Preface

The Helmholtz-Institute for Biomedical Engineering HIA represents a major hub for interdisciplinary basic research and development in biomedical engineering at RWTH Aachen University and beyond. This past September we hosted once more the Annual Conference of the German Society for Biomedical Engineering. More than 600 participants from 15 countries convened in the Central Auditorium for Research and Learning C.A.R.L., which had just opened as one of the latest additions to RWTH Aachen facilities. We are proud and honored to have hosted this major international conference for the second time.

We contribute to Bachelor and Master courses of the Medical, Engineering and Natural Sciences faculties of RWTH Aachen University. Members of the Helmholtz-Institute coordinate master courses related to all fields of biomedical engineering. 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. Biomedical Engineering, Medical Biology and Biointerface Science are steadily gaining importance and have in fact become compulsory or facultative subjects in study curricula of Biomedical and Engineering Master Courses. This development merely reflects the ever evolving Biomedical and Health Industries, technological innovation and societal needs.

Our bi-annual Helmholtz Symposium has become a prime meeting place fostering collaborations with partners from within and outside our University. The next meeting will be held on 14 June 2019.

Research projects target improved health care. Continuous refinement of methods and technologies helps to achieve optimized diagnostic and therapeutic options for patients. Networking and cooperation within RWTH Aachen University as well as with national and international clinicians, academic and industry researchers are key to our work. Members of the Helmholtz-Institute for Biomedical Engineering have been instrumental in securing funding for both coordinated teaching and research. In 2018, external funding alone has reached well over 9 Mio Euro.

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, April 2019

The Board of Directors

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

Events 2018

BMT 2018 – 52nd Annual Conference of the German Society for Biomedical Engineering (**DGBMT** within VDE).

Team building Events 2018
Christmas Party

Gene Function in Cell Growth, Differentiation & Development

Director

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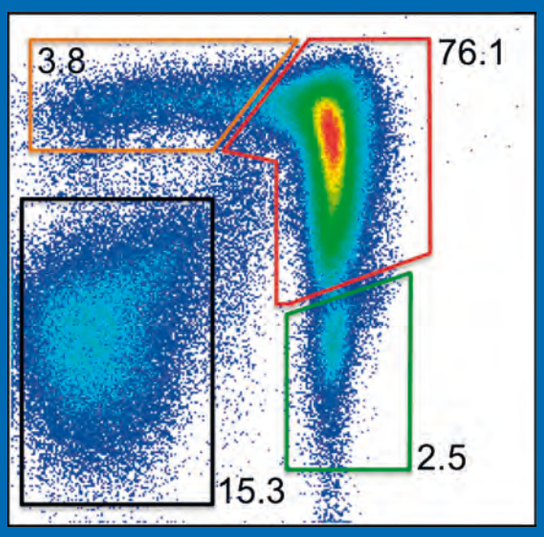

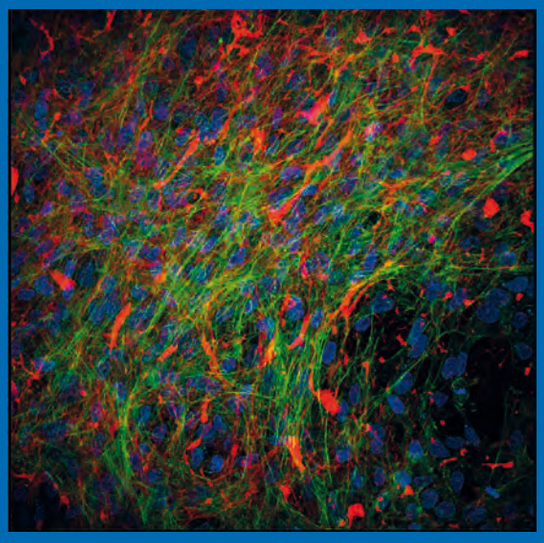

Stem Cell Biology and Cellular Engineering

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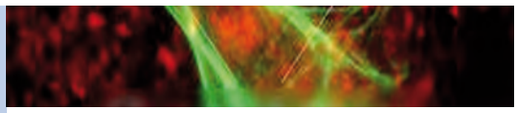

Introduction

The scientific progress made in recent years with both adult and pluripotent stem cells demonstrates the importance of stem cell research and its impact on biology and biomedicine. Additionally, engineering of stem cells possesses enormous potential for tailoring biomedical applications and cellular therapies towards precise and personalized medicine. This also demonstrates that engineering principles enter biology and biomedicine.

The institute studies genetic programs and epigenetic mechanisms that determine cell identity and developmental potential of stem cells and their differentiated progeny. A particular focus is on hematopoietic stem cells (HSC), mesenchymal stem cells (MSC), and embryonic stem cells (ES cells) and on stem cell differentiation towards specific lineages, such as antigen presenting dendritic cells (DC). In addition, pluripotent stem cells are generated from somatic cells by reprogramming, referred to as induced pluripotent stem cells (iPS cells; Fig. 1).

Novel technologies of genome editing including CRISPR/Cas have revolutionized both basic and applied research in many areas of biology and biomedicine. Stem cells are particularly well suited for genome editing. Thus, one objective of our research is on stem cell engineering and the generation of cells with wanted properties e.g. for disease modeling or drug testing.

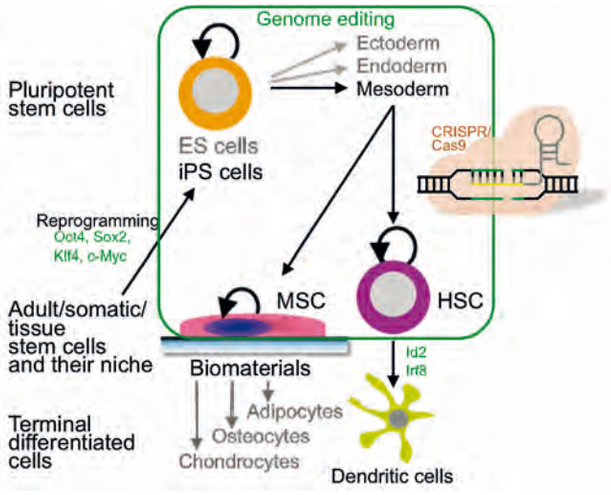

Fig. 1: Cellular and genetic engineering identifies genetic programs of cell fate. Transcription factors (green) are investigated and used to influence developmental programs. Mesenchymal stem cells (MSC) and hematopoietic stem cells (HSC) reside in the bone marrow niche and develop into cells of connective tissue and all cells in blood, such as dendritic cells, respectively. Biomaterials are used to emulate aspects of the niche and impact on cell growth, differentiation, and function. Induced pluripotent stem cells (iPS cells) are obtained from somatic cells by reprogramming. CRISPR/Cas technology is employed for precision genome editing of stem cells.

Stem cells and their differentiated progeny develop in a highly specialized microenvironment, referred to as stem cell niche. Thus, a further objective of our research is to employ biomaterials and/or specific factors to recapitulate conditions of the stem cell niche in vitro for optimal growth and differentiation of stem/progenitor cells. A particular focus is on DC development and DC migration. This includes research on molecular mechanisms of cell-to-cell and cell-biomaterial interaction and their impact on cell motility and adhesion. Furthermore, mechanisms of genetic and epigenetic regulation are investigated to address their impact on cellular senescence and aging of stem cells and on DC development. These studies are expected to provide valuable insights for cell and tissue engineering that may lead to novel replacement therapies in regenerative medicine.

Induced Pluripotent Stem Cells and Precision Genome Engineering

Patient specific iPS cells represent an essentially inexhaustible cell source for many biomedical applications. Additionally, iPS cells are ideally suited for genome editing with CRISPR/Cas, since the genetic changes introduced are propagated to the daughter generations, including differentiated cells (Zenke et al., 2018). We use patient and disease specific iPS cells and genome editing with CRISPR/Cas for studies on the impact of mutated KIT, JAK2 and calreticulin in leukemia and for compound screening (in collaboration with Department of Hematology, Oncology, Hemostaseology and Stem Cell Transplantation, RWTH Aachen University Hospital, and Organic Chemistry, RWTH Aachen University, and Department of Medicine I and Ludwig Boltzmann Cluster Oncology, Medical University, Vienna, Austria). In addition, iPS cells of patients with chronic pain were generated to study the pathophysiology of pain (Meents et al., 2018; in collaboration with Institute of Physiology, RWTH Aachen University Hospital).

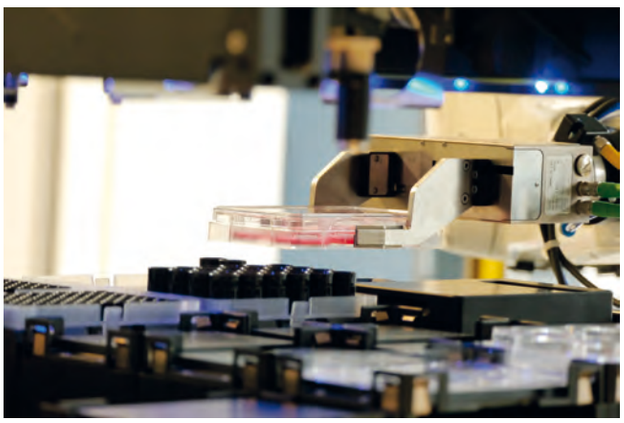

Fig. 2: Automatic cell production facility (iCellFactory)

Biomedical applications of iPS cells, and of cells derived thereof, require processing of large numbers of individual cell products. To meet these needs we followed up on our efforts to construct an automatic cell production facility (Fig. 2; in collaboration with Laboratory for Machine Tools and Production Engineering, WZL, RWTH Aachen University and Fraunhofer Institute for Production Technology, IPT, Aachen, Germany; Malik et al., 2018).

Chromatin Architecture of Dendritic Cells

DC are professional antigen presenting cells that develop from HSC in bone marrow through successive step of lineage commitment and differentiation. In our previous work by Lin et al. (Nucleic Acids Res., 2015) we studied gene expression in DC and several histone modifications. We have now extended this work to map the genome-wide open chromatin architecture by transposase-accessible chromatin using sequencing (ATAC-seq) technology (Fig. 3 and Li et al., 2018). Chromatin architecture, transcription factor binding and histone modifications are being integrated by bioinformatics to device the transcriptional circuitry of DC development and function.

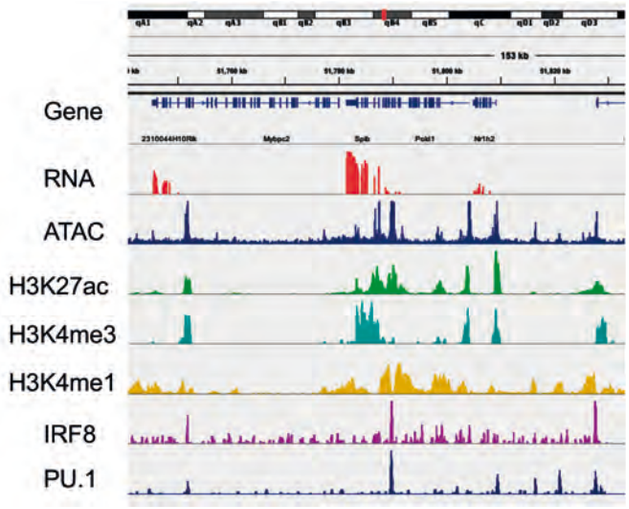

Fig. 3: SpiB locus in plasmacytoid DC subset was analyzed for gene expression (RNA), open chromatin (ATAC), histone modifications (H3K4me1, H3K4me3 and H3K27ac) and transcription factor binding (IRF8 and PU.1).

Cytokine Signals as Relays in Genetic Programs of EMT and MET during Dendritic Cell Development

DC develop from HSC in bone marrow (Fig. 1) and migrate as precursors into peripheral tissues, such as skin (Fig. 4). There, DC are embedded sedentarily and functionally to act as guardians of the immune system. Following antigen uptake, DC are activated, leave the peripheral tissue and migrate via lymphatic vessels to lymphoid organs for T cell stimulation (Fig. 4). We propose the concept that genetic programs of mesenchymal-to-epithelial transition (MET) and epithelial-to-mesenchymal transition (EMT) regulate homing and migration of DC, respectively (Hieronymus et al., Semin. Cell Dev. Biol., 2015; Sagi and Hieronymus, 2018). In EMT and MET programs distinct cytokine signals act as relays during DC development, function and migration. We particularly focus on investigating signaling via TGF-β receptor and hepatocyte growth factor (HGF) receptor, which have a differential impact on regulating homing and migration of DC (Fig. 4). The differential and sequential role of BMP7 and TGF-β1 in differentiation of Langerhans cells, the contingent of DC in stratified squamous epithelia, was identified (in collaboration with A.-H. Hovav et al., Hebrew University, Jerusalem, Israel; Capucha et al., 2018).

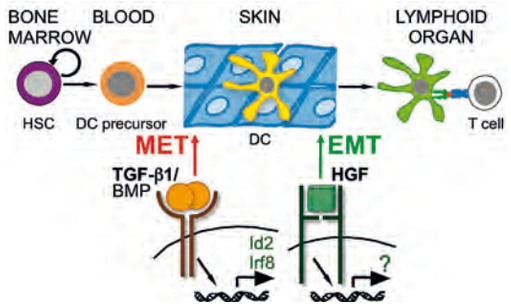

Fig. 4: TGF-β/BMP and HGF receptors are regulators of EMT and MET programs in DC development and migration.

Novel Infrared Cellulose Nanocrystals for Live Cell Imaging

Nanomaterials are highly tunable nanoscale objects, which have received remarkable attention in therapeutic and theragnostic applications. Cellulose nanocrystals (CNC) are a unique and promising natural material extracted from native cellulose. Due to their special surface chemistry, low toxicological risk, negligible inflammatory response and the ability to penetrate cells, CNC are promising candidates for biomedical applications. In this context, nanocellulose-based imaging probes have received considerable attention in recent years. However, CNC with near-infrared (NIR; λ=750-1400 nm) probes have not been reported to date. Higher tissue penetration, lower biological auto-fluorescence and reduced light scattering have greatly increased the interest of NIR fluorescent probes. Known limitations of these probes include dye aggregation, low solubility in water and undesired changes of photophysical properties. Thus, only a limited number of NIR dyes are available, most of them being not easily functionalized and too expensive.

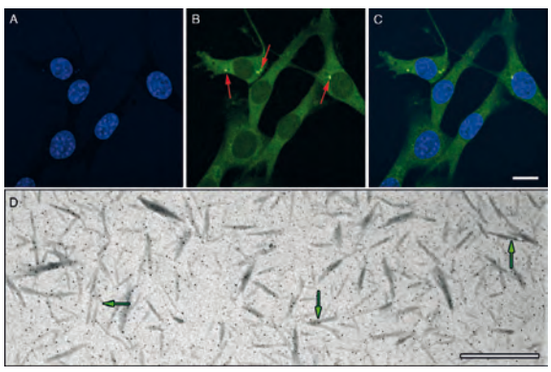

Fig. 5: Imaging of near-infrared cellulose nanocrystals (NIR-CNC). (A-C) Confocal imaging showing NIR-CNC (arrows) internalized by NIH-3T3 cells. Nuclei were stained with DAPI. Scale bar: 15 µm. (D) Transmission electron microscopy analysis of NIR-CNC showing their typical needle-like structure (arrows). Scale bar: 500 nm

To overcome these limitations, we are working on a joint project with Luiz H.C. Mattoso (LNNA, Embrapa Instrumentation, São Carlos, Brazil) centered on the development of near-infrared cellulose nanocrystals (NIR-CNC). NIR-CNC are fabricated via the covalent functionalization of water-soluble perylenediimide based NIR dyes on the surface of the CNC. Physical and chemical characterization of NIR-CNC is done by FT-IR, X-ray diffraction, scanning electron microscopy and X-ray photoelectron spectroscopy. Furthermore, live cell imaging studies (i.e., confocal laser scanning and total internal reflection fluorescence microscopy) are performed to determine the biocompatibility and suitability for short and long-term bioimaging (Fig. 5).

Epigenetic Age-Predictor for Mice

Specific cytosine residues of our DNA become either methylated or demethylated upon aging. It is yet unclear how these epigenetic modifications are governed, but they provide a very powerful biomarker to estimate the age of human donors. More importantly, the deviation between predicted and chronological age was shown to be affected by parameters that influence the aging process, indicating that epigenetic age is indicative of biological age. More recently, several groups described epigenetic age-predictors for mice based on genome wide deep sequencing data. These studies have raised a lot of attention because they facilitate assessment of age-intervention strategies in the murine model. However, the methods based on deep sequencing are relatively labor-intensive and cost-intensive and cannot be easily applied to large cohorts of mice.

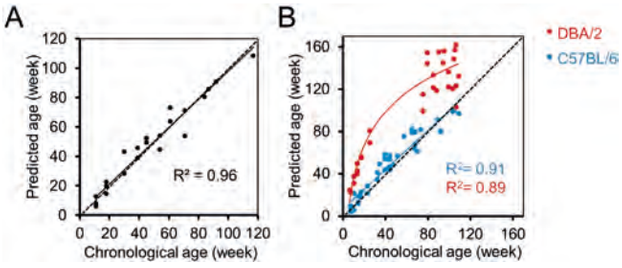

Fig. 6: (A) Three CpG multivariable epigenetic age-predictor for C57BL/6 mice. (B) Epigenetic age-predictions using the three CpG multivariable age-predictor for the C57BL/6 mice (blue) and DBA/2 mice (red) (Han et al., 2018).

Our group has described a bisulfite pyrosequencing approach to analyze the DNA methylation level at only three specific genomic sites in blood samples of mice (Fig. 6A). Notably, epigenetic aging varies between mouse strains and it is accelerated in DBA/2 strain with shorter life expectancy (Fig. 6B). The site-specific DNA methylation analysis at only three CpGs provides an easily applicable tool to further analyze how epigenetic aging is affected in knockout mice or in longevity intervention studies in mice (Han et al., 2018).

Does Soft Really Matter? Differentiation of Induced Pluripotent Stem Cells Towards Mesenchymal Stromal Cells on Soft Gels

Due to their functional plasticity MSC are very important for regenerative medicine, and they are studied in many clinical trials. However, primary MSC isolated from human tissue are very limited in cell numbers, they are highly heterogeneous and difficult to standardize. Therefore, alternative strategies have evolved to derive MSC from iPS cells (iMSC). However, the differentiation of iPS cells towards MSC remains incomplete. It has been suggested that mechanical cues can direct lineage-specific differentiation of stem cells and that particularly matrix elasticity is important for cell fate decisions.

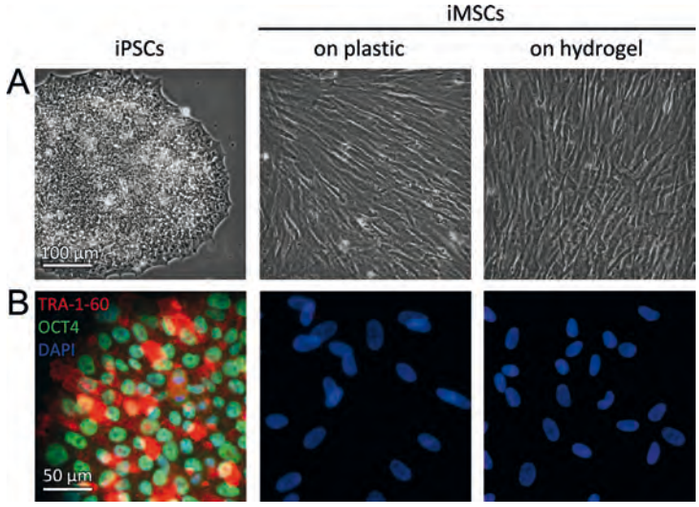

Fig. 7: iPS cells can be differentiated towards MSC on stiff plastic and on soft hydrogel. (A) After 35 days of differentiation, iMSC demonstrated MSC-like morphology. (B) The pluripotency markers TRA-1-60 (red) and OCT4 (green) were downregulated during differentiation (nuclei stained with DAPI, blue) (Goetzke et al., 2018).

We demonstrate that iPS cells can be effectively differentiated towards MSCs on fibrin-based hydrogels (Fig. 7; Goetzke et al., 2018). Unexpectedly, this complex differentiation process is not affected by the soft substrate: iMSC generated on plastic or hydrogel have the same morphology, immunophenotype, differentiation potential, and gene expression profiles. Moreover, global DNA methylation patterns of iMSC generated on plastic or hydrogel indicate that they are epigenetically alike. These findings add to recent controversy if and how mechanical stimulation impacts on cellular differentiation.

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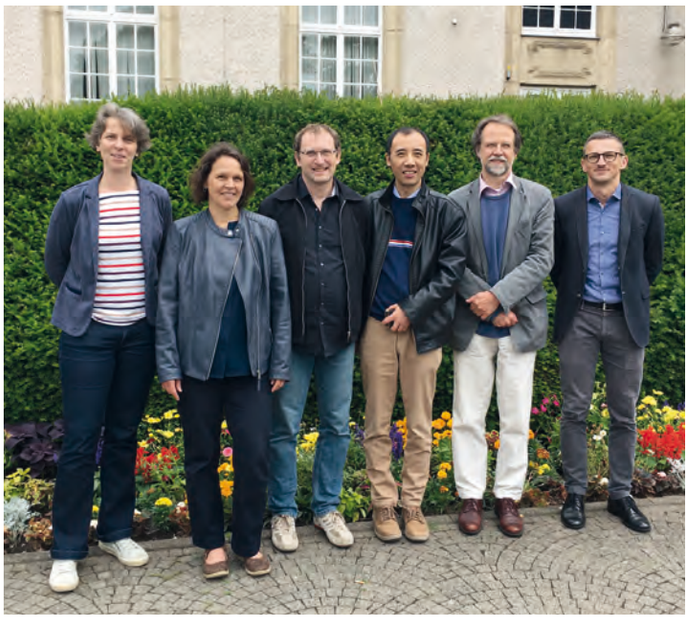
Team

Lab retreat in The Hague, Netherlands.

Stephanie Sontag, PhD, speaking to Professor Emmanuelle Charpentier, recipient of Aachen Engineering Award 2018, at the RWTH Aachen Graduation Celebration 2018.



Small lab reunion at the occasion of the 15th International Symposium on DC (DC2018) in Aachen, Germany. Kristin Seré, PhD, RWTH Aachen University; Sandra Diebold, PhD, National Institute for Biological Standards and Control (NIBSC), Hertfordshire, UK; Thomas Hieronymus, PhD, RWTH Aachen University; Xinsheng Ju, PhD, ANZAC Research Institute, Sydney, Australia; Martin Zenke, PhD, Professor, RWTH Aachen University; Nicolas Goncharenko, PhD, Institut National de Cancer, Luxembourg (from left to right).

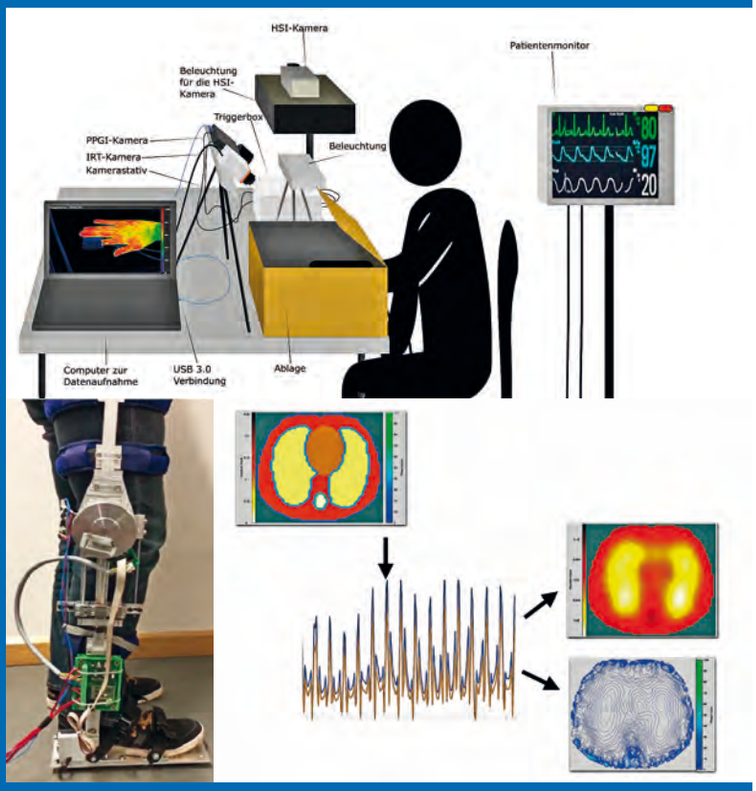
mediT

Medical Information Technology

Faculty of Electrical Engineering
and Information Technology

RWTH AACHEN UNIVERSITY

Smart Solutions for Advanced Healthcare



Director

Univ.-Prof. Dr.–Ing. Dr. med. Dr. h. c.
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Clever-Offermanns, Bettina, Secretary
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Thomas, Theo, IT Administrator

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Yu, Xinchi, M.Sc.

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Rahn, Hannah, Software Developer
Schröder, Kai, Software Developer
Schwarz, Frederic, IT Apprentice
Windeln, Fabian, IT Apprentice

Guests

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David Vrba, CTU Prague
Prof. Tarunraj Singh, University of Buffalo
Prof. Najib Jamaludi, UTM Malaysia
Dr. Shahliza Abd Halim, UTM Malaysia
Dr. Mohd Adham Isa, UTM Malaysia
Dr. Toni Anwar, UTP Malaysia
Rohiza Bt Ahmad, UTP Malaysia
Dayang Rohaya Bt Awang Rambli, UTP Malaysia
Dr. Xinyu Guan, Tsinghua University
Yinbo Li, Tsinghua University

Introduction

The Philips 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.

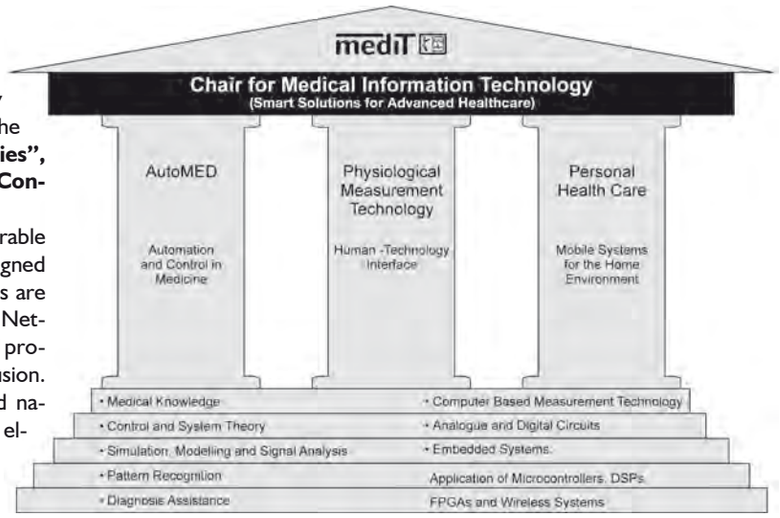

Fig. 1: *Research profile of MedIT.*

Ongoing Research – Selected Projects

Bioimpedance Volumetry for the Monitoring of Hydrocephalus

Hydrocephalus is a disease characterized by the abnormal enlargement of the ventricles of the brain. It occurs due to the disruption of the production-circulation-absorption cycle of cerebrospinal fluid (CSF) as a result of an obstruction in the CSF pathways. It is often associated with elevated intracranial pressure (ICP), although in those groups of patients suffering from Normal Pressure Hydrocephalus (NPH), the mean ICP remains mostly within physiological range. A reduction of the dynamic intracranial compliance plays an important role even the exact pathophysiology is still unclear.

Our aim is to investigate the feasibility of the bioimpedance technique for continuous ventricular volumetry. By integrating electrodes to the tip of the drainage catheter and taking advantage of the fact that CSF has a much higher conductivity (σ_{CSF} = 2.01 S/m) than its surrounding tissues ($\sigma_{parenchym}$ = 0.17 S/m), a combination of tetrapolar measurements might allow for a correlation to the amount of intraventricular CSF. We therefore focused on investigating, designing and testing the envisioned bioimpedance drainage catheter by conducting finite element (FE) simulation studies with anatomical and simplified anatomical models, shown in Figure 2.

Funded by: German Research Foundation (DFG)

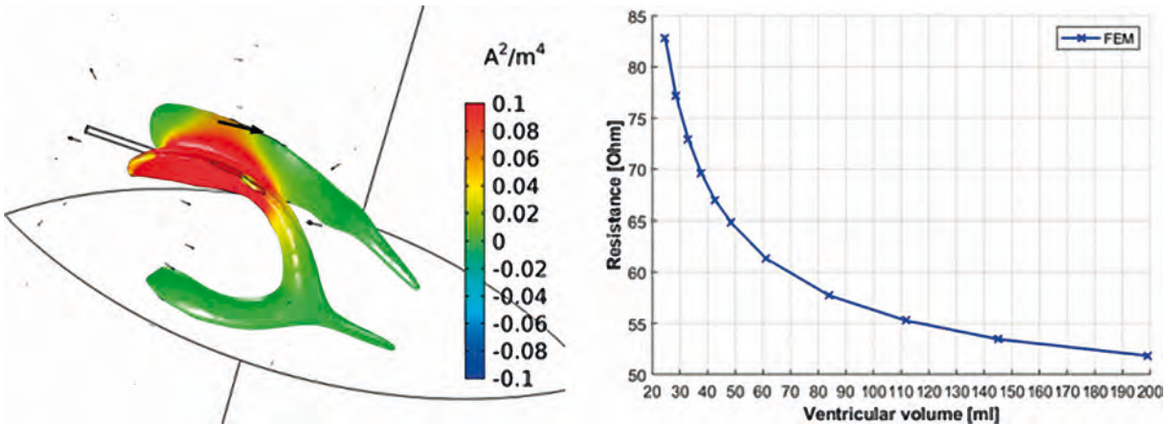

Fig. 2: Left: Sensitivity distribution [A2/m4] and Right: FE simulation results for the measured resistance [ohm] as a function of ventricular volume [ml].

Object-oriented Modeling of Cardiopulmonary Dynamics and Respiratory Diseases

In precision medicine, mathematical and computer-based models propose the customization of healthcare in terms of medical treatments as well as medical decisions for individual patient. Physicians can predict more accurately which treatment and prevention strategies for a particular disease should work in the defined groups of patients. In this project, we focus on medical modeling at the system/organ level and aim to develop a computational model of cardiopulmonary dynamics for analysis of respiratory diseases, i.e. cardiogenic pulmonary edema.

The lumped-element model was implemented in the object-oriented language based on Matlab Simscape, in which the system equations are presented by physical blocks and connections. The cardiopulmonary model includes more than 30 elements, which correspond to the same number of physiological functional components of the cardiopulmonary system. The cardiovascular system was developed based on the model of Smith et al. with the extension of atria and non-linear characteristics of the veins and lung capillaries. Nonlinear PV relationships were included to give the model a higher robustness against parameter uncertainties, especially at boundary conditions for the collapse of the capillaries or veins. The proposed respiratory model is a novel nonlinear model, which considered the bronchial collapse, pleural dynamics, and lung-chest wall interconnected elasticity.

Figure 3 represents the overall model of cardiopulmonary system including the fluid balance and the lymphatics. The proposed model provides physiologically stable results for cardiopulmonary interactions, which could be directly compared with clinical and animal data from literature. Pulmonary diseases such as heart failure, cardiogenic congestion and edema can be simulated in order to observe the system behavior and response. The model can be used as a simulator in a user-interactive software tool for educational and training purposes or as a bed-side model-based monitoring tool applied for personal health care.

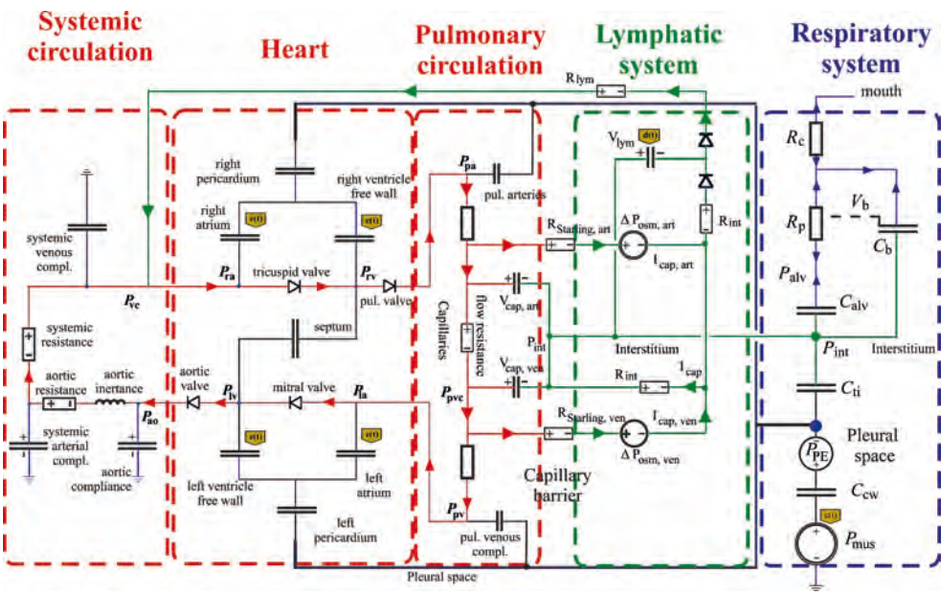

Fig. 3: Object-oriented modelling of the cardiopulmonary system.

MuSeSe – An Armchair for Unobtrusive Health Monitoring

The MuSeSe, a multi-sensor armchair developed at MedIT, is a research prototype that was built for the analysis of several technical aspects of unobtrusive sensing. It consists of different low-cost sensors to analyze cardiorespiratory activity which are integrated into back and seat, see Figure 4. Four different modalities are used, in particular, capacitively coupled electrocardiography (cECG), photoplethysmography (PPG), ballistocardiography (BCG), and high-frequency (HF) impedance. While cECG records the electrical activity of the heart, PPG measures pulse-synchronous optical changes. BCG records mechanical activity and HF impedance is very sensitive to changes in electrical conductivity inside the thorax, which are mainly induced by respiration.

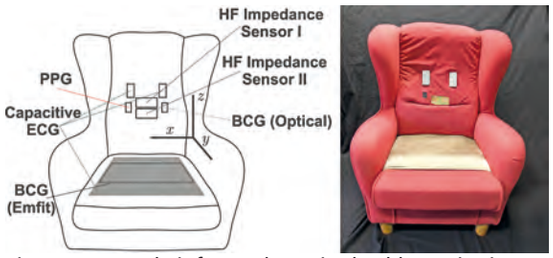

Fig. 4: An arm chair for unobstrusive health monitoring.

The selected modalities show different characteristics in terms of accuracy and robustness. For example, cECG gives the most precise cardiac signal but is easily disturbed by motion, while PPG is more robust in that aspect. BCG from the seat is obviously insensitive to the type of cloth worn on the torso. To exploit the respective strengths and compensate for weaknesses, concepts for sensor fusion were developed and evaluated on data acquired with MuSeSe. In particular, a powerful motion capture system of the Clinic for Internal Medicine and Geriatrics at the Franziskushospital Aachen was used as a reference to analyze motion tolerance. Larger studies including patients with a broad range of pathologies associated with old age need to be performed to proof the practical value.

Modelling of Heart Tissue using Customized Silicone

Cardiovascular disease remains the leading cause of death in developed countries. Due to diseases such as hypertension, atherosclerosis or other genetic risk factors as well as an unhealthy lifestyle in an aging society, more than 400 million people worldwide suffered from heart disease in 2015, resulting in the deaths of approximately 18 million people. Reduced perfusion of myocardial tissue caused by, for example, obstruction in the coronary arteries reduces the pumping performance of the heart. In severe cases, left ventricular assist device (LVAD) therapy can be used to sufficiently supply affected myocardial tissue with oxygenated blood to assist the heart muscle for recovering its functionality. In case of heart muscle recovery, it is desirable for the patient to wean from the device.

To date, there is no adequate method to detect heart muscle recovery in LVAD therapy. In order to establish a new method based on the measurement of electric conductivity, this project focuses on the development of customized silicone heart models to mimic the electrical properties of the heart in order to determine the recovery status of the heart muscle.

Previously, it has been shown that the electrical properties of myocardial tissue change during ischemia, so that these changes are a possible estimate for measuring the condition of myocardial tissue. To this purpose, initial attempts have been made to develop silicone models that mimic the electrical properties of heart tissue. This was done by mixing different carbon materials into the insulating silicone. Initial results showed that the higher the carbon concentration in the silicone, the higher the conductivity of the silicone samples.

In addition, cost-effective 3D casting moulds were developed to model the anatomy of the left ventricle. An internal paraffin wax core, which is removed during the casting process, ensures a hollow ventricle. Figure 5 (a) shows on the left side of a shell of the casting mould including the paraffin wax core, (b) represents the silicone ventricle mock-up and (c) presents silicone plus carbon ventricle mock-up with different electrical properties using customized silicone to model the heart muscle.

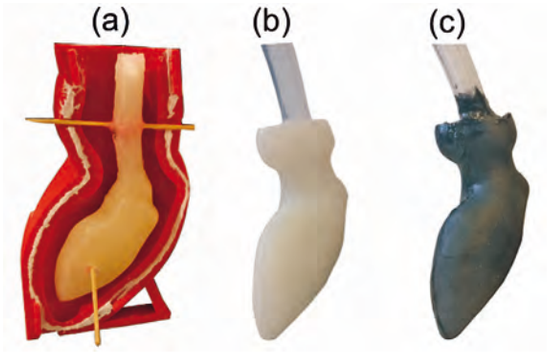

Fig. 5: a) Casting mould including the paraffin wax core fixed by wooden sticks in the center. b) Silicone ventricle mock-up. c) Silicone plus carbon ventricle mock-up.

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

The Smart Bandage – Multi Sensor Wound Monitoring

The continuous measurement and evaluation of chronic wounds could improve the treatment of patients with chronic venous insufficiency (CVI) significantly. Developing such a sensor device requires a deep understanding of the effects of local changes in hemodynamics as well as tissue properties, therefore our work follows a holistic approach covering five research topics: the identification of meaningful biological parameters that can be measured by sensors available on the market; the implementation of tissue and leg models for the simulation of wounds and their effect on those parameters; the measurement and evaluation of parameters using non-contact, camera based technologies; the design and manufacturing of a sensor device that can be integrated into a bandage; the fusion of the multi sensor data to allow for wound status diagnosis.

Wound diagnosis in clinical practice is still based on visual inspection and personalized patient survey. Potential biological indicators were identified in close cooperation with clinical partners within the project. Based on this, our research focuses on the measurement of temperature, perfusion, oxygen saturation and bio-impedance for wound diagnosis. Infrared thermograph (IRT) of wounds and surrounding tissues were recorded using thermal cameras in a clinical setting, where significant temperature drops have been identified inside chronic wounds – in contrast to the temperature of a healing wound of a healthy individual. Image processing algorithms are developed for the automatization of the parameter identification process, where non-physiological tissue regions are identified and temperature information is processed.

The effects of changes in tissue properties on the bio-impedance are simulated using a 3D-model of the human lower leg. Simulation results show that changes in tissue behavior can be identified, which are present during wound development as well as wound healing. Exemplary for the holistic approach, the multi sensor bandage design and the IRT data processing are displayed in Figure 6.

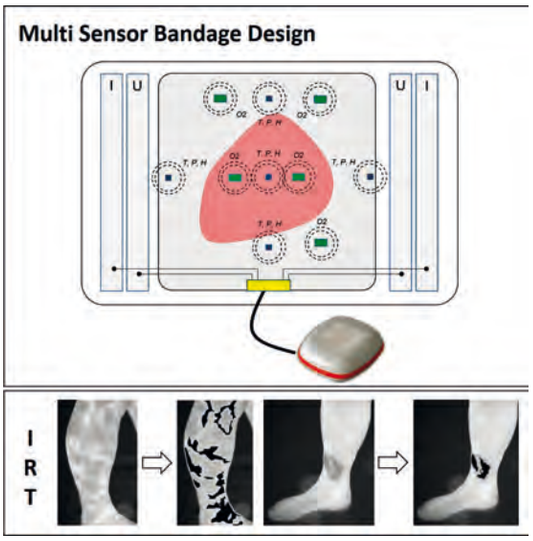

Fig. 6: Multi-sensor wound monitoring system.

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

Tissue Identification by Electrical Impedance Tomography

Electrical Impedance Tomography (EIT) is a radiation free imaging modality to represent impedance distributions inside the human body. Based on its principle, EIT injects a series of harmless sinusoidal current into the body around the thorax and measures the resulting surface potentials. 928 measurements can be acquired for a 32 electrode system. The reconstruction algorithm maps these voltage measurements to a 32x32-pixel image with high temporal resolution in real time. The traditional time-differential EIT uses these measurements to reconstruct conductivity changes over time at a single frequency e.g. ventilation and perfusion monitoring. A novel approach acquires transfer impedances at various frequencies, called multi-frequency EIT (mfEIT). Utilizing the frequency specific behavior of tissue, EIT has the potential to generate conductivity maps of the body including tissue specific information and to identify regional tissue types. Therefore, this project has two main aspects. On the one hand, a new measurement device, called AixTOM, is under development to satisfy the sophisticated requirements of mfEIT, which mainly imply frequency stability from a few kHz up to one MHz. On the other hand, the reconstruction itself is challenging and requires novel approaches for better image quality and usefulness in clinical interpretation. The reconstruction can be described as a least-square problem and the Gauss Newton algorithm is one way to find a stable solution. Optimizing the reconstruction parameters to find a suitable map of the measured transfer impedances onto a conductivity image is a complex and challenging task. Figure 7 shows the whole EIT acquisition chain (from left to right): The electrode belt around the chest is physically connected to the mfEIT device (AixTOM) via the cables. Within the AixTOM device, it consists of signal generator, signal acquisition unit, and signal processing unit, where field programmable gate array (FPGA) can be programmed and customized. Further computation and reconstruction of the image stream is then carried out in a laptop for data representation. The preprocessed signals are reconstructed to a map of complex conductivity differences, which contain tissue specific information. Possible applications are the early detection of extracellular water from an edema or secretion of a pneumonia in an early state of the disease.

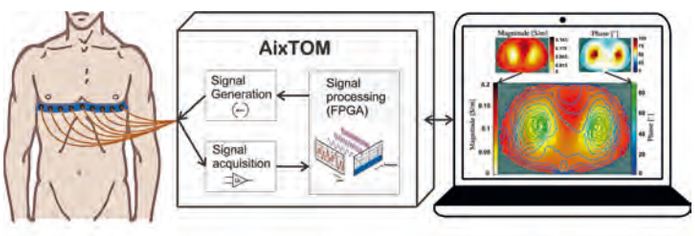

Fig. 7: The multi-frequency electrical impedance tomography (mfEIT) device, produced at MedIT, called AixTOM.

Automating Mechanical Ventilation for Better Patient Care

A patient is placed on mechanical ventilation when natural breathing is no longer able to ensure sufficient gas exchange (oxygenation and carbon dioxide elimination). The mechanical ventilator takes over the work of breathing, either completely or partially. Although often lifesaving, the mechanical ventilator can also further damage the lungs, if not correctly set by the clinician. The clinician therefore has to choose ventilator settings, such as peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), breathing frequency (f), inspiratory to expiratory ratio (I:E), and fraction of inspired oxygen (FiO_2), which ensure proper gas exchange and prevent ventilator induced lung injury (VILI), also known as protective ventilation. However, every patient is different and changing with time (due to illness progression for example) and as such these ventilator settings need to be updated continuously. In the present clinical environment, this is however not possible.
An option is to automate mechanical ventilation by using physiological closed-loop control. In this case, the targets for the oxygenation and carbon dioxide are to be controlled. By measuring physiological signals, such as oxygen saturation (SxO_2) and end-tidal CO_2 ($etCO_2$), and designing a suitable controller, ventilator settings can be optimized even when the clinician is not present. In todays' clinical environment, major focus is placed on protective ventilation, which also needs to be considered during the controller design. For this reason, medical expertise and optimisation strategies of tidal volume and applied pressures are incorporated into the controller design. An example for such a system is shown in Figure 8, where the individual controller aspects are grouped together in the controller and examples of physiological signals to be measured are given. By including the patient in the loop, using physiological feedback and medical expertise, the resulting ventilation therapy becomes more individualised for each patient and results in better patient care.

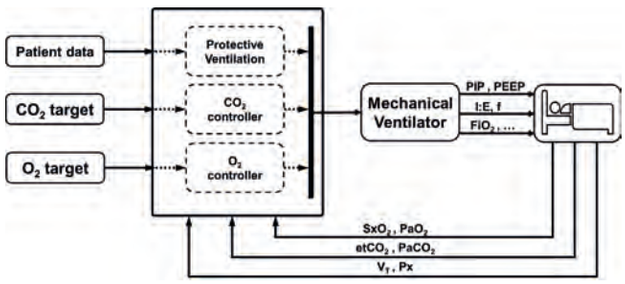

Fig.8: Physiological closed-loop control of mechanical ventilation concept.

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

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Selected References in 2018

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Prizes and Awards

- L. Korn was selected for the yESAO exchange award 2018 in Madrid, Spain.
- S. Leonhardt was awarded the title "Doctor Honoris Causa" in recognition of his scientific achievements in biomedical engineering at CTU Prague.
- D. Rüschen won the prize for best talk award at the "Regelungstechnisches Kolloquium", Boppard, Germany.
- P. von Platen was awarded the second prize in the Young Investigators Competition at the World Congress on Medical Physics and Biomedical Engineering in Prague, Czech Republic.
- B. Misgeld has received the best paper award at IFAC BMS 2018 in Sao Paulo, Brazil.

Conference Organization

[1] ICBEM and RGC, May 23rd -25th, 2018 at RWTH Aachen University, Aachen, Germany.

[2] DGBMT+Annual Conference of the DGBMT (HIA-all chairs)

People at MedIT

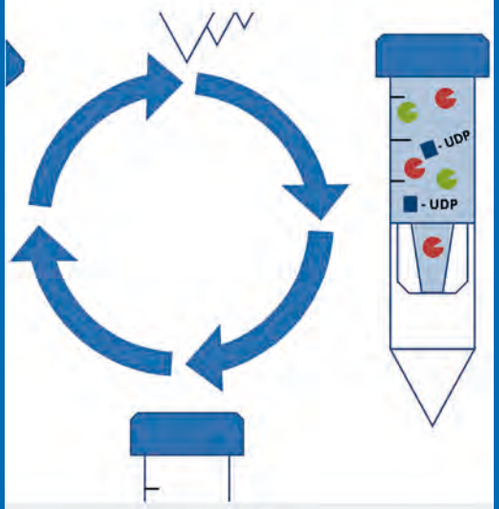
Lehr- und Forschungsgebiet Biomaterialien

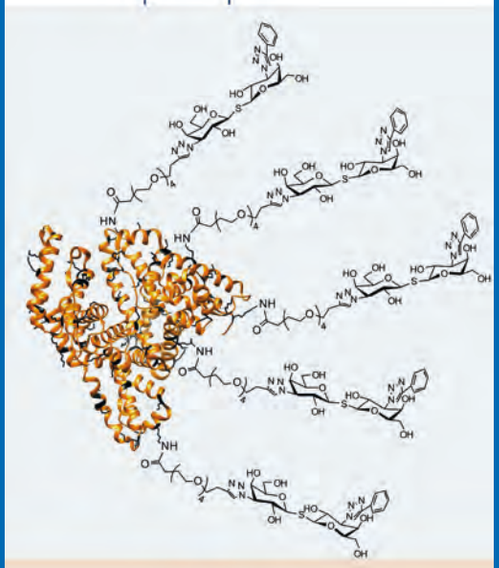
RWTH AACHEN UNIVERSITY

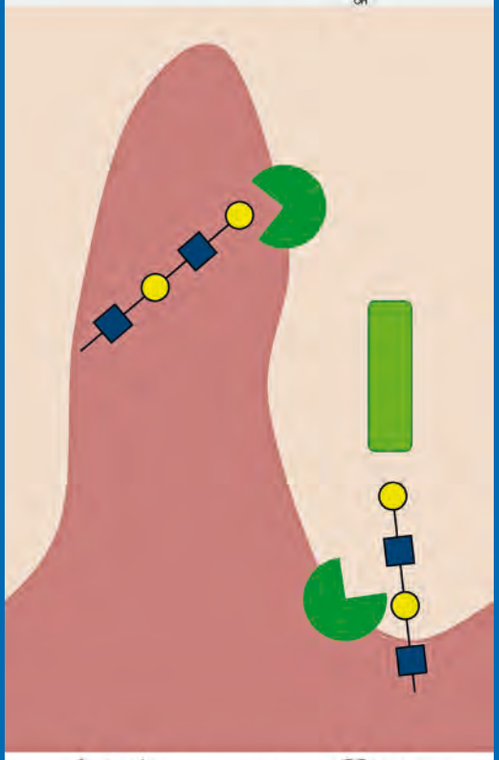
Laboratory for Biomaterials

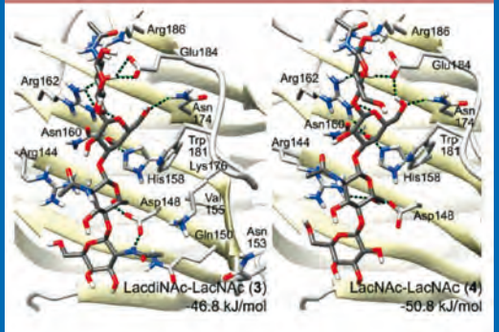
Faculty of Mathematics,
Computer Science and
Natural Sciences

From Genes to Glyco-conjugates









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RWTH AACHEN UNIVERSITY

Introduction

The cell surface and cell environment are 'sweet' – made of sugar structures (glycans) as part of glycoproteins, glycolipids, and proteoglycans. The complexity of glycans plays an important role in intercellular recognition events and for the contact of cells with the ECM, which are mediated by specific glycan binding proteins, the lectins. In disease state, glycan structures are altered and trigger specific lectin interactions. Sugar-based biomaterials, also named glycoconjugates, are therefore of special interest as diagnostic and therapeutic tools in biomedical research. Sugars are also important for the bioactivity of natural products, such as antibiotics and antitumor compounds, and for the detoxification of xenobiotics.
In 2018, we pursued our research studies on the synthesis and applications of glycoconjugates. Based on our enzyme toolbox we developed advanced synthetic enzyme cascades. High-throughput reaction analysis was key for fast optimization of reaction parameters resulting in the synthesis of complex glycan structures, glyco- and biopolymers as well as neo-glycoproteins. The evaluation of these glycoconjugates in binding studies with human and bacterial lectins identified high-affinity glycoconjugates. We focus our studies on glycan-based inhibitors for tumor-related galectins and glycopolymer toxin scavengers. This chapter compiles our most recent research results presented in our peer-reviewed publications in 2018.

Combinatorial Biocatalysis

a. The Golgi Glycan Factory (GGF)

The aim of our BMBF funded project 'The Golgi Glycan Factory (GGF)' is the development and optimization of enzyme modules for the synthesis of nucleotide sugars and glycans. Leloir-glycosyltransferases utilize nucleotide sugars for the formation of glycan structures. In GGF, enzyme modules are combined sequentially or in one-pot for the synthetic assembly of glycans. Modularization and flexibility are characteristic for these glycan production lines.
One focus of GGF is on the synthesis of human milk oligosaccharides (HMOS). Increased attention of nutrient industry to HMOS triggers studies on the identification and elucidation of complex HMO structures. We recently synthesized a library of more than 20 different HMOS to serve as glycan standards for the composition analysis of individual human milk samples. A second focus of GGF is on nucleotide sugars. Multi-gram scale synthesis of nucleotide sugars was realized by the repetitive batch mode technique (Fig. 1). The high enzyme stability of the applied enzyme cascades enabled us to reach high yields and productivities meeting the demands of industrial processes. With our cooperation partner a microfluidic reactor device was developed, which handles defined reaction compartments in combination with magnetic enzyme micro carriers. Proof-of-concept for this microreactor was demonstrated for the synthesis of a nucleotide sugar and a glycan structure. This is a first step towards automated enzymatic synthesis of nucleotide sugars and glycans.

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Financial Support

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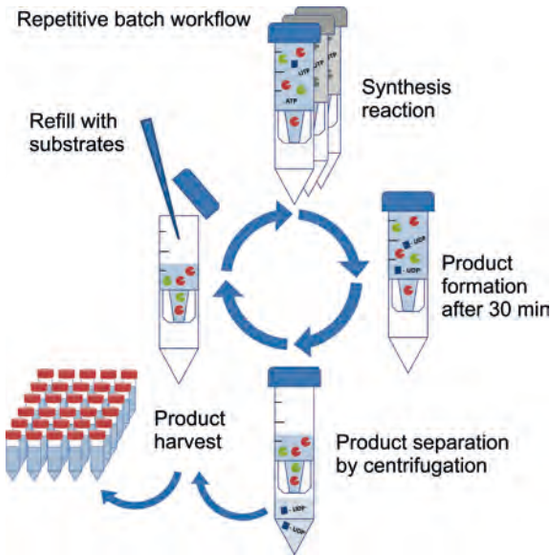

Fig. 1: Multi-gram synthesis of nucleotide sugars with enzyme modules in repetitive batch mode.

b. An economic multi-enzyme strategy for the *in vitro* synthesis of Hyaluronic acid from Sucrose and *N*-acetylglucosamine

Hyaluronic acid (HA) is a linear glycosaminoglycan polymer composed of up to 25,000 disaccharide units of *N*-Acetylglucosamine (GlcNAc) and Glucuronic acid (GlcA) with a molecular weight (MW) of up to 10 MDa. HA binds huge amounts of water making the non-immunogenic HA useful for medical and cosmetic applications (Fig.2). The quality parameters of HA are determined by MW and polydispersity; the required quality for both parameters is still challenging to achieve with current industrial processes like extraction from rooster combs or biotechnological production with *Streptococcus*.

Fig. 2: Applications of hyaluronan in medicine, cosmetics and food.

We developed an economic multi-enzyme strategy for the *in vitro* synthesis of high molecular weight HA (> 2 MDa) from cheap and sustainable substrates (sucrose and GlcNAc) (Fig.3). Modular enzyme cascades provide the precursors UDP-GlcA and UDP-GlcNAc for the hyaluronan synthase (HAS) module to produce HA in a one-pot synthesis.

Multiplexed capillary electrophoresis (MP-CE) was used for analysis and optimization of reaction cascades. A comprehensive reaction analysis approach was developed for reaction optimization in 96-well microtiter plate format to obtain high-MW HA (> 2 MDa) within a few hours. Key parameters influencing polymerization rate and MW of HA by HAS were metal ion co-factors, enzyme kinetics and substrate ratio. UDP-GlcA regeneration by sucrose synthase proved as highly favorable for HA polymerization. In summary, the presented optimized Enzyme Module System is an excellent starting point for cost-efficient HA synthesis from cheap and renewable starting materials.

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Financial Support

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

c. Hyperthermophilic Glycosidase for Glycoconjugate Synthesis

Hyperthermostable enzymes are biocatalysts with the ability to catalyze reactions at extremely high temperatures. These enzymes are most often found in thermophilic organisms which live under extreme conditions, such as volcanoes or hot springs. Enzymes with a high thermal stability

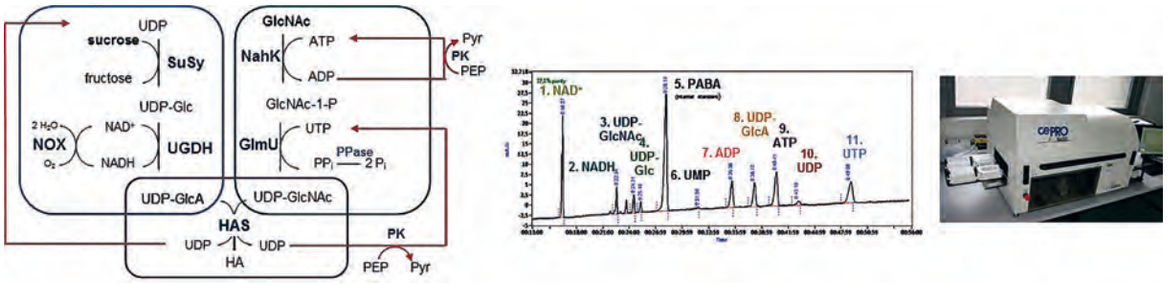

Fig. 3: In vitro one-pot synthesis of HA by modular enzyme cascades using sucrose and GlcNAc as cheap renewable substrates. MP-CE is used to monitor all analytes in enzyme reactions in a high-throughput manner.

also often display an increased resistance towards organic solvents. The catalytic properties of these enzymes turn them into attractive tools for reactions involving elevated temperatures, substrates with limited solubility or a low water activity.
We used a recombinant hyperthermo-stable β-glycosidase from the organism *Pyrococcus woesei* (PwGly) for the synthesis of a variety of amino-functionalized galactosides at 85° C. The enzyme's ability for transgalactosylation was previously exploited in our group for the synthesis of Galβ(1,4)GlcNAc-linker-tBoc (LacNAc-tBoc type II) [1]. Since sugar-functionalized amino-linker with the potential for immobilization are of high interest for the study of glycan-lectin interactions, the transgalactosylation reaction with amino-functionalized alkanols as acceptor substrates was examined with respect to the influence of their chain length and protection group (Fig. 4).

Substrate screening revealed a high enzyme flexibility regarding potential acceptor substrates. This turns it into an attractive tool for the synthesis of sugar-functionalized amines. The reaction products could serve as potential substrates for further chain elongation by glycosyltransferases, thereby paving the way for glycan functionalized polymers and proteins as scaffolds in biomedical applications.

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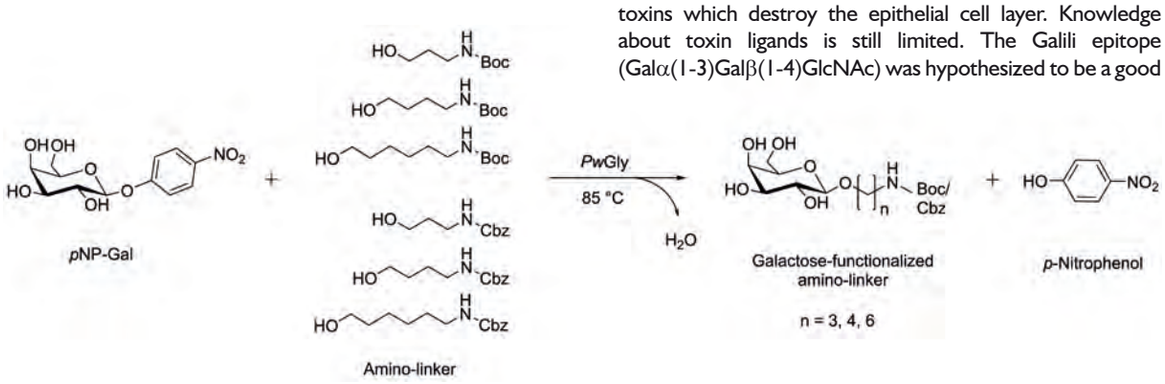

Figure 4: Substrate screening for the synthesis of galactose-functionalized amino-linker with acceptor substrates containing different chain lengths and protection groups.

Collaborations

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Selected Reference

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Financial Support

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The Glyco-BioInterface

a. Screening Libraries of Glycan Ligands for Binding of Bacterial Toxins

Clostridium difficile colonizes the human colon and secretes toxins which destroy the epithelial cell layer. Knowledge about toxin ligands is still limited. The Galili epitope (Galα(1-3)Galβ(1-4)GlcNAc) was hypothesized to be a good

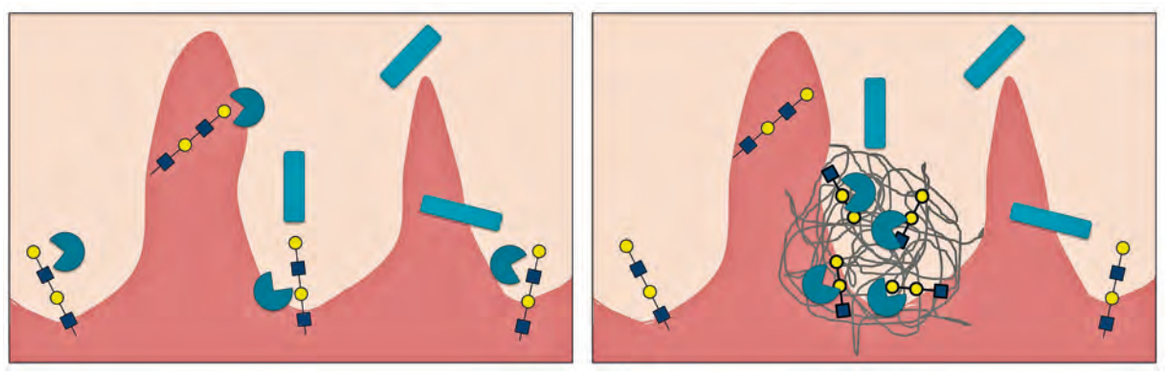

Fig. 5: Binding of C. difficile TcdA to epithelial cell surface glycans vs scavenging of TcdA with glycan-coupled microgels.

but artificial ligand for the toxin A receptor domain (TcdA-R). However, binding of the full toxin is still weak. Therefore, screening of a variety of glycan structures shall provide new insights into TcdA binding behavior regarding the structure of cell surface glycans. Coupling of promising glycan epitopes to microgels shall facilitate scavenging of the toxins from the colon and prevent destruction of the colon epithelium (Fig. 5).

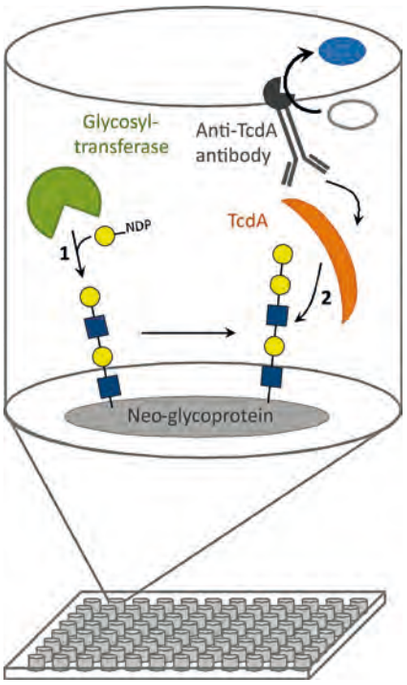

Fig. 6: Synthesis of glycan epitopes (1) and TcdA binding assay (2) in a microtiter-plate scale.

Glycan structures presented on colon epithelial cells were chosen for synthesis in a microtiter-plate scale ligand screening approach. Neoglycoproteins were chosen as scaffolds and multivalent glycan presentation. Specific glycan structures were generated by iterative synthetic cycles of a set of glycosyltransferases. Screening revealed several glycans that bind TcdA-R in an adequate manner; these ligands were selected for binding assays with the holotoxin (Fig. 6).

Together with our cooperation partners, we produce microgels [2] functionalized with the best TcdA glycan binders for further testing in cell-based assays to demonstrate scavenging efficacy of the respective glycan epitope.

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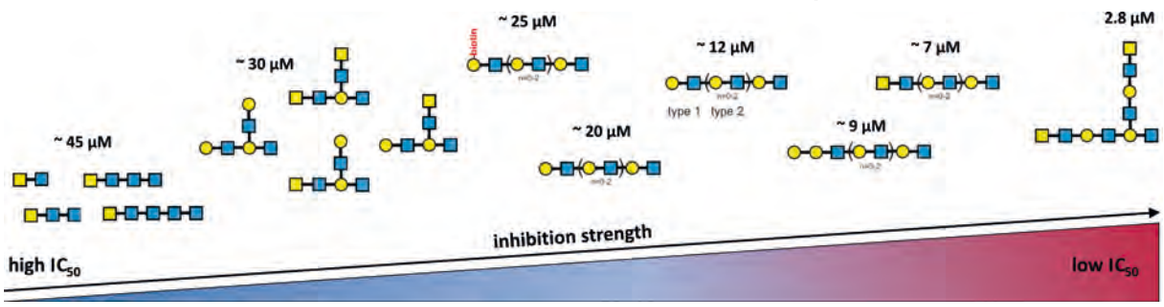
Financial Support

DFG in the framework of the SFB 985 “Microgels”

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

Galectins are β-galactoside-binding lectins that bridge glycoconjugates by their glycans, influencing signaling of cell surface receptors and cell adhesion. Altered glycosylation and galectin expression trigger cellular processes in tumorigenesis or cardiovascular diseases, making galectins attractive diagnostic and therapeutic targets. In our ongoing work, we developed advanced strategies for chemoenzymatic glycan synthesis resulting in novel multivalent (neo-)glycoconjugates for human galectin-1 and galectin-3 (Gal-3). In a series of glycans the branched LacdiNAc-LacNAc structure turned out to be the most efficient glycan inhibitor of Gal-3 (Fig. 7).

Fig. 7 (below): The inhibitory strength of synthesized glycans for Gal-3 binding.



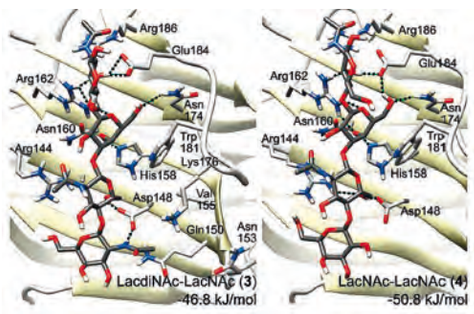


Fig. 8: Complexes of LacdiNAc-LacNAc (left) and LacNAc-LacNAc (right) in the Gal-3 CRD after 30 ns molecular dynamics simulation

Molecular dynamics simulation studies were performed to compare the binding free energies of the LacdiNAc-LacNAc with the LacNAc-LacNAc motif in the carbohydrate recognition domain (CRD) of human Gal-3 (Fig. 8). It turned out that Asp148 essentially contributes to the stabilization and tight binding of the LacdiNAc-LacNAc epitope. The flexible binding pocket in the concave-shaped carbohydrate recognition domain of Gal-3 accommodates the LacdiNAc in a highly efficient way. Multivalent glycan presentation in glycopolymers or neoglycoproteins is key to reach efficient binding of lectins with binding constants in the low μM and nM range. N-(2-hydroxypropyl)methacrylamide (HPMA) polymer carrying 10 mol% of LacdiNAc resulted in a 25-fold higher inhibition strength compared to the monovalent glycan. HPMA-based glycopolymers are of special interest due to their good water solubility and lack of toxicity and immunogenicity. Moreover, subnanomolar inhibition constants were reached with a multivalent neo-glycoprotein presenting the small molecule inhibitor thiodigalactoside on bovine serum albumin (BSA) (Fig. 9). Due to the benefit of multivalent glycan ligand presentation, the conjugate is currently one of the most potent multivalent Gal-3 inhibitors so far.

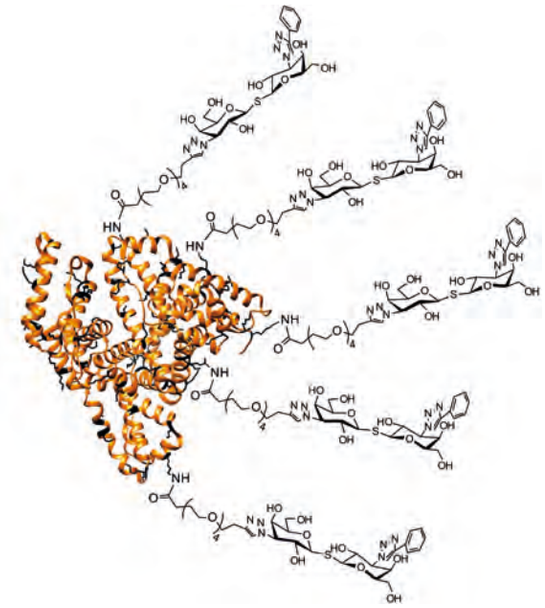


Fig. 9: Multivalent BSA-thiogalactoside neo-glycoprotein – a subnanomolar inhibitor of Gal-3.

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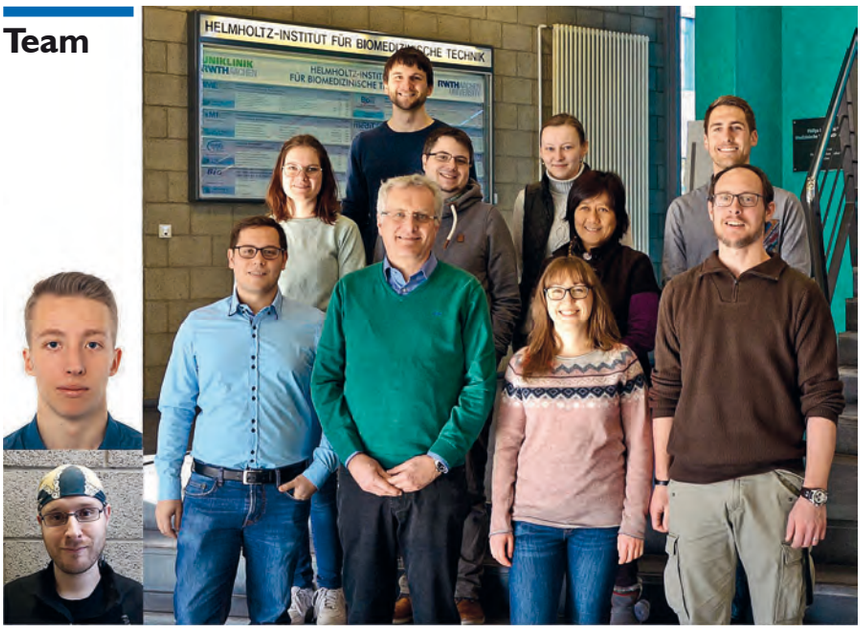

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Introduction

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. Focus areas of our research are:

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

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

Selected Projects

Biomechanics of the CSF System

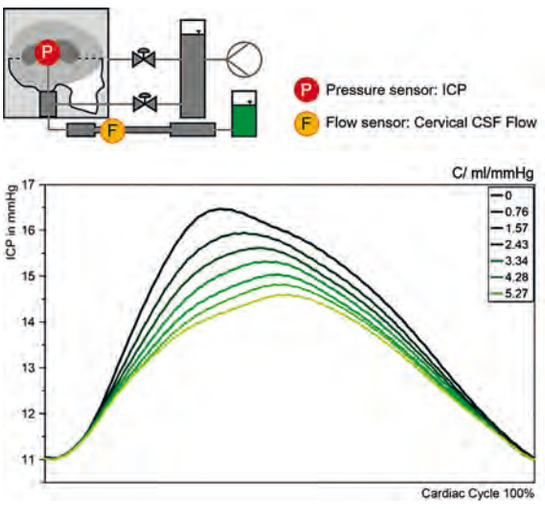

Fig 1: (Top) In-vitro setup and (bottom) impact of spinal compliance (C) on intracranial pressure (ICP) in the course of a cardiac cycle.

The etiology of Normal Pressure Hydrocephalus (NPH) is still not clear. However, it is known that a reduced compliance of the craniospinal system could be one key factor explaining typical NPH symptoms such as high intracranial pressure (ICP) amplitudes and a decreased cerebrospinal fluid (CSF) flow in the spinal canal. Nonetheless, so far the impact of the cranial or spinal compliance on the fluid dynamics is still unclear. An *in-vitro* model of the craniospinal system, including ventricles in a parenchyma, a cranial subarachnoid space connected to a first compliance chamber and a spinal canal including a second compliance was developed to investigate the impact of cranial or spinal compliance respectively. The ICP and the spinal CSF flow were measured (Fig. 1) and compared with in-vivo PC-MRI flow data. NPH patients with a reduced spinal CSF flow are likely to have a reduced spinal compliance. Whereas increased ICP amplitudes result from a decreased overall compliance.

Patient-specific Wrist Arthroplasty

The wrist is one of the most complex joint systems of the musculoskeletal apparatus. The wrist is prone to rheumatoid arthritis and is vulnerable to injuries due to its multi-layered ligament system. In contrast to knee and hip, wrist arthroplasty is much less established due to the short lifetime of the wrist implants.
Based on the review of current wrist implant designs and *in-silico* as well as *in-vitro* analysis of wrist biomechanics, new patient-specific concepts are evaluated taking the individual morphology and functional aspects into account (Fig 2). Furthermore, the use of additive manufacturing technologies for the production of patient-specific implants is investigated.

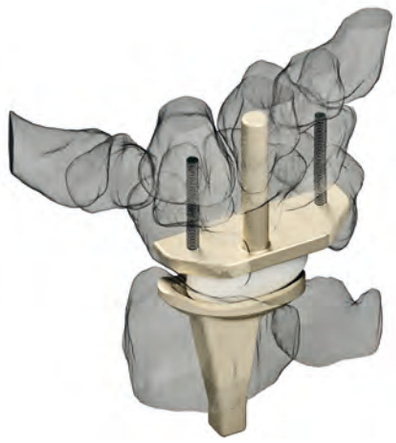

Fig. 2: Concept study on a parameterized, patient-specific adaptable wrist implant.

Morpho-functional Planning in THA

Edge loading is considered a major risk factor for a reduced lifetime of total hip endoprosthesis. Magnitude and orientation of the resulting hip joint force are inter-individually different and change during activities of daily living. Therefore, the prediction of the postoperative hip joint force has to consider the individual morphological and functional characteristics of the patient. Comparative studies with sophisticated inverse-dynamics models as well as less complex analytical models have been conducted in order to evaluate the validity of the models and their usability and scalability in clinical practice (Fig 3). Apart from edge loading, the outcome of total hip arthroplasty depends on several other parameters related to the alignment and design of the implant components. Unsuitable combinations of them could lead to impingement, dislocation, increased wear, and loosening. The prosthesis has to fulfil certain constraints that might be contradictory to each other. The components have to be properly fitted to the

Fig. 3 Comparative parameter studies using inverse-dynamic simulations and analytical models.

bony structures, the range of motion of both the prosthesis and the bones should be sufficient and the resulting hip force should not be too high in amplitude and not at the edge of the cup causing edge loading. A method for calculating a patient-specific target zone incorporating all the above mentioned criteria was developed (Fig. 4).

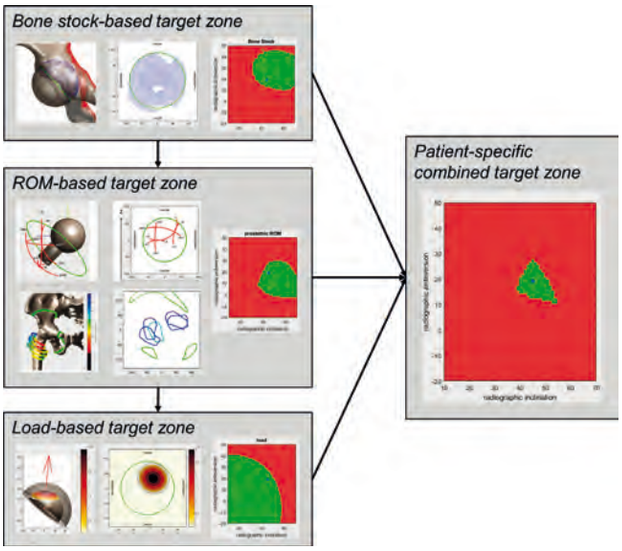

Fig. 4: Concept of a patient-specific combined target zone.

Morpho-functional Analysis of the Knee

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. In order to ensure a smooth transition between the implant and the bone, the design of the implant should be based on the morphology of the femur and tibia. A crucial investigation is whether there are several "morphotypes" of the involved bones, i.e. distinct shapes into which every bone can be classified (e.g. gender, age or ethnicity). In this case implant manufacturers could produce prosthesis that not only differ in size, but also match the different types or classes respectively.
Based on several hundred knee geometries obtained from CT-Scans, a set of shape features have been extracted and subjected to a cluster analysis. The distinctiveness of these clusters has been evaluated. Fig. 5 shows two cluster representatives found for the femur. The similarity of the two shapes as well as low cluster validity indices computed imply a high overlap of the clusters and therefore that no morphotypes exist.

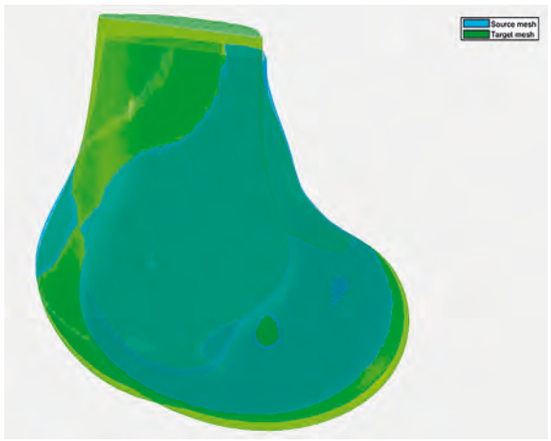

Fig. 5: Representative shapes of the cluster analysis of the distal femur.

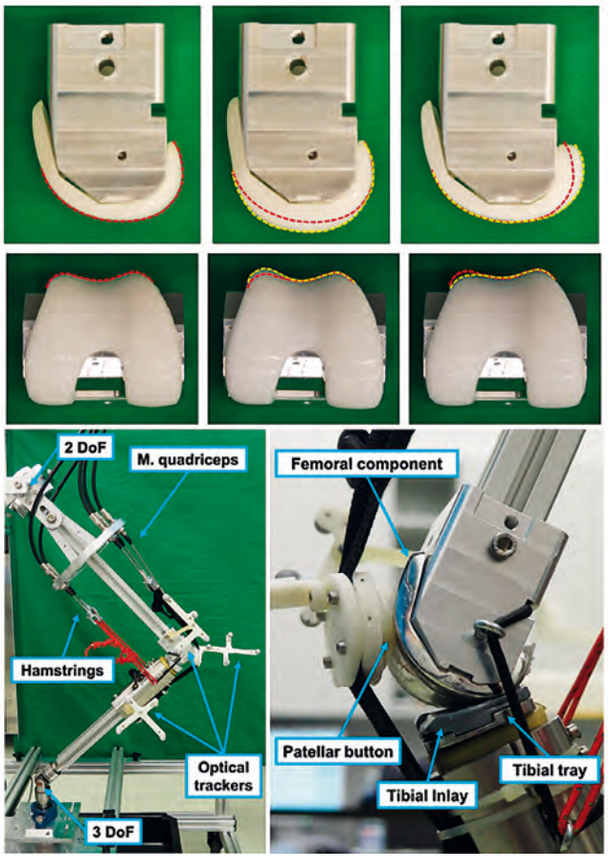

Fig. 6: Parameter variation of replica implants and experimental setup.

Apart from these morphological analyses, further implant design parameter studies regarding the relationship between morphology and (passive/semi-active/active) knee kinematics in *in-silico* multi-body simulations as well as in experimental testing rigs (Fig. 6) have been conducted.
Today, CT (and MR) are commonly used for the acquisition of 3D bone morphology. In order to reduce imaging cost and circumvent exposition of the patient to radiation, we are developing a demonstrator system for ultrasound based 3D-reconstruction of the knee (Fig. 7).

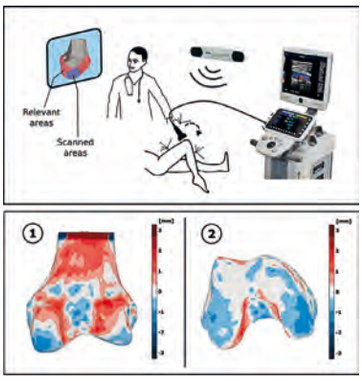

Fig. 7: Concept and first in-vivo results of US based 3D reconstruction of knee morphology.

Experimental Evaluation of Cavitation in ESWL

Cavitation is a major fracture mechanism in extracorporeal shock wave lithotripsy (ESWL). However, it can cause tissue trauma and its effects on kidney stones and surrounding tissue are not fully understood. Therefore, experimental setups enabling systematic parameter studies are crucial. We developed and evaluated a testing rig comprising three measuring methods in order to examine this mechanism. Cavitation was visualized by high-speed photography and B-mode ultrasound imaging (Fig. 8). Furthermore, stone comminution at different pulse repetition rates was investigated by fixed-dose fragmentation.

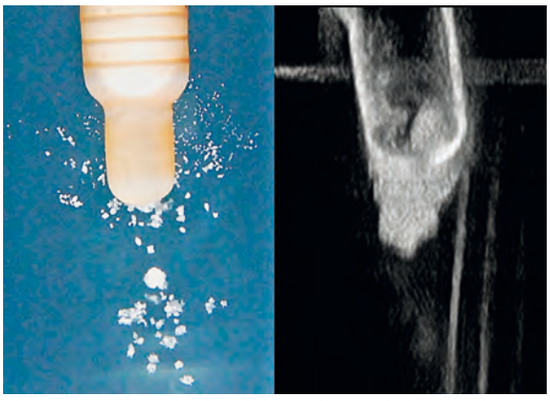

Fig. 8: Primary cavitation (left) and B-mode image of secondary cavitation (right).

The experimental setup provides reproducible results regarding the development of primary and secondary cavitation on the one hand and the fragmentation of phantom stones on the other hand. Therefore, it can be utilized to further investigate the effect of different boundary conditions and shock wave parameters on cavitation and stone comminution.

Modular Design of Cooperative Surgical Robots

Surgical robots have been introduced in the field of Computer Assisted Surgery to assist the surgeon by providing an accurate link between the computer-based plan and the exact (a) positioning or (b) dynamic path control of an instrument on the operating site respectively. Whereas initial systems mostly have been based on an active supervisory control scheme of industrial robots with large universal workspaces, later on specialized miniaturized kinematics have been proposed, with restricted workspaces adapted to specific applications in order to ease handling and provide inherent safety properties. However, this specialization resulted in even narrower fields of application, low quantities and higher costs. Modularization seems to be a key factor to combine the benefits of both approaches. Based on several proprietary developments and an in-depth literature review, concepts for a systematic modularisation scheme based on module indication matrices (Fig. 9) have been developed and evaluated.

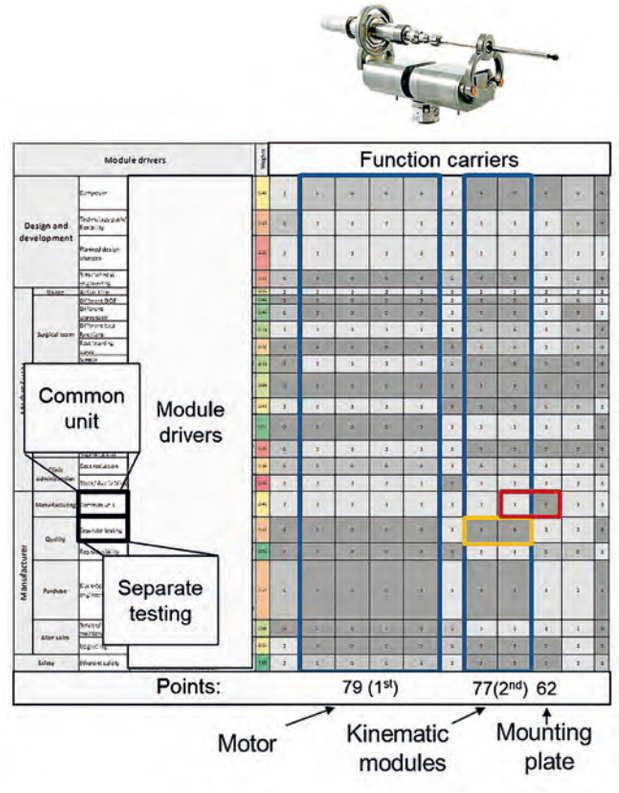

Fig. 9 Exemplary Module Indication Matrix for the MINARO modular minirobot system.

Modularity is also related to a flexible provision of cooperative robotics covering the entire spectrum from master-slave telemanipulator systems for endoscopic keyhole surgery to active autonomous robotic machining of structures for minimal invasive spine surgery. Haptic assistance seems to be a very promising option to reduce the complexity of a surgical control task while keeping the surgeon in-the-loop and allowing intervention at any time during surgery.
Based on experimental set-ups enabling the interactive simulation of different modes of feedback and levels of arbitration (Fig. 10) we perform user studies regarding different assistance functions to evaluate their effect on system usability. The aim is to identify appropriate configurations depending on the requirements of specific intraoperative scenarios as a basis for a comprehensive framework and modular user interfaces providing a flexible integration of cooperative robotic functionalities suited to the needs of a particular surgical scenario.

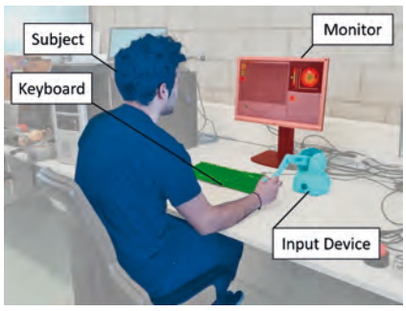

Fig. 10: Haptic Assistance Test Stand.

Interoperability in Open Medical Devices Networks

Based on the achievements of the BMBF flagship project OR.NET (2012-2016) our team continued its activities in the cooperative network of the OR.NET initiative (www.ornet.org). Initiated by OR.NET, the IEEE11073-20701 was approved as a new standard by the IEEE-SA Standards Board on September 27th 2018. The binding standard defines the interoperation of the participant and communication model defined in IEEE11073-10207 to the profile for transport over Web services defined in IEEE11073-20702. Thus, all substandards of the SDC standard family are approved by the IEEE and can be implemented by device and software vendors.

Fig. 11 (a): ZiMT surgical Workstation on the conhIT exhibition 2018, Berlin; (b) Tablet user interface with process-specific function group view.

In 2018, OR.NET related work was continued in the framework of the ZiMT project aiming to develop, evaluate and synchronize basic concepts with safe and usable human-machine-interfaces for the safe dynamic networking of components in operating theatres. ZiMT project results have been presented at the conhIT 2018, Berlin and the Medica 2018, Düsseldorf (Fig. 11a). The goal of the MoVE project is to research methods and testing procedures (conformity and interoperability tests) that support the approval and certification process and therefore especially the risk management of networked medical devices using IEEE 11073 SDC. For this, a simulation platform including test suite, test scenarios and device simulators is currently being developed, in order to provide future methods and tools for manufacturers, clinical operators and test institutions. Our team further develops inter alia a central surgical workstation for an open integrated operation room in the framework of the ZiMT project. This can either be controlled via a central touch display, which provides all relevant OR information and device panels, or by flexible remote controls (Fig. 11b). Numerous devices of different vendors have been integrated (e.g. OR light, 3D X-ray C-arm, OR table, RF devices, endoscopic devices, US-cutting device, different power tools such as high speed milling and shavers, an universal footswitch and an height-adjustable footboard).

Self-Balancing Mechatronic Rescue Aid (SEBARES)

Paramedics transport and monitor patients during 12 million deployments in Germany each year. Thereby, paramedics regularly lift and carry patients as currently available transport aids either do not offer any load reduction or have major other usability deficiencies. Therefore, paramedics frequently are overburdened due to high workloads far above ergonomic limits associated with unphysiological working postures. Therefore, the main objective of the SEBARES project is the development of an enhanced transport aid for paramedics with a self-stabilizing control. The goal is to simultaneously offer a universally applicable rescue aid with high mobility and a small footprint taking into account common constraints in patient transport. To be able to overcome stairs the transport aid shall incorporate a stair climbing mechanism which is currently developed based on a comprehensive market and literature analysis. Fig. 12 shows an exemplary scaled down functional model. These models are used to conduct first experiments on different staircase models and to identify issues and shortcomings early during the development process.

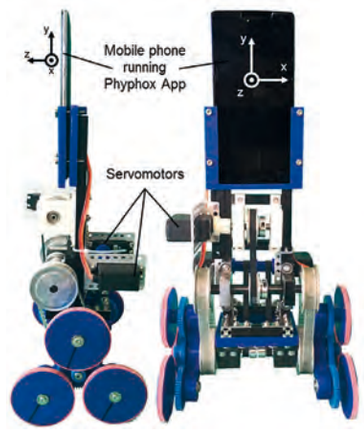

Fig. 12 Scaled Down Stair Climbing Mechanism.

Although self-balancing systems are in general well-analysed and described, the application as a patient transport system entails several specific requirements. For instance, about 25 % of the patients are not cooperative during transport and therefore might influence the stability of the control loop. To analyse this influence a parametric multi-body model was developed and validated experimentally (Fig. 13).

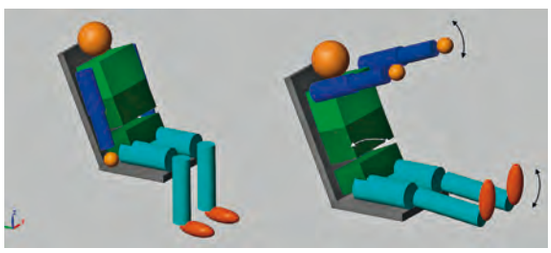

Fig. 13: Patient model, left: resting, right: seizure.

Simulation of different patient behaviors showed that the patient can critically influence the control loop especially by movements of his torso and introducing external forces such as holding onto a rail. Apart from system design modifications (e.g. for fixation of the patient), advanced control strategies which take possible movements of the patient into account are currently under development and evaluation.

Acknowledgements

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

Awards

- Philipp Schleer, M.Sc.: DAAD Travel Grant and IFAC CPHS 2018 Young Author Prize, 2nd Conference of International Federation of Automation Control on Cyber Physical & Human Systems 2018" in Miami, USA
- Anne Benninghaus, M.Sc.: DAAD Travel Grant and 3rd Prize - Young Investigator Award, Hydrocephalus 2018, Bologna, Italy
- Lukas Theisgen, M.Sc.: 3rd Prize – VDE Student Competition, Annual Meeting of the German Society for Biomedial Engineering – BMT2018, Aachen, Germany
- Dipl.-Ing. Malte Asseln: Travel Award of the German Society for Biomechanics - DGfB

Selected Publications

[1] M. Asseln, L. Berger, M. Verjans & K. Radermacher: Effects of the medial and lateral tibial slope on knee joint kinematics in total knee arthroplasty. Current Directions in Biomedical Engineering, 2018, 4(1), pp. 207-211
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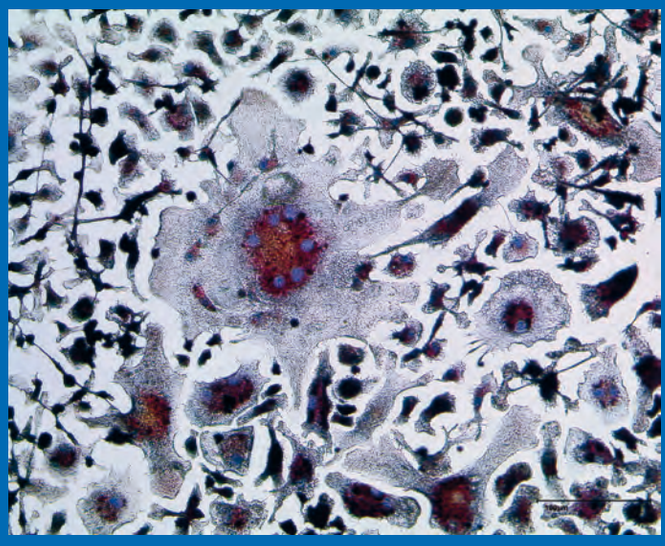
mediTEC-Team

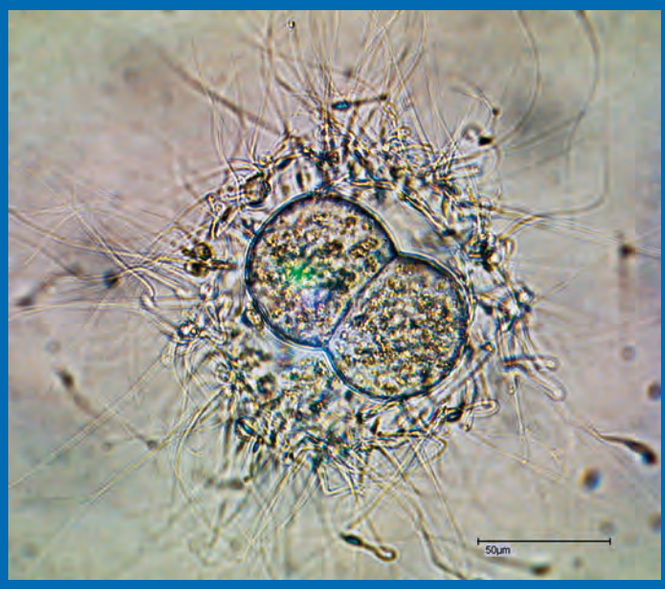
Biointerface Laboratory at Helmholtz-Institute for Biomedical Engineering

RWTH AACHEN UNIVERSITY

Faculty of Medicine

Cell-Material Interactions: Translating Basic Science Into Clinical Applications





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Cover Figures: *Top, large osteoclast-like cells with several cell nuclei differentiated from monocytic cells in culture. Osteoclasts mediate bone resorption. They may also be instructed to resorb calcifications. To this end they must be locally activated with the targeted cytokines. Bottom, Two-Cell embryo developed entirely outside the body. Immature oocytes were harvested from early follicles, matured, and fertilized in cell culture dishes. The cleavage of fertilized oocytes is living proof of favorable culture conditions. In vitro maturation and fertilization become a necessity, if oocytes cannot be naturally fertilized for medical reasons.*

Introduction

In this past year we continued our highly collaborative research on the biological role of fetuin family proteins [1-6]. In what follows, additional work will be presented by the people who actually did the work.

Mammalian Plasma Fetuin-B is a Selective Inhibitor of Ovastacin and Meprin Metalloproteinases

MSc Carlo Schmitz
Dr. Julia Floehr

Mammalian fetuin-A and fetuin-B are circulating hepatic glycoproteins of the cystatin-superfamily of cysteine proteinase inhibitors. Both fetuin proteins belong to type III cystatins and consist of two successive cystatin-like domains followed by a C-terminal region. While fetuin-A is a potent inhibitor of ectopic calcification, fetuin-B was identified as a potent and specific inhibitor of the zinc metalloproteinase ovastacin and plays an essential role in oocyte fertilization.

In cooperation with the group of Prof. Walter Stöcker (Johannes Gutenberg University Mainz) and Prof. Ralf Weiskirchen (RWTH Aachen University) fetuin proteins were produced in baculovirus transduced High Five insect cells, adenovirus transduced Cos-7 cells and in plasmid transfected CHO cells. Molecular masses of recombinant proteins varied according to their degree of N-linked glycosylation (Fig. 1A). Glycan analysis revealed that Cos-7 and CHO cell-derived proteins had complex glycosylation with and without terminal sialic acid, while High Five insect cell products typically had mannose-terminated N-glycans resulting in a lower molecular weight. To evaluate the effect of glycosylation on fetuin-B activity, fetuin-B was also expressed in the presence of tunicamycin, which prevents regular glycosylation. Also, the proteins were produced in glycosylation deficient CHO Lec 3.2.8.1 cells. Regardless of the cells employed for recombinant protein production, fetuin-B strongly inhibited ovastacin activity, indicating that neither glycosylation nor the expression system affected fetuin-B activity (Fig. 1B).

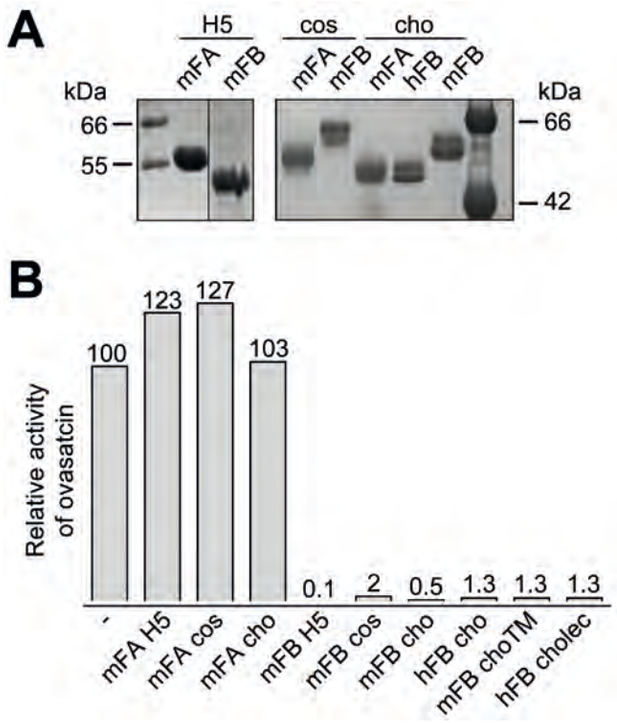

Fig. 1: Varying protein expression system does not alter inhibitory potency of fetuin-B.
(A) Recombinant fetuin-A and fetuin-B variants from human (hFB) and mouse (mFA, mFB) expressed in adenovirus transduced Cos-7 cells (cos), baculovirus infected High Five insect cells (H5) and plasmid transfected chinese hamster ovary cells (cho) were analyzed by SDS-PAGE followed by Coomassie staining. Molecular weight is indicated at both sides. (B) Inhibition of ovastacin by recombinant fetuin-B independent of the protein expression system. Glycosylation deficient CHO Lec 3.2.8.1 cells (cholec) were used to produce hFB; mFB was expressed in presence of tunicamycin (choTM) inhibiting N-glycosylation. The activity of ovastacin without additives was set to 100%.

Fetuin-B was the first known natural protein inhibitor of ovastacin, and is the first mammalian plasma protein that acts as a highly specific inhibitor of astacin metalloproteinases. We asked if further physiological target proteinases for fetuin-B exist. To this end we tested the inhibitory potential of fetuin-B against various metalloproteinases and cystein proteinases (Fig. 2).

Recombinant mouse fetuin-B inhibited mammalian astacin metalloproteinases meprin α and meprin β with similar potency like it inhibited ovastacin. Additionally, there was potent inhibition of non-mammalian astacins such as zebrafish nephrosin and crayfish astacin. Astacin family members tolloid-like protein 2 (TLL2) and bone morphogenetic protein-1 (BMP1) as well as various matrix metalloproteinases (MMPs) and cysteine proteinases were not inhibited by fetuin-B. Un-

like fetuin-B, fetuin-A did not inhibit any of the proteinases tested. While the regulated inhibition of ovastacin by fetuin-B is essential to maintain female fertility, the consequences of fetuin-B inhibition of meprin proteinases are less well understood. Meprins are pivotal in proteolytic networks controlling angiogenesis, immune defense, extracellular matrix assembly and general cell signaling. and therefor fetuin-B inhibition of these enzymes may affect many physiological pathways.

Class	Proteinase	fetuin-A K_i [nM]; IC_{50} [nM]	fetuin-B K_i [nM]; IC_{50} [nM]
Metalloproteinases	meprin α	n.i.	K_i 7±0.8
	meprin β	n.i.	K_i 33±2.4
	astacin	n.i.	K_i 16±1.5
	ovastacin	n.i.	IC_{50} 18±1.2
	nephrosin	n.i.	IC_{50} 0.6±0.1
	TLL2	n.i.	n.i.
	BMP1	n.i.	n.i.
	MMP-2/8/9/13	n.i.	n.i.
Cysteine proteinases	legumain	n.i.	n.i.
	papain	n.i.	n.i.
	cathepsin B/K/S	n.i.	n.i.

Fig. 2: Inhibition of proteinases by recombinant mouse fetuin-A and fetuin-B.
Proteinase activity assays were performed with fluorescent substrates. Due to detection limits of substrate hydrolysis at low enzyme concentrations, it was not possible to determine a Ki-value for ovastacin and nephrosin. Instead IC_{50} was calculated. n.i.: no inhibition.

Cellular Clearance and Biological Activity of Calciprotein Particles Depend on their Maturation State and Crystallinity


Ing. MSc Sina Köppert, MSc Andrea Büscher

The liver-derived plasma protein fetuin-A is a systemic inhibitor of ectopic calcification. Fetuin-A stabilizes saturated mineral solutions by forming colloidal protein-mineral complexes called calciprotein particles (CPP). CPP are initially spherical, amorphous and soft, and are referred to as primary CPP. These particles spontaneously convert into secondary CPP, which are larger and more crystalline. CPP mediate excess mineral transport and clearance from circulation.

We studied by intravital two-photon microscopy the clearance of primary vs. secondary CPP by injecting fluorescent CPP in mice. We analyzed CPP organ distribution and identified CPP endocytosing cells by immunofluorescence. Primary and secondary CPP were taken up by liver and spleen, but do not co-localize (Fig. 3 A, B). Only primary CPP were rapidly cleared by liver sinusoidal endothelial cells (LSEC) (Fig. 3 D), whereas primary and secondary CPP were cleared by Kupffer cells (Fig. 1 C, E). Cellular clearance was further studied using bone marrow-derived mouse wildtype and scavenger receptor A (SRA)-deficient macrophages, as well as human umbilical cord endothelial cells (HUVEC). Scavenger receptor A (SRA)-deficient bone marrow macrophages endocytosed secondary CPP less well than did wildtype macrophages. In contrast, primary CPP endocytosis did not depend on the presence of SRA, suggesting involvement of an alternative clearance pathway. We employed mouse wildtype and mutant immortalized macrophages to analyze CPP-induced inflammasome activation and cytokine secretion.

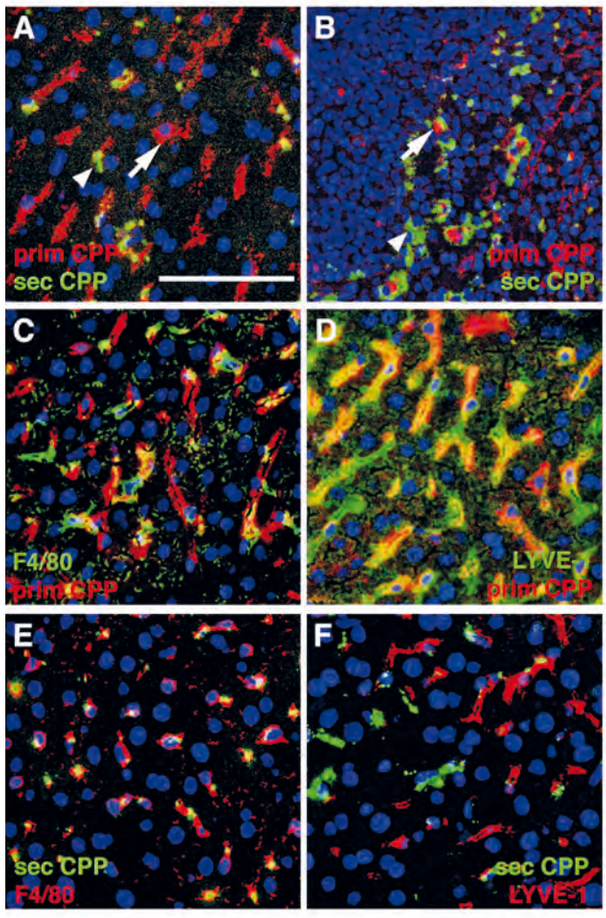

Fig. 3: Differential clearance of primary and secondary CPP.
Mice were injected with fluorescence labeled primary (red) and secondary CPP (green) and the major clearance organs liver (A, C-F) and spleen (B) were analysed for the presence of CPP, 10 minutes after injection. Primary CPP (prim CPP, arrows in A, B) and secondary CPP (sec CPP, arrow heads in A, B) showed distinct non-overlapping distribution in liver (A), and spleen (B). C-F, Co-localization with the macrophage-specific marker F4/80 and the liver sinusoidal endothelial LSEC-specific marker LYVE-1 suggested that primary CPP were predominantly cleared by LYVE-1-positive LSEC, and secondary CPP by F4/80-positive liver Kupffer cell macrophages. Scale bar: 25 µm. Figure taken from ref [8].

Figure 4 shows that CPP triggered TLR4 dependent TNF α and IL-1β secretion in cultured macrophages. Primary CPP treatment of macrophages caused low level TNFα secretion, yet strong IL-1β secretion. Primary CPP caused twice more IL-1β secretion than did secondary CPP (Fig. 4 C, D), which was associated with increased calcium-dependent inflammasome activation, suggesting that intracellular CPP dissolution and calcium overload may cause this inflammation. In comparison to primary CPP, secondary CPP caused five-fold increased TNFα secretion indicating preferential stimulation of preformed cytokine secretion.

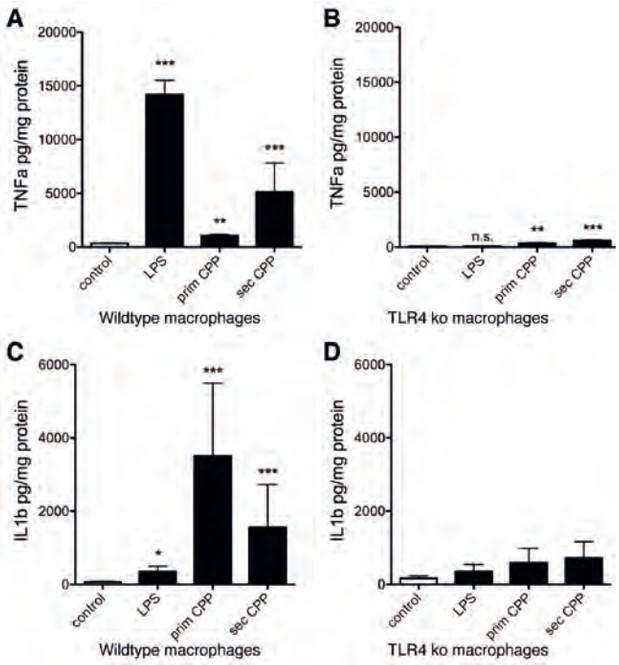

Fig. 4: CPP-induced inflammatory cytokine secretion by macrophages is TLR4 dependent.
*Wildtype and TLR4-deficient macrophages (TLR ko) where treated with LPS, primary or secondary CPP. (A, B) After 6 h stimulation, inflammatory cytokine TNFα secretion was determined in culture supernatants by ELISA. Secondary CPP caused stronger TNFα secretion than primary CPP. TLR4 ko macrophages showed 10-fold reduced TNFα secretion compared to wildtype macrophages suggesting a major contribution of TLR4 signaling in CPP-triggered TNFα secretion. Nevertheless, CPP-stimulated TLR4 ko still secreted higher amounts of TNFα compared to untreated control (prim CPP $p < 0.01$, sec CPP $p < 0.001$) suggesting a minor contribution of a TLR4-independent pathway. (C, D) After 16 h stimulation, supernatant IL-1β secreted by LPS-primed wildtype macrophages treated with primary CPP was twice as high as treated with secondary CPP Both values were significantly higher than in buffer control or with LPS treated. TLR4-deficient macrophages show a slight increase in IL-1β processing after the treatment with both types of particles. Overall, inflammatory cytokine secretion was strongly reduced in TLR4 ko. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Figure taken from ref [8].*

In contrast, primary CPP endocytosis did not depend on the presence of SRA, suggesting involvement of an alternative clearance pathway. CPP triggered TLR4 dependent TNF α and IL-1β secretion in cultured macrophages. Primary CPP treatment of macrophages caused low level TNFα secretion, yet strong IL-1β secretion. Calcium content-matched primary CPP caused twice more IL-1β secretion than did secondary CPP (Fig. 4 C, D), which was associated with increased calcium-dependent inflammasome activation, suggesting that intracellular CPP dissolution and calcium overload may cause this inflammation. In comparison to primary CPP, secondary CPP caused five-fold increased TNFα secretion indicating preferential stimulation of preformed cytokine secretion.

Stem Cells and Tissue Engineering

Prof. Dr. Sabine Neuß-Stein

In 2018, Sabine Neuss-Stein's group continued their research on physical and chemical cues directing stem cell behaviour [9-14]. Michaela Bienert received her PhD and moved to the Institute of Anatomy and Cell Biology as a Post-Doc. We wish her all the best for her future career. After focusing on stem cell-based bone tissue engineering using mesenchymal stem cells in the past, the group has now turned to cardiovascular tissue engineering. We secured funding by Deutsche Forschungsgemeinschaft for this work. Together with Andrij Pich (Institute of Textile and Macromolecular Chemistry) we develop fibrin-based hydrogels to direct cell answers on cardiovascular implants. In collaboration with Karolina Schickle, (Dept. of Ceramics and Refractory Materials) we test ceramic nanoparticles for stent coatings. We established hemocompatibility assays for cardiovascular implants including hemolysis and thrombogenesis. To this end we analyse blood cells (thrombocytes, monocytes, erythrocytes, Fig. 5), under static conditions as well as in flow conditions in a mechanoreactor.

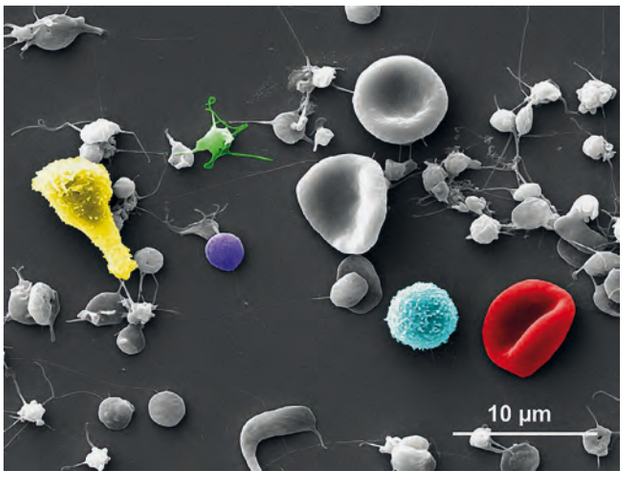

Fig. 5: SEM view of blood cells on glass slide.
Cell types are depicted by different colours: green – active thrombocyte; purple – resting thrombocyte; blue – monocyte; yellow – active monocyte; red –erythrocyte. Scale bar: 10 µm. Vuslat Parlak et al., submitted.

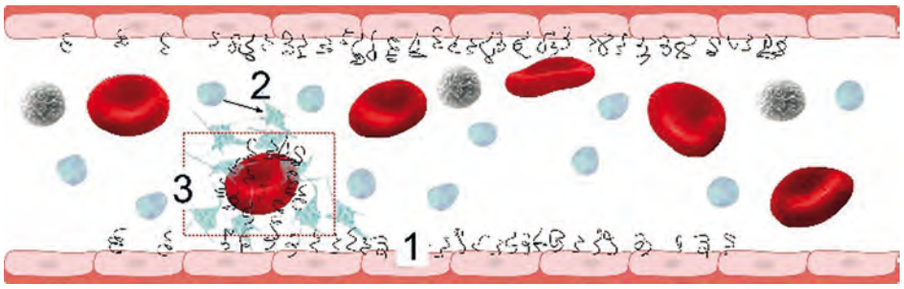

Fig. 6 (left): Start of thrombus formation within a vessel.
(1) Plasma protein deposition, (2) platelet activation, and (3) thrombus formation. Vuslat Parlak et al., submitted.

Major goals of this work are hemocompatible cardiovascular implants that prevent restenosis and allow for proper integration into the surrounding tissue while supporting endothelialization. (Fig. 6).

Development of Hemocompatibility Assays Using High-performance Ceramics

MSc Svenja Wein

Hemocompatibility is a salient feature of cardiovascular implants, e.g. stents. Platelet activation, a strong trigger of thrombosis causes stent occlusion. We studied the hemocompatibility of high strength ceramics, which can be used as nanoparticle coatings including alumina, zirconia, silicon nitride and silicon carbide. We measured the activation level of thrombocytes using platelets in static culture on the test materials. For comparison, Laminar flow conditions were also established using a bioreactor (MinuCell and MinuTissue perfusion chamber system, Munich). Platelet contact with test materials was maintained for 30 minutes at 37°C.

Figure 7 shows that all materials except Si_3N_4 and SiC (poly) activated platelets judged by the levels of CD62P and CD41a expression measured by ELISA. The number of adherent platelets, both inactive and activated, on Si_3N_4 and SiC (mono) was significantly lower than on Al_2O_3, ZrO_2, SiC (poly), glas and cupper as positive control. The positive control was generated by mechanical activation (centrifugal force) of all platelets in the sample. The highest adhesion was shown on Al_2O_3, followed by ZrO_2, SiC (poly) and glass, while SiC (mono) and Si_3N_4 showed the lowest adhesion (Fig. 7). Scanning electron microscopy (SEM) verified that more platelets adhered to samples in static conditions than in flow conditions. Platelet activation ranged from rolling to spherical and strongly adhering platelets as illustrated in Figure 8.

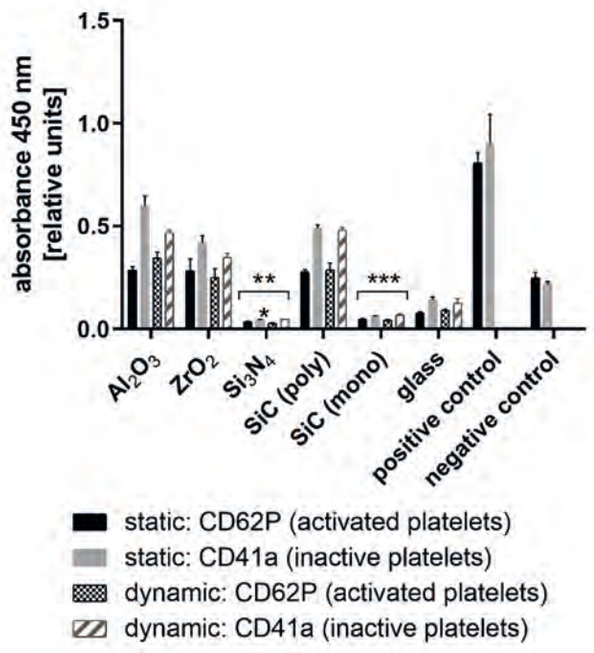

Fig. 7: Analysis of the activation stage of the thrombocytes on the ceramics determined by ELISA.
*Expression of CD62P vs. CD41a was measured for activated and non-activated platelets, respectively. Thrombocyte incubation was performed in comparison between static and dynamic conditions. There is a significant difference in activation between the amount of activated and inactivated platelets on Si_3N_4 and SiC (mono) compared to Al_2O_3, ZrO_2, SiC (poly) and glas. n=3, ***p<0.01.*

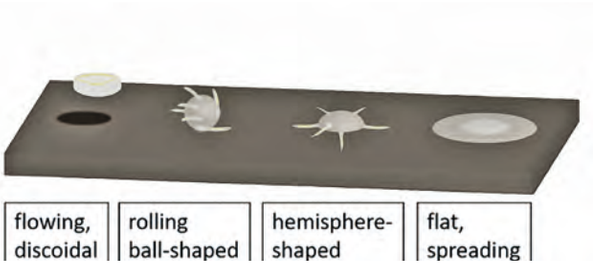

Fig. 8: Thrombocyte shape change during activation.
The shape change of platelets in response to a vascular lesion includes four stages ranging from non-activated discoidal platelets to adherent platelets. The coagulation of several adhesive thrombocytes could also be observed. A significantly lower platelet numbers could be detected under flow conditions, but there was still free material surface under static incubation conditions (Fig. 9).

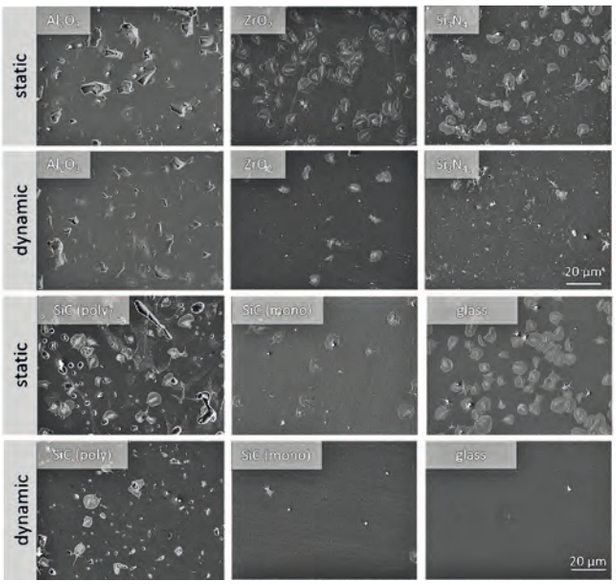

Fig. 9: Scanning electron microscopy of platelets on ceramics Al_2O_3, ZrO_2, Si_3N_4, SiC (poly), SiC (mono) and on glass.
More platelets adhered to the samples under static conditions than under flow (dynamic). Magnification: 1000x

The results of this work suggest that silicon nitride and silicon carbide in monocrystalline form should be used to coat cardiovascular implants.

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Team 2018

ExMI EXPERIMENTAL MOLECULAR IMAGING

Chair of Experimental Molecular Imaging
Faculty of Medicine

Improving therapy by integrated multiparametric imaging

Director

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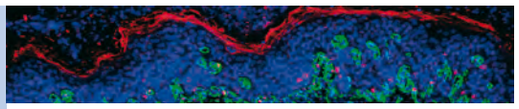

Introduction

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 projects are located at the interface between preclinical and clinical research. In this context, we typically follow a multimodal approach, based on combinations of MRI, CT, ultrasound, optical and photoacoustic imaging, nuclear medicine techniques (in particular PET-MRI), and MPI.

To develop image-guided therapies, we interconnect our pathophysiological and pharmacological research with 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 establish new diagnostic and therapeutic concepts. Imaging features and omics data are considered in concert, evaluated using radiomic and radiogenomic approaches, and are used to support mathematical disease models. In this context, ExMI initiated a strategic alliance with Fraunhofer MEVIS, resulting in the formation of a new MEVIS site in Aachen. Furthermore, Prof. Kiessling stimulated the foundation of the Comprehensive Diagnostic Center Aachen as an entity of the Medical Faculty to promote the clinical translation and implementation of new concepts for digital diagnostics.

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 tumor stroma to improve drug accumulation, penetration and efficacy. As a major achievement under coordination of ExMI the DFG-funded RTG "Tumor-Targeted Drug Delivery" was approved in 2018.

With the completion of the move of the ExMI institute to the Center for Biohybrid Medical Systems (CBMS) all expertises are now integrated under one roof.

Diagnostic and Therapeutic Ultrasound

Univ.-Prof. Dr. med. Fabian Kiessling

Quantitative multiparametric analyses may improve the diagnostic accuracy of ultrasound examinations and reduce user dependence. In this context, Theek at all evaluated, whether a radiomic assessment of contrast-enhanced ultrasound data can assign experimental tumors to their histopathological phenotypes. After the development of a semi-automated vessel segmentation method [1], he could fed 235 image features into the radiomics analysis and achieve a diagnostic accuracy of 82% [2]. A highly detailed tumor characterisation resulted from a collaboration with Prof. Schmitz from Ruhr University Bochum, in which a superresolution ultrasound method was developed to visualize the tumor vasculature at micrometer resolution [3]. Here, algorithms from GPS tracking were applied to assess the path of contrast molecules within consecutive images. The superiority of the method over standard ultrasound methods to characterize tumors was shown and - for the first time ever - superresolution ultrasound imaging was applied on patients [3].

While chemotherapy effects on breast cancers were successfully captured, clinical evaluation elucidated challenges that need to be addressed when translating the technology to hu-

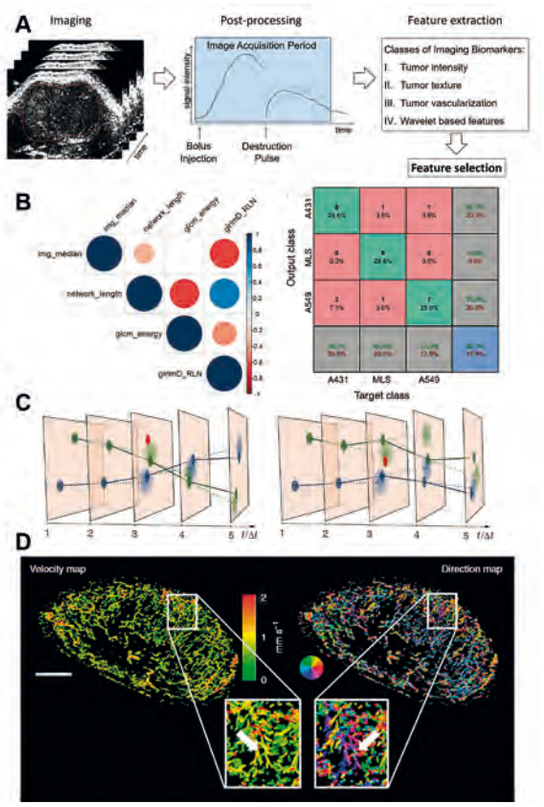

Fig. 1: A: Schematic presentation of the radiomics workflow performed on contrast-enhanced ultrasound data. Tumor intensity, texture, vascularization and wavelet-based features were extracted from the images and fed into a step-wise feature selection process. B: Supervised classification showed that imaging biomarkers enable the discrimination of different mouse tumor models. C: Principle of motion model Ultrasound Localization Microscopy (mULM). Filled circles mark the positions of detected microbubbles (MB). Red circles indicate detected MB are false alarms. The colors (blue/green) indicate the association of the MB to different tracks. One possible association of MB tracks is shown in the left diagram, another one in the right. The lighter ellipses indicate the probability density functions for the positions predicted by a linear motion model. From these, the likelihoods of the detected positions for an association are determined. In this example, the left association is more probable than the right one. D: Super-resolution ultrasound images of an A431 tumor. Functional information such as MB velocity and MB flow direction can be determined for each vessel and evaluated together with morphological characteristics. From [1,3]

mans [4]. Ultrasound does not only provide structural and functional features but can also contribute molecular information [5-10]. In this context, Curaj et al. completed a study in which JAM-A-targeted microbubbles were synthesized and evaluated as tools to study early vascular dysfunction [6]. Using these microbubbles, we showed in mouse carotid arteries that acute changes in blood flow and sheer stress induce JAM-A presentation at the luminal side of the endothelium, which rapidly normalizes under physiological conditions but remains enhanced during plaque development [6].

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Physics of Molecular Imaging Systems

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

In the last years, the PMI group jointly developed with Philips Research in Aachen the first fully-digital detector 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. Performance investigation according to the NEMA standard has been published by Hallen et al. [11].

The group is currently applying its expertise acquired in the field of PET/MR in the EU Horizon 2020 HYPMED project, for which a clinical PET/MR insert for human breast cancer is developed, cf. Fig. 2 (A).
Gross-Weege et al. characterized different shielding materials by measuring their gradient-induced response functions using an in-house developed MR field probe. Subsequently, gradient distortions caused by the PET insert Hyperion II were evaluated, yielding to the successful correction of gradient-induced image artefacts [12,13].

On the PET detector side, Schug et al. characterized the performance of a TOFPET-capable ASIC, determining an energy(timing) resolution of 10% (240 ps) [14], which is promising for application on system level. Müller et al. developed an AI-based (gradient-tree boosted) positioning algorithm for monolithic scintillators and applied it to the estimation of depth-of-interaction information [15,16].

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. In 2018, the group successfully conducted first experiments on a newly acquired preclinical MPI device.

To enhance the signal-to-background ratio of a 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 [17].

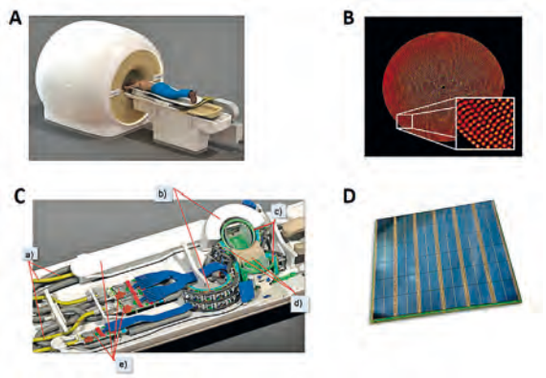

Fig. 2.: HYPMED Breast PET-MRI Insert, which turns a clinical MRI into a hybrid PET-MRI system. B: Simulated activity map of the HYPMED Insert (PET), indicating a spatial resolution of about 1.3 mm. C: Current construction of the HYPMED insert with cooling (a). movable PET 1/2-rings (b), two channel RF coil (c), fixed PET 1/2-rings (d), and readout electronics (e). D: Fully-digital sensor tile which will be used for the HYPMED scanner.

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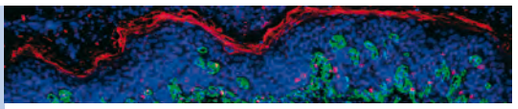
Nanomedicines and Theranostics

Univ.-Prof. Dr. Dr. Twan Lammers

Nanomedicines are carrier materials designed to improve the biodistribution of (chemo-) therapeutic drugs. By delivering drug molecules more specifically to pathological sites, and by preventing them from accumulating in healthy tissues, nanomedicines help to improve the balance between 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 is highly variable, in animal models and in patients [18-20]. Together with other working groups at ExMI and with international collaborators, we are establishing pharmacological and physical strategies to modulate EPR-mediated tumor targeting. These e.g. include the use of ultrasound and microbubbles (sonopermeation), as well as penetration-promoting peptides [21,22]. Within the framework of an ERC Proof of Concept grant, which started in October 2018, the latter are being coupled to PEG-pHPMA-Bz-baed polymeric micelles.

As part of the IZKF oncology initiative at UKA, we are extending previous work on vascular normalization. To systematically study this, in collaboration with Prof. Willi Jahnen-Dechent, we analyzed the effects of changing the expression levels of the histidine-rich glycoprotein (HRG) on the polarization of tumor-associated macrophages



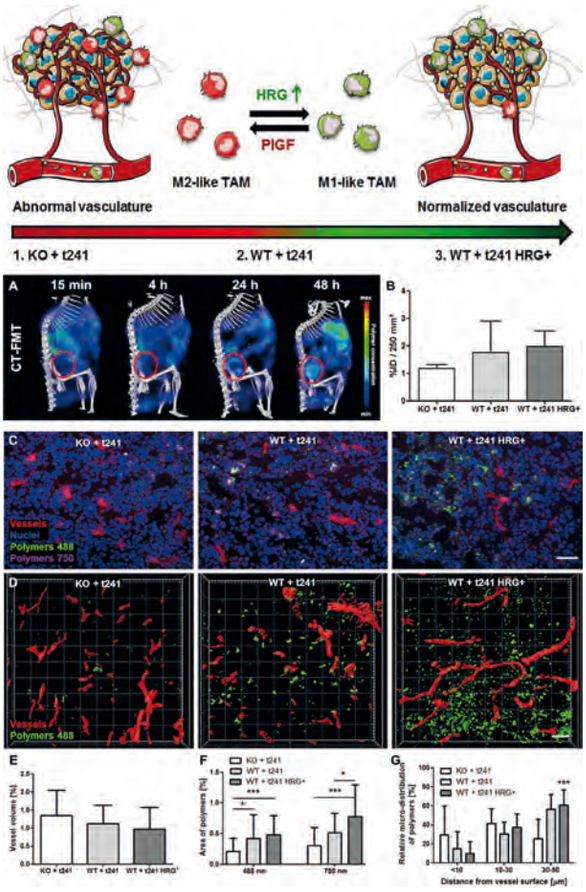


Fig. 3: HRG-mediated vascular normalization improves tumor-targeted drug delivery. A-B: CT-FMT imaging and quantification of the tumor accumulation of 10 nm pHPMA polymers. C-D: Fluorescence and two-photon microscopy analysis of polymer penetration out of the blood vessels into the tumor intertitium. E-G: Quantification of vascular volume (E), polymer accumulation (F) and penetration (G). From [6].

(TAM) and the impact of altering macrophage polarization on the tumor accumulation and penetration of polymeric drug carriers. HRG is known to induce a shift in TAM polarization from an M2-like phenotype, which promotes pathological angiogenesis, to an M1-like phenotype, which contributes to a more normalized vasculature. It was hypothesized that HRG-knockout mice present a lower accumulation of 10-20 nm-sized linear pHPMA polymers in t241 fibrosarcoma tumors as compared to wild type mice, and that wild type mice inoculated with HRG-overexpressing t241 tumors show the highest polymer concentration in tumors. Via multimodal and multiscale optical imaging, the accumulation and penetration of ATTO-488- and Alexa-750-labeled polymers was analyzed in the three abovementioned tumor models. Computed tomography-fluorescence mediated tomography demonstrated a trend towards the benefit of HRG-mediated vascular normalization on the macroscopic accumulation of the polymeric nanocarriers (Fig. 3A-B). These findings were verified and extend using fluorescent microscopy and two-photon laser scanning microscopy (Fig. 3C-D). Overall, it was found that HRG-mediated vascular normalization resulted in an increased accumulation and in improved penetration of polymeric nanocarriers (Fig. 3E-G) [23]. These findings exemplify that modulating the tumor vasculature may be valuable to improve tumor-targeted drug delivery and nanotherapy. Via priming of the microenvironment towards a more antitumor immune status, changing macrophage polarization, furthermore, holds potential to enhance the efficacy of nano-immunotherapy [24]. This concept is currently being explored as part of SFB 1066, in which we closely collaborate with scientists at Mainz University.

[18] Golombek et al., Adv Drug Deliv Rev (2018)
[19] Man et al., Mol Imaging Biol (2018)
[20] Lammers, J Control Release (2019)
[21] Snipstad et al., Exp Opin Drug Deliv (2018)
[22] Simon-Gracia et al., Oncotarget (2018)
[23] Theek, Baues et al., J Control Release (2018)
[24] Sun et al., Chem Soc Rev (2019)

Mechanisms of tumor progression and metastasis

Dr. Wiltrud Lederle

The group "Mechanisms of Tumor Progression and Metastasis" investigates the influence of the microenvironment on tumor growth and progression and stroma remodeling during tissue repair and inflammation using complementary non-invasive imaging techniques [7]. In addition, novel diagnostic and theranostic probes are evaluated in vitro and in tumor models in vivo.
Research activities were directed towards imaging of macrophages in the regenerating liver. Using a novel near infrared fluorescent imaging probe, time-dependent alterations in macrophage density were observed during liver regeneration (Figure 4).
In addition, we are investigating the interplay between inflammation and mesenchymal signalling in tumor progression and metastasis as part of the IZKF oncology initiative at UKA. In this context, different therapeutic drugs are applied that inhibit or modulate inflammation and fibrogenic signalling and their effects on tumor progression and heterogeneity are studied by non-invasive imaging.
In collaboration with Prof. Kühne, novel nanoparticles and π-conjugated molecules were investigated as photoacoustic imaging probes, e.g. with respect to imaging in the gastrointestinal tract [25,26].

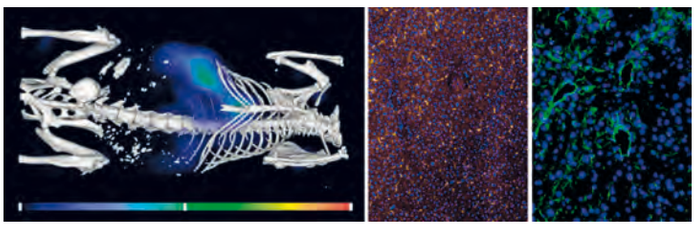


Fig. 4: 3D Rendering of reconstructed CT-FMT data showing macrophages in the regenerating liver of a mouse after injection of the optical probe (left). Immunofluorescent staining of macrophages (middle: macrophages in red, nuclei in blue) and blood vessels (right: vessels in red, nuclei in blue) in liver tissue during regeneration.

[7] Rix et al., J Nucl Med. (2018)
[25] Repenko et al., Adv. Funct. Materials (2018)
[26] Repenko et al., Photochem Photobiol Sci (2018)

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.
Together with companies MILabs B.V., Utrecht and Gremse-IT GmbH, Aachen, we developed and evaluated an integrated μCT-FMT which scans mice in both modalities in a single scan (Fig. 5). The device can be upgraded with SPECT and PET modules to acquire even more data and won the award for commercial innovation of the year at the World Molecular Imaging Conference 2018.
Our image reconstruction software benefits from innovative GPU-accelerated algorithms [27] and was used for 3D organ segmentation [28], bone structure analysis based on μCT data [29-31], and biodistribution analysis using μCT-FMT [23,32].

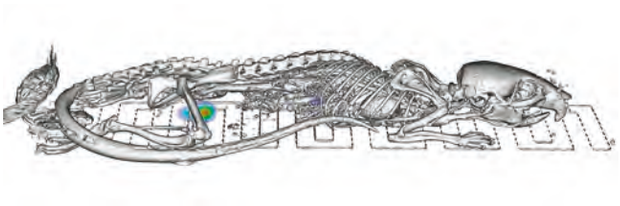


Fig. 5: 3D rendering of the a mouse scan acquired with the CT-FMT, which was developed in cooperation with MILabs B.V., Utrecht and Gremse-IT GmbH, Aachen. The image shows fluorescence in the urinary bladder as a consequence of renal elimination of a fluorescent probe.

[27] Gremse et al., SIAM J Sci Comput (2018)
[28] Rosenhain et al., Sci Data (2018)
[29] Kamal et al., J Craniofac Surg (2018)
[30] Kamal et al., J Biomed Mater Res B Appl Biomater (2018)
[31] Bohner et al., Ultrasound Med Biol (2018)
[23] Theek et al., J Control Release (2018)
[32] Wazecha et al., Adv Biosyst (2018)

Probe design for molecular imaging

Dr. Srinivas Banala

The research in the probe design group is focused on the development of novel diagnostic and theranostic agents. Our expertise is in multi-step organic synthesis, in particular in the development of novel chromophores for photoacoustic (PA) imaging and optical imaging (OI) 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 numbers of methyl groups generated highly bathochromic shifted PAI probes (Fig. 6). Moreover, in cremophore EL-H2O solution, these probes produced >4 times more intense PA signals than the gold standard indocyanine green.

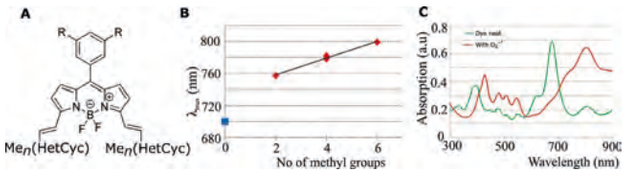


Fig. 6: A: Schematic presentation of the heterocyclics conjugated BODIPY. B: Overview of methyl group effect on the absorption maxima. C: Change in absorption spectra of a ROS-reactive BODIPY.

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) responsive BODIPY dyes. These dyes trap short-lived ROS and increase PA signals accompanied by a red-shift in PA maxima vs. the respective non-reactive chromophore (Fig. 6). These dyes might be interesting to probe pathological ROS generation, e.g. for the early diagnosis of inflammatory diseases.
In the development of optical probes for super-resolution imaging, we have developed a BODIPY based low-bleaching fluorescent dye. This probe survived hundreds of irradiation cycles in the 2-photon laser, thus can be useful as an alternative for cyanine dyes. Similarly, STED super-resolution microscopy has shown that this novel BODIPY is suitable for 660 nm depletion, surviving >85 irradiation cycles in 3-dimensional imaging.

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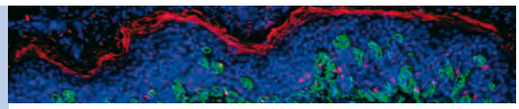
- F. De Lorenzi, M. Baues, S. Rosenhain and B. Theek: Travel stipend, World Molecular Imaging Congress (WMIC), Seattle
- N. Groß-Weege: Best Oral Presentation, PSMR 2018, Elba, Italy
- S. Banala: Travel grant, Indian Inst of Technologies
- Prof. T. Lammers: International ADRITELF Award, Maria Edvige Sangalli



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Team

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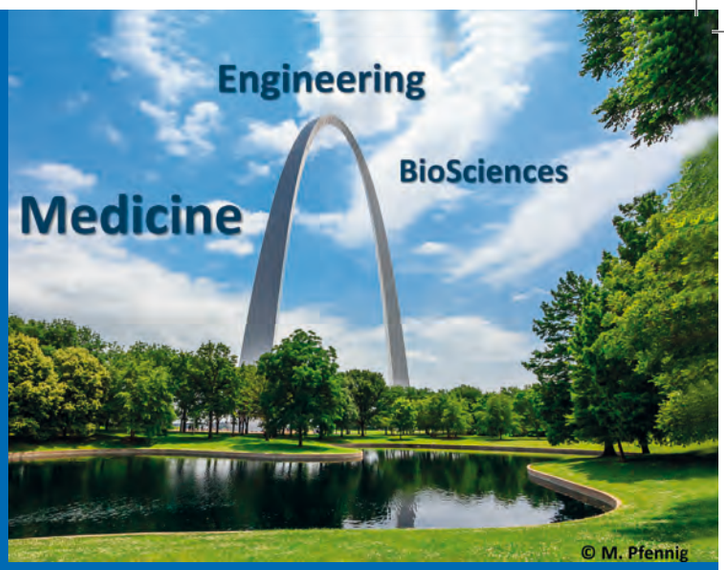
Institute of Applied Medical Engineering

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

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

Biophysical & Education Engineering (BEE)

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

Initiating new ways of collaborative learning in biomedical education

Motivation is one of the strongest success factors for self-directed and sustainable learning. Therefore, the BEE group took several approaches to integrate motivating learning scenarios in biomedical curricula. The most prominent makes use of media such as movies, literature or comic books. Interdisciplinary students groups (Fig. 2) are asked to identify scenes in these media with a connection to biomedical problems, e.g. what kind of forces must act upon a mandible before teeth are knocked out and which other injuries are caused by this impact (as to be seen in virtually every Asterix comic book). In the following course, groups train their skills on literature research, essay writing, interdisciplinary cooperation, discussion and feedback, teamwork methods, giving presentations and still others before they finally present their outcomes. This seminar showed outcomes above average and thus was integrated in the curriculum.

Nanomagnetic Medical Engineering/NME

Dr. Ioana Slabu

In patients with endoluminal tumors (e.g. trachea carcinoma, esophagus adenocarcinoma or bile duct Klatskin tumors), metallic stents are implanted to widen the occluded endoluminal site. However, after a while tumor tissue ingrowth takes place causing a re-closure, so-called restenosis, of the endoluminal organs. The group NME develops a hybrid stent made of fibers with incorporated magnetic nanoparticles (MNP) which allows performing local hyperthermia treatment and, in this way, destroying the tumor tissue in close vicinity to the stent (Fig. 3). Tumor damage by hyperthermia is generally expected for temperatures of about 43 °C, for which healthy tissue remains unharmed.

Fig. 2: Under supervision of a tutor, student elaborate self-chosen biomedical tasks.

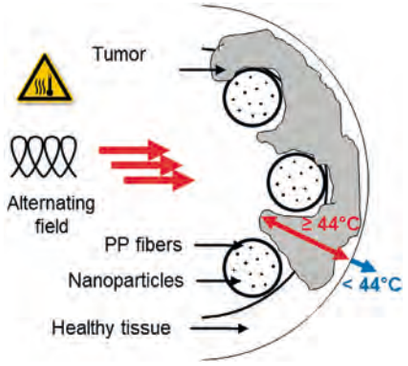

Fig. 3: Principle of hyperthermia tumor treatment using a hybrid stent with incorporated magnetic nanoparticles.

NRW Schwerpunktprofessur Biohybrid & Medical Textiles (BioTex)

Univ.-Prof. Dr. med. Stefan Jockenhövel

The *NRW-Schwerpunktprofessur* Biohybrid & Medical Textiles (BioTex) focuses on the development of viable biohybrid implants with the potential for remodelling, regeneration and self-repair. The mission statement of the *NRW-Schwerpunktprofessur* is "Innovation & Translation by Interdisciplinary Collaboration". Therefore, the department is organized as a bridging research group between the Aachen-Maastricht Institute for Biobased Materials (biomaterial research, Faculty of Science) via 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. Selected **research highlights** in 2018:

Fig. 4: The VascuTrainer bioreactor system with a medium reservoir, a centrifugal pump, pressure and flow sensors, a pump control unit and the tissue-engineered vascular graft (TEVG).

- Our group has successfully manufactured and conditioned **fibrin-based tissue-engineered vascular grafts (TEVG)** with a newly developed compact and mobile bioreactor system. The so-called **VascuTrainer** (Fig. 4) allows for the conditioning of TEVG under a wide range of hydrodynamic conditions, and enables production, subsequent storage and transportation to the patient in one device (Wolf et al. in *Annals of Biomedical Engineering*, funded by the Excellence Initiative of the German federal and state governments).
- **Macroporous constructs** (Fig. 5) and **electrospun fibers** (Fig. 6) produced from **elastin-like recombinamers (ELR)** have been demonstrated to be particularly suitable as a scaffold material for cardiovascular tissue engineering applications (Fernández-Colino et al. in *Macromolecular Bioscience* and *Materials Science and Engineering*, funded by the Excellence Initiative of the German federal and state governments).

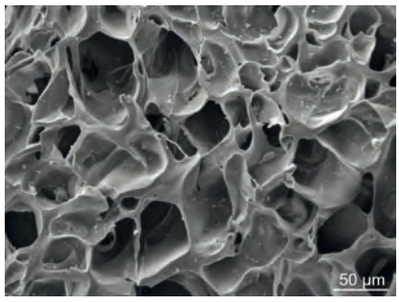

Fig. 5: SEM image showing the macroporous structure of the elastin-like recombinamers enabling cell infiltration.

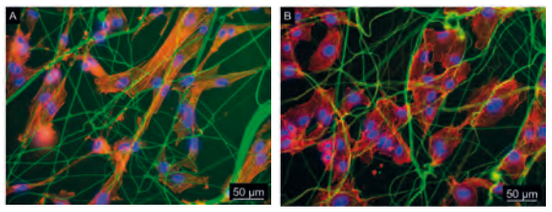

Fig. 6: Fluorescence microscopy images of electrospun elastin-like recombinamers fibers seeded with smooth muscle cells (A) and endothelial cells (B).

- The **BioPacer** project won the **KinderHerz Innovation Award NRW 2018** in the category "innovative research" for the development of a biological pacemaker for children. In this project, a small tubular hydrogel construct is populated with cardiomyocytes to generate a living conductive "wire" (Fig. 7) to treat heart rhythm disorders.

Fig. 7: Awardee Hans Keijdener (A). Tissue-engineered tubular structure populated with cardiomyocytes (B).

Cardiovascular Engineering (CVE)

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

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

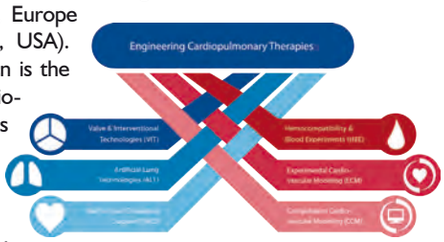

Fig. 8: Structure of the CVE.

The group Valve and Interventional Technologies (VIT) develops interventional medical devices as well as test methods for such devices. The group 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). Additionally, a patient-specific left atrial appendage (LAA) occluder (funded by the VDI) is being developed. The development of a tissue engineered endobronchial stent, the PulmoStent (funded by the VDI/VDE and PTJ, project lead: BioTex) has progressed and is on its way towards preclinical trials. 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, calcification testing on animal tissue and efficiency testing of cerebral protection devices. Additionally, employees of the CVE are involved in standardization committees regarding heart valve testing within ISO and DIN regulations. Fig. 9 gives an overview of some of the work conducted within VIT.

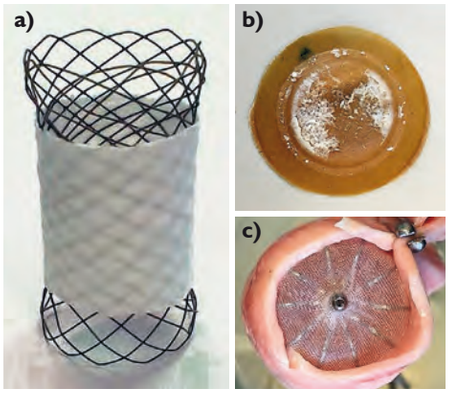

Fig. 9: a) PulmoStent prototype, b) bovine pericardial patch after calcification testing, c) LAA occluder in-vitro testing.

In the field of Artificial Lung Technologies (ALT), two research projects with funding from the German Research Foundation DFG researched the internal processes of gas exchange, flow distribution and hemocompatibility during pulsatile and non-pulsatile blood flows in oxygenators. Of these two, PulsOxy was successfully finished while OxySim is still ongoing. Within the DFG priority programme (#2014), the projects ConnLA and ConnExAL are working on novel cannulation methods for either peripheral or central longterm-connection, whereas 3D-ECMO focusses on the development of an improved membrane geometry for ECMO application. The ECCOR project develops a detoxification device for patients suffering from carbon monoxide intoxications, aiming to increase patients support during transport to a hyperbaric chamber.
The working group Mechanical Circulatory Support (MCS) investigates innovative blood pump concepts. The research project Scarabaeusherz has the objective to develop a total artificial heart based on the rotary piston principle. This pump type offers several clinical advantages compared to available blood pumps. However, one main hindrance prevented the clinical application for decades: insufficient seals. In order to overcome this technical obstacle, a seal-less drive was invented. In 2017, the first functional prototype, see Fig. 10, with a seal-less drive was completed. This proof-of-concept is a breakthrough in the development and forms the basis for the clinical application of rotary piston blood pumps.

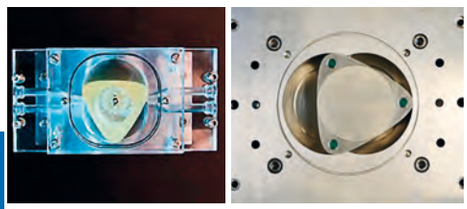

Fig. 10: The total artificial heart concept Scarabaeus. Left: early lab type; right: seal-free drive and bearing concept.

As an alternative to heart transplantation, the ReinHeart total artificial heart can completely replace the function of the natural heart, illustrated in Fig. 11. The durability of important components of the ReinHeart has already been proven in extensive laboratory tests, including the extremely low-wear drive concept. In addition, the fitting of the system has been optimized in anatomical studies.

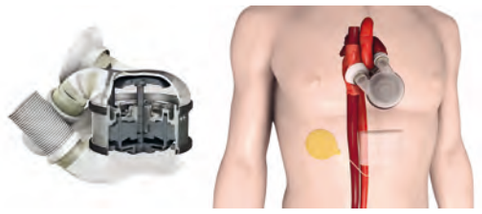

Fig. 11: The total artificial heart ReinHeart. Left: Inside view; right: Positioning of the pump and drive components.

The projects HOC Surf, GhostCells and Microstructures of the group hemocompatibility and blood experiments (HBE) are still ongoing. Within HOC Surf (EFRE funding), an optimized test setup for blood pump testing was developed and investigated in first in vitro trials. It aimed at reduced blood volume in the setup to reduce foreign surfaces at the same time. For the hemolysis analyses of the pumps, von Willebrand Factor is used as an additional marker.
The large batch production of GhostCells (DFG funding) was successfully realized and automated in terms of centrifugation, cell separation and reagent mixing (Fig. 12). This is the first step for spatially resolved hemolysis investigations of medical devices.

Fig. 12: Large batch production system for GhostCells.

For the 'Microstructures' project (START funding), master templates for mold casting of polymer foils with surface structures in the micrometer range were manufactured and a protocol for the mold casting procedure was established (Fig. 13). The microstructures increase the water contact angle of polymer surfaces, similar to the 'Lotus Effect'.

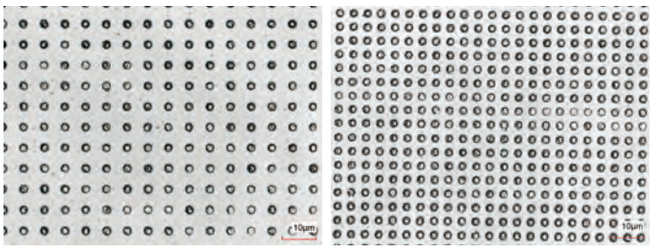

Fig. 13: Laserscanning images of microstructured polyurethane surfaces.

The thrombogenicity tester for mechanical aortic heart valve prosthesis was optimized in the course of the valve-related project 'PolyValve' (INTERREG funding). It allows for the evaluation of thrombi hotspots of aortic valve prostheses *in vitro*.
In the field of Experimental Cardiovascular Modelling (ECM), experimental simulation are used as a tool to support and optimize blood pumps, heart valve prostheses and artificial lungs.
Using experimental methods like Mock Circulatory Loops the group supports ongoing projects e.g. the ReinHeart TAH (EFRE funding) by evaluating different concepts of the right-left flow balance as part of a physiological control and

pump curve characteristics under various circulatory conditions.
Within the Cerebral Flow Model project (START funding) the development of a test bench for the *in vitro* testing and assessment of ischemic stroke treatment with endovascular aspiration methods is still ongoing (Fig. 14). We investigated cerebral hemodynamics by acquiring flow inside patient-specific arteries using Particle Image Velocimetry (PIV) (Fig. 15).

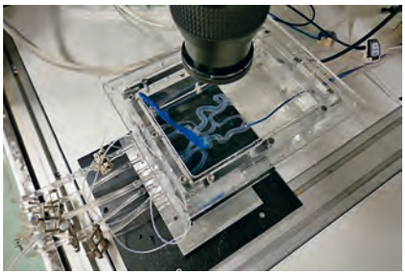

Fig. 14: Image of the test facility and occluded vessel.

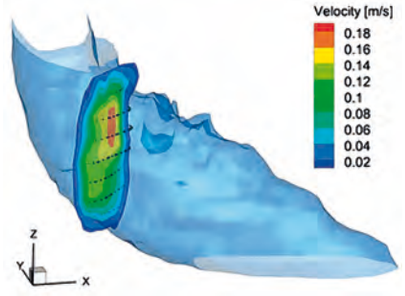

Fig. 15: Flow field inside a cerebral artery acquired by PIV.

In the new research project DurImplant, Sub-project P5 of PAK 961: DFG project "Towards a model based control of biohybrid implant maturation", the group supports the development of an *in vitro* methodology for the investigation of the durability of biohybrid implants with the main focus on the propensity to calcification as a decisive limiting factor of the implant lifetime and function.
In the field of Computational Cardiovascular Modeling (CCM), numerical simulation are employed as a tool to support and drive the development and optimization of cardiovascular devices as blood pumps, stents, heart valve prostheses and artificial lungs. High-resolution simulations and improved numeric predictions are made possible through high performance cluster computing.
The development of numerical, patient-specific evaluation and experimental validation methods are driven by the objective to quantitatively assess the device performance 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 for complex flows and dynamic shear stress exposure such as in 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.). The PolyValve project investigates an adapted stent design, as seen in Fig. 16, for a polymer prosthesis in the mitral valve position. A first concept for a transcatheter mitral valve stent model made of Nitinol has been developed by analysis of the anatomy, implantation and manufacturing conditions.

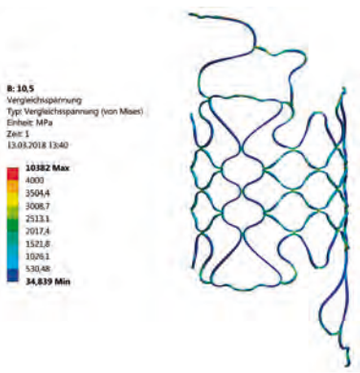

Fig. 16: Illustration of an expanded stent scaffold.

Rehabilitation and Prevention Engineering/RPE

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

Successful rehabilitation of musculoskeletal function depends not only on the quality of movement performance and the accuracy of clinical diagnosis but also on the amount and consistency of physiotherapeutic training. With more than 30 years expertise in engineering science and human motion analysis, the Department of Rehabilitation & Prevention Engineering (RPE) continues to successfully advance research, development and the realization of adaptive systems and methods that support the prevention, diagnosis and therapy of movement disorders.
In conjunction with clinical staff, RPE has gathered extensive knowledge regarding physiological and pathological function of the human musculoskeletal and neuromuscular systems. Biomechanical modelling and signal processing extracts and translates abstract sensor data into physiologically meaningful information about muscular coordination. On this basis, different assistive technologies have been developed which include the design of intelligent biofeedback training systems for extramural rehabilitation, novel orthoses, sensor-based movement analysis and robot-guided rehabilitation systems, which foster autonomous, customized physiotherapeutic exercise schemes for patients. Early consideration of quality management and adherence to clinical stipulations positively leverages the acceptance and success of technical innovations and systems while accelerating translation into usage.

Improving movement capacity in spasticity

Spasticity is a common symptom of a brain lesion and results in disrupted movement performance in children and adults who have had a stroke. The patient cannot control the occurrence of spasticity; movements are possible only under extremely forceful effort and sometimes with pain. Consequently, special emphasis has been placed on the detection, assessment and quantification of spasticity in patients presenting with infantile palsy and stroke. Specialist knowledge regarding muscular activity, muscular coordination and force regulation during spastic contractions has facilitated RPE's participation in smartMove, a multilateral cooperation project between Mexico and Germany which focusses on the development of a smart orthosis. The novel orthosis (Fig. 17) will support the execution of the movement in such a way that spastic contractures are avoided at the moment that the movement is performed.

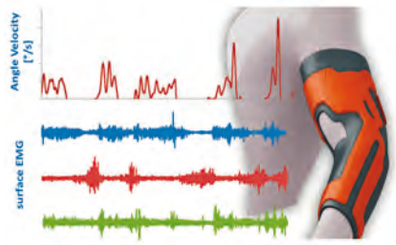

Fig. 17: Future smart orthoses will take advantage of knowledge regarding muscular activity and force regulation during daily movements to secure effective motor performance in patients with spasticity.

Wearable sensor-based movement analysis

Small, lightweight, smart sensors have been developed which allow the detection, tracking and recording of movement during the activities of daily living (ADL) outside of the research or clinical environment. Algorithms have been and continue to be developed in support of these wearable sensor systems to improve the remote assessment of movement quality. Such systems technologically support the quality assessment of daily and exercise movements, provide real-time biofeedback for users and facilitate accurate clinical supervision and individualized recommendations in both prevention and rehabilitation.

Fig. 18: Assessment and evaluation of movement quality e.g. in upper extremity using inertial sensors

*In*dividualized *Reha*bilitation therapy *R*obot assisted: *inRehaRob*

Robotically guided and assisted rehabilitation enables patients to take advantage of frequent, intensive, individualized rehabilitation while more effectively allocating the workload of therapists. These factors have been proven to be congruent with the best therapy practices and the optimization of quality outcomes. Rehabilitation robots offer tremendous benefits to their user groups: patients and therapists. They can be implemented to monitor movement quality, to assist patients as needed and provide specific feedback so as to accelerate patients' progress and maximize eventual functionality.

Fig. 19: Performance of a rehabilitation exercise using robotic guidance and assistance. Feedback about and real-time monitoring of movement paths is provided via the system's integrated display screen.

Within the BMBF founded project **inRehaRob** (Fig. 19) a consortium of research institutions, industry and rehabilitation centers have developed a rehabilitation robot which facilitates autonomous, individualized rehabilitation of patients. This system was presented at MEDICA 2018 and received an extremely positive response from various visitors at the expo.

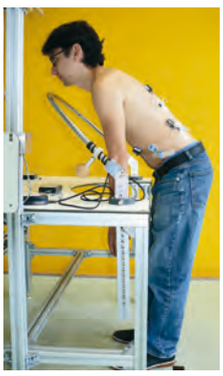

Fig. 20: The forward bending task is a typical ADL, which is difficult to perform in the presence of low back pain. sEMG was recorded and analyzed in order to assess movement performance.

Assessment of pain

Surface electromyography (sEMG) is used to investigate muscular activation in the presence of pain. Special emphasis is placed on 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 of pain during the activities of daily living (ADL) to be quantified.

Science Management (SCM)

Dr. Robert Farkas

Translational Research explores the enabling and accelerating discoveries to benefit human health. Currently there is a severe gap between increasing knowledge on the on hand and the consecutive introduction of novel therapies on the other hand. Too often, discoveries are getting lost in the so-called valley-of-death of innovation.
The Science Management department focus on the potential of Big-Data technologies e.g. text mining, machine learning of millions of patents and scientific publications to reveal technological concepts, which directly meet a clinical demand, or to identify an expert, who fits best to collaborate concerning a specified biomedical topic. Both automated reviewing of potential technologies and collaboration recommenders can speed up the transfer of knowledge into the clinical setup. However, even there, promising and mainly unused Big Data are available e.g. in diagnosis. Their use to support clincial decision making marks an upcoming field of research.

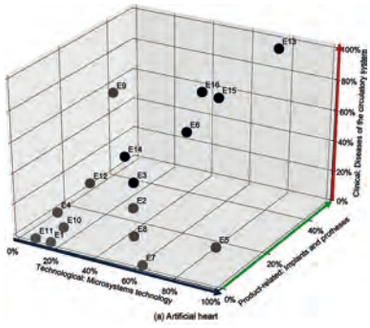

Fig. 21: Final profiling of experts (E1 …E16) for the development of artificial hearts according to the 3d-domain model of biomedical engineering.

Acknowledgements

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

Awards

- Jansen, Sebastian: Winner of the Silver ESAO PhD Award on the Congress of the European Society for Artificial Organs, ESAO for short, for his Dissertation entitled ‚Development of an *In vitro* Fluorescent Haemolysis Detection Method Using Ghost Cells'.
- Keijdener, Hans: Winner of the KinderHerz Innovation Award NRW 2018 for the project 'BioPacer: Entwicklung eines biologischen Herzschrittmachers'.

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Team

Facts

Third-party Funding gesamt 2018

	Number of Projects	Total Expense of Projects [EUR]
German Research Foundation (DFG)	3	2.345.782,00
German Federal Ministry of Education and Research (BMBF)	1	1.774.690,00
EU	3	1.442.538,00
Industry	6	1.090.100,00
Other	4	2.513.283,00
Sum	17	9.166.393,00

Theses

	Number
Student Mini-Thesis	
Bachelor	62
Diploma/Master	76
Doctoral	24
Habilitation	3
Sum	165

Staff

	Scientific	Non-Scientific
Total	171,6	36
Third party funded	162,6	11

in full-time equivalent (FTE)

Publications

	Number
Conference proceedings	99
Peer-reviewed journals	170
Books and book chapters	7
Sum	276

Patents and patent applications: 12

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