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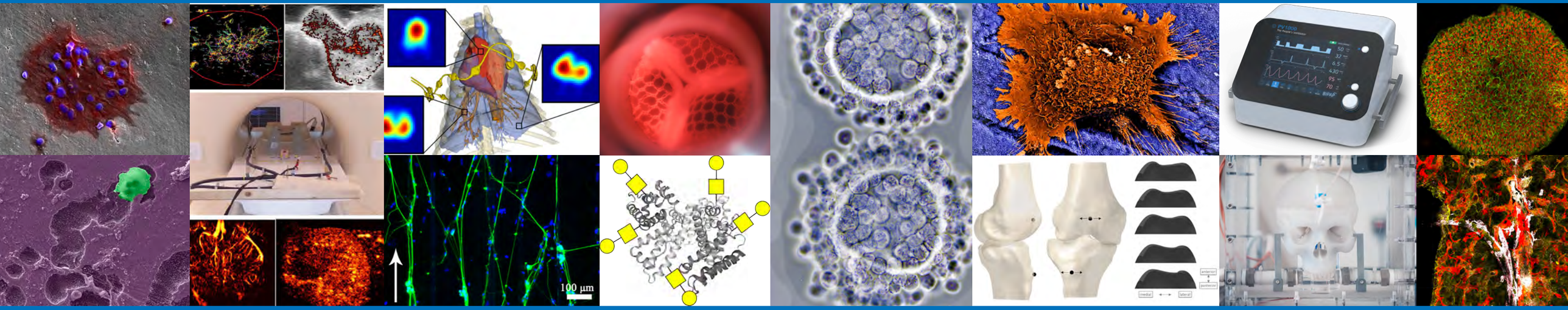
Helmholtz-Institute for Biomedical Engineering

Annual Report 2020



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Preface

The Helmholtz-Institute for Biomedical Engineering HIA represents a major hub for interdisciplinary basic as well as application-oriented research and development in biomedical engineering at RWTH Aachen University and beyond. In 2020, the Corona pandemic dominated our research and teaching activities. Video conferences and digital teaching were and still are the tools to interact with colleagues and students.

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

Research projects target improved health care. Continuous refinement of methods and technologies helps to achieve personalized diagnostic and therapeutic options for patients. Networking and cooperation within RWTH Aachen University as well as with national and international clinicians, academic and industry researchers are key to our work. Members of the Helmholtz-Institute for Biomedical Engineering have been instrumental in securing funding for both coordinated teaching and research. In 2020, external funding alone has reached well over 11.000.000 €.

This annual report is dedicated to our sponsors, partners, and friends for their support and cooperation and to all individuals that are interested in our institute. Enjoy reading our Annual Report 2020. We would be happy to provide further information on any of the topics reported herein and discuss future options of cooperation in the fascinating field of biomedical engineering.

Aachen, April 2021

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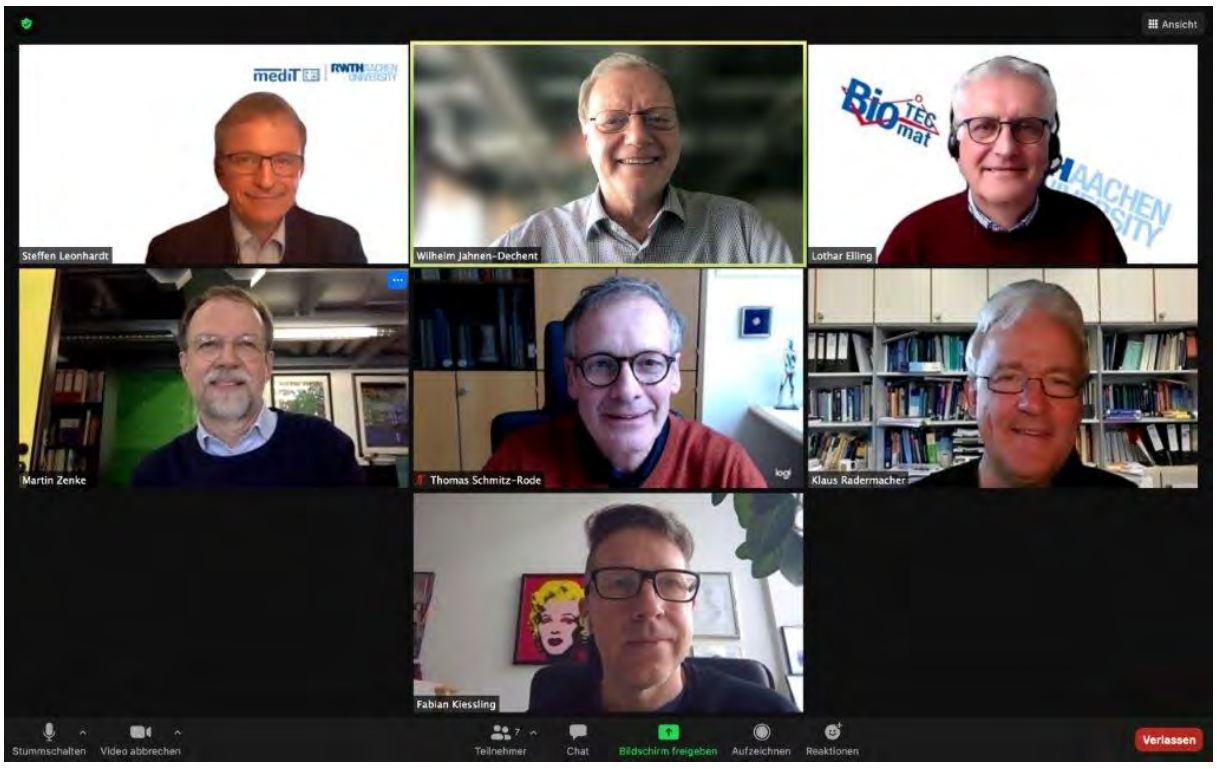
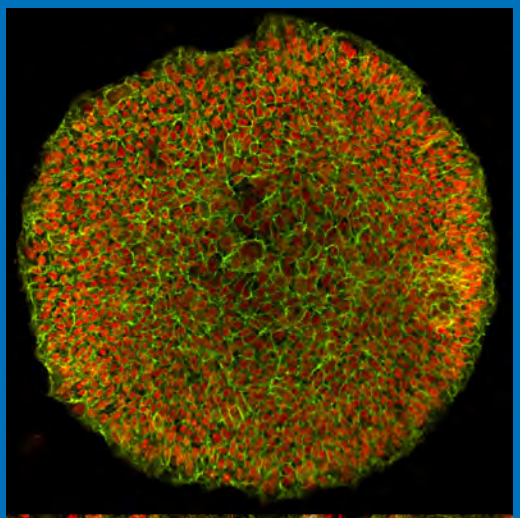
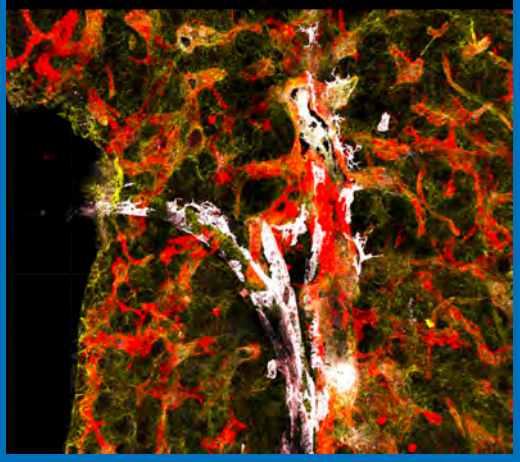


The Board of Directors of the Helmholtz Institute for Biomedical Engineering (from left to right – top down): Steffen Leonhardt , Willi Jahnen-Dechent, Lothar Elling, Martin Zenke, Thomas Schmitz-Rode, Klaus Radermacher, Fabian Kiessling

Cell Biology

Gene Function in Cell Growth, Differentiation & Development





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Introduction

Our studies during the year adressed pre-clinical biomedical research at various levels, ranging from subcelluar molecular mechanisms to in vivo drug testing (Fig. 1). They aimed at understanding basic cellular aspects like adhesion and migration of antigen presenting dendritic cells (DC) and macrophages, modeling of diseases (leukemia, premature aging syndromes) using induced pluripotent stem cells (iPS cells), improving diagnosis and identifying biomarkers via DNA methylation (DNAm) and single-cell RNA sequencing (scRNA-seq), and establishing novel therapies to treat patients.

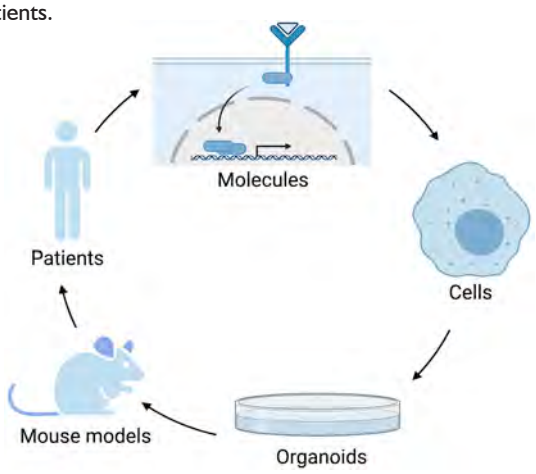

Fig. 1: Research topics of the year 2020 covered pre-clinical biomedical research at various levels (created with BioRender.com).

In 2020 we welcomed Rebekka Schneider, MD, PhD from Erasmus Medical Center, Rotterdam, The Netherlands as a new professor in the institute. Rebekka Schneider currently leads both her group in Rotterdam and her new group in the institute. Her primary focus is disease-oriented laboratory investigation of clonal myeloid neoplasms, employing a range of genomic technologies, specifically with single cell resolution, as well as classical cellular and molecular biology experimental approaches.

Drug Discovery with Patient Specific Induced Pluripotent Stem Cells (iPS Cells)

Patient specific iPS cells provide unique opportunities for disease modeling and drug screening, since they capture the disease-causing mutation(s), including disease-associated mutations, on the patient specific genetic background. We focused on advanced systemic mastocytosis (SM) and mast cell leukemia, and generated more than 1000 iPS cell lines from 14 patients with KIT D816V/H mutation (in collaboration with the Department of Hematology, Oncology, Hemostaseology and Stem Cell Transplantion, RWTH Aachen University Hospital). We also introduced the KIT D816V mutation in human embryonic stem cells (ES cells) by CRISPR/Cas9n editing.

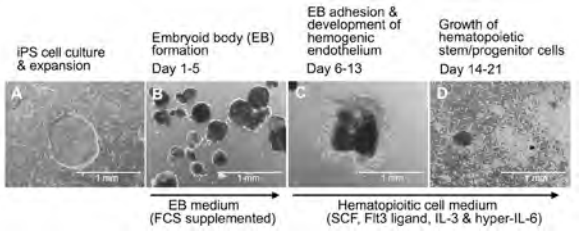

Fig. 2: Human iPS cells (A) are differentiated in an embryoid body (EB) protocol (B and C) toward hematopoietic cells (D). Scale bars: 500 µm.

KIT D816V hematopoeitic cells and mast cells obtained from KIT D816V iPS cells and ES cells recapitulated the pathology of mast cell disease in vitro, including patient-specific features (Fig. 2). Compound screening of KIT D816V cells identified nintedanib and its analogues as potent novel KIT D816V inhibitors (Fig. 3). Nintedanib efficacy was further validated in KIT D816V primary patient samples and in a murine KIT D816V model. Our work suggests nintedanib as a new drug candidate for KIT D816V targeted therapy of advanced SM (Toledo et al., Blood, in press).

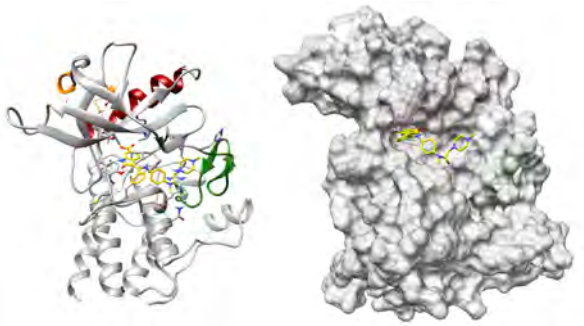

Fig. 3: Molecular docking shows KIT D816V ribbon structure with nintedanib in cartoon (left) and surface representation (right). Nintedanib is represented in yellow licorice.

The setting up of the automatic cell production facility for iPS cells (iCellFactory) we now completed. We expect the facility to meet the ever increasing need of patient specific iPS cells and derivatives thereof for compound screening (Fig. 4; see also above; in collaboration with Laboratory for Machine Tools and Production Engineering, WZL, RWTH Aachen University and Fraunhofer Institute for Production Technology, IPT, Aachen, Germany).

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

HGF Receptor/Met-signaling regulates Dendritic Cell Migration

DC are key regulators of adaptive immune responses and act as sentinels in almost all peripheral tissues of our body. DC originate from hematopoietic stem cells in bone marrow and leave it as precursors to immigrate into peripheral tissues, such as skin, where they become temporarily sessile. Following antigen uptake DC are activated, emigrate the peripheral tissue and travel via lymphatic vessels to lymphoid organs where they encounter T cells to present processed antigens. Thus, migration and homing of DC are closely interrelated to their development and function.

We previously identified HGF receptor/Met-signaling in DC as essential in the process of emigration from the skin tissue. We studied in more detail the role of Met-signaling on adhesion to extracellular matrix proteins and their degradation, which is in part mediated by podosome formation. We also addressed the response to chemotactic factors (Fig. 5) and the role of the Gab1-Ras-ERK-kinase pathway.

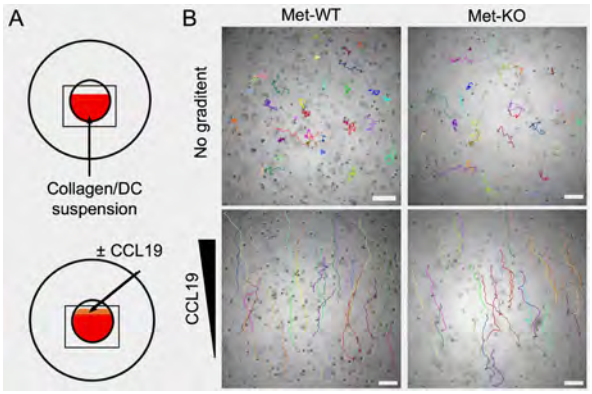

Fig. 5: Chemotaxis assay in 3D collagen gels. (A) Scheme of the experimental setup. (B) Met-signaling competent (Met-WT) and deficient (Met-KO) DC were applied on 3D collagen gels with or without a CCL-19 chemokine gradient. Migration of DC through the gel was recorded by time-lapse microscopy. Individual cells were tracked using the MTrackJ plugin tool of the Fiji software and were analyzed for velocity, distance and directional persistence. Scale bars: 50 µm.

Regulation of Cell Migration and Adhesion: Impact of Leukocyte-specific Protein 1 and Myosin 1e

Several cytoskeleton-associated proteins and signalling pathways work in concert to regulate actin cytoskeleton remodelling, cell adhesion and migration in normal and pathological processes. Among them, the leukocyte-specific protein 1 (LSP1) and myosin1e form a molecular complex thus working in concert to regulate actin cytoskeleton remodelling during phagocytosis, an early event of the immune response. We also demonstrated that LSP1 down regulation severely impairs cell migration, lamellipodia formation and focal adhesion dynamics in macrophages. Moreover, the inhibition of the interaction between LSP1 and myosin1e also impairs these processes resulting in poorly motile cells, which are characterised by few and small lamellipodia (Fig. 6). Cells in which LSP1-myosin1e interaction is inhibited are typically associated also with inefficient focal adhesion turnover. Our findings show that the LSP1-myosin1e bimolecular complex plays a pivotal role in the regulation of actin cytoskeleton remodelling and focal adhesion dynamics required for cell migration.

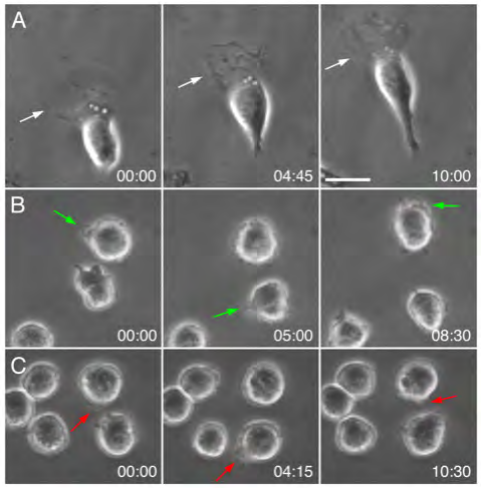

Fig. 6: LSP1 and myosin1e are essential for lamellipodia dynamics. (A-C) Time-lapse images showing lamellipodia morphology and dynamics in control (A), LSP1-deficient (B) and J774 cells expressing the LSP1 deletion mutant LSP1-ΔSBS (C). Note the large and very dynamic lamellipodium formed by control cells (arrows in A). LSP1-deficient cells or cells expressing an LSP1 mutant unable to interact with myosin 1e typically formed very small lamellipodia around their periphery (arrows in B, C). Numbers indicate the elapsed time in minutes and seconds. Scale bar: 10 µm.

S100A8/A9 as Novel Biomarker and Therapeutic Target for Disease Management of MPN

Myeloproliferative neoplasms (MPN) follow a biphasic disease course. The early phase is characterized by excess production of mature blood cells. The late phase shows hematopoietic insufficiency due to fibrosis of the bone marrow (myelofibrosis; MF). With progression from early to late phase, survival drops dramatically. Unfortunately, no biomarker exists to predict disease progression towards MF, moreover no specific anti-fibrotic therapies exist.

Our research aims at understanding the mechanisms that drive fibrosis. By applying single-cell RNA sequencing (scRNA-seq) we found that mesenchymal stromal cells (MSC) in bone marrow are functionally reprogrammed in a stage-dependent manner (Leimkühler et al., 2020). In the pre-fibrotic stage MSC lose their progenitor status and switch to differentiation. In the fibrotic stage MSC acquire an inflammatory, pro-fibrotic phenotype. Importantly, expression of the alarmin complex S100A8/S100A9 in MSC marks disease progression towards MF in mice and humans (Fig. 7). Tasquinimod, a small-molecule inhibiting S100A8/S100A9 signaling, significantly ameliorated the MPN phenotype and fibrosis in JAK2V617F-mutated murine models, highlighting that S100A8/S100A9 is an attractive therapeutic target in MPN.

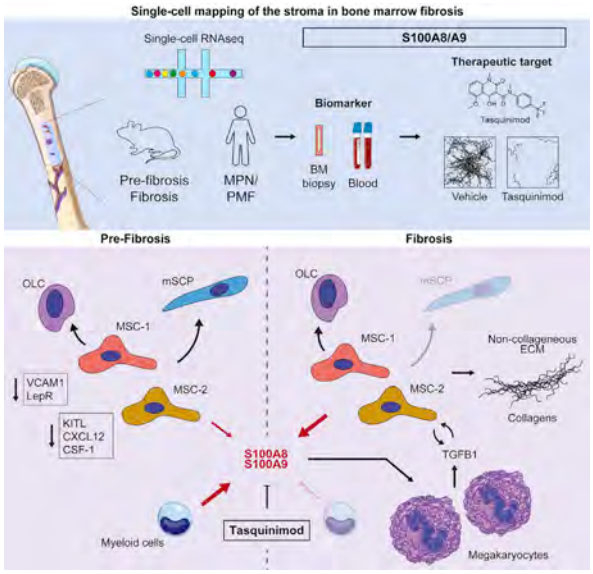

Fig. 7: Scheme showing the transition from a pre-fibrotic to a fibrotic stage in MPN, marked by expression of the alarmin complex S100A8/S100A9 (Leimkühler et al., 2020). Inhibition of S100A8/S100A9 by tasquinimod ameliorates the MPN phenotype.

This allows us to apply deconvolution on epigenetic profiles to estimate the composition of these cellular fractions in a given tissue. So far, deconvolution of DNAm profiles were performed with large signatures of many CG dinucleotides (CpGs). We investigated whether or not the characterization of cell types in tissue can also be achieved with individual cell type-specific CpG sites. This would allow us to use targeted analysis, such as pyrosequencing (Schmidt and Maié et al., 2020).

To identify cell type-specific CpGs, we collected 579 samples from 46 different studies, mostly generated with the Illumina 450K BeadChip technology. We developed and used an in-house analysis pipeline for the selection of CpGs based on high difference in mean methylation and low variance within the groups (Fig. 8). The mean DNAm levels from the training dataset were used as our reference matrix when applying the non-negative least squares (NNLS) deconvolution algorithm together with the eight selected CpGs. The results from the NNLS algorithm allows to estimate for the cellular composition of tissues or other DNA mixes. Our method can be used to gain insight into the composition of unknown tissue specimen or to correlate the percentage of specific cellular subsets with clinical parameters. Furthermore, this approach might provide estimates for the composition of cell-free DNA (cfDNA), which is increasingly relevant for liquid biopsy.

Deconvolution of Cellular Subsets in Human Tissue Based on Targeted DNA Methylation

It is not trivial to determine the composition of different cell types within a tissue. We identified characteristic DNA methylation sites for leukocytes, endothelial cells, epithelial cells, hepatocytes, glia, neurons, fibroblasts, and iPS cells.

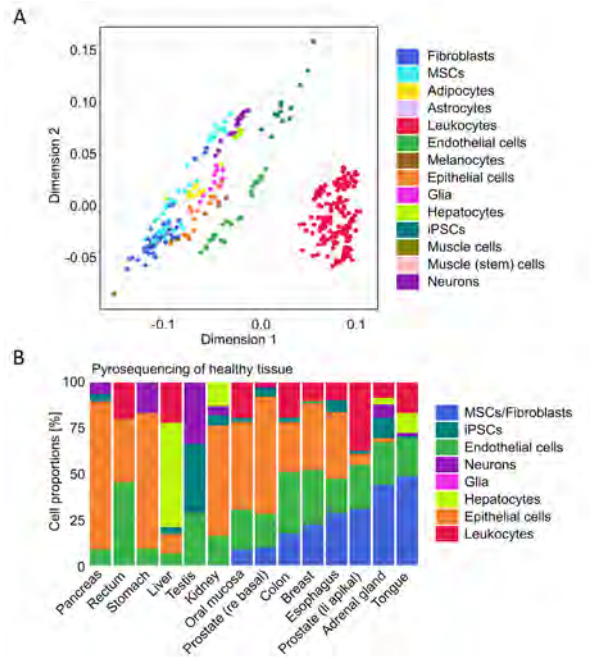

Fig. 8: Deconvolution of cellular subsets in human tissue. (A) DNA methylation profiles of various cell types of different studies are presented in a multidimensional scaling (MDS) plot. (B) Deconvolution of healthy tissues based on pyrosequencing of DNAm at the eight relevant CpGs.

Disease Modelling of Premature Aging Syndromes in iPS Cells

Dyskeratosis congenita and idiopathic aplastic anemia are bone marrow failure syndromes that provide aspects of premature aging syndromes. We have demonstrated that these patients reveal abnormal DNA methylation in a gene called PRDM8 (Fig. 9A).

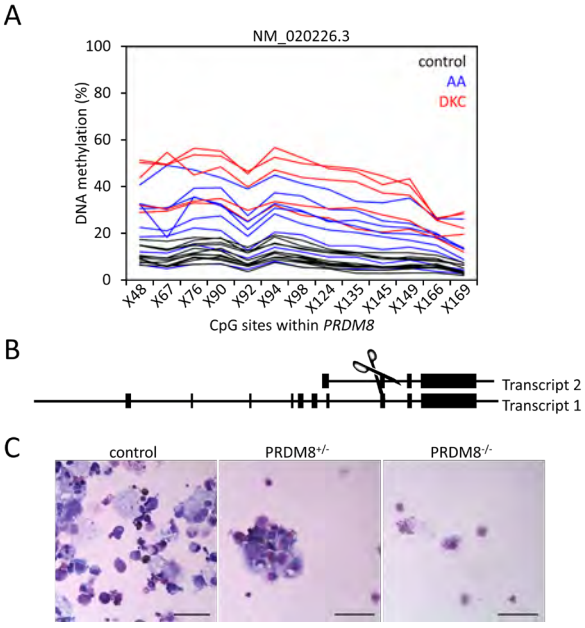

Fig. 9: PRDM8 is relevant for hematopoietic differentiation of iPS cells. (A) Aberrant hypermethylation in the gene PRDM8 was observed in patients with dyskeratosis congenita (DKC) and aplastic anemia (AA). (B) PRDM8 was knocked out in iPS cells with CRISPR/Cas9 technology. (C) PRDM8 knockout lines cannot be differentiated towards the hematopoietic lineage. Scale bars: 500 µm.

DNA methylation at this genomic region therefore provides a biomarker that can support diagnosis of these bone marrow failure syndromes and other premature aging syndromes. To further elucidate the biological function of PRDM8, we generated iPS cells without expression of this gene to investigate the effect on cellular differentiation. To this end, we used the CRISPR/Cas9 technology to knockout PRDM8 (Fig. 9B). Upon loss of PRDM8, iPS cells were hardly capable of differentiating towards the hematopoietic lineage (Fig. 9C). Furthermore, the neuronal differentiation potential was impaired as well. These results suggest that modulation of PRDM8 might play a role for premature aging syndromes, which often reveal hematological and neuronal defects (Cypris et al., 2020).

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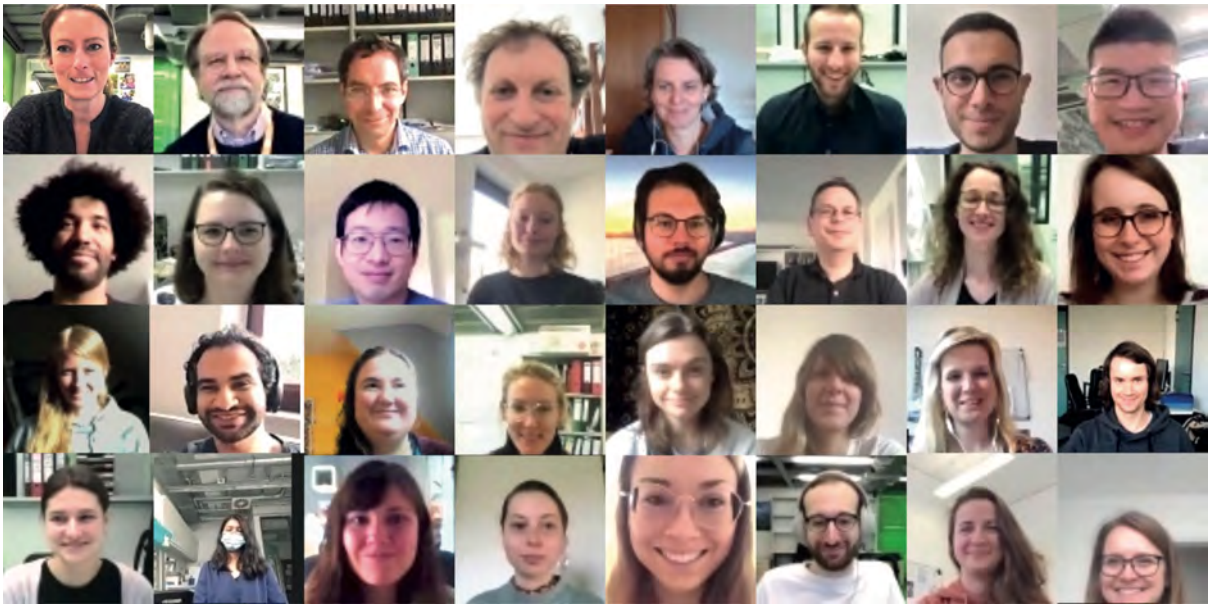

mediT

Medical Information Technology

Faculty of Electrical Engineering and Information Technology

Smart Solutions for Advanced Healthcare

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Introduction

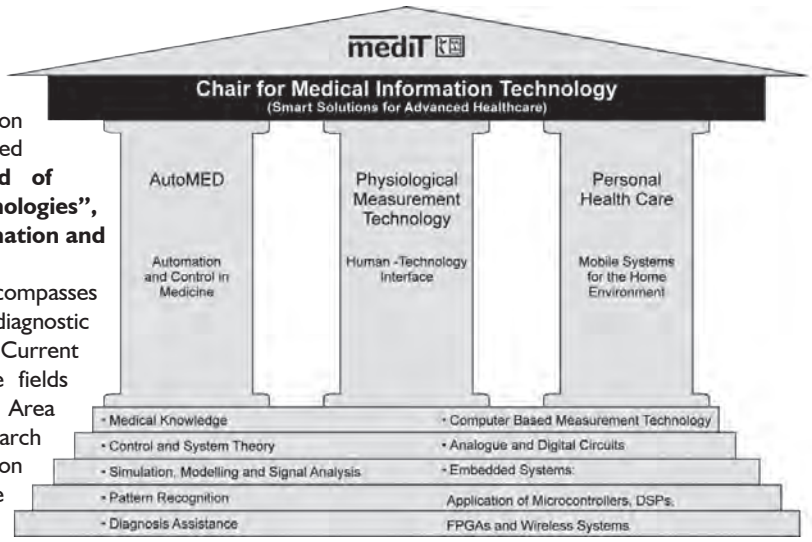

Fig. 1: Research profile of MedIT.

The Chair for Medical Information Technology is especially concerned with research problems in the **field of "Unobtrusive Measurement Technologies", "Personal Health Care", and "Automation and Control in Medicine".**

The topic Personal Health Care encompasses wearable medical devices, particularly diagnostic devices, designed for use at home. Current technological developments are in the fields of „Intelligent Textiles" and „Body Area Networks" (BAN), related basic research areas (e.g. signal processing and motion artifact rejection), and sensor fusion. Due to demographic trends, especially in developed nations, the laboratory also focuses on the needs of the elderly (e.g. enabling greater autonomy at home).

Automation and Control in Medicine is involved with the modeling of medical and physiological systems and the implementation of feedback controlled therapy techniques. Research topics include tools and methods for the modeling of disturbed physiological systems, sensor supported artificial respiration, active brain pressure regulation, and dialysis regulation and optimization.

Where necessary and sensible, sensors and measurement electronics are developed, for example, in the areas of non-contact sensing techniques (e.g. magnetic bioimpedance), bioimpedance spectroscopy and inductive plethysmography. Active research is currently conducted in biomechatronics.

Ongoing Research - Selected Projects

Contactless Control of the Incubator Temperature using Infrared Thermography

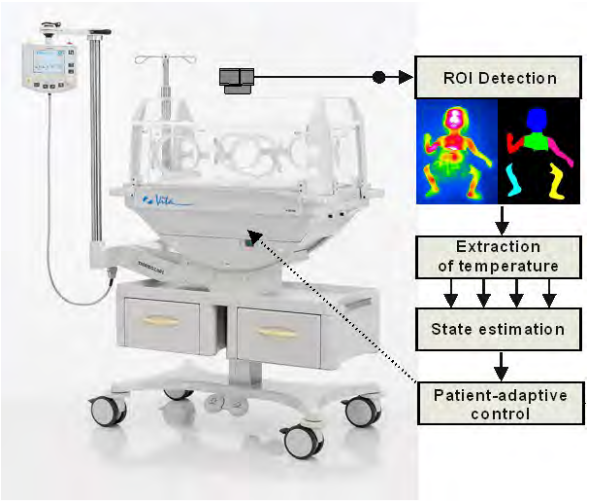

Fig. 2: Concept of contactless control of incubator temperature using infrared thermography [source: weyermed.com].

Since preterm infants are very delicate to heat loss after birth and the thermoregulation of their surrounding environment is crucial for the survival during neonatal intensive care. A neonatal incubator typically provides such regulation to newborn infants by monitoring body temperature and providing the needed warmth by heating the surrounded air. However, traditional monitoring systems usually require invasive or skin-contacted sensors, which can increase the risk of infection and damage the immature skin of neonates. In addition, the wiring of the sensors also complicates the work of the nursing staff and increases the psychological stress of the family. Parents often subjectively perceive the large number of sensors as an indicator of the severity of their child's care/illness.

The project aims to optimize the temperature control of the incubator using infrared thermography. Together with our project partners (Weyer GmbH, Dieter Richrath GmbH, and Uniklinikum Aachen), we want to develop a prototype that combines contactless temperature monitoring and individual thermoregulation inside the incubator. The use of infrared thermography makes it possible to measure the temperature not only at a few dedicated points, but also spatially resolved on the surface of the mattress. In particular, the measurement includes not only the temperature distribution on the mattress of the incubator, but also the temperature distribution of the patients themselves, becoming part of the control loop without contact. In this process, image processing algorithms are used to automatically detect regions of interest (ROIs) that serve as "virtual temperature sensors. This allows the monitoring of the temperature distribution of the neonate, which will be summarized in a novel „inhomogeneity index". Furthermore, the metabolic activity and the individual heat demand can also be estimated.

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

Data Fusion for Continuous Health Monitoring of Vehicle Drivers

Many traffic casualties can be traced back to driver fatigue, drowsiness or other critical physiological states such as heart attacks and strokes. Due to the aging demographics, the number of casualties can be expected to increase. Especially in partly autonomous vehicles, it is therefore crucial to monitor the fitness of a vehicle driver since the driver must be capable of taking control over the vehicle at any moment. With respect to the aging society, in-vehicle health monitoring also closes the gap of personal health care at home for early detection of various diseases. For personal health care applications, unobtrusive sensing technologies on different modalities are typically used, which can be invisibly embedded into fixed and secured objects, such as driver seats or driver cabins. These sensors include capacitive electrocardiography (cECG), ballistocardiography (BCG), magnetic induction (MI) sensors, radar and camera-based techniques.

Based on different sensor modalities, data fusion techniques can be employed on three different levels (see Fig. 3). First, signal-level fusion can be employed on the raw signals to increase the coverage and accuracy for the estimation of vital signs, such as cardiac and respiratory signals. Second, feature-level fusion can be applied on previously extracted features such as heart rate or breathing rate to classify the health status of a. Third, decision-level fusion can be used to decide whether the driver is fit for driving or not, and further measures can automatically be taken into action. These measures can include the coffee cup symbol, used often nowadays to point out drowsiness or fatigue with the recommendation to take a break. Yet telemedicinal approaches could also be a corrective measure in case of a heart attack or a stroke, wherein their detection might be combined with the automatic notification of an ambulance. In the latter case, the car could also automatically drive into a safe location to prevent possible car accidents.

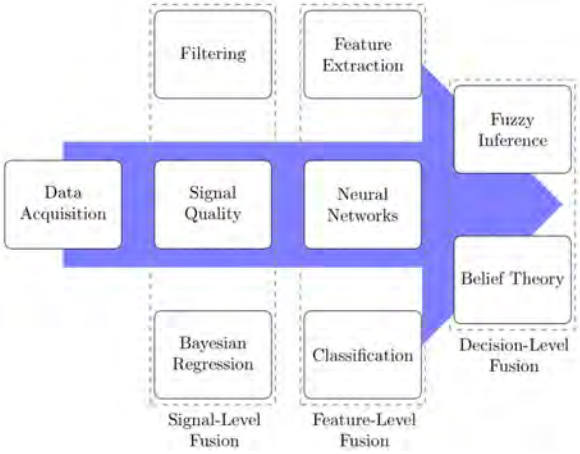

Fig. 3: Process of data fusion with examples for each level.

Automated Phrenic Nerve Stimulation with Mechanical Ventilation

The inactivity of diagphragm during traditional mechanical ventilation can lead to ventilator-induced diaphragmatic dysfunctions (VIDD), which are associated with 30 % of mechanically ventilated patients who are difficult to wean from the mechanical ventilator and to 10 % who face prolonged weaning. To ensure diaphragm activity, the phrenic nerve can be stimulated artificially. Together with Uniklinik RWTH Aachen, this project aims to develop a closed-loop system, which controls the phrenic nerve stimulation and the mechanical ventilation.

The closed-loop system must keep the patient in a safe condition and the diaphragm should be sufficiently stimulated to prevent VIDD. A configuration of the system is shown in Fig. 4. The stimulator generates electrical impulses, which are transmitted near to the phrenic nerve, causing a contraction of the diaphragm. The patient takes an artificially generated spontaneous breath. The real-time control system receives measurements from the stimulator, the mechanical ventilator and the patient monitor. The stimulator measures the voltage and current during the stimulation impulses whilst the mechanical ventilator measures the airway pressure and the flow in and out of the lung; the patient monitor measures the patient's condition such as the heart rate. Based on these measurements, the real-time control system adjusts the settings of the stimulator and the mechanical ventilator.

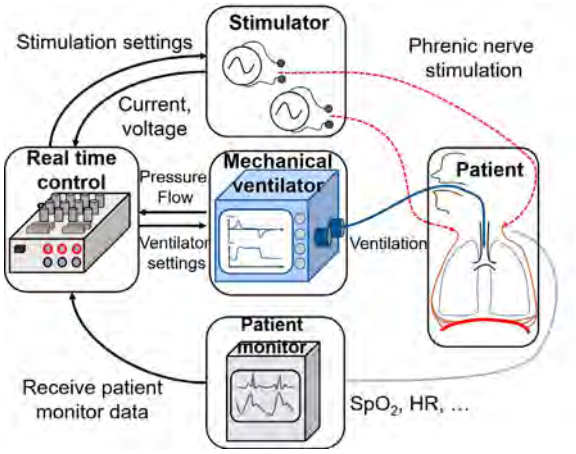

Fig. 4: Configuration of the closed-loop system with parallel phrenic nerve stimulation and mechanical ventilation.

This critical application imposes challenges on the overall system in terms of the least invasive method to place the electrodes near the phrenic nerve, an error of the stimulation and mechanical ventilation control algorithm, and an overstimulation that may lead to muscle fatigue.

Funded by: German Research Foundation (DFG)

Estimation of Force and Torque Development based on Dynamic Muscle Properties

Elders are suffering from a lack of mobility, typically resulting from ongoing age-related muscular atrophy. To relieve this process, early application of muscle development by training has proven as a valuable tool. Nevertheless, there is no feasible tool to assess the muscles force/torque development solely based on physiologic and dielectric tissue properties. One way to establish such a force/torque estimator is the algorithmic fusion of different measuring modalities, assessing indicators of physiological, morphological and metabolic aspects during muscle activity using the surface Electromyogram (sEMG) and Electrical Impedance Myography (EIM).

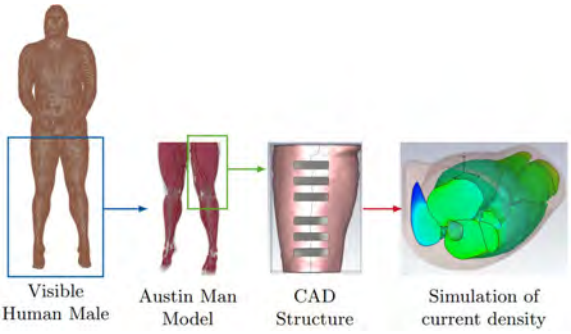

Fig. 5: Development of an FE-Model enabling simulation of current density within the upper leg.

A comprehensive analysis is investigated based on the physiological, morphological and metabolic processes of muscle activity and their impact onto the measured EIM and sEMG signals. Source separation strategies shall provide deeper insights into the superimposed processes shaping the signals, later approximating the dynamic process of muscle contraction and relaxation.

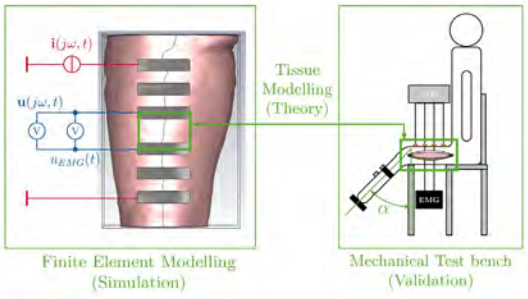

Fig. 6: Combination of theoretic knowledge, FEM and measurements to establish the basis of a force/torque estimation approach.

To realize this goal, an anatomical correct Finite Element Models (FEM) representing the human extremities are designed and consequently validated by measurements.

Funded by: German Research Foundation (DFG) and the Russian Foundation for Basic Research (RFBR)

Validation of Regional Lung Perfusion Monitoring using Electrical Impedance Tomography

For comprehensive cardiorespiratory monitoring of a patient, both the independent and synergetic knowledge of the pulmonary ventilation and perfusion status is imperative. As far as clinical practice is concerned, these two components are estimated resorting to techniques ranging from basic lung function tests to medical imaging. Despite the latter even being capable of estimating the invaluable ventilation-perfusion ratio, none grants us a chance of simultaneous, real-time, and non-invasive monitoring of ventilation and perfusion.

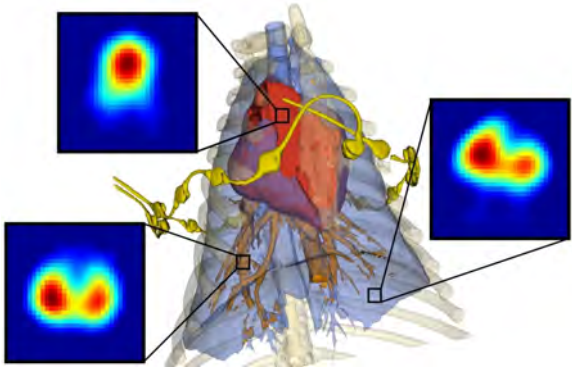

Fig. 7: Regional lung perfusion monitoring using electrical impedance tomography.

This project aims at validating electrical impedance tomography (EIT) as a perfusion monitoring technique, in the realm of ventilation-perfusion estimation. Therefore, the main mission is to compare the perfusion analysis promoted by EIT data with that of state-of-the-art Perfusion Computerized Tomography (CT-P), both simultaneously obtained from animal trials with an embolism-based damage model. Such endeavours will yield a thorough qualitative and quantitative characterization of the technique for perfusion using the challenging reference of CT-P, which, due to its invasiveness, cannot be used in clinical ventilation-perfusion practice, despite its superior accuracy.

Furthermore, the project seeks to investigate the underlying sources of this EIT perfusion signal. The signal is thought to result from the combined activity of single sources, like the movement of large calibre vessels, the pulsatile blood signal, down to the orientation of the blood cells. In this scope, we are constructing multi-physics models that can individually mimic these sub-components, allowing us to assess their influence. The perfusion signal is about an order of magnitude smaller than that from ventilation, with partially overlapping spectra, making it a non-trivial source-separation problem. We believe that the success of this work would provide the missing puzzle piece in the quest for the grail of cardiorespiratory monitoring.

Funded by: German Research Foundation (DFG)

Acquisition of Physiological Parameters for the Diagnosis of Affective Disorders

It is estimated that mental disorders account for 10% of the global burden of disease and are the leading cause of years lived with disability among all disease groups. Especially, affective disorders are the most important types of illness in terms of the duration of incapacity to work. Through acquisition of physiological data like photoplethysmography, skin response and temperature distributions, diagnostic markers will be defined that will allow a more precise diagnosis of the individual disorders. A more reliable differential diagnosis and improved monitoring of the course of therapy are the ultimate goal.

In this project not only contact based methods are used, but also the fusion of two inconspicuous measurement techniques, namely photoplethysmography imaging (PPGI) and infrared thermography are applied. PPGI enables the recording of heart rate and perfusion in the tissue as well as the quantification of the microcirculation, while infrared thermography shows the radiation of the patient's own heat. This enables local temperature distributions and central-peripheral gradients to be recorded and further analyzed. In addition, the system could enable the monitoring of a respiratory rate and other physical activities.

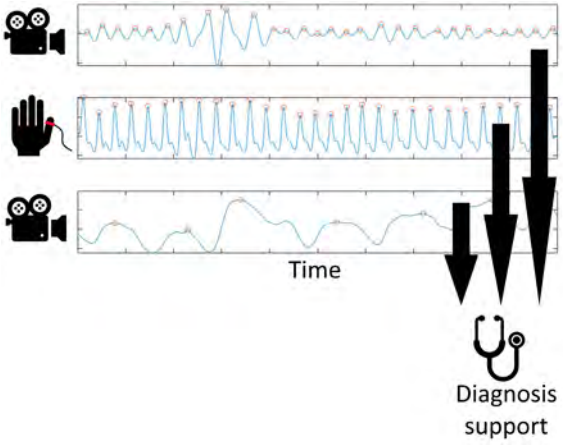

Fig. 8: Decision-based learning from sensor fusion for affective disorder classification.

Making use of predictive machine learning algorithms, both the individual and the combined predictive power for several relevant parameters can be determined. This requires the use of feature extraction, transformation and dimensionality reduction techniques combined with cross-validation of different learning paradigms including generative, discriminative, and deep learning approaches. This will help to increase diagnostic accuracy and improve treatment outcome for the depressive and schizophrenic patients, which seems highly relevant from clinical, scientific, and societal perspectives.

Funded by: European Regional Development Fund (ERDF)

Tremor Control using Deep Brain Stimulation

Related to the aging process of the population in western countries, researchers predict an increase of approximately 4.1 million Parkinson's patients worldwide in 2005 to 8.7 million Parkinson's patients in 2030. Since the treatment with medication often turns out to be insufficient or drug-resistant, Deep Brain Stimulation (DBS) is increasingly applied as an alternative treatment option.

DBS is also used to manage Tourette-syndrome, tremor, dystonia, and epilepsy. DBS is evolving as an effective treatment modality in certain neurological and psychiatric conditions. It has become an indispensable option for patients who have a poor response to medical therapy. During a neurosurgical intervention, small electrodes are implanted into specific regions of the basal ganglia, which are responsible for the control of motor functions. Through electrical impulses emanating from the electrodes, the regions of interest are excited such that symptomatic movement patterns are significantly reduced.

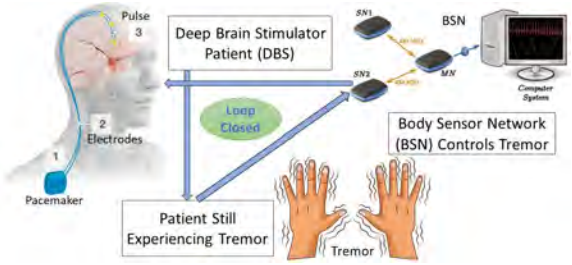

Fig. 9: Overview of tremor control using DBS.

The main risks of DBS are surgery itself, side effects after surgery, and side effects of stimulation. The side effects from stimulation could be managed with proper DBS control. Electrode polarity, stimulated frequency, pulse width, and current amplitude are stimulation parameters determining which neural elements in the surround of a stimulating electrode are being recruited. Although DBS is invasive with high risk and often associated with postoperative pain, it has been shown to have promising effects in some patients. With proper preoperative selection and follow-up, it can be the key for a better lifestyle for patients whose disability may not improve with medications. Controlling DBS automatically through an external programmable device that communicates with internal pulse generator (IPG) is the project's main idea. The IPANEMA body sensor network (BSN), containing motion sensors like accelerometer, gyroscope, and magnetometer, is also used as a tool for synchronized measurement for tremor monitoring in real time.

Funded by: German Academic Exchange Service (DAAD)

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Prizes and Awards

- C. Hoog Antink was admitted to the Young College of the North Rhine-Westphalian Academy of Sciences and Arts, January 2020.
- C. Ngo received the Borchers-Plakette 2020, ProRWTH.
- D. Rüschen won the 3rd prize for patient safety in medical technology, DGBMT, September 2020.

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Lehr- und Forschungsgebiet Biomaterialien

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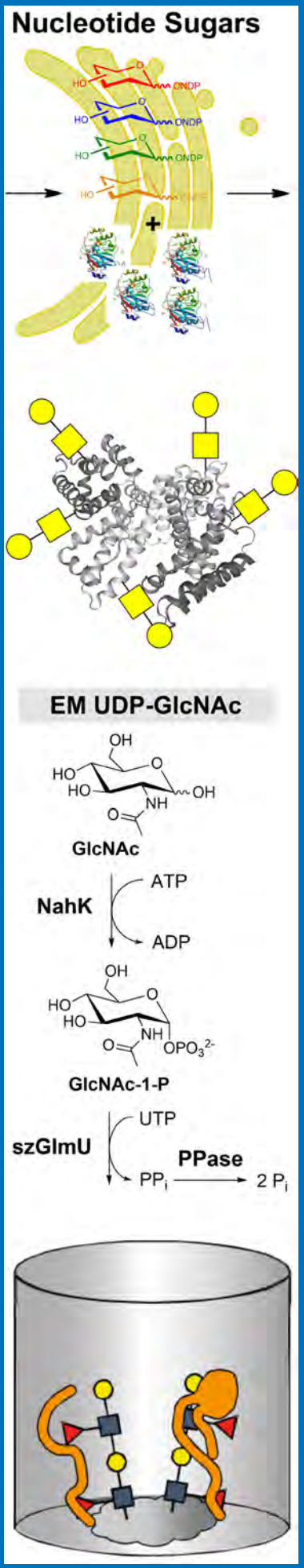
Laboratory for Biomaterials

Faculty of Mathematics, Computer Science and Natural Sciences

Synthesis and Application of Glycoconjugates



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Introduction

Sugar chains (glycans) of glycoproteins, glycolipids, and proteoglycans encode biological information on the cell surface and in the extracellular matrix (ECM). The complexity of glycans is the key for many cell-cell and cell-ECM interactions. Glycan-binding proteins, known as lectins, specifically decode the glycan information. In a disease-state, altered glycan structures of cell surface receptors trigger the binding of specific lectins with subsequent cell responses. Cell-surface glycans are adhesion points for specialized pathogens (bacteria, viruses) and bacterial toxins. Human milk glycans are essential for infant nutrition and intestinal protection against pathogens. Bioactivity and bioavailability of natural products, e.g. anti-oxidants, depend on their glycosylation. Polysaccharides are essential components of therapeutic and cosmetic products. With this background, sugar-based biomaterials are of special interest as diagnostic and therapeutic tools in biomedical research.

In 2020, the progress of our research projects was markedly hampered by the corona crisis. In this annual report, we provide an overview of our research efforts on the synthesis and applications of glycoconjugates. We summarize our general synthetic strategy using Leloir-glycosyltransferases. We expanded our enzyme toolbox by screening the microbiome. Optimization of enzyme-cascades was accelerated by high-throughput reaction analysis and resulted in the multi-gram-scale synthesis of nucleotide sugars as substrates for Leloir glycosyltransferases. The automated enzymatic glycan synthesis in a microreactor was realized as the next-generation strategy. Products are complex glycan structures, glyco- and biopolymers as well as neo-glycoproteins. Binding studies with human lectins revealed high-affinity glycoconjugates, e.g. glycan-based inhibitors for tumor-related galectins. This chapter summarizes the most recent results from our peer-reviewed publications in 2020.

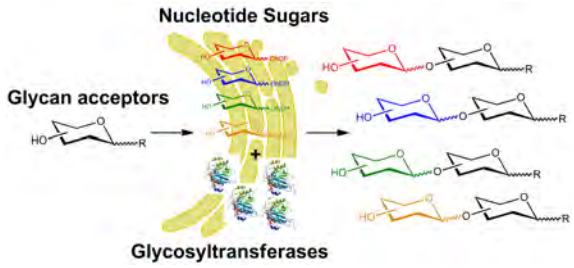

Fig. 1: Glycoconjugate synthesis with Leloir-glycosyltransferases.

Combinatorial Biocatalysis

a. The Golgi Glycan Factory (GGF)

In our BMBF funded project 'The Golgi Glycan Factory (GGF)', we produced nucleotide sugars and glycans. For *in vitro* glycan syntheses, a proper supply of nucleotide sugars and new Leloir glycosyltransferases is mandatory. There are only 5% of Leloir-glycosyltransferases (GTs) known. The pool of unknown GTs holds the potential for advances in the development of new synthetic processes (Fig. 1).[1]

However, there is a high demand for easily available nucleotide sugars. We utilized our IP-secured repetitive-batch-mode synthesis process to produce nucleotide sugars such as UDP-Gal, UDP-GlcNAc, or UDP-GalNAc in an industrially relevant scale (Fig. 2).[2]

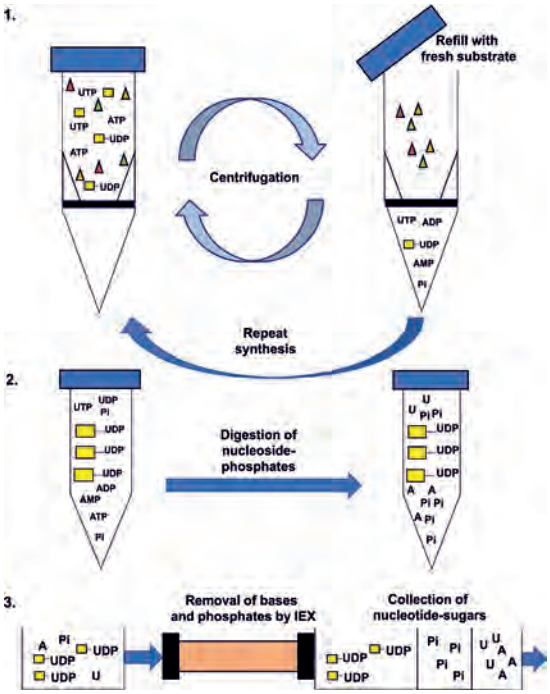

Fig. 2: Repetitive-Batch-Mode for g-scale enzymatic synthesis of nucleotide sugars. 1. Production of the nucleotide-sugar by re-usage of the synthesis enzymes. 2. To purify the nucleotide sugar, the remaining nucleotides must be removed by digestion. 3. Ion exchange chromatography is used for the separation of nucleotide sugar from the bases and phosphates.

We further developed processes for the synthesis of unnatural nucleotide sugar and sugar-1-phosphate derivates. They are precursors for the synthesis of unnatural glycoconjugates serving as drugs or analytical tools. In a cooperation project with Prof. Hanisch (Cologne University), 2-fluorinated galactose-1-phosphate was identified as potent inhibitor of the disease-related deficient human galactose-1-phosphate uridylyltransferase (hGALT).[3]

In cooperation with the group of Prof. Thomas Clavel (University Hospital Aachen), we were able to find novel lipases and glycosyltransferases in the intestinal pig microbiome.[4,5] By exceeding our view to the microbiome, we deepen the understanding of the role of *in vivo* glycosylation processes in the microbiome.[6] To foster the broad application, we joined expertise with Prof. Matthias Franzreb (KIT, Karlsruhe) to develop the technology for automated enzymatic glycan synthesis (Fig. 3).[7] The automated technology will supply glycoconjugate structures for studies promoting a deeper understanding of the gastrointestinal (GI) glyco-code and the interaction with its environment.

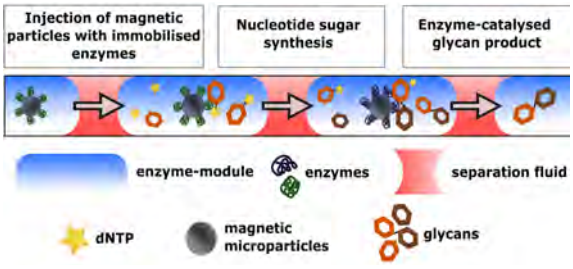

Fig. 3: Automated enzymatic glycan synthesis.

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Dr.-Ing. Raphael Heinzler, Prof. Dr. Matthias Franzreb, Karlsruhe Institute for Technology KIT.
Prof. Dr. Thomas Clavel, Dr. Thomas Hitch (Univerity Hospital Aachen)
Prof. Dr. Franz-Georg Hanisch (Cologne University)

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Financial Support

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b. Enzymatic Synthesis of Hyaluronic Acid and Glycosaminoglycans

Hyaluronic acid (HA) is a natural, non-sulfated, linear polymer consisting of repeating disaccharide units of [-3) GlcNAc(β1-4)GlcA(β1-]$_n$. with a molecular weight of size of up to 108 Da.

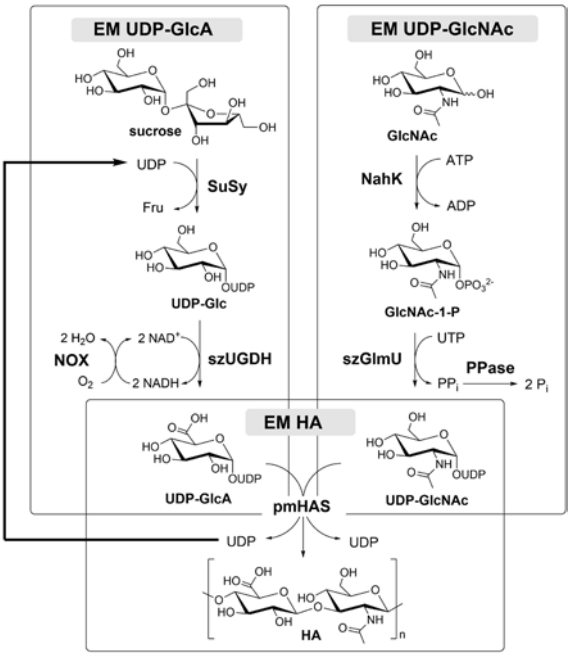

Fig.4: Enzyme cascade for the synthesis of hyaluronic acid from sucrose and N-acetylglucosamine.

As a polyanionic biopolymer, HA is a viscoelastic gel by binding large amounts of water. HA is widely used for medical and cosmetic applications such as drug/cosmetic agents, ophthalmic surgery, and tissue engineering. Current industrial production of high molecular weight (HMW) HA is based on harsh solvent-based extraction from rooster combs or bacterial fermentation with Streptococcus strains resulting in a highly dispersed HA product, which affects the biological properties of HA. Enzymatic *in vitro* synthesis has turned out as alternative for the synthesis of HA with defined HMW and low dispersity.[1,8] This was accomplished with hyaluronan synthase from *Pasteurella multocida* (PmHAS). However, *in vitro* HA production is limited by the availability and high consumption of the expensive substrates UDP-GlcA and UDP-GlcNAc.
We showed the production of UDP-GlcA and UDP-GlcNAc by enzyme cascades starting from renewable

substrates: sucrose (Fig. 4), glucuronic acid (GlcA, building block of pectin) (Fig. 5) and *N*-acetylglucosamine (GlcNAc, building block of chitin) (Fig. 4 and Fig. 5). In this respect, we optimized enzyme cascades for *in situ* generation of both nucleotide sugars and combined them with PmHAS in a one-pot synthesis of HMW HA (> 2 MDa) with a product titre of up to 4 g/L. For one-pot HA synthesis, reaction parameters were identified to set the ratio of the UDP-sugar substrates.[9] HMW HA with up to >2 MDa with low dispersity index (<1.1) and up to 4 g/L product titre was obtained. Starting the HA one-pot synthesis from GlcA and GlcNAc, the UDP-sugar ratio was adjusted by the concentration of magnesium ions (Mg^{2+}) resulting in HA MW of 1.55 MDa with low dispersity (1.05) and a HA concentration of 2.7 g/L.[9] Having the enzymatic tools and key parameters in hand, enzymatic HA synthesis shall now be lifted to the production scale.

Working Group

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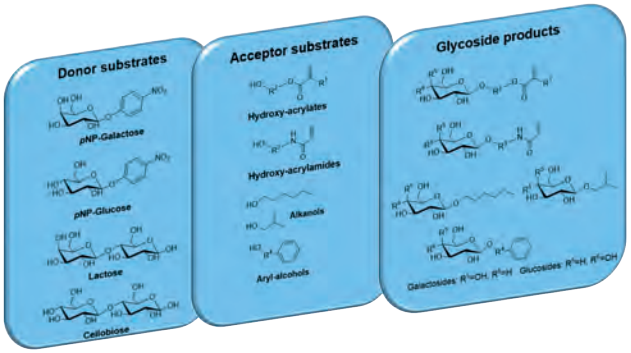

Fig.6: Substrate spectrum and prospective products of β-glycosidase from Pyrococcus woesei. [10, 11]

Collaborations

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M. Sc. Henning Zaun, Dr. J. Kuballa, GALAB Laboratories GmbH Hamburg.

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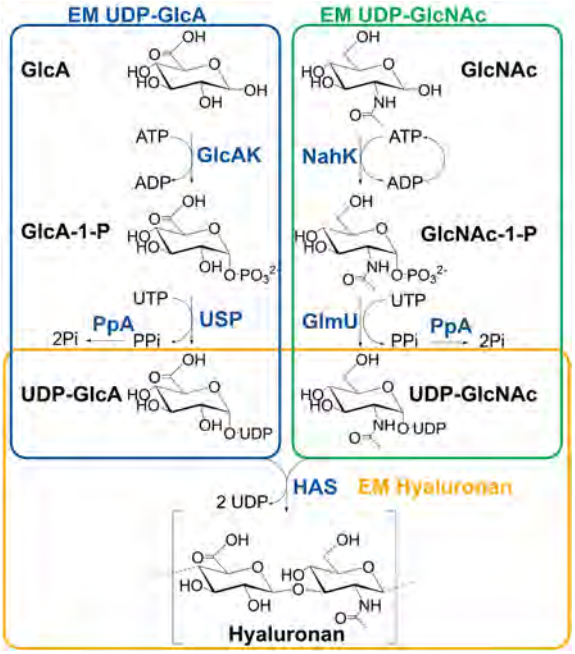

Fig.5: Enzyme cascade for the synthesis of hyaluronic acid from glucuronic acid and N-acetylglucosamine.

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c. Hyperthermophilic Glycosidase for Glycoconjugate Synthesis (GlycoHype)

Glycosidases from hyperthermophilic bacteria are of particular interest for reactions under extreme reaction conditions, e.g., in the presence of organic solvents and high temperatures. These characteristics facilitate the combination of bio- and chemocatalysis in chemical processes. In our project "GlycoHype" we characterized the substrate spectrum of the recombinant hyperthermostable glycosidase from *Pyrococcus woesei* (PwGly) in transglycosylation reactions (Fig.6). Besides p-nitrophenyl-β-D-galactopyranosid and -glucopyranosid (pNP-Gal, pNP-Glc), lactose and cellobiose serve as donor substrates. On the acceptor side, a broad spectrum of different hydroxyl-carrying substrates are accepted. Together with our cooperation partner Prof. Andrij Pich (DWI Leibniz Institute for Interactive Materials), we optimized the enzymatic synthesis and purification of 2-(β-galactosyl)-ethyl methacrylate (Gal-EMA) resulting in gram-scale amounts of the galactosylated monomer in high yield (Fig.7).[10] Gal-EMA was utilized for the chemical synthesis of sugar-functionalized acrylate polymers containing defined galactose amounts (0–100%). The resulting glycopolymers showed excellent nanomolar binding affinities for the lectin RCA_{120} from *Ricinus communis*.

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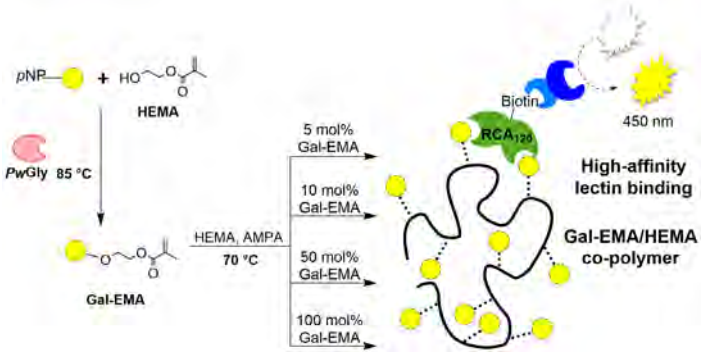

Fig.7: Synthesis of Gal-EMA based glycopolymers for scavenging of ricin toxin.

Collaborations

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Prof. Dr. Holger Gohlke, Nicola Porta, Institute for Pharmaceutical and Medical Chemistry, Heinrich-Heine University Düsseldorf.

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

The Glyco-BioInterface

a. Glycan Ligand Screening Assay and Biosensor

The binding behavior of pathogenic biomolecules is a field of research that permanently requires novel fast and feasible analysis and screening methods. Via optimization of these methods, therapy strategies are approached. We focused on the toxin A (TcdA) of *Clostridium difficile* that destroys the epithelial layer of the human intestine. The toxin contains a carbohydrate recognition domain and thus binds to cell-surface glycans on the intestinal cells. To find effective binders, we screened a variety of multivalent glycan ligands on immobilized neo-glycoproteins (NGPs) microtiter plates.[12] We applied our glycosyltransferase tool box to build glycan epitopes *in situ* on bovine serum albumin (BSA) (Fig. 8). Screening the NGPs, the Lewis^y-Lewis^x glycan epitope was proved as a highly efficient binder for TcdA. In cell culture experiments, Le^y-Le^x-NGPs protected human cells against TcdA mediated cell rounding and inflammation. We transferred the methodology to build a biosensor in cooperation with the group of Prof. Uwe Schnakenberg (IWE-1, RWTH Aachen University). The biosensor is based on electrochemical impedance spectroscopy (EIS) and enables the real-time monitoring of bio-molecular binding events on a bio-functionalized gold chip. First, the chemical binding of neo-glycoproteins to the gold chip surface was followed. Glycosylation of a neo-glycoprotein by a fucosyltransferase was kinetically monitored as well the subsequent binding of a Fucose-specific lectin.[13]

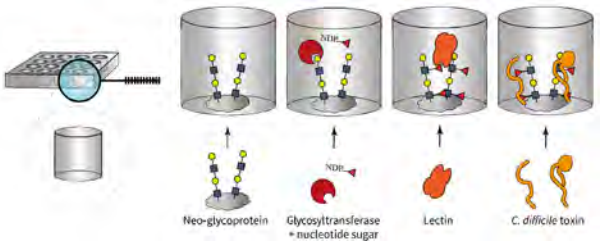

Fig.8: Glycan ligand screening assay for lectins and entero-bacterial toxins.

In this way, the encoding and decoding of glycan-related information in real-time is now possible. The EIS biosensor could be exploited for the detection of glycosyltransferases of pathogenic microorganisms that invade the human body.

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Dr. Tom Kremers, Nora Menzel, Prof. Uwe Schnakenberg (IWE-1, RWTH Aachen University.

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Financial Support

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b. Multivalent glycoconjugates for the Tumor-related Lectin Galectin-3

Galectin-3 (Gal-3), is a β-galactosyl binding protein that is highly relevant in cancerogenesis. The inhibition of Gal-3 binding to cancer-related glycan epitopes by multivalent inhibitors is an emerging tool in glycoscience and therapeutic applications. Recently, various approaches for the scavenging of Gal-3 were developed. We reported the efficient binding of Gal-3 to neo-glycoproteins presenting the tumor-related Thomsen-Friedenreich-(TF)-antigen (Fig. 9).[14]

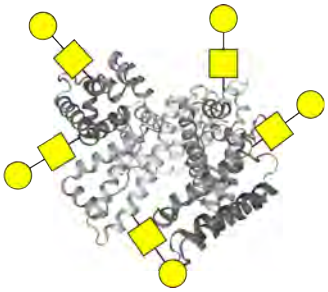

Fig.9: Neo-glycoprotein presenting the TF-antigen.

The enzymatically synthesized TF-antigen epitope was successfully coupled to alkynyl-functionalized lysine groups of bovine serum albumin and served as an efficient inhibitor for Gal-3 binding to asialofetuin (Fig. 10). Glycopolymers also play a crucial role in targeting Gal-3 for therapeutic applications. Our cooperation partners in Prague demonstrated nanomolar-affinity of Gal-3 towards clustered LacNAc epitopes on *N*-(2-hydroxypropyl) methacrylamide (HPMA)-based copolymers.[15]
Moreover, HPMA polymers containing a tetrasaccharide with a terminal LacDiNAc unit inhibited Gal-3 induced apoptosis of T lymphocytes and migration of tumor cells *in vitro*.[16] Our cooperation partner Prof. Laura Hartmann and coworkers reported the potential of heteromultivalent glycomacromolecules bearing lactose and non-glycosidic motifs as specific ligands for Gal-3.[17] In summary, multivalent glycoconjugates provide high potential in targeting tumor-related Gal-3.

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Prof. Dr. Laura Hartmann, Department of Organic and Macromolecular Chemistry, Heinrich-Heine-University Düsseldorf

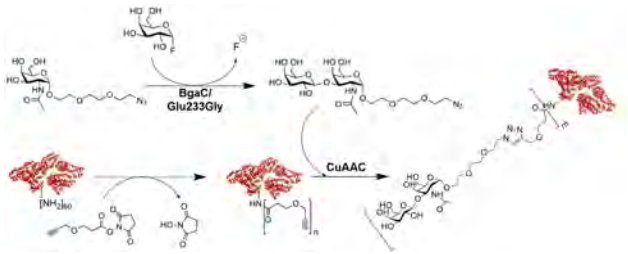

Fig.10: Synthesis of TF-antigen-azide and neo-glycoprotein.

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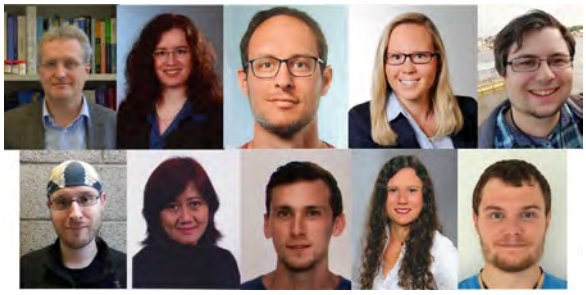
OUR TEAM



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Introduction

The mission of the Chair of Medical Engineering (mediTEC) of the RWTH Aachen University is to provide an active link between interdisciplinary basic sciences and application-oriented engineering research and development of innovative solutions for a better health care. Focus areas of our research are:
- Ultrasound & Shockwaves
- Biomechanical Modelling & Simulation
- Image & Model Guided Surgery
- Mechatronics & Robotics
- Integration, Usability & Risk Engineering

Apart from international publications and a practical transfer and implementation of scientific findings, the education of our students from different disciplines and specialties is a major objective. In addition to basic research grants, industrial cooperations, corresponding to about 50% of our annual turn-over, represent an important complementary application-oriented pillar of our work for the transfer of our research and developments into clinical applications.
In 2020 the pandemic situation forced our team to put a lot of efforts in the reorganisation of our teaching as well as of our research and development activities. However, based on established networks and in many cases long lasting cooperation with partners from research, industry and clinics, we have been able to continue major research projects as well as to successfully initiate new activities.
This annual report summarizes some examples of our project work.

Selected Projects

Ultrasound and AI

Medical ultrasound is a widespread imaging modality utilized in a variety of different diagnostic tasks, ranging from echocardiography and mammography over prenatal screening to orthopaedic applications like bone fracture detection. It offers real-time capabilities, which makes it especially useful for dynamic investigations. In contrast, other imaging alternatives like computed tomography (CT) or magnetic resonance imaging (MRI) are expensive and potentially dangerous for the patient as well as the clinical personal. Yet, ultrasound requires skilled personal due to the low signal-to-noise ratio and several other limitations.

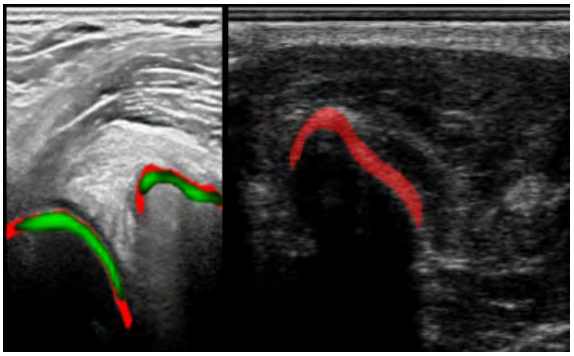


Fig. 1: Automatic segmentation of bone surface

Therefore, we develop image processing algorithms that allow for an automatic processing of ultrasound images, easing the task of image interpretation e.g. for a fully automatic classification of injuries like a tear of the anterior cruciate ligament. Furthermore, we develop a pipeline for full three-dimensional models for knee and wrist joint surgery, reconstructed solely from ultrasound images, potentially replacing CT for preoperative planning in orthopedics. The reconstruction process is based on a-priori knowledge incorporated with a statistical model as well as various neural networks specialized on image and sequence processing.

Extracorporeal Shock Wave Therapy

Extracorporeal Shockwave Therapy (ESWT) is used for treatment of Achilles tendinopathy. Line-focused ESWT is a novel technique treating a larger tendon area than point-focused ESWT. Monitoring capacities of clinical symptoms with ultrasound under ESWT treatment are unknown. We hypothesized that point-focused and line-focused ESWT have a superior outcome compared to placebo ESWT and that ESWT leads to tendon changes, which are detectable with ultrasound.
The present study is a single-blinded placebo controlled RCT. Three cohorts were compared: ESWT point, ESWT line and ESWT placebo. VISA-A score was measured before intervention (T0), after 6 (T1) and 24 weeks (T2). All cohorts performed daily physiotherapy for 24 weeks and received 4 sessions of point-focused, line-focused and placebo ESWT in the first 6 weeks. Ultrasound was performed with B-Mode, Power Doppler, Shear Wave Elastography (SWE) at T0 and T2 and with Ultrasound Tissue Characterization at T0, T1 and T2.

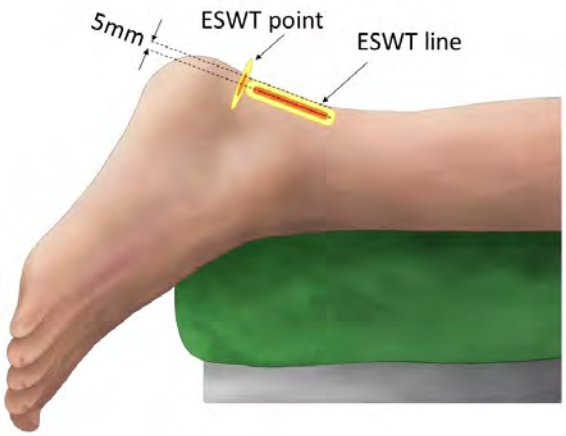


Fig. 2: The tendon volume treated with line-focused ESWT is larger than in point-focused ESWT. However, the maximum energy density is higher in point-focused ESWT than in line-focused ESWT.

There was a significant VISA-A improvement over time for all groups ($p<0.001$). ESWT point had the strongest VISA-A score improvement +23 (ESWT line: +18; ESWT placebo: +15), but there was no significant interaction between time and group. Ultrasound Tissue Characterization, Power Doppler and B-Mode could not show significant alterations over time. SWE revealed a significant increase of elastic properties for ESWT point in the insertion and midportion over time.

Morpho-functional analysis of the knee joint

Morphological parameters are considered in clinical practice for various reasons. For example, in the case of patellar instability and/or (recurrent) patellar subluxation, morphological parameters of the knee may support the decision for an adequate treatment option. The parameters considered include e.g. the femoral sulcus angle and the tuberositas tibiae to trochlear groove (TT-TG) distance. We investigate the relationship between such parameters used in clinical practice and knee kinematics e.g. by in silico analyses, both in the native knee and after knee arthroplasty. As an example, we evaluated the relationship between the TT-TG distance and patellar kinematics. The TT-TG distance is affected by various morphological parameters of the knee, including the mediolateral position of the tuberositas tibiae and the trochlear groove, as well as the relative rotation of femur to tibia. We considered various changes in the model setup, in order to represent changes in TT-TG distance. The described analyses are relevant both for a better understanding of the reasons for patellar instability as well as for implant design optimization.

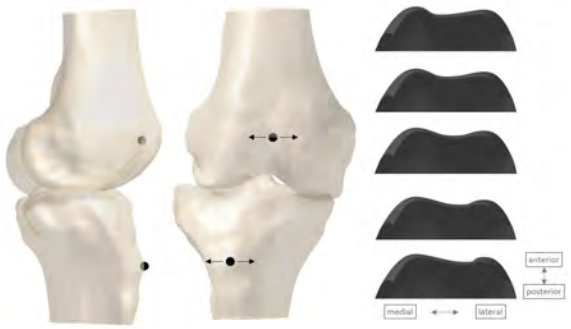


Fig. 3: (A) Native knee morphology with landmarks (tuberositas tibiae & trochlear groove point). (B) Parametrized surface models with changes in trochlea geometry.

CSF dynamics in NPH

As Normal Pressure Hydrocephalus (NPH) is associated with higher age, there might be a correlation with age-associated changes of vascular and craniospinal fluid (CSF) dynamics. To investigate this correlation of blood and CSF dynamics a computational model was developed, which can simulate the vascular pressure propagation inside the vessels with spatial and temporal resolution and its interaction with the CSF space and dynamics.

It consists of 11 compliant segments, from the bigger artery, to the capillaries and finally to the vein, which are all connected to the intracranial pressure (ICP). Input parameters are the venous pressure in the bridging veins and the pulsatile flow in the big arteries. The results show, that elevated capillary pulsations can damage the brain parenchyma and lead to higher aqueduct stroke volume as seen in NPH.
Further parameter studies of age associated geometric alterations, craniospinal compliance and blood pressure are part of our ongoing research.

MINARO HD – handheld mini-robotic bone milling

Current surgical robotic systems consist either of a large serial arm, resulting in higher risks due to their high inertia and no inherent limitations of the working space, or they are bone-mounted, adding substantial additional task steps to the surgical workflow.
To overcome these disadvantages, a robot was developed that has a handy and lightweight design and can be easily held by the surgeon. No rigid fixation to the bone or cart is necessary. A high-speed tracking camera together with a fast control system ensures the accurate positioning of the milling tool, while automatically compensating for movements of the surgeon or the patient's bone.

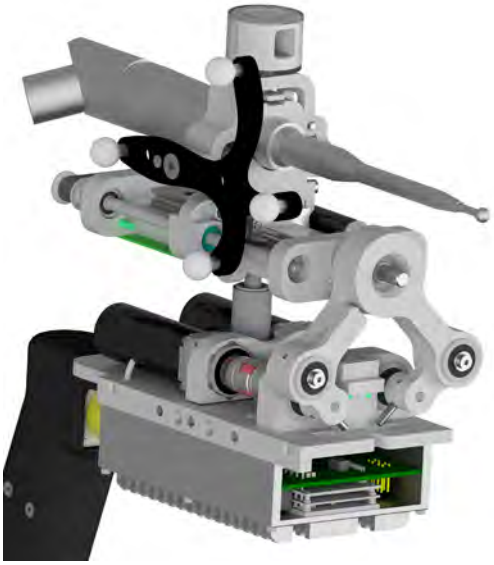


Fig. 5: Handheld robot Minaro HD

After the manipulator has been pre-positioned and activated by the surgeon, the milling tool is automatically moved by the robotic system along a previously planned trajectory with a latency of 24 msec and an offset of 0,044 mm. In case of any unforeseen event, the handheld manipulator can be stopped and reactivated at any time providing the benefits if robotic milling while avoiding the drawbacks of bulky robot arms.

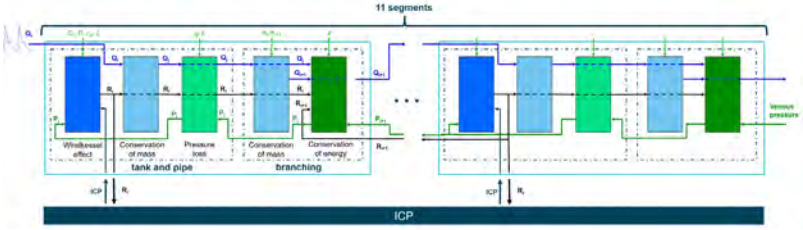
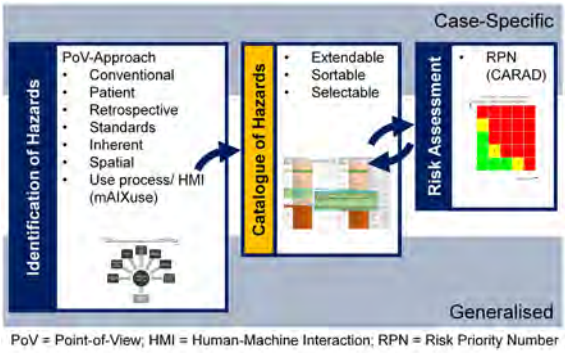


Fig. 4: MATLAB Simulink Model of cerebral vessels in connection with the intracranial pressure (ICP)

Catalogue of Hazards for Surgical Robot Design

Intrinsic safety is a major objective in surgical robot design. Inherently safe mechanisms can be based on modularity. Due to promising benefits of modularization approaches regarding safety, usability and costs, a design framework is being developed that streamlines the modular design of surgical robots wherein intraoperative safety is only one of many module drivers.
Furthermore, a multi-perspective method for hazard identification was established to make risk analysis as comprehensive as possible and easy to apply. Our Point-of-View (PoV) approach aims to capture relevant hazards by taking multiple overlapping perspectives. The perspectives are applied chronologically according to the degree of system determination. PoV1 and PoV2 relate to an early stage of development in which the functioning of the system is not need to be known. The subsequent PoVs require the stepwise development of scenarios and ease decision making during design. Each identified hazard is archived in a catalogue of hazards which can be accessed in subsequent developments.



PoV = Point-of-View; HMI = Human-Machine Interaction; RPN = Risk Priority Number

Fig. 6: Three stages approach for risk analysis

Cooperative Surgical Telemanipulation

Various cooperative strategies have been proposed to combine the individual strength of humans and machines to improve the surgical outcome. Based on the analysis of target applications in orthopedics and neurosurgery a cooperative surgical telemanipulator concept has been developed. The approach offers a variety of haptic assistances as well as haptic feedback, which are available based on the requirements of the underlying surgical application. The surgeon is then able to choose between applicable assistances based on his preferences and expertise.
Three experiments were designed with respect to different bone milling tasks. The implemented interaction modes avoid overlapping and masking of forces from haptic assistance and haptic feedback to avoid misinterpretation and confusion about the origin of the force information. The cooperative surgical telemanipulator was compared with the direct manual execution as well as automated milling. Results show that the cooperative surgical manipulator improves effectiveness, measured by the mean absolute depth and contour error, and efficiency close to an automated execution. In addition, the user satisfaction is increased compared to the direct manual process. Nevertheless, the surgeon is part of the control loop at all times and remains able to adjust the surgical plan according to the intraoperative situation and his/her expertise.

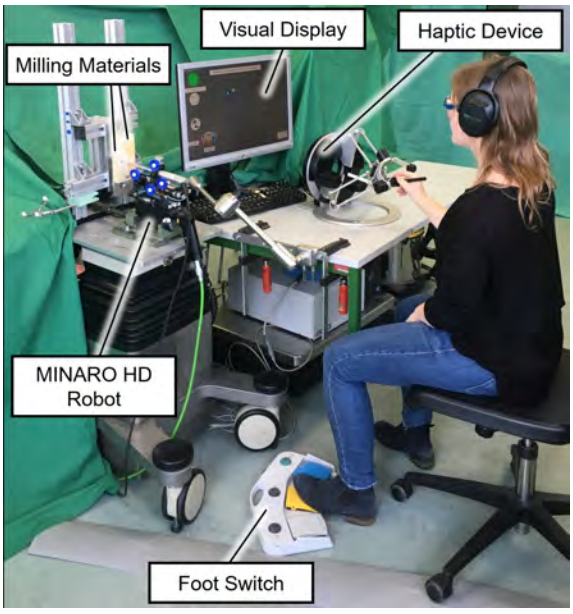


Fig. 7: Lab set-up of a cooperative surgical telemanipulator for bone milling tasks

SEBARES patient transportation aid

Patient transport in emergency medical services is a highly challenging task. The currently used transportation aids support the paramedics on flat surfaces but are not ergonomically applicable if obstacles, like stairs, occur. In these cases paramedics have to carry the patient, which leads to extreme physical stresses and short and long-term musculoskeletal injuries and diseases. A novel patient transportation aid, which can be used both on flat surfaces and a wide range of stairs was developed within the SEBARES project. To determine the actual loads for the paramedics and to compare the results to current transportation aids an ergonomic evaluation study was conducted. Twelve test participants performed a transport with the prototype and a simulated patient with a total transported mass of 137 kg, while force and posture data were recorded. The results show that over 90% of the time the loads were long-term acceptable according to ergonomic guidelines and a healthy upright posture of the back could be maintained at all times. In comparison to the currently most ergonomic tool, a caterpillar stair chair (according to a study of the Institute for Occupational Safety and Health of the German Social Accident Insurance), the forces could be reduced by 53%. Therefore, the study confirms the benefits of the novel approach and promotes further developments with our industrial partners to develop a sustainably effective solution for patient transportation in emergency medical services.

Fig. 8: Ergonomic evaluation of the SEBARES stair climbing patient transport aid

Risk Management in the Reprocessing Unit for Medical Devices (RUMED)

The quality of medical device reprocessing affects patient care in the operating theatre and, if deficient, can lead to nosocomial infections, as well as the prolongation or postponement of surgeries. Surgeons frequently complain about inadequately prepared or incomplete instrument sets. The processes in RUMED are partially standardized and automated, however, safety-critical work steps must be performed manually, which reduces the reproducibility and documentability of the results. For complex, high-risk applications, considering performance shaping factors (PSF) in the context of human reliability analysis (HRA) has proven effective in designing processes to support human performance and avoid errors. While human reliability analysis is already used in the field of nursing, no approaches have thus far been developed for RUMED.
A Germany-wide survey with RUMED executives identified PSFs suitable for reprocessing medical devices. In parallel, a Process-FMEA was performed to identify areas of particularly high risk due to potential for human error in RUMED. The next step is to apply the identified PSFs to the located risk areas to identify root causes of failures and develop potential solutions. The current approach in RUMED is related to the symptoms of process errors; knowledge of the underlying causes can enable process improvements and standardization that ultimately benefit the patient in the operating room.

Fig. 9: Exemplary performance shaping factors

Integrated Operating Room

Based on the OR.NET initiative (www.ornet.org), which has been significantly driven and supported by mediTEC, the ISO IEEE 11073-20701 SDC standard family (data model, protocol and architecture) for the open communication of medical devices has been approved in 2020.
The objective of the EFRE project PriMed in the pre-competitive area of medical technology research and development is to develop concepts and conduct feasibility studies for the optimization of perioperative workflows on the basis of SDC application.
Within PriMed devices like video-switch, OR-table, OR-light and patient monitor have been adapted and integrated into a surgical and anaesthetic SDC Workstation and can be controlled by using a tablet, a smartphone and a centralized cockpit including a universal foot switch. The OR personnel is supported by workflow specific dialogues and the OR management e.g. becomes more efficient due to the detailed information and overview, which is provided.

Fig. 10: Integrated surgical and anaesthetic workstation

Within the PriMed project user interface profiles (for standardized Human-Machine-Interaction in the open connected OR), which complement the technical profile of medical devices, are further developed and introduced into the supplementary standards (Base Key Purposes P11073-1070x) of the SDC series.
In cooperation with the nonprofit organization OR.NET e.V., mediTEC established a working group with the IG-NB (German Community of Notified Bodies) to develop guidelines for the approval of medical SDC devices.

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 2020 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 Ministry of Health (BMG)
- the German Research Foundation (DFG)

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

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

Awards

M. Asseln: Klee-Award 2020 of the German Society for Biomedical Engineering (VDE|DGBMT) and the Klee Family Foundation for his PhD-Thesis „Morphological and Functional Analysis of the Knee Joint for Implant Design Optimization“

Selected Publications

[1] M. Asseln, J. Eschweiler, A. Trepczynski, P. Damm & K. Radermacher: Evaluation and validation of 2D biomechanical models of the knee for radiograph-based preoperative planning in total knee arthroplasty. PLOS ONE, 2020, 15(1), pp. 1-16
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[13] P. Schleer, M. Vossel, L. Heckmann, S. Drobinsky, L. Theisgen, M. de la Fuente & K. Radermacher: Usability of cooperative surgical telemanipulation for bone milling tasks. International Journal of Computer Assisted Radiology and Surgery (IJCARS), 2020, Onlinefirst
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[19] O. Yilmaz, D. Wieschebrock, J. Heibeyn, K. Radermacher & A. Janß: Development and Evaluation of a Platform-Independent Surgical Workstation for an Open Networked Operating Theatre Using the IEEE 11073 SDC Communication Standard. Digital Human Modeling and Applications in Health, Safety, Ergonomics and Risk Management. Posture, Motion and Health, 2020, pp. 79-92

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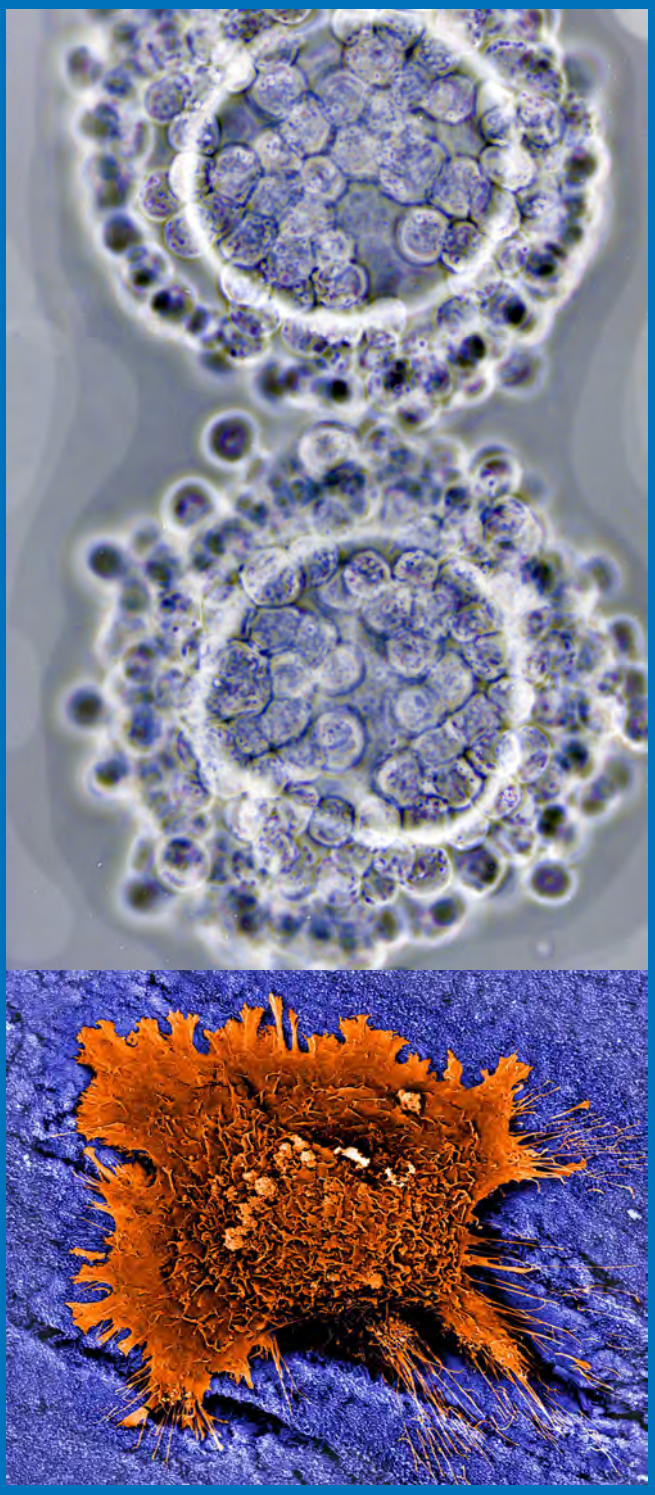
RWTH AACHEN UNIVERSITY

Faculty of Medicine

Cell-Material Interactions: Translating Basic Science Into Clinical Applications



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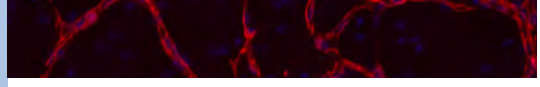


Cover Figures: Top *Mouse oocytes surrounded by follicle cells;*
Bottom *Bone marrow derived osteoclast with membrane ruffles.*

Introduction

Willi Jahnen-Dechent, Professor

The year 2020 was COVID front, back and center. Like everybody else, we had a hard time coping with the restrictions imposed by the pandemic. On the positive side we adopted online conference tools in a flash, distributed precious lab time between members to minimize contact time and adopted new teaching tools including Vlogging instructions. Miraculously, and thanks to a concerted effort of all, we actually got a lot of work done without anybody getting hurt! On the negative side, we dearly miss social interactions, we long for the yearly holiday events especially our yearly lab out – makes one cherish all the things we took for granted before COVID!
In these times of reckoning we reviewed our own and others' work. „The ONE" major goal of ours in the biomineralization field is the molecular structure of the plasma protein fetuin-A and its calcium phosphate cargo. Over the past years we showed that fetuin-A is a mineral chaperone preventing growth and precipitation of calcium phosphate mineral in extracellular fluids, hence our graphic phrase „mud in the blood". If or when we will actually determine this highly complex structure is uncertain, but for starters, we made ourselves a nice picture of where we are headed.

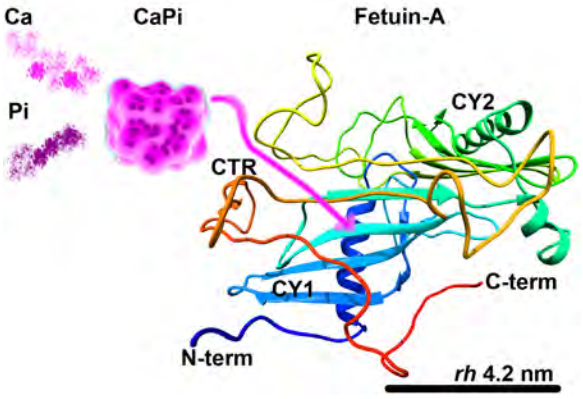
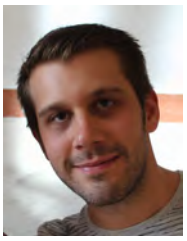


Fig. 1: Protein structure of fetuin-A.
Calcium phosphate (CaPi) binds an extended beta-sheet of the amino-terminal (N-term) cystatin-like domain of fetuin-A (CY1, blue). A second cystatin-like protein domain (CY2, green) connects to the carboxyl-terminal domain CTR (orange). CTR is intrinsically disordered and must be pried open to allow for mineral binding. rh, hydrodynamic diameter.

Oocyte Stiffness is a Quality Criteria



Carlo Schmitz, PhD

Julia Floehr, PhD

Mammalian eggs are surrounded by a protein matrix playing an important role in fertilization. Before fertilization, the protein matrix is soft and sperm can penetrate. Immediately after fertilization, this matrix is remodeled. It becomes hardened and sperm can no longer penetrate the egg. However, this matrix remodeling can also occur spontaneously before fertilization preventing the fertilization of the egg. Fertility clinics therefore require methods to assess egg quality to increase the chance of fertilization and ultimately of pregnancy.
By using nanoindentation technology we showed that fertilization-induced remodeling of the egg coat, a process called zona pellucida hardening, is indeed accompanied by an increase in the stiffness, the elastic modulus (E-modulus) of the egg coat. The coat of 2-cell embryos has an E-modulus of 454 ± 181 Pa, more than twice that of unfertilized eggs (155 ± 69 Pa). For E-modulus measurements by nanoindentation, the eggs were immobilized on a mesh and the measuring instrument, consisting of a cantilever probe, was placed in close proximity to the egg coat. The cantilever probe then indents 4 μm into the egg coat, to determine its mechanical hardness.

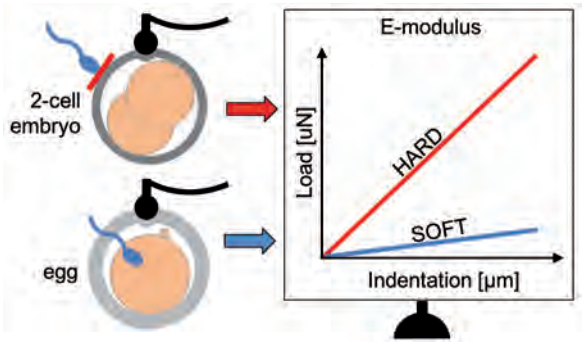


Fig.2: E-modulus measurement of eggs by nanoindentation, schematic overview.
Eggs were immobilized on a mesh and the cantilever with a spherical probe (black) of the indentation device was placed above. The cantilever probe indented 4 µm into the egg coat and measured a hardened egg coat for 2-cell embryos and a soft coat for unfertilized eggs. After hardening of the egg coat, no further sperm can penetrate the egg.

To test if mechanical indentation is suitable to assess egg quality, we used genetically modified fetuin-B deficient eggs with a predefined protein matrix structure. Those eggs have per se hardened coat that is known from eggs after fertilization – they represent fertilization failure. Using nanoindentation, we were able to clearly distinguish between the egg coat of wildtype eggs with a good quality and infertile fetuin-B deficient eggs. In numbers: compared to wildtype eggs, fetuin-B deficient eggs thus had a sevenfold higher

E-modulus (155 ± 69 Pa vs. 1104 ± 304 Pa). In conclusion, we established a method for egg quality determination that i) quantitatively measures individual egg hardness, ii) is non-destructively and iii) observer-independent.

Recombinant RANKL for Osteoclast Studies

Robert Dzhanaev, MD/PhD student

Mineralized tissues like bone can only be degraded by highly specialized cells called osteoclasts. These are giant multi-nucleated cells derived from myeloid precursors. Given the similarity of bone biomineralization and pathological calcification, we hypothesized that osteoclasts may also remove pathological calcification. Differentiation, survival and activation of osteoclasts critically depend upon receptor activator of nuclear factor κB ligand, RANKL. Together with its cell membrane receptor RANK, and the soluble decoy receptor osteoprotegerin OPG, RANKL plays a pivotal role in bone resorption. To study RANKL activation of osteoclasts, we produced recombinant RANKL in a mammalian cell line. Gel electrophoresis and immune blotting of the recombinant protein confirmed high purity of the product.

Fig. 3: Recombinant RANKL purification.
Gel electrophoresis revealed protein bands at approx. 25 kDa in the elution fractions E3-E9 (black arrowhead). Faint bands at 55 kDa in the fractions E5-E7 suggested the presence of RANKL dimers (red arrowhead). S – supernatant, FT - flow-through, W - wash fraction, DV - dead-volume column.

The biological activity of RANKL was confirmed in osteoclast cultures and bone resorption assays. Mouse bone marrow cells were treated with macrophage colony-stimulating factor (M-CSF) and commercial RANKL or homemade RANKL. The appearance of giant multinucleated cells in both RANKL-treated cultures demonstrated successful differentiation of viable osteoclasts.

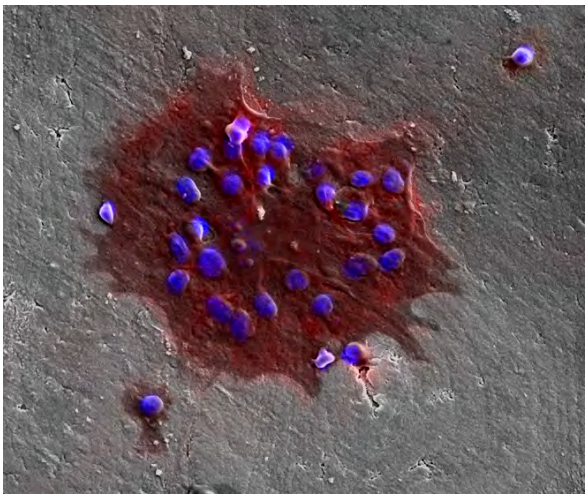


Fig. 4: SEM picture of a multi-nucleated bone marrow-derived osteoclast after 14 days of RANKL treatment.
Both commercial and homemade RANKL cytokine mediated osteoclastogenesis from bone marrow cells as indicated by the formation of multi-nucleated giant cells.

Bone resorption by differentiated osteoclasts was assessed using thin bovine cortical bone slices. Bone marrow-derived osteoclastic precursors were plated on bovine bone discs and stimulated with M-CSF and RANKL. Scanning electron microscopy confirmed the presence of multi-nucleated osteoclasts, which actively resorbed bone, forming resorption pits.

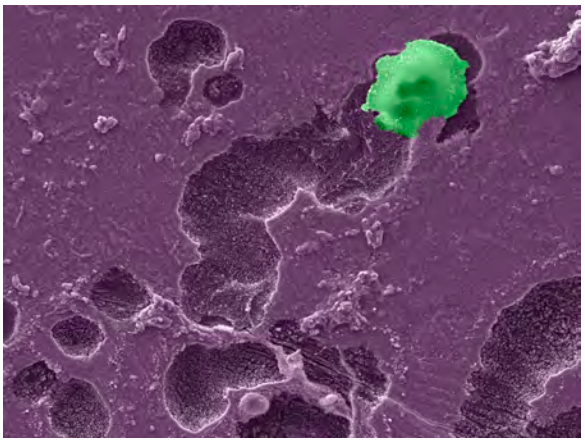


Fig. 5: SEM picture of an osteoclast on bovine bone disc.
An osteoclast (green) was observed during resorption of bone. Osteoclasts leave resorption pits and tracks while making their way through bone.

In conclusion, we produced biologically fully active RANKL that can be further developed into a theranostic agent to image and to treat pathological calcifications.

Stem Cells and Tissue Engineering

Sabine Neuß-Stein, Professor

The „Stem Cells and Tissue Engineering Group" pursued three major research topics: (i) mesenchymal stem cells (MSC) and periodontal ligament stem cells (PDL cells) in wound healing and tissue regeneration, (ii) bone tissue engineering and (iii) cardiovascular tissue engineering.

During the last two decades, we developed a recruitment system for endogenous MSC based on biomaterials releasing a potent chemoattractant to improve wound healing.

Together with Professor Michael Wolf, director of the Orthodontics Clinic at RWTH Aachen University Hospital, we study cellular mechanisms of PDL cells and cementoblast development, their cell-to-cell-communication and impact on wound healing, which is faster and more efficient in the upper jaw, than in the lower jaw. Hanna Malyaran reports on this work.

Together with Professor Andrij Pich, head of the research area Functional and Interactive Polymers at DWI - Leibniz Institute for Interactive Materials, we develop fibrin-based hydrogels. Depending on the kind and mixture of copolymers, a wide array of fibrin-based hydrogels form with different fiber sizes and elastic modulus, both of which are critically important in determining cell behavior. Svenja Wein presents this work in more detail.

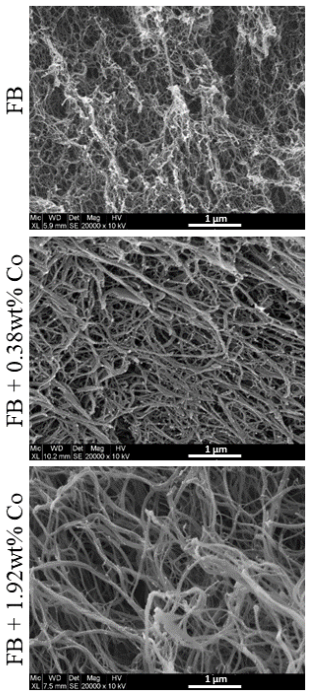


Fig. 6: Scanning electron micrographs of fibrin-based hydrogels. Fibrin-based (FB) hydrogels were synthesized with and without capolymers (Co). Increasing the copolymer concentration strongly increased fiber thickness.

Fibrin-based Hydrogels for Biohybrid Implants

Svenja Wein, PhD student

Biohybrid implants comprize a biomaterial scaffold and, ideally, the patient's own cells. Within a larger consortium of researchers, we develop fibrin gels with a textile support for biohybrid heart valve tissue engineering. We combine fibrinogen and poly(N-vinylcaprolactam) copolymers with smooth muscle cells, induced by adding TGF-β1 and BMP4 growth factors to the hydrogels. The contractile phenotype of smooth muscle cells is assessed as salient property of functional heart valve smooth muscle cells. Vascularization of the tissue engineered constructs is important. Therefore, we assess capillary formation and marker gene expression in vascular precursor cells.

Initial experiments show long-term stable hydrogels, which support the proliferation of human stem cells, so that the myogenic differentiation of the cells in the gels can be achieved in a subsequent step. The successful expression of contractile markers was demonstrated after 21 days of culture. Angiogenesis assays demonstrated formation of capillary-like structures in culture. In future we will analyze the influence of cyclic stretching on stem cell differentiation.

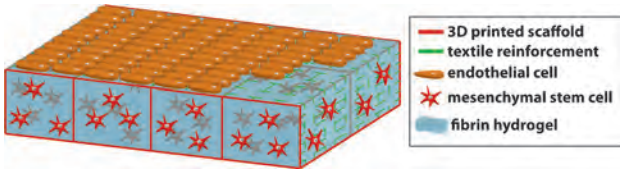


Fig. 7: Structural design of the biohybrid implant for a heart valve replacement built from a support structure coupled with the patient's own stem cells.

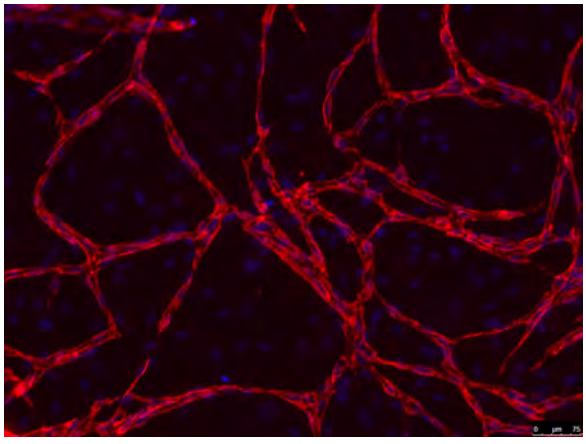


Fig. 8: Human umbilical cord vascular endothelial cells (HUVEC) form capillary networks when co-cultured with mesenchymal stem cells (MSC).

Impact of Stem Cells on Wound Healing and Integration of Tissue Engineered Alveolar Bone

Hanna Malyaran,
PhD student

Periodontal disease usually involves recession of the periodontal ligament (PDL) ultimately leading to tooth loss from the alveolar bone. The PDL plays an important role in physiological tooth function and is important for periodontal regenerative therapy. Clinical observations indicate that wound healing and bone formation in alveolar bone varies depending on the exact localization of the lesion. Wound healing is faster in the maxilla, the upper jaw, than in the mandible, the lower jaw.
Alveolar bone differs in composition, with 23% bone marrow and 46% lamellar bone in the upper jaw, and 16% bone marrow and 63% lamellar bone in the lower jaw. The PDL hosts endogenous stem cells. In 2004, PDL precursor cells were first isolated from extracted third molars, demonstrating self-renewal and differentiation capacity towards mesodermal cell fates, and therefore referred to as stem cells. Like mesenchymal stem cells (MSC), PDL cells are now extensively studied with respect to ligament and bone formation.
We isolated PDL cells from extracted third molars of young and healthy patients. Teeth were extracted from both upper and lower jaws to allow a comparison of maxilla and mandible-derived PDL cells. MSC isolated from the spongiosa of femoral heads served as the gold standard of MSC differentiation.
Like MSC, PDL cells were positive for CD73, CD90 and CD105, and negative for CD34 and CD45. PDL cells from the upper jaw showed more proliferation and differentiation when compared to PDL cells from the lower jaw. These results support the clinical hypothesis that wound healing of the upper and the lower jaw might differ due to different cell behavior. Next, we will identify regulatory gene networks involved in periodontal cell differentiation.

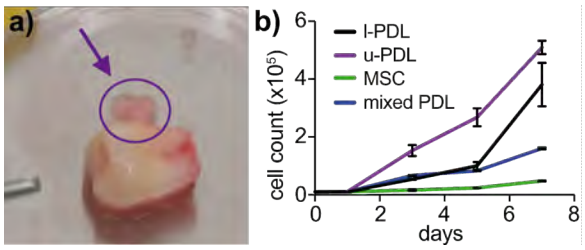


Fig. 9: Characterization of PDL cells from upper and lower jaw.
a) Periodontal tissue is scratched off the tooth with a scapel, digested in (FB) collagenase type 1 for one hour, centrifugated and seeded in a culture plate. b) PDL cells from the lower jaw (l-PDL), upper jaw (u-PDL), MSC and a mixed PDL population of 10 donors (Lonza, Cologne, DE) were seeded at a density of 5000 cells/cm². Proliferation rate was measured after 1, 3, 5 and 7 days.

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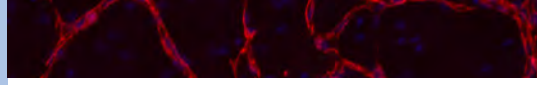

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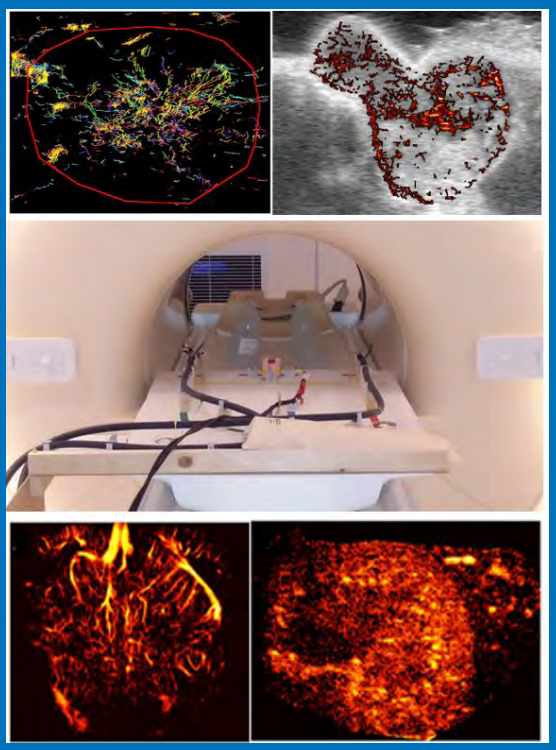
Team in February 2021

ExMI EXPERIMENTAL MOLECULAR IMAGING

Chair of Experimental Molecular Imaging Faculty of Medicine

Improving therapy by integrated multiparametric imaging



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Introduction

Univ.-Prof. Dr. med. Fabian Kiessling

The Chair of Experimental Molecular Imaging (ExMI) focuses on the development and evaluation of novel imaging methods, contrast agents and theranostics to characterize and treat cancer, cardiovascular and inflammatory disorders. ExMI has a translational scope and many projects are located at the interface between preclinical and clinical research. In this context, we often follow a multimodal approach, based on combinations of MRI, CT, ultrasound, optical and photoacoustic imaging, nuclear medicine techniques (in particular PET-MRI), and magnetic particle imaging (MPI). In order to develop image-guided therapies, we strongly interconnect our pathophysiological and pharmacological research with research in device engineering, image reconstruction, and data post-processing. Basic research on the tissue microenvironment (including the barriers for drug delivery) provides us with new imaging biomarkers and new mechanistic insights that can be used to identify diagnostic biomarkers. Here, imaging features and omics data are considered in concert, evaluated using radiomic and radiogenomic approaches, and used to support mathematical disease models.
As a second main focus, ExMI investigates materials and concepts to improve drug delivery to tumors. This includes the development and evaluation of novel biomaterials, including nanoparticles, polymeric carriers, liposomes, micelles and microbubbles as well as physical and biological treatments of the vasculature and the adjacent tumor stroma in order to improve drug accumulation and tumor penetration.
Research of ExMI has gained increasing international visibility. As major achievements in 2020, F. Kiessling and T. Lammers were for the second time recognized as Highly Cited Researchers by Clarivate Analytics, as was Magnus Rueping, who is co-affiliated with ExMI. Furthermore, F. Kiessling was appointed as a fellow of the World Molecular Imaging Society.

Diagnostic and Therapeutic Ultrasound

Univ.-Prof. Dr. med. Fabian Kiessling

In 2018 we presented the first in vivo application of superresolution ultrasound (US) imaging, i.e. motion model ultrasound localization microscopy. This year, together with most pioneers of this research field worldwide, a paper was published highlighting the advantages and disadvantages of the different superresolution US approaches as well as ongoing successes in its clinical translation [1]. Furthermore, this technology was applied in a larger clinical trial (clinicaltrials.gov: NCT03385200) trying to elucidate whether chemotherapy effects on breast cancer can be improved by manipulating tumor perfusion via contrast enhanced US (CEUS). We can already state that our diagnostic US setting with high mechanical index induces biological effects on tumor vascularisation and its response to chemotherapy. However, as data are still being analysed, we encourage the readers to wait until the study is published. Besides these translational and clinical activities, we continued our efforts to use CEUS to locally and temporarily open the blood-brain barrier and showed that even nanoparticles can efficiently be delivered to the brain tissue by this noninvasive intervention [2]. In addition, together with the Chair for Chemical Process Engineering of RWTH we found that electrical impedance spectroscopy is a favourable tool to monitor the disintegration of cellular monolayers by CEUS [3]. Furthermore, we generated an experimental setup that allows us to systematically study microbubble (MB) enhanced US settings for gene and drug delivery through a cell monolayer and into cells. Besides these theranostic projects, we continued our efforts in molecularly targeted US imaging [4] and highlighted its great translational potential for characterizing tumors [5], the cardiovascular system [5], and inflammatory diseases [6].
Besides these very focused research activities, in the context of a DFG Research Group about the severity assessment in animal-based research, we are also exploring how imaging with different modalities affects animal welfare and the outcome of oncological studies. While for MRI at 1T and 7T even after repeated exposure no critical influences on animal welfare and study results were found [7], immunological effects were observed for CT, CT-FMT and US.

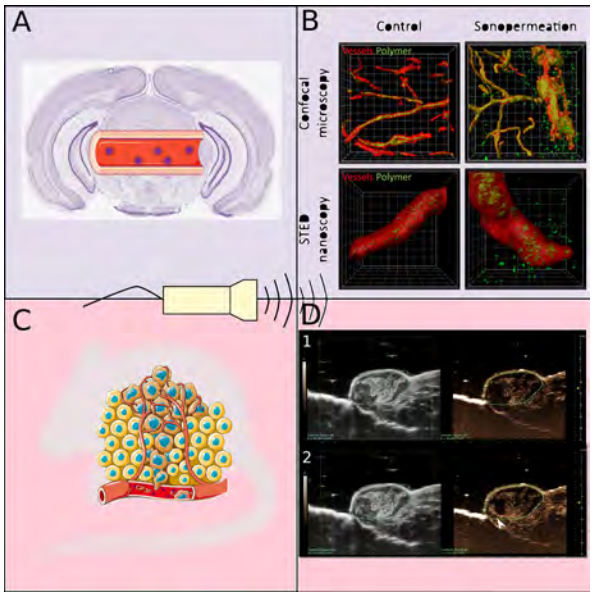

Fig. 1: A: US in combination with MB can open the blood-brain barrier to promote drug delivery. B: Confocal microscopy and STED nanoscopy of nanoparticles penetrating into the brain upon sonopermeation. In untreated brains, nanoparticles (green) are inside vessels (red); after sonopermeation they are found around them. C: CEUS can be used to analyze tumor perfusion. D: US images of a tumor before (1) and after (2) the injection of microbubbles are shown in B-mode (left) and contrast-mode (right). Arrow points to MB in vessels.

Physics of Molecular Imaging Systems

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

In 2020, the PMI group advanced their development for simultaneous Positron Emission Tomography (PET) and Magnetic Resonance (MR) imaging systems. This technology is being adapted for dedicated clinical PET/MRI systems: a brain insert (with the FZ Jülich), the EU H2020 HYPMED

project for breast cancer, and whole-body applications (with UMC Utrecht). Recently, a prototype PET insert for a split-gradient MR system was successfully installed at UMC Utrecht.
In the past year, the group developed an adaptable fan-beam collimator, which can reduce the calibration time of a PET detector from the order of weeks to one hour [8]. Further research was conducted on the evaluation methods for preclinical PET systems [9].

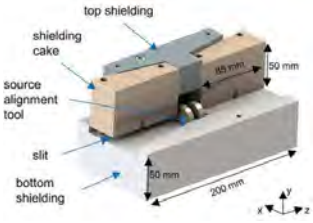

Fig. 2: Section view of the fan-beam collimator. From [8].

Apart from the digital silicon-photomultiplier-based detector developments, the group investigated analog detector concepts using the PETsys TOFPET2 ASIC and analog silicon photomultipliers. The successful investigations of 2019 on PETsys TOFPET2 ASIC were continued, especially for the characterization of PET detector read-out technology [10]. In parallel, these analog components were used to start the development of a PET/MRI insert for a preclinical 7T MRI.
In MR technology, the group developed a method to reduce fat blurring in MR fingerprinting (MRF) with spiral readout for female breast imaging [11]. MRF enables fast quantitative mapping, yet fat blurring might prevent correct identification of small tumors. A blurring correction using conjugate phase reconstruction was implemented and yields improved quantity maps.
The group furthermore focuses on Magnetic Particle Imaging (MPI) which detects magnetic fields generated by excited superparamagnetic nanoparticles (SPION). A novel approach to quantify flow velocities based on the principle of MPI and the well-known Doppler effect was developed, termed Doppler Magnetic Particle Spectroscopy (MPS). The method exploits the velocity-induced frequency shift of emitted tracer signal and was validated by simulations and measurements of moving SPION. Also, a technique to analyze 3D+t flow in-vivo based on MPI exploiting pulsed tracer information was presented [12]. Quantitative 3D+t flow information is combined with 3D anatomical information acquired with MRI.

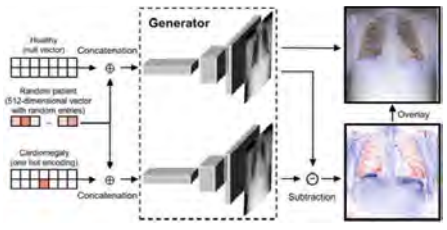

Fig. 3: Generation of the disease-specific pixel map. A healthy and a diseased radiograph of the patient (cardiomegaly in this example) were generated. From [13]

Additionally, the group developed a method to synthesize radiographs to improve computer vision (CV) algorithms to aid radiologists in diagnosis [13]. Many CV algorithms suffer from small and incomplete databases. High-resolution synthetic radiographs with high similarity to real images were created using generative models (GM) based on convolutional general adversarial networks. These synthetic images can be used to compensate for insufficient databases and improve the performance of CV algorithms. The method was validated by blind analyses of synthetic and real radiographs by CV and radiology experts.

Nanomedicine and Theranostics

Univ.-Prof. Dr. Dr. Twan Lammers

Nanomedicines aim to improve the biodistribution of systemically administered (chemo-) therapeutic drugs. By delivering drugs more specifically to pathological sites, and by preventing them from accumulating in healthy tissues, nanomedicines help to improve the balance between drug efficacy and toxicity.
We have a strong focus on cancer nanomedicine [X1]. We recently e.g. showed that polymer-prodrug vesicles can be employed for nanoimmunotherapy. Employing a TLR7/8 agonist, we provided proof of concept for potent and prolonged innate immune activation [14].
We also completed a 3-year collaboration with clinical colleagues from China aiming to develop taxane-loaded polymeric micelles for gastrointestinal (GI) cancer therapy (Fig. 4A-C). GI cancers are among the most lethal malignancies and very difficult to treat. We showed that ∏ electron-stabilized polymeric micelles can be loaded highly efficiently with the taxane drug docetaxel and potentiate chemotherapy responses in multiple advanced-stage GI cancer mouse models [X2]. Complete cures and potent tumor suppression were achieved in subcutaneous gastric cancer xenografts, patient-derived xenografts, and intraperitoneal and lung Metastasis. Mechanistically, micellar docetaxel modulated the tumor immune microenvironment, increasing the ratio between M1 and M2 macrophages. These findings exemplify that ∏-conjugated polymeric micelles loaded with docetaxel hold significant potential for the treatment of advanced-stage GI cancers.

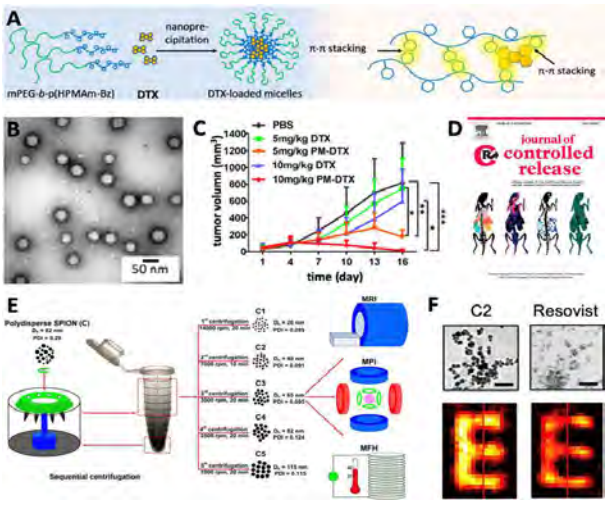

Fig. 4. A-C: mPEG-b-p(HPMA-Bz) polymeric micelles potently enhance the in vivo efficacy of docetaxel in advanced-stage gastrointestinal cancer. D: Artistic impression of the multimodal and multiscale optical imaging work done with clinical-stage mPEG-b-p(HPMA-Lac) polymeric micelles. E: Sequential size-isolation protocol to obtain iron oxide nanoparticles with enhanced performance in MRI, MPI and MFH. F: TEM images and MPI performance of size-isolated sample C2 versus the commercial control formulation Resovist. Images adapted from [X2], [15] and [17].

Using multimodal and multiscale optical imaging, we demonstrated that clinical-stage polymeric micelles developed by Cristal Therapeutics in Maastricht show a very favorable biodistribution (Fig. 4D), with strong accumulation in tumors at the whole-body level and prominent engagement of immune cells at the cellular level, providing opportunities to boost the immune system in case of cancer nanoimmunotherapy [15]. Conversely, we conceptualized that nanomedicines loaded with the potent corticosteroid dexamethasone may find application in the management of COVID-19, by virtue of their strong anti-inflammatory, anti-edema and anti-fibrotic effects [16].
In parallel, we worked on novel nanomaterials for imaging. With an interdisciplinary team of colleagues at HIA-AME, RWTH and UKA, we developed a sequential centrifugation protocol to obtain superparamagnetic iron oxide nanoparticles (SPION) with very well-defined sizes from a polydisperse SPION starting formulation, synthesized using co-precipitation (Fig. 4E) [17]. We showed that the SPION fractions obtained upon size-isolation are well-defined and almost monodisperse, resulting in excellent performance in magnetic resonance imaging (MRI), magnetic particle imaging (MPI), and magnetic fluid hyperthermia (MFH). This is exemplified in Fig. 4F, showing that the size-isolated SPION sample C2 outperformed the commercial control formulation Resovist in terms of MPI signal generation. We consequently conclude that the size-isolation protocol established, together with novel synthetic methods which we are currently exploring to prepare SPION, are attractive ways forward to obtain iron oxide nanoparticles with improved properties for diagnostic, therapeutic and theranostic applications.

[X1] Decuzzi et al, Nanotechnology 2021
[X2] Liang et al, Biomaterials 2021

Mechanisms of tumor progression and metastasis

PD Dr. rer. nat. Wiltrud Lederle

We investigate the influence of the microenvironment on tumor growth and progression. Noninvasive imaging techniques and tools are applied to characterize angiogenesis, stroma remodeling and inflammation during tissue repair and carcinogenesis [18].

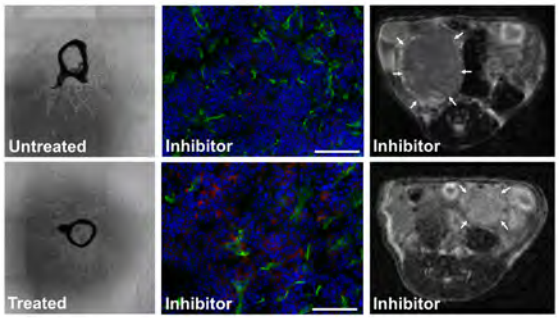

Fig. 5: Enhanced vascular sprouting is observed in response to a priming agent (treated) in the aortic ring assay (left). The amount of FAP-positive fibroblasts (middle panels, red: FAP, green: blood vessels) and tumor sizes (right, tumors marked by arrows on the MR images) differ between individual tumors upon treatment with immune checkpoint inhibitors.

As part of the RTG 2375, we aim at modulating the tumor microenvironment to improve nanodrug delivery and anti-cancer therapy efficacy. For priming tumor blood vessels towards an enhanced perfusion, the influence of clinically relevant agents on endothelial cell behaviour and vascular sprouting was studied in vitro and the most promising candidates were selected for in vivo application (Fig. 5). Moreover, we are exploring the effects of immune-modulatory drugs on colon cancer progression. In this context, we are investigating the heterogeneity in response to immune checkpoint blockade to gain better insights into the mechanisms that regulate treatment response (Fig. 5). In addition, FMT-CT was applied as a valuable tool for monitoring changes in apoptotic cell death in response to nanotherapy in advanced liver disease [19].
Furthermore, we contributed to the optimization of gold nanoparticle size and geometry for biomedical photoacoustic imaging [20].

Applied Medical Informatics

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

We develop and apply software tools for biomedical image analysis, segmentation, and visualization.
Together with cooperation partners, we applied our software tools to assess bone structures, based on in vivo and ex vivo μCT imaging, characterizing bone grafts and dental implants under different conditions [21,22,23]. Furthermore, we used our software for fat quantification in the context of infectious and inflammatory bowel diseases [24,25], liver vascular analysis [26] and calcification quantification [27].

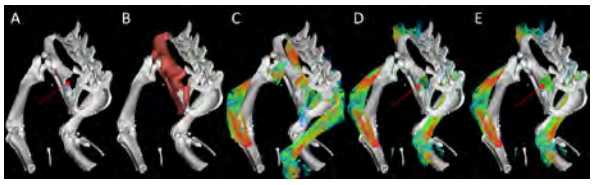

Fig. 6: Rat hip imaged in vivo (A). Left hip was segmented (B) to guide fusion of pre- and post-scans (C, D) to segment the harvested bone region (E).

Probe design for molecular imaging

Dr. Srinivas Banala

We design and synthesize organic chromophores for photoacoustic imaging (PAI), fluorescence microscopy and nanoscopy (STED) applications.
For PAI, we developed near-infrared (NIR) absorbing, highly photostable BODIPY and porphyrin dyes. [28, X3] We are also working on dyes for reactive oxygen species (ROS) detection. As ROS play important roles in inflammation and cancer therapy, non-invasive ROS detection is highly desired. To this end, a reversibly oxidizable ROS-BODIPY probe was developed that shifts its PAI signal from 680 nm to 800 nm. Due to reversible oxidation, it only detects overproduction of ROS. In addition, a non-reversible ROS sensor is also been prepared, based on the FDA approved dye methylene blue, to assess cumulative ROS production.

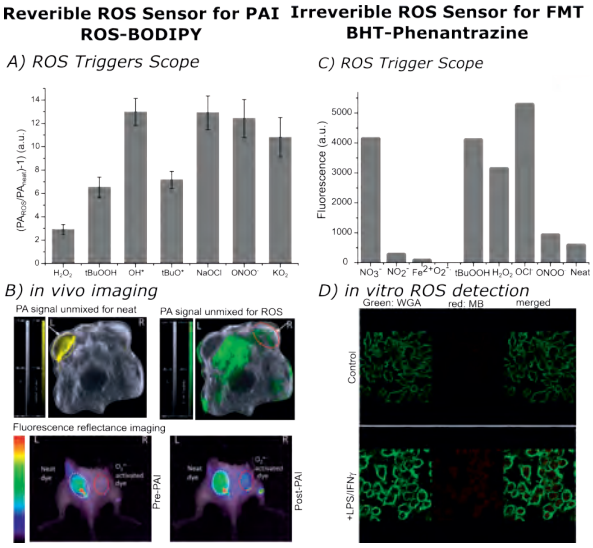

Fig. 7: In vitro and in vivo photoacoustic imaging of ROS species using the dye ROS-BODIPY.

Fluorescence imaging in the secound NIR-window (NIR-II, λmax: >1000 nm) enables in vivo imaging at high depths as NIR-II light penetrates deeper into tissue and is less scattered. Currently, only a few fluorophores are known with emission bands beyond 1000 nm. Thus, we initiated the synthesis of novel donor-acceptor dyes suitable for the NIR-II window. We furthermore recently patented a new class of bright and photostable dyes for nanoscopy [X4] and are working on advancing and expanding their application.

[X3] Merkes et al, ACS Sensors 2019
[X4] Merkes et al, WO2020120636A1

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• Funding Agencies: European Commission (H2020, EFRE), ERC, DFG, BMBF, ERS, IZKF, START, BMWI (AIF)

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- C. Hage: "Faculty price for an excellent dissertation" provided by Grünenthal GmbH
- C. Hage: "Friedrich-Wilhelm Award of the Friedrich-Wilhelm Foundation for an excellent dissertation"
- F. Kiessling: Fellow of the World Molecular Imaging Society
- F. Kiessling: Clarivate Analytics (Web of Science): "Highly Cited Researcher 2020" in cross-field category
- T. Lammers: International Award of the Belgian Society for Pharmaceutical Sciences (BSPS)
- T. Lammers: Clarivate Analytics (Web of Science): "Highly Cited Researcher 2020" in pharmacology and toxicology
- V. Pathak: Junior Investigator Award, Molecular Imaging in Nanotechnology and Theranostics, WMIC 2020Virtual
- V. Pathak: 2020 Vevo Travel Award in Molecular Imaging
- A. Rix: "Women in Molecular Imaging Network Scholar Award at the WMIC Virtual 2020"
- Y. Shi: best on-demand talk on "Targeting innate and adaptive immunity by polymeric nanomedicines". Controlled Release Society (CRS) Annual Meeting
- Y. Shi: Theodore von Kármán Fellowship

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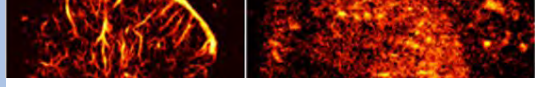

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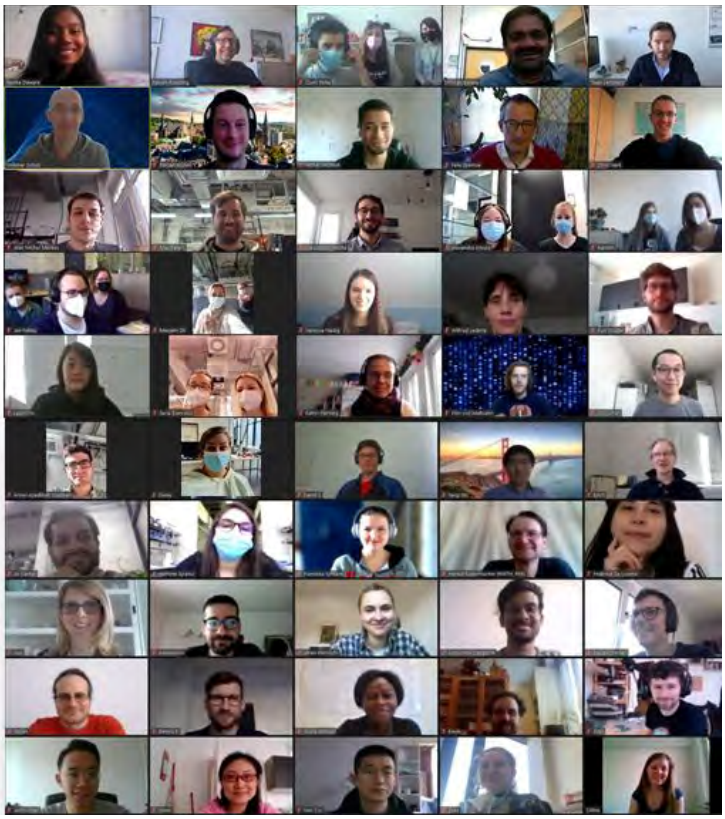
Gruppenbild



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Introduction

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

Our Institute of Applied Medical Engineering (AME) is a well-fitting example of the often cited "convergence of disciplines". In pursuing its research profile in biomedical engineering, the institute distinguishes itself through consistent and comprehensive interdisciplinarity. Our team consists of scientists and students from the fields of engineering, medicine, biology, life sciences, physics, materials science and computer science who work closely together on many research and development projects.
The interplay of highly innovative technologies in engineering with the latest knowledge and methods in the life sciences and medicine permeates all areas of activity and is characteristic of our undertakings and projects.
National and international industrial and academic partners are among our cooperation partners. These collaborations result in innovative diagnostic and therapeutic approaches, new impulses for teaching and an extensive catalog of jointly supervised engineering, natural science and medical dissertations.
The institute is located in the building of the Helmholtz Institute (HIA), in the Medical Technology Center (MTZ) and on two floors of the new Center for Biohybrid Medical Systems (CBMS), all of which are in close proximity to each other and to the University Hospital (UKA).

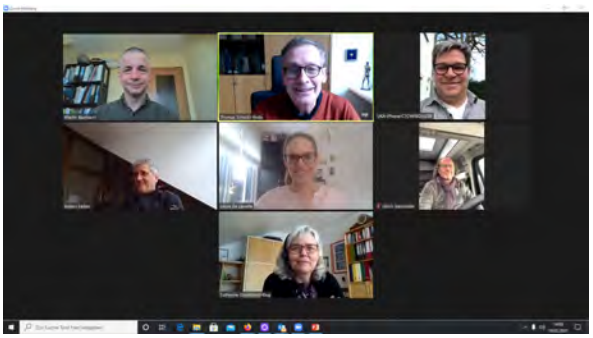


Fig. 1: AME Executive Team. Top left to right: Martin Baumann, Thomas Schmitz-Rode and Stefan Jockenhövel.
Middle from left to right: Robert Farkas, Laura De Laporte and Ulrich Steinseifer. Bottom Catherine Disselhorst-Klug.

Advanced Materials for Biomedicine (AMB)

Univ.-Prof.'in Dr.-Ing. Laura De Laporte

The Department for Advanced Materials for Biomedicine (AMB) focuses on the synthesis and (self)-assembly of synthetic molecules and micron-scale building blocks to create 3D constructs for tissue growth and regeneration. The research group forms a bridge between the University Hospital, the Chemistry Department of the RWTH, and the DWI-Leibniz Institute for Interactive Materials. Polymer synthesis is combined with in-mold polymerization techniques, microfluidics, and fiber spinning to achieve materials that can be injected in vitro or in vivo, or employed in bioprinting. By incorporating iron oxide nanoparticles or gold nanorods inside microgels or hydrogels, orientation and actuation is possible via external triggers, such as a magnetic field and light, respectively.

Selected **research highlights** in 2020:

Nanocellulose is an abundant natural material to fabricate regenerative scaffolds but can only be degraded by Cellulase. We found an easy way to create macroporous cellulose nanofibril hydrogels via a crushing step, followed by re-assembly of the formed granules. These constructs enabled efficient cell spreading in 3D hydrogels without the need for enzymatic degradation (doi: 10.1002/marc.202000191, Fig. 2).

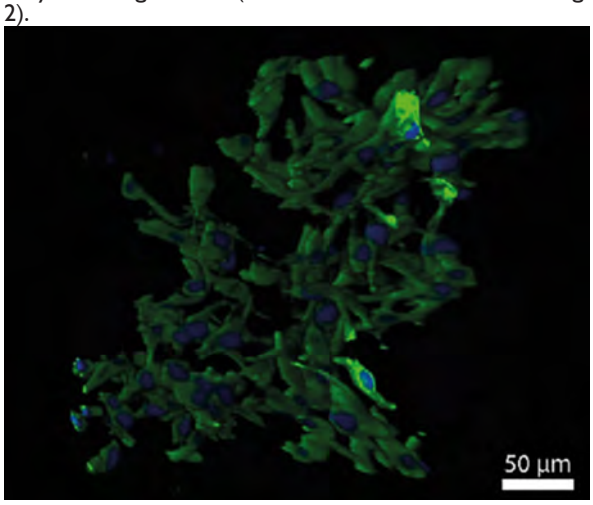


Fig. 2: Fibroblast spreading (green actin, blue dapi) in a 3D granular cellulose nanofibril hydrogel.

The Anisogel can form oriented anisotropic structures after injection, leading to cell and nerve alignment in between magnetically oriented anisometric microgels. After optimizing the inter-microgel distance, we found that thinner microgels result in enhanced nerve extension, while maintaining neurite alignment (doi: 10.1002/adhm.202000886, Fig. 3).

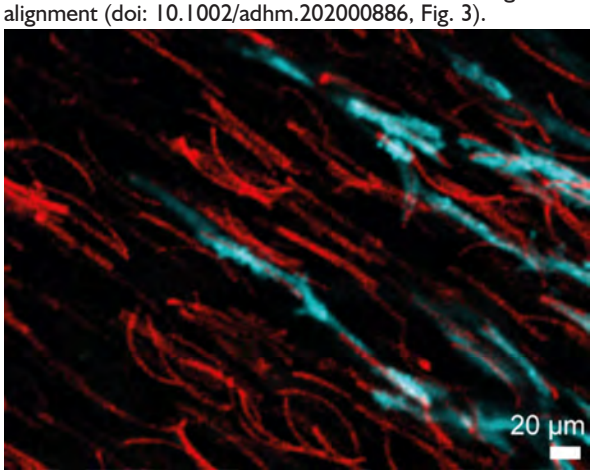


Fig. 3: Aligned neurons (blue) inside an Anisogel with 0.6 vol% oriented microgels (red, 2.5x2.5x50 µm).

Fibers with different topographies were produced via solvent assisted spinning and revealed how micro-/nano-scale topography and inter-fiber distance affect neuron alignment and branching in a synergistic manner (doi: 10.1016/j.actbio.2020.07.014, Fig. 4).

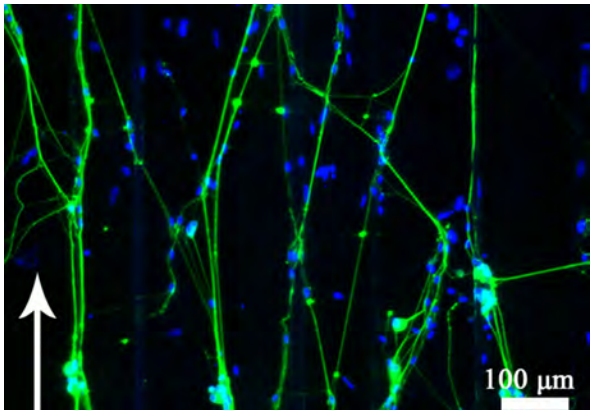


Fig. 4: Aligned neurons (green) and supporting cells (blue dapi) on oriented grooved fibers at ~100 µm inter-fiber distance.

Biophysical & Education Engineering (BEE)

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

Teaching goes online – Learning runs adaptive

As almost all university courses, the AME teaching formats also took the hurdles. Lectures have been adapted to digital formats, both synchronous and asynchronous. And even more, BEE took part in establishing online courses for lecturers to gain their personal digital experience, work with online collaboration tools and optimize the individual screen appearance. Blended learning was revised and turned to its genuine meaning. I.e. learning content was offered multi-layered and with different media: in real time, as simple recording, as semi-professional produced learning videos (Fig. 5) or interactively using breakouts on different levels. Thus, student learning could be supported actively, resulting in a still increasing number of student attendees. Practical courses which in the past were conducted group-based were redesigned to reach identical learning aims without personal contacts among students. We did the hurdling without major stumbles.

Fig. 5: Flipchart scribbles, video insets and demonstration materials support mnemonic and associative student learning.

Nanomagnetic Engineering/NME

Priv.-Doz. Dr. rer. nat. Dipl.-Phys. Ioana Slabu

Magnetic Nanoparticles in Theranostics

The research field of the NME group focuses on bionanomagnetism. The researchers use magnetic nanoparticles (MNP) for different applications in theranostics. The group develops different MNP formulations and uses them as tracers in magnetic resonance imaging (MRI) and magnetic particle imaging (MPI). MPI is a new imaging modality that directly detects MNP tracers at any point, space and time within the body. Both technologies, MRI and MPI, are employed for in vivo visualization of hybrid implants such as polymeric stents embedded with MNP and for the quantification of the implant functions. Further, the researchers manipulate MNP with magnetic fields in such way that controlled heat und drug release in the body is possible. For these therapeutic applications, drug loaded MNP are targeted at a specific region of interest in the body. To advance this therapeutic approach, the group develops models of MNP interactions with blood flow and magnetic fields (Fig. 6) and performs simulation of targeting scenarios in vivo, e. g. in a tumor. The tumor vessel networks are digitally reconstructed from histological images using advanced image-processing algorithms.

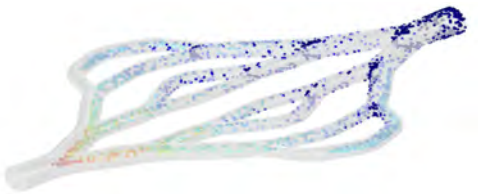


Fig. 6: Simulation of magnetic nanoparticles in a tumor vessel geometry.

NRW Schwerpunktprofessur Biohybrid & Medical Textiles (BioTex)

Univ.-Prof. Dr. med. Stefan Jockenhövel

The NRW-Schwerpunktprofessur Biohybrid & Medical Textiles (BioTex) focuses on the development of viable biohybrid implants with the potential for remodelling, regeneration and self-repair. BioTex wants to make a significant contribution to progress in (regenerative) medicine. We follow the mission to develop bioengineering solutions for clinical needs by combining functional materials and biological components towards biohybrid systems. Therefore, we have set up the institute along the value chain from material development and processing to biohybrid implant development and biofunctionalization and into (pre) clinical testing. BioTex is in a strong collaboration with the Aachen-Maastricht Institute for Biobased Materials (Director: Prof. Jockenhövel) and the DWI Leibniz Institute for Interactive Materials. In the close collaboration with the DWI, we were able to make a significant contribution to raise the necessary third-party funds for the construction of the Leibniz Joint – Lab for first-in-translation (fiT) at the DWI Leibniz Institute. In autumn 2020, construction of the fiT began, which will enable us to produce our current pre-developments under GMP and GLP-compliant conditions and validate them in first clinical trials from 2022 on.

Fig. 7: Under Construction: The Leibniz Joint-Lab first-in-translation (fiT) at the DWI Leibniz Institute.

Research Highlights of 2020:

BioPacer - Biological Pacemaker for Pediatric Application

Treating AV blocks (malfunction of heart's conductive system) in children using standard pacemakers is still unsatisfactory for different reasons (finite battery life, size requirements and necessity for lead readjustment during child growth). Therefore, the BioPacer project aims to develop a permanent treatment solution (Fig. 8A). Cardiomyocytes combined with endothelial cells (ECs) form a living conductive 'wire' bypassing the non-function area of the heart. (Fig. 8B).

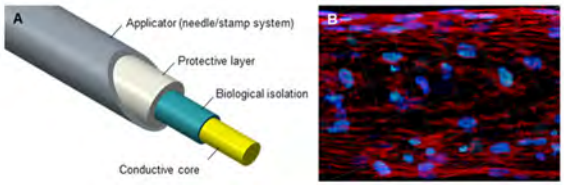


Fig. 8: A: Concept of the BioPacer device with a conductive (cardiomyocytes), prevascularized (ECs) core surrounded by biological isolation (fibroblasts), protective layer and applicator. B: Longitudinal section of conductive core. Nuclei of ECs and fibroblasts stained blue. Fibroblasts stained red.

in vitro Differentiation of Airway Epithelium

Reproducible cell culture of primary human respiratory epithelial cells (HREs) is crucial for reliable disease models and tissue engineering approaches. Creating a ciliated, physiologically functional epithelium remains a great challenge. To address this, different cell culture media were evaluated in an air-liquid interface (ALI) setting. Among the tested conditions, modified Airway Epithelial Cell Growth Medium was identified to most reliably raise a mucociliary phenotype (Fig. 9, Lüngen et al.).

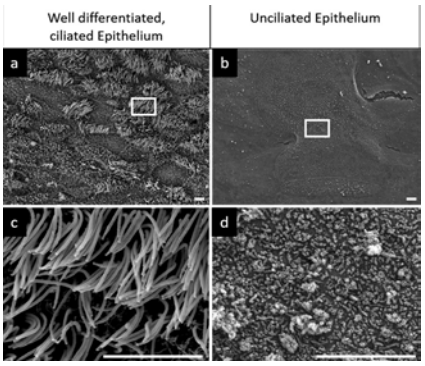


Fig. 9: After four weeks of ALI in different media, SEM images revealed cilia formation using modified Airway Epithelial Cell Growth Medium (a, c) and microvilli formation without ciliation using the other media (b, d). Representative images of two different magnifications are shown. Scale bar: 5 µm.

EndOxy - Endothelialized Oxygenator
Shortcomings of conventional extracorporeal membrane oxygenation include thromboembolism and bleeding. For the development of a biohybrid lung for long-term support, gas exchange membranes were seeded with endothelial cells (ECs) to establish a physiological, hemocompatible surface (Fig. 10). Mid- and long-term stability of the EC layer at physiological flow rates as well as gas transfer across the cell-seeded membranes were demonstrated (Klein et al. & Hellmann et al.).

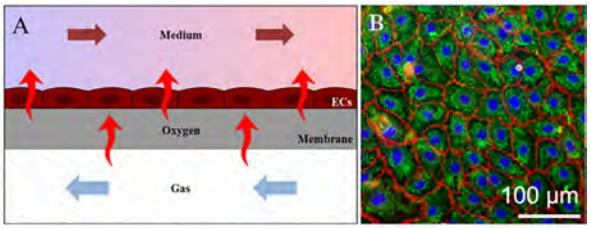


Fig. 10: A: ECs seeded on gas exchange membranes allowing gas transfer. B: Layer of ECs (top view) stained with DAPI (blue), CD31 (red) and von Willebrand factor (green).

Tissue Engineered Heart Valves
Using bioreactors, living heart valve transplants can be created (constituting a promising alternative to less durable valves with animal origin). They undergo a three-week cultivation phase under dynamic flow mimicking fetal environment. Controlling and optimizing the maturation will enable reliable automation of this process. Therefore, a new bioreactor is developed enabling valve monitoring, recording and regulation of biomechanical and -chemical parameters during the maturation to achieve optimal process conditions.

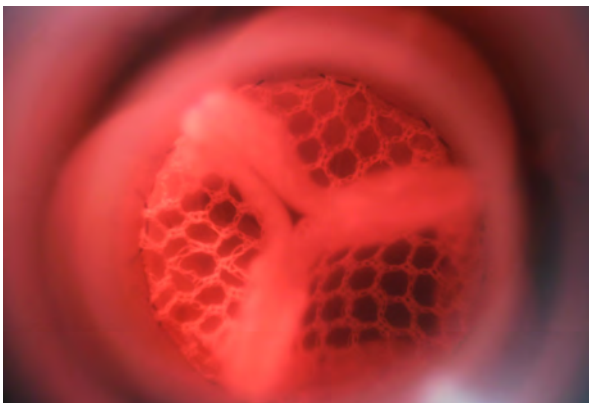


Fig. 11: Tissue engineered heart valve during maturation in the bioreactor. The trileaflet aortic valve (closed state) is fixed inside a silicone tube (blurred) mimicking the human aorta.

Regenerative Endodontic Therapy
Extracellular vesicles (EVs) have potential to support dental pulp regeneration due to their potent proangiogenic effects. An EV-fibrin gel composite as injectable delivery system was developed and investigated (Fig. 12). EVs isolated from dental pulp stem cells enhanced cell growth and migration and facilitated vascular-like structure formation in less than seven days (Zhang et al.).

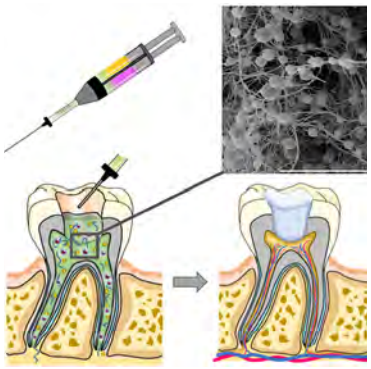
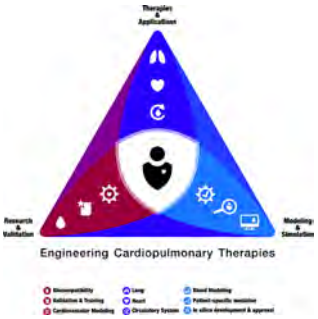


Fig. 12: Using a dual chamber syringe, EV-loaded fibrin gel can be applied into the root canal system. SEM image shows polymerized EV-loaded fibrin gel (Scale bar: 10 µm).

Cardiovascular Engineering (CVE)

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

In 2020, the restructure of CVE's research activities in the fields Application & Therapies (Dr. Sebastian Jansen) and Research & Validation (Dr. Johanna Clauser) was completed by the arrival of Dr. Michael Neidlin as Chief of the field Modeling & Simulation and Marie-Luise David as Research Manager, assuring the mission "Engineering cardiopulmonary therapies for the benefit of patients."



Research & Validation concentrates on the in-vitro evaluation of interactions between biological and technical systems for cardiopulmonary applications.

Within the project Ghost Cells, the large-scale Ghost Cell production is validated enabling spatially resolved hemolysis detection in blood-bearing medical devices (Fig. 14).

Fig. 14: Large-Scale Ghost Cell production facility.

In a similar project Ghost Blood, transparent erythrocytes free of hemoglobin are enhanced with coagulation properties of platelet rich plasma as blood analogue for particle image velocimetry (PIV).

The project TIBET aims at developing an in-vitro thrombogenicity test method for membrane oxygenators. A validated in-vitro method would significantly reduce the number of in-vivo experiments. Another in-vitro thrombogenicity setup is the THIA II, a test bench for heart valve evaluation (Fig. 15).

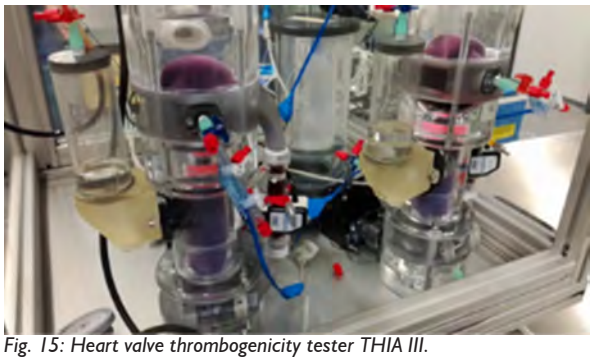


Fig. 15: Heart valve thrombogenicity tester THIA III.

Within the project PolyValve, the above-mentioned setup was modified to investigate not only mechanical, but also polymeric heart valve prostheses. Within a Hirsch Foundation project, the tester will further be enhanced to biological valves.
The project EduDerm continues research on skin models for medical students to train basic surgical skills as suturing or cannulation (Fig. 16).

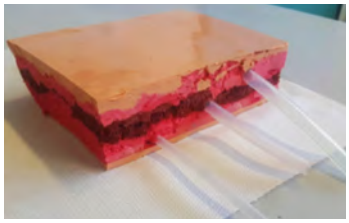


Fig. 16: Skin model for basic surgical education.

Within the field **Modeling & Simulation**, the gas transfer across oxygenator fibers using in-silico and in-vitro methods is investigated in OxySIM II. Small-scale oxygenator modules with different fiber orientations are constructed and tested with in-vitro blood experiments (Fig. 17a). Then, an existing CFD model of gas transfer is expanded to consider the different gas exchange ratios for various fiber geometries (Fig. 17b). Finally, the insights are upscaled to full-sized oxygenator modules.

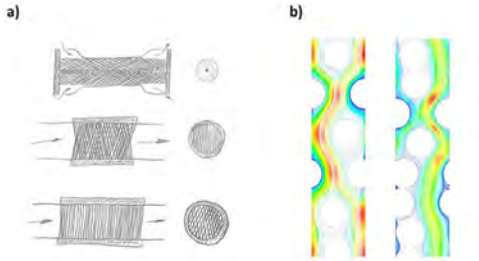


Fig. 17: a) Concepts for modules with different fiber orientations. b) microscale CFD simulations of gas transfer along fiber geometries.

In a second project, the blood flow within univentricular hearts was investigated using a self-developed moving mesh methodology. Time-resolved 3D-ECG images of ventricular movement were acquired for healthy subjects and patients with a singular right ventricle pathology by the University Hospital Bonn. Then, ventricular movement was interpolated and transferred to CFD models of the ventricles. Finally, fluid dynamic markers such as vortex formation, kinetic energy and ventricular washout were compared between left and single right ventricles (Fig. 18). Significant differences in the vortex structures and in the washout performance were observed, pinpointing the intriguing role between ventri-cular motion, fluid dynamics and cardiac function.

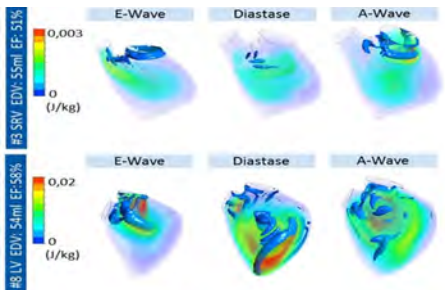


Fig. 18: Turbulent kinetic Energy (J/kg) and vortex structure formation with Q-value 6000 (1/s) for subject #3 (SRV) and subject #7 (LV) during diastole.

Therapies & Applications focuses on innovative therapies and devices and their potential transfer into the clinic. In Perinatal Life Support (PLS), a European consortium investigates two approaches to improve survival of extremely pre-term neonates. In both approaches, the lungs of neonates remain filled with artificial amniotic fluid to maintain the fetal circulation and avoid mechanical ventilation. Oxygenation is performed by extracorporeal oxygenators via the umbilical cord (Fig. 19). The two approaches differ by either completely submerging the neonate in the amniotic fluid or by just flushing the lungs.

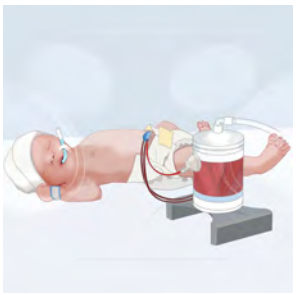


Fig. 19: Life Support for pre-term neonates by oxygenation via the umbilical cord.

The ReinHeart TAH project presents a new method for the adjustment of the Total Artificial Heart's (TAH) left-right flow balance. This is a persistent challenge for all TAHs with a coupled driving mechanism for the left and right side. An adjustable left-right flow balance was achieved through control of the right diastole duration.
The project 3D-Membranes investigates triply periodic minimal surfaces (TPMS) as new membrane shapes for their use in artificial lungs. Compared to state-of-the-art hollow fiber geometries, TPMS can be freely designed towards a completely homogeneous blood flow while also providing a significant higher gas exchange.

Rehabilitation and Prevention Engineering (RPE)

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

The Department of Rehabilitation & Prevention Engineering (RPE) has extensive expertise in the development and use of biomechanical models, feature extraction algorithms for prevention and diagnostics, as well as technical devices ranging from sensor- to robotic-systems for therapy support and the rehabilitation of patients with movement disorders.

Analysis of human movement and coordination

Autologous bony tissue from the pelvic crest or fibula may be used in mandibular resection. The effect of this orthopaedic procedure on the long-term postoperative gait of patients was investigated using clinical gait analysis (Fig. 20).

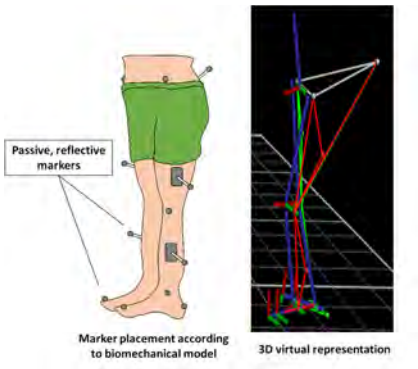


Fig. 20: Clinical gait analysis.

Knowledge of the physiological and pathological movement patterns of the elderly is required to better adapt rehabilitation methods and aids to their movement abilities. An on-going 'START' project employs 3D motion analysis to investigate such subjects' movement patterns during selected exercise tests (Fig. 21).

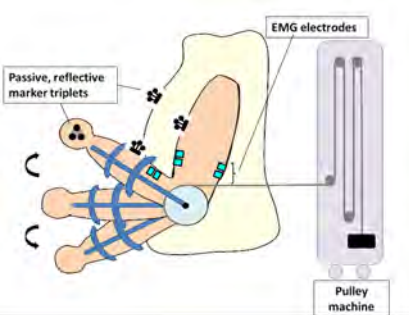


Fig. 21: Motion analysis in the elderly. Arm movement test at a pulley-machine.

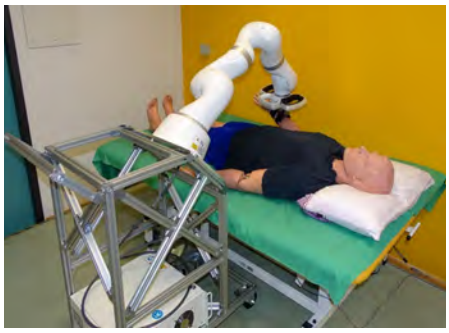


Fig. 25: PfleKoRo prototype. Its robotic arm holds the arm of a simulated patient.

Intelligent rehabilitation aids & cooperative robotics

An assistance system, based on inertial measurement units (IMUs), was developed in the **autoPräz** project to support the autonomous rehabilitation of patients with lower back pain (Fig. 22). The system detects patients' mistakes during their performance of therapeutic exercises and thus supports remote patient rehabilitation in healthcare.

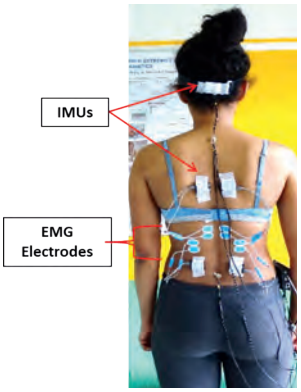


*Fig. 22: **autoPräz** IMU-based assistance system: Testing.*

In a bilateral project with Mexico, **DeMaPro**, a bespoke prosthesis is being developed, which will be controlled by surface electromyography (sEMG) signals. Usage of the prosthesis will require patients to independently position sensors on the arm so that muscular activation can be detected. Initial tests on a newly developed sEMG sensor system (Fig. 23), comprising dry-electrodes, have detected muscular activation with sufficient accuracy.

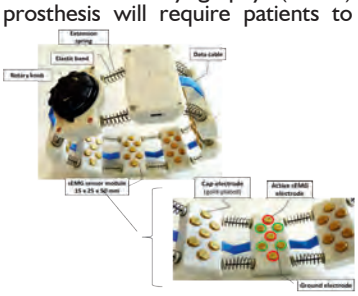


Fig. 23: sEMG sensor system (8 modules, each with 7 dry electrodes).

inRehaRob (BMBF funded project) resulted in an autonomously useable robotic rehabilitation system that monitors, and provides feedback to both patient and therapist during therapy (Fig. 24). By incorporating the sEMG sensor system above, continuous information about patients' muscle activation during therapy tasks can be provided to refine the system's assist-as-needed feature for individualized rehabilitation.

*Fig. 24: **inRehaRob**.*

An iterative process was utilized in the **PfleKoRo** project to develop a needs-oriented robotic system to support caregivers (Fig. 25). During patient care, the **PfleKoRo** system can take over the physically-taxing holding and repositioning tasks normally performed by caregivers, freeing them to focus on dedicated patient care.

Science Management (SCM)

Dr. Robert Farkas (Head)

Translational Research aims at accelerating the process from invention to clinical application. However, increasing complexity of technology and regulatory affairs slows down the pace of innovation. To tackle this challenge a promising mean among other is to intensify collaboration. Thus we investigated the potential of an AI based collaboration recommender for profiling medical technology experts according to their scientific publications and their patents. Trained machine learning classifier (Support Vector Machines) mapped the published work of experts to our domain model of medical technology consisting of three major dimensions (clinical field, key technology and field of innovation) and 21 subgroups. The respective task, a collaborator is searched for, can be categorized to the domain model as well, so that a match between the experts profile and the given task can be visualized by computing the euclidian distance (Fig. 26). Our feasibility study showed, that all tested experts were able to identify their own profile among a stack of ten anonymized expert profiles, which proves the validity of our approach of profiling the expertise of a biomedical scientist. Encouraged by these findings, the future task now is to scale our approach from a handful of subjects to all scientists of the medical faculty or the entire RWTH Aachen University or even beyond.

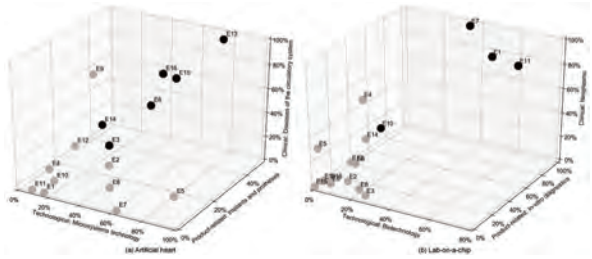


Fig. 26: Position of 16 experts (E1...E16) after activity-based profiling using their publications and patents in the requirements cube for the development of an artificial heart (left) or a lab-on-a-chip system (right). The domain model of medical technology forms the basis; black dots mark the experts suitable for the task according to external validation (see Bukowski et al. 2020).

Acknowledgements

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- Excellence Initiative of the German federal and state governments
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- German Federal Ministry for Education and Research BMBF
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- INTERREG

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- Maquet Cardiopulmonary GmbH / GETINGE SA
- „START-program“ of the Faculty of Medicine, RWTH Aachen University
- Stifterverband für die Deutsche Wissenschaft

Awards

- Thiebes, Anja Lena, Dr.rer.medic: Award of the Westdeutsche Gesellschaft für Pneumologie (WDGP) in January 2020 for her scientific work with the title “Comparison of Covered Laser-cut and Braided Respiratory Stents: From Bench to Pre-Clinical Testing”.

Selected Publications 2020

[1] Besomi M, Hodges PW, Clancy EA, van Dien J, Hug F, Lowery M, Merletti R, Sögaard K, Wriglesy T, Besier T, Carson RG, Disselhorst-Klug C, Enoka RM, Falla D, Farina D, Gandevia S, Holobar A, Kierman MC, McGill K, Rerreault E, Rothwell JC, Tucker K: Consensus for experimental design in electromyography (CEDE) project: Amplitude normalization matrix. Journal of Electromyography and Kinesiology 53: 102438-102454, 2020.

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Team (Photos taken before Corona).

Facts

Third-party Funding gesamt 2020

	Number of Projects	Total Expense of Projects [EUR]
German Research Foundation (DFG)	49	2.476.900
German Federal Ministry of Education and Research (BMBF)	34	2.878.500
EU	16	975.300
Industry	23	1.918.100
Other	49	3.078.200
Sum	171	11.327.000

Theses

	Number
Student Mini-Thesis	14
Bachelor	61
Diploma/Master	82
Doctoral	26
Habilitation	2
Sum	185

Staff

	Scientific	Admin.&Techn.
Total	234	47
Third party funded	173	12

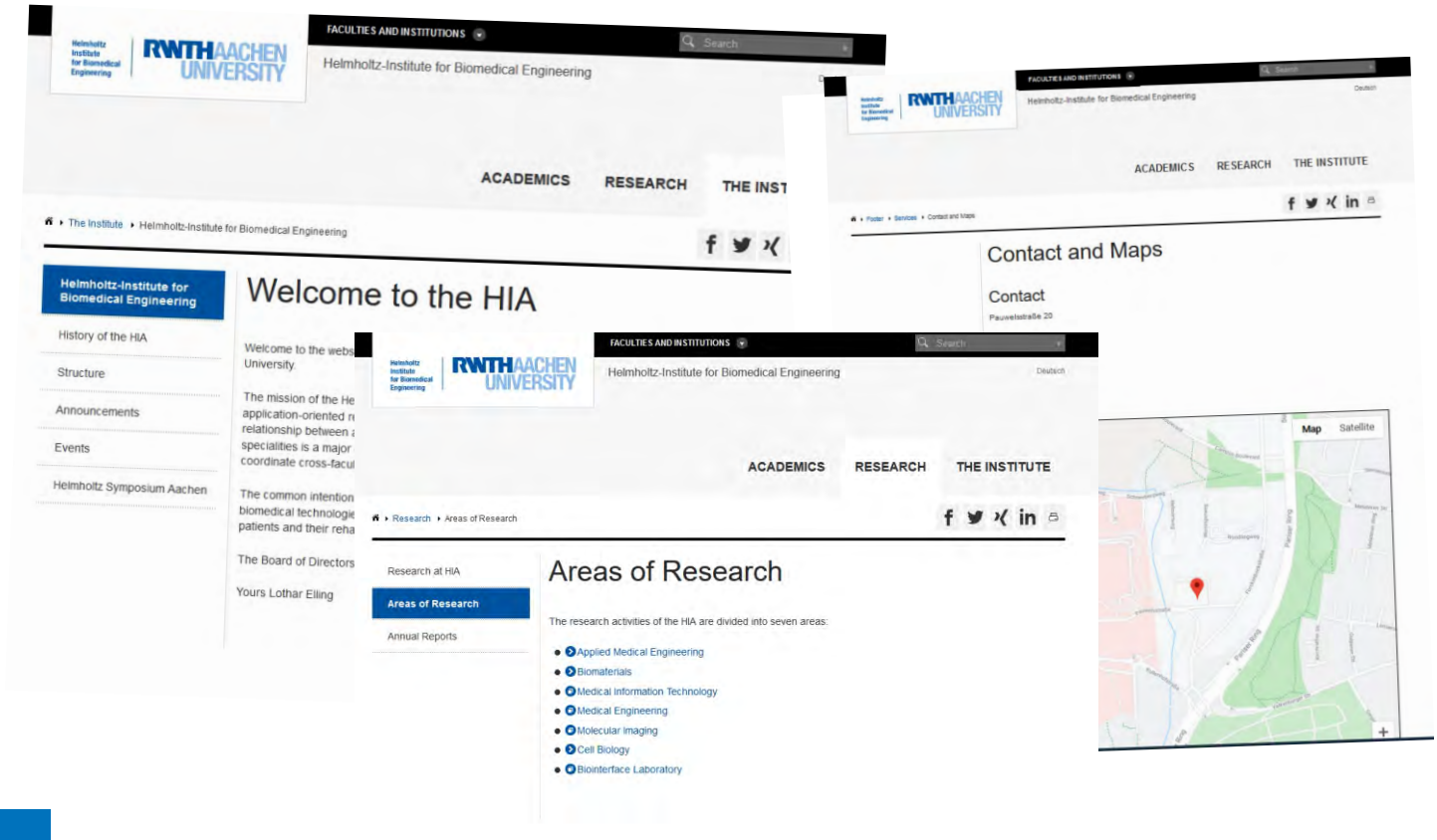
in full-time equivalent (FTE)

Publications

	Number
Conference proceedings	19
Peer-reviewed journals	175
Books and book chapters	9
Sum	203

Patents and patent applications: 7

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



Content

Annual Report
2020
Helmholtz-Institute for Biomedical Engineering
RWTH Aachen University

How to reach us

Address

Helmholtz-Institute for Biomedical Engineering
Pauwelsstrasse 20
52074 Aachen
Germany

By car

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

By train/bus

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

By plane

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

- From Düsseldorf airport the travel time by car is approxi - mately 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.