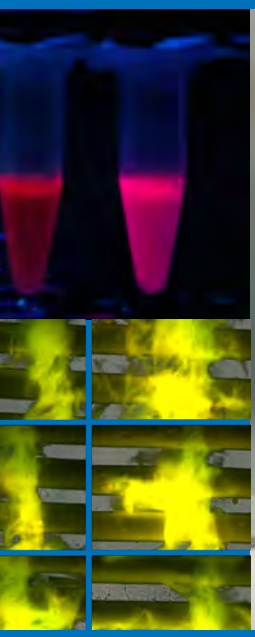
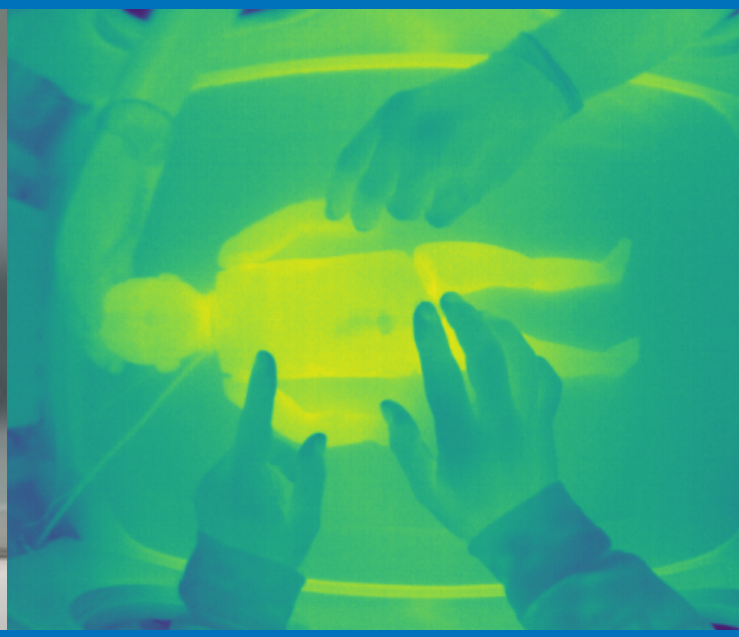
Helmholtz-Institute for Biomedical Engineering

Annual Report 2023





RWTH AACHEN UNIVERSITY

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Content

Preface

The Helmholtz-Institute for Biomedical Engineering, Aachen (HIA) is a nucleus for interdisciplinary basic and applied research and the development in biomedical engineering at RWTH Aachen University and beyond. Our research projects aim to improve health care. The continuous development of methods and technologies contributes to achieving personalized diagnosis and therapy options for patients. The Helmholtz-Institute realizes the vision of interfaculty research that is promoted by RWTH's profile areas (www.rwth-aachen.de/cms/root/Forschung/Strukturen/~ptz/Profilbereiche). In this context, the directors of the Helmholtz-Institute are taking leading roles in the profile areas Medical Science and Technology and Molecular Science and Engineering. In this regard, networking and cooperation within RWTH Aachen University and with national and international clinicians, academic and industrial researchers are key to our work.

The Helmholtz-Institute continuously evolves, we are excited that with Prof. Dr. Ioana Slabu and Prof. Dr. Yang Shi, both ERC awardees, two new professors were appointed to our institute. In addition, Ioana Slabu received an RWTH Innovation Award for the development of nanomodified stents to treat hollow organ tumors (ProNano). Besides this, Prof. Kiessling and his team received the 4th Aachen Animal Welfare Award for an advanced in vitro tumor model. Furthermore, the two Clarivate Highly Cited Researchers of RWTH Aachen University (Prof. Dr. Fabian Kiessling and Prof. Dr. Twan Lammers) are both members of our institute. Prof. Dr. Catherine Disselhorst-Klug has been awarded with the John Basmajian Award for outstanding scientists in the field of electrophysiology and kinesiology. In addition, for the second time Prof. Leonhardt was appointed "Distinguished Professor" at IIT Madras (2023-2028), RWTH Aachen's sister University, in Chennai, Tamil Nadu, India. Prof. Laura De Laporte became part of the Board of Directors of the International Society for Biofabrication. Prof. Stefan Jockenhövel and Prof. Steffen Leonhardt were appointed to the German National Academy of Science and Engineering (acatech) and Prof. Thomas Schmitz-Rode to the German National Academy of Sciences Leopoldina.

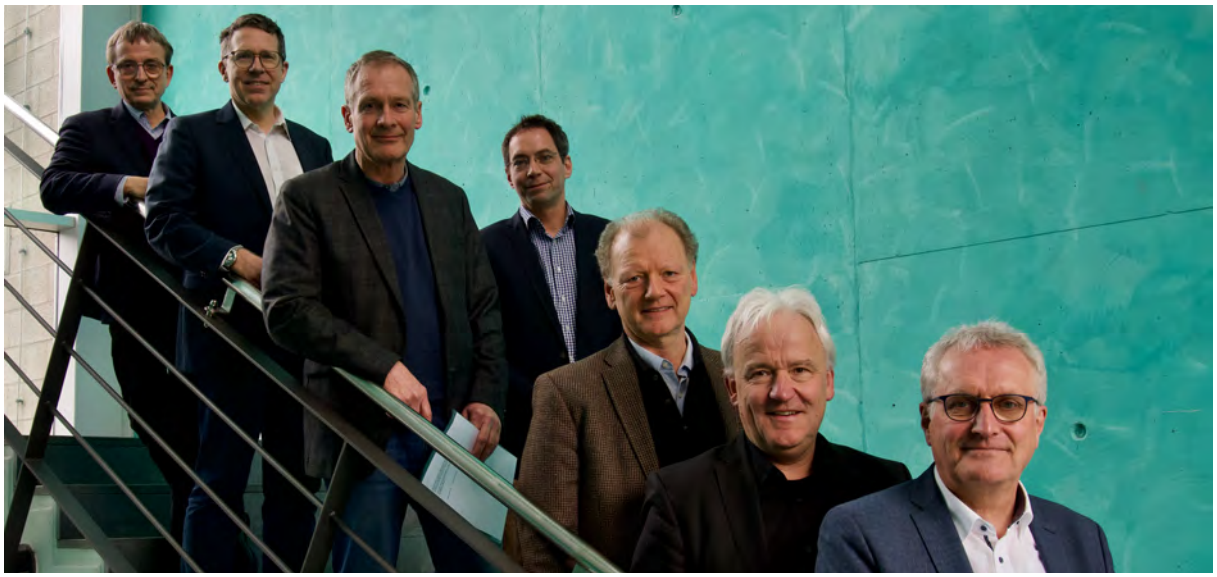
Researchers at the Helmholtz-Institute for Biomedical Engineering were instrumental in raising funds for research and coordinating teaching. In 2023, third-party funding alone reached well over 13 Mio. Euro.

The professors of the Helmholtz-Institute are internationally highly visible and take responsibility in international research communities. For example, in 2023 Prof. Kiessling became the President of the European Molecular Imaging Society, Professor Lammers the President of the Controlled Release Society, and Professor Steinseifer the President of the European Society for Artificial Organs ESAO. He will also host the 50th annual congress of the ESAO in Aachen this year. Prof. Schulz and Dr. Slabu hosted the International Workshop on Magnetic Particle Imaging (IWMPI) 2023 in Aachen, drawing over 200 attendees from 20 countries. In June 2023, Prof. Steffen Leonhardt and his team organized and hosted the 23rd International Conference on Biomedical Applications of Electrical Impedance Tomography in Aachen, with more than 100 participants attending.

As in the past, researchers from the Helmholtz-Institute have successfully participated in the bachelor, master and doctoral programmes of the medical, engineering and natural science faculties of RWTH Aachen University, coordinating studies in all areas of biomedical engineering. The practical training of students in parallel with academic teaching has proven to be essential for successful international careers in industry and academia. Biomedical Engineering, Medical Biology and Biointerface Science are becoming increasingly important and have become major subjects in biomedical and engineering master's programmes. This development reflects the constantly evolving biomedical and healthcare industry, technological innovations and societal needs.

This 2023 Annual Report is dedicated to our funders, partners and friends for their support and collaboration, as well as to all those interested in our Institute. Enjoy reading and please do not hesitate to contact us! We look forward to providing you with further information and discussing future opportunities for collaboration in the fascinating field of biomedical engineering.

Aachen, March 2024
The Board of Directors



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

Helmholtz Institute for Biomedical Engineering | RWTH AACHEN UNIVERSITY

HELMHOLTZ INSTITUTE 50 YEARS ANNIVERSARY

Dear Colleagues,

For the past 50 years, the **Helmholtz Institute for Biomedical Engineering** has been committed to pioneering solutions for improving patient diagnosis and therapy. We are delighted to invite you to join us in celebrating this significant milestone at a one-day symposium!

28 June 2024

09:00 – 13:00 **Welcome and Talks; RWTH Main Building, Templergraben 55 – Aula 1**

15:00 – 17:30 **Tours, Posters and Get Together, HIA, CBMS, Pauwelsstrasse 20. 52074 Aachen**

Poster registrations are welcome and possible for all RWTH institutes. Details for submission will be communicated soon. Please let us know by **February 1, 2024** whether we can expect you at our anniversary via **info@hia.rwth-aachen.de**

With Kind Regards,

The HIA Board of Directors

Institute for Stem Cell Biology
Medical Faculty

Epigenetic regulation of cell function

Director

Univ.-Prof. Dr. med. Dr. rer. nat. Wolfgang Wagner

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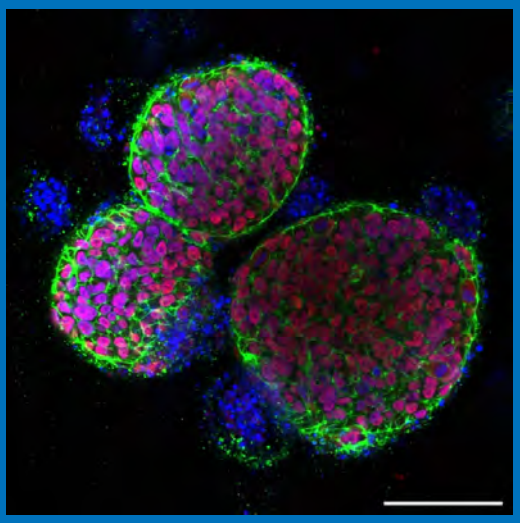


Introduction

The Institute for Stem Cell Biology focusses particularly on understanding of the molecular mechanisms governing pluripotency and differentiation in human stem cells. These processes are controlled by epigenetic changes in the genome, such as DNA methylation of specific CG dinucleotides (CpGs). We use these site-specific DNA methylation changes as biomarker for quality control of induced pluripotent stem cells (iPSCs) to characterize their differentiation potential toward the three germ layers: endoderm, mesoderm, and ectoderm. Notably, DNA methylation signatures do not only evolve during early cell differentiation, but also during maturation of each specific cell type, they change during aging, and acquire aberrations during development of many diseases. Consequently, we use such epigenetic modifications to develop a wide range of biomarkers. For example, we track DNA methylation changes to characterize malignant diseases such as myeloproliferative neoplasms (MPN) and acute myeloid leukemia (AML) or to calculate leukocyte cell counts in human blood samples. This involves close collaboration with various other institutes at RWTH Aachen, particularly at the University Hospital of RWTH Aachen, which provide patient samples. Furthermore, we are external member of the research unit "Aging at Interfaces" (CRU 1506) in Ulm, and lead a consortium on "Genome Wide Analysis of Epigenetic Changes in Aging". We utilize a broad range of next generation sequencing and microarray technologies in combination with genome editing tools like CRISPR-Cas9 to investigate how cell fate decisions are triggered. Using CRISPR-Cas9 editing in somatic cells, we induce targeted DNA methylation to analyze its effects on the control of molecular mechanisms and generated CTCF-deficient stem cell lines to determine its impact on pluripotency and differentiation.

Since, in vitro culture conditions create an artificial cellular environment, we furthermore draw on our interdisciplinary knowledge in collaboration with the DWI Leibniz-Institute for Interactive Materials and the Institute for Molecular and Cellular Anatomy at the University Hospital of RWTH Aachen. Together, we examine the influence of biomaterials and surface structure on the self-organization and differentiation of stem cells. Modulation of surface topography, adhesive properties, and elasticity is evaluated to further optimize culture conditions for tailored cellular products. Our research provides insights into aging processes, establishing biomarkers for iPSC quality control and clinical diagnostics, and advances the generation of cell products for regenerative medicine.

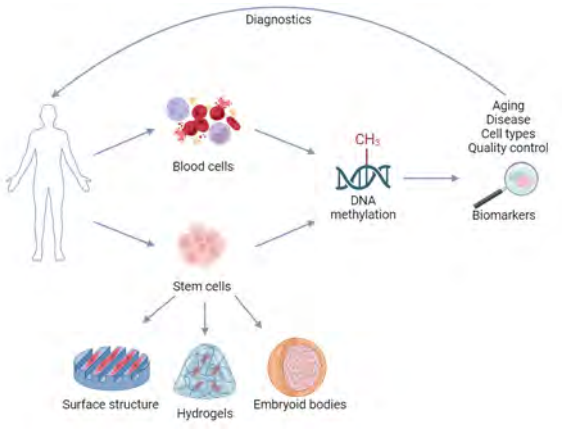


Fig. 1: Schematic overview of different research approaches. We aim to better understand underlying epigenetic mechanisms of aging and diseases to develop new diagnostics, by culturing stem cells on biomaterials, creating organoids, or by disease modeling with patient-specific mutations. In addition, we develop robust epigenetic biomarkers for pluripotent and differentiated cells to determine the cellular composition in a specimen, biological age, or cancer.

PluripotencyScreen – Improving the quality control of pluripotent stem cells and their derivatives

Cells from our tissues can be reprogrammed into induced pluripotent stem cells (iPSCs) by overexpressing specific transcription factors. Such reprogrammed iPSCs have the ability to differentiate into the cell types of our body. Thus, iPSCs are defined by their potential to give rise to cells of all three embryonic germ layers: mesoderm, endoderm, and ectoderm. As a quality control for this ability, gene expression patterns and immunofluorescence images are commonly used. However, there remains an urgent need to better track early cell fate decisions and to improve quality control of iPSCs.

DNA methylation (DNAm) has been shown to be involved in cellular differentiation and manifests throughout development. Hence, it can be used to classify cell types and to estimate the composition of tissues. To better understand epigenetic changes in early differentiation events, we investigated DNAm changes during endodermal, mesodermal, and ectodermal differentiation of iPSCs in monolayer culture, as well as in 3D culture as embryoid bodies. Based on these epigenetic changes, we were able to derive a pluripotency score and differentiation scores for the individual germ layers, each consisting of three specific genomic regions (CpG sites). These epigenetic markers can support the quality control of pluripotent stem cell preparations and possibly also estimate their propensity to differentiate into specific germ layers (Fig. 2; Schmidt et al., Stem Cell Reports, 2023).

While the selected sites have been established on different cell lines and differentiation conditions, the next step is to further validate this assay on more cell lines and differentiation protocols to make them universally applicable. To this end, we received funding by the Bundesministerium für Bildung und Forschung (BMBF) for the VIP+ research project

PluripotencyScreen (1.4 mio €), to further develop this application into a service or kit that facilitates quality control of iPSCs for other scientists.

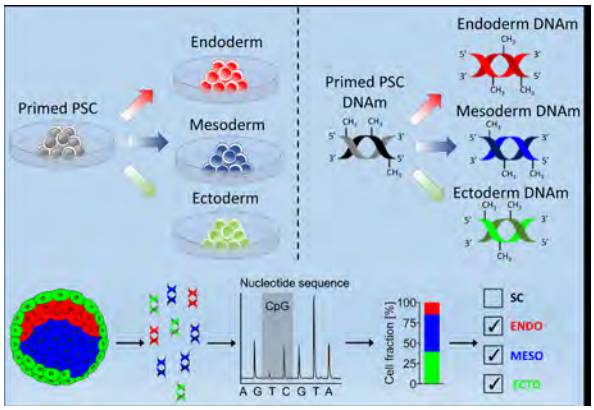


Fig. 2: Quality control of pluripotent stem cells. Adapted from the graphical abstract in Schmidt et al., Stem Cell Reports, 2023 depicting the selection of methylation sites for PluripotencyScreen.

CTCF deletion alters the pluripotency of human iPSCs

Pluripotency and cell fate decisions are mediated by epigenetic mechanisms that include long-range chromatin interactions. One of the key players regulating these interactions is a zinc finger-containing DNA-binding protein CCCTC-binding factor (CTCF). Using CRISPR-Cas9-mediated gene editing, we generated human induced pluripotent stem cell (iPSC) lines with deletions in the protein-coding region of CTCF and found these cells exhibit slower growth and an altered DNA methylation and transcription profile. Further analysis revealed that CTCF deletion leads to a reduced expression of the pluripotency protein OCT4 and to a bias toward endo-mesodermal lineage and a defect in ectodermal differentiation (Fig. 3). Our study provides novel insight into the role of chromatin-modifying proteins in pluripotency and differentiation of iPSCs (Puri et al., Frontiers in Cell and Developmental Biology, 2023).

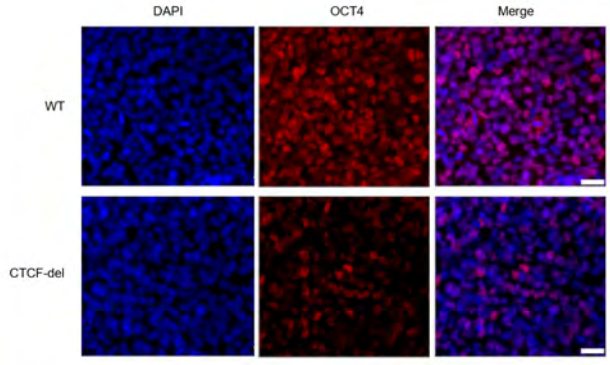


Fig. 3: Comparison of wildtype (WT) and modified CTCF-del cells by immunofluorescence analysis of the pluripotency protein OCT4 in iPSCs. The CTCF-del lines show reduced pluripotency. Scale bar: 50 µm. Adapted from Puri et al., Frontiers in Cell and Developmental Biology, 2023.

Targeted manipulation of biomarkers in aging and disease

Can we rejuvenate cells by directly interfering with the epigenetic program? The epigenetic landscape changes continuously during aging. Accelerated epigenetic aging is associated with shorter life expectancy and various diseases. Thus, epigenetic signatures were suggested as biomarkers for biological aging. However, it is so far not understood how age-associated DNA methylation (DNAm) is regulated and if it is relevant to the cell function. To address this question, we used new methods to directly modulate DNAm levels at specific sites in the genome. This was performed using two different approaches (CRISPR-mediated epigenome editing) to methylate genomic regions that either gain or lose DNAm with human age (Fig. 4a). Pyrosequencing and bisulfite amplicon sequencing were performed to validate the successful modulation of the epigenetic profiles. We could demonstrate that targeted modulation of age-associated DNAm remains stable for up to three months (Fig. 4b). Furthermore, we analyzed how this treatment affected genome-wide methylation levels. Even the effects beyond the target regions of epigenome editing were highly reproducible and systematically distributed. We are now using this model system for a better understanding of the molecular sequel of age-associated DNA methylation. Eventually, this might bring us in the position to interfere with epigenetic clocks and find out if directed modulations are suitable for rejuvenation.

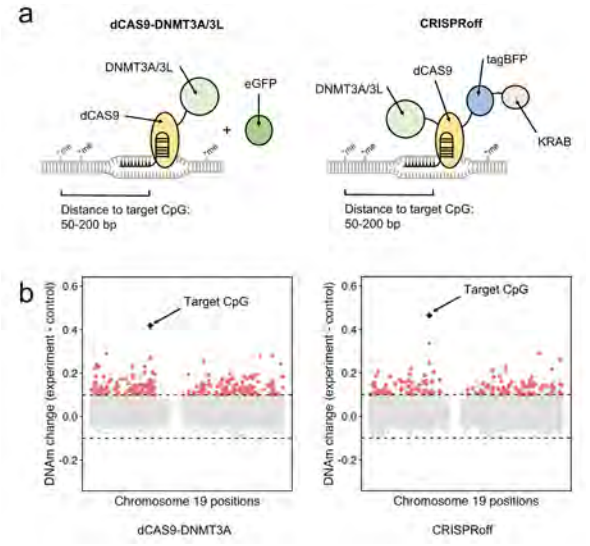
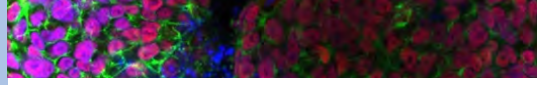


Fig. 4: CRISPR-Cas9-mediated epigenome editing. Scheme of two alternative CRIPSR-guided constructs (a). Fusion-proteins selectively change DNA methylation levels at one exemplary CpG-site on chromosome 19 (b).

Cellular aging is accelerated in myeloproliferative neoplasm

Myeloproliferative neoplasms (MPNs) are a family of clonal hematopoietic disorders, including polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). Somatic mutations such as JAK2V617F may not only



drive proliferation, but also accelerate replication and cellular aging, as well as genetic instability, potentially contributing to disease progression. Since MPNs are more frequently observed in the elderly and accelerated cellular aging has been shown for other types of cancer, we wanted to better understand if MPN is also associated with increased cellular aging. To this end, we used different models to study the molecular sequel of the JAK2V617F driver mutation. First, we used peripheral blood cells from MPN patients (Fig. 4a) and single cell-derived colony forming units (CFUs; Fig. 5b), which offer the possibility to study malignancy at the single cell level. In addition, we studied the impact of mutation using syngeneic iPSC models with JAK2 V617F upon short-term hematopoietic differentiation and mouse models. Our results show that cellular aging is accelerated in MPN compared to healthy individuals, which is particularly pronounced in specific clones carrying the JAK2V617F mutation. Furthermore, we analyzed the heterogeneity of aging in MPN patients and explored how this can be used to selectively target malignant cells with senolytic drugs or telomerase inhibitors (Vieri, Tharmapalan et al., Blood Cancer Journal, 2023). This research is performed within the Clinical Research Unit CRU 344, which is funded by the Deutsche Forschungsgemeinschaft (DFG).

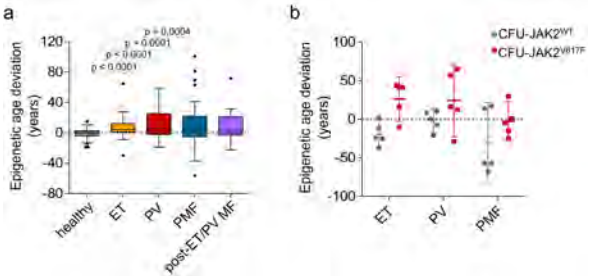


Fig. 5: Cellular aging is accelerated in MPN entities and prominently in malignant clones. Epigenetic age prediction in peripheral blood derived cells (a) and colony forming assay (CFU) (b). Adapted from Vieri, Tharmapalan et al., Blood Cancer Journal, 2023.

DNA methylation signatures in hematological malignancies

DNA methylation (DNAm) is a highly dynamic modification and plays an important role in regulating gene expression and cellular differentiation, including differentiation towards the different types of blood cell. On the other hand, the DNAm pattern changes in a very characteristic manner during development of leukemias, such as myeloproliferative neoplasms (MPN) or acute myeloid leukemia (AML). AML is the most common type of leukemia in adults and presents normally alterations in DNA methylation modifier genes. Our studies aim to conduct a comprehensive methylation analysis to better understand the underlying epigenetic changes in these diseases and establish epigenetic biomarkers.

Little is known about the sequence of events that lead to the altered methylation landscape or the impact that these changes have on the disease. It is also unclear to what extent epigenetic aberrations differ between hematological malignancies and if their aberrant methylation marks correlate - or if they are even coregulated. Our preliminary results show that methylation dysregulation in MPN is independent from driver mutations (JAK2, CALR, and MPL), suggesting a general molecular mechanism promoting the epigenetic alterations found between healthy and diseased samples (Fig. 6). Results with AML data shows high correlation between altered methylation marks. Furthermore, our predictive models have high accuracy determining the beta values of a certain position using just the beta values of other positions from the same samples. This suggests a common regulation between CG positions across the genome.

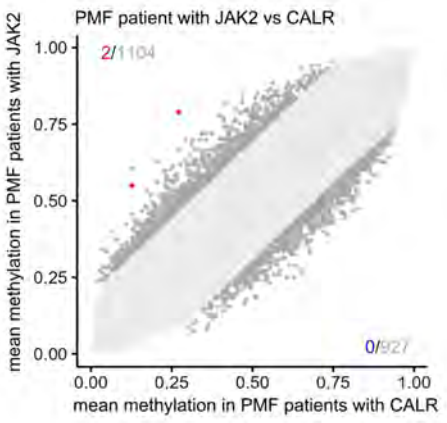


Fig. 6: Disease associated epigenetic patterns in myeloproliferative neoplasms. Scatter plot of differentially methylated CpGs in MPN blood samples with different driver mutations. There are hardly any epigenetic differences in samples with JAK2 and CALR, indicating that driver mutations have relatively little impact on the epigenetic aberrations in MPN.

A blood test from blood spots – Targeted analysis of DNA methylation facilitates leukocyte counts

Physicians measure the composition of white blood cells (granulocytes, monocytes, lymphocytes, CD4+ T cells, CD8+ T cells, B cells, NK cells) for diagnosis of a wide range of diseases, or to track therapeutic response. To this end, the patients have to visit the clinic because the currently established methods can only be performed with fresh blood. In particular for elderly patients with restricted mobility or patients that need regular screening this can be an issue. As part of a translational research project – initially funded by a VIP+ grant of the BMBF and then by ForTra GmbH for research transfer from the Else Kröner-Fresenius Foundation – we developed EpiBlood: an alternative method to count white blood cells based on DNA methylation. Publicly available DNA methylation data from 1,303 immune cells was analyzed to pinpoint genomic regions (called CpG sites) that are uniquely methylated in each cell type. We demonstrated that by measuring the methylation levels at these CpGs by digital droplet PCR it is possible to predict the relative composition of white blood cells (Hubens et al., Clinical Chemistry, 2023). In contrast to conventional methods, EpiBlood does not require fresh blood and could also provide accurate predictions from dried blood spots (Fig. 7a). By adding a reference plasmid, we could additionally calculate the absolute cell numbers (Fig. 7b). We are currently optimizing this absolute quantification and are additionally validating EpiBlood for pediatric samples. We aim to develop this method into a cli-

nically approved test that enables analysis of white blood cell counts from samples collected at home from a finger prick.

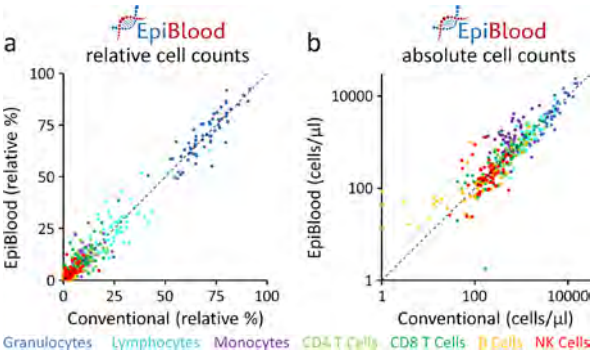


Fig. 7: The composition of white blood cells was estimated in dried blood spots with EpiBlood. DNA methylation was measured at seven CpG sites by digital droplet PCR to accurately estimate the relative amounts of white blood cells in dried blood spots of 75 patients (a). For absolute quantivation we added a reference plasmid during DNA isolation, which can be used to calculate the absolute amount of cells present (b). Adapted from Hubens et al., Clinical Chemistry, 2023.

Acknowledgements

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- Deutsche Krebshilfe
- Interdisciplinary Centre for Clinical Research Aachen (IZKF Aachen)
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- Donation by Vision4 Life Sciences

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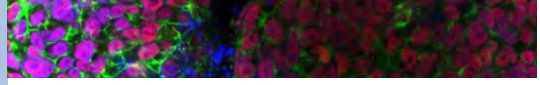

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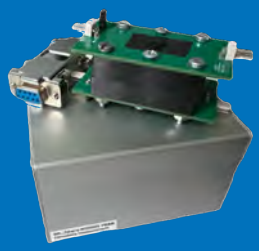
Team

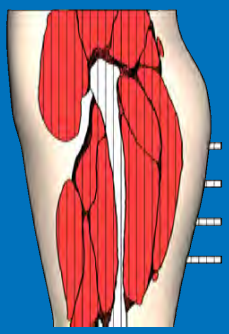
Dragon Boat race on the Mosel in Trier during our Labout in June 2023.

Medical Information Technology

Faculty of Electrical Engineering and Information Technology

Smart Solutions for Advanced Healthcare





Director

Univ.-Prof. Dr.–Ing. Dr. med. Dr. h. c. (CTU Prague)
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Trödel, Cedric, Software Developer
Warkentin, Astrid, Software Developer

Dissertations
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10.03.2023: Yu , Xinchi
21.04.2023: Uguz , Umutcan

Guests
01.04.2023 till 30.09.2023
Shubhanshu Sharma, M. Sc. (IIT Madras, India)
23.07.2023 till 23.09.2023
Prof. Qasem Qananwah (Yarmouk University, Jordan)
01.09.2023 till 01.03.2024
Dr. Kazi Jabed Akram (IIT Madras, India)

Delegations and events

- Between 12.06.2023 and 14.06.2023, the EIT conference has been hosted by the MedIT in Aachen.
- On 23.07.2023 the Indian Consul General Dr. Amit Telang visited the MedIT.
- On 15.09.2023 the MedIT celebrated its 20th anniversary.
- Between 18.09.2023 and 22.09.2023, a delgation of the MedIT visited the IIT Madras for coordinating the concept for an Indo-German Graduate College.
- On 29.09.2023 a delegation of the Tokyo Institute of Technology in Japan visited the MedIT.
- Between 13.11.2023 and 17.11.2023, the MedIT was visited by a student delegation from CTU Prague in Czechia.

Introduction

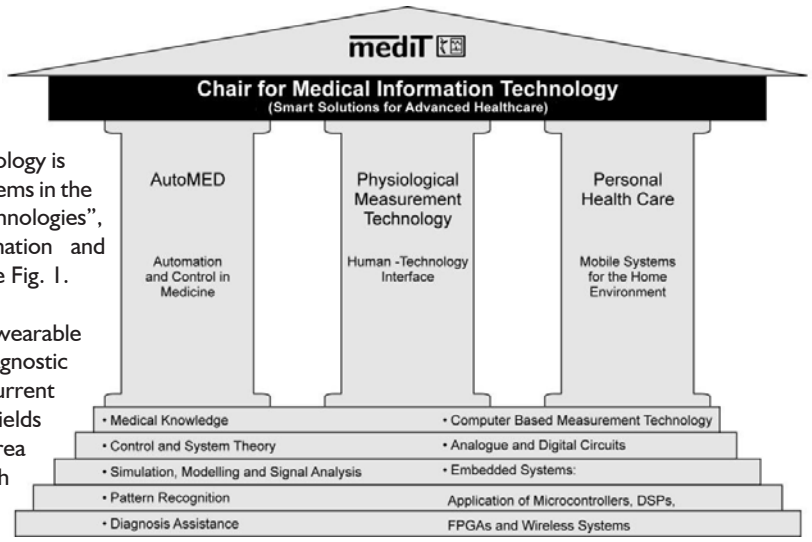

Fig. 1: Research profile of MedIT.

The Chair for Medical Information Technology is especially concerned with research problems in the fields of "Unobtrusive Measurement Technologies", "Personal Health Care", and "Automation and Control in Medicine". For illustration, see Fig. 1.

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, our chair 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, unobstrusive measurement technologies (sensors and 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

Since preterm infants (neonates) can't regulate their body temperature on their own, they are susceptible to heat loss after birth. Thus, the thermoregulation of their surrounding environment is crucial for the infant's survival during intensive care. A neonatal incubator typically provides such regulation to newborn infants by constantly 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 or damage the neonate's immature skin.

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 or illness. However, a non-invasive, non-contact measurement of temperature (regulation) as an essential control element of the incubator temperature has not yet been included in the control loop yet.

Our project aims to optimize the temperature control of the incubator using infrared thermography. Together with our project partners (Weyer GmbH, Dieter Richrath GmbH, 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 neonate's themselves, becoming part of the control loop without physical contact. In this process, image processing algorithms are used to automatically detect „Regions of Interest" (ROI) that serve as „virtual temperature sensors", enabling the temperature measurements on the head, torso and extremities, see Fig. 2.

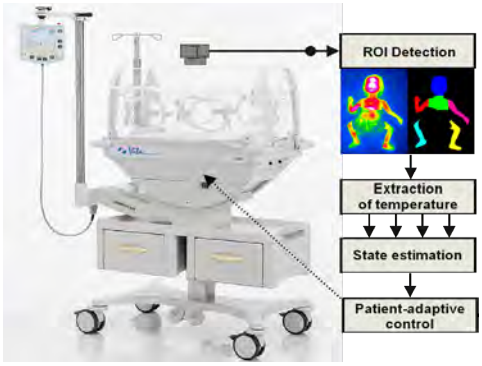

Fig. 2: Schema of the applied neonatal incubator, temperature extraction and patient-adaptive control.

This allows not only the monitoring of the temperature, but of the temperature distribution of the neonate, which will be summarized in a novel „inhomogeneity index", providing information about the health of the neonate. Furthermore, the metabolic activity and the individual heat demand can be estimated. Finally, the number of skin-contacted sensors, which can damage the immature skin of the neonate and lead to the invasion of germs, can be reduced. Thus, we hope for a significant reduction in the risk of infectious diseases and their associated, sometimes life-threatening, consequences.

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

Lower Limb Hybrid Exoskeleton with Functional Electrical Stimulation

Clinical and postoperative rehabilitation play a crucial role in maintaining the health of patients, particularly the elderly. Among the prevalent impairments, lower limb and upper limb paresis are common challenges. Functional electrical stimulation (FES) and exoskeletons are recognized as indispensable approaches for facilitating body motion rehabilitation. However, relying solely on these methods falls short of achieving optimal control over gait motion. An emerging and promising solution for enhancing body rehabilitation is a hybrid electromechanical system. Therefore, the aim of this project is to develop and assess a hybrid robotic system, integrating FES technology, a body motion tracking system, and various sensors, as illustrated in Fig. 3.

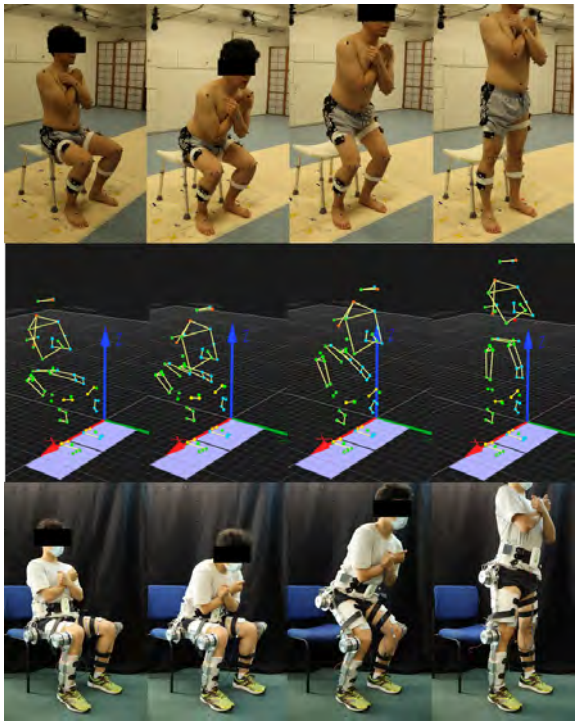

Fig. 3: Four phases of Sit-to-Stand movement in motion lab, simulation, and exoskeleton.

To achieve this objective, the motion capture system is initially employed to capture precise trajectories of fundamental body movements such as walking and sit-to-stand transitions. Exoskeletons, equipped with four motors, are specifically designed and attached to the hips and knees to stabilize the body and provide torque assistance during movement. The FES system, comprising four channels, is applied to the tibialis muscle, soleus muscle, gracilis muscle, and rectus femoris muscle. Unlike direct muscle stimulation, stimulating the muscles' nerves induces full muscle contractions. Additionally, considerations are given to muscle fatigue and electromyography (EMG) signals in the rehabilitation process. The integration of exoskeletons with neurological methods and sensors serves to enhance the closed-loop system's overall performance. This hybrid system holds potential applications in rehabilitation centers, with ongoing research and applications aimed at evaluating its efficacy and control strategy through clinical trials.

Funded by: Chinese Scholarship Council (CSC)

Impedance-Based Hemodynamic Monitoring

Cardiovascular diseases remain the leading cause of death in the developed world. Due to conditions such as high blood pressure, atherosclerosis or other genetic risk factors, as well as an unhealthy lifestyle in an aging society, more than 400 million people worldwide suffered from heart diseases in 2022, resulting in the death of approximately 18 million people. Reduced perfusion of heart muscle tissue caused by, for example, obstruction in the coronary arteries reduces the pumping performance of the heart. The standard of care for these patients consists of drug therapy or support with a heart pump, such as a left ventricular assist device. In both cases, a careful monitoring of the patient's heart function is required.

Currently, there is no satisfactory method for determining cardiac function and measuring the cardiac output; available techniques are either inaccurate or complex, and unsuitable for continuous monitoring. One promising new method is based on measuring electrical conductance with an electrode catheter from inside the ventricle, as shown in Fig. 4.

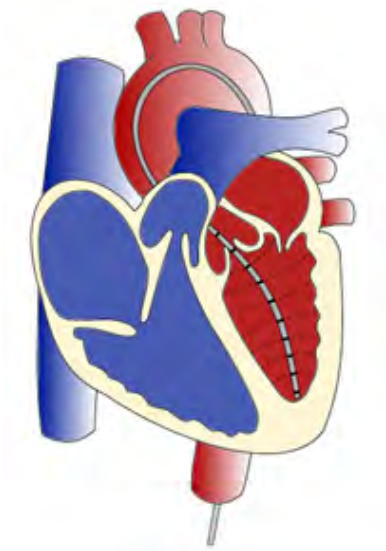

Fig. 4: Schema of impedance measurement in the heart with an electrode catheter.

Due to the higher conductivity of blood compared to the surrounding tissues, the conductance correlates with the ventricular volume. With an appropriate algorithm, it is therefore possible to calculate the volume of the ventricle. From the ventricular volumes in systole and diastole the stroke volume can be calculated and thus, the volume of blood pumped into the aorta. At present, the available algorithms require an elaborate calibration for accurate measurements, which thus limits their practicability. The aim of this project is to develop a new algorithm that avoids manual calibration and thus enables automated continuous monitoring. To this end, we are improving impedance measurement instrumentation using a multichannel setup to perform many impedance measurements, supported by computer simulations of the electrical fields and simulated impedance measurements in the heart.

Funded by: German research foundation (DFG)

Regional Lung Perfusion Monitoring with Electrical Impedance Tomography

In the pursuit of regionally monitoring lung perfusion and ventilation, a longstanding aspiration has been to unlock capabilities that facilitate the diagnosis and monitoring of a broad spectrum of perfusion, ventilation, and gas exchange disorders. Established technologies, such as dynamic or single photon emission computed tomography (DCE-CT and SPECT), have provided accurate estimates of these components. However, their cost and invasive nature limit them to intermittent measurements with low temporal resolution.

In contrast, electrical impedance tomography (EIT), a relatively inexpensive technique, offers the ability to reconstruct the spatial conductivity distribution of the inner thorax through non-invasive current injections from an electrode belt, see Fig. 5. Among its benefits, EIT provides continuous regional information related to blood and air volume movements.

In collaboration with the Department of Radiology at the University Hospital Aachen and the Department of Anaesthesiology and Intensive Care Medicine at the University Hospital Bonn, extensive animal studies were conducted to explore the feasibility of EIT as a non-invasive monitoring tool for regional lung perfusion. Central to peripheral lung perfusion impairment states were surgically induced and recorded by the gold standard contrast-enhanced CT and EIT after the injection of radio dense and electrically conductive media, respectively. Having verified statistically significant strong agreement between both techniques, we were able to prove the effectiveness of contrast-enhanced EIT as a minimally invasive method for the derivation of regional lung perfusion information, see section 1 of Fig. 5.

To completely overcome the invasiveness of contrast enhancement, we are also developing a real-time system to simultaneously monitor pulmonary ventilation and perfusion. This requires separating cardiac and ventilation-related signal components in the raw data, identifying the strongest predictors of perfusion and ventilation from the signals, and training robust statistical models to map them onto lung perfusion/ventilation heat maps, see section 2 of Fig. 5.

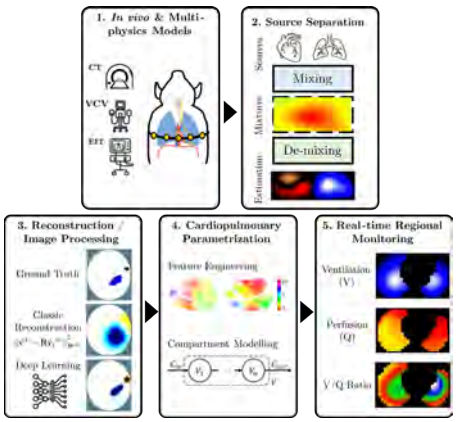

Fig. 5: Workflow of the research activities within the project.

The complexity and novelty of these challenges often surpass the capabilities of traditional signal and image processing techniques. Pure machine learning applications also face limitations due to a lack of training data. It is therefore required marrying both approaches and leveraging prior physiological modelling concepts in the hope to unlock the potential of EIT as a tool for continuous regional lung perfusion monitoring in intensive care units, see sections 3, and 4 of Fig. 5.

Funded by: German research foundation (DFG)

Fusion of Electrical Impedance Tomography and Ultrasound Tomography

Electrical Impedance Tomography (EIT) and Ultrasound Tomography (UST) both are lesser-known, but already clinically used tomography techniques. UST basically works similarly to the well-known CT, just with ultrasound instead of X-ray. A slight difference is that you can not only take the transmission into account, but also the reflected part of the injected ultrasound, see Fig. 6.

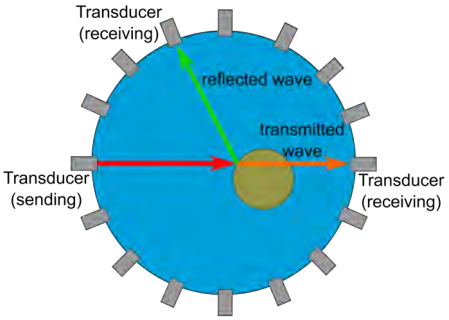

Fig. 6: Functional principle of UST.

In EIT, a harmless alternating current is applied to the surface of the patient's body, which leads to a potential distribution on the surface that depends on the body's inner composition. The current injection as well as the voltage measurements are normally done using an electrode belt, with the current being fed in from different positions so that as many linearly independent measurements as possible are obtained. Finally, a tomogram of the body can be calculated from this series of measurements, see Fig. 7.

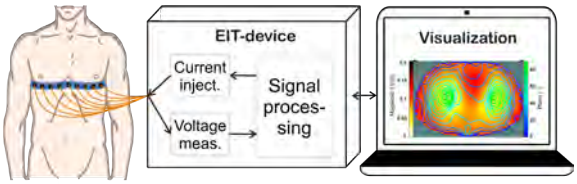

Fig. 7: Typical EIT arrangement.

Both modalities have a considerably lower resolution than the CT or MRI, but are characterized by portable, inexpensive hardware and the fact that they work without ionizing radiation. These properties make them attractive, especially for constant patient monitoring at bedside, in cases where the low resolution is sufficient. For instance, one of the main applications of EIT is determining how well the different regions of the lung are ventilated.

From a diagnostic point of view, the distinction or – even better - the identification of tissue types is particularly interesting, as it would enable i. e. identifying the reason for non-ventilated lung areas. That's why multi-frequency EIT (mfEIT) is an ongoing research topic, where currents with different frequencies are applied and the responses are compared. As the electrical impedance of the respective tissues has a characteristic frequency dependence, this method makes it possible to distinct different types of tissue. Bringing mfEIT and UST together probably has the potential of further improving the tissue recognition, as it enables a finer analysis that takes both electrical, and acoustic properties of the tissue into account.

Additionally, for current medical ultrasound, the lung is said to be inaccessible, since the strong change in impedance between body tissue and air leads to total reflection. However, more recent research suggests that lower frequencies (than the ones commonly used in medical US) somehow are capable of penetrating the lung. Here, further research is needed to fully understand the underlying mechanism and to assess the diagnostic potential lying in this approach.

For these purposes, it is planned to build a tomography system that can do mfEIT and UST all in one. As patient interface, a belt featuring alternatingly arranged EIT electrodes and US transducers will serve. An early prototype of this is shown in Fig. 8.

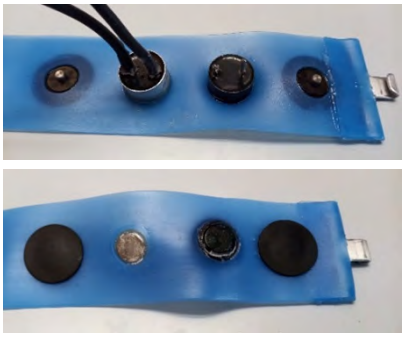

Fig. 8: Belt prototype for combined EIT and UST. EIT electrodes outside, ultrasonic transmitter \& receiver inside.

Modeling and Removal of Physiological Motion Artifacts in Capacitive ECG

Capacitive electrocardiogram (cECG) is an unobtrusive measuring approach that have gained interest in the last two decades, as they can extend cardiac monitoring to everyday life and might even replace classical electrocardiogram in some instances. However, with every new application scenario proposed for cECG, the limitations of this modality are becoming more evident. Literature suggests various improvements and modifications in the sensor design. Similarly, numerous signal processing techniques have been proposed to tackle the biggest challenge of cECG, namely motion artifacts. So far, most solutions revolve around increasing the signal coverage so that cECG can be used to monitor the heart rate and the heart rate variability in various non-medical settings, while ignoring the potential of cECG for diagnostics.ECG is an essential tool for diagnosing arrhythmia, and its waveform is of utmost importance for medical diagnosis. However, the deformation processes of the cECG signal are not well understood yet.

Our research group has been trying to explain the deformation of cECG signals by identifying the origin of artifacts. By identifying the mechanical vibrations originating from cardiac and respiratory activity, a distortion in the coupling impedance of cECG measurement can be observed, even when there is no active movement of a limb or the torso. This interference from the cardio-mechanical signals into the cECG has been called "physiological motion artifacts", in order to distinguish them from the classical motion artifacts that do not share the same origin as the cECG signal. As ballistocardiography (BCG) signals are time-lagged synchronous with the cECG signal, their artifacts appear as a part of the cECG, likely deteriorating the identification of essential features.

This project aims to model and quantify physiological motion artifacts by by gaining a deeper understanding of the interaction of cECG and BCG. Therefore, a test bench is designed to mimic the cECG-measurement scenario under influence of physiological motion artifacts. Furthermore, the test bench can be used to evaluate different experimental designs of cECG electrodes under constant conditions, see Fig. 9.

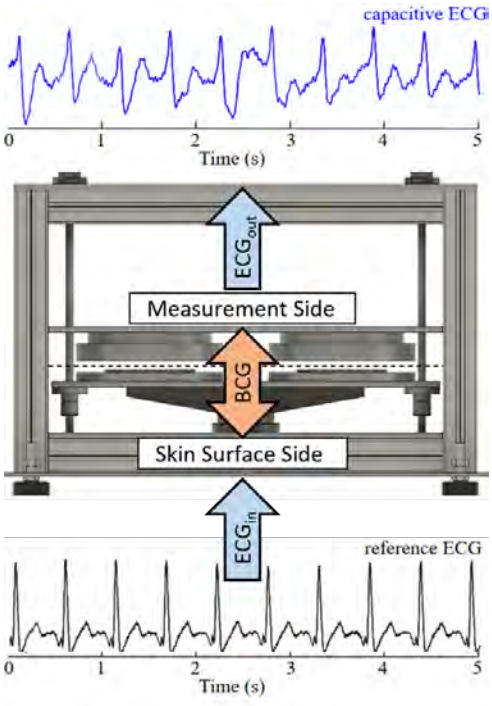

Fig. 9: Scheme of the cECG test bench: The reference ECG is fed into the testbench and applied to the skin surface side of the system. The capacitive ECG electrodes are placed on the measurement side. A reference BCG signal is modulated on the contact pressure between the two sides of the test bench. Thereby, the effects of the mechanical heart activity are simulated to further investigate the interference between BCG and cECG.

By modeling the interaction of different influences on cardiac signals in multi-modal sensors, the deformation in cECG will be reduced to regain the diagnostic power of cECG.
Such an improvement would enhance the quality of cECG recordings, e.g., a future home-monitoring system for older adults or standardized cECG screening in a patient chair during anamnesis.

Funded by: German research foundation (DFG)

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Prizes and Awards

1. The MedIT was honored with a commemorative medal during its 20th anniversary by Prof. Dr. Ing. Stefan Borik (University of Zilina, Czechia).
2. Election of Prof. Leonhardt as fellow of the Deutsche Akademie der Technikwissenschaften (actech).
3. The MedIT archived the 4th place at the faculty football tournament and 2nd place at the Institute Olympiad during RWTH FH Sports Day.
4. During the 27th International Student Conference on Electrical Engineering POSTER, the medIT has been rewarded with the 1st (S. Lyra and C. Weiss), 3rd (U. Jacobs) and 3rd (C. Weiß) price.
5. The Stiftung Universitätsmedizin Aachen donated financial resources for two projects „Contactless Monitoring of Premature Infants“ and „Non-invasive temperature monitoring“.
6. Starting in winter semester 2023 / 24, Dr. Markus Lüken offers a new lecture „Unobtrusive Monitoring of Vital Signs“ for Master's degree course.

The MedIT Team

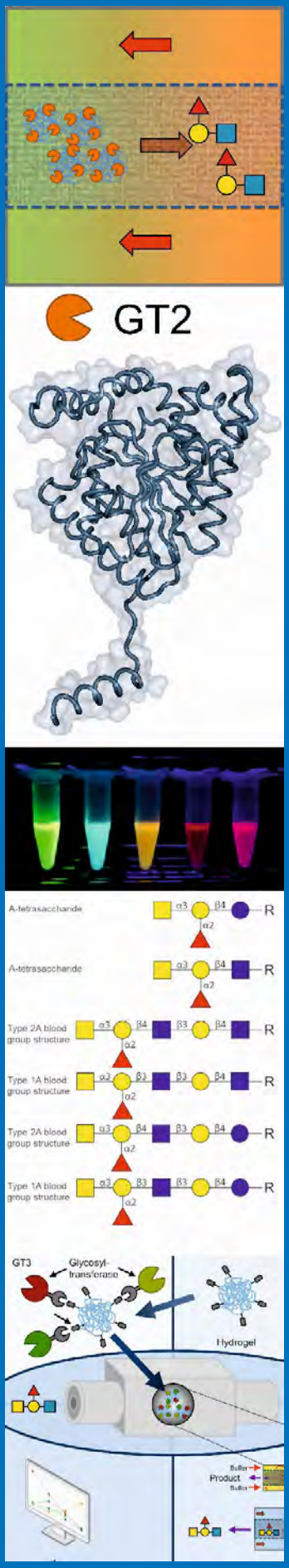
Lehr- und Forschungsgebiet Biomaterialien

RWTH AACHEN UNIVERSITY

Laboratory for Biomaterials

Faculty of Mathematics, Computer Science and Natural Sciences

Synthesis and Application of Glycoconjugates



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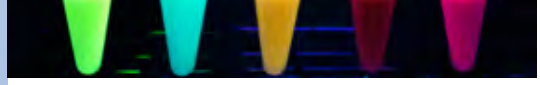

Introduction

Glycans are present on glycolipids, glycoproteins, and proteoglycans and consist of covalently bonded monosaccharides. The extracellular matrix (ECM) is made up of a complex network of glycans that regulates several interactions between cells and between cells and the ECM. Glycan-binding proteins, such as galectins, recognize glycan patterns unique to tumors and pathogens (viruses, bacteria), thereby initiating the corresponding cellular response. They also function as tools for glycan structure analysis and detection. Human milk oligosaccharides (HMOs) are important for developing an infant's digestive resistance against infections and have a significant market in the food industry. Therefore, research on sugar-based biomaterials is crucial in bio- and material sciences and can expand knowledge through new methods and technologies. We ramped up our studies on glycoconjugate synthesis and applications in 2023.

We transferred our enzyme cascades to new large-scale and automated operations by creating enzyme reactors and novel enzyme fusion proteins for covalent immobilization. Our efforts on the large-scale manufacturing of nucleotide sugars is prerequisite for the development of an automated platform for glycan synthesis with Leloir-glycosyltransferases. We have created new galectin-fusion proteins providing a protein-based color code for glycan pattern binding on cell surfaces. The most current findings from our peer-reviewed publications in 2023 are compiled in this chapter.

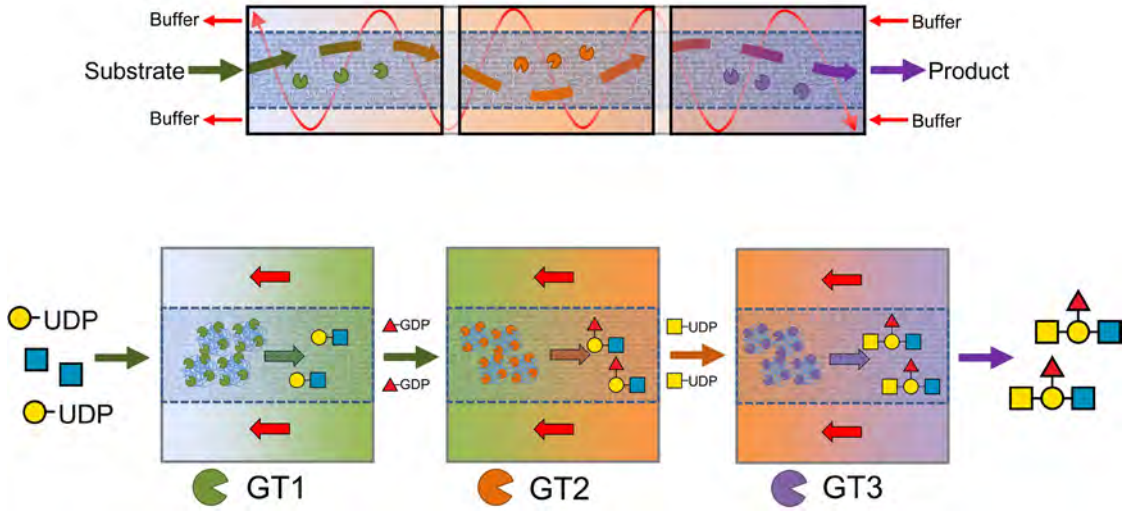

Fig. 1: Production of the blood group antigen A epitope with glycosyltransferases and nucleotide sugars in a continuous counter-current flow reactor system.

Combinatorial Biocatalysis

Enzymatic Synthesis and Production of Nucleotide sugars

Leloir-glycosyltransferases play a predominant role in constructing glycan chains, utilizing nucleotide-activated monosaccharides for specific glycan chain formation. However, nucleotide sugars are very costly substrates for the usage in larger scales (>1g). This is particularly relevant in the characterization and application of Leloir-glycosyltransferases, as it becomes an ecological concern due to the high quantities of nucleotide sugars that are required. In recent years, an increasing number of enzymatic processes for producing nucleotide sugars at a gram-scale have emerged. The key benefits of chemoenzymatic nucleotide sugar synthesis include high yields and the use of renewable and cheap compounds. Nucleotide sugars can be synthesized through either *de novo* or salvage pathways. While the *de novo* synthesis creates sugars from basic monosaccharides like glucose or fructose, the salvage pathway recycles the monosaccharide released from the degradation of e.g. polysaccharides. The *de novo* synthesis uses a multitude of enzymes as sugars undergo numerous processing steps. In contrast, the salvage pathway utilizes only two to three enzymes for nucleotide sugar synthesis (Fig. 2). In our recent review we evaluated the most recent enzymatic synthesis processes which use the salvage pathway for nucleotide sugar production.[1]

In addition, we focused our attention in particular on the role of ATP as a cofactor of sugar kinases in the synthesis of nucleotide sugars. While ATP is a relatively cost-effective substrate, challenges arise also from feedback inhibition by the product ADP, impacting optimal productivity. Therefore, efficient regeneration systems for ATP are of crucial importance, considering aspects such as enzyme kinetics, cost efficiency and donor stability. Pyruvate kinase (PK) and phosphoenolpyruvate (PEP) are widely used in the regeneration of ATP and other nucleotides. An innovative solution involves the utilization of polyphosphate (polyP) and polyphosphate kinases (PPKs) (Fig. 3) to enhance ATP regeneration, thereby reducing nucleotide expenses and mitigating inhibitory effects.

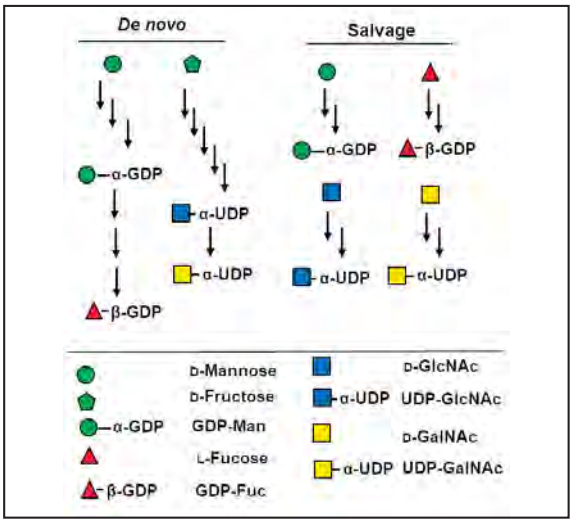

Fig. 2: Comparison of the de novo synthesis and salvage pathway exemplarily for the synthesis of GDP-Man, GDP-Fuc, UDP-GlcNAc and UDP-GalNAc.

We have demonstrated the efficacy of PPK/polyP systems in the synthesis processes of UDP-Gal, GDP-Man and CMP-Neu5Ac.

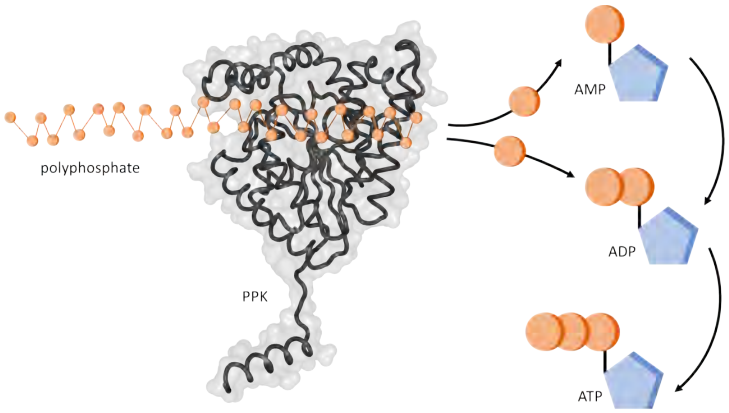

Fig. 3: Synthesis of the nucleotide ATP from AMP by a polyphosphate kinase (PPK) from polyphosphate.

Moreover, integrating enzyme cascades feature for nucleotide synthesis contributes to the development of cost-effective and efficient pathways for nucleotide sugar production. Nucleotide sugars produced by our technology platform are commercially available (www.biolog.de).

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Selected Reference

[1] Frohnmeyer, H., Elling, L., 2023. Enzyme cascades for the synthesis of nucleotide sugars: Updates to recent production strategies. Carbohydr. Res. 523, 108727. https://doi.org/10.1016/j.carres.2022.108727.

Financial Support

Financial support by the German Federal Ministry of Economic affairs and Energy (BMWK) in the frame of the ZIM project: "Entwicklung einer enzymatischen Syntheseplattform 'NukZuk' für Nukleotidzucker und funktionalisierte Nukleotidzuckerderivate"(ZF4788501AJ9) and by the German Federal Ministry of Education and Research (BMBF) for funding the project "BoostLab1-8 - BioProNuk, Biokatalytische Produktionstechnik für Nukleotidzucker - Valorisierung von nachwachsenden Rohstoffen" (AZ: 031B1146BX and 031B1146B) within the Competence Center for Biological Transformation of material sciences and production engineering (Bio4MatPro).

Automated Enzymatic Glycan Synthesis

Glycans, oligosaccharide structures varying from simple linear chains to intricate branched forms, are linked to glycoproteins and glycolipids, exhibiting specificity to distinct species, tissues, and cell types. Present on the surfaces of both eukaryotic and prokaryotic cells, glycans play crucial roles in fundamental physiological processes such as cell-cell interactions, viral and bacterial attachment, cancer evasion, metastasis, and immune responses. Moreover, accurate glycosylation is a basic requirement for properly functioning glycoproteins and the mediation of intracellular and extracellular processes involving soluble glycoproteins, therapeutics, or prebiotics.
Given that the majority of recombinant production of therapeutic proteins and monoclonal antibodies occurs in hosts lacking human glycosylation patterns, there is a growing interest in industrial-scale post-translational *in situ* glycosylation. Two general approaches have been established: chemical glycan synthesis, relying on complex multi-step reactions in harsh conditions, resulting in low yields and generating toxic by-products; and enzymatic glycan synthesis, considered a more promising strategy by recent research.[2]

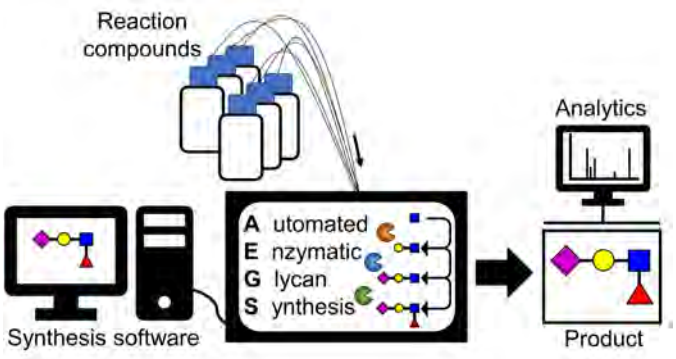

Fig. 4: Automated Enzymatic Glycan Synthesis (AEGS) involves mixing reaction compounds in a software-supported bioreactor. The final product is then analyzed using a suitable device.

Enzymatic glycan synthesis involves the stepwise construction of structures through reactions catalyzed by different enzymes, namely glycosyltransferases, glycosidases, or glycosynthases. Unlike chemical synthesis, enzymatic strategies offer advantages like achieving regio- and stereoselective glycosylation in single-step reactions under natural, non-toxic conditions. The combination of multiple enzymes leads to the production of various sugar structures in cascades (Fig. 4). While step-by-step synthesis poses challenges, automated synthesis emerges as a valuable alternative to established one-pot strategies.
The BMBF-funded project „**mi**crogel countercurrent flow **r**eactor for automated **g**lycan synthesis with immobilized

enzymes“ (**MiRAGE**) is a collaborative project with partners from academia and industry.
Our envisioned aim towards automated glycan synthesis is depicted in Figure 5. Here, immobilized enzymes, embedded in a countercurrent flow reactor for simultaneously production of glycans and removal of by-products. Compartmentation allows serial connection of different modules towards enzymatic cascades for complex glycans.

Andreas Bock, Max Frick (glyXera GmbH, Magdeburg).

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[2] Hussnaetter, K.P., Palm, P., Pich, A., Franzreb, M., Rapp, E., Elling, L., 2023. Strategies for Automated Enzymatic Glycan Synthesis (AEGS). Biotechnol. Adv. 67, 108208. https://doi.org/10.1016/j.biotechadv.2023.108208.

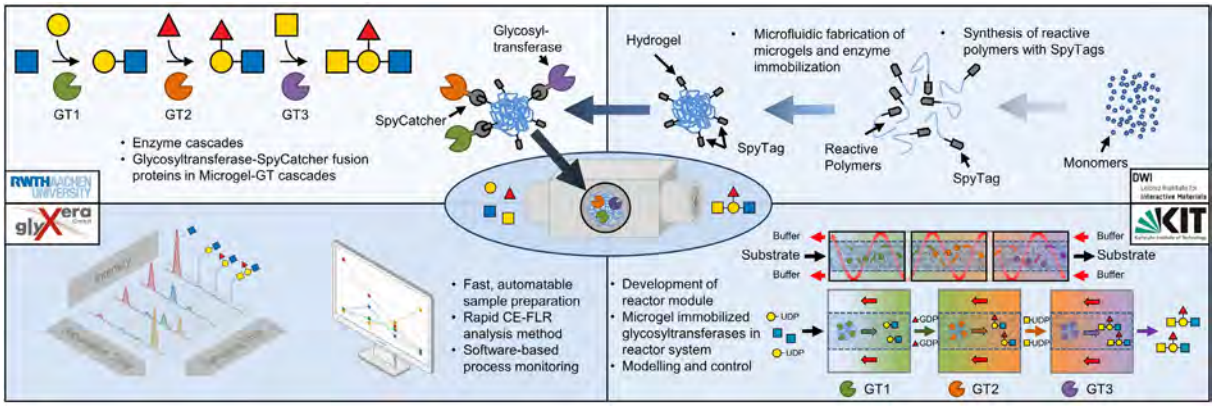

Fig 5: Concept of MiRAGE. Microgel-immobilized glycosyltransferases are embedded in a microreactor. Fast at-line analysis allows in-process monitoring and intervention of synthesis.

In the **MiRAGE** project, we aim to establish an automated counter current flow reactor for enzymatic glycan synthesis using microgel-immobilized glycosyltransferases (Fig. 5). Collaborators from RWTH Aachen University, DWI Leibniz Institute for Interactive Materials, Karlsruhe Institute of Technology (KIT), and glyXera GmbH, from both academia and industry, contribute to different aspects of this collaborative effort. Our solutions encompass scalable methods for enzyme immobilization, incorporating compartmentalization of enzymatic cascades for glycan production and simultaneous, continuous removal of by-products, integrated into an automated counter current flow reactor (Fig. 5). Within our group, we are developing an enzymatic toolbox comprising different Leloir-glycosyltransferases for synthesizing complex glycan structures in cascades (upper left). DWI partners provide microgels for enzyme immobilization in an aqueous environment (upper right), and the KIT partner has developed a bioreactor for embedding microgel-immobilized glycosyltransferases (lower right). Additionally, glyXera GmbH facilitates fast at-line analysis of glycan products and intermediates (lower left).

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The Glyco-BioInterface

Galectin fusion proteins for targeting cells and Glycoproteins

Galectins, members of the carbohydrate-binding lectin family, play crucial roles in various physiological functions such as cell-cell interaction and cell signalling. Dysregulated galectin expression often contributes to cancerogenesis or inflammatory diseases. In the realm of biomedicine, galectins emerge as valuable tools for the development of biomaterial coatings by the incorporation of functional domains. In our research, different galectins (Gal-1, Gal-3, Gal-8N/C) were utilized as fusion proteins with intrinsic color-coding, featuring a His_6-tag for purification, a fluorescent protein for imaging applications, and a SNAP-tag for immobilization (Fig. 6). We accomplished the purification of active galectin fusion proteins with glycoprotein-presenting affinity resins. Exploring the interactions between galectins and glycomaterials is essential for understanding their binding specificities. Throughout the years, various methods for studying galectin-glycomaterial

interactions have evolved in glycoscience.[3] In our studies, we verify galectin affinity parameters for binding different natural glycoproteins, such as laminin or fibronectin, through *in vitro* binding and crosslinking assays, which helps classify galectin targets on cell surfaces and glycoproteins.[4]

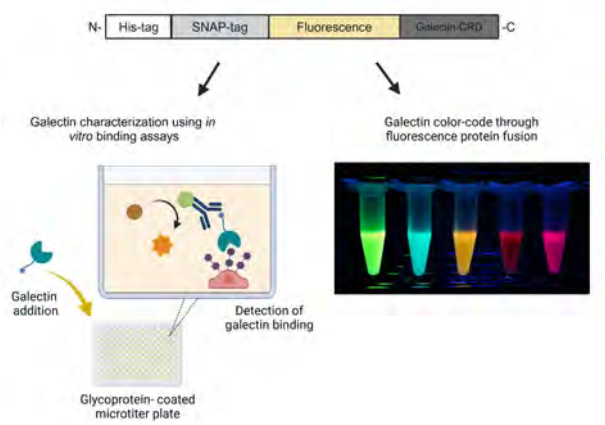

Fig. 6: Galectin fusion protein structure, characterization and fluorescent color code (created with BioRender.com).

Synthesis of Multivalent Glycoconjugates for the Inhibition of Galectin-4

Human tumor development and progression are also influenced by galectins. For example, expression of Gal-4 is associated with increased metastasis and progression in liver and lung cancer. Inhibition of Gal-4 binding to cancer-relevant glycan epitopes by multivalent inhibitors has the potential for therapeutic and diagnostic applications. Gal-4 can cross-link sulfated glycosphingolipids and *N*- and *O*-glycosylated proteins that carry blood group antigens. To this end, Lewis-type blood group antigens were developed in our previous studies and linked to form novel multivalent neo-glycoconjugates. The study of two mutant α3-fucosyltransferases (α3-FucT) from *Helicobacter pylori* showed that various parameters influence the fucosylation pattern, such as the type of glycosidic bond within the lactosamine (LN) subunits, the location of the LN subunits, and the additional α2-fucosylation at the terminal galactose.[3] Furthermore, we successfully identified *N*',*N*''-diacetyllactosamine (LacdiNAc) as a new substrate for the α3-FucTs and optimized the synthesis for quantitative yields.[5] The focus is now on the synthesis of blood group antigens (ABH) (Fig. 7). Here, too, fucosyltransferases are crucial for the enzymatic synthesis of fucosylated glycans on a large scale. The investigation of two α-1,2-fucosyltransferases (WbgL and FutC) shows different preferences for substrates. Thus, successful syntheses could be developed using FutC, which produces the H-antigen analogs 2'-fucosyllactose and 2'-fucosyl-*N*-acetyllactosamine (type 2). The successful production of the H-antigen analogs precursor is an important step for the further synthesis of blood group structures A and B. The aim is to build up an ABH blood group antigen library and to test its specific binding to Gal-4. Further, neo-glycoproteins will be generated by multivalent coupling of such glycans to human serum albumin, providing specific and selective detection of Gal-4 in body fluids and inhibition of Gal-4 binding to cell surface glycans.

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[3] Heine, V., Dey, C., Bojarová, P., Křen, V., Elling, L., 2022. Methods of in vitro study of galectin-glycomaterial interaction. Biotechnol. Adv. 58, 107928. https://doi.org/10.1016/j.biotechadv.2022.107928.

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[5] Heine, V., Pelantová, H., Bojarová, P., Křen, V., Elling, L., 2022. Targeted Fucosylation of Glycans with Engineered Bacterial Fucosyltransferase Variants. ChemCatChem 14, e202200037. https://doi.org/10.1002/cctc.202200037.

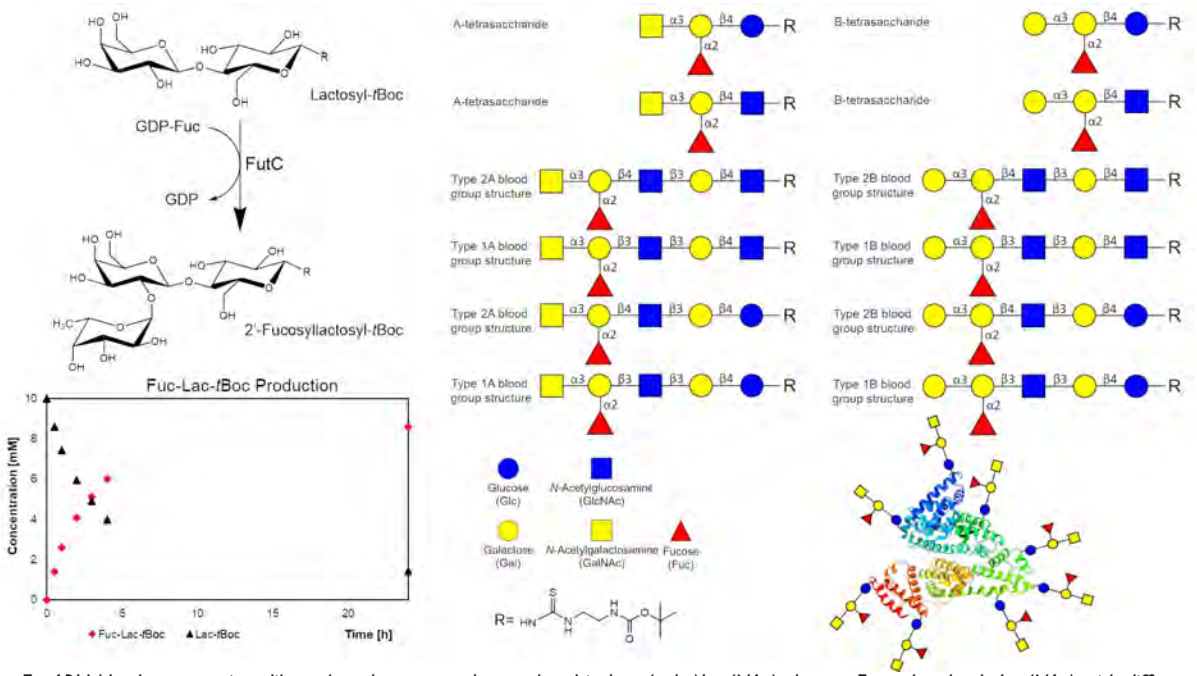

Fig. 7: ABH blood group antigen library based on monovalent and multivalent (poly-)Lac(NAc) glycans. Fucosylated poly-Lac(NAc) with different terminal glycan epitopes and hybrids of LacNAc type 1 and type 2 synthesized with FutC. Conjugation to human serum albumin results in multivalent neo-glycoconjugates.

Financial Support

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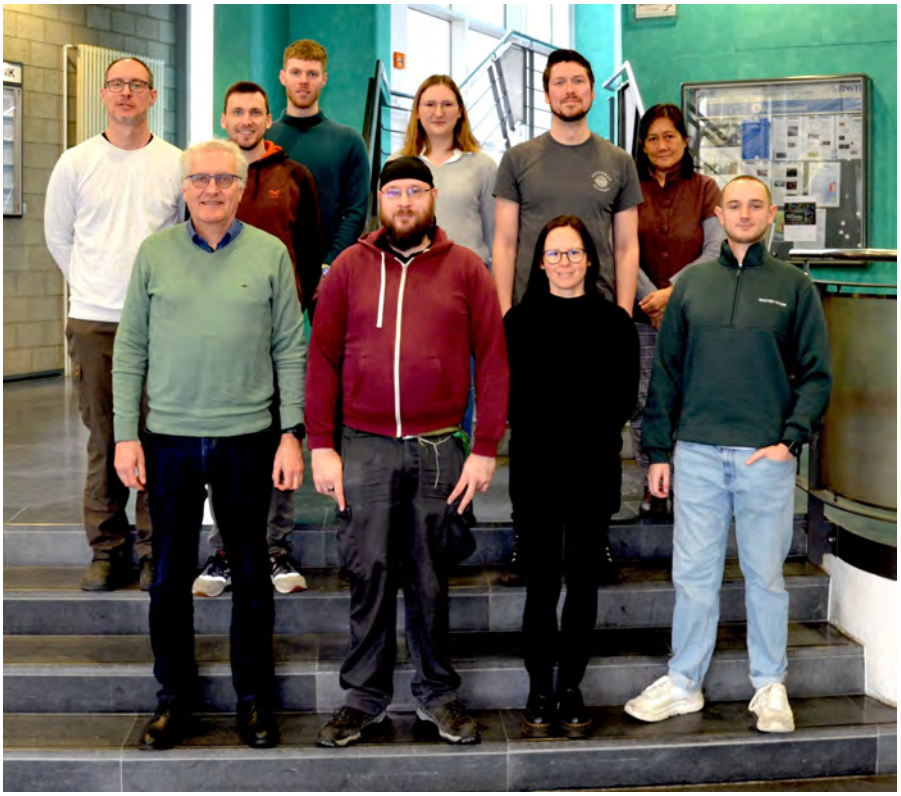
OUR TEAM



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Chair of Medical Engineering
Faculty of Mechanical Engineering

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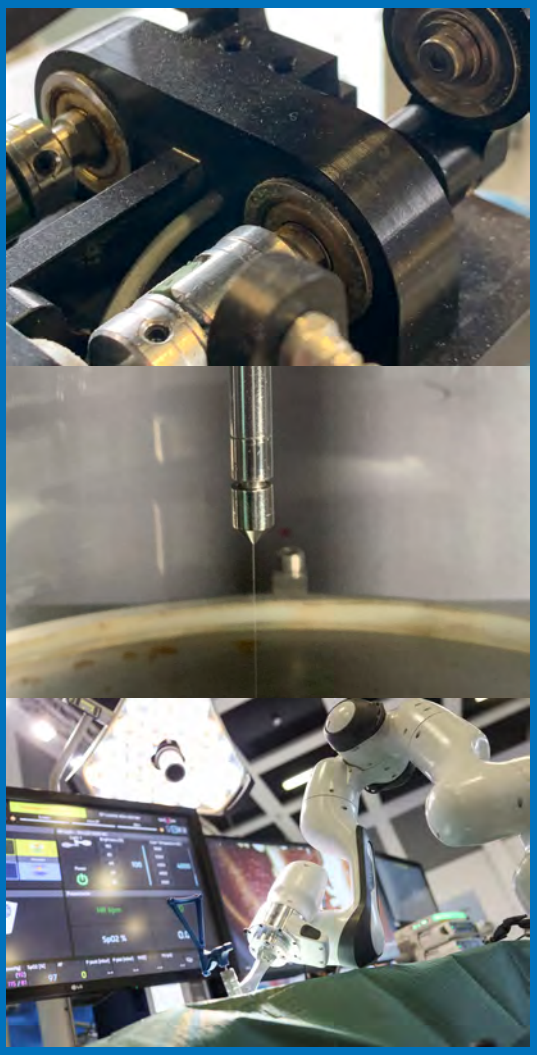

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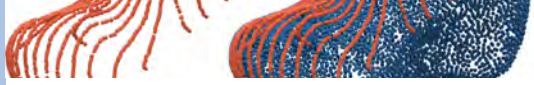

Introduction

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

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

Apart from international publications and a practical transfer and implementation of scientific findings, the education of our students from different disciplines and specialties is a major objective. In addition to basic research grants, 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.
After the years of pandemic, we were pleased to restart in 2023 to make greater use of scientific exchange in face-to-face meetings as part of bilateral contacts and international conferences. We are back to life! Based on networks with international partners from research, industry and clinics, existing collaborations were reenforced and a wide range of new projects were initiated or started.
This annual report summarizes some examples of current project work in 2023.

Selected Projects DFG-Project MOFUMO – THA Biomechanics

Based on recent developments and demographic trends, an increase in the number of Total Hip Arthroplasty (THA) patients can be expected in the future. These patients tend to be younger, more active and have higher requirements on the prosthesis. Therefore, detailed preoperative planning becomes more important. With our clinical partners from Niigata Hip Joint Center (Niigata, Japan) and Charité Medical University Center (Berlin) we work on the integration of patient specific morpho-functional conditions and requirements for activities of daily living (ADL) into preoperative planning for THA. One aspect of this current research is the evaluation of range of motion (ROM) and hip joint forces for different ADLs.

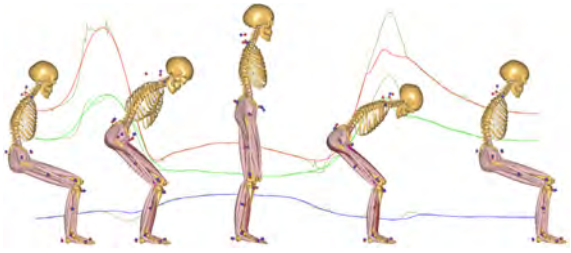

Fig. 1: Hip joint force evaluation for the process of getting up from a chair and sitting down again

Patient Specific Optimization of TKA Implants

In the case of advanced knee osteoarthritis in combination with pain and functional impairment, total knee arthroplasty (TKA) is indicated. However, potential osteoarthritis-related deformities as well as genetic deformities should not be reconstructed in the design as they have been reported to have a detrimental effect on knee function. Therefore, they must be corrected prior to a patient specific evaluation of different OTS implant designs or a design of optimised patient-specific implants. For this purpose, we developed a fully automated workflow including a parameter-based deformity check and various methods for subsequent deformity correction, including a twin search, multiple linear regression and neural networks. After the deformity correction, adapted joint surfaces are created using previously published parameter models. The functional effects of the deformity correction on the knee kinematics are then evaluated using patient-specific biomechanic simulation.

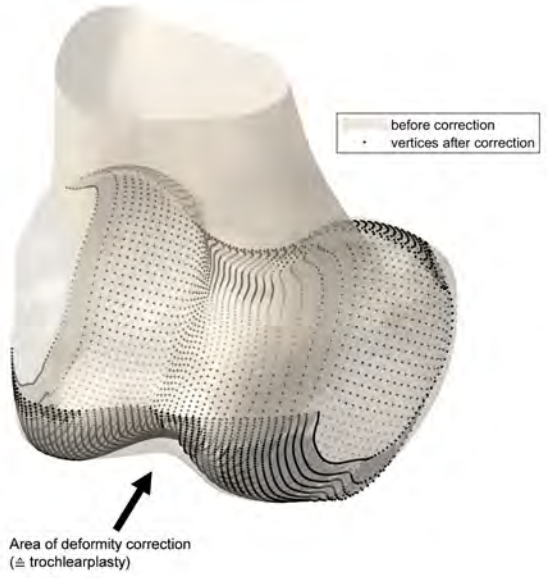

Fig. 2: Exemplary case with trochlear dysplasia before and after parameter-based deformity correction.

Biomechanics of the RNR

So-called “Redundant Nerve Roots” (RNR) are tangled, hypertrophied and accumulated nerve fibers in the area of stenoses of the spinal canal. Since the development of RNR is not entirely understood, a modular in vitro model being developed to investigate mechanical effects. The flexible model allows the variation of different pathological changes (e.g. osteophytes). Furthermore, a model of the spinal canal is integrated into an existing cerebro-spinal fluid (CSF) dynamics in vitro model in order to investigate hydrodynamic effects as part of our ongoing research on RNR and Normal Pressure Hydrocephalus (NPH).

Fig. 3: In vitro model of the lumbar section of the spinal canal with intervertebral discs and nerve fibers.

Cooperative Surgical Robotics

Although surgical robots have the potential to improve safety and surgical outcomes in neurosurgery and orthopedic surgery, their clinical adoption remains limited. One key reason for the limited adoption of current robotic systems is their restricted application scope. Further limitations arise from safety issues due to over-dimensioned kinematics, that contradict established safety standards for cooperative robotic systems. To address these challenges, we developed a modular dual robot system. The systems consists of an off-the-shelf lightweight carrier robot for pre-positioning and an in-house developed, highly dynamic, application-specific miniaturized tooling robot. The tooling robot compensates for patient breathing motion and robot elasticity. An admittance control allows the user to move the burr within pre-planned virtual fixtures. For the use case laminectomy, a formative usability study was conducted on a spine phantom, comparing the dual robot system with manual milling. Seven surgeons successfully performed a planar laminectomy with an accuracy better than 0.3 mm. Most surgeons rated the proposed dual robot system's safety, usability, and workload positively compared to manual milling.

Fig. 4: Cooperative robotic laminectomy on a spine phantom

Robotic Ultrasound System for TKA

For patient specific implants for TKA 3D bone models are required. These are typically generated by computer tomography (CT), causing significant additional costs and radiation exposure.
We investigate the use of ultrasound (US) imaging as a potential alternative for PSI design in TKA. But conventional US imaging results are highly user dependent and computer-aided recognition of bone is more challenging. Furthermore, the 3D reconstruction of bone requires 3D registration of the entire set of 2D US images. Using a robot equipped with an ultrasound probe, position information can directly be obtained for 3D reconstruction and an optimal path control with high reproducibility can be achieved.
In a fully autonomous process, initially the knee region to be scanned is recorded with a depth camera. This information is used as a basis for an autonomous path planning with an automatic model based optimization of the robotic scanning process with respect to the iteratively refined bone surface estimation. Subsequently, the robot follows the planned path and maintain a defined contact to the skin, while neural networks are used for an automatic bone surface segmentation and reconstruction.

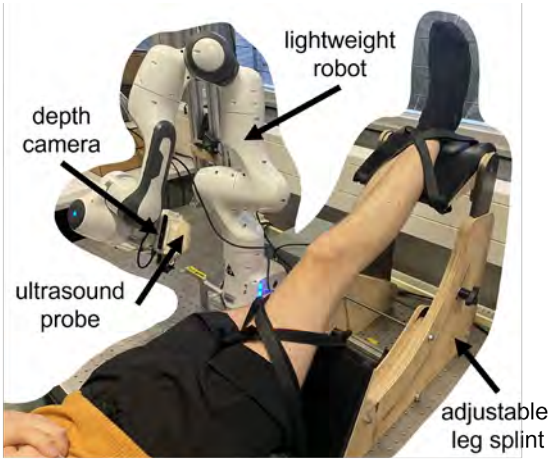

Fig. 5: Autonomous robotic ultrasound scanning of the knee

Ultrasound-based Fixation of Scaphoid Fractures

For the computer-assisted percutaneous fixation of scaphoid fractures, a patient-specific bone model is required for screw planning. This bone model is typically derived from pre-operative CT data, which exhibits the patient to radiation and moreover requires an intraoperative registration step. Conventionally repeated intraoperative fluoroscopic control induces significant radiation exposure for the patient as well as for the surgical staff. Alternatively, a 3D bone model for planning and intraoperative navigation of the screw may be derived from intraoperative ultrasound data directly. Since the scaphoid is only partially depicted in ultrasound images, statistical morphological knowledge is incorporated for the completion of partial bone surfaces. For this purpose, deep learning based approaches are employed.

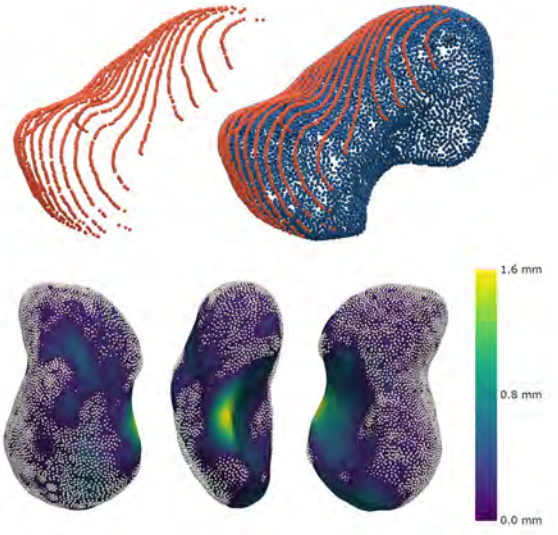

Fig. 6: Partial input and completed output point cloud (top), error between completed point cloud and ground truth mesh (bottom).

Modelling Piezoelectric Transducers for TUS

Piezoelectric Transducers are used in therapeutic ultrasound (TUS) for generating self-focusing shock waves. Designing transducers for this application is time-consuming as there are no readily available methods of simulating the transducer and its electrical and acoustical behaviour. Therefore, extensive iterative testing is required.
We developed a transducer model which can simulate the electrical and acoustical behavior of piezoelectric transducers dependent on time or frequency. The model can be combined to include control circuits and can be used to provide surface pressures for wave-field simulations as well.
By combining electrical and acoustical simulation, the model can simplify the design process of transducers and improve the understanding of related piezoelectric effects.

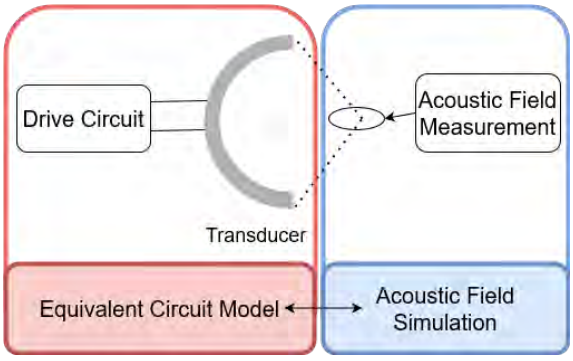

Fig. 7: Diagram of the shock wave generation simulation setup. The new equivalent circuit model can simulate both drive circuit and transducer, a second program can then simulate the acoustic field.

Benchmarking of Reprocessing Facilities

Previous field studies have revealed significant differences in the Performance Shaping Factors (PSFs) of German reprocessing facilities despite the uniform necessity to supply the operation theatres with clean and sterile medical devices. We developed the first German reprocessing benchmark in cooperation with the "Deutsche Gesellschaft für Sterilgutversorgung e.V." (DGSV) to facilitate the exchange and shared learning of the reprocessing facilities. 50 reprocessing facilities participated in the first benchmarking initiative. Our ongoing work focuses on statistical analysis of the retrieved data to identify PSFs with an especially strong influence on the reprocessing key performance indicators (KPI) and, therefore, patient safety.

Fig. 8: Visualisation of the first statistical analysis with brighter colours indicating stronger correlations

Automation in Surgical Instrument Reprocessing

Reprocessing of surgical instruments after use is essential for a continuous supply of the operation theatres and includes the manual opening of hinged standard instruments for cleaning. This manual interaction poses a severe risk to cleaning personnel, as reaching into contaminated instrument sets and respective handling of the different instruments is necessary. In the context of our broader R&D activities related to automated surgical instrument reprocessing, we investigated the feasibility of automating this handling task. We analysed a caesarean section set to consider various forms and sizes of hinged instruments. We developed and evaluated an automated device able to handle and open all instruments with or without locking mechanism.
Moreover, we conducted an interaction-centered user study with 13 participants performing typical reprocessing tasks using different assistance approaches. Digital assistant systems (DAS) and cyber-physical assistance systems (CPAS), including cooperative robots, have the potential to enhance usability and safety in complex tasks such as surgical instrument reprocessing. Various metrics were measured and documented, including time required, user errors, the criticality of errors and perceived workload.
In first trials the CPAS improved usability the most, improving effectiveness (number of errors) while maintaining the same efficiency (total duration). This ongoing study will provide comparative data on usability across different levels of assistance and automation for complex and workpiece-specific tasks in surgical instrument reprocessing.

Wireless Tracking Systems for the Integrated OR

Navigated and robotics have been established in recent years. However, the use of additional medical devices and especially tracking systems is necessary. Consequently, each navigation or robot system comes along with its wired (in most cases optical) localizer system. As operating rooms are crowded already, there is often a noticeable decrease in ergonomics and safety when more devices are added, especially ones that need both wired power and network connectivity. Our wireless tracking system (Fig. 1) is a novel battery-powered development which can operate for up to 24 hours on a single charge without any cable connections necessary. The device is easily manoeuvrable and creates less constrictions around the operating table. The data is transferred via WiFi or local 5G to the operating room network, where it can be harnessed by applications such as the surgical navigation software or robotic system. The communication of the wireless tracking system conforms to the open ISO/IEEE 11073 Service-oriented Device Connectivity (SDC) standard family. This means that the tracking is no longer a static component that comes bundled with only one software. Instead, the tracking data may be used by multiple applications even from different vendors, as long as the standard is safely implemented. This makes the tracking camera a modular component and decreases the cost while providing more benefits and flexibility to the surgical team.

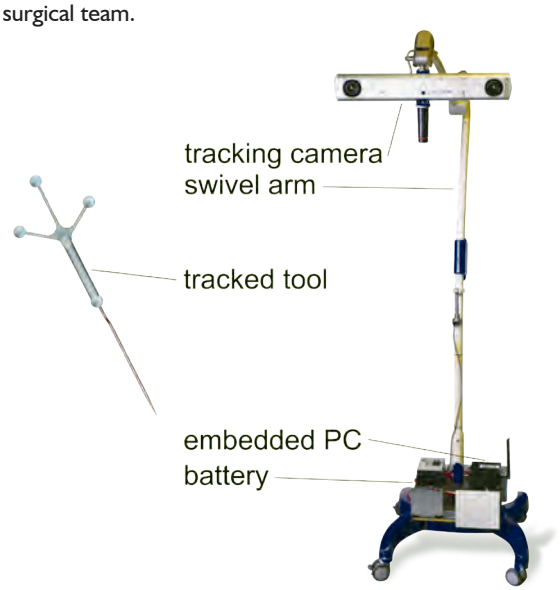

Fig. 9: Wireless tracking system with labelled components (right) and example of tracked pointer tool (left).

UI Profiles for the Open Networked OR

Safe and user-friendly interfaces are crucial in open networked operating rooms, where various medical devices communicate via the ISO/IEEE 11073 SDC protocol. The transmitted data currently contains technical device values and their descriptions but misses standardized human-machine interface (HMI) information, which is crucial for developing user interfaces. Categories such as grouping, visibility level, control speed or criticality could help designers build more useable and safer interfaces. Without that information, creating safe user interfaces is a challenging task. We developed a UI description language containing rules and design requirements for UI intended to increase usability for healthcare professionals and patient safety.

Scalable Cloud Architecture for 5G/6G RAN

In the framework of the CLOUD56 project, we are contributing virtualized clinical assistance functions for the operating room and the entire hospital to demonstrate the benefits of 5G campus networks and vRAN (virtualized Radio Access Network) implementations. In this context, we leverage SDC as a vendor-independent network protocol for medical devices. Clinical assistance functions are provided as containerized services within hybrid cloud-edge infrastructures and utilize intelligent interaction and data exchange of different medical devices (medical device ensembles). This approach enables the availability of vast computational performance for intensive and multimodal tasks, such as image or audio processing, from all connected areas in and around a clinic. New services can be dynamically integrated, and computing capacities can easily be adapted to the current and future demands. In addition, we investigate the specific requirements for forming ensembles of wireless medical devices and ensuring their seamless and secure transmission. To ensure security in device-to-device communications that require the formation of ensembles based on location or patient information before and after network changes, we develop and analyze specific processes and strategies. This includes linking ensembles based on the tracked locations of users and medical devices. At the same time, we optimize traditional manual processes for wireless workflows. The use of 5G offers the potential to ensure proper authentication and identification of users and devices, which is crucial for maintaining IT security, especially when dealing with wireless medical devices and mobile patient beds.

Fig. 10: DMEA 2023 – SDC OR Demonstrator.

Awards

We also congratulate Sonja Ehreiser for the Best Technical Podium Presentation (1st place), Lovis Phlippen for the Best Technical Podium Presentation (3rd place) and Luisa Berger for the Best Clinical Poster Presentation (2nd place) – all funded by the ISTELAR foundation - , 22nd Annual Meeting of the International Society for Computer Assisted Orthopaedic Surgery - CAOS 2023, Pattaya,

Thailand

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

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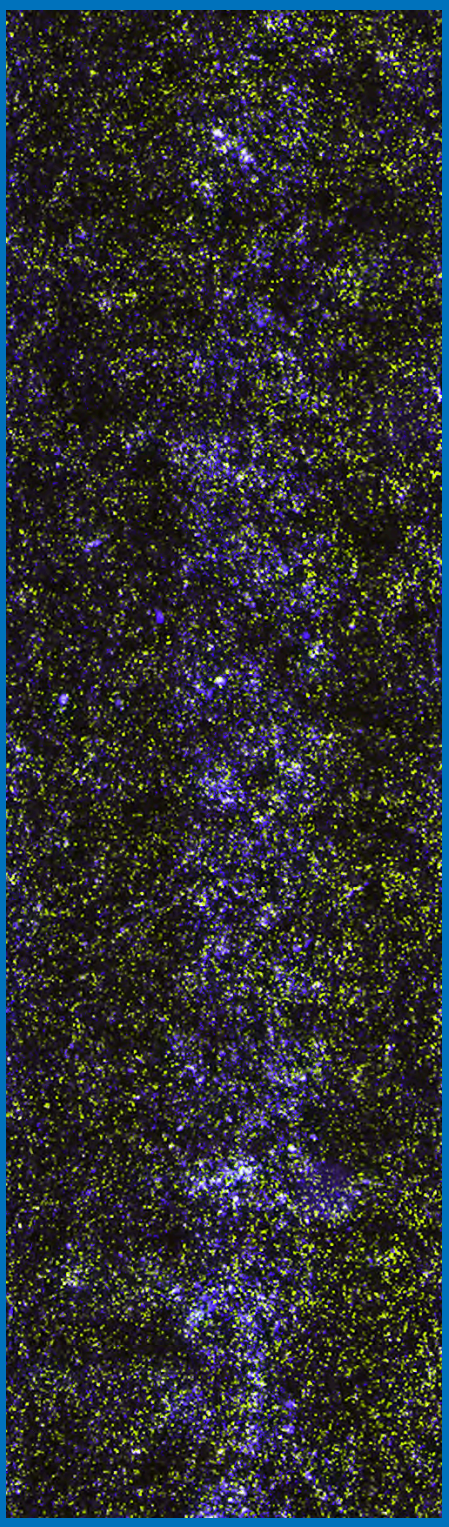
RWTH AACHEN UNIVERSITY

Faculty of Medicine

Cell-Material Interactions: Translating Basic Science Into Clinical Applications



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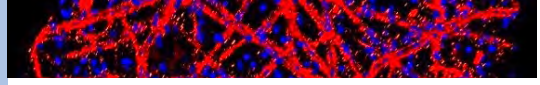


Cover: Members of the group trying to sledge down the milky way. In fact, we made good use of the only day where we had snow (top). The stary picture below shows a flow chip colonized with endothelial cells that were subject to calcification fluids. Details of this work are presented by Aaron Morgan and Robert Dzhanaev below.

Introduction

Willi Jahnen-Dechent, Professor

All hands are back on deck and we are completing funded projects that we started several years ago. The group is now shrinking in anticipation of my imminent retirement next year. Fetuin research is down to Fetuin-A. We cryo-conserved all our mouse strains as we plan no further animal experiments. Thus, our research fully focussed on Biomineralization and Stem Cell-Tissue Engineering, both of which yielded some fine results in the past year. As always, the research will be presented by the people performing it.

Stem Cells and Tissue Engineering

Sabine Neuß-Stein, Professor

The working group "Stem Cells and Tissue Engineering" continued research projects funded both externally (DFG and BMBF) as well as in house funding through IZKF and ERS.
Our interest in mesenchymal stem cells and their role in wound healing and regeneration now also includes periodontal ligament stem cells (PDLSC). We studied cell growth in polymeric and ceramic scaffolds meant for bone tissue engineering. We focussed on capillary formation as a proxy of sufficient vascularization. Using MSC or PDLSC as stromal cells we achieved robust capillary formation of endothelial cells. The work of Hanna Malyaran and Chloe Radermacher in fact constitutes the first demonstration of PDLSC as stromal cells and Svenja Wein went on to demonstrate capillary formation in collagen and fibrin gels, and in gels from human platelet lysate (HPL). Hanna and Svenja tell their stories in more detail.

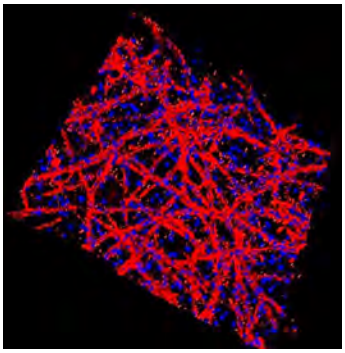


Figure 1: 2-Photon Microscopy of a fibrin gel with capillaries formed by endothelial cells (red, CD31 staining) and supported by mesenchymal stem cells (blue nuclei, DAPI staining). Scale bar is 200 µm.

We engineered the potent chemoattractant, hepatocyte growth factor (HGF), to be released from biomaterials to attract endogenous MSC towards damaged tissues. This is a so-called in situ tissue engineering approach that may be used to avoid the resource-intensive in vitro culture of autologous cells. In the past, we successfully employed HGF-based cell recruitment scaffolds based on silk, collagen, and fibrin. Now we improved release kinetics by creating hierarchically structured fibrin gels with encapsulated microgels loaded with HGF. This strategy is illustrated in the following figure.

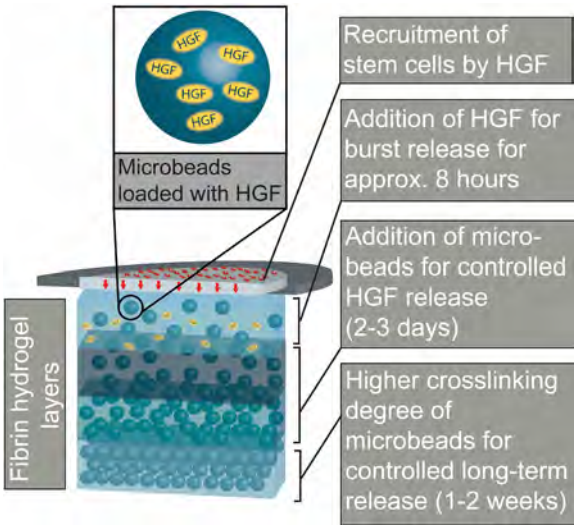


Figure 2: Schematic view of MSC recruitment system using hierarchically structured fibrin gels with encapsulated microgels loaded with HGF.

Just before Christmas, we farewelled Norina Labude to parental leave. Meanwhile she is mum of a lovely baby daughter, and we look forward to her return in 2025!

Comparative analysis of human periodontal ligament stem cells from maxillary and mandibular molars

Hanna Malyaran, MSc

Clinical experience holds that the precise localization of periodontal defects greatly influences the velocity and effectiveness of wound healing and bone remodelling. Periodontal healing is quicker and more efficient in the maxilla (upper jaw) than in the mandible (lower jaw). Differences in blood supply, innervation, and odontogenesis of upper vs. lower jaw may all influence healing, but cell-intrinsic differences may also exist. The overall goal of my project is to characterize PDL cells from third molars of the upper (u-PDL) and lower jaw (l-PDL) and compare them with MSC in terms of proliferation, plasticity, trophic phenotype (via transcriptome and proteome analyses).
In 2023, we were able to unravel differences in molecular mechanisms and pathways in PDLSC using kinomics technology. Kinase analysis revealed two Ephrin A, EphA

receptors that were significantly stronger expressed in the mandible compared to maxilla. EphA4 signalling is known to inhibit osteogenic differentiation. Pathway analysis revealed that PI3K-Akt pathway is more active in the lower jaw (Figure 3 A). This hints to differential activation of gene regulatory pathways in PDLSC from upper vs. lower jaw, which should be considered in studies regarding the regenerative capacity of PDLSC.
We also investigate the angiogenic potential of u-PDLSC and l-PDLSC and compare the results to well-established mesenchymal stem cells. Periodontal stem cells from the upper jaw showed a higher proliferation capacity, secreted more VEGF, and formed faster capillaries and a denser capillaries network than l-PDLSC (Figure 3 B). In cooperation with the working group of Prof. Dr. Horst Fischer, Department of Dental Materials and Biomaterials Research, (OC1-14) we continued the investigations of PDLSC cells in 3D hydrogel-based microenvironments (Figure 3 C).

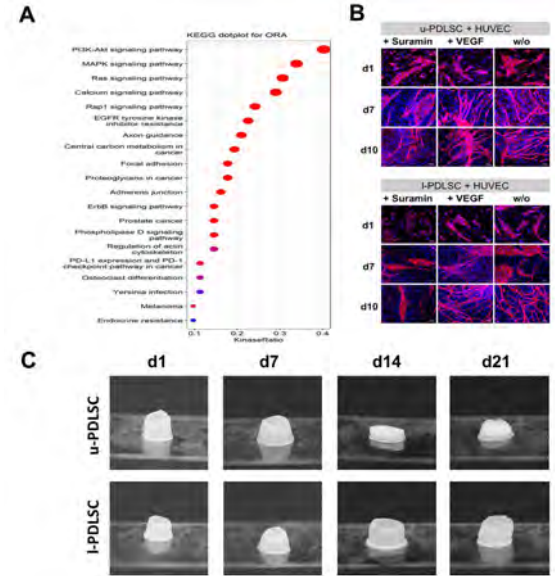


Figure 3: Characterization of PDLSC from upper and lower jaw. Kinase analysis of PDLSC from upper (u-PDLSC) and lower jaw (l-PDLSC) (A). Formation of capillaries was stained with CD31 over 10 days (B). PDLSC in 3D hydrogels over 21 days (C).

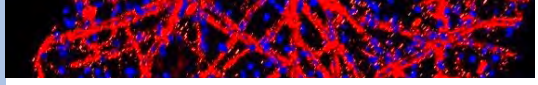
Fibrin-based hydrogels with reactive amphiphilic copolymers for mechanical adjustments allow for capillary formation in 2D and 3D environments

Svenja Wein, MSc

The focus of my project is on the development of a mechanically controllable hydrogel that is to be supplied with capillaries by means of cells and adapts perfectly to the respective conditions of the application. Exploring the incorporation of a novel copolymer into fibrin-based hydrogels enhances their adaptability for cell-based angiogenesis while addressing challenges in Tissue Engineering. Issues concerning nutrient supply and waste disposal beyond the diffusion limit are common, and angiogenesis becomes pivotal in overcoming these obstacles for larger constructs. The copolymer integration significantly improves the mechanical aspects of the hydrogel, fostering angiogenesis and resulting in more extensive and intricately branched capillary networks.
The attachment of the copolymer to fibrin fibers allows for a targeted adjustment of hydrogel properties, introducing a novel approach applicable to various Tissue Engineering applications. Demonstrating the copolymer‘s effectiveness in both 2D and 3D environments underscores its potential to address critical aspects of functionality, biocompatibility, and longevity in biohybrid implants. Conclusive evidence of the positive impact of copolymer-modified fibrin hydrogels on capillary growth, with potential implications in wound healing and the development of artificial organoids was shown. The copolymer‘s ability to enhance mechanical controllability and support angiogenesis unveils new opportunities for biohybrid implants. In Tissue Engineering, the fusion of patient-derived cells with bioactive materials aims to create biohybrid constructs for tissue replacement. Nevertheless, oxygen supply remains a challenge, particularly for larger constructs, necessitating strategies to promote vascularization. In vitro pre-vascularization using endothelial cells in a fibrin gel matrix emerges as a plausible solution.

The distinctive properties of fibrin gels make it an ideal matrix for angiogenesis. The exploration of copolymer-modified fibrin hydrogels aims to tackle challenges linked to oxygen supply and mechanical adaptability. The incorporation of copolymers enhances the hydrogel‘s mechanical properties, offering a promising strategy for clinical applications.

Fibrin-based hydrogels, prepared with and without the copolymer PVP12400-co-GMA10mol%, and the co-culture of human umbilical vein endothelial cells (HUVEC) and mesenchymal stem cells (MSC), were employed to scrutinize angiogenesis behaviour. Rheological analysis confirmed improved mechanical properties in copolymer-modified hydrogels. Capillary-like structures displaying a distinct parallel orientation on hydrogel surfaces suggest the influence of the hydrogel‘s 3D network. This alignment persisted even in the presence of angiogenesis inhibitors. In this study, we successfully adapt the angiogenesis protocol to a 3D context, demonstrating the hydrogel‘s robust support for capillary network formation (Figure 4). Transmission electron microscopy verifies the existence of functional capillaries with closed lumina, illustrating the potential for blood flow (Figure 5). The addition of the copolymer enhances the material‘s mechanical properties and alters its ultrastructure, resulting in a more controlled angiogenic environment.
In summary, the copolymer-modified fibrin hydrogel emerges as a versatile platform for Tissue Engineering, offering improved mechanical properties and robust support for angiogenesis. The findings suggest promising applications in wound healing and the development of biohybrid implants. The potential for 3D capillary network formation underscores the hydrogel‘s versatility, paving the way for future research in biohybrid medical systems.



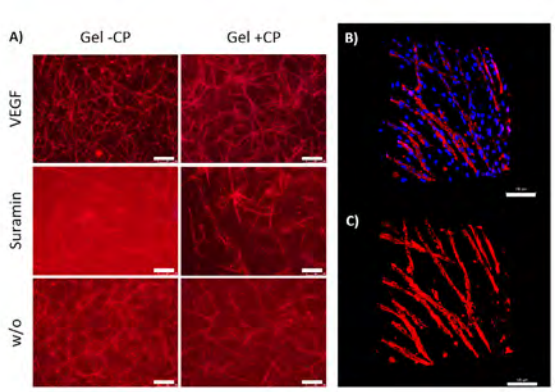


Figure 4: Angiogenesis in a 3D context with VEGF as promotor of angiogenesis and suramin as an inhibitor. The fibrin-based hydrogel in combination with the copolymer (CP) enhances angiogenesis even in the inhibitor and unconditioned samples. A) Fibrin hydrogel with a co-culture of HUVEC and MSC, treated with different supplements to enhance or inhibit angiogenesis B) 2-photon microscopy pictures of 3D cultured co-culture of HUVEC and MSC stained with CD31 and DAPI, C) 2-photon microscopy pictures of 3D cultured co-culture of HUVEC and MSC stained with CD31 (technically enhanced illustration); Scale bars: 100 µm

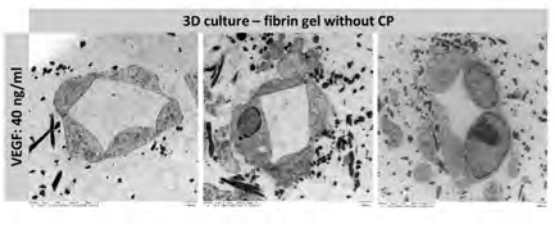


Figure 5: Transmission electron microscopy shows that the resulting capillaries have a real lumen, and that blood flow would therefore be possible in the hydrogel-embedded capillaries. VEGF: 40 ng/ml; scale bar: 5000 nm

The function of fetuin-A as a „mineral transporter" depends on the post-translational modifications (PTMs). Fetuin-A is glycosylated and, depending on the species, has up to 7 phosphorylation sites. Phosphorylation is known to increase the binding affinity of mineral binding proteins, and this is also true for Fetuin-A. We hypothesize that reversible phosphorylation regulates mineral binding in the blood and its release in bone during physiological bone mineralization, as well in soft tissues during pathological calcification.
To illustrate the role of fetuin-A as a transport protein, a 3D structure of the fetuin-A is shown with calcium phosphate mineral attached (Figure 6 A). Phosphorylation strongly enhances Fetuin-A mineral binding (Figure 6 B).

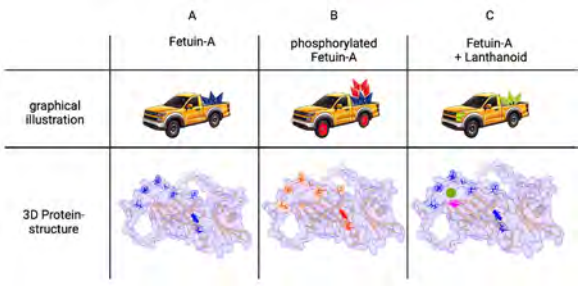
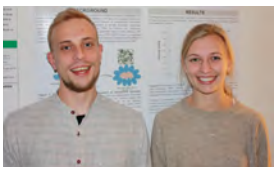


Figure 6: Graphic representation of fetuin-A and its cargo. Fetuin-A is a mineral binding protein with a high affinity for calcium phosphates. Calcium phosphate binds to the residues shown in blue (A), depicting putative serine/threonine phosphorylation sites. When these residues are phosphorylated (B, red residues), fetuin-A affinity for calcium phosphate is strongly increased. Fetuin-A lanthanide binding triggers luminescence depicted in green (C).

Fetuin-A binds and transports primarily calcium phosphates. In addition, Fetuin-A was also shown to transport actinides uranium and plutonium, and lanthanides. Figure 6 C illustrates lanthanide terbium and europium binding, triggers robust luminescence.

Functions of the blood protein Fetuin-A



Christian Hasberg, MSc

Camilla Winkler, MSc

Calcium and phosphate are present in the blood in concentrations far above the solubility product and would precipitate immediately without the presence of proteins preventing tissue mineralization known as pathological calcification.
Chief among these proteins is the hepatic plasma protein fetuin-A. Fetuin-A is found particularly in foetuses in high concentrations of up to 2.5 mg/mL and thus its name is derived from it (lat. fetus). In the early stages of development, a lot of bone mass is built up, which contains, not least, calcium phosphates. Fetuin-A is believed to carry calcium phosphate rich mineral precursors through the blood to newly forming bone. The targeted deposition of mineral in the bone is called biomineralization, in contrast to pathological calcification elsewhere in the body.

Clearing up muddy waters- live imaging of calcifycing cells

Aaron Morgan, MSc

Robert Dzhanaev, Dr med Dr rer medic

Mineralization is the process by which organisms reinforce their bodies with calcium salts, making bones and teeth. Under pathological conditions, the mineralization process can get out of control, and then ectopic calcification, or soft tissue calcification, can develop in the body. The study of calcification offers insights into the processes accompanying and complicating many common disorders such as atherosclerosis and chronic kidney disease. As technology advances, so does our ability to peer into the microscopic world of living cells, unravelling the complexities of calcification over time.
Historically, scientists could only capture snapshots of mineralized tissues and cells. Early imaging techniques

required fixation and application of multi-step staining methods that would help to reveal the presence of mineral deposits within cellular structures. However, these static images failed to capture the dynamic nature of calcification. Fetuin-A based probes enable high sensitivity, live analysis of the process of calcification. The probes are non-toxic, so they can be used in live cell cultures over extended periods of time. By capturing sequential images, it is now possible to observe the initiation, progression, and resolution of calcification events, revealing how these small mineral deposits affect cellular biology.

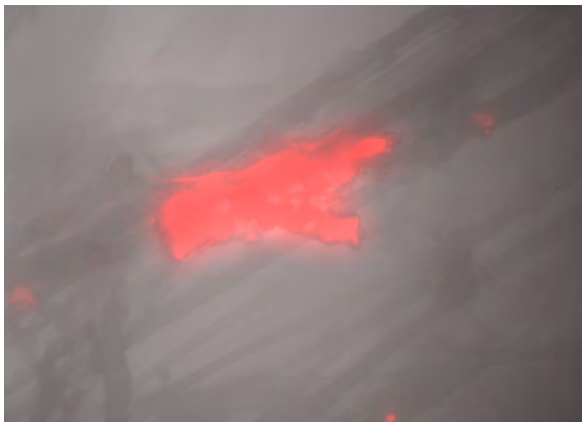


Figure 7: Calcified bovine pericardium after 7 days in calcification medium. Collagen fibers can be seen in the brightfield. A large, calcified lesion is seen in red, labelled with fluorescent Fetuin-A-mRuby

With this new ability for real-time monitoring, it is now possible to gain insights into the mechanisms behind cellular calcification. For example, pathological calcification commonly occurs in the vessel walls of patients suffering from chronic kidney disease (CKD), due to impaired kidney function and poor clearance of mineral from the blood. While this is a very common disease, there is currently no good cell model for studying the mechanisms behind this pathology in more detail. By utilizing our novel calcification probes in combination with live-imaging technology and specially designed flow chambers, we can observe the process of cellular calcification in real-time.

Figure 8: A live-imaging compatible flow chamber for testing biohybrid implant materials. A roller pump drives a closed fluid loop containing calcification medium, while the flow chamber exposes the sample within to physiological shear stresses like those seen in the vessel wall.

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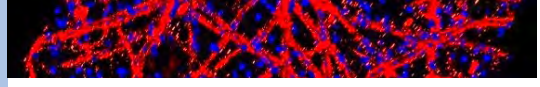

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Team

Labout at Gmünd Youth Hostel in the Eifel Mountains

Outdoors on a “Beaver Hunt” – got em…

Christmas dinner at “Zum Wehrhaften Schmied” downtown Aachen.

ExMI EXPERIMENTAL MOLECULAR IMAGING

Chair of Experimental Molecular Imaging Faculty of Medicine

Imaging, engineering, and nanomedicine technologies to improve diagnosis and therapy

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Introduction

Univ.-Prof. Dr. med. Fabian Kiessling

The Chair of Experimental Molecular Imaging (ExMI) develops and evaluates novel imaging modalities, contrast agents and theranostics for the characterization and treatment of cancer, cardiovascular and inflammatory diseases. ExMI has a translational focus and many projects are at the interface between preclinical and clinical research. In this context, we often adopt 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). To develop image-guided therapies, we combine our pathophysiological and pharmacological research with research in device engineering, image reconstruction and advanced data analysis. Basic research into the tissue microenvironment (including barriers to drug delivery) is providing 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 together, evaluated using radiomic and radiogenomic approaches, and used to support mathematical disease models.
The second focus of ExMI is on materials and concepts to improve drug delivery to tumors. This includes the development and evaluation of novel biomaterials, nanoparticles, polymeric carriers, liposomes, micelles, microbubbles and multi-scale hydrogels, as well as physical and biological manipulation of the vasculature and adjacent tumor stroma to enhance drug accumulation and penetration.
ExMI's research has gained increasing international visibility. In 2023, Prof. Kiessling and Prof. Lammers were recognized by Clarivate Analytics as Highly Cited Researchers (5th time). In addition, Prof. Kiessling became President of the European Society for Molecular Imaging (ESMI) and Prof. Lammers of the Controlled Release Society (CRS). Finally, we are pleased to welcome our ERC Starting Grant awardee, Prof. Dr. Yang Shi, as the new W2 Professor for „Polymer Therapeutics" at ExMI.

Diagnostic and Therapeutic Ultrasound

Univ.-Prof. Dr. med. Fabian Kiessling

The diagnostic and therapeutic ultrasound (US) group focuses on four major topics: 1. Molecular US imaging, 2. Superresolution US imaging, 3. Sonoporation and US-mediated drug/gene delivery, and 4. Radiomics analysis of US data. In this context, we further explored molecular ultrasound imaging to elucidate vascular tumor biology [1]. Using our PBCA-based polymeric microbubble platform for the first time non-spherical microbubbles were produced that promise improved vascular targeting and sonoporation efficiency [2]. Furthermore, we started to refine targeted microbubbles for clinical use in context with the BMBF CLIMBING Crohn project that aims to explore molecular ultrasound imaging in a bi-centric study on inflammatory bowel diseases. Clinical translation was also promoted in superresolution ultrasound imaging, where we refined our clinical protocol for breast cancer imaging, identified important clinical challenges, and demonstrated its complementarity with sheer wave elastography [3]. Furthermore, within the DFG funded FOR2591 we assessed the impact of several imaging modalities on animal welfare and study results [4]. While animal welfare was not affected by ultrasound [5], we found a significant influence on immune cell migration into tumors. Although medical research still requires laboratory animals in many regards, there is a high ethical demand to replace animal experiments. Therefore, we worked on advanced in vitro models as an alternative [6]. In this context, a new imageable bioreactor was developed, in which vascularized tumors spontaneously grow to a mesoscopic scale, showing comparable stromal and metastatic characteristics as their in vivo counterparts [7]. This work was honored with the 4th Aachen Animal Welfare Award.

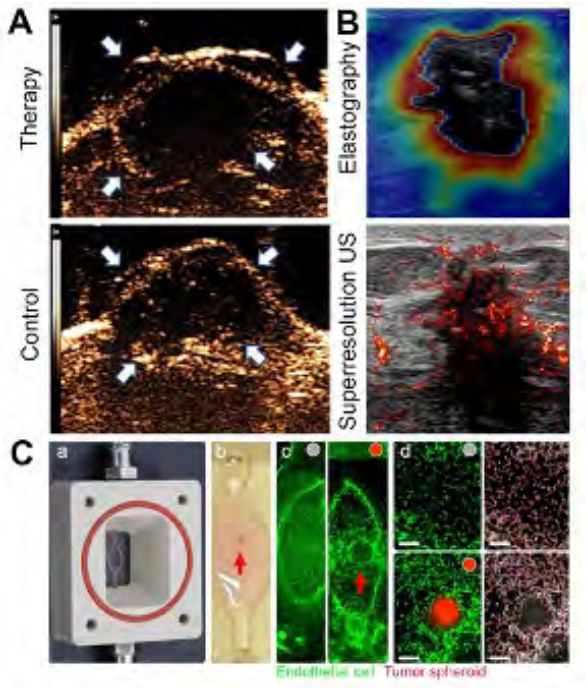

Fig. 1. A: Molecular ultrasound images of murine breast cancers using VEGFR2-targeted microbubbles highlight the inhibitory effect of acetylsalicylic acid on tumor angiogenesis [1]. B: Superresolution ultrasound and sheer-wave elastography images of a human breast cancer after protocol refinement [3]. C: Advanced in vitro tumor models [7]. a: Bright field images of the bioreactor where branched gelatin strands are 3D-bioprinted. b: In a fibrinogen-collagen hydrogel blend containing endothelial cells (GFP) and stromal cells, tumor spheroids (red arrow) vascularize and grow to mesoscopic scales. c, d: After dynamic cultivation, a dense vascular network between the two branched feeding vessels has only formed in the presence of tumor spheroids. Scale bar = 200 µm

Nanomedicine and Theranostics

Univ.-Prof. Dr. Dr. Twan Lammers

Nanomedicines are designed to help deliver drugs to pathological sites, thereby enhancing therapeutic efficacy and reducing systemic side effects. At RWTH Aachen University, we have an increasingly strong focus on materials

and methods to promote interfacial drug delivery, aiming to modulate biological barriers in a temporally and spatially controlled manner [8]. For drug delivery to the brain, we have been generating polymeric microbubbles (MB), which in combination with transcranial focused ultrasound (FUS) can be employed to open the blood-brain barrier [9]. When heating these PBCA-based polymeric MB above their glass-transition temperature, they can be mechanically stretched, to obtain rods [2]. In the blood stream, rod-shaped MB flow in closer proximity to the margins of the vessels, thereby promoting US-mediated model drug delivery to the brain (Fig. 2A) [10]. In 2023, we also expanded our work on polymeric micelle and liposome production and translation [11,12,13]. Most prominently, together with colleagues from the Medical Clinic IV at UKA, we provided first-in-men proof-of-concept for the safety and potential therapeutic use of liposomal dexamethasone phosphate in patients with multiple myeloma (Fig. 2B,C) [14].

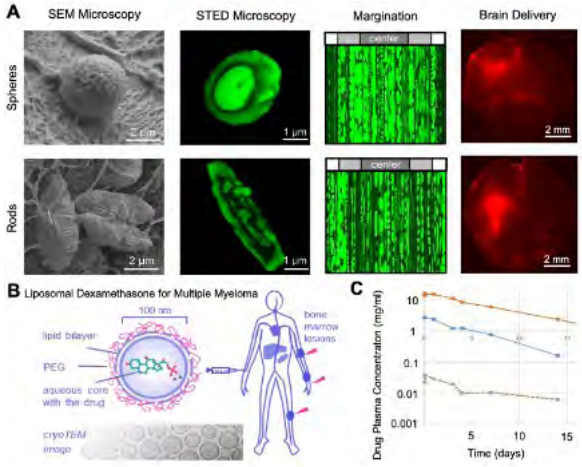

Fig. 2. A: Nonspherical polymeric MB were generated via 1-dimensional mechanical stretching. The rod-shaped MB were shown to marginate in microfluidic flow devices (in green), and to enhance model drug delivery (in red) specifically in US-treated areas within the brain of mice. B: Pegylated liposomal dexamethasone was evaluated in multiple myeloma patients, showing prolonged presence of liposomal drug (full lines) and free drug (dashed line) in plasma after i.v. administration at a dose of 10 mg (blue) and 40 mg (orange). Images are reproduced from [2,10,14].

models [16], see Fig. 1. PET in-system calibration was addressed using angular irradiation methods. These methods serve as a convenient 3D positioning calibration for clinical systems, to enable, e.g., (semi-)monolithic detector designs in commercial devices [17]. Unprecedented performance benchmarks for a novel silicon photomultiplier technology and fast scintillators have been established using emerging high-frequency (HF) concepts [18]. Two different options of encoding the depth of interaction within the scintillator have been tested [19,20], resulting in sub-150 ps TOF resolution. In addition, the HF readout circuit has been scaled up to a 16-channel prototype, leading to a deep understanding of the multi-photon time resolution of the TOFPET2 ASIC [21]. The group has researched the timing performance of alternative scintillators with fast light emission such as the cross-luminescence emitter BaF2, also considering material properties such as absorption probability and photofraction for a TOF-PET system [22].

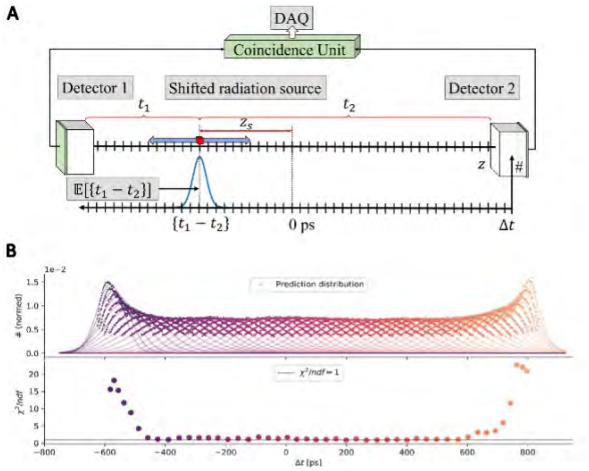

Fig. 3. Besides usually used data scientific metrics (e.g., MAE), trained models were also checked for their consistency with fundamental laws of physics. A: Setup with two detectors in coincidence and a source that is moved to discrete known positions between the detectors. B: The predicted distributions of time difference spectra. CC BY 4.0.

Physics of Molecular Imaging Systems

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

The PMI group researches, develops, and evaluates medical imaging systems ranging from established techniques like Positron Emission Tomography (PET) to the emerging method Magnetic Particle Imaging (MPI). Within the field of Time-Of-Flight (TOF)-PET, the group published an analytical timing calibration concept, which addressed the fundamental issues regarding the TOF calibration of light-sharing-based PET detectors [15]. Furthermore, a novel approach for general calibration problems was developed using the principle of 'Residual Physics', aiming to combine prior domain knowledge with machine learning. The overall goal is to estimate corrections for effects of higher order, which are not or very complex to be described purely by analytical

Polymer Therapeutics

Univ.-Prof. Dr. Yang Shi

Polymers, characterized by their high-molecular weight macromolecules with repeating units, offer a unique ability to impart rich functionalities to biomaterials, setting them apart from conventional small molecules. From traditional pharmaceutical dosage forms like tablets to cutting-edge applications such as the development of COVID-19 mRNA vaccines, polymers play a diverse and crucial role in investigational therapeutics for disease treatment and diagnosis. The Department of Polymer Therapeutics is dedicated to designing and engineering polymer-based biomaterials with a clinical translation focus. Our innovative polymer biomaterials are meticulously crafted to facilitate the targeted delivery of cancer chemotherapeutic drugs and/or to engineer the immune system for enhanced therapeutic outcomes. Within the framework of the ERC Starting Grant BeaT-IT, we are engineering biomaterials to target extracellular and intracellular receptors of immune cells

(23, 24). We have designed nanovesicles for B cell activation and have tested the in vivo immunization effects of the nanovesicles. We have demonstrated that the nanovesicles potently stimulate B cells and successfully engineered B cells into antigen-presenting cells to prime both cytotoxic and helper T cells. In vivo application of the nanovesicles stimulated germinal center B cell and follicular helper T cell responses and antibody production.

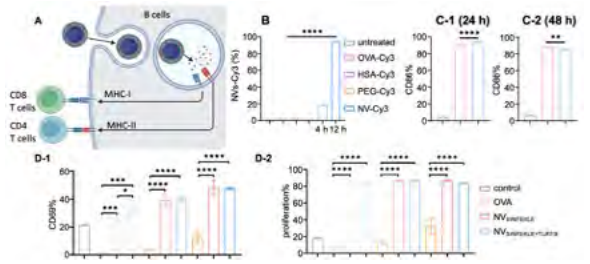

Fig. 4. A: B cell engineering by nanovesicles to be potent antigen-presenting cells to prime T cells. B and C: Efficient uptake of nanovesicles by B cells and B cell activation by the nanovesicles. D: Cytotoxic T cell priming by nanovesicle-treated B cells.

Biohybrid Nanomedical Materials

Dr. Roger Molto Pallares

The Biohybrid Nanomedical Materials group focuses on developing new solutions to improve the diagnosis, prognosis, and treatment of challenging diseases by combining elements of bio-inspired technology and nanomedicine. Hence, we engineer (nano)materials with unique characteristics, e.g. radiological, optical, magnetic, or acoustic, with the functionality of biological (or bio-inspired) agents to provide localized diagnostic and/or therapeutic responses [25,26].
For instance, the group has recently engineered new plasmonic nanoconstructs based on gold nanostars for enhanced photoacoustic imaging and photothermal therapy [27,28]. Furthermore, to ensure the safety of clinically relevant materials, we are applying -omics approaches to characterize their toxicity/safety and biological behavior in different models [29,30]. Lastly, we have been able to design new hybrid Janus composites for applications beyond healthcare, such as high-performing nanocatalysts for sustainable green chemistry [31].

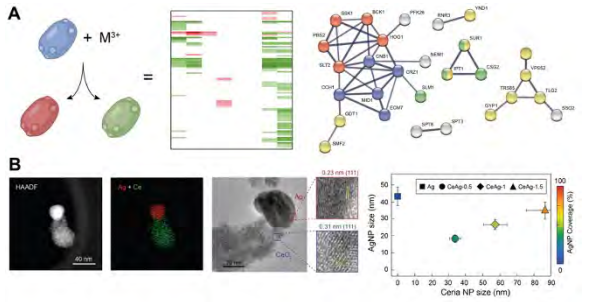

Fig. 5. A: Genome-wide toxicogenomic analysis of critical metals [29]. B: Structural characterization of Janus hybrid nanocomposites with enhanced optoelectronic properties [31].

Immune cell targeting and imaging

Dr. Alexandros Marios Sofias

Within our research group, we embrace a paradigm shift in cancer nanomedicine, moving beyond the traditional approach of targeting cancer cells alone to encompass the targeting and manipulation of immune and fibrogenic cells in circulation, primary tumors, and hematopoietic organs. This targeted approach serves both diagnostic and therapeutic purposes. In terms of diagnostics, we employ molecular imaging contrast agents or nanoparticles [32] to precisely target and quantify cell populations responsible for disease development and progression. Simultaneously, therapeutic nanomedicines are designed to target specific cell populations, leveraging them as carriers to transport nanomedicine to distant tissues, essentially using these cells as „chariots“. This approach also allows for the in situ modulation of their behavior and functions [8]. We investigate these innovative methodologies in the context of triple negative breast cancer, hematological malignancies, and liver cancer. To evaluate the in vivo performance of nanomedicines, we employ a comprehensive strategy that includes whole-body imaging techniques (e.g., FLT/CT and MRI), state-of-the-art intravital microscopy, as well as ex vivo flow cytometry and histological approaches.

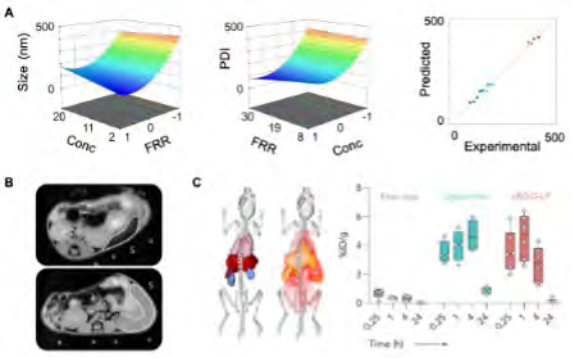

Fig. 6. A: Development and prediction of nanoparticle (NP) properties and characteristics. B: Non-invasive assessment of disease progression via imaging. C: In vivo assessment of NP biodistribution and targeting specificity.

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Awards

- Prof. Fabian Kiessling and Prof. Twan Lammers: Highly Cited Researchers 2023 by Clarivate.
- Prof. Volkmar Schulz: elected IEEE Senior Member; Fraunhofer Attract Award
- Dr. Alexandros Marios Sofias: Scientific Ambassador of Euro-BioImaging; Director of Abstracts for CRS 2024 Annual Meeting; Chair of Oncology for EMIM 2024.
- Asmaa El Shafei: Young Investigator Award at EMIM 2023; Audience Award at the Young Scientist Workshop at CRS Annual Meeting 2023.
- Katrin Herweg: Second-best oral presentation and third place in the Student Paper Award competition of the NSS.
- Stephan Naunheim: Award for the best poster presentation and second place in the Student Paper Award competition of the MIC.
- Katrin Herweg, Vanessa Nadig, Stephan Naunheim, Yannick Kuhl and Florian Mueller: NSS MIC Trainee Grants.
- Vanessa Nadig: IEEE Glenn F. Knoll Graduate Educational Grant.
- Anshuman Dasgupta, Shiva Khorshid and Karina Benderski: CLINAM Poster Awards.
- Dr. Roger Molto Pallares: Umbrella Award.
- Karina Benderski: Poster Award at EMIM.
- Anshuman Dasgupta and Asmaa El Shafei: Vevo Research Award, sponsored by Fujifilm | Visualsonics.
- Vedangi Kulkarni: Merck-GRADS Research Award at CRS Annual Meeting 2023.
- Dr. Quim Pena: Poster award at CRS Annual Meeting 2023.
- Aachen Animal Welfare Award to the authors of doi: 10.1002/adma.202303196

Publications

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Faculty of Medicine

Building Bridges, Creating Innovation

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Introduction

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

Dear readers,
the distinctive guiding principle of our Institute of Applied Medical Engineering (AME) is to address urgent medical needs and specific healthcare challenges using the principle of convergence of disciplines („convergence research"). This explains why we have an intellectually diverse team of scientists and students from engineering, natural sciences and medicine working closely together on many research and development projects.

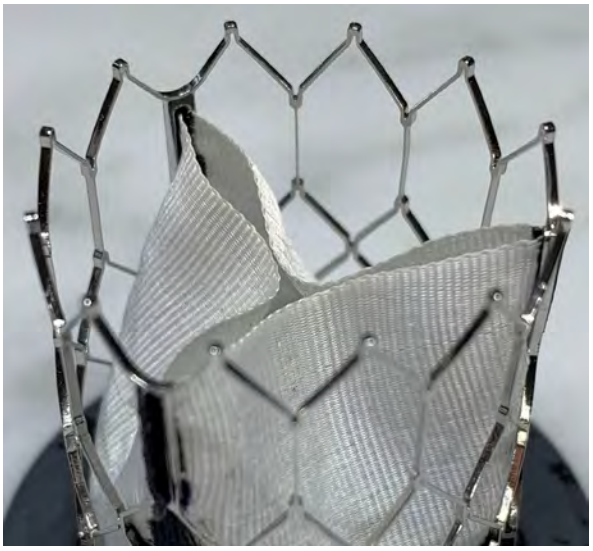

Fig. 1: Materials for Medical Devices:
Textile heart valve tested with 200 million load cycles

The interaction of cutting-edge technologies from engineering and materials science with the latest findings and methods from the life sciences and medicine runs through all areas of activity and determines the innovative spirit of our undertakings and projects (Fig. 1). The influence of materials science on medical engineering has steadily increased and thus also determines our participation in current consortium projects.

The AME institute consists of 6 departments, whose 2023 research activities are described below. RPE, BEE, SCM and parts of AMB are located in the building of the Helmholtz Institute (HIA), another part of BEE in the Medical Technology Center (MTZ). BioTex and CVE as well as other parts of AMB are located on two floors of the Center for Biohybrid Medical Systems (CBMS). All locations are part of the RWTH Biomedical Engineering Cluster, are in close proximity to each other and to the University Hospital Aachen (UKA).

Advanced Materials for Biomedicine (AMB)

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

The Department of Advanced Materials for Biomedicine (AMB) focuses on the synthesis and (self)-assembly of synthetic molecules and micron-scale colloidal 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 Aachen University, and the DWI-Leibniz Institute for Interactive Materials. Polymer synthesis is combined with in-mold polymerization techniques, microfluidics, and fiber spinning to create pre-programmed, responsive, and interactive 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 of 2023:
Vascularization is still one of the largest challenges in the field of tissue engineering. In our study, we found out that sequential application of Angiopoietin 1 + PDGF-BB followed by Angiopoietin 2 in Endothelial Growth Media-2 generated long, thick, branched structures in our PEG-based hydrogel compared to conditions where Ephrin-B2 or no growth factors were used (Fig. 2). We demonstrated that inside our Anisogel system, vascular structures grew following the direction of the guiding cues, represented by magnetically aligned rod-shaped microgels. This may permit the creation of directed vascular networks, reaching out to media inlets/outlets of dynamic flow systems to develop specific tissue models for in vitro and in vivo applications. [doi: 10.1002/adtp.202300091]

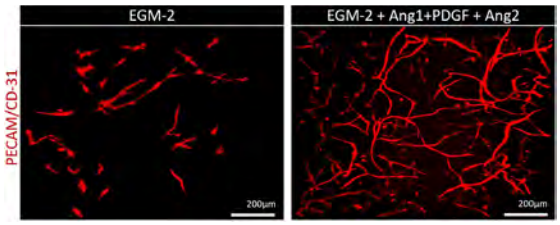

Fig. 2: Normal human dermal fibroblast + Human umbilical cord vascular endothelial cells (3:1 ratio) grown in media with and without the sequential delivery of specific growth factors.

Rod-shaped microgels are unique colloidal building blocks to create scaffold materials for tissue engineering and regenerative medicine. In this paper, the microgels are produced via a microfluidic technique and light-induced crosslinking of a polymer precursor solution. Their stiffness, degree of swelling, and mesh size depends on their polymer architecture, crosslink density, and fabrication method (Fig. 3). These parameters influence cell behavior and tissue formation by dictating not only the physical, mechanical, and biochemical properties of the cell substrate but also influencing diffusion of nutrients, waste material and other biomolecules. Therefore, we investigated how the architecture and molar mass of polyethylene glycol acrylate (PEG-Ac) precursors, in combination with their concentration, affect the internal structure of rod-shaped microgels to identify optimal parameters to design new materials for tissue growth. [doi: 10.1002/anie.202309779]

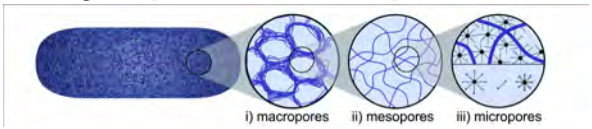

Fig. 3: The microgel internal structure can be tailored using different precursors to achieve the properties needed for specific applications.

Scaffolds are designed to provide a stable matrix for cells to grow, but what if we just offer the cells the building blocks and allow them to design their own house? We established a cell-induced interlinking method for Macroporous Annealed Particle (MAP) scaffold formation where cells self-organize together with the microgels creating dynamic tissue constructs. Dextran-based microgels bearing RGD motives are the building blocks "glued" by the cells, resulting in a homogenous cell distribution throughout the scaffold with efficient cell–cell interactions (Fig. 4). Microgel properties, cell/microgel ratio, and well shape are used to control the 3D assembly. This platform can be used to build to build in vitro model systems in a simple and automated manner by relying on and influencing cellular self-organization. [doi: 10.1002/adhm.202302957]

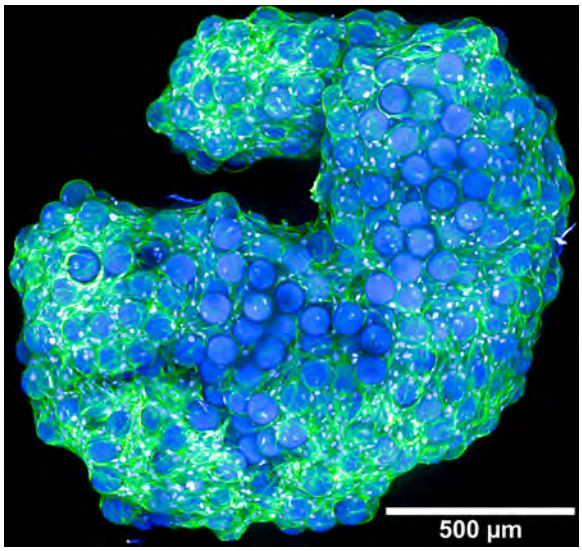

Fig.4: Cells organize the microgels to create 3D structures according to their needs.

Biophysical & Education Engineering (BEE)

Priv.-Doz. Dr. rer. nat. Dipl.-Phys. Ioana Slabu
Prof. Dr. rer. nat. Dipl.-Ing. Martin Baumann, MME

Research Highlights in 2023

Electromagnetically heatable nanomodified stents for the treatment of hollow organ tumors
NME develops nanomodified magnetically responsive hybrid materials for theranostic applications. In 2023, the project ProNano received the RWTH Innovation Award for the development of hybrid stents that can treat hollow organ tumors. For this, magnetic nanoparticles (MNP) are

incorporated into polymeric fibres and then braided to stents. Placed inside the hollow organ, the stents are exposed to a magnetic field that heats them up and, in this way, destroys the tumor in the surrounding area. An exemplary stent and the heat induced is shown in Fig.5. Exploiting MNP properties optimized towards theranostic applications, the combination of magnetic particle imaging MPI with magnetic hyperthermia promises huge possibilities for image-guides therapies (Mues et al. 2021a; Mues et al. 2021b; Mues et al. 2022).

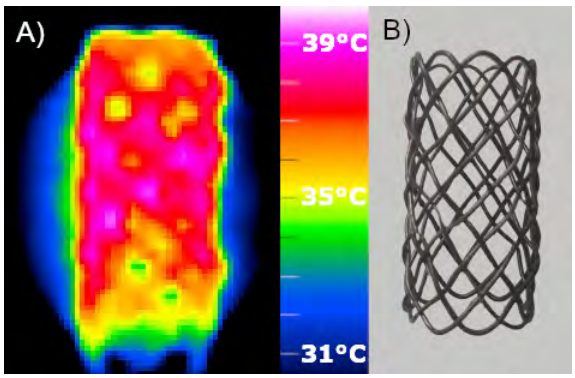

Fig. 5: A) Thermographic picture of a MNP loaded hybrid polymeric stent activated in a magnetic field. The measurement was started at an average stent surface temperature of 23°C. B) Image of a hybrid stent.

High-scale production of magnetic nanoparticles
Using a continuous, highly scalable, and automated approach, NME produces MNP and tailors their properties for specific applications (Fig. 6) (Göpfert et al. 2022). Powerful in-line measurement techniques are used to control the manufacturing parameters to customize MNP properties. Accordingly, MNP can be used as contrast agents for resonance imaging (MRI) and as tracers in magnetic particle imaging (MPI) as well as heating agents in magnetic hyperthermia and as magnetic carrier for drug delivery.

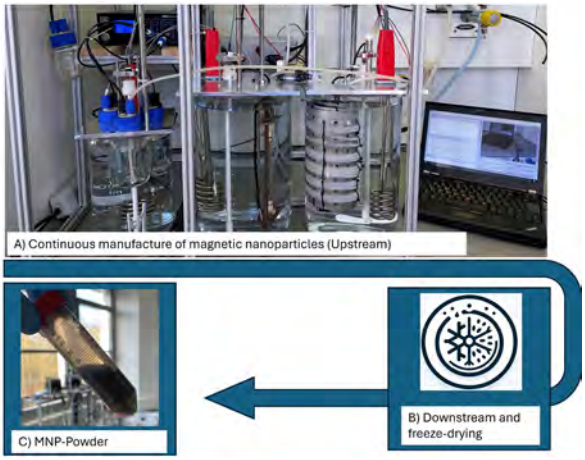

Fig. 6: A) Continuous production of magnetic nanoparticles and B) further processing. C) Resulting MNP powder. The powder is used to produce MNP incorporated implants.

Teaching Highlights in 2023

In our department, we also focus on research in teaching. In 2023, we received funding to extend our project to train teachers and scientist in "Giving professional talks", which depicts a three-module workshop curriculum. More than 1800 lecturers, postdocs, doctoral students and students have enrolled in these workshops in the recent years to rehearse and improve their presentation skills. Based on their evaluations and feedbacks, we developed a fourth workshop to practise those skills "on the fly": A group between four and eight participants was invited for a walk in the University Hospital park, during which they had to give talks according to different instructions (Fig. 1). The given tasks are escalating, i.e. they are becoming increasingly difficult. Videorecording and post-workshop feedback enhanced the learning outcomes. This concept of "learning along the way" is acknowledged and financially supported by the RWTH Aachen University.

Fig. 7: Talk scene. Persons were made unrecognisable.

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 strives 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 to (pre)clinical testing. The BioTex Institute works in a strong collaboration with the Aachen-Maastricht Institute for Biobased Materials and the DWI Leibniz Institute for Interactive Materials.

Fig. 8: The BioTex team during the LabOut event at the „Dreiländereck".

Research Highlights in 2023:

Bio-Inspired Fibre Reinforcement for Aortic Valves
The application of tissue-engineered heart valves in the high-pressure circulatory system is still challenging. One possible solution is the development of biohybrid scaffolds with textile reinforcement to achieve improved mechanical properties. We invented a manufacturing process of bio-inspired fiber reinforcement for an aortic valve scaffold. The reinforcement structure consists of polyvinylidene difluoride monofilament fibers that are biomimetically arranged by a novel winding process. The fibers were embedded and fixated into electrospun polycarbonate urethane on a cylindrical collector.

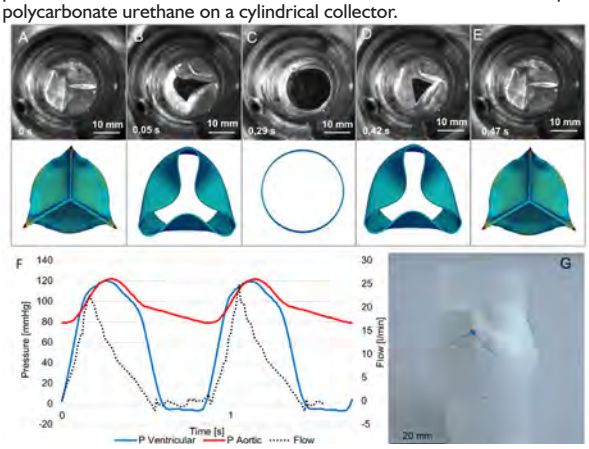

Fig. 9: Boehm et al showed a new model based approach of producing aortic heart valves with fibre reinforcement and characterized the hemodynamic behaviour of the fashioned heart valves.

Inaugural lecture by PD Dr. med. Christian Cornelissen and PD Dr. rer. medic. Anja Lena Thiebes
PD Dr. med. Christian Cornelissen and PD Dr. rer. medic. Anja Lena Thiebes held their inaugural lecture on the 8th of September 2023 with the topics "Umwelt, Abgas und der menschliche Körper" and "In-vitro-Modelle – Die Lunge in der Petrischale", respectively.

Launch of the new braiding machine
As part of the reACT ("resorbierbare Lösungen aus der Aachener Technologieregion") research project, capabilities in the field of textile engineering were expanded to include circular braiding. The new circular braiding machine enables us to research and develop wire-based stent structures, which are used as biohybrid vascular or airway stents and as structural frames for heart valves. The main focus of the reACT research project is on the development of partly resorbable implant structures, which is achieved through a selective combination of different wire materials (e.g. nitinol and magnesium) in the stent structure.

New Projects

Drug delivery to the airways – Evaluation of underlying mechanisms in a transparent airway model
The application of liquid therapeutics into the lung is associated with complex transport mechanisms depending on the application method used. In this project, we aim at a direct visualization and quantitative comparison of fluid dynamics and deposition using an innovative lung model for different application techniques. Complementary to the investigations on the model, the influence of the different application methods on the functionality of different therapeutic classes, stem cells and extracellular vesicles were analyzed.

Extracellular Vesicles for the Functionalization of Polymers – New Biohybrid Materials for the Regenerative Medicine in the Head and Neck Area
Extracellular vesicles (EVs) were incorporated into the silk fibroin material as a carrier for wound healing applications. For this purpose, EVs were isolated from cells by differential ultracentrifuge and characterized. Silk fibroin material was processed in different structures and characterized to achieve controlled degradation time for wound healing applications.

Julian Gonzales-Rubio is a part of the Strategic Alliance Committee
Julian Gonzales-Rubio was elected as chair of the Strategic Alliance Committee of the Tissue Engineering and Regenerative Medicine Society (TERMIS), EU Chapter, Student and Young Investigator Section.Additionally, Julian Gonzales-Rubio has been awarded the "Wissenschaftspreis" (2nd place) of the "Westdeutsche Gesellschaft für Pneumologie" (WDGP) for his work on the relationship between Sars-Cov-2 particles and the differentiation and ciliation of airway epithelium.

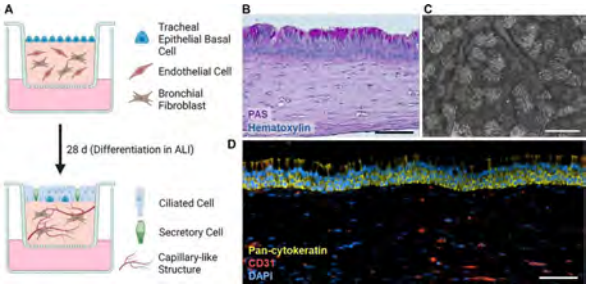

Fig. 10: Gonzales-Rubio et al. showed the influence of SARS-CoV-2 particles on epithelial cells cultured in an air-liquid interface leading to ciliation and differentiation of the epithelial basal cells in a Tri-culture model.

Cardiovascular Engineering (CVE)

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

In 2023, there were a number of changes in clinical areas relevant to us at our university hospital, which led to closer integration with our clinical partners. Besides our ongoing activities, this will lead to a more targeted future focus of our research work on clinical issues.

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

Therefore, alternative blood fluids are developed and investigated. One approach is the validation of porcine abattoir blood as fluid for material thrombogenicity evaluation. A new project funded by the Hirsch Foundation focusses on the comparison of the hemorheology of porcine and human blood.
Another approach focusses on the development of blood analog fluids such as the "Ghost blood" – a clottable, transparent blood build of plasma and ghost cells (hemoglobin-deprived erythrocytes). Fig. 11 shows a technical aneurysm model with an inserted flow diverter perfused with ghost blood.

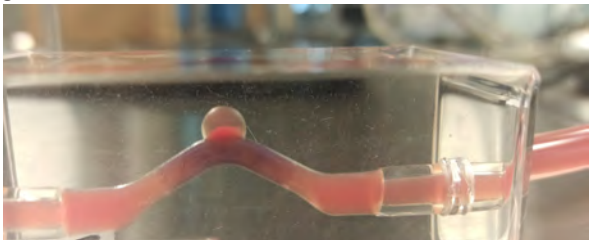

Fig. 11: Testing of an aneurysm model with flow diverter with Ghost Blood.

The DFG-ANR cooperation ThromboSurf deals with the impact of surface structures on blood flow and platelet behavior. The combined numerical and experimental approach tries to unravel the underlying mechanisms of improving material hemocompatibility by means of surface structures. In Fig. 12, the newly designed flow chamber is shown in a μPTV system, which is aimed to enable real time observation between particles and the structured surfaces. In the future, the system will used washed and labelled platelets as tracking particles.

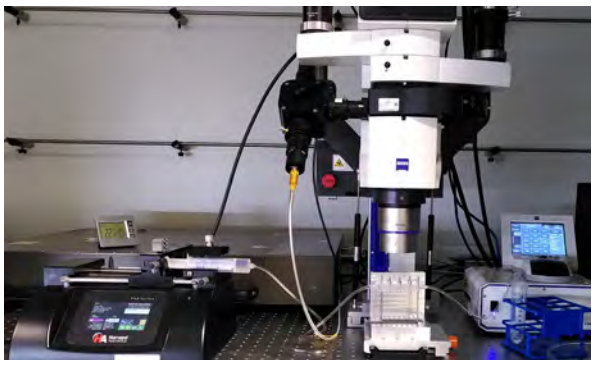

Fig. 12: Test setup with flow chamber in μPTV system for real-time platelet observation.

In DurImplant2, which is part of the PAK 961, a new calcification fluid and test system that is cell compatible is developed to investigate biohybrid heart valve prostheses in vitro. Fig. 13 displays the newly established test system for calcification testing of c cellularized biomaterial.

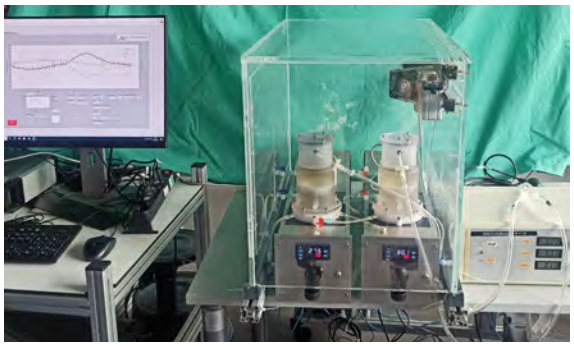

Fig. 13: Calcification test system for cellularized biomaterial.

In cooperation with an industry partner, an in-vitro thrombogenicity assessment of oxygenators was further developed and expanded to compare coated and uncoated oxygenators as well different operating points. Further, the analysis of blood parameters and the oxygenator fiber mats was improved. Fig. 14 shows a dissected fiber mat from an oxygenator after blood contact.

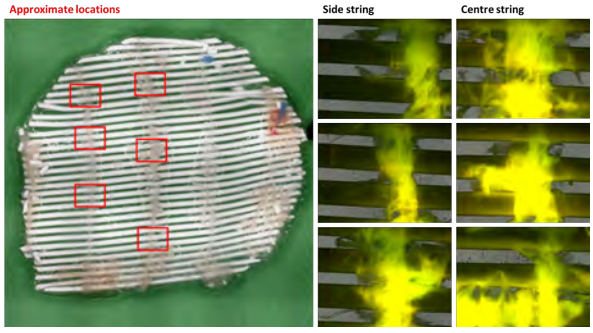

Fig.14: Sample from dynamic preparation scheme. Left: Dissected fiber mat from the RatOx oxygenator in macroscopic image. Right images: Fibrin depositions at and around the warp threads that hold together the individual fibers. Left three images: Thread at the side of the sample. Right three images: Thread in the middle.

Within the field **Modeling & Simulation**, a novel computational methodology for the development of accelerated computational fluid dynamics through non-intrusive polynomial chaos expansion (NIPCE) was created. This technique allows an instant determination of pressure-flow relationship within rotary blood pumps and the calculation of blood damage potential over the entire operating range of the devices.

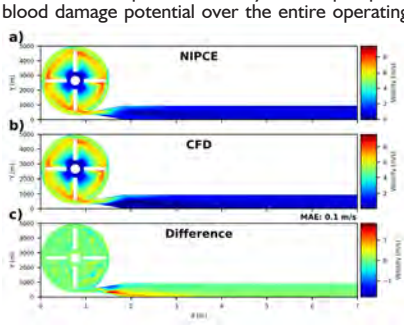

Fig. 15 shows the comparison of the NIPCE methodology with full scale CFD simulations.

Fig. 15: Two dimensional NIPCE prediction of the velocity field (a) on the plane Z = 0.0065 m at the operating point 4 L/min and 3000 rpm. In (b) the corresponding velocity field from the test simulation is shown,where

(c) shows the subtraction from NIPCE and CFD and indicates the mean absolute error of all mesh elements of this plane.

In a second project, performance and hemocompatibility of extracorporeal rotary blood pumps was investigated for low flow operating conditions. For this, a fully parametrized blood pump was developed which allows automatic parameter variation and prototype generation for in-vitro testing, Fig. 16. This setup allowed a systematic evaluation of gap sizes on pump performance for a broad range of operating conditions.

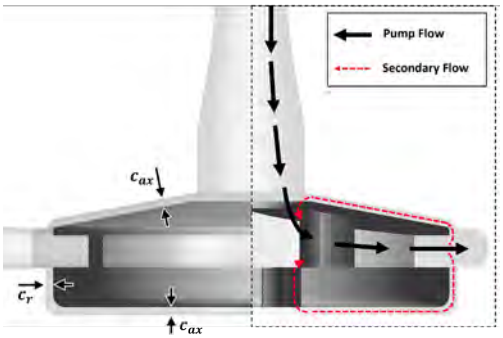

Fig. 16: Cross sectional view of the generic parametric blood pump model used in this study. The lefthand side highlights the adjusted clearance parameters cax and cr for axial gap and radial gap, respectively. The righthand side shows a schematic of the expected blood streams within the pump.

Within the field of **Therapies & Applications**, an optimization algorithm for local variation of structure permeability in 3D TPMS membrane oxygenators (SPP2014 – Towards an implantable lung) was successfully developed. Local flow resistance is altered to achieve homogeneous flow through the oxygenator module. Respective simulations could be validated by the manufacturing of a prototype oxygenator and CT measurement of transient contrast agent distribution (Fig. 17) in comparison to a predicate device (Maquet Quadrox small adult).

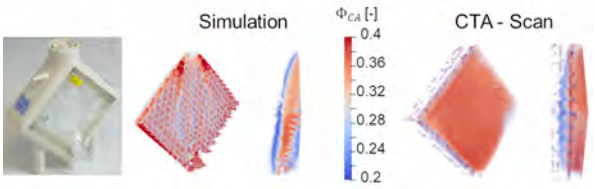

Fig. 17: Simulation and CT scan measurement to assess flow-homogeneity through the oxygenator module of a TPMS prototype with local variation of flow resistance compared to a clinically known predicate device.

As part of a European Consortium within the Perinatal Life Support project, a prototype of the Liquid Filled Chamber approach of the artificial uterus could be successfully manufactured and validated in in-vitro test series. The innovative multi-compartment oxygenator design for artificial placenta application that can account for an increase of oxygen demand due to the growth of the neonate, was successfully tested for gas-transfer and hemolysis levels. Gas-transfer performance exceeded expectation and requirements while maintaining less than 20 mmHg of pressure gradient over the oxygenator, allowing for a pump-less operation of the artificial placenta. Hemolysis levels were found to be comparable to predicate devices but room for improvement was identified. Since the tests were performed using porcine blood, comparability of porcine blood and neonatal blood is currently going to be investigated. An ex-vivo test stand (Fig. 18) for the hydrodynamic testing and ECMO cannulation procedures using donated human umbilical cords was successfully build up and validated. A current study investigates the mechanical properties of human umbilical cords to lay the foundation for future cannula development with respect to artificial placenta applications.

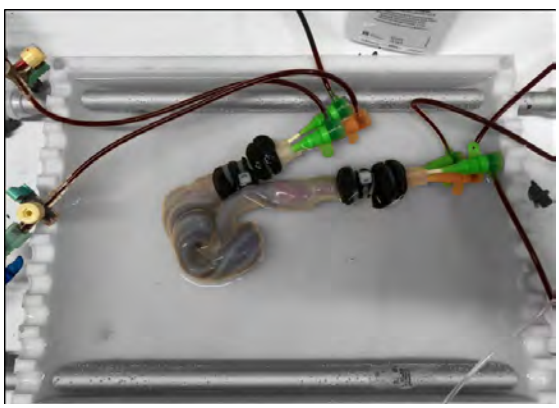

Fig. 18: Ex-vivo test stand for donated human umbilical cords.

An innovative adjustment mechanism of the blade geometry inside a centrifugal blood pump for low flow conditions in Extracorporeal Life Support applications was manufactured and verified in a proof-of-principle experiment. Adjustment of the impeller's blade geometry during operation was found to affect hydraulic performance and to provide the possibility to operate the pump at the highest hydraulic efficiency for each flow setting in contrast to conventional fixed centrifugal blood pumps. Because hydraulic efficiency is associated to blood damage, the active pump adjustment might allow for minimal blood damage over a wide range of flows and reduce current clinical complications in ECMO applications where flow variation is a clinical reality.

Rehabilitation and Prevention Engineering (RPE)

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

The ability to perform controlled movements is the basis for interaction with our environment. The high precision of this interaction results from a complex interplay among the central nervous system, muscles, and environmental feedback and is referred to as Neuromechanics. Analysing physiological and pathological human movements the Department of Rehabilitation & Prevention Engineering (RPE) continuously adds to neuromechanical knowledge and constantly extends its own expertise in this field. This neuromechanical expertise is increasingly being utilized when developing robot-assistive systems for rehabilitation and care. Along with stringent user-centered design, this approach promotes a systematic translation of robotics into clinical application.

The management of muscle activation, learning of new motor skills and ensuring joint stability during the execution of movement is coordinated by the central nervous system (CNS). When performing unfamiliar tasks, the CNS employs two strategies: increased activation of individual muscles (muscular coactivation) or considering a modular approach (muscle synergies). A recent study aimed to examine how muscle synergies and muscle coactivation vary in young adults during familiar and unfamiliar tasks. Findings indicate that in unfamiliar tasks, the CNS mainly relies on muscular coactivation for controlling position and velocity, with muscle synergies becoming less relevant (Fig. 19). Future work aims to assess these changes across age groups and potentially in patients with neuromuscular disorders, providing deeper insights into physiological and pathological muscular control.

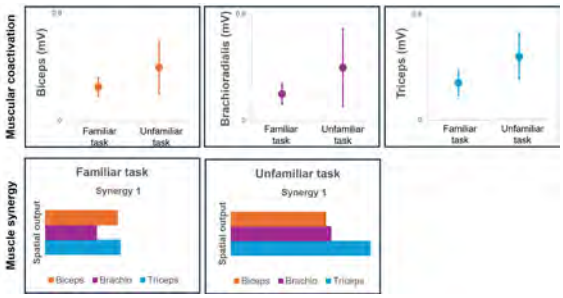

Fig. 19: Muscle activation and synergy for biceps, brachioradialis and triceps during familiar and unfamiliar tasks.

Another study investigated the change in muscular activation due to the use of an end-effector robot-based assistance system during movement tasks involving the upper extremities (Fig. 20). Robot-based assistance systems also offer persons with neurological disorders the opportunity to independently, intensively and accurately to practice their rehabilitation exercises. In order to guarantee fast and successful re-learning of functional movements, the influence of such systems on the motor control of the user must be examined. Using 3D-motion analysis and electromyography, the performance of simulated daily activities was investigated in 3 scenarios: passive, active and no robotic support. During the study, the movement tests presented a challenge for healthy test subjects in terms of both the performance of and adaption to the robot-supported tasks. It was found that robot-assisted tasks presented unfamiliar exteroceptive stimuli, which have a marked effect on the test subjects' muscular activation patterns and thus impact both motor control and motor learning.

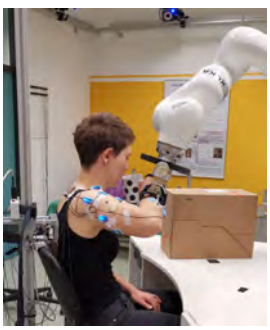

Fig. 20: Usage of an end-effector robot-based assistance system during a movement task.

In the first project phase, PfleKoRo, a robot-based assistance system, was successfully developed to support caregivers during physically demanding tasks e.g. "lifting and holding a patient's limb" and "turning a patient onto her/his side" (Fig. 21). Transferring the results of the prior investigation of the change in muscular activation during rehabilitation exercises, a follow-up study was performed to investigate similar effects during caregiving tasks. Video recordings of caregivers performing the selected activities showed a high degree of compliance and mobility on the part of the carer. It was investigated whether the robotic system should provide a similar degree of compliance to reduce muscular activity.

Fig. 21: PfleKoRo, a robot-based assistance system to support caregivers.

Overall, the results showed lower muscular activation during robotic assistance compared to human assistance. Furthermore, a decrease in muscular activation with low compliance was demonstrated, which was therefore favoured in the system design. The results confirm that assistive robots influence the muscular activation of care recipients and thus have an impact on their comfort during care tasks. The results were directly incorporated into the development of the robot control and the gripping system. In keeping with the project's focus on user-centered design, an evaluation study gathered feedback from caregivers, patients and patients' relatives. Caregivers saw the greatest benefit in particular in the reduction of physical strain, especially on the back, and in the independence from other colleagues. They lauded the approach, the ease of system-handling patients and a willingness to use such a robot-based assistance system in their daily work. While the PfleKoRo system can reduce the physical strain on caregivers during care tasks, the strain of the manual handling of the cart also needed to be addressed. The robotic system is mounted on motorized cart (Fig. 22) for easy maneuverability, to reduce load-bearing and postural adaptations of the spine and to support the daily workflow.

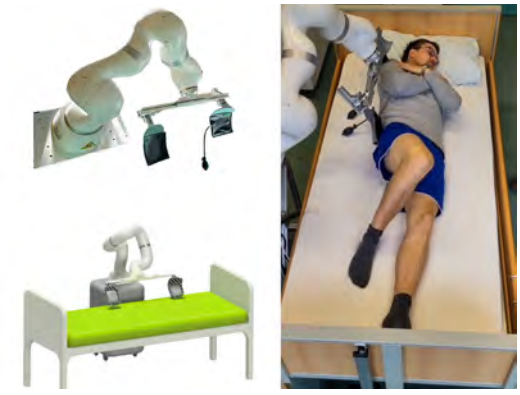

Fig. 22: Implementation of PfleKoRo during a possible caregiving activity.

The effect on spinal curvature of the load pushed and gait velocity was investigated during pushing tasks. 30 healthy participants pushed a handle against varying load resistance while walking at different gait velocities (Fig. 23). The kyphosis angle and lordosis angle, which describe the thoracolumbar curvature of the spine in the sagittal plane were recorded using video raster stereography.

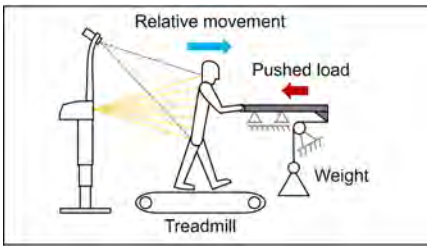

Fig. 23: Experimental set-up to investigate spinal curvature during load pushing.

The results revealed alterations in spinal curvature, including a significant reduction in thoracic kyphosis with increasing load. This study contributes valuable insights into the biomechanics of the spinal curvature during pushing tasks, helping to mitigate the risk of musculoskeletal injuries in manual material handling.

Science Management (SCM)

Dr. Robert Farkas

Artificial intelligence (AI) is arguably one of the most promising innovation for future medicine and technology. Moreover, AI will even advance the innovation process ifself, especially in Translational Science being more than just clinical trials. According to NIH this is about "…investigation to understand the (…) principles underlying each step of the translational process." (https://ncats.nih.gov/translation/spectrum) including the dissemination of findings.
In 2022, the new Medical Device Regulation (MDR) came into force across the EU, which essentially aims to increase patient safety, but threatens the existence of many companies and manufacturers with drastically increased requirements, not least in clinical evaluation.
Thus, we have developed both an AI-based text mining framework that provides initial insights and orientation into the state of clinical knowledge about a medical device in a simple way, and a time-saving service process for interested companies, called 'Digital Compass'.
Inspired by the success with Digital Compass', we conceptualized a novel approach of different search steps, e.g. using Bidirectional Encoder Representations from Transformers (BERT), on different data sources (publications, patents) to finally obtain an AI powered ideation using seed document-based TAR (Technology Assisted Review) innovating medical devices from unmet medical needs (see Fig. 24).
In addition, we continued the collaboration with the local Clinical Department of Internal Medicine I (MK1) focussed on heart failure with preserved ejection fraction (HFpEF), developing of a digital decision support system for early diagnosing HFpEF. Using artificial intelligence and the terminology standard SNOMED CT, structured as well as unstructured data (text) will serve as fundament to train cutting-edge machine learning algorithms for the explainable prediction of the patients risk suffering from HFpEF. The project named DARIO is funded by the German Federal Ministry of Education and Research – BMBF.

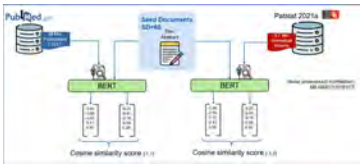

Fig. 24: BERT semantic Search – Implementation on document similarity of publication and patents to enable innovation from unmet medical needs.

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She also won the Research Prize of the West German Respiratory Society (1st Prize).
Claudio Luisi:
yESAO Exchange Award 2023

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Team

Third-party Funding

	Number of Projects	Total Expense of Projects (€)
German Research Foundation (DFG)	56	4.508.951,82 €
German Federal Ministry of Education and Research (BMBF)	31	5.985.652,34 €
EU	10	1.030.869,12 €
Industry	25	753.745,16 €
Other	34	1.276.107,88 €
Sum	156	13.555.326,32 €

Theses

	Number
Bachelor	60
Master	125
Doctoral	21
Habilitation	2
Sum	208

Staff

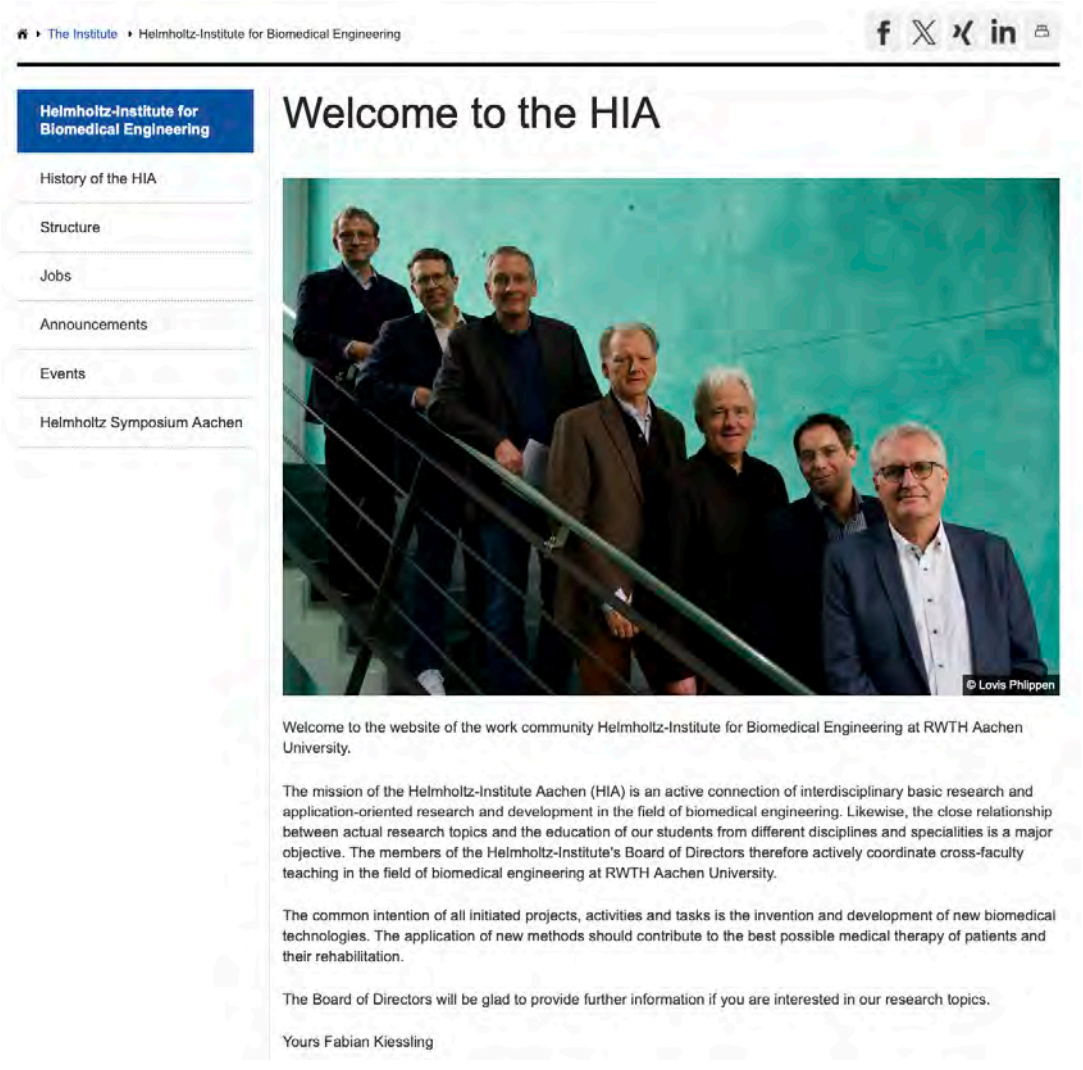
	Scientific	Non-Scientific
Total	194,2	44,6
Third party funded	135,9	11

in full-time equivalent (FTE)

Publications

	Number
Conference proceedings	104
Peer-reviewed journals	187
Books and book chapters	5
Sum	296

Patents and patent applications	19



The Institute › Helmholtz-Institute for Biomedical Engineering

Helmholtz-Institute for Biomedical Engineering

- History of the HIA
- Structure
- Jobs
- Announcements
- Events
- Helmholtz Symposium Aachen

Welcome to the HIA

Welcome to the website of the work community Helmholtz-Institute for Biomedical Engineering at RWTH Aachen University.

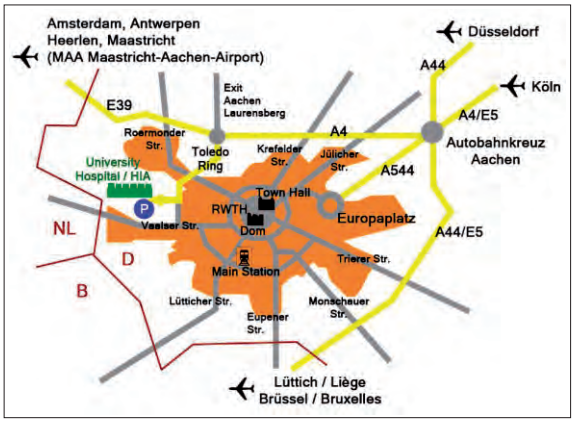
The mission of the Helmholtz-Institute Aachen (HIA) is an active connection of interdisciplinary basic research and application-oriented research and development in the field of biomedical engineering. Likewise, the close relationship between actual research topics and the education of our students from different disciplines and specialities is a major objective. The members of the Helmholtz-Institute's Board of Directors therefore actively coordinate cross-faculty teaching in the field of biomedical engineering at RWTH Aachen University.

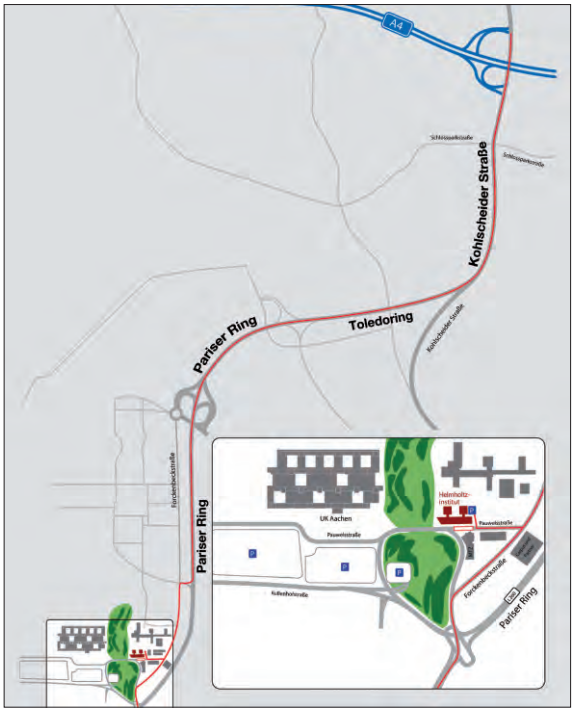
The common intention of all initiated projects, activities and tasks is the invention and development of new biomedical technologies. The application of new methods should contribute to the best possible medical therapy of patients and their rehabilitation.

The Board of Directors will be glad to provide further information if you are interested in our research topics.

Yours Fabian Kiessling

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 (bus stop „Worringer Weg"), the other lines stop in front of the main entrance of the University Hospital (bus stop „Uniklinik"). A short walk (150 m) 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.

Contact

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