assessment of spasticity:

Spasticity is a common consequence in patients with brain lesions. Thus, special emphasis is given to the detection and analysis of spasticity. Information extraction procedures are constantly being developed and refined which allow the assessment and quantification of spasticity in patients with stroke and infantile cerebral palsy.

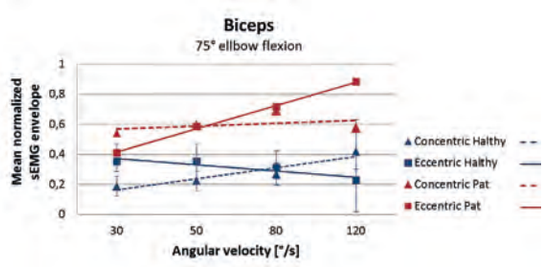

Figure 9: Differences between spastic and voluntary biceps activation with respect to movement velocity.

Furthermore, the central nervous control loop has been investigated at the level of the single motor units to gain better insight into force regulation in spastic contractions.

Assessment of pain

Surface electromyography (sEMG) is used to investigate muscular activation in the presence of pain. Special emphasis is given to low back pain in which pain-related changes in muscular activation can be found. Features have been extracted from sEMG-signals which allow the amount pain during activities of daily life (ADL) to be quantified.

***Fig. 10**: Sit-to-stand task is a typical ADL causing problems in the presence of low back pain. sEMG has been recorded and analyzed with respect to movement performance.*

*In*dividualized *Reha*bilitation therapy *Ro*bot assisted: *inRehaRob*:

Technical assistance enables patients to perform their exercises autonomously. This is a prerequisite for increasing the amount of exercises performed by the patient without increasing the work load of the therapists. Within the BMBF founded project inRehaRob (Figure 11) a consortium of research institutions, industry and rehabilitation centers aim to develop a rehabilitation robot which facilitates individualized rehabilitation performed autonomously by the patient.

***Fig.11**: Robot guiding the therapeutic exercises of stroke patients while sensors assess the movement performance of the patient.*

Ambulatory movement analysis:

Smart sensors have been developed which allow the detection of movement constraints and coping movements during daily activities. These sensors are used to detect e.g. limping during gait or a modified range of motion in the upper extremities. Additionally, algorithms have been developed which allow the assessment of the quality of movement.

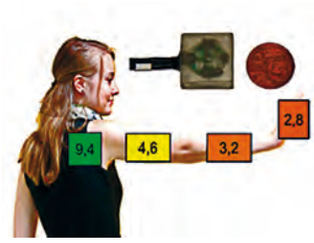

Fig. 12: *Assessment and evaluation of quality of upper extremity movement performance based on inertial sensors.*

Biophysical & Education Engineering/BEE

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

Nanomagnetic Medical Engineering/NME

Dr. rer. nat. Ioana Slabu

The group NME explores magnetic nanoparticles (MNP) for their use in medicine basically for two applications.

1. Design of intelligent magnetic hybrid materials

MNP are used in combination with other substances to create new materials with adjustable features which can be controlled by external magnetic fields. Such hybrid materials can be used e. g. for the manufacture of tissue engineered implants. In a static magnetic field of an MRI device, the MNP inside the implant act as sensors giving information about the position and functionality of the implant. In an alternating magnetic field, the MNP are used for tumor ablation as they cause an effective temperature rise of the implant destroying cancer cells in its close vicinity. For these applications the particle properties must be tuned in order to insure a good response of the hybrid material to the magnetic fields (Figure 13).

Figure 13: Benedikt Mues (left) and Dr. Ioana Slabu (right) observing a step of MNP synthesis

2. Modeling of magnetic carrier systems with temperature triggered drug release

Magnetically controlled transport and release of drugs bound to MNP can be used e. g. to increase the local dose of chemotherapeutica in tumor therapy. In cooperation with the Department of Surgery at the Aachen University Hospital, biophysical models for the optimization of drug delivery with MNP are developed based on individual patient data (Figure 14). These models take into account the interaction of MNP with the blood flow and with cancer cells under the influence of an external static magnetic field. When exposed to an alternating magnetic field, the MNP cause a local overheating inducing cancer cell death. The heat is also used for local release of drugs which have a temperature sensitive bond to the surface of the MNP.

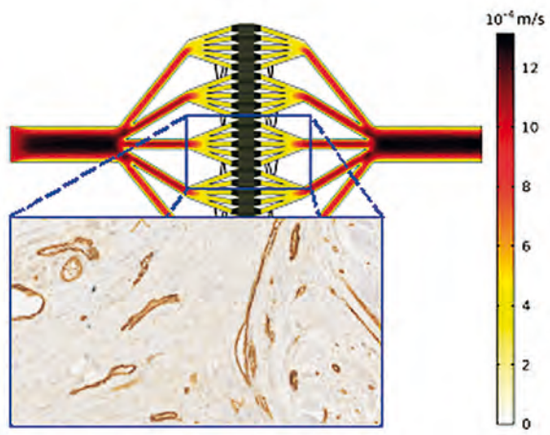

Fig. 14: *Simulation of magnetic targeting in a tumor. The tumor capillaries are modeled based on histological data. The zoom shows stained capillaries (~ 40-100 µm) of a human pancreatic tumor.*

NRW-Schwerpunktprofessur Biohybrid & Medical Textiles/ BioTex

Univ.-Prof. Dr. med. Stefan Jockenhövel

The *NRW-Schwerpunktprofessur* Biohybrid & Medical Textiles focuses on the development of viable implants with the potential for remodeling, 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 the Institute for 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).
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.

Science Management/SCM

Dr. Robert Farkas

Although interdisciplinary collaboration is considered to be the most promising tool to tackle the braking effect of the increasing complexity in developing innovative medical devices, finding the most suitable partners for an effective R&D-cooperation is often haphazard or done in a laborious manual way.
So we analyzed published documents of different sources to extract the professional competencies of a small sample of biomedical experts using Information Retrieval tools. Although some specific issues (e.g. author disambiguation, profiling) need further research, the approach in general turned out to be feasible and promising.

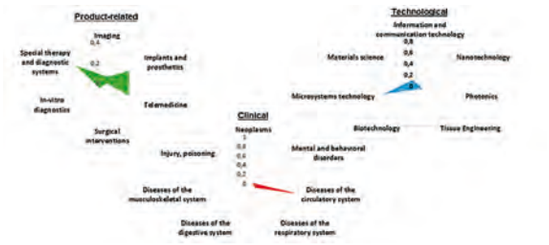

Figure 15: Example of a domain specific competence profile as part of a biomedical collaboration recommender system. (see details in M. Bukowski et al., ACM RecSys 2017, Como.)

Of course we continued in fostering cooperation within the I3TM, a measure of the Excellence Initiative, and traditionally at RWTH Aachen Campus within the Biomedical Cluster expanding the partnerships and research space (see Figure 16).

***Fig. 16:** 'Lights on!' Users' take-over of the new Center for Biohybrid Medical Systems CBMS. (Picture by Stefan Jockenhövel)*

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Journal Publications 2017

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Team

Facts

Third-party funding

	Number of Projects	Total Expense of Projects [EUR]
German Research Foundation (DFG)	41	2.836.165
German Federal Ministry of Education and Research (BMBF)	27	4.010.940
EU	17	2.631.296
Industry	25	1.238.565
Other	39	5.800.185
Sum	149	16.517.151

Theses

	Number
Bachelor	63
Diploma/Master	74
Doctoral	14
Habilitation	0
Sum	151

Staff

	Scientific	Non-Scientific
Total	204,5	38
Third party funded	167,5	10,5

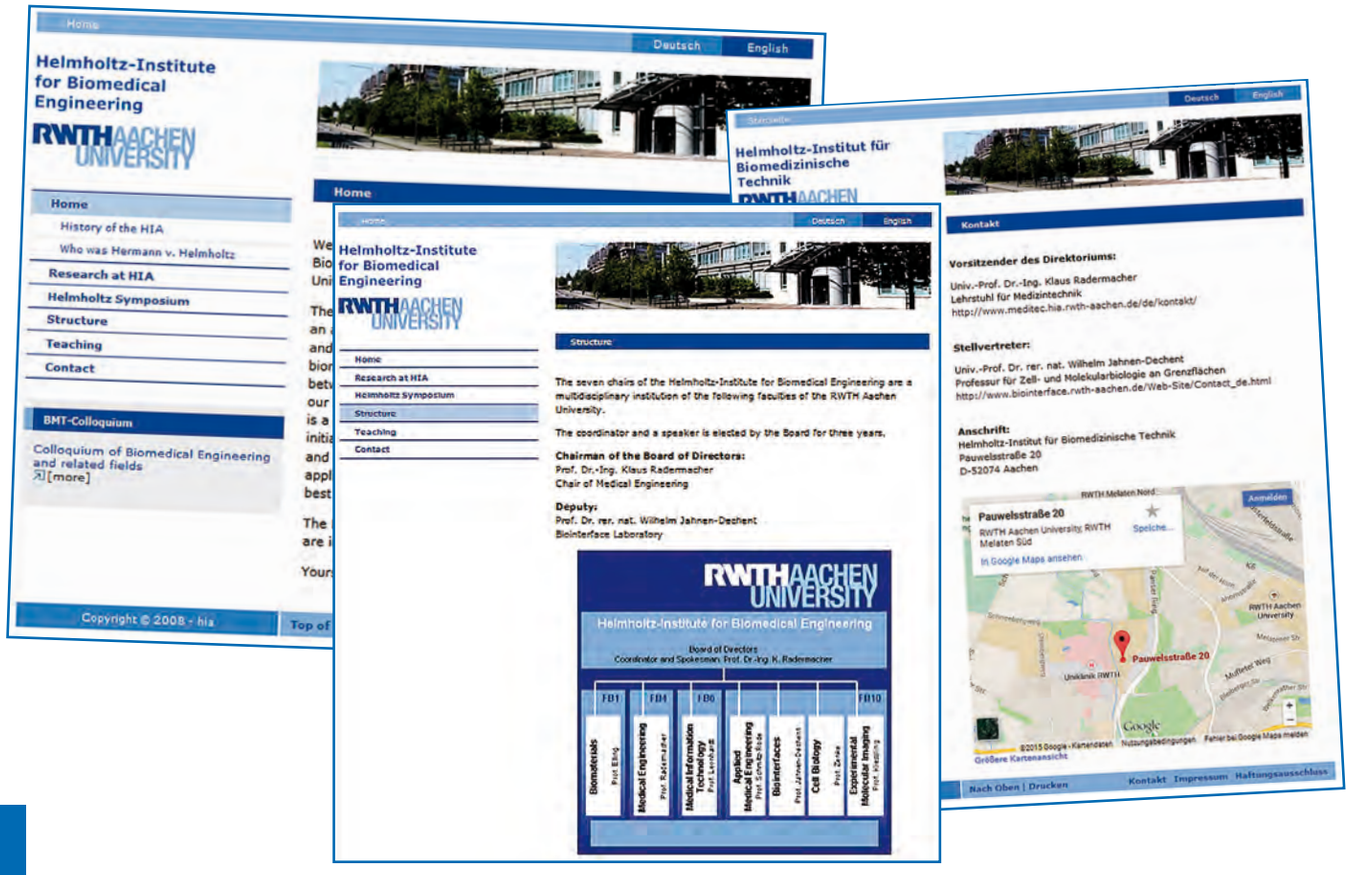
in full-time equivalent (FTE)

Publications

	Number
Conference proceedings	112
Peer-reviewed journals	179
Books and book chapters	7
Sum	298

Patents and patent applications: 22

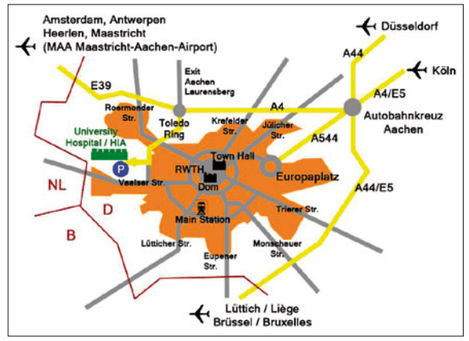
Web Contact: *www.hia.rwth-aachen.de*

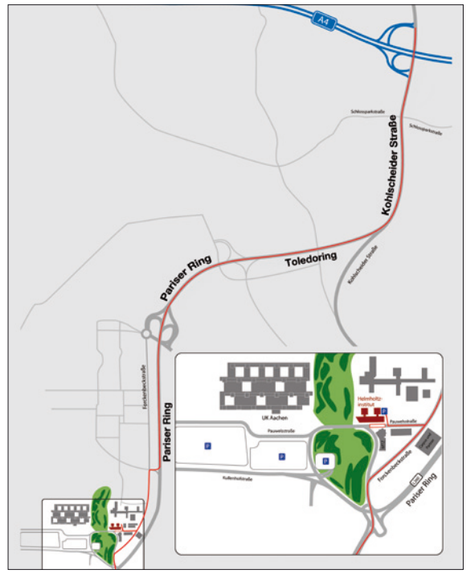


Content

Annual Report
2017
Helmholtz-Institute for Biomedical Engineering
RWTH Aachen University

How to reach us





Address

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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.