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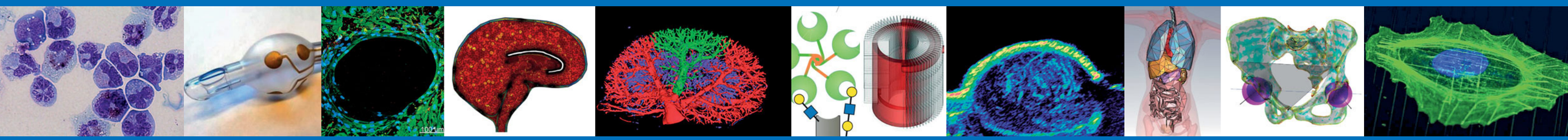
Helmholtz-Institute for Biomedical Engineering

Annual Report 2016



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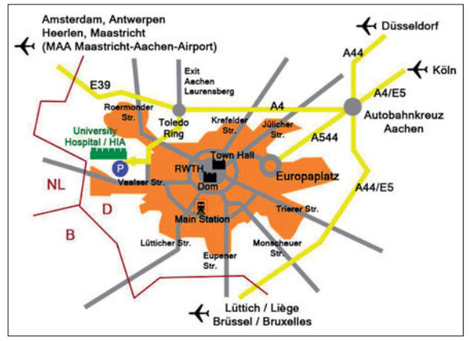
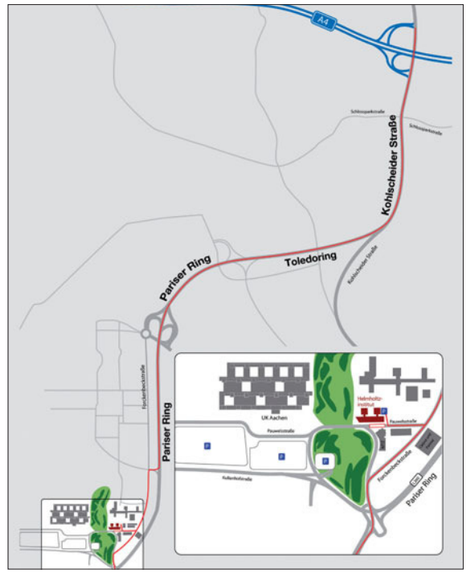
Content

Annual Report
2016
Helmholtz-Institute for Biomedical Engineering
RWTH Aachen University

How to reach us





Address

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By car

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

By train/bus

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

By plane

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

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

Preface

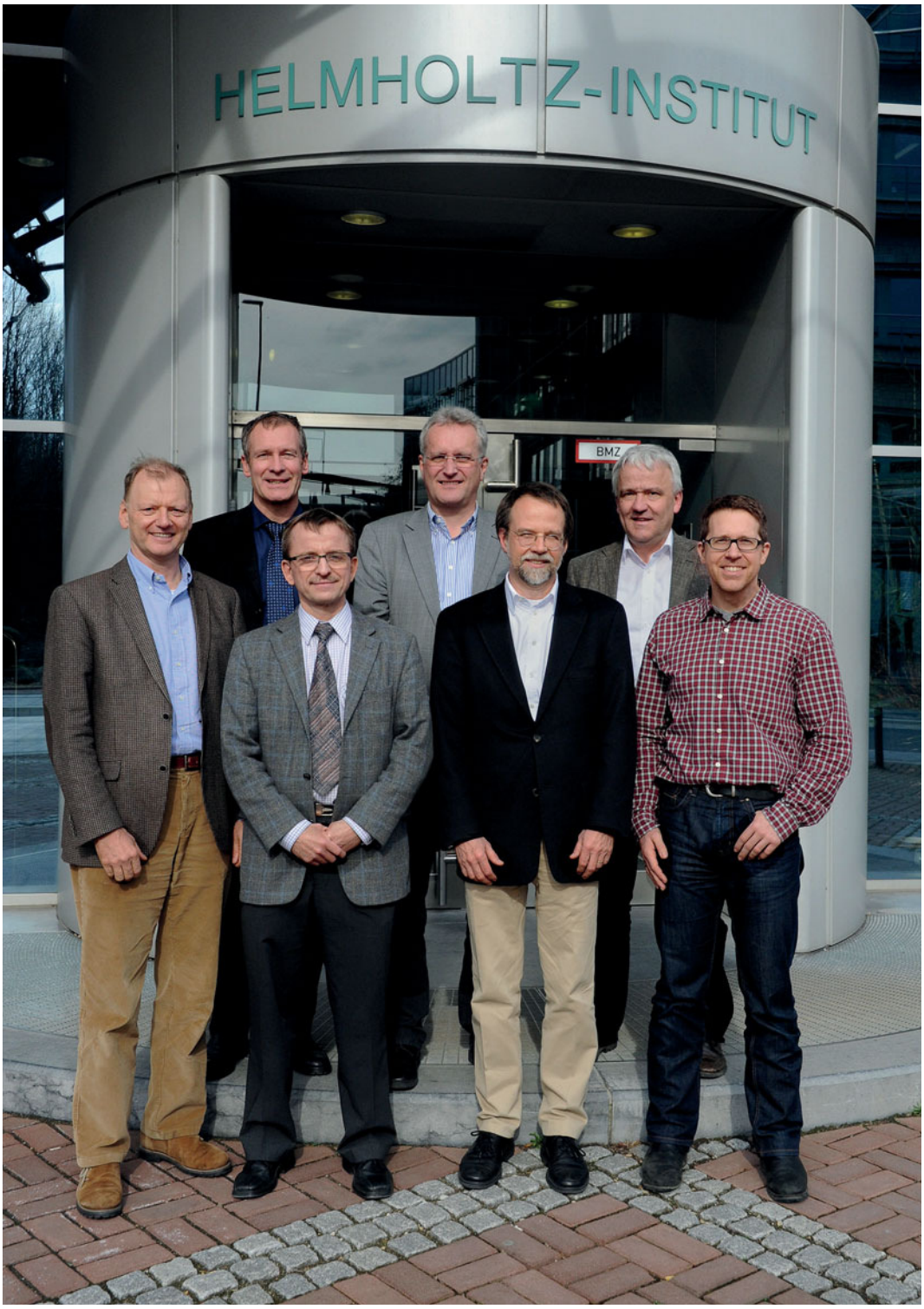

Fig 1: The HIA Board of Directors (from left to right):
Prof. Jahnen-Dechent, Prof. Schmitz-Rode, Prof. Leonhardt, Prof. Elling, Prof. Zenke, Prof. Radermacher, Prof. Kiessling

The mission of the Helmholtz-Institute for Biomedical Engineering of the RWTH Aachen University is interdisciplinary basic research and development for personalised biomedical engineering solutions. The common objective of all initiated projects, activities and tasks is to create innovation for better health care. The application of new methods and technologies should contribute to the best possible diagnostic means and better therapy options for each individual patient. Networking and cooperation within the RWTH Aachen University as well as with experts from clinics, research and industry on a national and international level are key factors of our work.

We contribute to bachelor and master programs of different faculties of the RWTH Aachen University, including the coordination of 3 different master programs related to the field of biomedical engineering. The tight connection between actual research topics and the theoretical as well as practical education of our students from different disciplines and specialities is an essential basis for the success of our alumni in their international industrial as well as academic careers.

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

Aachen, January 2017

The Board of Directors

Events 2016




The **Annual Conference of the German Society for Biomaterials** was held from 29 September – 1 October 2016 at RWTH Aachen University and was hosted by Prof. Jahnen-Dechent. Several talks and posters were presented by members of the Helmholtz-Institute for Biomedical Engineering. *First row, above from left: Conference opening with invited speakers and Pro-rector of RWTH Aachen University (left to right David Grainger, Andres Garcia, Doris Klee, Willi Jahnen-Dechent, Seeram Ramakrishna); centre left: session talk; centre right: participant discussion during coffee break; centre right: conference dinner at Couven Hall*
Second row, left: During the meeting Prof. Jahnen-Dechent was elected President of the German Society for Biomaterials, and later on awarded the presentation prizes.

Team building Events 2016






Gene Function in Cell Growth, Differentiation & Development

Director

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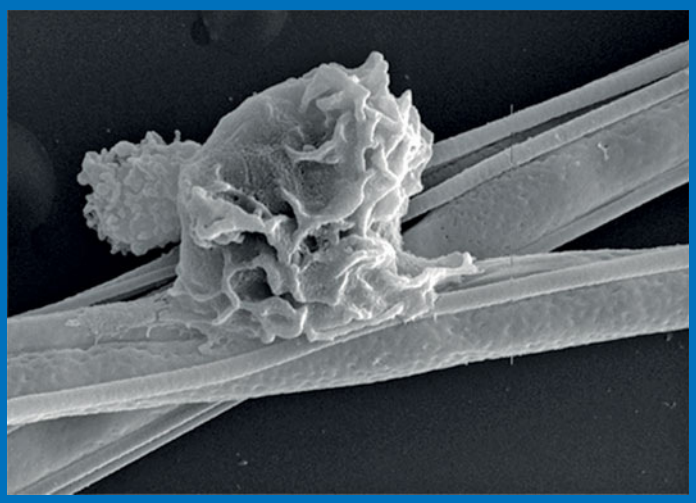

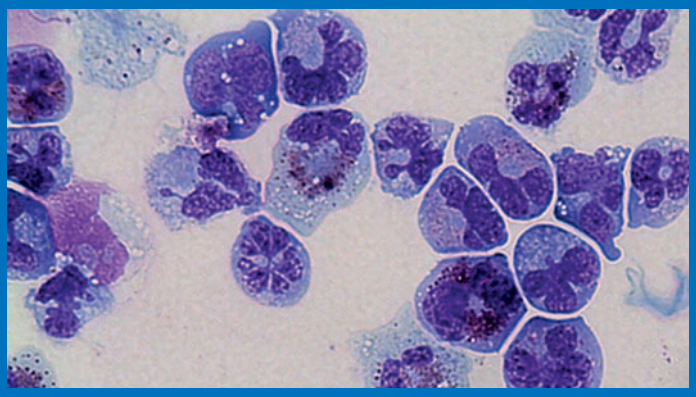

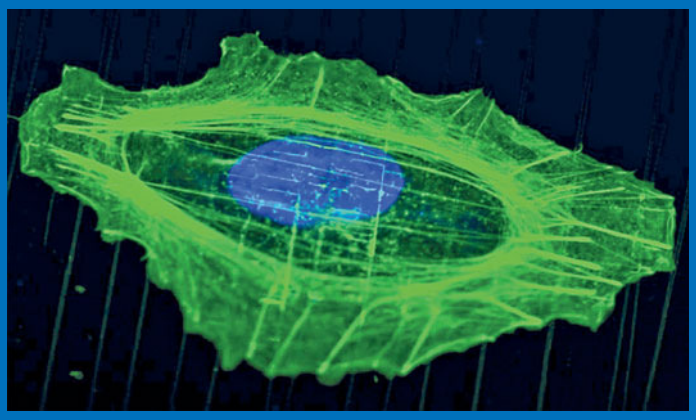

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Introduction

In cells a specific grammar of DNA and chromatin modifications determines gene expression and thus cell identity and function. We aim at elucidating how gene networks direct cell fate and specific cellular activities, using a rich toolbox of bioinformatics and computation for analysis and predictions of sequencing data (Fig. 1). The laboratory studies stem cells both in the normal physiological and in the diseased state. This includes blood stem cells (hematopoietic stem cells, HSC), mesenchymal stem cells (MSC), embryonic stem cells (ES cells) and also engineered stem cells, such as induced pluripotent stem cells (iPS cells), and their differentiated progeny. We use genome precision engineering with CRISPR/Cas to generate cells with desired properties. A particular focus is on antigen presenting dendritic cells (DC). We also study stem cell aging, magnetic nanoparticles for cell tracking and the influence of biomaterials and surface topology on cell growth and cell behavior.

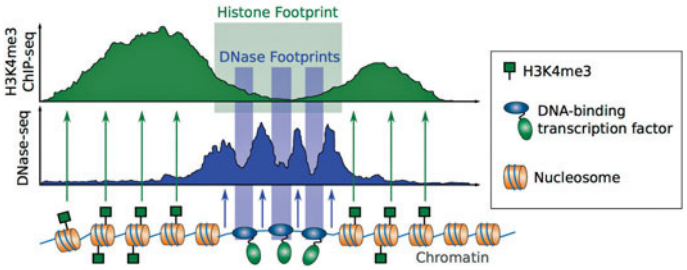

Fig. 1: The histone modification H3K4me3 is indicative of active genes. The binding of transcription factors to the promoters of these genes leaves histone and DNase footprints.

Engineered IRF8-/- iPS Cells by CRISPR/Cas Genome Editing

Human iPS cells can differentiate into cells of all three germ layers, including hematopoietic stem cells and their progeny. Interferon regulatory factor 8 (IRF8) is a transcription factor, which acts in hematopoiesis as lineage determining factor and autosomal recessive or dominant IRF8 mutations in patients cause severe monocytic and DC immunodeficiency.

To study IRF8 in human hematopoiesis we generated human IRF8–/– iPS cells and IRF8–/– ES cells using RNA guided CRISPR/Cas9n genome editing (Sontag et al., 2016, in press). We differentiated iPS cells and ES cells into hematopoietic stem/progenitor cells and further into DC. IRF8 deficiency caused a bias towards granulocytes at the expense of monocytes and compromised development of specific DC subsets (Fig. 2). Additionally, IRF8–/– DC showed reduced MHC class II expression and were impaired in cytokine responses, migration and antigen presentation. Thus, this human IRF8 knockout model allows studying molecular mechanisms of immunodeficiencies in the human system.

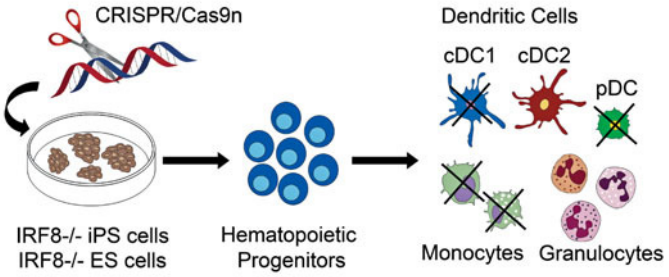

Fig. 2: IRF8–/– iPS cells and IRF8–/– ES cells were generated by CRISPR/Cas9n and differentiated into hematopoietic progenitors and further into mature blood cells. Deletion of IRF8 compromised development of specific dendritic cell subsets (classical DC1 and plasmacytoid DC, cDC1 and pDC, respectively) and monocytes, while enhancing the frequency of granulocytes (Sontag et al., 2016, in press).

Senescence-associated Epigenetic Modifications of Cells in Culture

MSC represent the cell type that is currently used in most clinical trials – but this necessitates *in vitro* culture expansion to achieve clinical relevant cell numbers. During the *in vitro* expansion, MSC acquire large and flat morphology, lose differentiation potential, and ultimately enter proliferation arrest – a state defined as replicative senescence. Interestingly, replicative senescence is reflected by continuous and highly reproducible DNA methylation (DNAm) changes at specific CpG dinucleotides in the genome. We developed a deep sequencing method based on six CpGs to precisely reflect the state of replicative senescence in MSC and human umbilical vein endothelial cells (HUVEC) (Fig. 3; Franzen et al., 2016; patent pending).

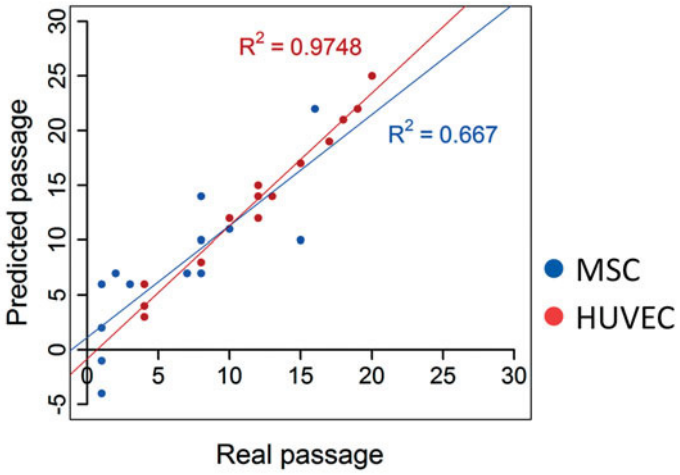

Fig. 3: Epigenetic-Senescence-Signature based on six CpG dinucleotides to predict the number of passages of cell preparations of MSC and HUVEC (Franzen et al., 2016).

It is still unclear whether the senescence-associated DNAm changes are directly regulated by a targeted molecular process. During the last years long non-coding RNA (lncRNA; >200 nucleotides) have emerged as

potential epigenetic modifiers. We demonstrated that the HOX transcript antisense RNA (*HOTAIR*) binds preferentially to genomic *loci* that become hypermethylated during replicative senescence. Gain- and loss-of-function approaches indicated that *HOTAIR* expression contributes to regulation of cellular senescence by changes in gene expression and DNAm. Notably, *in silico* and subsequent *in vitro* analysis indicated that targeting of *HOTAIR* to specific genomic *loci* is mediated by triple helix formation (Fig. 4; Kalwa et al., 2016).

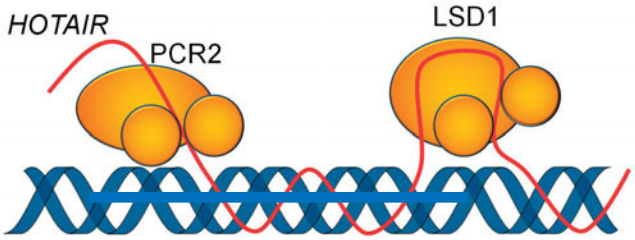

Fig. 4: Schematic representation of the triple helix formation. The lncRNA HOTAIR targets specific genomic locations and interacts with epigenetic modifiers, such as PCR2 and LSD1 (Kalwa et al., 2016).

Polyelectrolyte Coating of Magnetic Nanoparticles for Cell Labelling and Tracking by MRI

Translation of cell-based therapies into clinical applications is hampered due to the lack of tools to monitor cell fate and function after transplantation. Labelling of cells with engineered magnetic nanoparticles (MNP) before implantation shows great promise in tracking cells *in vivo* using magnetic resonance imaging (MRI).

We study the tailoring of MNP using layer-by-layer assembly of polyelectrolytes (PE) for enhanced labelling of hematopoietic stem/progenitor cells and DC and their tracking using MRI (Schwarz et al., Nanomedicine, 2012; Celikkin et al., J. Magn. Magn. Mater, 2015; in collaboration with W. Richtering and J. E. Wong, Institute of Physical Chemistry, RWTH Aachen University, Aachen, Germany and M. Hoehn, In vivo NMR Research Group, MPI for Metabolism Research, Cologne, Germany). Recent studies revealed a differential impact of specific PE coatings on labelling and cellular responses of different DC subsets under steady state and inflammatory conditions (Celikkin et al., manuscript in preparation; Fig. 5).

Regulation of Cell Motility and Adhesion by Surface-grafted Nanogel Arrays

Cellular functions, including cell adhesion and migration, are controlled by the precise spatio-temporal regulation of cytoskeleton dynamics. Several interdisciplinary studies have demonstrated that material chemistry and topology can be exploited to modulate cell adhesion and migration.

In this project, we developed highly functional and stimuli-responsive poly(*N*-isopropyl acrylamide) nanogel arrays grafted onto glass surfaces by a printing process using wrinkled polydimethylsiloxane (PDMS) templates (Sechi et al., 2016). Using low-temperature plasma treatment, nanogels were chemically grafted onto glass supports thus leading to highly stable nanogel layers in cell culture media.

We demonstrate that surface-grafted nanogels can serve as novel substrates for the analysis of cell adhesion and migration (Sechi et al., 2016). Nanogels have a strong impact on size, speed and dynamics of focal adhesions and cell motility causing cells to move along straight trajectories (Fig. 6). In addition, modulation of nanogel swelling state or spacing serves as an effective tool for regulation of cell motility.

Our study demonstrates that nanogel arrays deposited on solid surfaces can be used to provide a precise and tunable system to understand and control cell migration. We anticipate that our surface-grafted nanogel system will contribute to the development of implantable systems aimed at supporting and enhancing cell migration and adhesion.

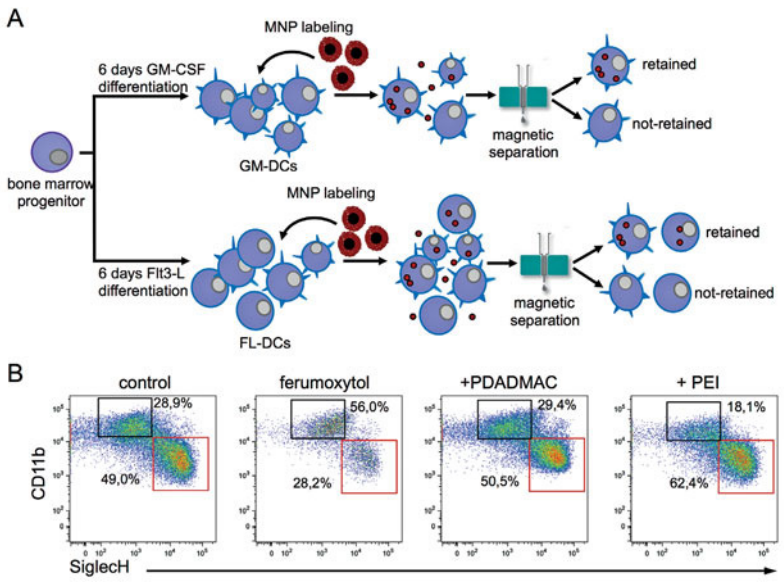

Fig. 5: Labeling of inflammatory (GM-DC) and steady state (FL-DC) DC with PE-coated and uncoated ferumoxytol particles. (A) Schematic representation of magnetic separation after labelling with MNP. (B) FL-DC after uptake of respective MNP were analyzed by flow cytometry. Representative dot plots show MNP-labeled cDC (black boxes) and pDC (red boxes) subsets.

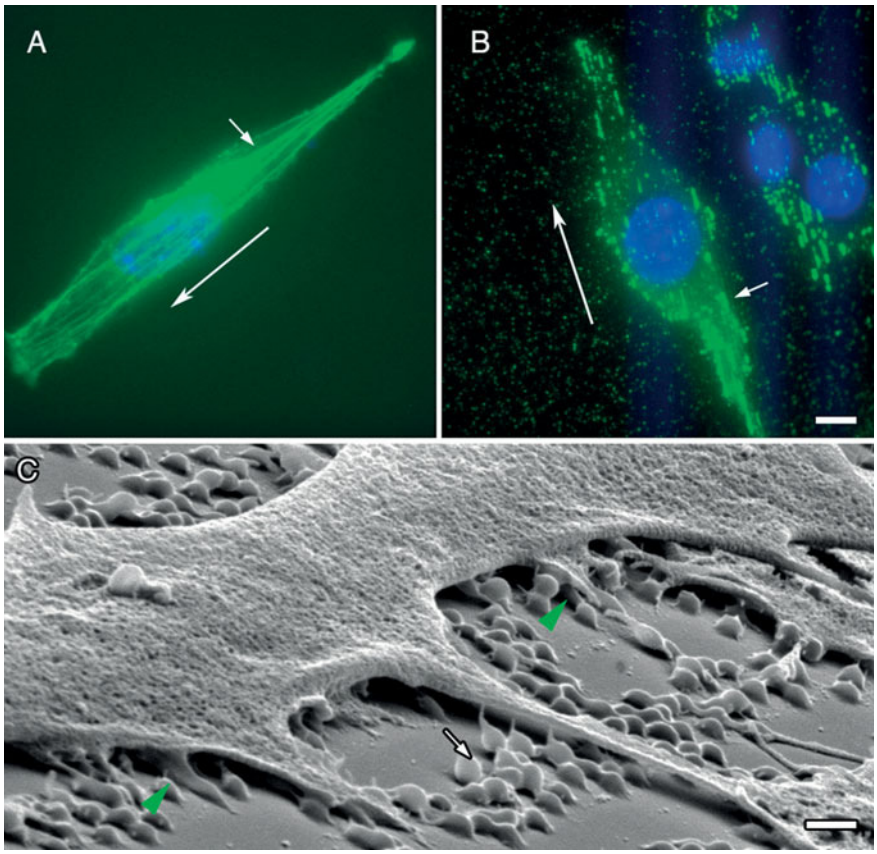

Fig. 6: Impact of surface-grafted nanogels on cell morphology and cytoskeleton organisation (A-C). The microfilaments (A, green, arrow) and focal adhesions (B, green, arrow) of mouse melanoma B16F1 cells aligned along the major axis of nanogel arrays (long arrows). Cell nuclei were stained with DAPI (blue). Scale bar: 10 µm. Scanning electron microscopy of B16F1 cells seeded on nanogel arrays (C). Note the interaction of cell projections (green arrows) with the underlying nanogel arrays (white arrow). Scale bar: 0.25 µm (Sechi et al., 2016).

Computational Detection of Cell Specific Binding Sites

One of the main molecular mechanisms controlling the temporal and spatial expression of genes is transcriptional regulation. In this process, transcription factors bind to the vicinity of a gene to recruit (or block) the transcriptional machinery. The identification of transcription factor binding sites is a first step to understand regulatory networks driving cellular processes, such as cell differentiation and the onset of diseases. Cell specific binding sites can be predicted by the analysis of sequencing protocols measuring open chromatin with computational footprinting methods (Fig. 7).

We have revisited the problem of binding site detection from computational footprinting in Gusmao *et al.*, 2016. We showed that several state-of-the-art methods (including our own method) can detect cell specific binding sites with very high accuracy. Moreover, we demonstrated how to correct for experimental artefacts, such as DNase I enzyme cleavage bias, thereby settling a long-standing scientific discussion about computational footprinting (see also Editorial Nat. Methods 13, 185, 2016). In practical examples, we have applied computational footprint to dissected NF-kB regulation during inflammation in HUVEC (Kolovos et al., 2016) and to uncover regulatory roles of Tbx3 in pancreas development (Perkhofer et al., 2016).

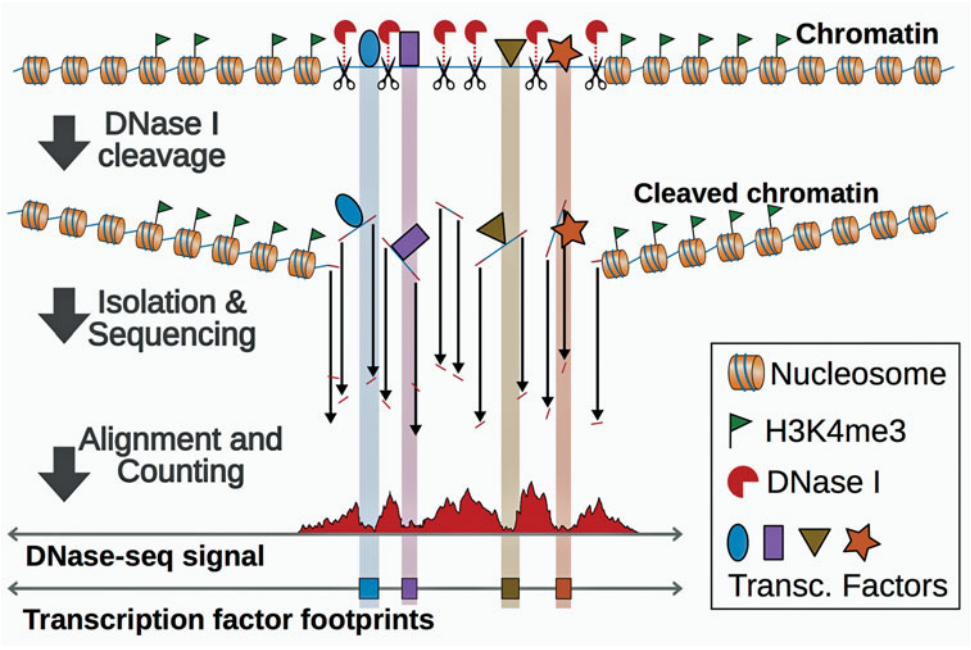

Fig. 7: Workflow of the computational analysis of the open chromatin protocol DNAse-seq (Gusmao et al., 2016).

Acknowledgements

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[1] Epigenetic classification of human mesenchymal stromal cells; 2016; EP 16152198.4 (Wagner W, de Almeida DC)

[2] Method for analysis of the cellular composition in buccal swabs; 2016; DE 10 2016 109 291.6 (Wagner W, Eipel M)

Team

At the Top and right: Best Paper Award to Eduardo Gusmao, PhD (right) and Poster Award to Thomas Hieronymus, PhD (top, second from left) at Medical Sciences Day 2016, Medical Faculty RWTH Aachen University.

Below: Lab retreat at Mosel river.

mediT

Medical Information Technology

Faculty of Electrical Engineering
and Information Technology

Smart Solutions for Advanced Healthcare

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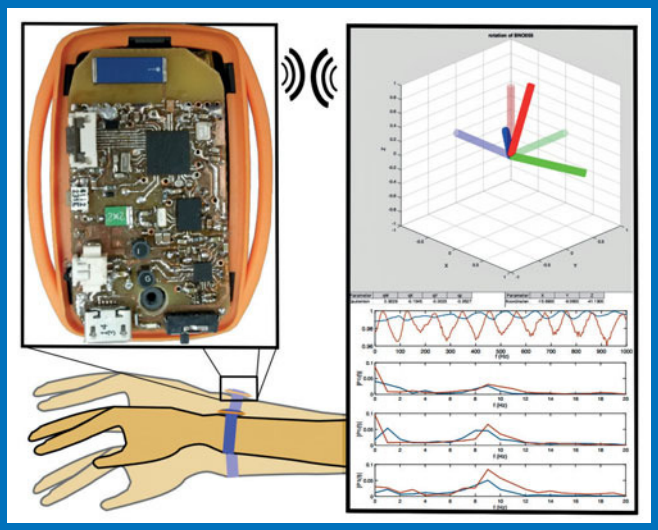

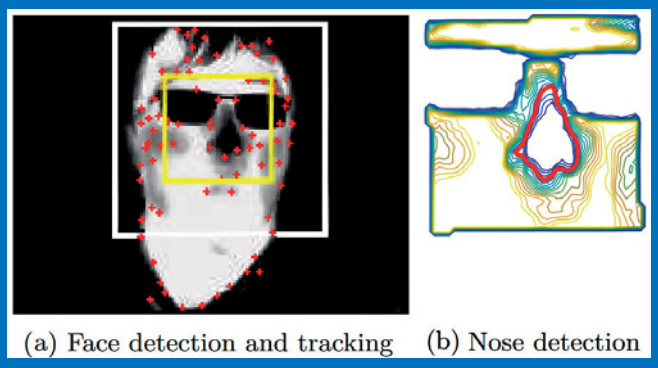

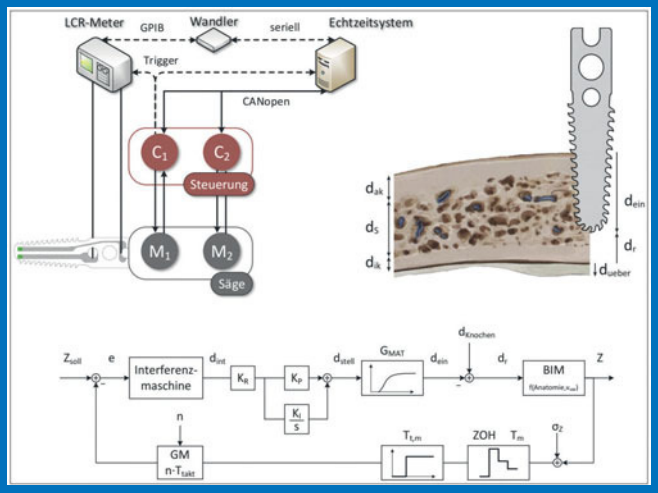

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RWTH AACHEN UNIVERSITY

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.

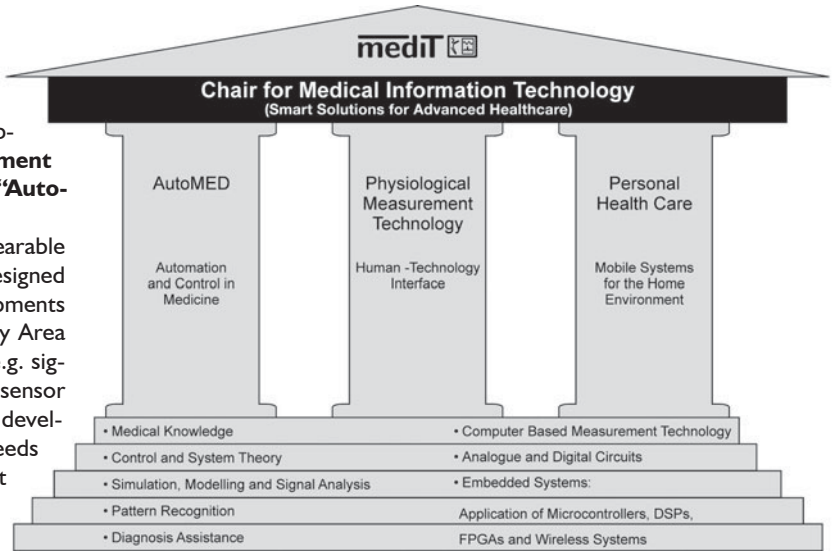

Fig. 1: Research profile of MedIT.

Selected Ongoing Research Projects

Monitoring of Respiratory Rate in Newborn Infants using Thermal Imaging

Respiration is one of the most important physiological processes. Principally, respiratory rate (RR) can be used as an early and solid predictor of cardiopulmonary arrest, intensive care admission or death. However, it is one of the most frequently undocumented and underestimated vital signs. According to the literature, RR is usually neglect due to shortcomings of current clinical monitoring techniques. These modalities require attachment of sensors to the infant's body leading to stress and discomfort. Moreover, removal of adhesive electrodes in preterm babies induce pain and epidermal stripping. In recent years, there has been an increasing interest for unobtrusive, contactless and reliable monitoring modalities to estimate RR. They aim to improve patients' quality of life as well as the use of medical resources. Thermal imaging is a remote and passive technique, which detects the radiation naturally emitted from an object, in this case the human skin, and does not use any harmful radiation. Moreover, thermal imaging does not need a light source. This particular characteristic is one of the biggest advantages of infrared tomography (IRT) over other imaging technologies.
There are different approaches to estimate RR in thermal videos. The most common is based on the fact that temperature around the nostril oscillates during the respiratory cycle. It consists of one inspiration, where cold air from the environment is inhaled, followed by one expiration, where warm air from the lungs is exhaled. Thermal imaging can be used to accurately detect these temperature fluctuations. Thus, the nose (region of interest - ROI) must be automatically located in the first frame. Forthwith, a rough tracking of the ROI must be performed to compensate motion artefacts. Lastly, the breathing waveform can be extracted and used for estimation of RR.

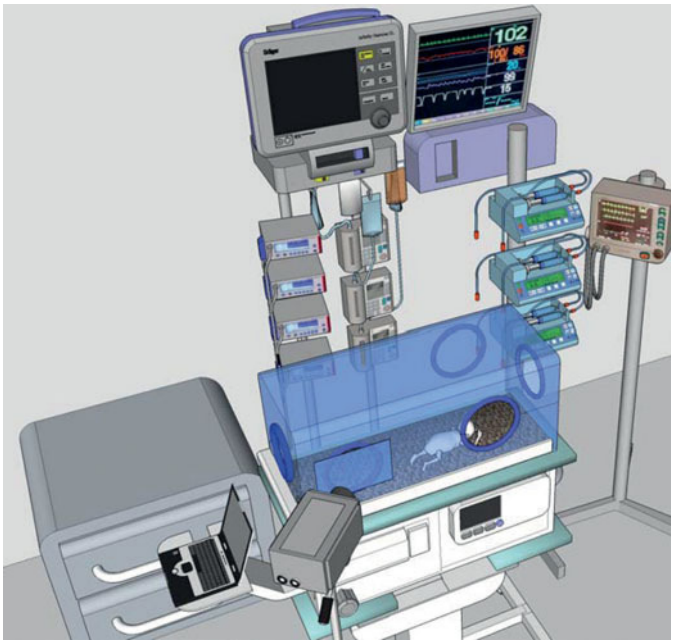

Fig. 2: Monitoring system of respiratory rate based on thermal imaging in a newborn infant.

Funded by: Fundação para a Ciência e a Tecnologia (FCT Portugal)

Smart Dialysis – Optimization of Hemodialysis by means of Multimodal Monitoring

Over the last few decades, continuous advances in dialysis technologies have increased the safety and efficacy of hemodialysis (HD). Nevertheless, the improved patient care has not translated into a clear improvement of survival rates. At present, the most common acute complications during hemodialysis are hypotension (20 - 30 %), muscle cramps (5 - 20 %), nausea and vomiting (5 - 15 %), and headache (5 %). Intradialytic hypotension (IDH) is defined as a symptomatic drop in systolic blood pressure of more than 25 mmHg or as an absolute systolic blood pressure below 90 mmHg. The causes of IDH are multifactorial. Main underlying factors are volume depletion induced by rapid removal of plasma volume with an ultrafiltration rate (UFR) higher than the plasma-refilling rate as well as impaired compensatory mechanisms. Negative effects of intradialytic hypotension include patient discomfort, a decrease in hemodialysis efficacy, and an increase in the need for medical interventions. More importantly, IDH-prone patients exhibit a higher mortality than those without intradialytic hypotension.
Thus, the project aims at integrating continuous BIS measurements into the clinical dialysis procedure, in order to establish a diagnostic method for the early detection of blood pressure instability and the prediction of dialysis outcome. This method is planned to be combined with non-contact vital sign monitoring to produce a real-time multimodal monitoring system. Our hypothesis is, that this multimodal system can predict IDH episodes and, if needed, support the adjustment of ultrafiltration profile and dialysate fluid composition. A further aim of the project is to develop a model, which is able to explain the hypotensive reaction. Such a model will serve as a basis for the establishment of early warning predictors of hypotensive episodes. These predictors will be based on vital signs like electrocardiogram (ECG), photoplethysmography (PPG), breathing and facial temperature imaging.

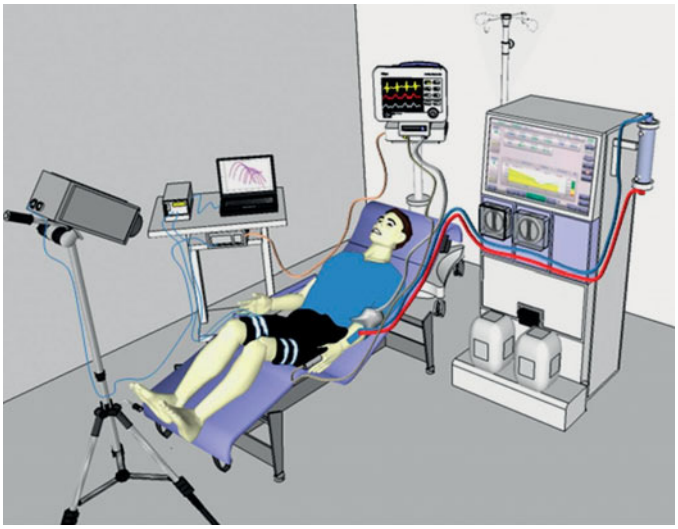

Fig. 3: Smart dialysis system with multimodal monitoring.

Driver State Monitoring

Self-driving cars become reality in the automotive industry. The first test vehicles already find their own way on highways and in dense rural areas. It is expected that, in 2025, this will be a normal course of life. One crucial part of autonomous driving is the so-called handover, so that the automatic driving mode hands over all control to the human driver, for example in a difficult traffic situation that exceeds the capabilities of the automated system. But how can it be guaranteed that the driver is capable of taking over the steering wheel? In some situations such as sleeping or unconsciousness, a monitoring of the driver status is necessary, including driver's behaviour and driver's condition. Especially, the medical condition of the driver is of great interest.

Fig. 4: Automated monitoring of driver state.

Driver state monitoring has its own history at MedIT. In 2007, we first introduced non-contact ECG in a car, demonstrating its feasibility for heart rate monitoring and detection of driver stress. Since 2013, the project has been extended to assess driver states with respect to distraction and workload, being two risk factors for car accidents. Currently, the project incorporates a larger portfolio of different sensors, in particular cameras, recording physiological and behaviouristic driver data. All sensors have been integrated into a test vehicle offering an interesting and unique research platform. Using data recorded during test drives on a dedicated test facility with a well-defined distraction and workload profile, we intend to derive metrics to assess and predict driver states. This metrics can be used not only for securing handover procedures, but also for risk mitigation. For example, the exhaustion of human driver should be detected and autonomous driving systems can take over the control.

Funded by: Ford Motor Company, European Commission

Oscillatory Electrical Impedance Tomography (oEIT)

Assessment of mechanical lung properties is of prime importance for respiratory monitoring and diagnosis of lung diseases. Oscillatory Electrical Impedance Tomography is a new technology combining two non-invasive methods, the lung function test forced oscillation technique (FOT), and the electrical impedance tomography (EIT) for respiratory online monitoring. FOT is based on measurements of the complex respiratory impedance over a frequency range between 4 and 30 Hz, where sinusoidal forced pressure signals created by the FOT device are superimposed on the patient's spontaneous breathing. By capturing the responding flow at the airway opening, the frequency response of the system and lung parameters can be estimated.

The basic principle of EIT is based on the injection of a harmless alternating current into the human thorax through a 16-electrode belt. By rotating the injecting current based on the adjacent electrode pair and measuring the resulting voltages, an impedance distribution can be scanned with a high dynamic frequency (50 Hz). EIT provides dynamical information about global and regional ventilation by reconstructing 2D cross-sectional images, which are strongly correlated with the regional ventilation lung volume. Performing EIT simultaneously during a FOT measurement provides additional 2D EIT images at different frequencies. Each pixel of the image includes three frequency components: the spontaneous breathing, the heartbeat and the oscillation. New features such as oscillatory tidal image and phase delay distribution should provide useful information on detection and localization of lung diseases. A measurement system was constructed and illustrated in Fig. 5. Oscillatory tidal image shows how oscillation signals are distributed in lung and heart regions.

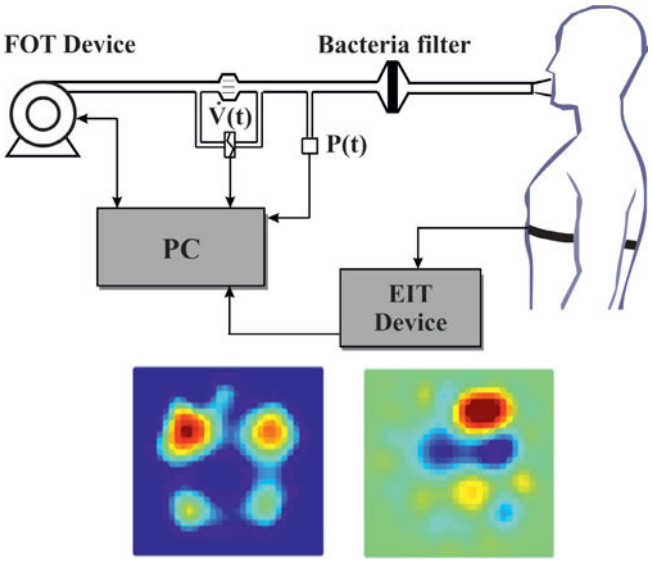

Fig. 5: System configuration of oEIT.

Robust Physiological Control of Rotary Blood Pumps

Ventricular assist devices (VADs) are increasingly used to treat advanced stage heart failure. If the native heart is unable to maintain a sufficient blood flow to the organs, a VAD can be used to restore this function and relieve the heart. However, setting the appropriate VAD speed for a particular heart failure patient requires lots of experience. We thus use robust control methods to automatically adjust the pump flow such that the patient's blood flow demand is satisfied. Our system, called Assistance, offers the treating physician a single, intuitive setting option for continuous-flow left VADs (LVADs).

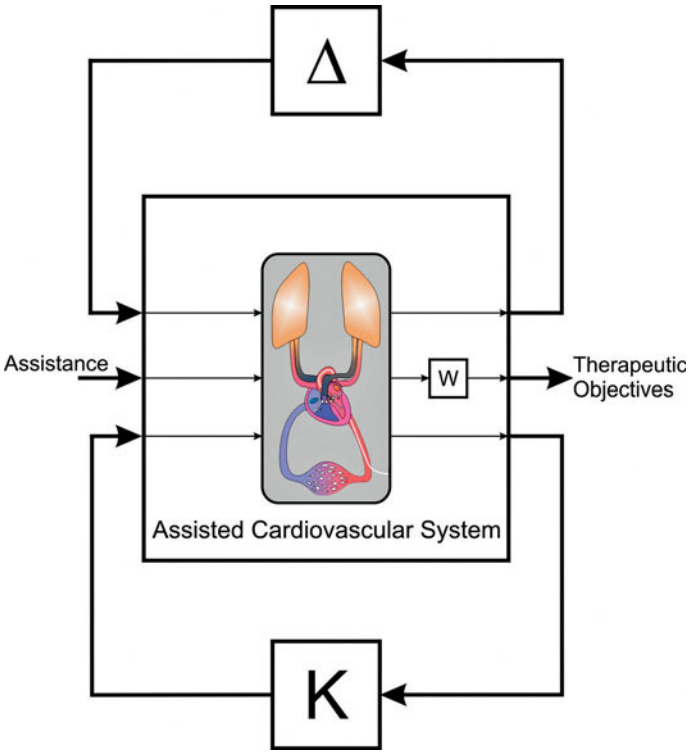

Fig. 6: Robust control of rotary blood pump.

The Assistance is defined by the time-averaged ratio of LVAD flow and total cardiac output. A proportional-integral controller sets the pump speed to keep the Assistance at the predefined level. The LVAD amplifies the remaining physiological control loops and supports the native heart function. The controller optimally complements the native blood flow and pressure regulation by including a frequency domain descripition in the controller synthesis. The system is implemented using a dSPACE real time system with Abiomed Impella CP in an ovine animal model for acute myocardial infarction. A continuous measurement or estimation of pump flow and total cardiac output is then required. However, for the case that the control loops affecting the cardiac output are unimpaired, the Assistance control strategy can sufficiently maintain the systemic circulation. Therapies with targets such as recovery or weaning can be acheivable.

Funded by: German Federal Ministry of Research (BMBF)

Mechatronics in Rehabilitation

Robot-aided rehabilitation can be classified as an intelligent mechatronic system. In this work, three main aspects, namely mechanical design, electronics and patient-cooperative control strategies are of concern. The challenge of rehabilitation robot is to design a light-weight actuator for wearing comfort. The development of a variable stiffness actuator (VSA) is carried out and integrated into robot-aided rehabilitation. The benefit of this subsystem is to adjust the stiffness automatically in order to interact with an unknown dynamical environment.

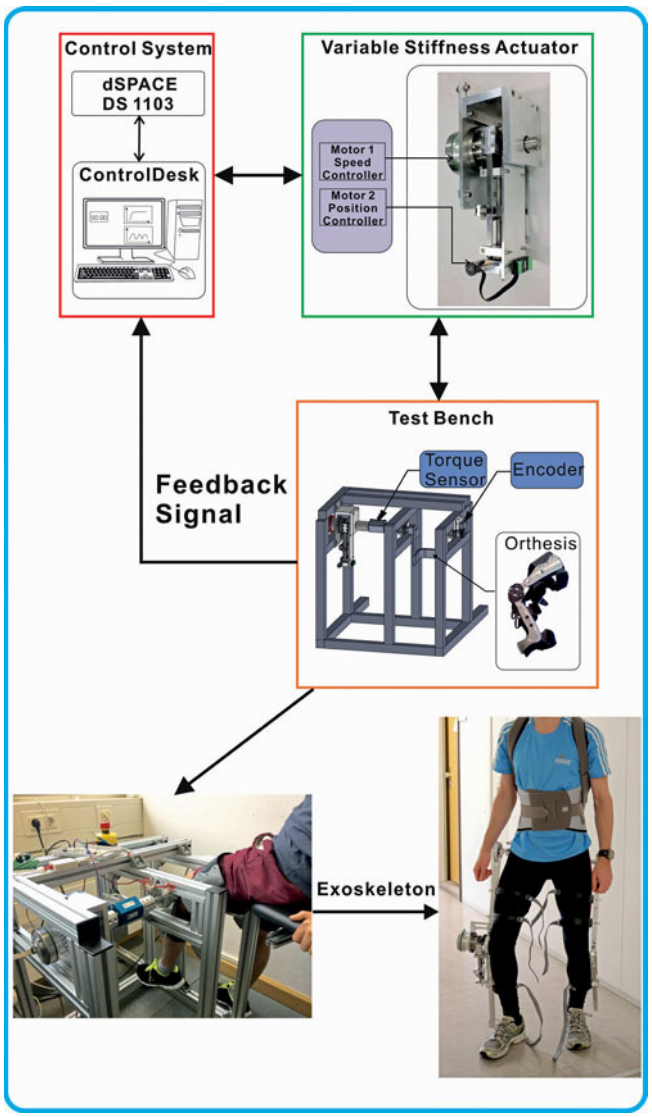

Fig. 7: Mechatronics in rehabilitation.

Moreover, a control strategy should be designed to avoid possible oscillations, which might occur, due to the time-varying stiffness coefficient. Hence, different control methods such as robust and gain-scheduling controller were investigated to ensure good stability margins and tracking performance. To enable a patient-cooperative control, bio-feedback information is required during the training process. In this scope, movement support is tested by human-in-the-loop configuration as an active part in the loop.

The testing environment is depicted in Fig. 7, where a one degree-of-freedom (DOF) knee orthosis is designed to realize similar test condition compared to a swing phase during a healthy gait-cycle. In addition, we can use the observable joint torque to tune the controller gains and change the actuator stiffness in real time. Thereby, a control of human movement effort during training can be achieved, whilst simultaneously saving the power of actuator in order to track the stiffness variation. Further research works will include bio-feedback based trajectory estimation and exoskeleton with treadmill training.

Funded by: Chinese Scholarship Council (CSC)

Sectoral Bioimpedance Spectroscopy

The early detection of lung pathologies such as pneumonia or pulmonary edema is of great importance for the outcome of the patient, especially in ventilated patients. Currently, a combination of x-ray and blood gas analysis is used to detect such pathologies. However, these technologies have two major disadvantages as they do not provide continuous results and potentially harm the patient. Thus, the goal of this project is to use bioimpedance spectroscopy (BIS) in order to detect pathologies in local sectors of the lung. BIS measurements are principally performed by injecting a small current (with a compliance to the safety standard) into the body and measuring the resulting impedance in a frequency range from 1 kHz to 1 MHz. Typically, transthoracic or hand-to-hand electrode configurations are used that do not provide any local information. In order to find electrode positions that allow a regional lung monitoring, a complex simulation study was intensively performed. For this, a finite-element model as shown in Fig. 8 was used and the effect of electrode positions on the acquired impedance data was analyzed. The sensitivity of BIS measurements can be focused to desired lung regions using both external and internal electrodes, which can be for example integrated in breathing tubes (Fig. 8). Our preliminary results indicate that the electrical properties of healthy and pathological lung differ. Thus, we expect to be able to detect lung pathologies from BIS data.

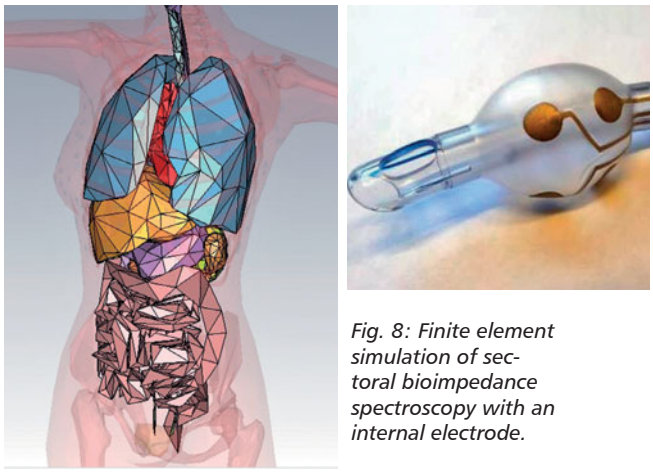

Fig. 8: Finite element simulation of sectoral bioimpedance spectroscopy with an internal electrode.

Funded by: German Research Foundation (DFG)

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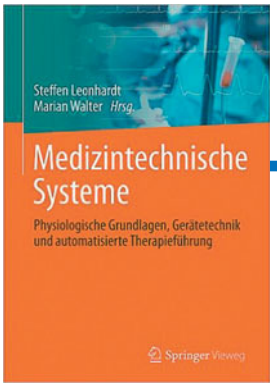
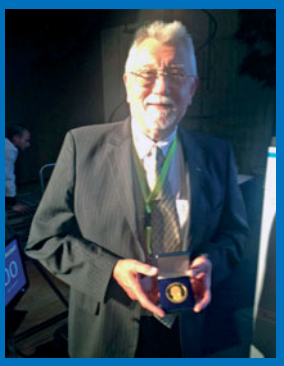


Prizes and Awards

- S. Leonhardt: appointed "Distinguished Lecturer" of the IEEE "Enginieering in Medicine and Biology Society (EMBS)", term 2015-2016.
- P. Vetter won 1st Poster-Award whilst X. Yu & C. Pereira and C. Castelar shared 2nd Poster-Award in session "Biomedical Engineering" at POSTER 2016, Prague.
- I. Elixmann: Aschoff-Prize 2016 from Christoph Miethke GmbH & Co. KG and Aesculap AG, Germany.
- V. Blazek: Erich Krieg Medal from the German Society of Phlebology, Dresden, Germany.
- A. Böhm, X. Yu and W. Neu (Multichannel ECG-T-Shirt) and S. Weyer and F. Weishaupt (RheoDetect) were the Top 21 participants at Texas Instruments Innovation Challenge (TIIC) – Europe Design Contest.
- C. Hoog Antink: 1st Prize for patient safety 2016 from DGBMT, Germany.
- B. Venema and D. Teichmann: Borchers Plakette 2016 from ProRWTH.
- S. Leonhardt: invited guest professor as part of the Global Initiative of Academic Networks (GIAN) program, Indian Institute of Technology (IIT) Madras, India.

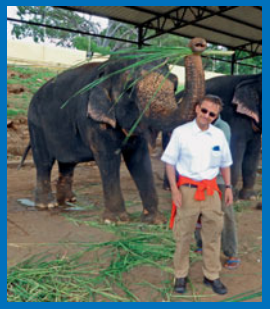
People at MedIT









Lehr- und Forschungsgebiet Biomaterialien

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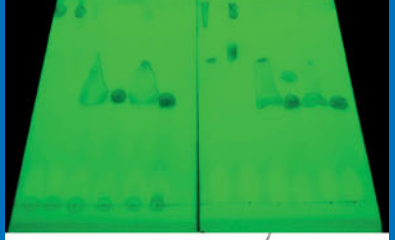

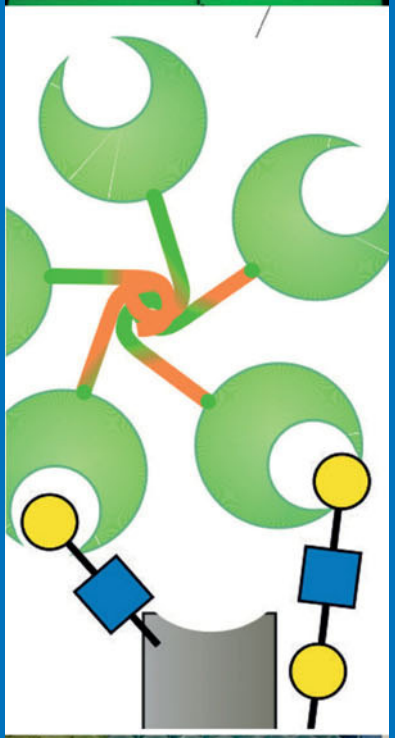

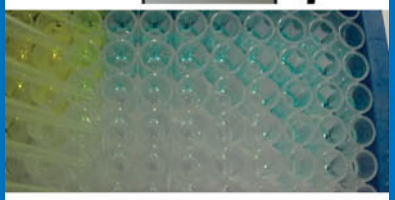

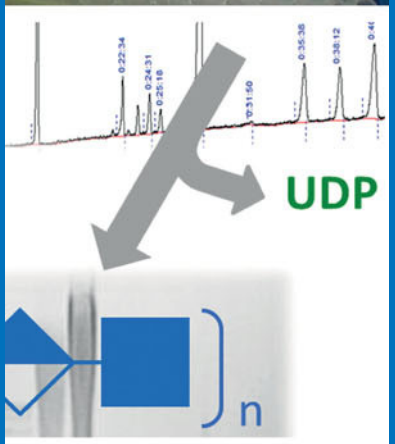

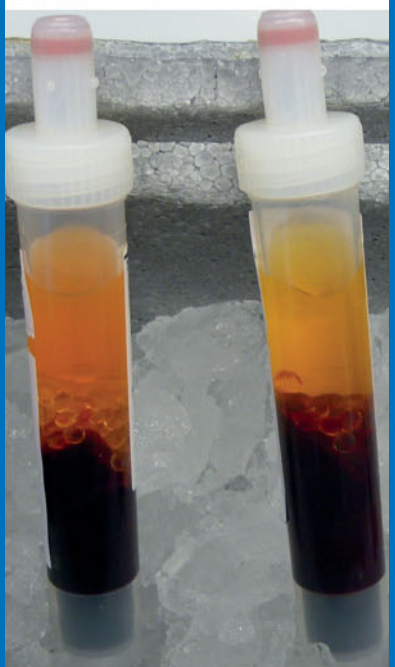

Introduction

Glycans, saccharides, sugars or carbohydrates are all designations for one and the most versatile biomolecule class. They appear as mono-, oligo or polysaccharides and fulfill a myriad of functions in all domains of life. Among their roles as energy source and structural elements they most importantly serve as information carriers in cell-cell communication. Cells and extracellular proteins are covered with distinct glycan structures which depend on e.g. the cell type and differentiation state. The presented sugars are recognized by special proteins (lectins) which can appear in free form or on the surface of other cells. These carbohydrate-lectin interactions trigger cell-signaling cascades and mediate numerous events like cell-adhesion, -migration or pathogen binding.
Novel functionalized biomaterials or therapeutics increasingly need to be modified with glycans to mimic an extracellular environment or to imitate their natural state. For this reason our working group has specialized in the synthesis of glycans by "combinatorial biocatalysis" and their application to build up a "Glyco-Biointerface". Thereby, a constantly growing toolbox of recombinant enzymes is applied for the *in vitro* synthesis of nucleotide sugars (the activated form of monosaccharides), glycans and (neo-)glycoconjugates. A high-throughput analytical technique allows a fast and thorough optimization of enzymatic reactions. Recombinant lectins, especially galectins, are produced in native or modified form and tested for interactions with the synthesized sugars in order to e.g. identify galectin inhibitors. Finally, interdisciplinary work with polymer chemists and engineers allows the immobilization of sugars in microgels and the synthesis of glycopolymers on biosensor surfaces. These glycofunctionalized materials serve to study and exploit carbohydrate-lectin interactions.

Combinatorial Biocatalysis

a. The Golgi Glycan Factory (GGF)

For biomedical applications and research, glycan structures are very promising targets. For instance, they can affect the biocompatibility of implants or the effectiveness of vaccines and anti-tumor drugs. Thereby, a rising need for efficient large scale production is implicated to provide these target structures. Due to a high stereo- and regioselectivity, Leloir-glycosyltransferases are used as common biocatalysts for the synthesis of complex glycan structures. However, their requirement of expensive and partly poorly available nucleotide sugars as precursors is frequently mentioned as an obstacle, especially for large scale syntheses. The usage of multi-enzyme cascade reactions can solve this bottleneck by starting from cheap and renewable substrates (Fig. 1).

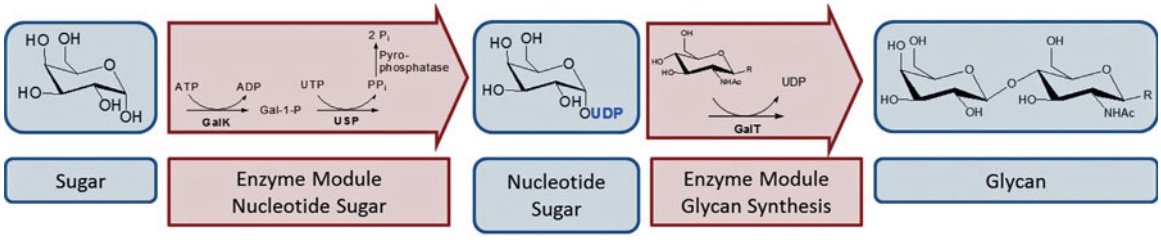

Fig. 1: Reaction scheme of a multi-enzyme cascade reaction for the glycan synthesis.

To avoid inhibitory effects and achieve high product yields, broad data sets of the involved biocatalysts must be available. Within the "Golgi Glycan Factory" project, the multiplexed capillary electrophoresis (MP-CE) was developed and established as an analytical platform technology for the high-throughput screening of reaction parameters (Fig. 2). Optimized parameters for enzyme modules allows the synthesis of various nucleotide sugars, e.g. UDP-α-d-glucuronic acid (UDP-GlcA) and UDP-α-d-galactose (UDP-Gal), leads to high space-time-yields and makes the large scale productions feasible.

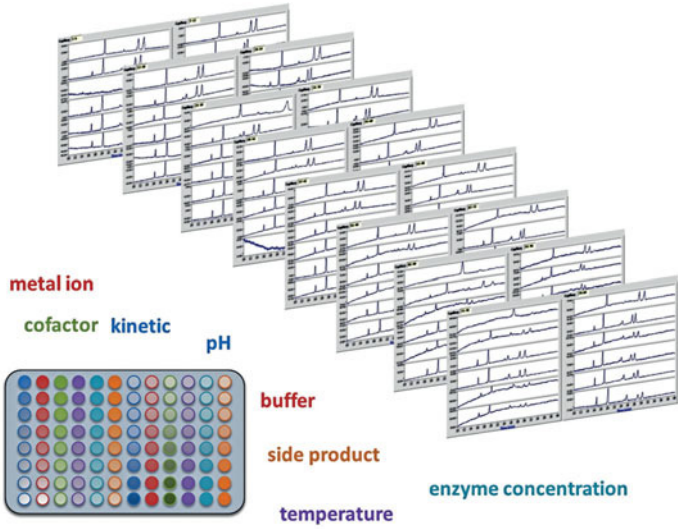

Fig. 2: Multiplexed capillary electrophoresis (MP-CE) as an analytical platform technology for the high-throughput parameter screening of enzymatic reactions.

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b. Enzymatic Synthesis of Hyaluronic Acid Polymer

Hyaluronic acid (HA) is a long-chain sugar polymer produced by vertebrates and some pathogenic bacteria. It consists of the alternating monosaccharides GlcA and GlcNAc. The enzyme responsible for the polymerization from its nucleotide sugar precursors UDP-GlcA and UDP-GlcNAc is the plasma membrane associated HA synthase.
The non-immunogenic HA is a favorable biomaterial and is widely used in medicine, cosmetics and food industry. HA is mainly obtained by either streptococcal fermentation or by extraction from rooster combs. Two characteristics determine the quality of commercial HA: its molecular weight and polydispersity. However, the regulation of both parameters is still a challenge.
We developed a novel multi-enzyme system for the synthesis of HA with *in situ* production and regeneration of expensive UDP-sugars from cheap and sustainable substrates. Our novel reaction analysis approach is based on a combination of methods including multiplexed capillary electrophoresis. It allows for the first time to take into account not only the HA product but also the UDP-sugar substrates and the UDP coproduct. Thus, our system provides new insights into the regulation mechanisms of HA synthases and serves as model for the metabolic engineering of a potential HA producing microorganism.

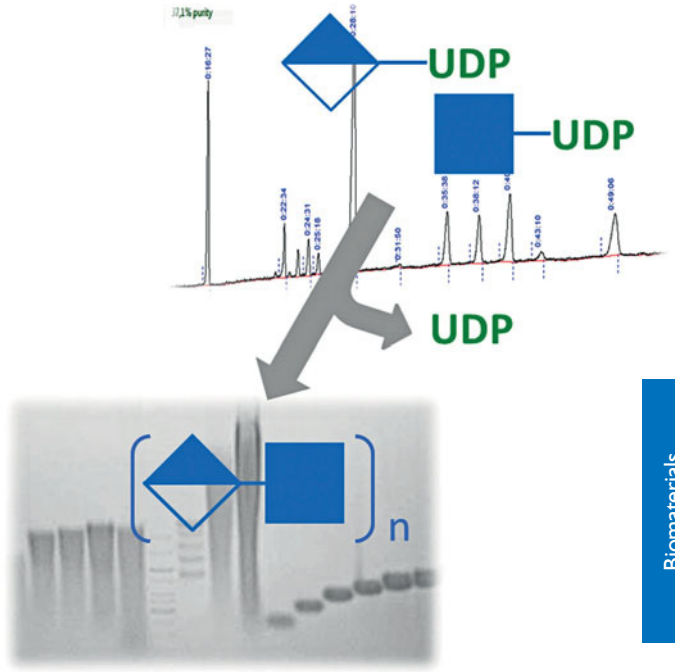

Fig. 3: Combined reaction monitoring of the enzymatic in vitro hyaluronic acid synthesis including MP-CE measurement of nucleotide sugars and agarose gel electrophoresis analysis of the HA polymer (diamond: GlcA, square: GlcNAc).

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c. Microwave-Assisted Synthesis of Glycoconjugates

Microwave irradiation (MWI) has been demonstrated to be beneficial for synthetic chemical reactions resulting in reduction of waste and reaction time. In biocatalysis, MWI has been employed in transglycosylation reactions of glycosidases, with beneficial activity and selectivity.

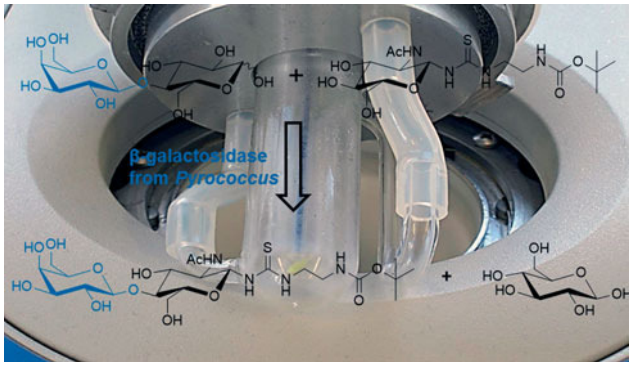

Fig. 4: MWI assisted enzymatic synthesis of glycoconjugates with a hyperthermophilic glycosidase.

We report for the first time on microwave-assisted transglycosylation reactions with a hyperthermophilic glycosidase from *Pyrococcus*. With MWI reactions at temperatures far below the temperature optimum (85 °C) of the glycosidase gave higher product yields and minor amounts of side products. MWI is useful as a novel experimental set-up for the synthesis of defined glycoconjugates. Glycosylation reactions under MWI at low temperatures are in general favorable for higher regioselectivity using heat-labile substrates.

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Selected Reference

Henze, M., Merker, D. and Elling, L.: Microwave-Assisted Synthesis of Glycoconjugates by Transgalactosylation with Recombinant Thermostable β-Glycosidase from *Pyrococcus*. International Journal of Molecular Sciences, 2016, 17, 210-221. doi:10.3390/ijms17020210

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The Glyco-BioInterface

a. Screening for Natural Galectin Ligands

Lectins are ubiquitously distributed carbohydrate binding proteins. Members of the galectin subfamily are specialized in recognition of β-galactose providing sugars. As essential part of glycosylated macromolecules found in the extracellular space, *N*-acetyllactosamine (LacNAc) was identified as major interaction partner of galectins. Thus, there is no doubt that galectins fulfill important functions with regard to cellular communication and cell-matrix interaction. During the last decades, scientists have also gained deeper insights into the involvement of galectins into the pathophysiological role of galectins, e.g. tumor development, progression and spreading. Galectin-3 (Gal-3) is one of the most extensively studied galectins as it is a promising drug target and considered as cancer biomarker (Fig. 5).
Our aim is the synthesis of extended β-galactoside sugars with high amounts of LacNAc or derivatives and their evaluation as Gal-3 ligands. Various eukaryotic, bacterial as well as parasitic glycosylation motifs represent promising candidates for generation of selective Gal-3 ligands of high affinity. For this purpose, we use selected recombinant glycosyltransferases, known as sugar transferring enzymes. Enzyme production is carried out by large scale cultivation of genetically manipulated microbial host strains (e.g. *Escherichia coli*). After purification (e.g. affinity chromatography), valuable catalysts can be applied for (chemo-)enzymatic syntheses. The ultimate goal with regard to *in vitro* sugar assembly would be the generation of glycans related to those found on erythrocytes (I-antigens), which comprise a linear poly-LacNAc

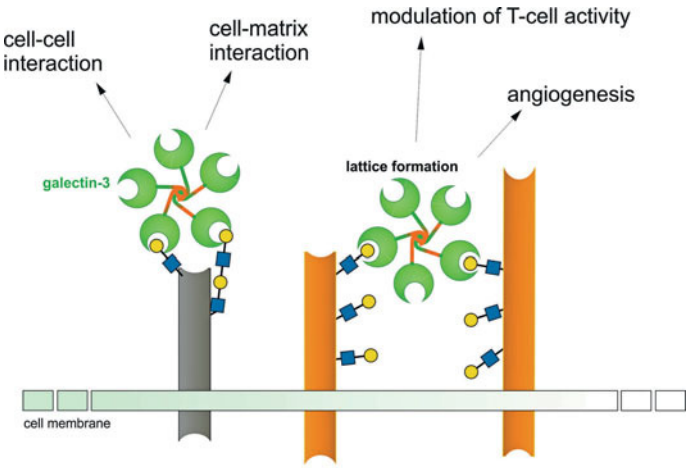


Fig. 5. Multimeric Gal-3 as important molecule in the extracellular space.

chain with certain branches of (poly-)LacNAc. I-antigens or related compounds offer multiple galectin interaction sites in close proximity that may lead to an augmented binding strength of Gal-3. Terminal glycosylation motifs may further be enzymatically modified for individual needs.
Whenever a biomedical application is aimed for, a preferably nature-approximated environment must be generated. On the cell surface and throughout the extracellular space, glycan moieties are present in a multivalent mode. For this reason, so called glycomimetics on the base of neo-glycoproteins (Fig. 6) were synthesized to raise the galectin affinity many hundred fold. Non-glycosylated serum proteins serve as natural scaffold for the attachment of glycan moieties by amidation of selected amino acids (lysine residue). Multivalent neo-glycoproteins can be utilized as selective Gal-3 inhibitors and as theranostic tools for cancer-related biomedical research.

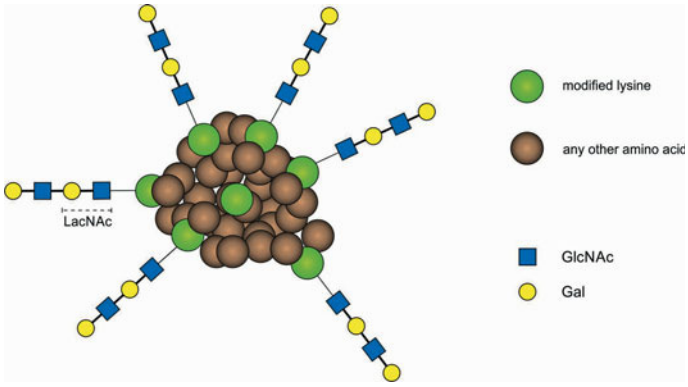
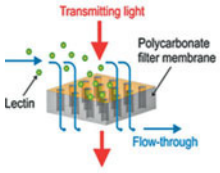


Fig. 6. Artificial glycosylation of protein scaffolds result in a multivalent neo-glycoprotein.

A different approach focuses on modified galectin proteins applicable as instruments for drug delivery or imaging purposes in tumor therapy and diagnostics. By recombinant DNA-technology, Gal-3 protein sequence was either fused to protein-tag (SNAP), or a fluorescence protein (e.g. YFP) or both artificial add-ons. In total, fifteen different Gal-3 constructs were successfully produced in appropriate bacterial host strains and efficiently purified using affinity chromatography. In some cases, binding properties of truncated Gal-3 variants could be improved and identified to be comparable to full-length Gal-3. To conclude, the synthesized fusion proteins represent biotechnologically engineered and sophisticated tools for biomedical research.



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Böcker, S. and Elling L.: Binding characteristics of galectin-3 fusion proteins. Glycobiology, 2017. doi: 10.1093/glycob/cwx007.

Financial Support

DFG project (EL 135/1-12): Modified multivalent poly-*N*-acetyllactosamine glycans as novel ligands of human galectin-3.

b. Glycopolymer Brushes and Biosensors

The affinity of lectins towards glycan ligands is enhanced in orders of magnitude by multivalent presentation of glycans which is called the "cluster glycosidic effect". Thus, the understanding of protein-carbohydrate interactions requires a platform providing multivalent ligand presentation.
In collaboration with the DWI Leibniz-Institute for Interactive Materials, glycopolymer brushes were prepared by surface-initiated atom transfer radical polymerization (SI-ATRP) grafted from a silicon surface as multivalent platform in combination with enzymatic glycan synthesis which allow the investigation of specific lectin-glycan cross-talk. Based on this, biosensor chips were developed allowing the investigation of lectin-carbohydrate binding. In cooperation with the Institute of Materials in Electrical Engineering I and the DWI-Leibniz-Institute for Interactive Materials, glycopolymer brushes of different lengths grafted from a gold biosensor were developed. Lectin binding was analyzed with electrochemical impedance spectroscopy (EIS) enabling the analysis of topology-dependent lectin binding to glycans. Glycopolymer brushes were also built up on a local surface plasmon resonance (LSPR) biosensor enabling a label-free kinetic analysis of lectin binding in a flow-through configuration (Fig. 7). The LSPR biosensor enabled the determination of kinetic parameters of TcdA-R (*Clostridium difficile* Toxin A) binding to the Galili glycosylation motif in a multivalent environment for the first time.

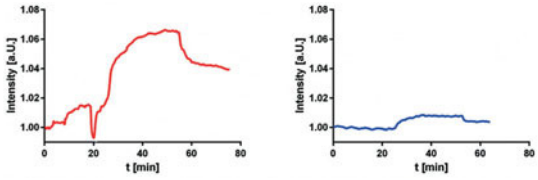

Fig. 7: LSPR biosensor setup and sensorgrams for binding of TcdA-R to Galili presenting brushes and GlcNAc presenting brushes as negative control (PhD thesis R.R. Rosencrantz).

Our work with the DWI-Leibniz-Institute for Interactive Materials, the Institute of Physical Chemistry (RWTH Aachen) and the Fraunhofer Institute for Applied Polymer Research (University of Potsdam) resulted in the synthesis of self-assembling glycopolymer micelles which were utilized as sugar binding scaffolds. These micelles are synthesized from

double-hydrophilic diblock copolymers enabling the analysis of lectin binding in a multivalent manner by two-focus fluorescence correlation spectroscopy (2fFCS) with high IC_{50} values (Fig. 8).
In cooperation with the Institute of Materials in Electrical Engineering I a novel flow-through biosensor was developed for analyzing biomolecular interactions by simultaneous use of EIS and LSPR. This biosensor enables ELISA-type assays and SPR measurements in one single experiment. Due to the different origin of the EIS- and LSPR-signals, information about the binding of lectins like GS-II under flow and static conditions were provided (Fig. 9).

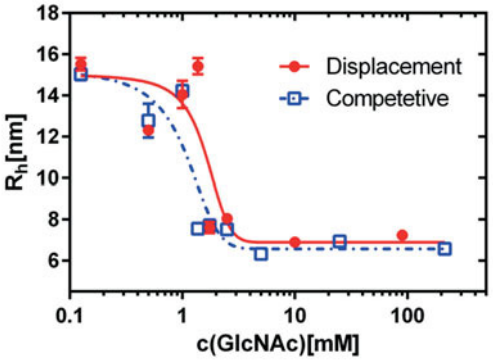

Fig. 8: Inhibition of the binding of the lectin GS-II to GlcNAc glycopolymer-micelles via displacement and competition (PhD thesis R.R. Rosencrantz).

In 2016, a further collaboration with the DWI Leibniz Institute and the Clinic of Gastroenterology (University Hospital RWTH Aachen) was started within the SFB 985. In this interdisciplinary project, glyco-functionalized microgels are developed to capture the enterotoxins TcdA and TcdB from the intestinal bacterium *Clostridium difficile*. The effectivity of these toxin scavengers will be tested in a mouse model.

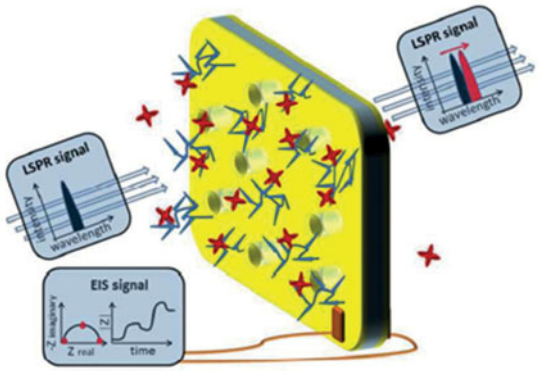

Fig. 9: Double-side gold-coated perforated microfluidic biosensor for analyzing biomolecular interactions with EIS and LSPR under flow and static conditions. Reprinted with permission from Anal. Chem. 2016, 88, 9590-9596. Copyright 2016. American Chemical Society.

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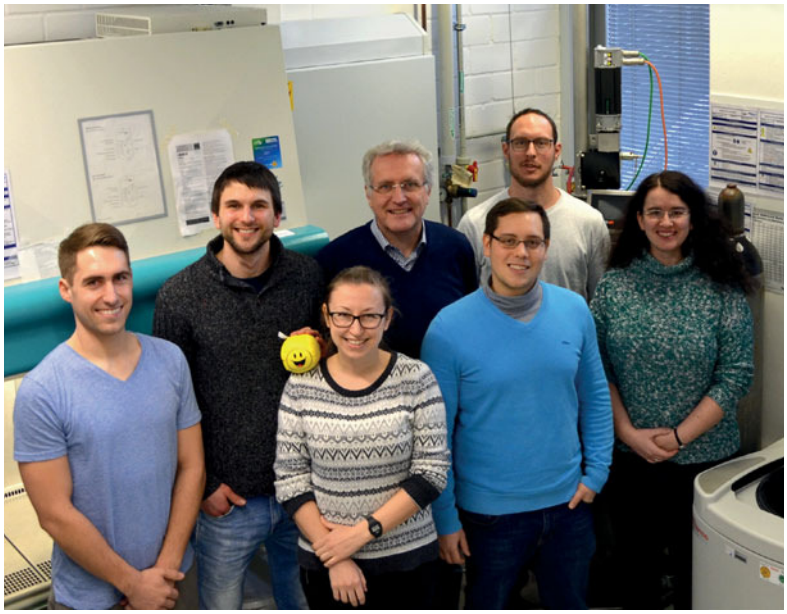

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DFG in the framework of the SFB 985

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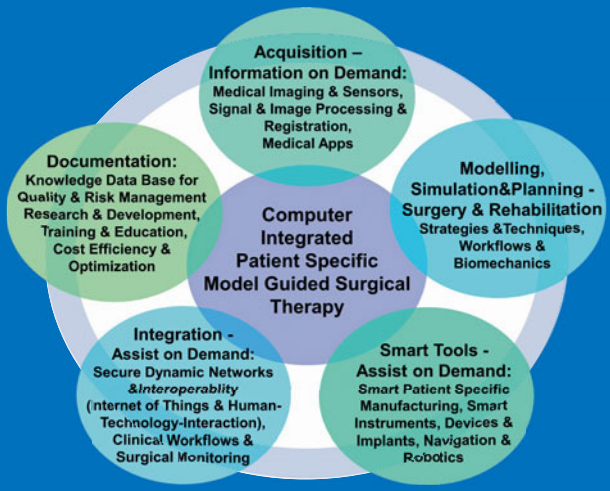

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Introduction

The main objective of our research activities is the development of new approaches for efficient and smart health care. In cooperative projects with national and international partners from clinics, research and industry, the topics range from basic research to application oriented developments with the aim to find, validate and transfer new solutions for clinical applications. However, in many cases technical solutions remain worthless in a clinical context without an in-depth understanding of related boundary conditions, requirements, clinical processes and workflows. Therefore, one major focus is the optimization of clinical usability of complex human-technology systems by efficient integrated risk management and usability engineering methods.

Actual trends towards personalized medicine (including e.g. biomechanical modelling and patient specific implants) are based on modern technologies such as 3D-imaging or sensor technologies, image processing and statistical morphological and functional modelling as well as additive manufacturing technologies ("3D-printing"). The numbers and complexity of technical components, e.g. in the operating room, are rapidly increasing, which requires the integration of smart communication concepts and technologies as well as open medical networks ("internet of things").

In this context, our activities cover a wide range of topics from feasibility studies to usability testing and clinical trials e.g. in orthopedics, traumatology, neurosurgery, general surgery, interventional radiology and cardiology in close cooperation with academic, clinical and industrial partners. Current projects range from the acquisition, segmentation and reconstruction of relevant information, its registration and integration for patient specific modelling and simulation, to adequate technical (software or mechatronic) means for model guided therapy.
In 2016, the OR.NET project on secure dynamic integration of modular OR-systems, a flagship project of the German Ministry for Education and Research (BMBF) has been officially concluded successfully with a symposium and demonstrator presentation at the conhIT 2016 trade fair and conference in Berlin. At the same time, continuity and sustainability of the OR.NET project has been assured by the successful acquisition of follow-up project grants as well as by the foundation of charitable OR.NET association by partners of the OR.NET project from industry, clinics and research.

Based on the results of our initial BMBF project IDA (Medical Technology Innovation Award 2008 of the BMBF), members of the mediTEC team founded the Whitesonics GmbH (www.whitesonic.com) and received substantial funding of the Federal Ministry of Economic Affairs and Energy (BMWi) and the High-Tech Gründerfonds (HTGF) for the transfer of our basic research and development of a dental ultrasound microscanner to its clinical application.
Additionally, various projects related to basic research issues (e.g. funded by the German Research Foundation (DFG)) as well as industrial co-operations in different focus areas have been continued or started by our team. International cooperations, publications of our research, the market applications of products originally developed in our lab as well as international patent applications continuously confirm our general concept of combining basic as well as problem oriented medical engineering research and application development. Last but not least, this also provides a sound basis for the education of our students.

Fig. 1: mediTEC-team members engaged in workshops, field trips and public hands-on demonstrations.

We contribute to bachelor and master programs of different faculties of the RWTH Aachen University, including the coordination of the master program for general mechanical engineering of the Faculty of Mechanical Engineering. Apart from these educational programs and internships we offer field trips and hands-on workshops to get young pupils, students and future researchers hooked on the fascinating field of medical engineering (Figure 1).
The tight connection between actual research topics and the theoretical as well as practical education of our students from different disciplines and specialities is an essential basis for the success of our alumni in their international industrial as well as academic careers.

Selected Projects

Modelling and Analysis of Shoulder Biomechanics

Understanding biomechanics of the shoulder is essential to cope with current shoulder problems. To investigate shoulder biomechanics we developed an ex-vivo shoulder-simulator. Our shoulder simulator comes with an innovative "teach-in" function which allows us to investigate the behaviour of the shoulder in any assigned free spatial movement without the need of EMG data or external input. Moreover, the simulator allows us to conduct parameter studies and evaluation of various shoulder implant designs which shows very promising results. The experimental results are also useful in the multi-body in-silico simulations for shoulder model verification or analysis. This could lead to a better understanding of the shoulder behaviour and related innovative implant concepts.

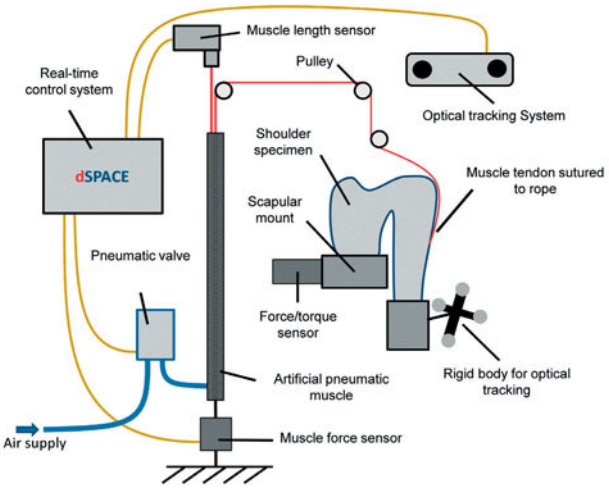

Fig.2: Simplified schematic of the shoulder simulator.

Patient-specific Safe Zone in THA

In total hip arthroplasty procedures, standard values are often used for component positioning and orientation alignment. Despite high success rates, complications such as dislocations, wear and loosening still occur. They could be reduced by considering patient-specific parameters. In this project, a planning procedure based on the definition of a so-called patient-specific safe zone will be developed. This includes the consideration of anatomical as well as functional parameters such as the required range of motion and resulting hip forces. Furthermore, concepts for integrating this process into the clinical workflow will be developed and analysed.

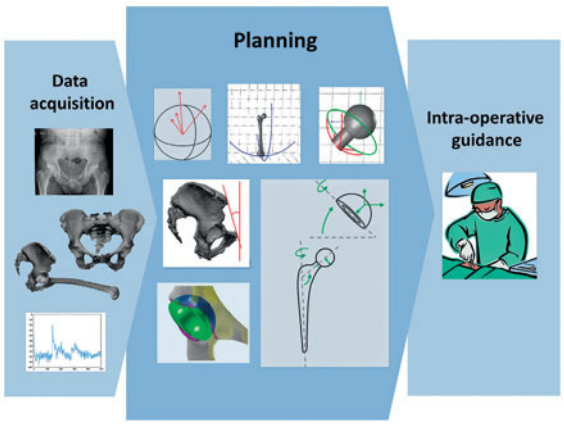

Fig. 3: Clinical workflow of optimized patient-specific planning of THA.

Simulation of the Craniospinal Fluid Mechanics

The craniospinal fluid (CSF) system is a very complex part of the nervous system and until today its dynamics is not fully understood. Since flow and pressure measurements in the brain ventricles or the subarachnoid space are highly invasive, it is inevitable to simulate the biomechanics of the fluid system in the context of parameter studies and developments of innovative implant solutions. Using simulation tools, such as MATLAB Simulink or COMSOL Multiphysics®, enables us to reproduce the CSF dynamics including the significant mechanisms: compliance, vascular pulsation, CSF production and absorption. The gained knowledge about the CSF system can be used to find alternative therapies for treating e.g. normal pressure Hydrocephalus.

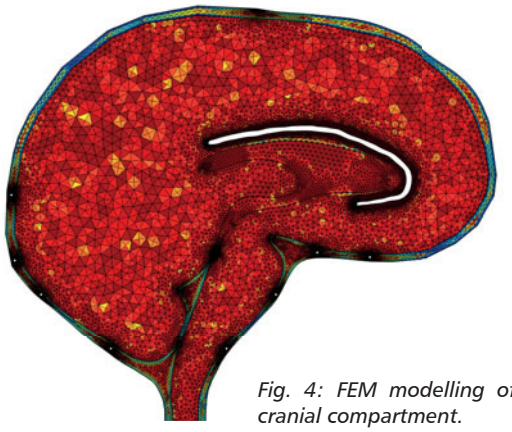

Fig. 4: FEM modelling of the cranial compartment.

Parametrization of the Pelvis for Morpho-functional Analysis

Total hip arthroplasty is the most frequently performed artificial joint replacement in the human body. During the planning phase it is necessary to identify anatomical parameters and landmarks to take the individual anatomy and biomechanics of the patient into account. A manual identification requires medical knowledge, is time-consuming and error-prone. Therefore, a robust, automatic detection process is preferable and was developed to determine patient specific parameters and landmarks of the pelvic bone. This is the basis for sensitivity analysis regarding the correlation of morphologic and functional parameters.

Fig. 5: Automatic alignment, landmark detection and acetabular analysis of a patient specific surface model of the pelvis.

3D-US imaging of the Knee

There are numerous applications like biomechanical simulations or implant design and planning that need patient specific bone surface information. This information is mostly extracted from CT data associated with ionizing radiation. Alternatives such as MRI are expensive or suffer from distortions. Therefore, ultrasound is investigated as an alternative imaging modality. It has a high resolution, is cheap, and it is widely available. Its drawbacks, however, are a small field of view, acoustic shadowing, and a low signal-to-noise ratio. Thus, established segmentation algorithms do not work and new algorithms must be developed.

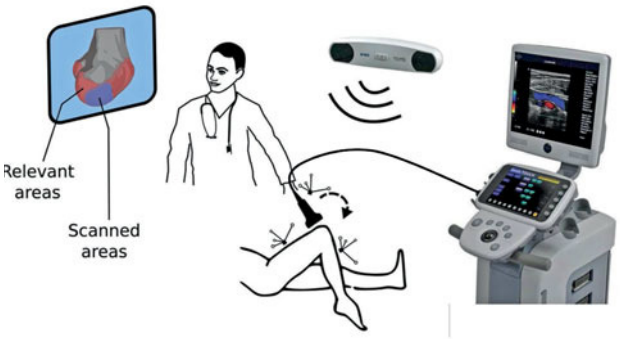

Fig. 6: A clinician records 3D ultrasound data from the knee. The probe, as well as the upper and lower leg are tracked.

We develop methods that allow clinicians to scan the knee from various sides using a 3D ultrasound probe. The probe is tracked as well as the upper and lower leg. A statistical shape model trained from semi-automatically segmented CT data is used to adapt to all ultrasound images. The entire information is combined to reconstruct the bone surfaces. Current in-silico and in-vitro investigations are very promising and yield reconstructions that deviate only in the sub-millimetre range from the real geometry.

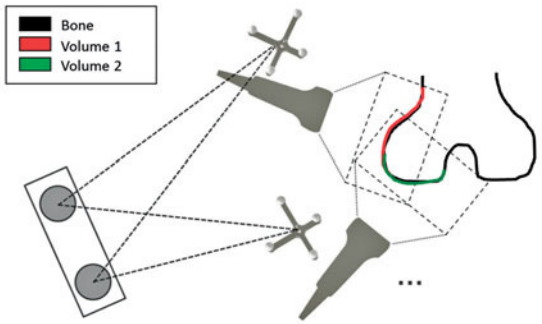

Fig. 7: Various parts of the bone are recorded with a 3D ultrasound probe from different perspectives. The probe is tracked as well as the bone.

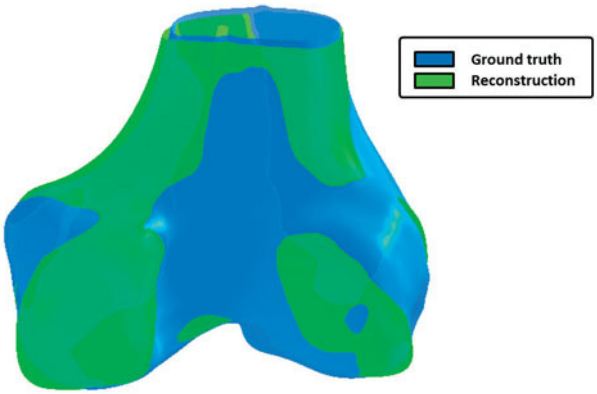

Fig. 8: The reconstruction of the femoral bone surface.

Enhanced Skin Regeneration by Shockwaves

Shockwaves are high intensity focused acoustic waves with a high bandwidth from about 100 kHz to 100 MHz. They are used in medicine for the treatment of several indications like the disintegration of kidney stones, bone growth stimulation for non-unions and skin regeneration, especially for diabetic ulcers. As the effective mechanisms are yet not well understood, and shockwave treatment effectiveness for some indications is not proven, most indications are still under investigation.

Together with the Department of Dermatology and Allergology (RWTH Aachen University Hospital) we investigate skin regeneration in-vitro. We use a 3D model which consists of dermis and epidermis as well as the main dermal cell types. Thereby, it represents a functional model of the skin with a realistic geometry and wound healing process. The 3D model is wounded, then treated with shockwaves and afterwards the histology and gene expression are investigated.

For undisturbed and reproducible sound propagation towards the cells, we developed an experimental setup. It consists of the 3D skin model which is submerged in cell culture fluid. A silicone insert was build, which fits on the cell model and ensures the constant positioning of the focal point on the cells. Thereby, we achieve a reproducible sound field reaching the cells, which gives us the possibility to correlate our sound field measurements with the biological results.

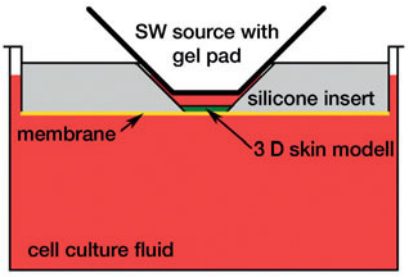

Fig. 9: Experimental setup.

SICOSI – Smart Impedance Controlled Osteotomy Instrumentation

Cutting of bone tissue (osteotomy) is a frequently performed surgical procedure which often carries the risk of damaging sensitive soft tissue underneath the bone. Especially the craniotomy and re-sternotomy, which are standard surgical procedures to enable access to intra-cranial or intra-thoracic structures respectively, carry a high risk of causing serious damage on the vessels and meninges which leads to worse surgical outcomes. Within the SICOSI project (funded by the German Research Association (DFG)) the feasibility of a novel hand guided, sensor integrated instrument for craniotomies is investigated. To achieve better cutting results the concept is based on a thin ceramic sawing blade equipped with electric conductors to perform a live bioimpedance spectroscopy of the treated bone during the operation to determine the minimum required sawing depth. Results of simulations and first laboratory trials suggest that the use of bioimpedance measurements is practicable to build a system which automatically adjusts to the minimum sawing depth during the operation without the need for any additional imaging or external sensor information

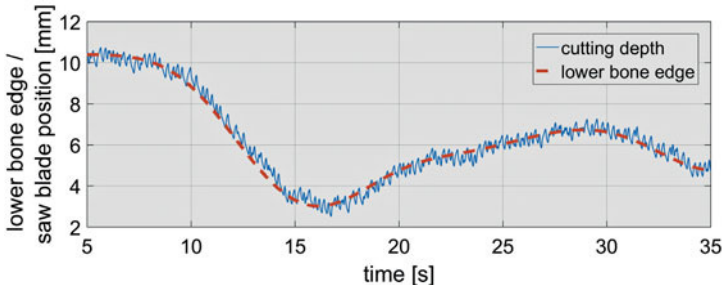

Fig. 10: HiL simulation for cutting with bipolar saw blade.

Open Medical Devices and IT-System Networks in OR and Clinic

The coordination and conduction of the OR.NET project on the open integration of OR-systems, a flagship project of the Federal Ministry for Education and Research (BMBF) with an overall budget of 18,5 M EUR (2012-2016) and finally more than 100 project partners from industry, research, clinics and associations has been a major challenge in the last 4 years. The overall concepts for integrated OR-systems is based on the open communication standard IEEE 11073 and further established standards. The extended medical device and service profile developed in OR.NET complement the standardization activities in the OR.NET project especially regarding the ISO 11073 extensions for the data model and especially for safety aspects of medical device communications. Medical Device User Interface Profiles (MDUIP) have been developed in order to extend the technical device profile, enabling an automatic optimized selection and composition of various user interfaces and an integrated human risk analysis in terms of quality assurance in human-machine interaction.
On this basis we developed a surgical workstation with an integrated graphical user interface including numerous device panels (e.g. 3D X-ray C-arm, OR-table, high-frequency cutting devices, endoscopic devices and ultrasound-cutting device). In conventional operating rooms, e.g. in neurosurgery, up to 10 foot switches are used to operate different devices. Unintentional displacement or confusion of footswitches may cause serious adverse events. In contrast, the OR.NET demonstrator system includes a universal footswitch optionally integrated onto a motorized positioning platform for the surgeon. Usability evaluations in cooperation with industrial and clinical partners showed very promising results.

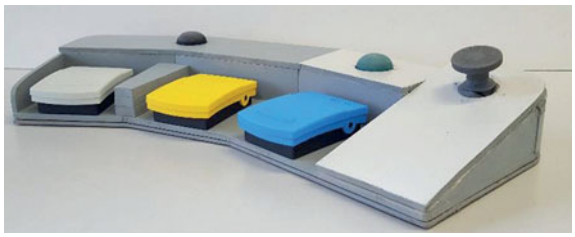

Fig. 11: Prototype of the Universal Footswitch.

Moreover, the integrated system enables direct access to clinical KIS and PACS systems. The alarm concept and surgical workflow navigation provide the OR team with valuable information, surgical checklists and surgical monitoring features.

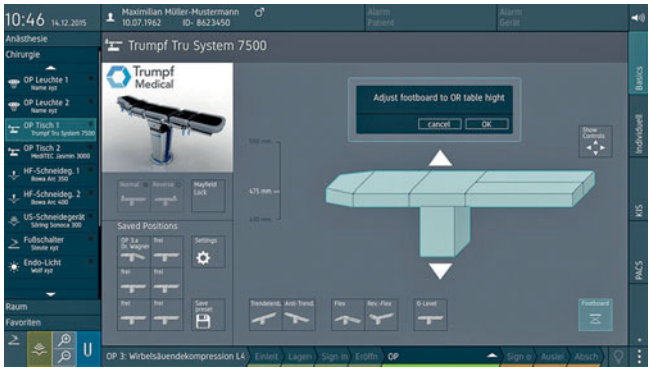

Fig. 12: Graphical user interface of surgical workstation.

The final OR.NET demonstrator system has been successfully presented on the conhIT (Connecting Health Care IT) conference and exhibition in April 2016 in Berlin. Together with OR.NET partners, sustainability of the project work and continuing research and development will be assured by the OR.NET association founded in March 2016 (for more information: www.ornet.org) and the follow-up project ZiMT funded by the European Regional Development Fund (EFRE) and the State of North-Rhine-Westphalia (NRW)

Fig. 13: OR.NET demonstrator on the conhIT exhibition 2016, Berlin.

SEBARES – Self balancing rescue aid

Annually in Germany 10 Million patients are transported by emergency services. In a great number of cases the patients have to be transported over stairs, which is associated with enormous physical effort for the paramedics and longer mission times. Currently available rescue aids are often unsuitable because of structural circumstances, lack of dynamism or insufficient compactness. Because of this in most of the cases the paramedics have to carry the patients' weight resulting in an increasing rate of work-related injuries and premature incapacity to work. In combination with an increasing rate of obese patients the transport is a rising problem for emergency services.
In the context of the project SEBARES a novel mechatronic rescue and transport aid is under development. An innovative self-balancing concept enables high mobility, compactness and speed for the transport of patients via staircases. Together with a compact patient chair and a docking interface in the ambulance a universal rescue and transport aid may help to speed up the transport and to re-duce the physical effort of paramedics, and there-fore improve the working conditions in emergency services.

Team

Acknowledgements

We would like to thank all our clinical, technical and industrial partners for the fruitful cooperation*.
Apart from basic funds and industrial cooperation, in 2016 our research has been substantially funded by:

- the German Federal Ministry of Education and Research (BMBF)
- the German Federal Ministry of Economic Affairs and Energy (BMWi)
- the German Research Foundation (DFG)
- the START program of the Medical Faculty of the RWTH Aachen University
- the European Union, the European Regional Development Fund (EFRE), the Ministry of Innovation, Science, Research and Technology and the Ministry of Economic Affairs North-Rhine-Westphalia
- ERS@RWTH Aachen

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.

Selected Publications

[1] J. Dell'Anna, A. Janß, H. Clusmann & K. Radermacher: A Configurable Footswitch Unit for the Open Networked Neurosurgical OR – Development, Evaluation and Future Perspectives. i-com, 2016, 15(3), pp. 227-247
[2] K. Dietz-Laursonn, R. Beckmann, S. Ginter, K. Radermacher & M. de la Fuente: In-vitro cell treatment with focused shockwaves—influence of the experimental setup on the sound field and biological reaction. Journal of Therapeutic Ultrasound, 2016, 4(10)
[3] J. Eschweiler, J.-P. Stromps, M.C.M. Fischer, F. Schick, B. Rath, N. Pallua & K. Radermacher: A biomechanical model of the wrist joint for patient-specific model guided surgical therapy: Part 2. Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, 2016, 230(4), pp. 326-334
[4] J. Eschweiler, J.-P. Stromps, M.C.M. Fischer, F. Schick, B. Rath, N. Pallua & K. Radermacher: Development of a biomechanical model of the wrist joint for patient-specific model guided surgical therapy planning: Part 1. Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, 2016, 230(4), pp. 310-325
[5] J. Hsu, M. de la Fuente & K. Radermacher: Determination of the mechanical axis of the femur using 3D-2D model to X-Ray registration. Bone Joint J, 2016, 98(SUPP 5), pp. 35-35
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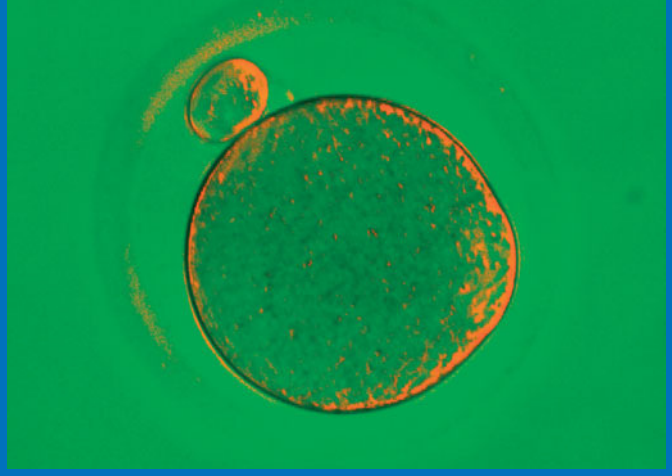
[10] M. Verjans, N. Siroros, J. Eschweiler & K. Radermacher: Technical concept and evaluation of a novel shoulder simulator with adaptive muscle force generation and free motion. Current Directions in Biomedical Engineering, Band 2, Heft 1 (Sep 2016), 2016, pp. 61-67

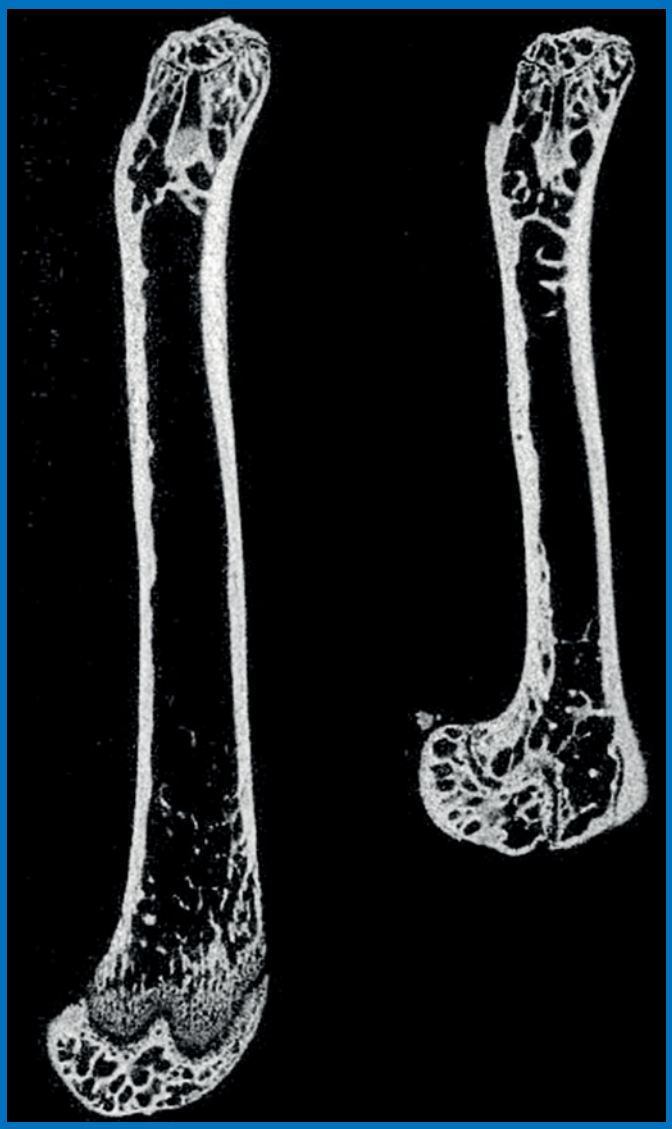
Biointerface Laboratory at Helmholtz-Institute for Biomedical Engineering

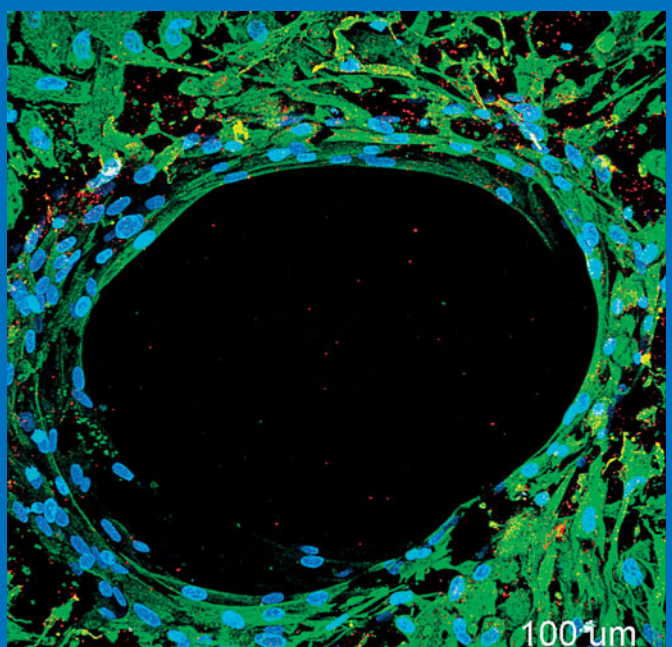
RWTH AACHEN UNIVERSITY

Faculty of Medicine

Cell-Material Interactions: Translating Basic Science Into Clinical Applications







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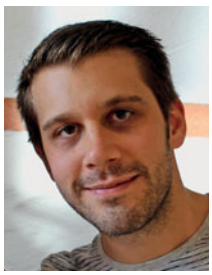
Introduction

This year marks the completion of Julia Floehr's and Laura Brylka's PhD work. They both earned their degrees with distinction. Congratulations! Enjoy their contributions to this report. Kathrin Olschok finished her Bachelor Thesis, Andrea Büscher, Sina Köppert, Eva Wölfel, and Clara Carvalho (Univ. Minho, Portugal) finished their Master Theses. Andrea and Sina continue their work with a PhD thesis, and will report in due course. At the end of the year, Eileen Dietzel moved with her family to the Karolinska Institute in Stockholm, Sweden to spend a post-Doc. We wish her well and many happy returns. Student teaching, graduate training, paper and grant writing is what keeps us busy throughout the year. We secured a training grant that will fund altogether 15 PhD students at University Hospital Aachen, University of Maastricht, The Netherlands, and at the Karolinska Institute, Stockholm, Sweden. Willi Jahnen-Dechent is local coordinator of the Marie Skłodowska Curie training grant IntriCARE that is funded under the Horizon 2020 program. Surely, we will all benefit from this training network. Let us start with a short update on a fruitful area of our lab, fertility research.

Fetuin-B Increases Artificial Fertilization Rate and Is a Target for Contraception

MSc Carlo Schmitz, Dr. Julia Floehr, Dr. Eileen Dietzel



Fetuin-B is a liver-derived serum protein, which diffuses freely from the blood into ovarian follicles[8]. Thus during the development of mammalian oocytes and after fertilization in the oviduct, Fetuin-B is present close to the oocyte. Fetuin-B is an inhibitor of the proteinase ovastacin rendering the *zona pellucida* (ZP), a layer of extracellular matrix surrounding the oocyte, in a hardened state due to proteolytic cleavage of ZP glycoproteins[6]. As a potent inhibitor of ovastacin Fetuin-B prevents premature ZP hardening before fertilization. Thus Fetuin-B keeps the ZP penetrable for sperm until fertilization and maintains female fertility. After fertilization the proteinase ovastacin mediates definitive ZP hardening. It prevents further sperm attachment and penetration, and protects the pre-implantation embryo.

To study Fetuin-B/ovastacin interaction *in vivo*, we generated mice that were deficient for both proteins[3]. While Fetuin-B single deficient female mice (*Fetub*$^{-/-}$) were infertile, due to premature ZP hardening, additional ovastacin deficiency (*Astl*$^{-/-}$) restored fertility (Fig. 1). *Fetub*$^{-/-}$, *Astl*$^{-/-}$ double deficient female mice were fertile. *Fetub*$^{-/-}$, *Astl*$^{-/-}$ females produced offspring, confirming ovastacin proteinase as a prime molecular target of Fetuin-B. Thus, in the absence of the target proteinase ovastacin, the lack of the regulating inhibitor is of no further consequence. The recovery of fertility in *Fetub*$^{-/-}$, *Astl*$^{-/-}$ females underscored the decisive role of Fetuin-B in fertilization, rendering Fetuin-B a potential target for contraception.

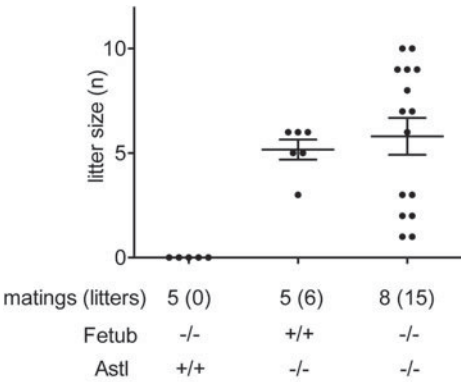


Fig. 1: Fetuin-B / ovastacin double deficiency restores fertility of fetuin B deficient female mice. *Mating study shows that Fetuin-B deficient females (Fetub−/−, Astl+/+) were infertile. Double deficient (Fetub−/−, Astl−/−) females had litters in a comparable size to ovastacin single deficient (Fetub+/+, Astl−/−) females.*

Classical hormone-mediated contraception has intrinsic disadvantages despite proven success and worldwide application in human and animal medicine. Nevertheless, there is an urgent need for contraception to reduce the high number of unintended pregnancies noted in the USA (50%) and worldwide (40%). Contraception should prevent pregnancies, be reversible and well tolerated. Considering these requirements, we studied if Fetuin-B down-regulation could be used for non-hormonal contraception. To achieve this, we analyzed the fertility of female mice undergoing Fetuin-B down-regulation by antisense oligonucleotide treatment. The immunoblot in figure 2A illustrates a typical serum Fetuin-B down-regulation within 50 days and the following washout period during the recovery

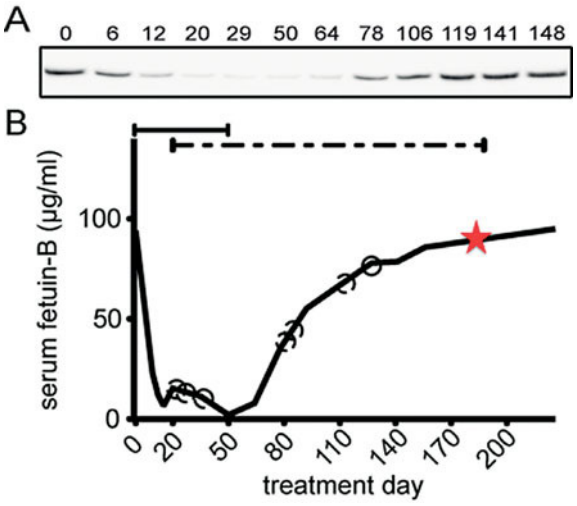


Fig. 2: Fetuin-B* antisense oligonucleotide-*mediated down-regulation of serum Fetuin-B causes infertility. *(A) Representative mouse Fetuin-B immunoblot shows serum Fetuin-B level during (day 0–50) and after the antisense oligonucleotide treatment. (B) Serum Fetuin-B decreased during antisense oligonucleotide treatment (continuous line). Mating (dashed line) was from day 20 onwards. Black circle indicates vaginal plug without pregnancy. Red star symbolizes a vaginal plug followed by pregnancy.*

time course. Upon mating the Fetuin-B antisense oligonucleotide-treated females (11/12) did not become pregnant while PBS-treated females (10/10) had litters. Furthermore, the antisense oligonucleotide treatment was reversible. When the antisense treatment was stopped and serum Fetuin-B returned to the base level, females became pregnant. Consequently, we showed that pharmacological Fetuin-B down-regulation by antisense oligonucleotide therapy results in reversible infertility in female mice and can be used for contraception.

Besides the usefulness of ZP hardening for contraception, it is also a common complication in assisted reproductive medicine. To keep the ZP unhardened and penetrable, it is common practice to use serum-derived factors as media supplements. Common additives include fetal calf serum, bovine fetuin and human serum or human follicular fluid, all of which contain Fetuin-B. Lot-to-lot variation, in for example human serum and human serum albumin, has been blamed for low pregnancy rates following assisted reproductive techniques. Strict quality control must ensure that media are free of infectious proteins and viruses. Thus, we studied the addition of recombinant Fetuin-B protein instead of sera to inhibit premature ZP hardening and to obtain defined media[4]. Figure 3A shows that when sperm were added to oocytes immediately after isolation (0 hours of *in vitro* culture), embryos developed to the two-cell stage in comparable numbers regardless of supplementation of the IVF medium with recombinant mouse Fetuin-B. However, when *in vitro* culture was increased for up to one or five hours, addition of recombinant mouse Fetuin-B to the IVF medium increased the IVF
rate. Two-cell embryos (Fig. 3B, E) de veloped into four-cell embryos (Fig. 3C, F) and further into blastocysts (Fig. 3D, G). Embryos that were fertilized in recombinant mouse Fetuin-B containing medium had larger numbers of sperm attached to them, suggesting that recombinant mouse Fetuin-B inhibited fertilization-triggered ZP hardening, which normally prevents further sperm attachment. Thus recombinant mouse Fetuin-B inhibited ZP hardening as expected but did not increase embryo loss despite multiple sperm binding.

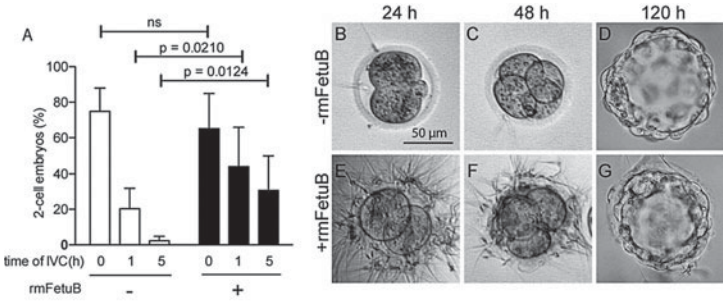


Figure 3: Recombinant mouse Fetuin-B (rmFetuB) increases in vitro fertilization (IVF) rate for up to five hours of in vitro culture (IVC). *(A) IVF was performed in medium without rmFetuB (white columns) or in medium containing 0.05 mg/ml rmFetuB (black columns). Embryos developed normally without (B-D) or with added rmfetuB (E-G) according to developmental stage at 24 hours post fertilization (B, E), 48 hours (C, F) and 120 hours (D, G). All micrographs were taken using the same magnification.*

The Role of Fetuin-A in Endochondral Ossification

Dr. Laura Brylka

Using genetically engineered mouse models, we established that the main function of the hepatic plasma glycoprotein Fetuin-A is to inhibit ectopic calcification. Fetuin-A deficient mice (*Ahsg*$^{-/-}$) on the calcification-sensitive genetic background DBA/2 develop extensive soft tissue calcification in almost all major organs. In patients suffering from chronic kidney disease, which leads to extensive vascular calcification, high Fetuin-A levels correlate with increased survival rates. Through its capacity to bind calcium phosphate mineral, Fetuin-A facilitates the clearance of excess mineral from the body. As mineralized bone tissue contains huge amounts of calcium phosphate, it is not surprising, that Fetuin-A accumulates in bone in high abundance. Fetuin-A is indeed one of the most highly abundant non-collagenous proteins in bone. Fetuin-A deficient mice on the genetic background C57BL/6 and to a lesser extent also on DBA/2 background develop a bone phenotype anomaly. In adult mice, the femoral bones are shorter and their growth plates are disordered, while all the other bones are normal in size.
Long bones develop through endochondral ossification. This process starts with the aggregation of mesenchymal stem cells and their differentiation into chondrocytes. The resulting cartilaginous bone template increases in size and is gradually replaced by bone through continuous proliferation, cell maturation, and vascular invasion. In order for the bone to grow in length, cartilaginous regions remain at opposite ends of the long bone, the so-called growth plates. These growth plates contain chondrocytes of different maturation stages arranged in distinct zones. In the reserve zone, immature chondrocytes serve as a reservoir. Then, chondrocytes start to proliferate, forming neatly ordered stacks of cells.

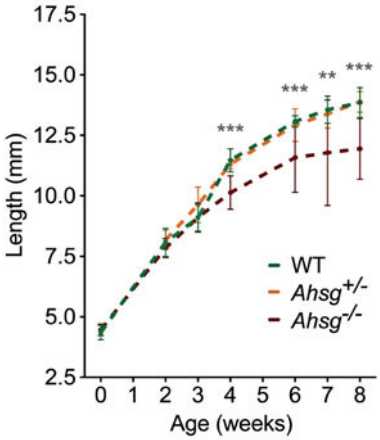


Fig. 4: The development of femur length over time. *While femur growth was similar in wildtype and Fetuin-A heterozygous mice, femur length was significantly decreased in Ahsg*$^{-/-}$ *mice, starting from four weeks of age.*

Subsequently, the chondrocytes become hypertrophic. Late hypertrophic chondrocytes mineralize their matrix. Finally, the chondrocytes either differentiate into osteoblasts or they undergo apoptosis. The calcified cartilage is replaced by bone. Continuous proliferation and differentiation of growth plate chondrocytes and subsequent remodeling of the growth plate cartilage lead to an elongation of the bone.

To investigate the bone phenotype anomaly in Fetuin-A deficient mice, and thus the role of Fetuin-A in longitudinal bone growth, we studied the development of the femur in wildtype, heterozygous (*Ahsg*$^{+/-}$) and homozygous Fetuin-A deficient (*Ahsg*$^{-/-}$) mice, starting from newborn mice until eight weeks of age. While femur growth was similar in wildtype and *Ahsg*$^{+/-}$ mice, femur length was significantly decreased in Fetuin-A deficient *Ahsg*$^{-/-}$ mice, starting from four weeks of age (Fig.4). To better understand the morphological changes in femora from *Ahsg*$^{-/-}$ mice, femora from eight weeks old mice were measured using micro-computed tomography (μCT) (Fig. 5). Femora from *Ahsg*$^{-/-}$ mice were notably bent in their distal region. Also, their growth plates were angularly deformed (Fig. 5F). Taken together these results suggest that at the age of four weeks the distal femur had started to deform.

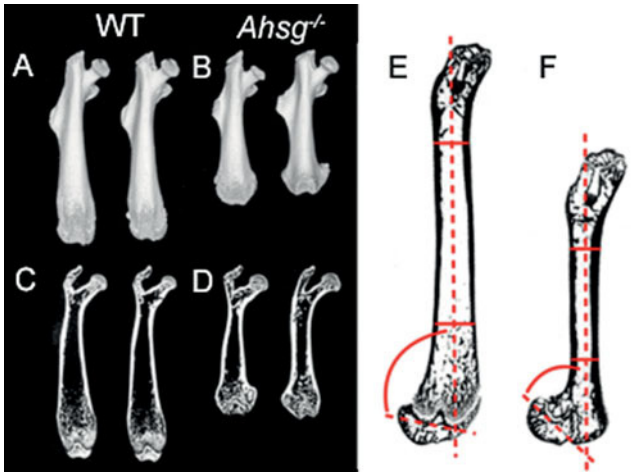


Fig. 5: Micro-computed tomography (µCT) reveals morphological features in femora from eight weeks old Fetuin-A deficient mice. *Three-dimensional reconstructions of bones from wildtype (A) and Ahsg*$^{-/-}$ *mice (B) and the respective two-dimensional cross-sections (C, D) show morphological changes in Ahsg*$^{-/-}$ *femora. The growth plates from Ahsg*$^{-/-}$ *bones (F) were deformed in such a way that the angle of the growth plate with respect to the shaft was decreased (E).*

In order to understand the development of the bone dysplasia in *Ahsg*$^{-/-}$ mice, we studied histological sections from mice of different ages. Starting from newborn mice, until about three weeks of age, the zone of hypertrophic chondrocytes was elongated (Fig. 6). At three weeks of age, the elongated hypertrophic zone disappeared. At this time point cellular infiltrates localized in growth plates between the proliferative and hypertrophic zone. These infiltrates were not only found in *Ahsg*$^{-/-}$ mice, but also in heterozygous *Ahsg*$^{-/-}$ mice. To investigate the underlying mechanisms leading to cellular

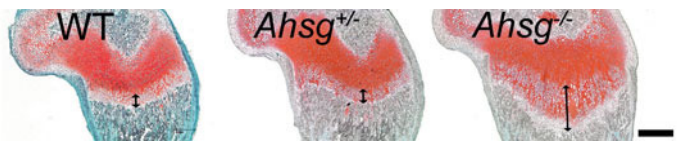


Fig. 6: Elongated hypertrophic zones in bones from 13 days old Ahsg*$^{-/-}$ *mice. *Histological femur sections were stained with safranin O and fast green FCF. The two-sided arrow marks the length of the hypertrophic zone, which was severely elongated in Ahsg*$^{-/-}$ *mice. Scale bar is 200 µm.*

infiltration and growth plate deformation, we performed a microarray analysis on growth plate cartilage in collaboration with the Genomics Facility of the IZKF Aachen. Using laser capture microdissection of frozen bone section, we isolated whole growth plates from 13 days old wildtype, *Ahsg*$^{+/-}$ and *Ahsg*$^{-/-}$ mice. RNA was extracted from the isolated growth plate cartilage and used for microarray analysis. Gene enrichment analysis showed that in the growth plates of *Ahsg*$^{-/-}$ mice, genes involved in the regulation of the immune response were highly overexpressed. The most highly upregulated genes were mainly regulated by interferon signaling, as shown by a comparison of the data to the interferome database. The single most highly upregulated gene, with an upregulation of about 560-fold, was the chemokine CXCL9. This chemokine is predominantly expressed during inflammation and it recruits effector T cells to the site of inflammation. The high upregulation of CXCL9 in the growth plates of *Ahsg*$^{-/-}$ mice points to a specific inflammatory mechanism.

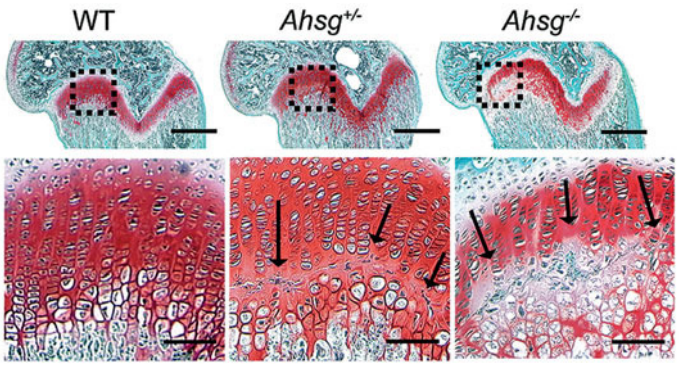


Fig. 7: Cellular infiltrates in the growth plates of three weeks old Fetuin-A deficient mice. *Histological femur sections stained with safranin O and fast green FCF show the presence of cellular infiltrate located between the proliferative and the hypertrophic zone (arrows) in the growth plates of both, Ahsg*$^{+/-}$ *and Ahsg*$^{-/-}$ *mice. Scale bars upper panels are 200 µm, lower panels 50 µm.*

Taken together, our results suggest an anti-inflammatory role for Fetuin-A in endochondral ossification. We will further investigate the mechanisms leading to the inflammatory response in the growth plates of Fetuin-A deficient mice. This will deepen our understanding not only of fetuin biology, but also of growth plate physiology and pathology.

Stem Cells and Tissue Engineering

PD Dr. Sabine Neuß-Stein

In 2016 members of the group „Stem Cells and Tissue Engineering“ published data gained in long-lasting cooperations with clinicians and basic scientists. Together with Bernd Lethaus from the Department of Oral and Maxillofacial Surgery, tissue engineered bone constructs were proved to be functional for the first time in a large animal model. Therefore, ovine

MSC (oMSC) were isolated, expanded and characterized before they seeding on 3D Poly-D-L-Lactid acid (PDLLA), Poly-Ether-Keton-Keton (PEKK) and silk (± hydroxyapatite (HA)) scaffolds. The tissue engineered constructs were autologously transplanted in critical size defects in an ovine calvarial model for three months. Histological stainings and microradiographic analyses identified PEKK scaffolds as suitable biomaterial for bone tissue engineering (Fig. 8).

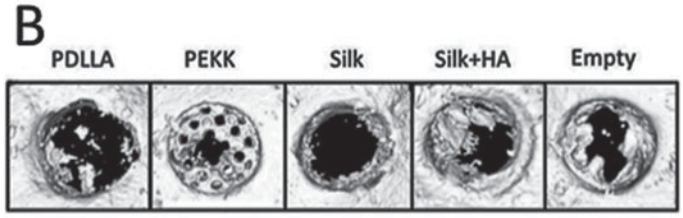


Fig. 8: Tissue engineered bone constructs seeded with autologous ovine mesenchymal stem cells. *A) Critical size defects in a calvarial sheep model were filled with in vitro derived bone constructs for three month. B) Microradiographic analysis demonstrates highest amounts of newly formed bone in PEKK transplants.*

Besides advancing bone tissue engineering strategies from cell culture to large animal models, the group used the biomaterial test platform – established in 2007 – to unravel further biomaterials suitable for bone tissue engineering in combination with human dental pulp stem cells (DPSC). This work was done in cooperation with Christian Apel (Department of Tissue Engineering and Textile Implants). Here, DPSC were seeded on 17 different polymers for 21 days either in osteogenic induction medium or in stem cell expansion medium followed by RealTime PCR of osteogenic marker genes, Alizarin red staining and analysis of alkaline phosphatase secretion. Surprisingly, on the molecular level, alginate, hyaluronic acid and Polyvinylidenfluoride (PVDF) initiated osteogenic differentiation of DPSC without addition of induction factors.
Together with Andrij Pich (DWI) and Georg Conrads (Oral Microbiology and Immunology) the group was successful in developing Isoeugenol-based nanogels for implant coatings repelling microorganisms – here antibacterial activity against oral pathogens was demonstrated - and in parallel exhibiting cell adhesive properties. Such functional nanogels can be used to design implant coatings preventing biofilm formation during tissue regeneration and wound healing processes. (Fig.9).

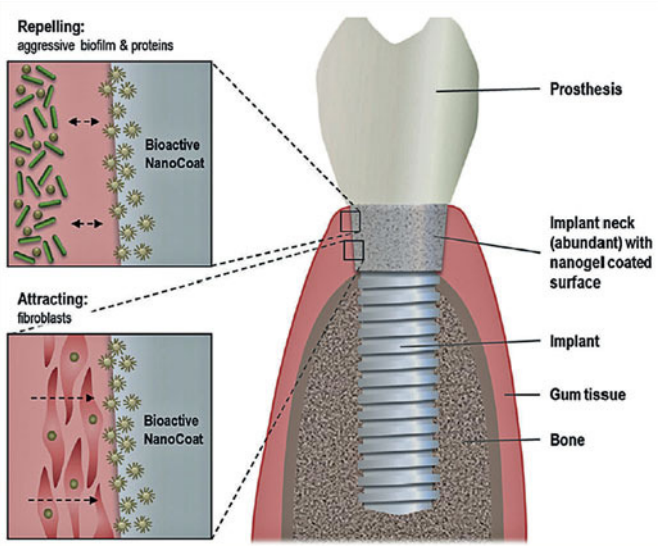


Fig. 9: Concept of bioactive nanogel coatings for (dental) implants. *Kather* et al., *Angew Chem Int Ed, 2016.*

Increasing Biocompatibility of Patient-Specific PEO-Coated Implants Using Endothelial Progenitor Cells and Mesenchymal Stem Cells in Bone Defects

MSc Michaela Bienert

Bone graft vascularization is a main challenge in tissue engineering to improve biocompatibility. Osseointegration and reconstruction of function after implantation can be achieved by support of a bone environment rich in vascular networks. In our study, structural and vascular integration was achieved by using plasma electrolytic oxidation (PEO)-coated magnesium grafts cultured with autologous mesenchymal stem cells (MSC) and endothelial progenitor cells (EPC) from peripheral blood. Magnesium grafts were designed in a patient-specific way using selective laser melting (SLM) data from the Fraunhofer ILT Aachen. Materials were bated before PEO-coating and coated grafts were compared to non-coated grafts. To enable EPC and MSC culture, graft materials needed to be sterile before they were used in cell culture. In figure 10 four different prevalent sterilization methods were shown.
Color changes in the implants could be observed when materials were autoclaved or treated with EtOH. No color changes could be observed when implants were heated or exposed to UV-C light. Compared to the other methods UV-C provided a gentle method for sterilization. For further studies materials are sterilized using UV-C light.
For cytotoxicity studies of magnesium grafts with or without PEO-coating, grafts were incubated for 24 h in cell culture media. Human vein endothelial cells (HUVEC) or human MSC were seeded on cell culture plastic. Media

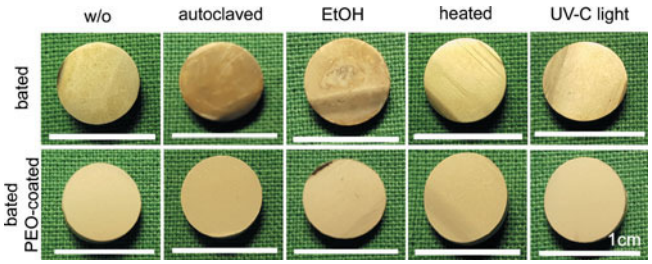


Fig. 10: Comparison of different sterilization methods for bated magnesium implants with and without PEO-coating. *Bated implants or bated PEO-coated implants were either autoclaved for 120 min at 121 °C and 2.12 bar, washed for 5 min in 70 % EtOH followed by washing in PBS for 5 min, heated for 3 h at 160 °C or exposed to UV-C light for 25 min and compared to non-treated materials (w/o). Scale bar indicates 1 cm.*

incubated with grafts were added to respective cells and incubated for 24 h. Afterwards cells were stained with fluorescein diacetate (FDA) and propidium iodide (PI). Figure 11 shows fluorescence microscopy pictures of live/dead staining of the respective materials with viable cells in green and dead cells in red.

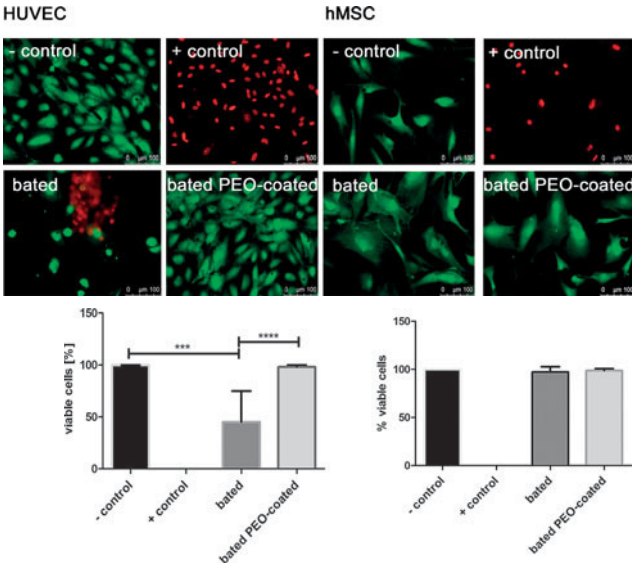


Fig. 11: Cytotoxic effects of magnesium grafts coated with or without polyethylene oxide (PEO). *Grafts with or without PEO-coating were incubated for 24 h in cell culture media. Subsequently HUVEC or hMSC were incubated with this media for 24 h. Afterwards live/dead staining occurred using FDA (green/viable cells) and PI (red/dead cells). Quantification performed using, t-test, CI 95 %, p***= 0.0007 and p****< 0.0001, representative for n=3.*

Bating of the magnesium grafts significantly reduced HUVEC viability compared to negative control and PEO-coated material. This indicates that PEO-coating is essential for HUVEC viability. In contrast PEO-coating is not essential for MSC viability.

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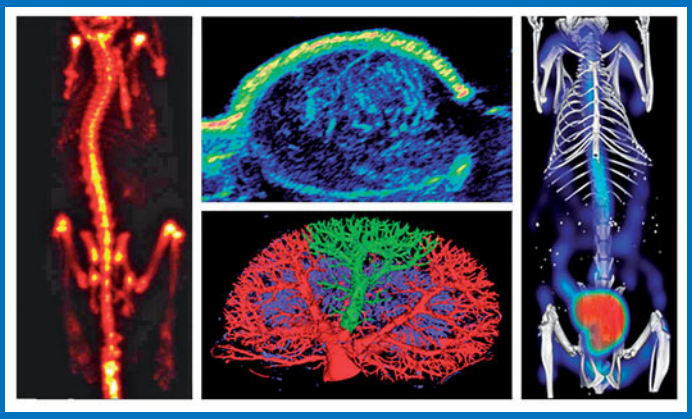

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Introduction

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. For this purpose, basic research on the tissue microenvironment including the barriers for drug delivery is combined with innovative image-guided targeting concepts. In this context, novel biomaterials, including nanoparticles, polymeric carriers, liposomes, micelles and microbubbles play a major role. Their delivery and therapeutic efficacy is studied by functional and molecular imaging, which has become an established tool in preclinical research.
ExMI follows a multimodal approach, based on combinations of MRI, CT, ultrasound, optical and photoacoustic imaging, nuclear medicine techniques (in particular PET-MRI) and magnetic particle imaging (MPI). Image fusion, hybrid imaging as well as multimodal contrast agents and advanced (radiogenomic) data analysis are in the research scope. Research projects at ExMI usually have a translational scope and increasing efforts are currently taken to initiate and perform first in man trials with new diagnostic and therapeutic tools.
Currently, the institute consists of 2 departments and 4 research groups working on the biological mechanisms of tumor progression, on novel imaging agents, on medical informatics, on nanomedicines and theranostics, diagnostic and therapeutic ultrasound imaging, and on the development of novel tools for MR-PET hybrid imaging and MPI.

Diagnostic and Therapeutic Ultrasound

Univ.-Prof. Dr. med. Fabian Kiessling

In this new research group, advanced ultrasound technologies that can be used for diagnostic and therapeutic purposes are explored. In particular, we focus on contrast-enhanced ultrasound and the refinement of microbubbles (MB) [1] to derive vascular tissue characteristics, but also use MB to transmit acoustic power to the vascular wall and thus increase vessel leakiness to improve drug delivery [2]. Using human breast samples, VEGFR2 and $\alpha v\beta 3$ integrins were validated as promising targets to distinguish benign and malignant tumors with molecular ultrasound imaging [3]. Encouraged by these findings clinical scale MB targeted against the VEGFR2 were applied in mice bearing breast cancer xenografts and it was shown that the combined functional, and molecular characterisation of tumor vascularisation enabled an early and sensitive assessment of antiangiogenic therapy effects [4]. Furthermore, B. Theek could show that the controlled destruction of MB in the tumors increased vascular leakiness and enhanced the stromal penetration of liposomal drug carriers [5].
Molecular ultrasound imaging was also successfully applied in the cardiovascular field. In this context, it was shown that MB targeted against $\alpha v\beta 3$ could depict vascular damages after catheter-based interventions in pigs and allowed to faithfully monitor the vascular healing process, which could be useful to adapt anticoagulant therapies that are frequently required after radiological interventions [6].

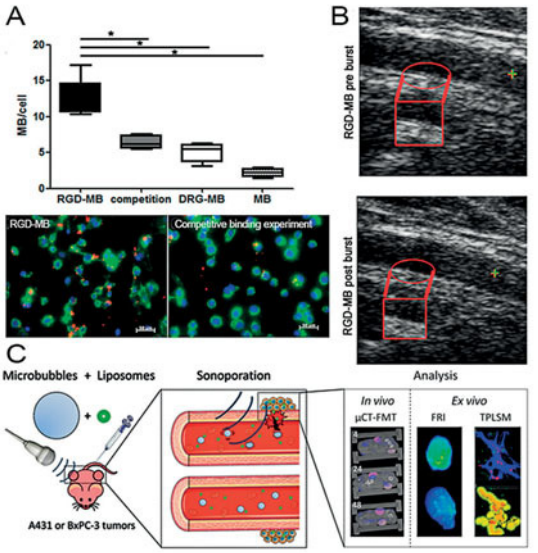

Fig. 1: A: Quantification of the binding of fluorescent $\alpha v\beta 3$-integrin-targeted (RGD-MB) and control microbubbles (DRG-MB and MB) to endothelial cells. Corresponding fluorescence images are shown below (red = RGD-MB; green = cell surface; blue = nuclei). B: Binding of RGD-MB to an injured carotid artery in a pig before and after MB destruction by US. C: Scheme explaining sonoporation in peripheral tumors and fluorescence-based analyses illustrating the enhanced accumulation and penetration of liposomes. Image taken from [5].

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Physics of Molecular Imaging Systems

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

In the last years, the PMI group and Philips Research Aachen have jointly developed the first fully-digital detector concept for simultaneous Positron Emission Tomography (PET) and Magnetic Resonance (MR) imaging. The team succeeded in integrating this new detector technology in a preclinical PET/MR insert (Fig. 2 A, left) for a human 3T MR system [7]. The sensitivity, spatial resolution and timing resolution of the scanners have been investigated outside and inside the MR system [8]. Simultaneous acquisition has been shown to work without major degradation of either modality [9]. Preclinical studies were already conducted with the scanner, e.g. for human breast cancers (Fig. 2 A, right).
One important focus in the development of our software toolbox is the real-time capability of the software-based data acquisition and processing architecture [10]. The so-called maximum likelihood algorithm increases the

sensitivity of our system [11]. Research was also done in FPGA techniques to reduce radiofrequency interferences between the PET and the MRI [12].

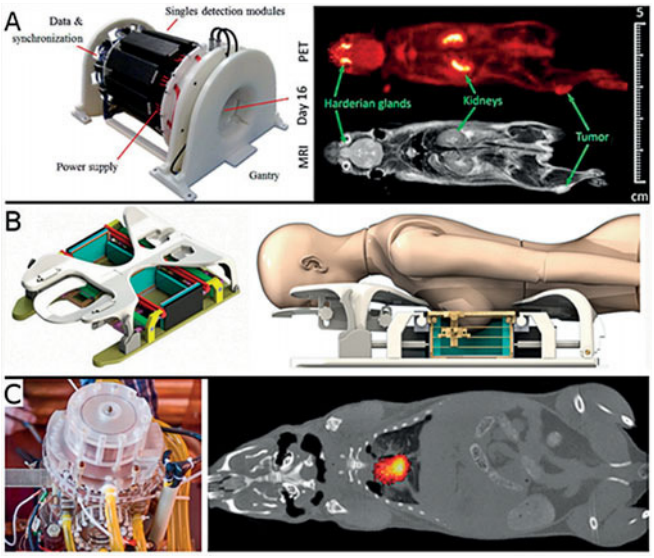

Fig. 2: A: Simultaneous PET/MR device with digital PET detector technology (left). Simultaneously measured whole-body PET and MR mouse image (right, adapted from [7]). B: Prototype sketch of the HYPMED breast PET/MR insert [13]. C: MPI system (left) and the first in-vivo MPI image of a mouse heart overlayed with a CT image (right).

The knowledge, which was gained in the development of the preclinical PET/MR system, is now transferred into clinical projects. Within the EU Horizon 2020 HYPMED project we are working on a clinical PET/MR insert for human breast cancer [13]. A sketch of the system is shown in Fig. 2 B. The system aims to improve the diagnoses and treatment response monitoring of breast cancer.
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 as tracers. In the last years, the team built up and developed an MPI scanner (Fig. 2 C, left). The group invented a new method to enhance the sensitivity of the scanner and recorded an in-vivo image of a beating mouse heart (Fig. 2 C, right) [14].

[7] Weissler et al., "A Digital Preclinical PET/MRI Insert and Initial Results." IEEE Trans Med Imag (2015)
[8] Schug et al, Phys Med Biol (2016)
[9] Dueppenbecker et al., Biomed Phys Eng Express (2016)
[10] Goldschmidt et al.., IEEE TBME (2016)
[11] Gross-Weege et al., Med Phys (2016)
[12] Gebhardt et al., Phys Med Biol (2016)
[13] http://www.hypmed.eu/about-hypmed (2016)
[14] Franke et al., IEEE TMI (2016)

Nanomedicines and Theranostics

Univ.-Prof. Dr. Dr. Twan Lammers

Nanomedicines are 1-1000 nm-sized carrier materials designed to improve the biodistribution of systemically administered (chemo-) therapeutics. By delivering drug molecules more specifically to pathological sites, and by preventing them from accumulating in healthy tissues, nanomedicines are able to improve the balance between drug efficacy and toxicity.
The majority of projects in our department deal with drug targeting to tumors, which is based on the Enhanced Permeability and Retention (EPR) effect. The EPR effect, however, is highly variable, both in animal models and in patients [15]. We are working on strategies to address this variability [16,17]. As part of ERC Proof-of-Concept grant, theranostic tools are being developed to monitor EPR-mediated tumor targeting. By using theranostic nanomaterials, i.e. delivery systems combining both diagnostic and therapeutic properties within a single nanomedicine formulation, the EPR effect can be visualized and quantified in individual patients. On the basis of this, patients showing good accumulation in tumors and metastases can be preselected for subsequent nanomedicine treatment, while

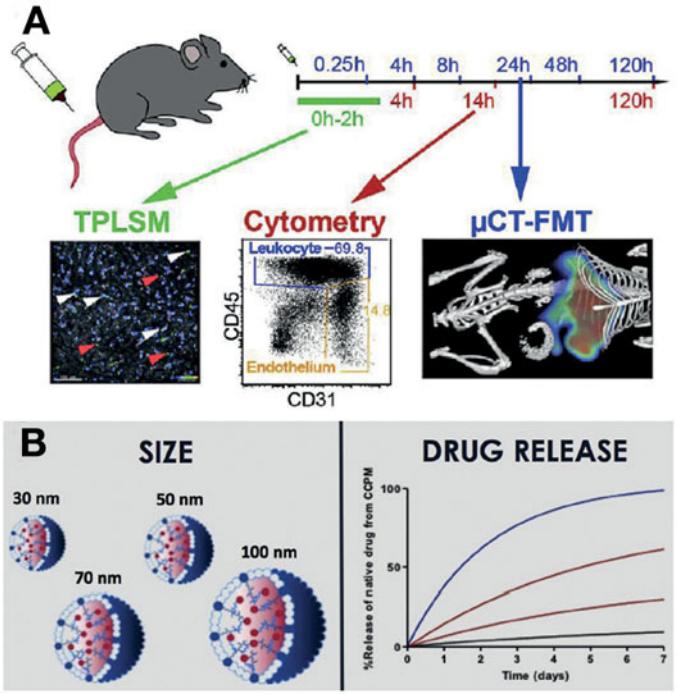

Fig. 3: A: Multimodal and multiscale optical imaging is employed to evaluate the biodistribution of prototypic drug delivery systems. B: Efforts are invested in developing nanomedicines with tailorable sizes and drug release kinetics. Images adapted from [18,19].

patients showing low or no EPR-mediated tumor targeting can be excluded. This leads to more efficient clinical trials, and to more effective and more precise tumor-targeted treatments.
We recently established multimodal and multiscale optical imaging for monitoring nanomedicine biodistribution. This was done in collaboration with Prof. Tacke (MedIII-UKA), showing that combining CT-FMT, two-photon microscopy and FACS enables the assessment of the biodistribution of fluorophore-labeled polymers (10 nm), liposomes (100 nm) and microbubbles (2000 nm) from the whole-body level down to the cellular level [18]. Furthermore, we worked on protocols to reduce the size and control the drug release kinetics of core-crosslinked polymeric micelles [19]. These are developed in cooperation with Cristal Therapeutics (Maastricht) and Utrecht University,

and they have recently successfully completed phase I clinical trials for solid tumor treatment. In parallel, we have also worked on PEGylated liposomes for the targeted delivery of corticosteroids. Liposomes containing prednisolone, developed by Enceladus Pharmaceuticals and group leader Dr. Josbert Metselaar are in clinical trials for the treatment of arthritis and inflammatory bowel disease. In collaboration with Prof. Bruemmendorf (MedIV-UKA) and with the Clinical Trials Center at the UKA, a first-in-man study with liposomal dexamethasone in patients suffering from multiple myeloma will start in Aachen in the beginning of 2017.

[15] Lammers et al., Nat Rev Mater (2016)
[16] Hare et al., Adv Drug Deliv Rev (2016)
[17] Arranja, Pathak et al., Pharmacol Res (2017)
[18] Ergen et al., Biomaterials (2017)
[19] Hu et al., J Control Release (2016)

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. Non-invasive imaging techniques are combined with ex vivo and in vitro analyses in order to characterize the interplay between the tumor and the microenvironment and to investigate the effects of anti-cancer drugs.

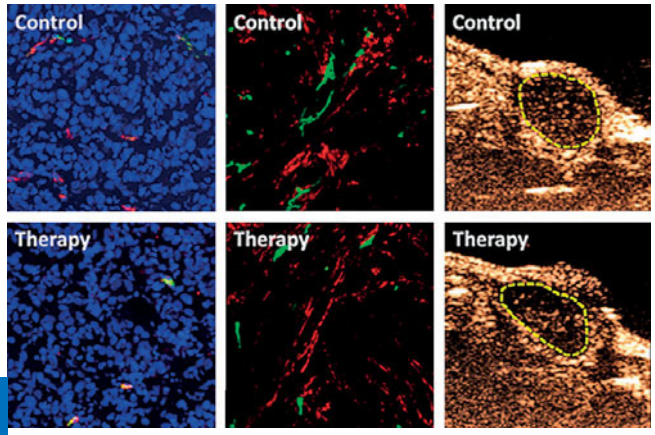

Fig. 4: A: Immunostainings (left: CD31-green; VEGFR2-red, middle: SMA-red, CD31-green) demonstrating reduced angiogenesis and vessel density in treated tumors, while vessel maturation is not markedly altered. Accordingly, molecular ultrasound imaging shows reduced signal intensities of bound VEGFR2-targeted microbubbles in treated tumors (right: tumors encircled in yellow).

For this purpose, imaging approaches are directed towards targeting cellular key players involved in tumor progression and towards monitoring molecular and functional alterations that occur during tumor progression or that are induced in response to anti-tumor therapies. In different tumor models that were treated with drugs affecting the tumor vasculature, alterations in the endothelial VEGFR2-expression levels occurred earlier and were more pronounced than functional changes in the tumor vessels [20]. Thus, the reduction in the VEGFR2-levels in response to VEGF-blockade was depicted with high sensitivity by molecular ultrasound imaging using target-specific microbubbles [20]. Even low doses of microbubbles targeting the vascular inflammation marker E-selectin could be used for discriminating tumors based on the differential expression of the inflammation marker and for detecting anti-angiogenic therapy effects [21]. Currently, we are combining molecular ultrasound imaging with other modalities in order to investigate mechanisms of tumor progression to metastasis.

[20] Baetke et al., Radiology (2016)
[21] Spivak et al., Mol Imaging Biol (2016)

Applied Medical Informatics

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

Our aim is to develop and apply innovative and useful software for data- and computer-related problems which arise while performing clinical and preclinical imaging studies. This includes the development of quantitative reconstruction algorithms [22], efficient software tools for interactive image analysis [23], and their application for molecular imaging studies [24]. A particular focus is on multimodal imaging where the strengths of two imaging modalities are combined, e.g. fluorescence-mediated tomography (FMT) and micro-computed tomography (μCT). FMT provides highly sensitive molecular information about the distribution of fluorescence and μCT delivers anatomical information at high resolution. In contrast to planar fluorescence reflectance imaging, FMT applies multiple illumination patterns and allows the assessment of deep fluorescence sources by means of tomographic reconstruction (Fig. 5). Reconstruction was performed at increased resolution using GPU-accelerated algorithmic differentiation [22].

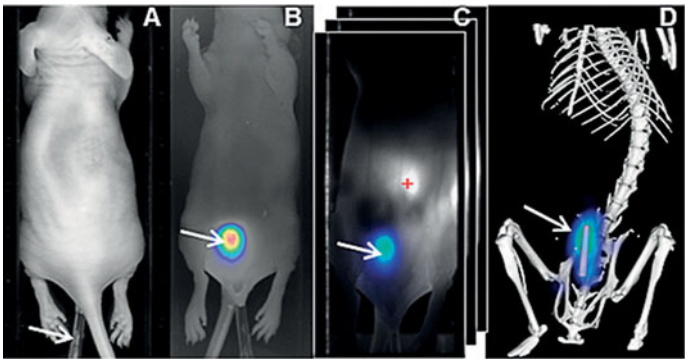

Fig. 5: Planar fluorescence imaging and multimodal fluorescence-mediated tomography. (A) A Mouse is positioned in a multimodal mouse bed after insertion of a rectal probe containing both CT-contrast agent and a NIRF-dye (white arrow). (B) Planar reflectance image. The diffuse signal of the rectal insertion shines through the mouse body (arrow). (C) The FMT captures multiple images using a servo-mounted laser. (D) The reconstructed three-dimensional fluorescence distribution on top of the anatomical μCT image.

The anatomical μCT data is useful for fluorescence reconstruction and analysis, and we used it to assess sensitivity and accuracy of the fluorescence reconstruction [24]. A rectal probe containing both μCT and fluorescent contrast agent was inserted into anaesthetized nude mice to show that our improved fluorescence reconstruction increases sensitivity and accuracy of the 3D fluorescence image.
Furthermore, our GPU-accelerated software for interactive image analysis and visualization was used for several imaging studies, e.g. to quantify the amount of fat [25], to assess the vascularization in murine kidneys [26], and to measure organ sizes [27].

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[23] Gremse et al., Theranostics (2016)
[24] Rosenhain et al., J Biophotonics (2016)
[25] Gautheron et al., Nat Commun (2016)
[26] Ehling et al., J Am Soc Nephrol (2016)
[27] Brinkmann et al., Sci Total Environ (2016)

Probe design for molecular imaging

Dr. Srinivas Banala

Research in the probe design group focuses on the development of novel diagnostic and theranostic agents. Our expertise is in multi-step organic synthesis, in particular the development of novel chromophores for optical and photoacoustic (PA) imaging applications.
We have designed and synthesized probes based on porphyrins and BODIPYs, which can work as stand-alone PA probes with increased PA signal (Fig 6). In porphyrin modification, fusing quinone conjugation to the dye core shifted absorption into the near-infrared (NIR) range and also increased PA efficiency, up to 4 times higher than that of the current 'gold standard' indocyanine green (ICG). Similarly, in BODIPYs, fusing with photo-electron transfer groups increased their PA efficiency, which also resulted in over 4 times higher signal intensities as compared to ICG. We furthermore explored BODIPYs tethered with reactive functional groups, which can increase their PA signal and shifts the PA maxima in response to chemical and biochemical triggers. These dyes may be interesting to trap short-lived reactive oxygen species (ROS), and might therefore be suitable for PA imaging of inflammatory diseases. Further work in shifting absorption and PA maxima towards the NIR-II window (up to 1064 nm) is currently being explored. Similarly, optimization studies to improve the aqueous solubility and biocompatibility of these probes were carried out.
Non-bleaching NIR fluorescent dyes are useful for fluorescence image-guided surgery (FIGS). We conceived to combine photodynamic therapy (PDT) with FIGS. As both modalities use a non-thermal laser, differing in light fluence, they can be combined, employing PDT as a post-surgical tool to eradicate remaining tumor cells. These theranostic probes will be based on NIR-absorbing and emitting BODIPY dyes. We have already synthesized heavy atom substituted chromophores showing absorption and emission in the 700 nm range, and good PDT activity. As the current FIGS devices are mostly designed for 800 nm, further fine-tuning of absorption is in one of our future aims.

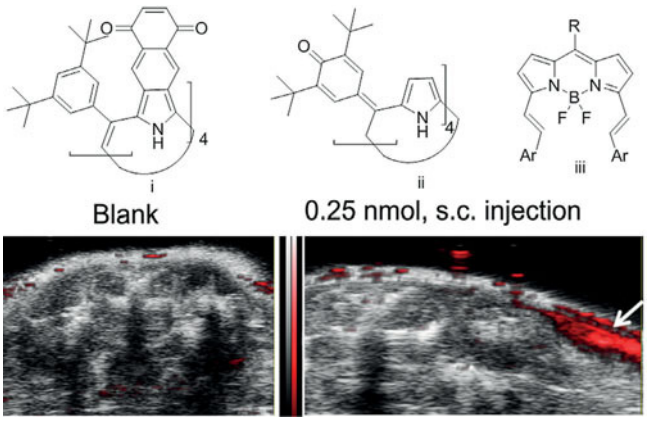

Fig. 6: Chemical structures and photoacoustic images of an optimized BODIPY after subcutaneous injection in a dead mouse.

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Awards

- Dr. Yannick Berker: Friedrich Wilhelm Award
- Maike Baues: DGBM Outstanding Oral Presentation
- Maike Baues: EMIM Poster Award
- Susanne Golombek: EMIM Poster Award
- Larissa Rizzo: EMIM Travel Support
- Dr. Wa'el Al Rawashdeh: WMIC Student Travel Stipend
- Maike Baues: WMIC Student Travel Stipend
- Larissa Rizzo: GlaxoSmithKline Travel Stipend
- Maike Baues: WMIC Women in Molecular Imaging Award

Selected publications

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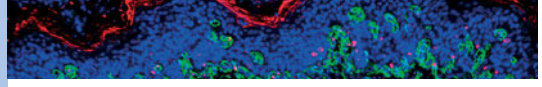

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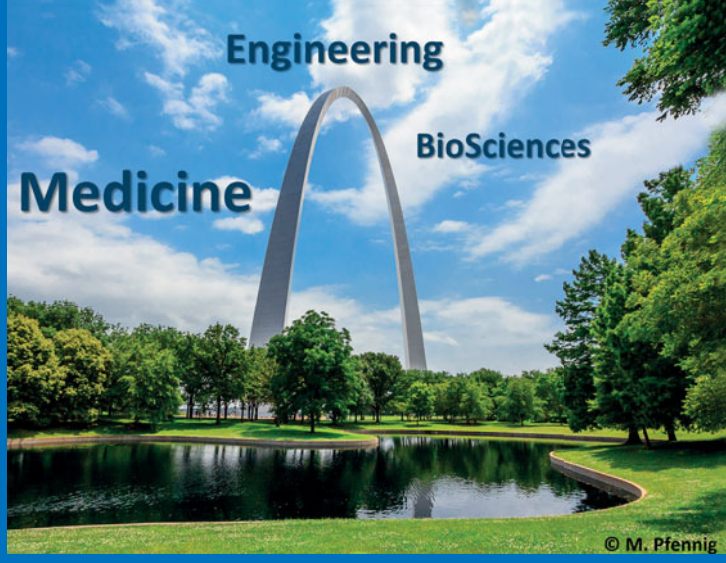

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Introduction

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

A multidisciplinary approach to medical engineering constitutes our innovative power: in the Institute of Applied Medical Engineering about 100 medical scientists, engineers, biologists, physicists, information scientists and chemists are working closely together in approximately 80 R&D projects, spanning over the entire technology transfer chain from ideas to the generation of innovative and beneficial clinical products. We focus on a combined theory-based and practice-oriented scientific education of students and employees. We prepare highly-motivated young investigators for industry, healthcare sector and academia. The AME Executive Team consists of the director and five department heads (Fig. 1). The following portraits of our five AME departments describe our areas of R&D.

Fig. 1: Robert Farkas, Martin Baumann, Ulrich Steinseifer, Thomas Schmitz-Rode, Catherine Disselhorst-Klug, Stefan Jockenhövel

Cardiovascular Engineering/CVE

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

In 2016, the Department of Cardiovascular Engineering continuously strengthened its research activities in the fields of cardiac assist and replacement, artificial lung, and valve replacement and interventions with a strong focus on the development of new methods and technologies.
In the field of **cardiac assist and replacement systems** the total artificial heart project "ReinHeart" and the in 2015 established spin-off company received an NRW-grant for the next research and development steps towards clinical application.
For the rotary piston total artificial heart "Scarabaeus" different drive concepts were evaluated based on the Wankel motor principle (Fig. 2). The joint project with the Department for Thoracic and Cardiovascular Surgery of the University Hospital received a START grant from our medical faculty.

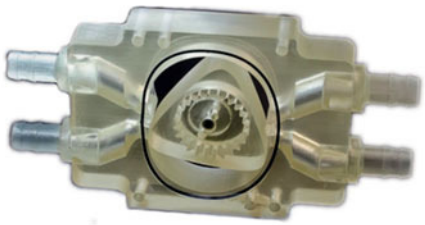

Fig. 2: "Scarabaeus" Heart lab-type

The development of the minimal invasive right ventricular assist device MIRVAD is still ongoing with university funding. With its foldable rotor MIRVAD allows for placement in the pulmonary artery at an earlier state than common RVADs. This project is supported by a START grant in order to develop a hydraulic circuit model with integrated anatomical modeling for the examination of cardiovascular mechanical support devices such as the MIRVAD (Fig. 3).
In the field of **artificial lung systems**, the development projects MobiLung and EndOxy are still ongoing. MobiLung is the acronym for a wearable ECMO system for better mobilization of bridge-to-lung-transplant patients, whereas the EndOxy stands for an endothelialized oxygenator membrane, developed in close cooperation with the BioTex department. In order to better understand the internal processes

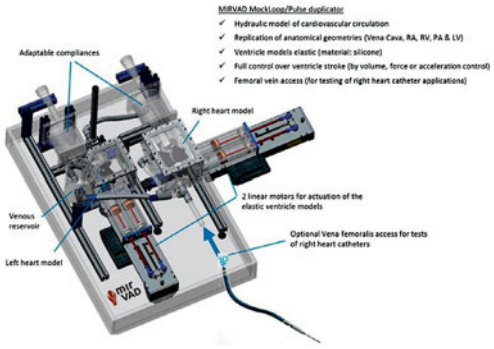

Fig. 3: Hydraulic circuit model with integrated anatomical modeling

of gas exchange, flow distribution and hemocompatibility during pulsatile and non-pulsatile blood flows in oxygenators, the research projects PulsOxy and OxySim were launched with funding from the German Research Foundation DFG. They include the implementation of a multiphase blood model that represents blood plasma and red blood cells as two separate phases. Further improvements consist of implementing a pulsatile flow, different fiber materials and arrangements. For validation purposes, an experimental method was developed to analyze the flow within an oxygenator with particle image velocimetry (Fig. 4).

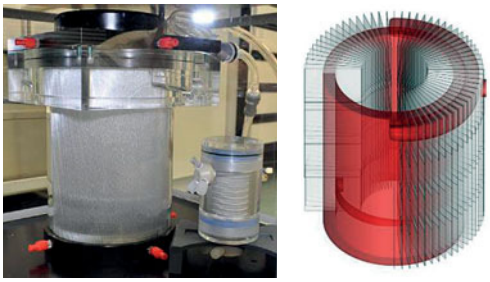

Fig. 4: PIV-Model of neonatal oxygenator and post-processing schematics.

Within the area of **valve replacement** and interventions, CVE supports the startup company Protembis in the development of a polyurethane-based embolic-protecting device. The project is funded by the Federal Ministry of Education and Research. For the development and the approval of safe repair and replacement devices several anatomically and functionally representative in-vitro models are being developed at the CVE: a model for the mitral valve will be incorporated into a pulse duplicator to allow for hydrodynamic measurements and ultra-sonic as well as flow visualization studies. A model for left atrial appendage (LAA) occluders is used to

quantify the respective tug force, sealing, and effect on the atrial flow field of an occluder in different LAA anatomies (Fig. 5). Additionally, CVE staff is involved in the standardization process for heart valve testing within ISO and DIN.

Fig. 5: Occluder inside LAA anatomy

Basic research activities were mainly focused on computational cardiovascular modelling and experimental validation technologies, including blood testing. Among others, a mock heart was developed, which does not only correspond to the anatomy but also simulates the actual contraction of a native heart (axial, radial, torsional). This enables in-vitro analyses of clinical scenarios as well as the validation of multiscale numerical approaches, such as cannulation methods of ventricular assist devices under physiological and pathophysiological conditions. 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.). In a perioperative study in cooperation with the Department of Thoracic, Cardiac and Vascular Surgery of the UKA, the CVE looks for a way to define intraoperatively the development of the acquired von Willebrand syndrome in order to optimize anticoagulation therapies and to reduce the increased risk of bleeding of heart support patients in the future. Blood testing mainly focused on optimizing the hemocompatibility of medical devices. This includes analyses of protein adsorption, platelet activation and adherence on artificial surfaces, development of species-specific diagnostic assays and real-time visualization of hemolysis using calcium-loaded, hemoglobin-free red blood cells (ghost cells) and a suitable fluorescent indicator.
A new project HOCSurf was started in cooperation with two Aachen based start-up companies (Rein-VAD and Meotec) in order to investigate the increase in hemocompatibility by

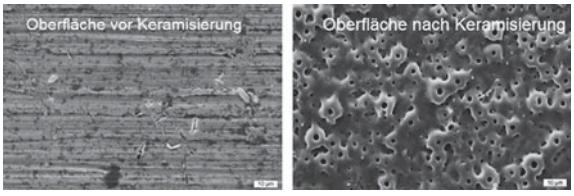

Fig. 6: Surface before (left) and after (right) ceramization.

the ceramization of heart support pumps (Fig. 6). A model for the prediction of haemocompatibility is developed, which in the future allows optimal design and thus improved patient care during component planning

Rehabilitation and Prevention Engineering/RPE

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

Development of technical devices assisting prevention, diagnosis and therapy of musculoskeletal and neuromuscular disorders needs a comprehensive knowledge about the physiological and pathological function of the neuromuscular and musculoskeletal system. To be successful aspects of biomechanics of movement, muscle biomechanics and central nervous control have to be combined with knowledge about how to integrate the devices in the clinical workflow, how to meet patients' and therapists' demands and how to achieve user acceptance. The department of Rehabilitation- and Prevention Engineering (RPE) has the needed expertise in its disposal in order to develop novel devices for prevention, treatment, rehabilitation and care which can be taken out from the research laboratory into patients' everyday life.

Muscular control and coordination:

During freely performed movements synergistic and antagonistic muscles are activated by the central nervous system (CNS) in a well-controlled pattern resulting in a precise execution of tasks relevant for various activities for daily life. However, up to now even in physiological movements it is not completely understood how the CNS activates different synergistic muscles during everyday movements. Information extraction procedures have been developed, which allow identifying the muscular activation strategy used by the CNS to control freely performed every day movement tasks. The physiological control strategies synergistic and antagonistic muscles used by the CNS have been investigated and are used as a baseline to identify pathological deviations in movement control (Fig. 7).

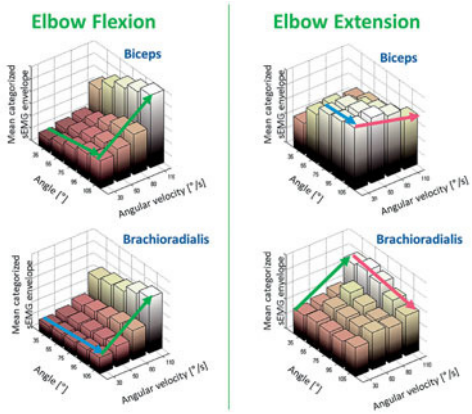

Fig. 7: Activation of elbow flexors.

Additionally, the central nervous control loop has been investigated on the level of single motor units to get closer insight into the physiological and pathological activation pattern chosen by the CNS to control force generation.

Individualized Rehabilitation therapy Robot assisted *inRehaRob*:

The outcome of rehabilitation efforts of neuromuscular and musculoskeletal disorders depends mainly on the amount of exercises performed by the patient. This can be significantly increased if technical assistance enables patients to perform their exercises autonomously. Robots are ideally suitable for this task, but to be efficient they have to adapt their given assistants to the instantaneous needs of the patient.

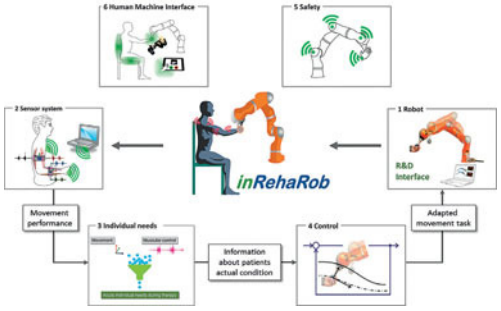

*Fig. 8: **inRehaRob** – individualized rehabilitation-therapy by means of a self-adapting robotic assistance*

Within the BMBF founded project inRehaRob (Fig. 8) a consortium of research institutions, industry and rehabilitation centres aim to develop a rehabilitation robot which facilitates individualized rehabilitation performed autonomously by the patient.

Ambulatory movement analysis:

Both interpretation of muscular co-ordination as well as the self-adaption of assistive devices to the patient needs require the information about the movement performed. Therefore, the assessment of movement by accelerometry has been improved. Fig. 9 shows an example how the patient's active range of motion can be measured by accelerometers for diagnosis purpose.

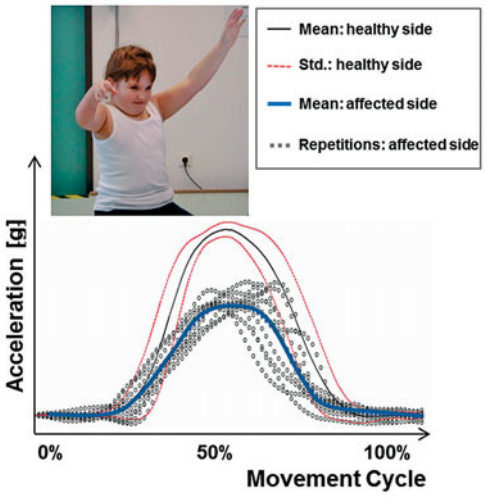

Fig. 9: Measurement of range of motion with accelerometers

Biophysical & Education Engineering/BEE

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

Towards business-adapted learning and digital implementation:

Nowadays business and industry require skills beyond knowledge reproduction, as team collaboration, soft skills and flexible implementation of digital information escalate. These requirements are met in problem-based learning (PBL), an approach confronting student-groups with assignments entirely new to them, which must be solved in group work solely. Two such PBL-based-projects were successfully undertaken in 2016: In the first, lecturers of the RWTH Aachen University have been trained in cooperation with the University of Maastricht to implement PBL in their lectures. In the second, existing PBL-courses (as part of BEE lecture "Introduction to Medicine") where successfully supplemented by digital collaboration tools, in order to adapt to students digital learning and communicating habits. This blended PBL approach was rated highly successful by participants in generating a realistic setting and conveying practical knowledge to prepare for the challenges of the digital business world. Taking both implementations together, we increased the PBL-impact RWTH-wide and improved concept reception by blending in digital awareness

Fig. 10: PBL-study group: Students work independently of the tutor (left-hand person) on a challenging assignment.

Nanomagnetic Medical Engineering (NME)

Our work addresses the use of magnetic nanoparticles (MNP) for diagnosis and therapy. As a diagnostic tool MNP are used as contrast agents in magnetic resonance imaging (MRI).
After their incorporation into surgical implants, the MNP facilitate the delineation of the implants from the ambient tissue with MRI. To guarantee for accurate MR images, we investigated the morphology and crystal structure as well as the magnetic properties of MNP aggregates inside the implants (Fig. 11).

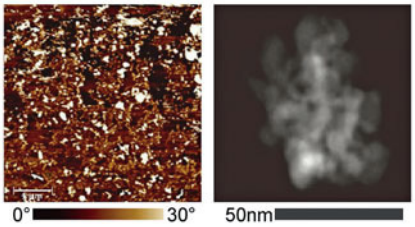

Fig. 11: Left: Magnetic force microscopy image of MNP agglomerates (white spots) inside the implants. Right: Electron tomography picture of a typical agglomerate consisting of individual MNP (in collaboration with Central Facility for Electron Microscopy, RWTH Aachen University).

Further, MNP are used for therapeutic applications as drug carriers in magnetic drug targeting. Drug targeting describes the selective targeting of therapeutics in a tumour by an external magnetic field in order to allow a controlled drug release. A controlled drug release is ensured if a sufficient amount of nanoparticles is internalized in the tumour cells. To analyse this, we quantified the MNP uptake inside and on the surface of pancreatic tumour cells (Fig. 12).

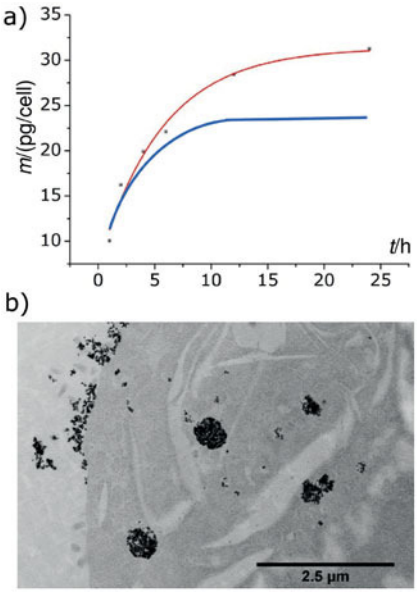

Fig. 12: a) Quantification of MNP internalization in pancreatic human cells as a function of time (in collaboration with Physikalisch-Technische Bundesanstalt, Berlin). Red line: exponential fit of the measured data. Blue line: uptake kinetics of MNP only on the surface of the cells. b) TEM image of cells with internalized and surface bounded MNP.

NRW-Schwerpunktprofessur Biohybrid & Medical Textiles/ BioTex

Univ.-Prof. Dr. med. Stefan Jockenhövel

The *NRW-Schwerpunktprofessur Biohybrid & Medical Textiles* focuses on the development of viable implants with the potential for remodeling, regeneration and self-repair.
The mission statement of the NRW-Schwerpunktprofessur is **"Innovation & Translation by Interdisciplinary Collaboration"**. Therefore, the department is organized as a **bridging research group** between the *Aachen-Maastricht Institute for Biobased Materials* (biomaterial research, Faculty of Science) via the *Institute for Textile Engineering* (biomaterial processing and textile reinforcement, Faculty of Mechanical Engineering) towards the clinical application at the *Institute for Applied Medical Engineering* (biohybrid implant development and (pre-) clinical evaluation, Medical Faculty). Regarding the translation into clinic, the biohybrid approach focuses on the optimal combination of a (i) (non-biodegradable) technical component to guarantee a high (re)producibility with a (ii) cellular component to guarantee an optimal biological performance. Therefore, we have introduced the biomimetic textile-reinforcement in the field of regenerative medicine.
Selected **research highlights in 2016**:

- Using **hybrid elastin-like recombinamer-fibrin gels** for cardiovascular tissue engineering applications (Gonzalez de Torre et al. Biomaterials science 2016)
- Development of a vital endobronchial stent with a **flexible endoscopic spray applications of respiratory epithelial cells** as platform technology to apply cells in tubular organs (Thiebes et al. Tissue engineering part c-methods 2016 and Ann Biomed Eng. 2016) (funded by EU-Project PulmoStent)

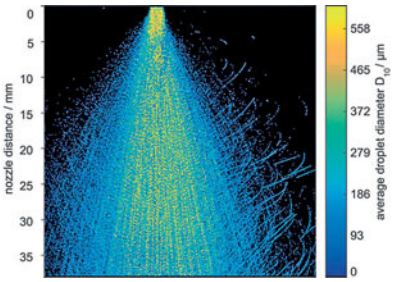

Fig. 13: Droplet distribution in the endoscopic cell seeding process.

- Development of a **bioengineered vascular test set-up as living models for in vitro cardiovascular research (Wolf et al. Drug discovery today 2016) (funded by the BMBF)**
- Development of Tissue-Engineered **Fibrin-Based Heart Valves with Bio-Inspired Textile Reinforcement** (Moreira et al. Advanced healthcare materials 2016).
- **Festive Opening of the *Aachen Maastricht Institute for Biobased Materials*** on the Brightland Chemelot Campus in Geleen, Sittard, The Netherlands.

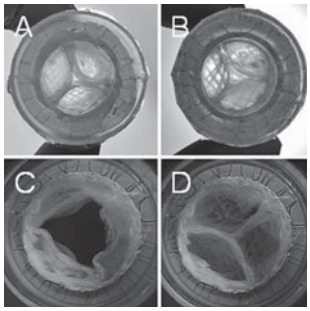

Fig. 14: Textile-reinforced biohybrid heart valve for aortic valve replacement.

Science Management/SCM

Dr. Robert Farkas

Although interdisciplinary collaboration is considered to be the most promising tool to tackle the braking effect of the increasing complexity in developing innovative medical devices, finding the most suitable partners for an effective R&D-cooperation is often haphazard. But little is known about the time course between idea and a successful product in medical technology.

So we analyzed the time gap of biomedical innovation using our recently established information retrieval framework of the textual outcome of research and development, e.g. patent documents, publications etc. Supported by the German Patent and Trademark Office and DIMDI we successfully elaborated specific time lags depending of the risk class of the device (Fig. 15).

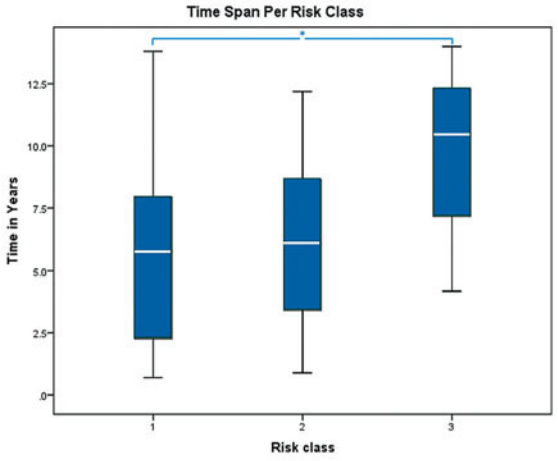

Fig. 15: Time lag in biomedical innovation as a function of risk class assigned to the products.

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

Fig. 16: The new Training-Center of the Medical Faculty, to be opened in 2017. (Illustration by Frauenrath and sop-Architects).

Acknowledgements

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Awards

- Dr. Roland Graefe: Ph.D. Award of the European Society for Artificial Organs ESAO
- Dipl.-Ing. Indra Mueller: Exchange Scholarship of the European Society for Artificial Organs ESAO

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Team

Facts

Third-party funding

	Number of Projects	Total Expense of Projects [EUR]
German Research Foundation (DFG)	54	1.783.201
German Federal Ministry of Education and Research (BMBF)	36	2.181.949
EU	13	973.892
Industry	31	1.450.216
Other	40	1.006.264
Sum	174	7.395.522

Theses

	Number
Bachelor	64
Diploma/Master	81
Doctoral	29
Habilitation	1
Sum	175

Staff

	Scientific	Non-Scientific
Total	187,50	47,80
Third party funded	133,50	10,00

in full-time equivalent (FTE)

Publications

	Number
Conference proceedings	78
Peer-reviewed journals	189
Books and book chapters	9
Sum	276

Patents and patent applications: 16

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