Helmholtz-Institute for Biomedical Engineering

Annual Report 2022

RWTH AACHEN UNIVERSITY

UNIKLINIK RWTH AACHEN

Content

Preface

Dear reader, as every year, you receive our annual research report, which presents the achievements of the Helmholtz Institute for Biomedical Engineering, Aachen (HIA) as a hotspot for interdisciplinary basic and applied research and development in biomedical engineering at RWTH Aachen University and beyond. Despite the fact that, as in the previous two years, the Corona pandemic continued to impact our daily life, we can report on many successes in research and teaching in 2022.

After 20 years as chair of the Institute of Biomedical Engineering – Cell Biology, Prof. Dr. Martin Zenke will continue his successful research as senior professor of RWTH Aachen in the Department for Hematology, Oncology, Hemostaseology and Stem Cell Transplantation (Med IV). His position in the board of directors at HIA was taken over by Prof. Dr. Dr. Wolfgang Wagner. Prof. Wagner was since 2009 heading the subunit "Stem Cell Biology and Cellular Engineering" at HIA and since 2022 he is director of the new Institute for Stem Cell Biology. His research team continues to provide expertise and multiple cooperation at RWTH and beyond to control and define cellular differentiation, in aging and disease.

We are happy to announce that two of our researchers, Priv.-Doz. Dr. Ioana Slabu and Dr. Yang Shi, were awarded ERC starting grants in the fields of Applied Medical Engineering and Experimental Molecular Imaging, respectively. We are also pleased about the successful evaluation of the DFG Research Training Group „Tumor Targeted Drug Delivery" and the approval of the second funding phase of the DFG PAK 961 „Model-based Control of Biohybrid Implant Maturation". Moreover, both Clarivate Highly Cited Researchers of RWTH, Prof. Dr. Fabian Kießling and Prof. Dr. Twan Lammers, are members of our institute.

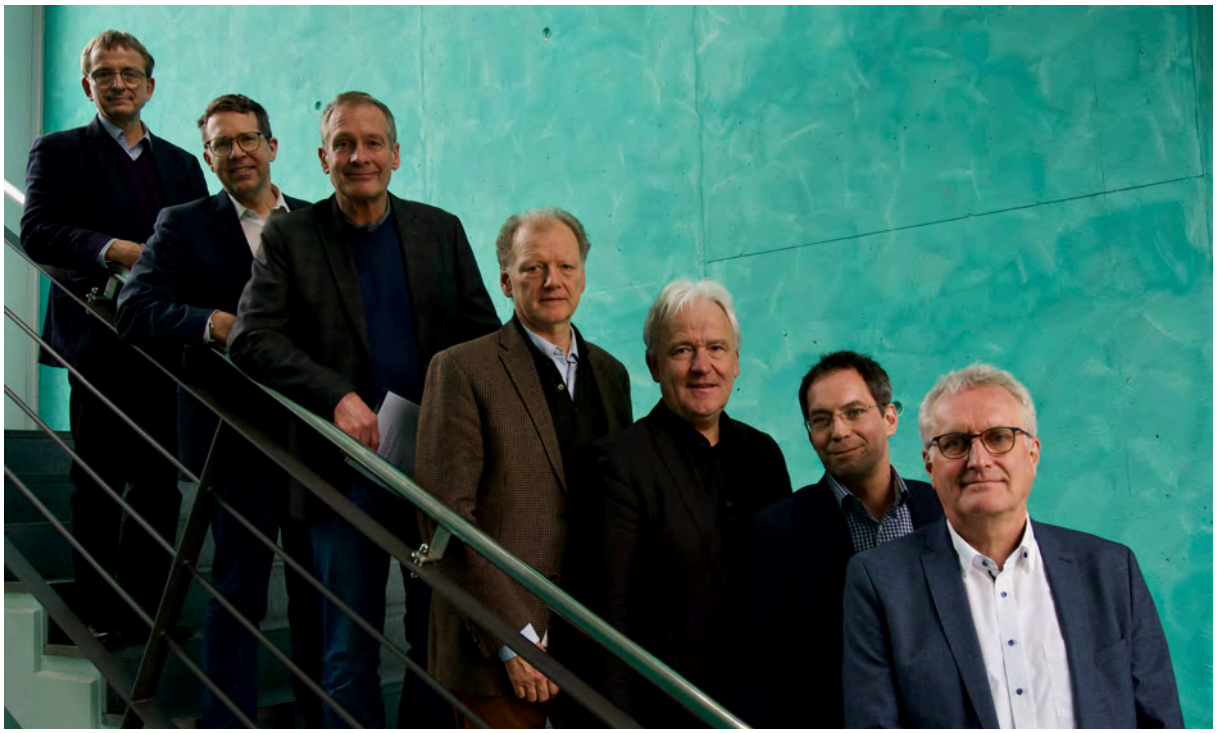
As in the past, the researchers of the Helmholtz Institute have successfully participated in the bachelor's, master's degree and doctoral studies' programs of the medical, engineering, and natural science faculties of RWTH Aachen University and coordinated studies in all areas of biomedical engineering. The practical training of students, conducted in parallel to academic teaching, has proven 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 the biomedical and engineering Master's curricula. This development merely reflects the ever-evolving biomedical and healthcare industry, technological innovations, and societal needs.

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. Networking and cooperation within RWTH Aachen University and with national and international clinicians, academic and industrial researchers are key to our work. Researchers at the Helmholtz Institute for Biomedical Engineering were instrumental in raising funds for research and coordinating teaching. In 2022, third-party funding alone reached well over 13,4 Mio. € .

This 2022 annual report is dedicated to our funders, partners, and friends for their support and cooperation, as well as to all people interested in our institute. Enjoy reading! If you are interested we would be happy to provide you with more information and discuss future opportunities for collaboration in the fascinating field of biomedical engineering.

Aachen, March 2023

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, Willi Jahnen-Dechent, Klaus Radermacher, Wolfgang Wagner, Lothar Elling

STEM CELL SYMPOSIUM

A JOURNEY TO STEMNESS (AND BACK AGAIN)

June 3rd 2022

Lecture Hall 5, University Hospital RWTH Aachen, Pauwelsstrasse 30, 52074 Aachen

Program

14:00 **Welcome**

14:15 **Hans Schöler**
Department of Cell and Developmental Biology, Max Planck Institute for Molecular Biomedicine, Münster, Germany.
Pluripotent Stem Cells: An incredible Journey.

14:45 **Petr Bartůněk**
Institute of Molecular Genetics of the Czech Academy of Sciences, Prague, Czech Republic.
How to change the fate of blood cells.

15:15 **Mathias Heikenwälder**
Division of Chronic Inflammation and Cancer, German Cancer Research Center (DKFZ),Heidelberg, Germany.
"Role of immune cells in driving NASH and in affecting liver cancer therapy response". Learning from a modest giant!

15:45 **Friedemann Zenke**
Computational Neuroscience Group, Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland.
Learning, self-calibration, and neuronal identity in plastic neural network models.

16:15 **Get-together**

This symposium is in honor of the scientific achievements of Prof. Dr. Martin Zenke, who was director of the Institute for Biomedical Technologies - Cell Biology from 2003 to 2021.

Registration

https://forms.office.com/r/2CMETSQF1z

Cell Biology

UNIKLINIK RWTH AACHEN



Institute for Stem Cell Biology

Epigenetic regulation of cell function

Director

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

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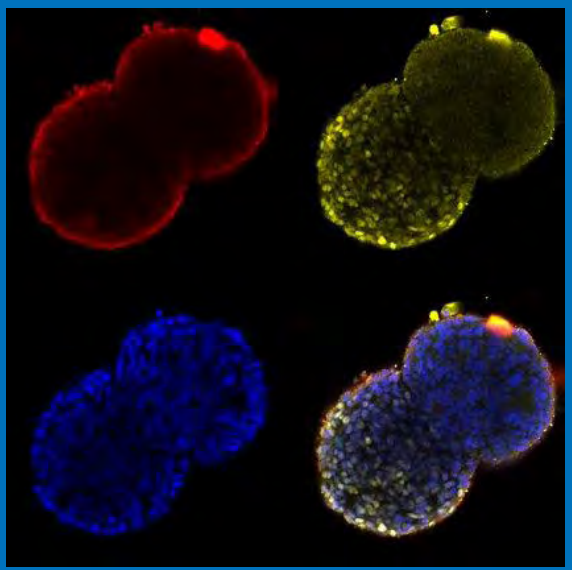


Introduction

Since 2022, the Department for Stem Cell Biology and Cellular Engineering, became the Institute for Stem Cell Biology at the Helmholtz Institute for Biomedical Engineering. Our research aims for a better understanding of how differentiation of stem cells can be directed toward specific cell types. We use healthy and patient-derived induced pluripotent stem cells (iPSCs), as well as somatic stem cells from human tissues. These cell preparations provide powerful model systems to understand molecular mechanisms involved in development, aging, and diseases. A challenge of stem cell research is that the cells are grown and maintained in an artificial in vitro environment. We therefore investigate how culture conditions and biomaterials affect stem cell function. Modulation of surface topography, adhesive properties, and elasticity is evaluated to further optimize culture conditions for tailored cellular products. This research provides insight into how substrates can affect cell growth and differentiation, also for implants in biomedical applications.

Another focus of our work is on epigenetic modifications on the DNA strand. Such modifications ultimately govern processes of cellular differentiation. We utilize a broad range of next generation sequencing and microarray technologies in combination with genome editing tools, such as CRISPR-Cas9, to investigate how cell fate decisions are triggered. The DNA methylation (DNAm) pattern changes at specific sites in the genome during cellular differentiation, ageing of the organism, and cancer development. We utilize these site-specific DNAm changes to establish biomarkers for the cellular composition of cells and tissue, aging processes, and malignant diseases such as acute myeloid leukemia (AML) and myeloproliferative neoplasms (MPN). To this end, we are closely collaborating with various other institutes at RWTH Aachen, particularly at the University Hospital of RWTH Aachen, that provide biomaterials and patient samples. Furthermore, we are external member of the research unit "Aging at Interfaces" (CRU 1506) in Ulm, and leading a consortium on "Genome Wide Analysis of Epigenetic Changes in Aging". We use high throughput multiomics analysis to determine comprehensive epigenetic ageing signatures in mice and human samples. Systematic integration of such data will provide new insights into the interplay of age-associated epigenetic changes and new approaches for healthy aging.

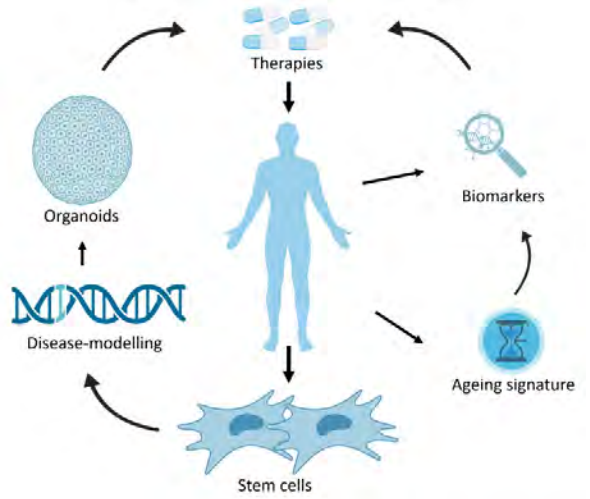


Fig. 1. Schematic overview of different research lines. We aim to better understand underlying molecular mechanisms of diseases to develop new therapies, by culturing stem cells, creating organoids, or by disease modeling with patient-specific mutations. In addition we develop robust epigenetic biomarkers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

In June, we hosted a scientific stem cell symposium "A Journey to Stemness – and Back Again". Four renowned speakers gave fascinating talks that provided new perspectives of pluripotent stem cells, the regulation of the immune system, and neuronal networks for regenerative medicine. This symposium was in honor of the scientific achievements of Prof. Dr. Martin Zenke, who was director of the Institute for Biomedical Technologies – Cell Biology from 2003 to 2021. Prof. Zenke was awarded as senior professorship at RWTH Aachen and remains active in research at the Department for Hematology, Oncology, and Stem Cell Transplantation.

Fig. 2. Speakers at the Stem Cell Symposium. Dr. Friedemann Zenke,

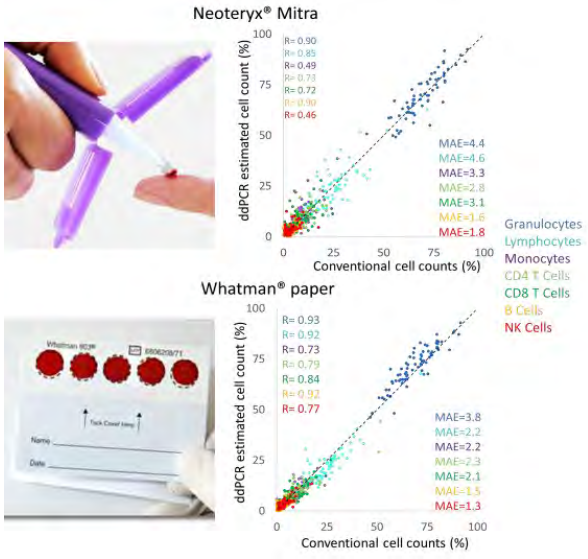
Prof. Dr. Petr Bartunek, Prof. Dr. Martin Zenke, Prof. Dr. Hans Schöler, Prof. Dr. Mathias Heikenwälder

Counting white blood cells by DNA methylation – an innovative method facilitates remote diagnostics from a finger prick.

The composition of white blood cells gives physicians insight into various diseases or infection in a patient. Measuring of these blood cells, such as granulocytes, monocytes and lymphocytes (CD4+ T cells, CD8+ T cells, B cells, NK cells), reflects functions of the immune system. Currently, such analysis can only be performed with fresh blood and therefore patients have to come to the physician in person, which can be an issue for the elderly with restricted mobility. We have developed an alternative approach, referred to as "Epi-Blood-Count" to determine the composition of white blood cells based on DNA methylation at specific sites in the genome (so called CpG sites). We demonstrated that Epi-Blood-Count can accurately estimate leukocyte counts in venous blood (Sontag, Bocova et al., Clin. Chemistry, 2022). To facilitate remote diagnostics, we are now further optimizing the method for dried blood. We first selected new CpG sites based on publically available methylation data from 1303 sorted leukocytes. These were measured in 75 venous blood samples (up to 30μl) dried on Neoteryx® Mitra micro-sampling devices and dried on Whatman® paper (Fig. 3). We could accurately predict cell counts from dried blood with slightly less variation for Whatman paper. The method is currently further optimized to also obtain absolute cell numbers and to validate the remote diagnostic approach with capillary blood obtained from a finger prick. This translational research was initially funded by a VIP+ Project by the BMBF (Bundesministerium für Bildung und Forschung) and now by the Else Kröner Fresenius Stiftung. The method shall be further deve-

loped toward a diagnostic test that enables easy and reliable blood tests for clinical analysis.

Fig. 3: The composition of white blood cells was estimated with Epi-



Blood-Count. Here, capillary blood was taken from 75 patients, comparing Neoteryx® Mitra micro-sampling devices and Whatman paper. DNA methylation was analyzed at specific sites in the genome with digital droplet PCR (ddPCR). Based on the dried blood samples we could accurately predict cell counts for both drying devices. Pearson correlation r is given for each cell type.

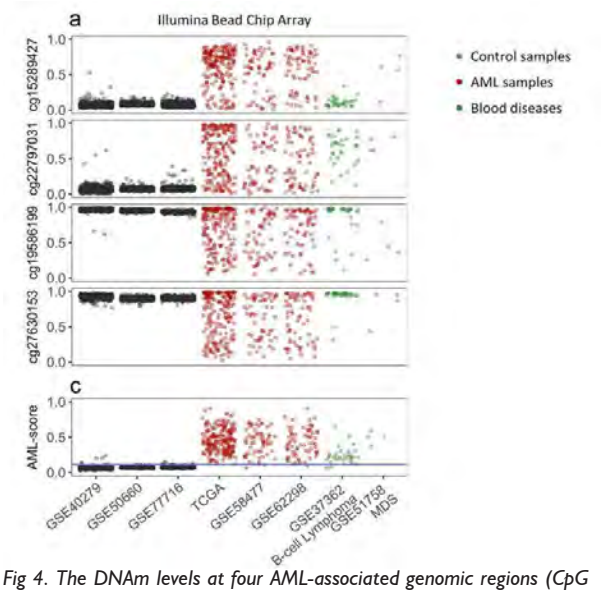


Fig 4. The DNAm levels at four AML-associated genomic regions (CpG sites are indicated by cg15289427, cg22797031, cg19586199, and cg27630153). The AML samples reveal clear differences as compared to control samples of healthy donors (Bozic T, Kuo C-C et al., Leukemia, 2022)

DNA methylation biomarkers to track acute myeloid leukemia

DNA methylation (DNAm) is not only regulating normal cellular differentiation - it is also impacted by many diseases and during cancer development. The most common type of leukemia in adults is acute myeloid leukemia (AML), which originates in the marrow and rapidly spreads to the blood. The disease is often caused by mutations in enzymes that modulate the epigenetic landscape. In fact, aberrant DNAm is a hallmark of AML. With our research, we try to establish reliable biomarkers for disease stratification and prognosis in AML. DNAm data is more stable than other types of biological data (such as gene expression data) but it is largely unclear how the complex epigenetic patterns are co-regulated and how they affect the disease. Using public DNAm data, we identify CpGs positions that frequently reveal aberrations in AML. This is then followed by computational methods, from simple scores based on 4 CpGs (Fig 4) to sophisticated machine learning algorithms to integrate DNAm patterns from neighboring CpGs to develop robust prognostic tools for AML progression. This research shall provide a better understanding how epigenetic aberrations contribute to development of malignancies and provide biomarkers to support diagnosis and for early detection of relapse after treatment.

GermLayerTracker – A new method for quality control of pluripotent stem cells and embryoid bodies

Somatic cells can be reprogrammed into induced pluripotent stem cells (iPSCs), by overexpression of specific transcription factors. One of the hallmarks iPSCs is their ability to differentiate into cell types of all the three embryonic germ layers: mesoderm, endoderm and ectoderm. Quality control of reprogrammed iPSCs should therefore include this trilineage differentiation. Currently, gene expression patterns and immunofluorescence are commonly used for qualitative and quantitative assessment of differentiation, but there is a general need to improve tracking of differentiation potential in vitro. DNA methylation (DNAm) has been shown to be involved in cellular differentiation and manifests early in embryonic development. Hence, it can be used to classify cell types and to estimate tissue compositions. 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 (embryoid bodies). These findings were complemented by gene expression profiles (RNA-seq) and expression of canonical germ layer markers. Based on these datasets, 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 quality control of pluripotent cell preparations and possibly also estimate their propensity to differentiate into specific germ layers. The selected sites are currently validated on different cell lines and differentiation conditions.

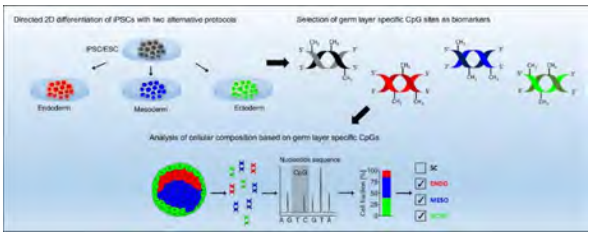


Fig. 5: Adapted from the graphical abstract in Schmidt et al., 2023 depicting the selection of methylation sites for the GermLayerTracker.

Predictors of epigenetic age in mice

Epigenetic changes at specific sites in the genome, particularly in the DNAm pattern, can also be used to monitor the aging process. We have used such epigenetic clocks to estimate the donor age of humans. Such epigenetic predictors can be used in forensics, to estimate the age of unknown blood specimen, and they are also indicative for biological age. A better understanding of epigenetic changes during aging can therefore also provide insight into parameters that impact on the aging process – and thereby support healthy aging. Mice are a frequently used model system for aging research. We used the recently released Infinium Mouse Methylation BeadChip to compare these epigenetic changes in two of the most widely used inbred mouse strains in research: C57BL/6 (B6) and DBA/2J (DBA). We found significant variations in age-related DNAm between these two strains, indicating that epigenetic clocks must be adopted for such inbreed mouse strains. Notably, CpG sites with the strongest age-correlation were overlapping in B6 and DBA – and the homologous regions showed also age-association in humans. Based on these results, we developed a new pyrosequencing-based targeted epigenetic clock for mice with the four relevant regions with very high correlation with chronological age in independent cohorts of B6 and DBA (Fig. 6), which provides a versatile tool for other researchers analyzing aging in mice.

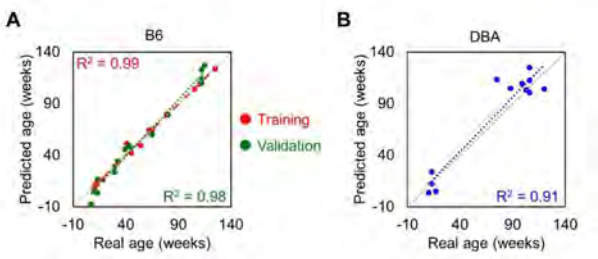


Fig 6. Epigenetic clocks for mouse strains. (A) Chronological age versus predicted age based on a 4 CpG model in the training (n = 15) and validation sets (n = 16) of mice of the C57BL/6 (B6) strain. (B) The same 4 CpG predictor was then applied to DBA/2J (DBA) mice (n = 12). (Adopted from Perez-Correa et al., Front Cell Dev Biol 2022)

YAP1 regulates self-organized differentiation of pluripotent stem cells

Induced pluripotent stem cells (iPSCs) form aggregates that recapitulate aspects of self-organization in early embryogenesis. Within few days, cells undergo a transition from epithelial-like structures to organized 3D embryoid bodies (EBs) with upregulation of germ layer-specific genes. The Yes-associated protein 1 (YAP1) has been suggested to play a crucial role for early embryo development. To gain insights into the function of YAP1 for early cell-fate decisions of human iPSCs, we generated YAP1 knockout (YAP-/-) iPSC lines with CRISPR/Cas9 gene editing and analyzed transcriptomic and epigenetic modifications. YAP-/- iPSCs revealed a normal phenotype in pluripotency, growth, and self-organization of 2D colonies. Gene expression changes – particularly upregulation of NODAL, an important regulator of early differentiation – and epigenetic modifications already pointed to modification of germ layer differentiation. Notably, while directed differentiation could be induced in YAP-/- iPSCs, germ layer specification was clearly impaired upon self-organized differentiation in EBs. This phenotype was rescued via lentiviral re-expression of YAP1 and also by NODAL inhibitors. Our results demonstrate that YAP1 plays a critical role during self-organized germ layer specification of iPSC aggregates and this is at least partly attributed to activation of NODAL signaling.

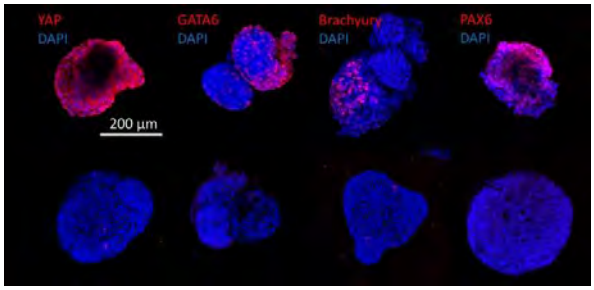


Fig. 7: YAP1 is required for early germ layer differentiation in EBs. Wild-type and YAP-/- EBs were differentiated for five days in serum-containing medium. EBs were stained for YAP1, GATA6 (endoderm), Brachyury (mesoderm), or PAX6 (ectoderm). Nuclei were counterstained with DAPI. YAP-/- EBs do not express germ layer markers. (Adopted from Zeevaert et al., Biomaterials Advances 2023)

Scalable generation and differentiation of size-controlled EBs

Induced pluripotent stem cells (iPSCs) offer several opportunities for drug screening, regenerative medicine, and disease modelling. We are interested in studying the cell fate of iPSCs during early differentiation to various germ layer lineages (endoderm, mesoderm and ectoderm). We developed a system of geometrical pattern of iPS cell culture using micro-contact printing approach with iPSCs. Using this system, we discovered that iPSCs cultured under conditions of geometrical confinement spontaneously detach to form embryoid bodies (EBs) without the need for enzymatic or mechanical treatment (Mabrouk M. et al., Biomaterials 2022). This system allows scalable generation of size-controlled EBs which can be further differentiated to the three embryonic germ layers. Additionally, we are currently employing this approach to study the effect of mechanical cues resulting from hydrogel encapsulation on early germ layer differentiation. Subsequently, we aim to study the impact of externally-applied shear stress on the early differentiation patterns of iPSCs and EBs. However, while EBs closely replicate the temporal events of in-vivo embryonic differentiation, they lack the highly-conserved spatial organization observed during this process. Hence, in parallel, we are establishing a 3D cellular model called Gastruloid from iPSCs which shows both the spatial and temporal aspect of early germ layer differentiation. This research is partly supported by the graduate school "Mechanobiology in Epithelial 3D Tissue Constructs" (ME3T) supported by the DFG.

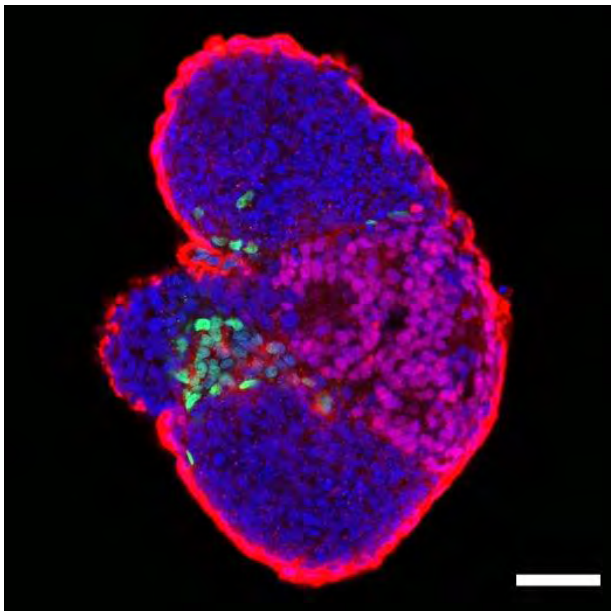


Fig 8: Confocal fluorescence image of spontaneously detaching EBs showing expression of germ layer markers PAX6 and GATA6 (scale bar: 100 µm).

Acknowledgements

This work was supported by:
- German Research Foundation (DFG)
- German Federal Ministry of Education and Research (BMBF)
- German Cancer Aid
- Interdisciplinary Centre for Clinical Research Aachen (IZKF Aachen)
- Else-Kröner-Fresenius Foundation
- Donation by Vision4 Life Sciences

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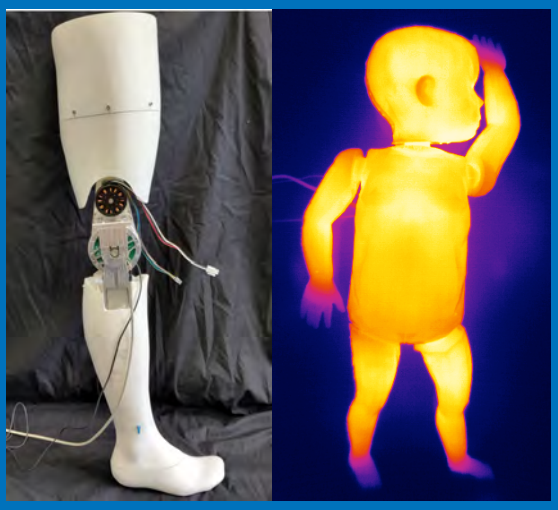
Team

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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Kaufmann, Jan, Electronics Technician
Noor, Soufian, Software Developer
Trödel, Cedric, Software Developer
Warkentin, Astrid, Software Developer
Weike, Katharina, Software Developer

Guests

Prof. Stefan Borik (UNIVERSITY OF ZILINA) visited the chair from the 1st of July to the 31st of October 2022.

Introduction

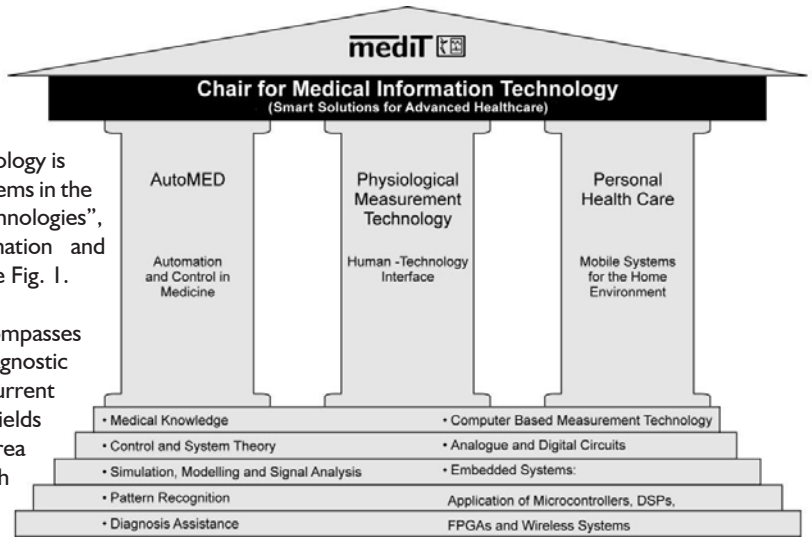

Fig. 1: Research profile of MedIT.

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.

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

Camera-based Early Detection of Blood Poisoning in preterm infants

The occurrence of sepsis in preterm infants is one of the most critical complications in the neonatal intensive care unit (NICU) and poses a major threat to mortality and long-term morbidity. Due to the rapid progression, the mortality rate increases by 7.6 \% every hour in which the therapy is delayed. Therefore, advanced monitoring systems are crucial for an early prediction of the sepsis onset.

Today, various vital parameters are recorded using contact-based measurement techniques such as ECG and PPG. In this context, the immature skin of the preterm patients and the associated inefficient barrier to the environment are major issues, because the infant can be additionally injured or infected during the replacement of the adhesive electrodes. The use of non-contact techniques for continuous monitoring of vital signs can facilitate the situation for both the medical staff and the patients by measuring the medical parameters without direct skin contact with camera-based devices. These systems could therefore reduce the prevalence of diseases such as sepsis. By using a camera-based system for vital parameter monitoring, the first signs of septic shock could be detected automatically.

The project SIRIO focuses on the fusion of two unobtrusive measurement techniques, Photoplethysmography Imaging (PPGI) and Infrared Thermography, which can be applied in the NICU, see Fig. 2. While PPGI enables the recording of heart rate and perfusion in the tissue and additionally a quantification of the microcirculation, Infrared Thermography indicates the radiation of the body's own heat of the patient. This allows local temperature distributions and central-peripheral gradients to be recorded and analyzed for sepsis prediction. Furthermore, the system could enable the monitoring of respiration rates and physical activity, which provides further information about the medical condition. In combination with data-driven Deep Learning-based algorithms for real-time image processing, the data fusion of the camera system enables the derivation of an early warning parameter directly at the incubator. Therefore, an early start of therapy can be realized, which significantly improves the healing and survival chances of neonatal patients.

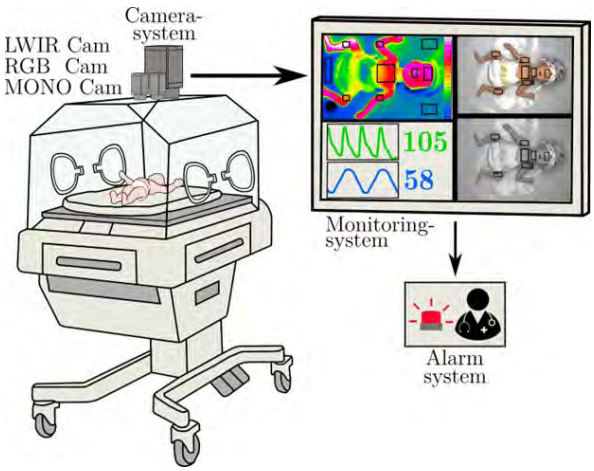

Fig. 2: Schema of the SIRIO project, combing Photoplethysmography Imaging (PPGI) and Infrared Thermography.

Funded by: German Research Foundation (DFG)

Non-invasive Monitoring of the Peripheral Arterial and Venous Oxygen Saturation with contact-based and camera-based Photoplethysmography

Deficient oxygenation in tissues causes hypoxic cell damage, which is critical in vital organs such as the heart and brain. Under normal physiological conditions, oxygen delivery and consumption relate to each other; however, microcirculatory dysfunctions such as diabetes mellitus and sepsis can alter the cohesion between oxygen supply and consumption. Thus, determining these factors is crucial for the early diagnosis of tissue abnormality. In blood circulation, blood flows to the organs via arteries and returns to the heart and lungs through veins. Therefore, oxygen consumption in the organs can be determined by the difference between its saturation in arteries and veins.

In this project, we are developing a non-invasive monitoring system for arterial and venous blood to estimate oxygen saturation and further detect circulatory diseases. For that, photoplethysmography (PPG) is used, a technique in which the skin is illuminated with two specific wavelengths to distinguish the absorbing properties of oxygenated and deoxygenated hemoglobin. PPG is obtained through contact-based sensors and through video images from a commercial webcam, which works as a PPG sensor that captures reflected red, green, and blue light. The novelty of our technique to monitor venous blood relies on the „venous muscle pump“, which considers dorsal ankle extensions at a fixed frequency for generating easily identifiable venous blood volume variations, see Fig. 3.

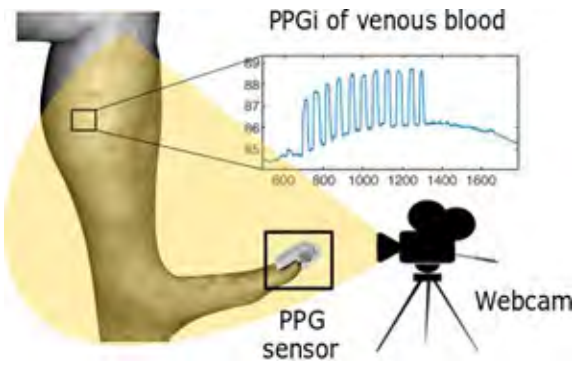

Fig. 3: Venous blood volume variations acquired through a contact-based PPG sensor and a commercial webcam during the „venous muscle pump test“ (dorsal ankle flexion) to estimate the venous oxygen saturation.

Several aspects are investigated within this project. Firstly, image and signal processing are needed to acquire the PPG signals of arterial and venous blood pulsations, plus filtering and a removal of motion artifacts, through conventional and machine learning-based algorithms. Secondly, physiological and mathematical models based on Monte Carlo simulations need to be developed to estimate the oxygen saturation from the signals. Besides, a pressure cuff placed on the calf/finger can be controlled through a self-made hardware system to artificially generate venous blood pulsations at a regulable frequency and pressure. Finally, the arterial and venous blood circulations must be simulated on a mock loop with a regulable blood pump, ECMO oxygenators, a pressure cuff, and an artificial dynamic skin consisting of many layers and blood vessels, see Fig. 4. Thus, the arterial and venous oxygen saturations can be monitored with PPG under in-silico configurable circulatory and skin conditions.

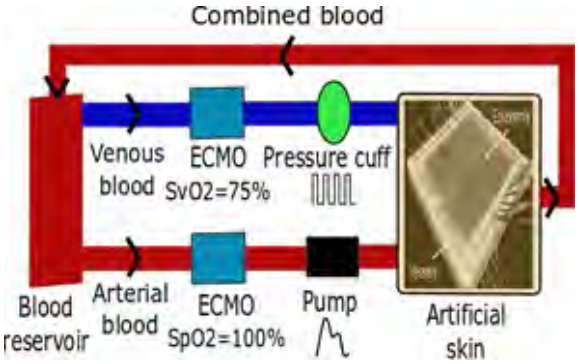

Fig. 4: Blood circulation simulating mock-loop with a regulable blood pump, ECMO oxygenators, and an artificial dynamic skin and blood vessels to monitor oxygen saturation with a PPG sensor under configurable conditions.

Funded by: German Federal Ministry of Economic Affairs and Energy (BMWi)

Automated Phrenic Nerve Stimulation with Mechanical Ventilation

Humans use primarily their diaphragm to breath, but it is not active during traditional mechanical ventilation. This inactivity can lead to ventilator-induced diaphragmatic dysfunctions (VIDD) which is associated with 30 \% of mechanically ventilated patients who are difficult to wean from the mechanical ventilator and to 10 \% who face prolonged weaning. These patient types account for 40 \% of total intensive care unit (ICU) patient-days. To ensure diaphragm activity, the phrenic nerve (nerve of the diaphragm) can be stimulated artificially. Together with Uniklinik RWTH Aachen, this project aims to develop a closed-loop system, which controls the phrenic nerve stimulation and the mechanical ventilation. The closed-loop system has to keep the patient in a safe condition and stimulate the diaphragm adequately to prevent VIDD. An overview of the closed-loop system is shown in Fig. 5. The stimulator generates electrical impulses, which are transmitted through electrodes near the phrenic nerve.

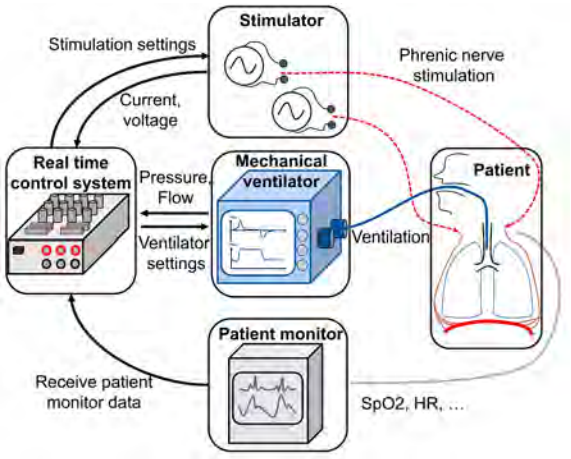

Fig. 5: Overview of the closed-loop system with parallel phrenic nerve stimulation and mechanical ventilation.

These impulses cause the diaphragm to contract, and the patient takes an artificially generated spontaneous breath. The real-time control system receives measurements from the stimulator, the mechanical ventilator and the patient monitor. The stimulator measures the voltage and current during the stimulation impulses; the mechanical ventilator measures the airway pressure and the flow in and out of the lung; the patient monitor measures the patient's condition such as the heart rate (HR) or the peripheral oxygen saturation (SpO2). Based on these measurements, the real-time control system adjusts the settings of the stimulator and the mechanical ventilator.

This critical application imposes challenges on the overall system. The least invasive method to place the electrodes near the phrenic nerve must be found. An error of the stimulation and mechanical ventilation control algorithm could be fatal. An over stimulation may lead to muscle fatigue in the diaphragm. The stimulator and the mechanical ventilator must act coordinated to prevent further damage to the lungs and the diaphragm. To overcome these challenges, several control techniques like robust control, adaptive control or model predictive control are considered.

Funded by: German Research Foundation (DFG)

Hemocompatibility of left ventricular assist devices under pulsatile operating conditions

Heart failure is one of the main causes of mortality in the developed world. Nowadays, heart transplantation is the gold standard therapy for terminal-stage heart failure. However, the number of donor hearts is significantly lower than the existing need. Therefore, heart failure patients are frequently treated by implanting a mechanical left ventricular assist device (LVAD). An LVAD supports the failing heart by pumping an additional amount of blood from the left ventricle to the aorta. Nowadays, most LVADs are rotary blood pumps, which are operated at a constant speed.

One of the most important parameters to assess the hemocompatibility of LVADs is hemolysis. LVAD-induced hemolysis denotes the destruction of red blood cells due to their exposure to the artificial pumping mechanism. Much work has been dedicated in the past to optimize the pump geometry in this respect. Within this research project, we now want to investigate if hemocompatibility can be improved by optimizing the dynamic control of the LVAD.

Fig. 6 depicts a mock circulatory loop according to the ASTM F1841 standard, which can be utilized to assess the hemocompatibility of LVADs. The blood flow within the loop is controlled by the rotational speed of the LVAD and the head pressure by an automatic tube clamp. Typically, porcine blood is circulated for 6 hours within these loops and blood samples are drawn once per hour. The blood samples are then assessed for plasma-free hemoglobin, which is a marker for hemolysis. In the future, these loops will be utilized to assess the hemocompatibility of LVADs under pulsatile operating conditions. At first, we will analyze isolated pump speed pulsatility and subsequently, the loop will be extended to also mimic remaining heart activity.

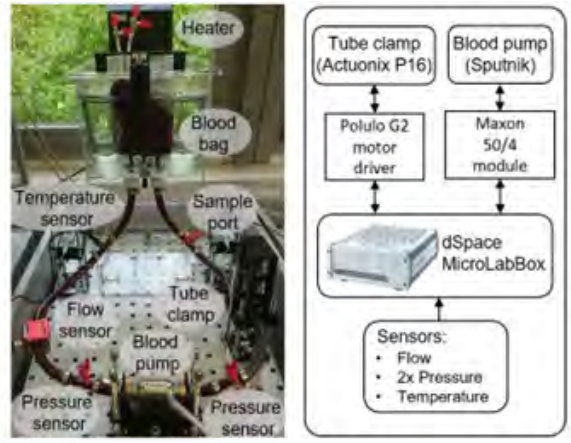

Fig. 6: Mock circulatory loop according to the ASTM F1841 standard equipped with an axial-flow LVAD. The operating conditions (head pressure and pump flow) are automatically controlled using a dSpace MicroLabBox.

Funded by: German Research Foundation (DFG)

Estimation of Force and Torque Development based on Dynamic Muscle Properties

Especially in old age, the decline of muscular units for example due to Sarcopenia results in a significant decrease of independence and thus, life quality. Besides, the constant increase in life expectancy in wealthy countries establishes new challenges for the health case systems. Therefore, non-invasive measuring modalities to assess the muscle's condition and performance are highly demanded for therapy planning.

Recently, a combination of Electrical Impedance Myopgrahy (EIM) and Electromyogram has shown to be promising to assess the muscles geometric, physiological, and metabolic

properties. Nevertheless, both approaches are highly sensitive to the applied electrodes placement. Accordingly, we performed comprehensive Finite Element Method (FEM) modelling analysis to define an optimal electrode placement, focusing on the activity of one specific muscle group, see Fig. 7.

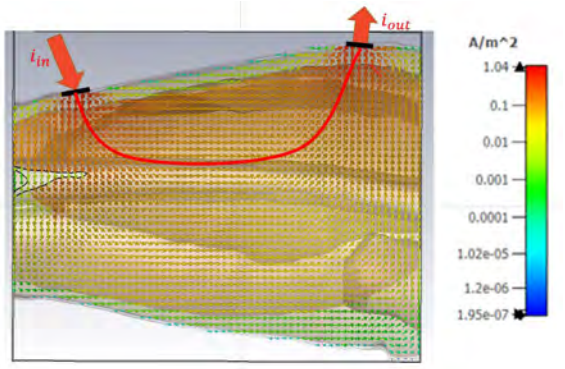

Fig. 7: Simulation of the impact of the applied current feeding on the resulting current density distribution.

Another interesting question is the impact of different kinds of muscle activity on the measured EIM and EMG signal. For instance, a passive lifting assess the state of minimal contraction, contraction without lifting quantifies the muscle's contraction mechanism, and most other daily movements are combinations of both. To enable a delimitation of passive and active forms of muscle contractions, we designed and assembled a passive test-bench for the lower extremities, enabling continuous monitoring of torque, angle, EMG and EIM signals during leg curls, see Fig. 8.

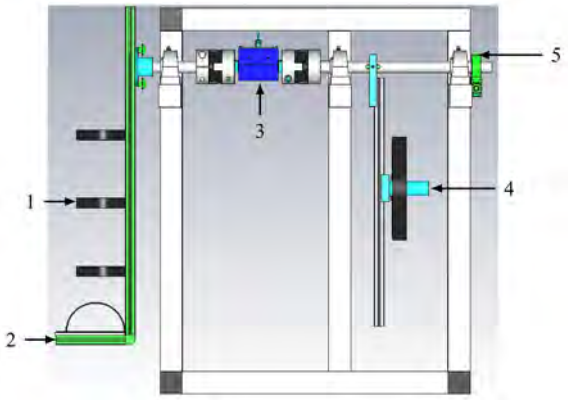

Fig. 8: Schematic of the assembled test-bench, consisting of fixation belts (1), foot-attachment (2), torque sensor (3), counterweight (4) and angle sensor (5).

In combination, the fine-tuning of electrode placement and the performance of guided movements in a limiting environment shall provide deeper insights into the superimposed geometrical and physiological processes, shaping EIM and EMG signals. In the future, their relation to the dynamic process of muscle contraction and relaxation potentially paves the way for new kinds of muscle function tests.

Funded by: German Research Foundation (DFG)

Data fusion for continuous health monitoring of vehicle drivers

Many traffic casualties can be traced back to driver fatigue, drowsiness or other exceptional physiological states such as heart attacks and strokes. Due to the ageing demographics, such physiological problems can be expected to increase. Especially in partly autonomous vehicles, it is crucial to monitor the fitness of a vehicle driver, since the driver must be capable of taking control over the vehicle at any moment. With respect to the elderly, in-vehicle health monitoring also closes the loop of personal health care at home for early detection of diseases.

For personal health care applications, unobtrusive sensing technologies on different modalities are typically used and are embedded into everyday objects, such as driver seats or driver cabins. Such sensors can include capacitive electrocardiography (cECG), ballistocardiography, magnetic induction sensors, radar and camera-based techniques. Due to their unobtrusiveness, these sensors often suffer from a reduced signal quality and motion artifacts.

Apart from developing new, improved sensors, the measured signals must be processed accordingly to extract as much information as possible. For that, data fusion techniques can be employed on three different levels to combine the different sensor modalities, see Fig. 9.

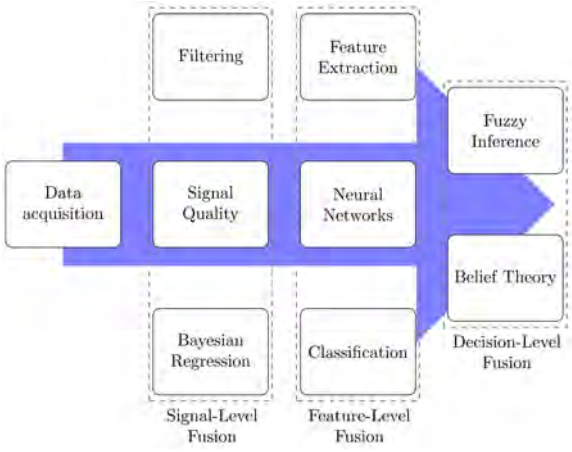

Fig. 9: Process of data fusion with examples for each level.

First, Signal-Level Fusion can be employed on the raw sensor signals to increase the coverage and accuracy of the estimation of vital signs, such as heart rate and breathing rate. Second, Feature-Level Fusion can be applied on previously extracted features such as heart rate, breathing rate or ECG shape to classify the health status of a driver with respect to different diseases. Third, Decision-Level Fusion can be used to decide whether the driver is fit for driving or not, and further measures can automatically be taken into action. These measures can include the coffee cup symbol, often used nowadays to point out drowsiness or fatigue, with the recommendation to take a break. Yet, telemedicinal approaches could also be an appropriate measure in case of a heart attack or a stroke, wherein their detection might be combined with the automatic notification of an ambulance. In the latter case, the car could also automatically drive into a safe location to prevent car accidents.

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Prizes and Awards

- K. Weike has been awarded the graduation award 2022, by IHK Aachen.
- M. Walter and the team of the PV1000 have been awarded with the Best Paper Award, by VDI Mechatronik.
- The medIT team have been awared with the 2-nd place, during the RWTH FH Sportsday
- During the 26th International Student Conference on Electrical Engineering POSTER, the medIT has been rewarded with the 1-st (P. Borchers), 2-nd (I. Badiola) and 3-rd (F. Röhren) place in the session Biomedical Engineering. Besides, in the session Informatics and Cybernetics the 3-rd (L. Bergmann) and in the session History of Science with the 3-rd place (C. F. Benner).

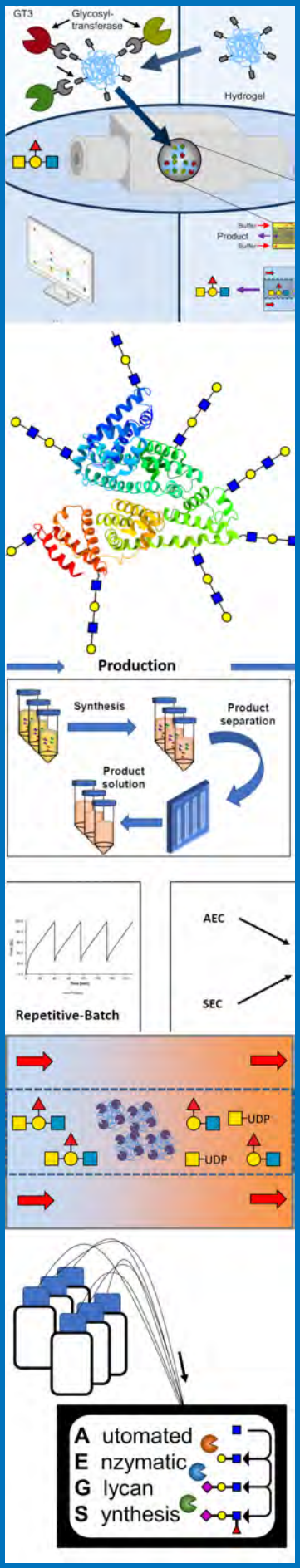
The MedIT Team

BioTEC mat 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 a group of covalently attached monosaccharides that are carried on glycoproteins, glycolipids, and proteoglycans. The complex glycan structure constitutes the extracellular matrix (ECM) and coordinates many cell-cell and cell-ECM interactions. Glycan-binding proteins such as galectins decode glycan-specific tumor and pathogen (bacteria, viruses) glycan patterns and trigger the respective cell response. They serve also as tools for analyzing and detecting glycan structures. Human milk oligosaccharides (HMOs) are essential in building the intestinal defense against pathogens in infants and display a considerable market in the food industry. Polysaccharide biopolymers are widely used in cosmetic products and the pharmaceutical industry. Sugar-based biomaterials are therefore a vital topic in material sciences and biomedical research with the potential to support the scientific community with intriguing new technologies and methods. In 2022, we intensified our research projects on the synthesis and application of glycoconjugates. We started to transfer our enzyme cascades to new large-scale processes starting with developing new techniques for enzyme immobilization and stabilization. We aim to conduct continuous production platforms of oligosaccharides with Leloir-glycosyltransferases (Fig. 1), supported by our projects on the large-scale production of nucleotide sugars. We further developed novel galectin-based biosensors to enhance the analytical variety of glycan patterns. This chapter summarizes the most recent results from our peer-reviewed publications in 2022.

Combinatorial Biocatalysis

Enzymatic Synthesis and Production of Nucleotide sugars

Nucleotide sugars are precious products and are used for a variety of glycosylation reactions conducted by Leloir-glycosyltransferases. They are mainly obtained by chemical synthesis but can also be deducted from large cell culture lysates. However, even if the synthesis pathways for the nine main nucleotide sugars are known, enzymatic production processes are still scarce. Furthermore, most of the established enzyme cascades lack industrial-relevant information such as space-time yield ($gxL^{-1}h^{-1}$), the substrate conversion rate (yield), and total turnover numbers (gP/gE).
In addition, only a few examples demonstrate the gram-scale production of nucleotide sugars. Enzyme cascades of the nucleotide sugar salvage pathways are mostly applied and start from simple sugars. This eases most of the processes with a small set of different enzymes and opens the window of opportunity to assess critical process parameters as such as pH, buffer, and temperature. In our recent review, we displayed the synthesis cascades for the nine main nucleotide sugars and gave more profound insights into the workflow of nucleotide sugar production and purification (Fig. 2)[1]. We performed the gram-scale synthesis of GDP-fucose (GDP-Fuc) in a repetitive batch mode. Here, GDP-Fuc was either produced with an ATP regeneration system using polyphosphate or with ATP excess to maximize the synthesis productivity. With ATP excess, ADP-activated fucose (ADP-Fuc) appeared as a side product, which diminished GDP-Fuc production. However, the repetitive batch mode demonstrated that GDP-Fuc could successfully be produced on the gram scale[2].

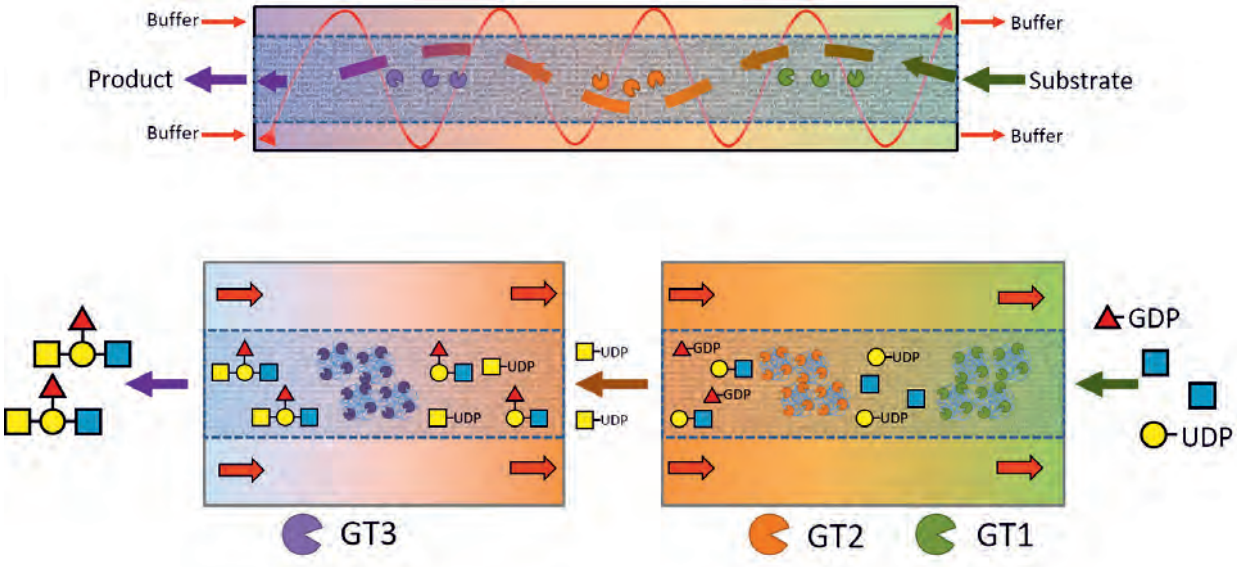

Fig . 1: Production of the blood group antigen A epitope with glycosyltransferases and nucleotide sugars in a continuous counter-current flow reactor system.

In contrast to these repetitive batch processes, in which dissolved enzymes are retained by a membrane and are thus reusable, another way to reuse enzymes is through their immobilization. A simple method is to use the His_6-tag of the enzymes, which is mostly already used for purification via IMAC for immobilization

on magnetic beads. This has the advantage that the enzymes can be quickly and efficiently retained via magnetism and separated from the reaction mixture (Fig. 3). By immobilizing the enzyme cascades for the production of UDP-GlcA and UDP-GlcNAc on magnetic beads, we achieved full turnover for the two nucleotide sugars in a repetitive batch process [3].

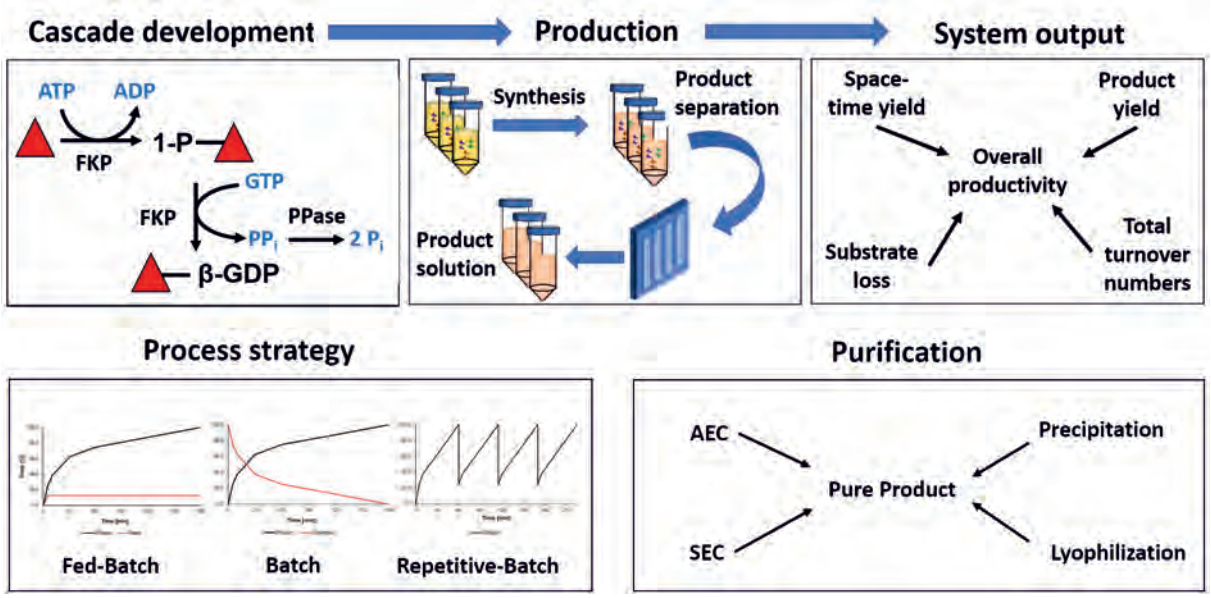

Fig. 2: Process development of an enzymatic cascade for the production of nucleotide sugars.

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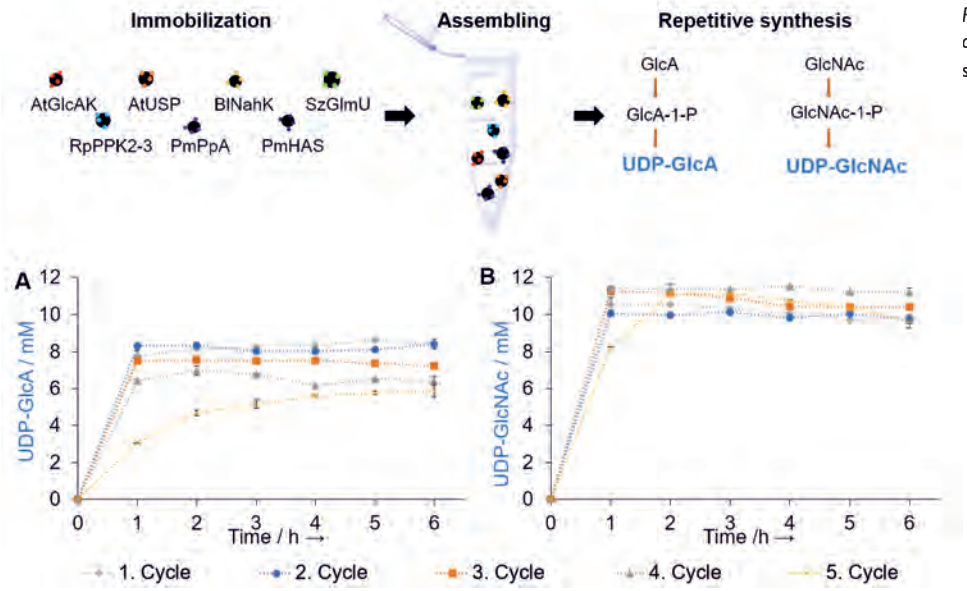
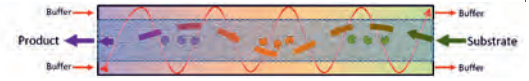


Fig. 3: Immobilization of enzymes on magnetic beads for nucleotide sugar synthesis.



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) and the KMU-Innovative-17 project: "Multi-Enzym-Membranreaktor für die Synthese von hochmolekularen Hyaluronsäure-Polymeren für Kosmetik und Medizin" (AZ: 031B0104B).

Automated Enzymatic Glycan Synthesis

Glycans are oligosaccharide structures that range from simple linear chains to branched moieties with high complexity. They are bound to glycoproteins and glycolipids and are specific to species, tissues, and cell types. Glycans, which are found on the surfaces of eukaryotic and prokaryotic cells, play a crucial role in essential physiological processes like cell-cell interactions, viral and bacterial attachment, cancer escape, and metastasis. They are also involved in the immune response. Moreover, the proper function and mediation of intracellular and extracellular processes of soluble glycoproteins, therapeutics, or prebiotics are highly dependent on the correct glycosylation.

Due to the fact, that the majority of the recombinant production of therapeutic proteins and monoclonal antibodies takes place in hosts that do not glycosylate proteins with human glycosylation patterns, post-translational *in situ* glycosylation on an industrial scale has gained increasing interest in recent years. Here two different general approaches were established. While chemical glycan synthesis relies on complex multi-step reactions in extreme conditions and produces only low product yields but also a lot of toxic by-products, enzymatic glycan synthesis is viewed as a more promising strategy by recent research.[4] Here, different structures are built stepwise by reactions catalyzed by different enzymes, namely glycosyltransferases, glycosidases, or glycosynthases. The composition of different sugar chains or branches is determined by the respective enzyme, sugar acceptor, and sugar donor.

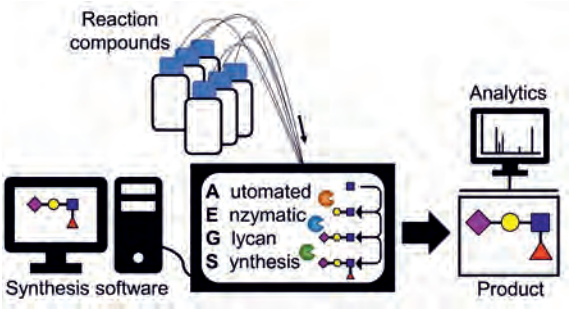


Fig. 4: Overview of Automated Enzymatic Glycan Synthesis (AEGS). Reaction compounds are mixed in a bioreactor. The reaction parameters are controlled by synthesis software. The final product is analyzed in a suitable device.

In contrast to the chemical synthesis of glycans, enzymatic strategies have the advantage of achieving regio- and stereoselective glycosylation in single-step reactions and under natural non-toxic conditions, superseding excessive protection of different sugar groups and a global deprotection of the product. The combination of multiple enzymes leads to the production of different sugar structures in cascades (Fig. 4). Step-by-step synthesis can be a tremendous challenge; therefore, automated synthesis is a valuable alternative to established one-pot strategies[5].

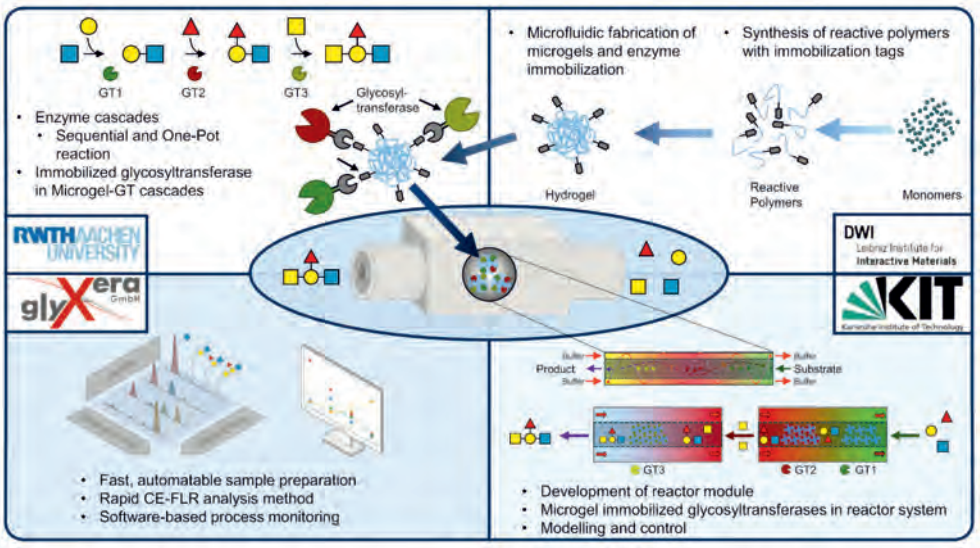


Fig. 5: Concept of MiRAGE. Microgel-immobilized glycosyltransferases are embedded in a microreactor. Fast at-line analysis allows in-process monitoring and intervention of synthesis.

The BMBF-funded project "microgel countercurrent flow reactor for automated glycan synthesis with immobilized enzymes" (MiRAGE) is a joint effort with collaboration partners from academia and industry.
Our envisaged solutions include scalable concepts for the immobilization of enzymes with compartmentation of enzymatic cascades for the production of glycans and simultaneous, continuous removal of by-products, combined in an automated, countercurrent flow reactor [6].
In the interdisciplinary project MiRAGE we aim to establish an automated countercurrent flow reactor for enzymatic glycan synthesis by microgel-immobilized glycosyltransferases (Fig. 5). Industry and academia partners from the Laboratory for Biomaterials of the RWTH Aachen University, the Institute for Technical and Macromolecular Chemistry of the DWI Leibniz Institute for Interactive Materials, the Institute of Functional Interfaces of the Karlsruhe Institute of Technology (KIT), and the glyXera GmbH work on different tasks in this collaboration. Our solutions include scalable concepts for the immobilization of enzymes with compartmentation of enzymatic cascades for the production of glycans and simultaneous, continuous removal of byproducts, combined in an automated, countercurrent flow reactor (Fig. 5). In our group we establish an enzymatic toolbox of different glycosyltransferases for the synthesis of complex glycan structures in cascades. Partners from the DWI provide microgels for the immobilization of enzymes in an aqueous environment. Microgel-immobilized glycosyltransferases are embedded in a bioreactor, developed by the KIT partner. Fast at-line analysis of glycan products and intermediates is realized by glyXera GmbH[6].

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Financial Support

Financial support from the Federal Ministry for Education and Research (BMBF) for the project "Microgel countercurrent flow reactor for automated glycan synthesis with immobilized enzymes (MiRAGE)" (AZ: 031B1116A) as part of the BMBF program "Future Technologies for the Industrial Bioeconomy: Focus on Biohybrid Technologies"

The Glyco-BioInterface

Galectin fusion proteins for cell and tissue targeting

Galectins belong to the family of carbohydrate-binding lectins that fulfill essential physiological functions. The upregulation and overexpression of galectins frequently point to cancerogenesis or inflammatory processes. Galectins are useful tools in biotechnology for the development of biomaterial coatings. The thorough investigation of interactions between galectins and glycomaterials provides the foundation for our understanding of the binding specificities of galectins. At various molecular levels, several solid-phase, in-solution, and structural methods have emerged in recent years[7]. The biotechnological application of galectins often necessitates the addition of functional domains. Different galectins (Gal-1, Gal-3, Gal-8N/C) were used in our research as fusion proteins with a His_6-tag, a fluorescent protein, and a SNAP-tag [8] (Fig. 6). We created glycoprotein-decorated affinity resins to obtain pure and active binding fusion galectins. In addition, we used binding assays to investigate the galectin's binding to extracellular glycoproteins like collagen IV, demonstrating their potential for upcoming applications in cell and tissue targeting.

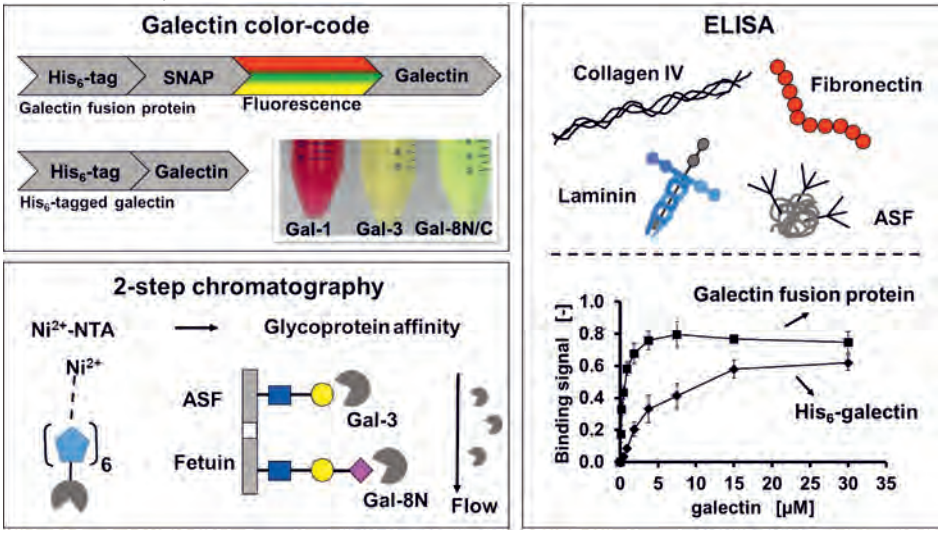
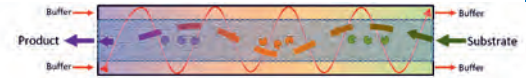


Fig. 6: Galectin fusion proteins (structure, purification, and binding analysis).



Synthesis of multivalent glycoconjugates for the inhibition of Galectin-4

Gal-4 is associated with increased metastasis and cancer progression in liver and lung cancer. Thus, inhibition of Gal-4 binding to cancer-related 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 carrying blood group antigens. Our group developed syntheses for Lewis-type blood group antigens resulting in novel multivalent (neo) glycoconjugates. Fucosyltransferases are critical for the large-scale enzymatic synthesis of fucosylated glycans.

The study of two mutant α3-fucosyltransferases (α3FucT) from *Helicobacter pylori* showed that various parameters influence the behavior and fucosylation pattern, such as the type of glycosidic bond within the LN subunits, the location of the LN subunits, and the additional α2-fucosylation at the terminal galactose[9]. Furthermore, we successfully identified *N*',*N*''-di-acetyllactosamine (LacdiNAc) as a new substrate for the α3FucTs and optimized the synthesis for quantitative yields [9]. With the start of the DFG project "GlycoMatGal", the poly-*N*-acetyllactosamine (poly-LacNAc) based library will be extended chemo-enzymatically by ABH blood group antigens (Fig. 7).

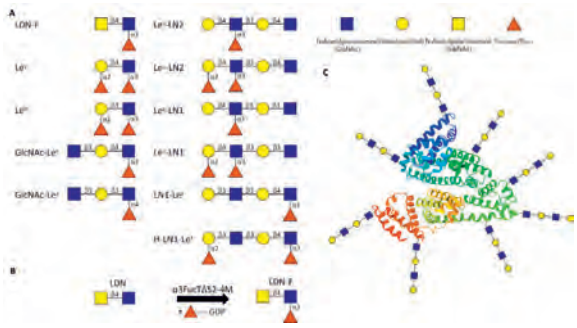


Fig. 7: Blood group antigens and multivalent glycan presentation on human serum albumin for Gal-4 inhibition.

These will be tested for their specific binding to Gal-4. Multivalent coupling of such glycans to human serum albumin will provide neo-glycoproteins for specific and selective detection of Gal-4 in body fluids and inhibition of Gal-4 binding to cell surface glycans.

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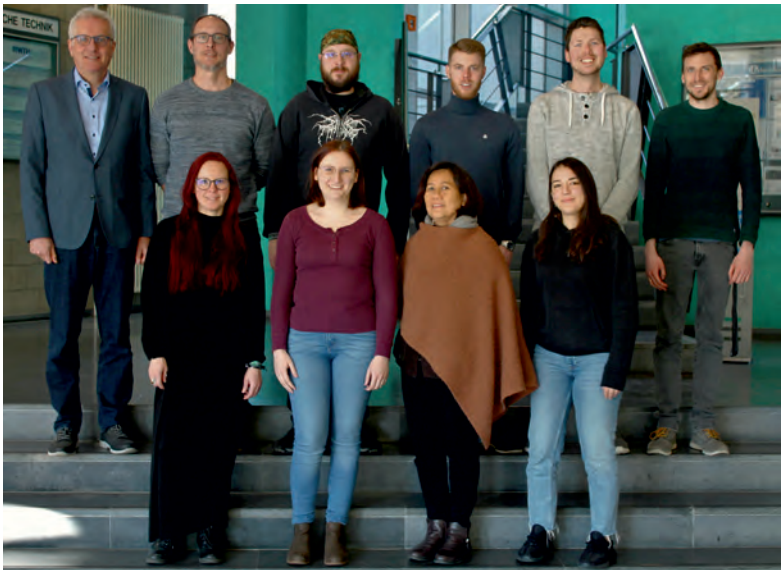
Financial Support

Financial support from the Deutsche Forschungsgemeinschaft (DFG) within the framework of the Collaborative Research Center (SFB 985) – Functional Microgels and Microgel Systems as well as from the DFG and GAČR (Czech Republic) within the bilateral project "Chemoenzymatic synthesis of selective multivalent neo-glycoproteins for galectin-4 inhibition – GlycoMatGal (EL 135/19-1, GAČR 21-00505J) and networking support from the EU-COST action CA18103 is gratefully acknowledged.

OUR TEAM



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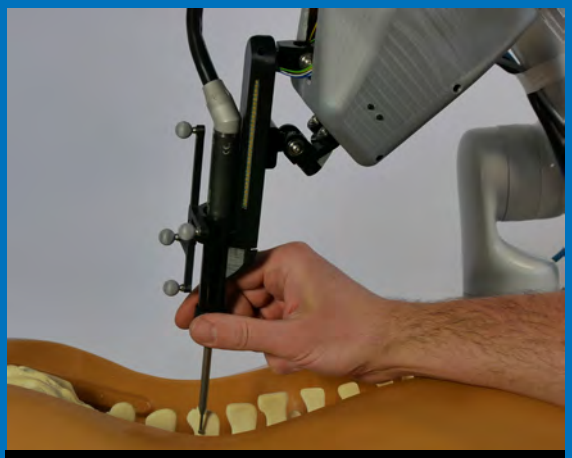

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Introduction

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.
In 2022 the pandemic situation continued to challenge our team regarding teaching as well as research and resumed international conference activities. Especially our novice students and younger colleagues, even not knowing "normal" live and cooperative work, suffered from the ongoing demanding boundary conditions. However, based on established networks and our long-lasting cooperation with international partners from research, industry and clinics, we have been able to succeed in creating fertile ground for diverse ongoing as well as new projects.
This annual report summarizes some examples of our project work.

Selected Projects
Biomechanics of HTO

Open-wedge high tibial osteotomy (OWHTO) is used for the treatment of unicompartmental (medial) osteoarthritis in varus knees, especially in young to middle-aged, active patients. The procedure represents a relevant alternative to unicompartmental knee arthroplasty (UKA) and total knee arthroplasty (TKA). Advantages of OWHTO include joint preservation (delay of TKA) and a higher functionality e.g., a higher range of motion postoperatively. However, HTO is more challenging and requires extensive planning. Due to limited resources and methods, the biomechanical effects of the different HTO variants are not comprehensively considered in the planning process. Therefore, a workflow for easy and fast simulation of (OW)HTO biomechanical outcome could substantially support the planning process, and may help to find individualized targets for (OW)HTO cutting parameters. Together with our clinical partners (MUM-LMU, Munich), we perform simulation analyses of knee kinematics and loading after different OWHTO variants. With the simulation of the biomechanical outcome, the surgeon can be supported in decision-making during the planning of the deformity correction.

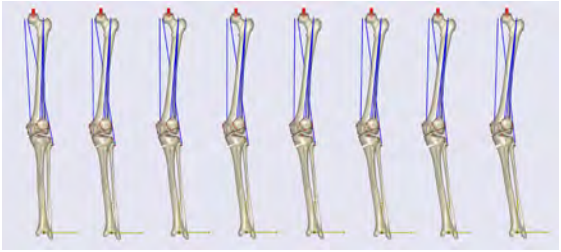


Fig. 1: Individualized simulation models for one cadaveric knee for different OWHTO variants

3D robotic ultrasound of the Knee

Surgical interventions on the knee joint such as for example personalized implants for the hip (THA) and knee (TKA) or deformity correction surgery can benefit from 3D imaging and 3D reconstruction of surface models of bone structure. In order to plan the correct shape and position of implants or cuts, a 3D model is required. Gold standard for its acquisition is computed tomography (CT), which exposes the patient to radiation. Ultrasound (US) is investigated as an alternative imaging modality that provides fast, inexpensive and widely available imaging. A pipeline for fully automatic and robust bone modelling was developed and evaluated in a small-scale in-vivo study with 10 probands together with our clinical partner (Luisenhospital, Aachen).

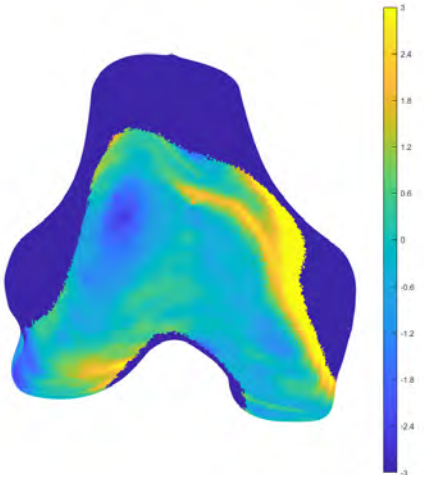


Fig. 2: Distal femur reconstruction based on free hand ultrasound imaging compared to the MRI reference.

However, free hand ultrasound imaging results are highly user dependent and continuous image-based probe pose optimization with respect to the scanned bone surface is very demanding. In contrast, a near real time image processing and automatic robotic probe guidance based on machine learning algorithms can address these bottlenecks. Position information can directly be obtained for referencing of the images and a high reproducibility is feasible.
Initially, for a fully autonomous process, the region to be scanned has to be recognized and autonomous robot path planning must be performed. Subsequently, the robot must follow the path and maintain a defined contact to the skin, while optimizing its orientation for optimal ultrasound-based acquisition of bone surface.

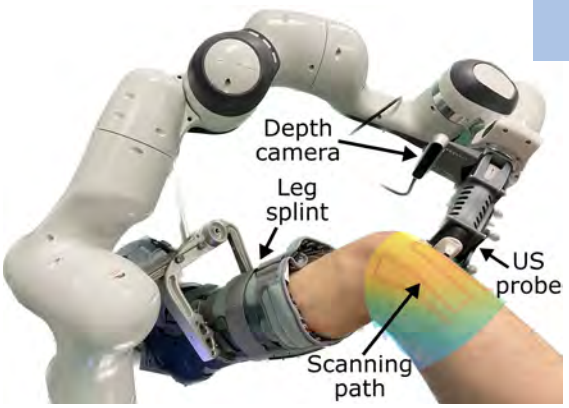


Fig. 3: Setup for autonomous robotic ultrasound scan of the knee

Ultrasound-assisted Scaphoid Fixation

Scaphoid fractures are predominant in young males and are often caused by a fall on the outstretched hand. For the percutaneous fixation of scaphoid fractures with an osteosynthesis screw, fluoroscopy is conventionally used to guide screw placement. However, screw placement based on projective imaging is challenging and furthermore exposes patient and medical staff to harmful radiation. To address these drawbacks, we proposed a fast and fully automated, navigated approach based on intraoperative ultrasound imaging. Recently, this approach was evaluated in an in-vitro study on carpal phantoms together with our clinical partners (UKB, Bonn), which demonstrated the successful and seamless integration to a surgical workflow. Pre-clinical ex-vivo and in-vivo studies are subject of ongoing work.

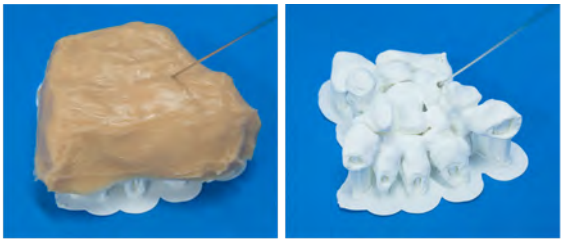


Fig. 4: Carpal phantom with (left) and without (right) silicon soft tissue model overlay as used in the in-vitro study.

Morpho-functional analysis for THA

Morpho-functional preoperative analysis for total hip arthroplasty (THA) is an important aspect to enable an optimal planning and implantation of the hip prosthesis. In order to investigate the impact of patient specific preoperative pain and movement restrictions subjectively assessed by the patient, score values from questionnaires, such as the Harris Hip Score can be used. In retrospective clinical studies, the relationship between these parameters and the postoperative functional parameter pelvic tilt have been investigated. The analysis of the impact related to further activities of daily living (ADLs) is subject to ongoing studies with our clinical partners (Nigata Hip Joint Center, Niigata, Japan and Charité Medical University Center, Berlin).

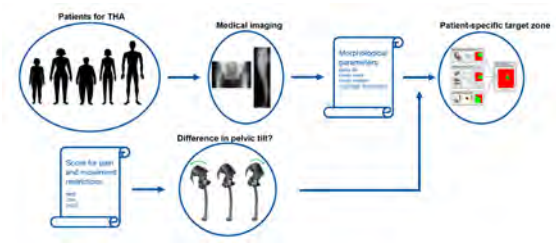


Fig. 5: Workflow for integration of pain and movement restrictions in the preoperative planning process for THA

Robotic Gripper for Surgical Instrument Handling

Robotic handling of contaminated surgical instruments during cleaning and sterilization could protect staff from infection risk and compensate for staff shortage. The robotic gripper handling the instruments are contaminated, leading to potential risks of cross-contamination between instruments. Therefore, the gripper must be cleaned regularly. Ideally, the cleaning can be automated and can take place after one shift of 8-9 hours. The duration of usage contradicts the requirement to clean surgical instruments 5 hours after use, after which dried contamination might make cleaning impossible. Therefore, we investigated if we could design a robotic gripper enabling a secure gripping and handling of contaminated instruments while being optimized for cleanability. We developed a gripper design for toolless disassembly and cleanability. Afterward, we tested the design according to DIN EN IST 15883-1 by applying sheep blood, cleaning the gripper using a standard cleaning cycle in a cleaning and disinfection machine, and taking samples by applying sodium dodecyl sulfate to the surfaces of the gripper.

Fig. 6: Gripper designed for toolless disassembly (left), test contamination with sheep blood (right)

The samples were evaluated using a fluorescence measurement. The results showed a protein level below the required threshold of 100 μg, even after a drying time of 10 hours. The gripper is an integral part of the ongoing development of a robotic workstation for pre-processing contaminated instruments.

MINARO DRS: A Dual Robot System with Haptic Control

Combining the high dynamics of a miniature application-specific parallel robot for machining of bone, with the large workspace of a serial robot arm for prepositioning, the Minaro DRS enables flexible use in the OR. The demonstrator system incorporates an off-the-shelf light-weight serial cobot arm and the custom developed

distal parallel mini-robot for a burring task in case of laminectomies for spinal decompression.

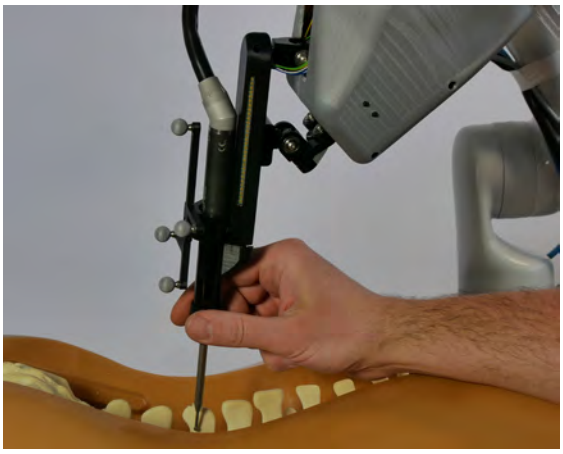


Fig. 7: Hands-on Minaro DRS for spinal decompression.

In order to preserve the sensitive structures right underneath the bone (dura mater and spinal cord) while removing the thin laminae efficiently, highest accuracy of the robotic system together with efficient surgical control is essential. Cooperative control was implemented to transcend the accuracy boundaries of computer-assisted surgery from image acquisition, planning, and registration. The robotic system's precision, which is much higher than its accuracy due to the abovementioned issues, is combined with the intra-operative visual control of the surgeon during hands-on or optionally telemanipulated synergistic control.

Model Based Risk and Usability Engineering for Cooperative Surgical Robotics

In bone surgery specialties like orthopaedic-, maxillo-facial-, and neurosurgery cooperative robotic assistance can support surgeons by reducing task workloads and support surgical plan implementation. Internal and external performance shaping factors (PSFs) need to be considered when designing cooperative robotic assistance systems. Design decisions during early development phases have a large impact on final device usability and cost. Modelling the of the underlying processes and systems potentials can support the identification of risks and support evidence-based design decisions in early development stages. Analyses are performed based on a common process description, which allows to identify application requirements and analyse system integration. Standardized ranking scales were derived by engineers and surgeons that allows to assess the characteristic workload of surgical tasks with respect to human resources and performance shaping factors to find root causes of excessive workloads and latent error conditions. Modelling the clinical work system and workflows in Matlab Simulink and System Composer, the modular approach allows to separately parametrize surgical process requirements and system properties and analyse system behaviour with respect to defined hazards. Standardized process macros on the one side and variant system components for different technical assistance systems on the other allow iterative system adaptations and tests in early design stages. Model validation is possible in later-design phases when data from unit tests is available. The modular approach allows to flexibly extend the model quality with respect to prediction scope and accuracy.

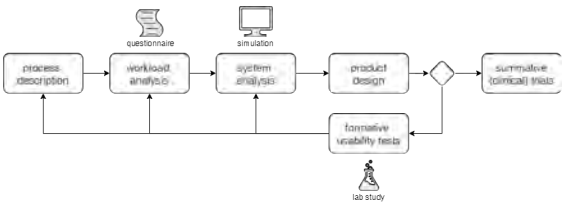
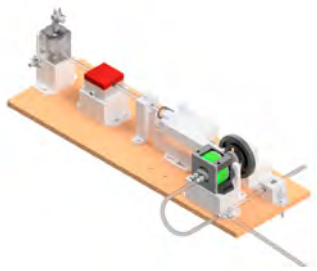


Figure 8: Workflow for process-based risk and usability analysis during early stages of cooperative robotic assistant development

MR compatible pump for PC-MRI flow validation

Phase-contrast MRI (PC-MRI) enables non-contact flow measurement of blood or cerebrospinal fluid. Conclusions about pathological changes can help to diagnose diseases (e.g. normal pressure hydrocephalus). Although measurements have been performed on both healthy subjects and patients for many years and significant changes have been seen, the accuracy of PC-MRI was questioned. In order to be able to quantify the accuracy of the measurement method, an MR-compatible pump was developed together with our clinical partners (CHU, Amiens, France). The drive was realized by a pneumatically driven pump using rapid prototyping. The entire setup is composed of 3D printed MRI compatible components. In addition, the speed can be adjusted by the air pressure and the flow profile can be modified by the cam geometry.

Fig. 9: Pump-setup PC-MRI flow validation.



Design method for acoustic lenses for piezoelectric shock wave transducers

The increasing number of indications for extracorporeal shock wave therapy (ESWT) makes it necessary to adapt the generated sound field to the specific requirements of the treatment. In wound treatment, for example, a more extensive area is treated, whereas in tissue ablation a defined treatment area can be advantageous. We developed and evaluated an acoustic lens design method to arbitrarily adapt the sound field used for ESWT. An iterative method for lens design using the principle of phase shift was adapted and validated for spherical piezoelectric ESWT transducers. It offers the possibility to create both symmetrical and asymmetrical target sound fields. Additionally, the acoustic properties of various lens materials were determined. Sound field simulations with MATLAB k-wave and in-vitro measurements in water were performed to evaluate three different lenses.

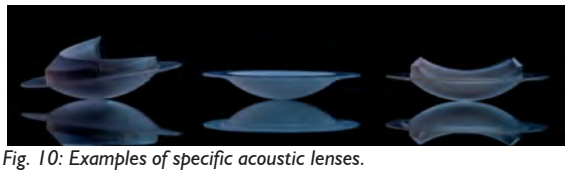


Fig. 10: Examples of specific acoustic lenses.

The validation of the new method using a complex target image showed comparable results to an iterative method for planar sources reported in the literature. Three lenses were designed to shift the focal position and to enlarge the treatment area and were fabricated using rapid prototyping. The simulated and measured sound fields were in good accordance. With the lenses, 80-90% of the energy of the original sound field was obtained in the target plane. However, the lenses distributed the energy of the originally highly focused sound field more widely. Nevertheless, clinically relevant peak pressures were reached. The new method is well suited for spherical sources and arbitrary target images, with asymmetric solutions leading to improved results. The designed lenses show good results for transient input signals such as those generated by ESWT devices and thus provide a cost-effective and easily interchangeable option for sound field adaptation.

Safe and ergonomic control of surgical devices through recommendation software

This increases complexity and number of technical devices in the OR can lead to confusing or dangerous situations. For example, many devices come with their own foot switch unit, which occupies floor space and creates tripping hazards. Surgeons have to observe the situs and therefore may confuse foot pedals, leading to erroneous triggering of functions. Timely access to a function like bipolar coagulation is paramount to patient safety. The ISO IEEE 11073 SDC standard for interoperable medical device communication is key standard to address the related issues. Human-Machine interfaces can now address multiple manufacturer's devices and interact with them reliably. However, the enormous potential of this technology raises new questions. In an OR setup where various device functions can be controlled through multiple user interfaces, defined restrictions must be applied so that control is safe, usable and complies with existing regulations. Therefore, an automated recommendation system for surgical control interfaces is one objective of our research. It builds on specifying user interface profiles. With this new software tool, surgeons and other clinical staff can configure their control inputs prior to surgery, associate mappings with different workflow steps and save everything to their own user profile which can be deployed to any operating room. Changes during surgery are possible unless any safety-critical function would be made unavailable through that change. The system's knowledge of the ongoing procedure, involved medical devices, critical steps and even patient state can be incorporated to optimize controls and risk management.

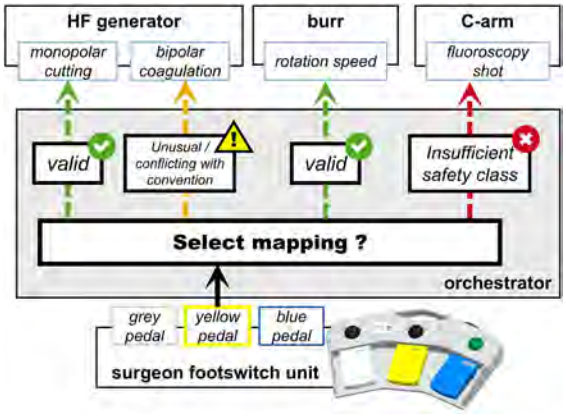


Fig. 11: Mapping options for a control element.

To assure that a certain mode of operation has been considered during risk management and usability engineering, the manufacturer may provide a machine-readable „rule book" for their device. It lists the requirements for each controllable parameter or human interface element. The rule book may include hard limits as well as dissuasive notifications for mappings which are not strictly forbidden but may lead to subpar usability. The tool may also serve the purpose of checking the compatibility of a newly compiled ensemble prior to surgery. The objective is, to decrease the time needed to configure medical devices and human interfaces for surgery, while maintaining inherent usability and risk engineering standards. The evaluation of this approach is subject to ongoing studies together with our industrial and clinical partners (University Clinic Aachen) as well as in close contact with notified bodies and FDA.

Process Optimization through Integrated medical devices in the operating room and clinic

Several studies identified the Operating Room (OR) as costly to maintain, but on the other hand the OR is also the most profit generating department. In the PriMed research project concepts to increase the overall efficiency and patient safety have been developed and evaluated. Medical device manufacturer can now be interoperable by following the 2019 approved ISO IEEE 11073 SDC communication standard. SDC defines the syntax and semantic, the technical description of medical devices as well as responsibilities and requirements network participants have to fulfil, to be an interoperable network participant. Workflow analysis have been performed with the OR-management and surgeons (University Clinic Aachen). Functional models of user interfaces have been developed and evaluated as part of a central surgical SDC workstation. Presently, using proprietary systems does not allow to collect relevant data and therefore i.a. hinders the preparation of protocols during an operation. Automatic documentation through interoperability helps to save important time, and potentially improves clinical processes by increasing the efficiency and safety. A concept for workflow step specific device settings has been developed and evaluated with clinical users. Further optimization and implementation into OR.NET demonstrator OR in our institute is subject to ongoing work.

Fig. 12: Evaluation setup in our OR.NET demonstrator

Awards

We congratulate Sergey Drobinsky for the award for patient safety in medical engineering of the Action Alliance Patient Safety. We also congratulate Sonja Grothues for the Emerging Researchers Award of the ISTELAR Foundation.

Acknowledgements

We would like to thank all our clinical, technical and industrial partners for the fruitful cooperation*.
Apart from basic funds and industrial cooperations, in 2022 our research has been substantially funded by:

- the German Federal Ministry of Education and Research (BMBF)
- the German Federal Ministry of Economic Affairs and Energy (BMWi)
- the German Research Foundation (DFG)
- the European Union, the European Regional Development Fund (EFRE), the Ministry of Innovation, Science, Research and Technology and the Ministry of Economic Affairs North-Rhine-Westphalia

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

Selected Publications

[1] M.C.M. Fischer, P. Damm, J. Habor & K. Radermacher: Effect of the underlying cadaver data and patient-specific adaptation of the femur and pelvis on the prediction of the hip joint force estimated using static models. Journal of Biomechanics, 2022, 139, pp. 110526

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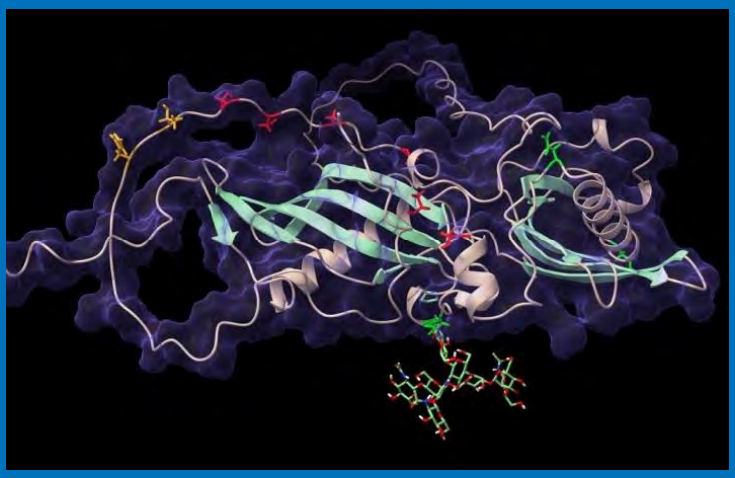
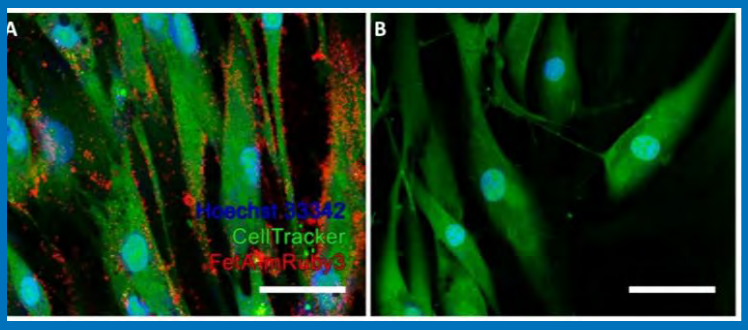
Biointerface Laboratory at Helmholtz-Institute for Biomedical Engineering

RWTH AACHEN UNIVERSITY

Faculty of Medicine

Cell-Material Interactions: Translating Basic Science Into Clinical Applications





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Cover Figures:

***Cover Figure Top**, it happens to the best, it happens to the rest – and it takes a while to recover from COVID, in this case 10 days to be exact, until the antigen test turned negative. Back to work!*
***Second from above**, getting an ever more detailed view of our poster child protein - Fetuin-A modelled with Alphafold including post-translational modifications glycosylation and phosphorylation*
***Third from above**, back to work as well for recombinant Fetuin-A-mRuby fusion protein, an excellent probe to stain early stage mineralization in cell based mineralization and calcification assays.*
***Bottom**, woman without fear - PhD student Anna Bartz casually handling a female Nephila spider. This animal will procure hundreds of meters of silk thread for three-dimensional scaffold materials if handled tender and with care.*

Introduction

Willi Jahnen-Dechent, Professor

We finally made it through the COVID pandemic, taking shots and required precautionary measures. Still, many of us eventually succumbed to the virus and whoever has not, will certainly do in the near future. COVID has lost its sting. I wish we could say the same of the war in Ukraine, which hopefully will also end sooner than later. In this case however, precaution and protective measures don't cut it – we just have to be patient, resolved and united until this madness ends.
Right here and now we continue to study the structure and function of the mineral chaperone Fetuin-A, the development of devices and assays for calcification testing, the role of stem cells and precursors in tissue healing as well as the study of innovative biomaterials to improve tissue engineering, all of which is presented below.
We welcome Sarah Kellner to the office. She took over from Renate Sous who for 20 years flawlessly administrated in our group personnel, reporting, student teaching, exams, research funds and social events. Renate will fill in once a week to secure a smooth transition. A big Thank You, Renate! Sabine Neuß-Stein and her team moved from the Institute of Pathology to the Biointerface labs and offices, a very welcome move indeed. This marks a renewed interest in cell-material interactions fully in line with our very label "Biointerface Laboratory".

Stem Cells and Tissue Engineering

Sabine Neuß-Stein, Professor

In 2022, we could further develop our MSC recruitment system for in situ tissue engineering, which avoids the time- and money-intensive conventional tissue engineering approach with isolated and expanded cells that are seeded on a three-dimensional scaffold to substitute a tissue function. The main research focus of the group is still the role of human mesenchymal stem cells (MSC) in wound healing and tissue engineering. To more accurately release MSC chemoattractants and direct the stem cells towards a damaged location, we now use this recruitment approach for endogenous MSC to several scaffold materials based on ceramics and polymers with adjusted elasticity and degradation durations.

Besides, we gained further knowledge on cell types of the alveolar bone, in particular on periodontal ligament stem cells (PDLSC). Hanna Malyaran a PhD student in a project funded inhouse by the Interdisciplinary Center for Clinical Research IZKF showed marked differences in proliferation and differentiation capacity between PDLSC from the upper and lower jaw of the same patient. PhD student Chloé Radermacher went on to show that PDLSC secrete more vascular endothelial growth factor VEGF than MSC and thus support more efficiently endothelial cells in forming capillaries. In addition, we found out that stroma-derived stem cells including MSC from bone marrow and adipose tissue, and PDL cells from upper and lower jaw differentially respond to mechanical forces. This research added to our molecular understanding of mechanobiology the influence of the mechanical environment on cell behaviour in the body. Now that we better understand PDLSC, we turn to the isolation and characterization of human cementoblasts of alveolar bones, a challenge which as part of a project is funded by the Deutsche Forschungsgemeinschaft DFG.

Together with Karolina Schickle from the GHI of the RWTH Aachen, we investigated monocrystalline ceramic scaffolds and could demonstrate that hemocompatibility and endothelialization are related to the atomic composition of the upper surface of the scaffold and we could successfully publish a patent application (EP21722810.5) with ceramic nanoparticles integrated in cardiovascular stents to improve hemocompatibility and reduce the risk of thrombocyte aggregation and activation.

PhD student Anna Bartz continues her crowd-funding campaign to support the study of spider silk as a biomaterial. Anna employs spider silk to produce three-dimensional scaffolds for bone tissue engineering. In her quest for innovative biomaterials Anna recently also included in her cytocompatibility testing fish skin from an Islandic fishing consortium. She demonstrated that MSC and endothelial cells preferentially adhere to specific side of the skin, discriminating the external side originally covered I scales from the side facing the muscle tissue, respectively. Stay tuned to learn more about this exciting biomaterial next year J

Last but not least, we are pleased that PhD candidate Svenja Wein has rejoined the lab following her parental leave. As part of a different DFG-funded research, she keeps working on fibrin-based scaffold materials and vascularization.

Periodontal ligament stem cells vs. mesenchymal stem cells as stromal support for angiogenesis

Chloé Radermacher, PhD candidate

Periodontitis is the most common reason for tooth loss in adults and affects around 11.2% of the world´s population. The periodontal ligament contains stem cells which are known to have similar characteristics to mesenchymal stromal/stem cells (MSC). The aim of the study is to investigate the angiogenic support of periodontal ligament stem cells (PDL cells) from the upper and lower jaw (u-PDL cells and l-PDL cells, respectively), since there is clinical evidence for differential speed and efficiency in wound healing and regeneration processes and angiogenesis in general plays an important role in regeneration processes of wounds. Bone marrow-derived MSC (BM-MSC) served as controls, since they possess a well-known supporting function for capillary formation of endothelial cells. Here, PDL cells from the upper and lower jaw are co-cultured with human umbilical vein endothelial cells (HUVEC) to compare them with each other and with mesenchymal stromal cells. The increased capillary formation has been demonstrated in PDL cell co-cultures compared to MSC co-cultures by immunofluorescence staining (Fig. 1). This phenomenon can be explained by the higher VEGF (vascular endothelial growth factor) secretion of PDL cells compared to BM-MSC. Indeed, 2ng/mg more VEGF was secreted in the medium supernatant of PDL cells than in BM-MSC. Lastly, slightly increased capillary formation was seen in the co-culture with PDL cells from the maxilla compared to the co-culture with PDL cells from the mandible of the same donors. In the present study, we could demonstrate for the first time, that PDL cells are able to support endothelial cells in the capillary formation process. These pilot experiments showed that u-PDL cells have higher angiogenic potential compared to l-PDL cells. This observation may help to explain the clinical observation, that wounds in the maxilla tend to close faster than in the mandible.

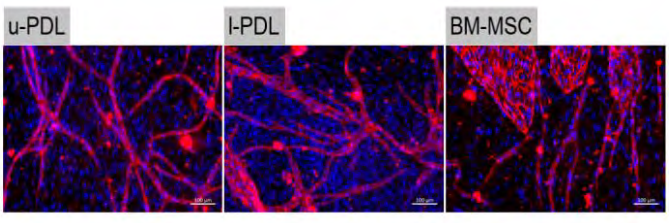

Fig. 1: Representative immunofluorescence pictures from the co-culture of human umbilical vein endothelial cells and periodontal ligament stem cells from the upper (u-PDL) and lower jaw (l-PDL) and from bone marrow-derived mesenchymal stromal cells (BM-MSC). The endothelial cells are stained with CD31 and nuclei of both cell types in co-cultures are stained with DAPI

Comparative analysis of proliferative and multilineage differentiation potential of human periodontal ligament stem cells from maxillary and mandibular molars

Hanna Malyaran, PhD candidate

Clinical experience indicates that wounds in alveolar bone and periodontal tissue heal faster and more efficiently in the maxilla compared to the mandible. Since stem cells are known to have a decisive influence on wound healing and tissue regeneration, the aim of this study was to determine whether differences in proliferation and differentiation of periodontal ligament stem cells from upper (u-PDLSC) and lower jaw (l-PDLSC) contribute to the enhanced wound healing in the maxilla. U-PDLSC and l-PDLSC from the same donor were harvested from the periodontal ligament of extracted human maxillary and mandibular third molars. Cell characteristics of u-PDLSC and l-PDLSC of the same donors were assessed by analysing stem cell markers, proliferation rate and multilineage differentiation and compared to bone marrow-derived mesenchymal stem cells (MSC, Fig. 2). Successful differentiation of PDLSC and MSC towards osteoblasts, adipocytes and chondrocytes was analysed via RT-qPCR and histochemical staining (Alizarin Red, Oil Red O, Toluidine Blue). PDL cells expressed the MSC-markers CD73+, CD90+, and CD105+ and lacked expression of CD34- and CD45-. Proliferation was significantly higher in u-PDLSC than in l-PDLSC, regardless of the culture conditions. Osteogenic (ALP, RunX2 and Osteocalcin) and chondrogenic (SOX9 and ACAN) related gene expression as well as staining intensities were significantly higher in u-PDLSC than in l-PDLSC. No difference in adipogenic differentiation was observed. Thus, we could identify differential cell characteristics of PDL cells from maxilla and mandible of the same donor which might be a first hint towards the mechanism behind the differential wound healing within the upper and lower jaw.

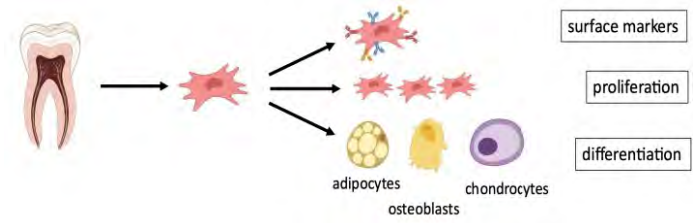

Fig. 2: Periodontal stem cells were isolated from third molars of the upper and lower jaw of the same patient and characterized in terms of surface markers, proliferation and differentiation capacity.

Structure-function analysis of Fetuin-A

Christian Hasberg, Camilla Winkler, PhD candidates

Our research team has a long-standing interest in Fetuin-A protein structure and function. Fetuin-A regulates mineral metabolism especially in conditions of mineral supersaturation. To prevent ectopic calcification, Fetuin-A stabilizes excess calcium phosphate as a colloid and mediates its distribution to target organs or its elimination from the body. Fetuin-A has three folding domains. The first two domains are cystatin-like CYS domains, which include five antiparallel beta sheets covering an alpha helix. The third domain is the C-terminal region CTR, which is intrinsically disordered. Post-transcriptional modifications phosphorylation and glycosylation likely regulate Fetuin-A function (Fig. 3).

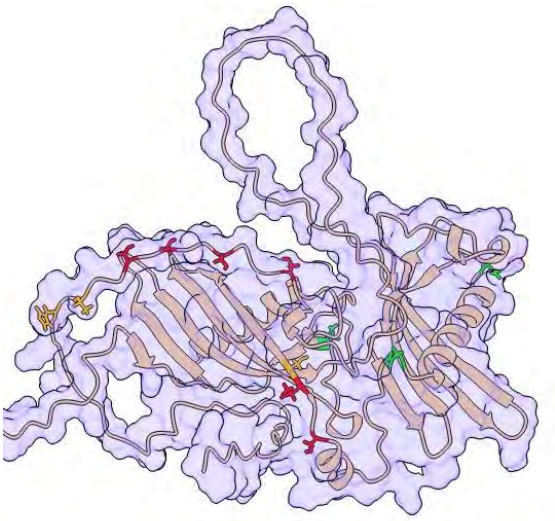

Fig. 3: A model of murine Fetuin-A was developed using the program AlphaFold. A volume model of the peptide backbone is displayed in transparent purple. Secondary structure is depicted as helix and loop cartoons. Putative phosphorylation sites are highlighted in yellow and red, and N glycosylation sites are indicated in green.

A program called AlphaFold, an artificial intelligence (AI) system developed by the company DeepMind predicts the three-dimensional structure of proteins based on their amino acid sequence, evolutionary data and deep learning from established protein folds. Alphafold has drawn a lot of interest because it predicts protein structures with remarkable precision. Nevertheless, protein structures must be experimentally validated. To establish the 3D structure of proteins, experimental methods like X-ray crystallography, NMR spectroscopy, and electron microscopy are commonly employed.

Fetuin-A has conformational flexibility, especially in the CTR domain, which makes it near impossible to generate crystals of sufficient size and quality.
Therefore, we choose cryo-electron microscopy (Cryo-EM) instead of X-Ray crystallography for structure determination of Fetuin-A. To determine the structure of Fetuin-A by cryo EM, we teamed up with expert structural biologists from the nearby Forschungszentrum Jülich , Professor Carsten Sachse and Alexandros Katranidis PhD.

Cryo-EM uses an electron microscope to capture images of proteins that have been rapidly frozen at - 180°C to retain their native structure. Several hundred 2D images are computationally grouped and superimposed for contrast enhancement, then matched and rotated to derive a full 3D structure. Figure 4 illustrates how Cryo-EM arrives at protein 3D structures.

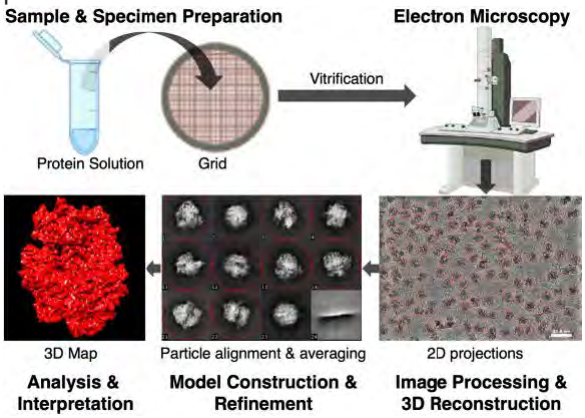

Fig. 4: Workflow of cryo-EM structure determination.
1. Sample Preparation: *To prepare a sample for cryo-EM, the quality of the sample has to be optimized by purification steps as well as adjusting the concentration.*
2. Specimen Preparation: *Ensuring that the sample is as preserved as possible prior to imaging, the sample is mounted on a cryo-EM grid and vitrified by ultrafast freezing.*
3. Image Acquisition: *Transmission electron micrographs are recorded in vacuum at ultralow temperatures maintaining the frozen state of the sample and thus an electron-dense environment.*
4. Image Processing and 3D Reconstruction: *The images are processed to create a 3D reconstruction of the sample based on the 2D projections.*
5. Model Construction and Improvement: *A model of the protein structure is constructed and iteratively improved.*
6. Analysis and Interpretation: *To comprehend the structure and function of the protein, analysis and interpretation must be done on the model.*

Fetuin-A is involved in mineral transport, it likely plays an important role in diseases involving mineral dysbalance like chronic kidney disease (CKD) and cardiovascular disease (CVD). Alterations in the metabolism of calcium and phosphate in CKD and CVD can result in pathological calcification of blood vessels and other soft tissues. Thus, understanding the molecular mechanics of Fetuin-A and its associated metabolic pathways may point to novel therapies for CKD and CVD patients.

Vessel-On-A-Chip: A miniaturized device for calcification testing

Aaron Morgan, PhD candidate

To facilitate the testing of cellularized biohybrid materials and implants, current calcification testing devices needed to be miniaturized and made to be compatible with cell culture conditions. A miniaturized, dual-channel flow device was developed that mimics the flow found in arterial vessels, with one side under high flow (vessel lumen) and one side under perfusion conditions (vessel wall).

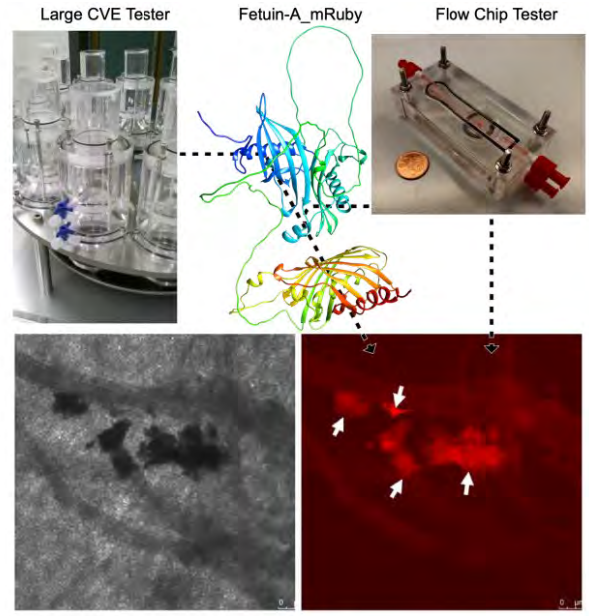

Fig. 5: Workflow of device miniaturization, using fluorescence-labelled Fetuin-A to identify calcifications in vitro.

The miniaturized flow device shown in Fig. 5 is used together with the protein Fetuin-A, a mineral chaperone found in the blood. Fetuin-A selectively binds to nascent mineral and, by attaching fluorescent labels to the protein, can be used to stain any calcifications in the sample. The transparent body of the device allows for live microscopy during experiments to monitor the progression of these calcifications. This method can be used to test the calcification propensity of materials, as well as cellularized tissue constructs.

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Team

RWTH SportsDay

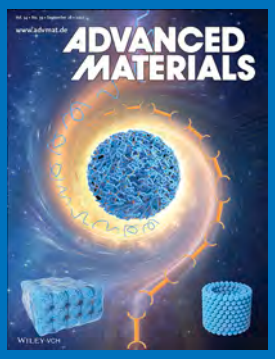
Gordon Conference for Biomineralization

Christmas Dinner at "Golden Pig", Aachen

ExMI EXPERIMENTAL MOLECULAR IMAGING

Chair of Experimental Molecular Imaging Faculty of Medicine

Improving therapy by integrated multiparametric imaging



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Introduction

Univ.-Prof. Dr. med. Fabian Kiessling

The Chair of Experimental Molecular Imaging (ExMI) focuses on the development and evaluation of novel imaging methods, contrast agents and theranostics to characterize and treat cancer, cardiovascular and inflammatory disorders. ExMI has a translational scope and many projects are located at the interface between preclinical and clinical research. In this context, we often follow a multimodal approach, based on combinations of MRI, CT, ultrasound, optical and photoacoustic imaging, nuclear medicine techniques (in particular PET-MRI), and magnetic particle imaging (MPI). In order to develop image-guided therapies, we strongly interconnect our pathophysiological and pharmacological research with research in device engineering, image reconstruction, and advanced data analysis. Basic research on the tissue microenvironment (including the barriers for drug delivery) provides us with new imaging biomarkers and new mechanistic insights that can be used to identify diagnostic biomarkers. Here, imaging features and omics data are considered in concert, evaluated using radiomic and radiogenomic approaches, and used to support mathematical disease models.
As a second main focus, ExMI investigates materials and concepts to improve drug delivery to tumors. This includes the development and evaluation of novel biomaterials, nanoparticles, polymeric carriers, liposomes, micelles and microbubbles as well as physical and biological treatments of the vasculature and the adjacent tumor stroma for improving drug accumulation and tumor penetration.
Research of ExMI has gained increasing international visibility. In 2022, Prof. Kiessling and Prof. Lammers were recognized as Highly Cited Researchers by Clarivate Analytics (4th time). Also, Prof. Kiessling was elected as incoming president of the European Society for Molecular Imaging (ESMI) and Prof. Lammers as incoming president of the Controlled Release Society (CRS). Finally, Prof. Kiessling was awarded as fellow of the RWTH Aachen University and Prof. Lammers received the Journal of Nanobiotechnology Trailblazer award.

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 delivery, and 4. Radiomics analysis of US data. In many publications, we already showed that our PBCA-based microbubble platform can be successfully applied for molecular imaging. In 2022, we were able to acquire the BMBF CLIMBING Crohn project, which enables us to transfer our microbubbles into clinical trials for the first time and to evaluate them in a bi-centric clinical study on inflammatory bowel diseases. Furthermore, we used integrin-targeted microbubbles in a multimodal imaging approach to characterize biohybrid vascular grafts with respect to their remodelling [43]. New aspects on microbubble- drug delivery showed that therapeutic gases can be transported and released via microbubbles [40]. In this theranostic study, MRI was used to detect gas release via responsive manganese complexes. With respect to super-resolution ultrasound, we are focusing on clinical translation and are recruiting patients for its application in imaging chronic kidney disease and breast cancer [42]. In further clinical studies, we are developing methods to automatically detect and characterize pathologies of the female breast on ultrasound images using artificial intelligence. Here, we emphasize a potential real-time capability to provide the physician with information already during the examination [21].

[*1] Dencks et al, IEEE Trans Ultrason Ferroelectr Freq Control, 2019.

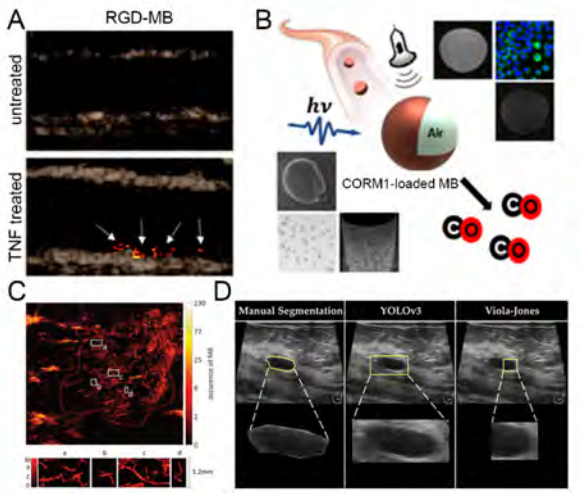

*Figure 1. A: Molecular US imaging of αvβ3 integrin expression in tissue-engineered vascular grafts. While there is hardly any RGD-microbubbles (RGD-MB) binding to untreated tissue-engineered vascular grafts, TNF-α induced inflammation results in strong MB attachment (modified from [43]). B: Air-filled polymeric microbubbles were loaded with the carbon monoxide (CO) releasing molecule CORM-1, which enables local light-triggered CO generation. Triggered generation of CO was monitored via US and MRI and assists in suppressing inflammation and hypoxia-induced cell death in immune and heart muscle cells [40]. C: Superresolution ultrasound image of a human breast cancer [42,*1]. D: Examples of detected lesions in US images obtained by (left) expert radiologist, (middle) YOLOv3 and (right) Viola–Jones detection models. The bottom row shows magnifications of areas that were considered for further classification [21].*

Nanomedicine and Theranostics

Univ.-Prof. Dr. Dr. Twan Lammers

Nanomedicines help to deliver drugs to pathological sites, thereby enhancing therapeutic efficacy and reducing toxic side effects [6]. We develop different types of nanomedicines, focusing mostly on polymeric micelles and liposomes, and we use them for the treatment of cancer, inflammation and fibrosis [45].
In recent work, we co-loaded polymeric micelles with drugs and imaging agents, and we demonstrated that the extent of nanomedicine tumor targeting correlates with therapeutic

outcome (Fig. 2A) [7]. We also for the first time showed that the heterogeneity in EPR-based nanomedicine tumor targeting increases during treatment. In a clinical study with zirconium-labeled micelles, which was performed together with Cristal Therapeutics and the Amsterdam University Medical Center, we exemplified the feasibility of visualizing and quantifying polymeric micelle targeting to tumors and metastases in patients (Fig. 2B) [24].
We furthermore provided proof-of-concept for the use of nanoformulated corticosteroids for the treatment of arthritis. In a clinical trial, the efficacy of liposomal prednisolone (Nanocort) was compared to standard-of-care methylprednisolone (Depo-Medrol) [23]. Nanocort was found to be significantly more effective than Depo-Medrol in reducing pain (Fig. 2C). Extending these efforts, with colleagues from the Medical Clinic IV at UKA, we completed a clinical study in which liposomes loaded with dexamethasone were shown to be efficient and safe in patients with multiple myeloma [1*].

[*1] Metselaar et al, Drug Delivery and Translational research, 2023.

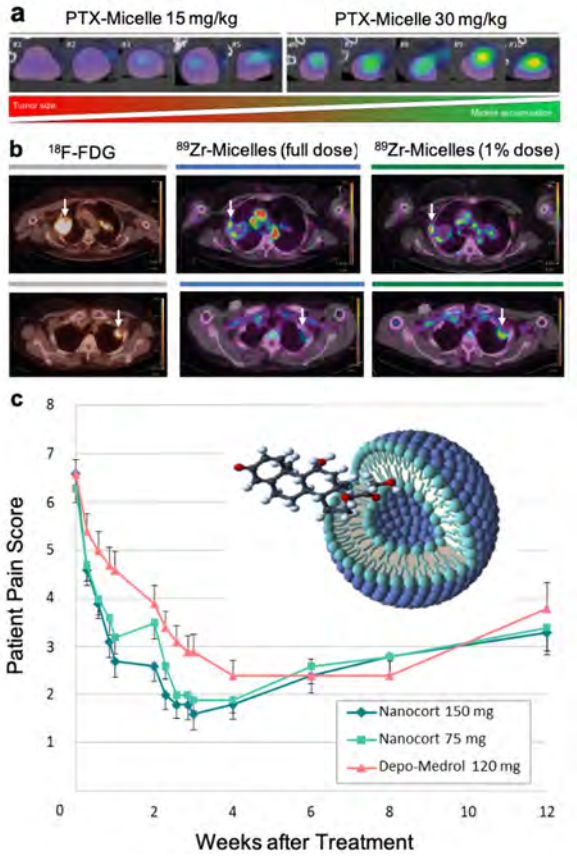

Figure 2. A-B: Tumor accumulation of Cy7- and paclitaxel-loaded micelles after 3 weeks of treatment, showing correlation of tumor targeting with therapeutic efficacy (A) and increase in targeting heterogeneity upon treatment (B). C: Visualization of zirconium-labeled micelles accumulation in lung metastases in a patient. Images reproduced from [7, 24].

Physics of Molecular Imaging Systems

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

The PMI group develops medical imaging systems ranging from established techniques, like MRI and PET, to the emerging method of Magnetic Particle Imaging (MPI). The field of PET research stays a vivid community, aiming for higher system sensitivity as realized with total-body PET [29]. We expanded our strong focus on detector research. So-called semi-monolithic scintil¬lators were proposed for clinical whole/total-body PET [28]. We investigated silicon photomultipliers in combination with the PETsys TOFPET2 ASIC and high-frequency read-out. Studies comparing both approaches [30], as well as improvements on the power consumption of the high-frequency read-out were conducted [18]. For MPI, the passive Dual Coil Resonator, a purely passive coil insert for a preclinical MPI system was characterized [39]. The device is easy to handle and cost-efficient. Deep learning was applied to implement super-resolution of measured system matrices [51].
Machine and deep learning are making their way into all areas of medical imaging. Computer vision tech¬nolo¬gies make predictions that determine individual treat¬ment plans and outcomes [*1]. So far, advan¬ces in disease recognition and progression prediction have been based on end-to-end learning, with challenges due to discontinuous and heterogeneous patient trajectories in longitudinal data. With the UKA [13], we demonstrated that a latent search algorithm combined with generative models efficiently analyzes longitudinal data. In detail, we utilized a self-supervised generative model to explore latent temporal trajectories of patients whose longitudinal radiographs infered model-based prognostication of osteoarthritis onset and progression (Fig. 3A). The model only utilizes temporal information embedded in longitudinal datasets from different patients, without any requirements for labels used in supervised learning (Fig. 3B). It outperformed all seven radiologists in determining the progressive cohort within a time window of up to eight years. This approach can pave the way for the broad usage of generative latent searching in predicting Alzheimer's disease and macular degeneration [13].

[*1] Han et al, Nature communications, 2021.

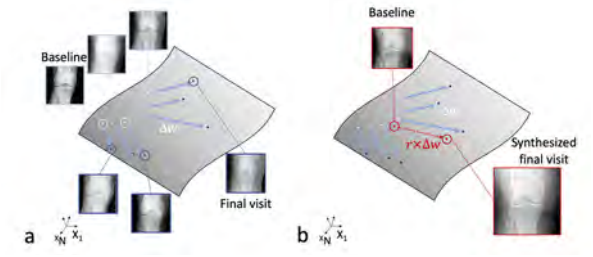

Figure 3: Synthesizing follow-up radiological scans via latent nearest neighbor navigation. (A) Encode possible OA progression scenarios from individual participants to latent trajectories in the learned manifold. (B) Generation of the predicted follow-up.

Polymer Therapeutics

Dr. Yang Shi

Polymers play important roles in a large number of therapeutics for various diseases, and they are the cornerstone of many treatment strategies. The research group "Polymer Therapeutics" focuses on developing translatable cancer treatment strategies based on own-designed synthetic polymers. These strategies include: (1) clinical translation of polymeric nanomedicines for combination therapy based on a patented ∏-∏-stacking-stabilized micelles. (2) Engineering of self-assembled immuno-prodrug vesicles for immune-activation via intracellular pattern recognition receptors in antigen presenting cells. The vesicles are produced from amphiphilic conjugates of hydrophilic polymers and hydrophobic prodrugs of low MW immunostimulants, (e.g., Toll-like receptor and STING agonists). The vesicles are highly efficient in activating antigen-presenting cells through enzyme-triggered intracellular drug release. (3) Development of nano-to-macroscale hydrogels based on methacrylamide polymers, which are used to deliver small or macromolecular drugs and cells via systemic or local routes of administration. Major achievements of 2022 include: (1) A novel concept in polymeric materials engineering, leveraging newly discovered covalent polymer self-assembly, has been established to construct nano-to-macroscale biomaterials (cover in Advanced Materials) [3]. (2) Investigated the influence of the polymer polydispersity on the formation and properties of ∏ electron-stabilized polymeric micelles. This work is an important contribution to the upscaled manufacturing and clinical development of this type of polymeric micelles [*1].

[*1] Shi et al, Biomacromolecules, 2023.

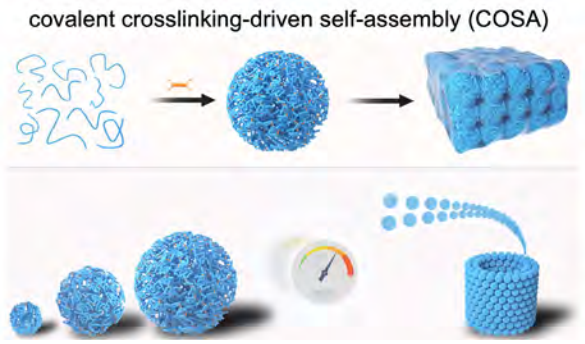

Figure 4: Illustration of the covalent crosslinking-driven self-assembly (COSA) of a homopolymer.

Biohybrid Nanomedical Materials

Dr. Roger Molto Pallares

The Biohybrid Nanomedical Materials group was established in September 2021 and is funded by the competitive RWTH Aachen-sponsored Junior Principal Investigator Fellowship. The group focuses on developing hybrid materials, such as polymeric microbubbles and inorganic nanoparticles, for biosensing, imaging and smart drug delivery applications [38,*1]. To this end, the group has recently developed new routes to manipulate the chemistry of polymeric microbubbles, maximizing their performance as ultrasound contrast agents and drug delivery vehicles [4]. New aspects on microbubble bioconjugation were also explored, providing microbubbles with targeting capabilities and enhanced nonlinear responses for molecular imaging applications [5]. Moreover, to develop highly-responsive nanoprobes for optoacoustics, we are synthesizing gold nanoconstructs with finely tuned optical properties [60]. Lastly, we are applying -omics approaches to characterize the safety/toxicity and biological behavior of clinically relevant materials [33,34,37].

[*1] Zhang et al, Drug Delivery and Translational Research, 2023.

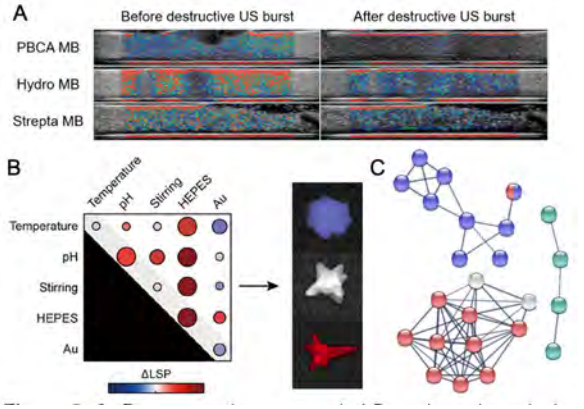

Figure 5. A: Representative gray-scaled B-mode and overlaying color-coded nonlinear contrast mode images (left) and stable cavitation indexes (right) of plain, hydrolyzed and functionalized microbubbles (PBCA MB, Hydro MB and Strepta MB, respectively). B: Manipulation of morphology and optical properties of gold nanostars via colloidal chemistry. LSP stands for localized surface plasmon resonances. C: Protein-protein interaction network analysis of gene products disrupted by gadolinium exposures. Images reproduced from [5,33,60].

Immune cell targeting and imaging

Dr. Alexandros Marios Sofias

Twenty-five years after the approval of the first nanomedicine, we have to refine tumor-targeted drug delivery alongside advances in immuno-oncology. Given that cancer is characterized by an immunological imbalance, we should focus on targeting, engaging, and modulating cancer-associated immune cells inside and outside the tumor microenvironment (TME). When designed and applied rationally, nanomedicines will assist in restoring the immunological equilibrium at the whole-body level, which holds potential for the treatment of a range of other disorders [*1]. Within our group, we are focusing on the development of myeloid immune cell targeting nanomedicines, aiming to the development of nano-immunotherapeutic solutions in triple negative breast cancer (TNBC), hematological malignancies, and liver cancer. To assess the nanomedicine in vivo performance, we utilize a highly complementary strategy composed of whole-body imaging techniques (e.g., FLT/CT, MRI), and state-of-the-art intravital microscopy, supplemented with ex vivo flow

cytometry and histological approaches [*2,10,27]. The group was established in March 2022, and is funded by the DFG Excellence Initiative – JPI fellowship 2021, the DFG Clinical Research Unit 344, the DFG Collaborative Research Center 1066, the German Cancer Aid, and the Euro-BioImaging.

[*1] Sofias et al, Drug Discovery Today, 2021.
[*2] Sofias et al, Advanced Science, 2021.

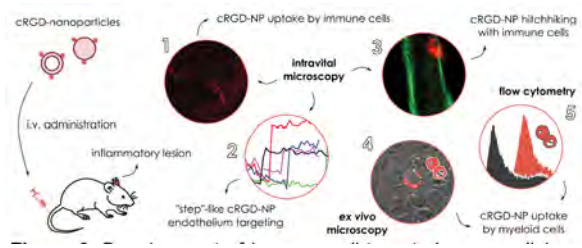

*Figure 6. Development of immune cell-targeted nanomedicines, followed by their in vivo tracking and tracing via multiscale imaging at different levels of spatial and temporal resolution [*2].*

Acknowledgements

Companies: Gremse IT, invivoContrast, Hyperion, Enceladus Pharmaceuticals, MILabs, Roche, AstraZeneca, Bayer, Bracco, Bruker, BiOrion, Cristal Therapeutics, Merck-Serono, Merck Darmstadt, Molecular Targeting Technologies, Nano4Imaging, Novartis, Philips, Siemens, VisualSonics.

Funding Agencies: EC (Horizon 2020, EFRE), ERC, DFG, BMBF, ERS, IZKF, START, BMWI (AIF), Euro-BioImaging.

Awards

- Prof. Kiessling and Prof. Lammers were recognized as Highly Cited Researchers 2022 by Clarivate in the Pharmacology and Toxicology category.
- Prof. Kiessling appointed RWTH Fellow 2022.
- Prof. Kiessling elected new president of the European Society for Molecular Imaging (ESMI).
- Prof. Lammers won the Springer Trailblazer award.
- Prof. Lammers elected new president of the Controlled Release Society (CRS).
- Dr. Shi received the highly prestigious ERC starting grant
- Dr. Pallares received the „Fonds Der Chemischen Industrie“ grant.
- Dr. Sofias received a research grant by the DFG Clinical Research Unit (CRU344 – P4).
- Dr. Sofias received a mobility grant by the Euro-BioImaging.

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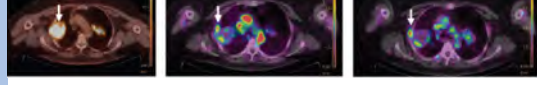

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Lindemann, Max, M.Sc. Wirt.-Ing.
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Reisen, Oliver, M.Sc.
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Prof. Dr. med. dent. Christian Apel (Deputy Head)
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Cornelissen, Christian, PD Dr. med.
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Fernández-Colino, Alicia, Ph.D.
Ghazanfari, Samaneh, Ph.D.
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Lubig, Andreas, M.Sc.
Lüngen, Anja, M.Sc.
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Numan, Jacquelien, CTA
Ramakers, Richard, Dr.-Ing.
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Sandhoff, Cilia, M.Sc.
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Schmidt, Amanda, M.Sc.
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Singh, Abhishek, M.Sc.
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Heyer, Jan, M.Sc.
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Menne, Matthias, Dr. rer. medic. M.Sc. M.Sc.
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Ritter, Jan, M.Sc.
Roggenkamp, Jan, Dipl.-Ing.
Sauren, Fabio
Secer, Muhammet Ali, CTA
Schadow, Marlene, M.Sc.
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Strudthoff, Lasse, M.Sc.
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Dr. Robert Farkas (Head)

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Tang, Fu-sung Kim-Benjamin, M.Sc.

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Dietmar Faßbänder (Head)

Baldin, Thomas
Lipka, Jürgen
Mangartz, Dominique
Niens, Marcel

Introduction

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

Dear readers,
this is the umpteenth issue of our HIA Research Report, which in our view is not quite up to date in this form. But since the majority of the HIA Board of Directors still wants it in this way, we naturally join in and present our Research Achievements of the year 2022 as a contribution to this issue that you now hold in your hands.

As in all the previous years, 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, medicine, biology, life sciences, physics, materials science, and computer science working closely together on many research and development projects.

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.

The institute continues to consist of 6 departments, whose 2022 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 new 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 (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, 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 in 2022:

The Anisogel successfully induces anisotropic cell growth to mimic aligned tissues. In this work, we demonstrate that by pre-aligning ellipsoidal maghemite nanoparticles during microgel production, we can pre-program the angle of orientation of the microgels. This enables the creation of Anisogels with multiple discrete directionalities while under the influence of a single static magnetic field. Anisogels made using such microgels, pre-programmed to orient in mutually perpendicular directions, induce cell growth in the two orthogonal directions. This demonstrates a new enhanced level of complexity in Anisogels, which enables cells to respond to discret pre-defined guiding cues within the same material.

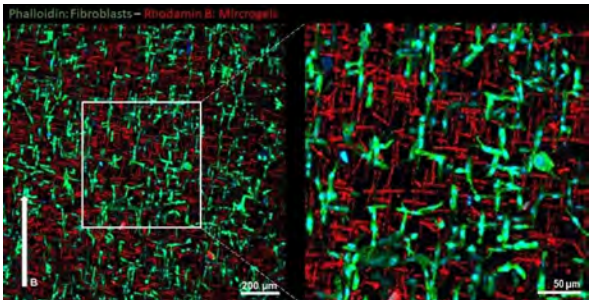


Fig. 1: Fibroblasts (green) growing along the two mutually perpendicular directions of microgel (red) orientation.

A light triggered hydrogel system is used to locally induce small, time dependent mechanical forces on C2C12 myoblasts cells growing on the surface of a soft, patterned NIPAM/NEAM hydrogel, which we call our 'in vitro gym'. We show that short-term actuation (5 h) enhances cell proliferation, increases nuclear translocalization of YAP and MyoD and reduces ECM secretion. When cells actuate for longer time (17 h), their cell area is increased, MyoD and YAP reverse back to the cytoplasm and proliferation slows down, which suggests a transition of the myoblasts to start differentiation. The actuation time ('time in the gym') affects proliferation and differentiation of myoblasts, underlining the importance of a dynamic system for muscle culture in vitro.

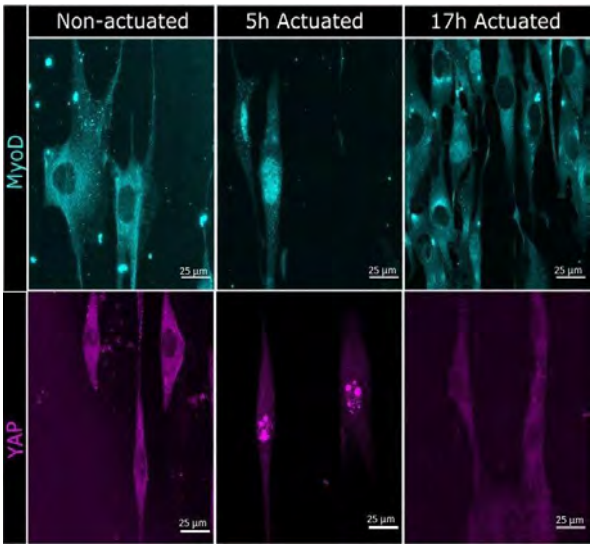


Fig. 2: MyoD (cyan) and YAP (pink) are shuttling to the nucleus due to short-term actuation and going back to the cytoplasm after long-term actuation.

Microporous annealed particle (MAP) scaffolds are mostly fabricated from spherical microgels. By using rapidly interlinking rod shaped microgels, it is possible to achieve larger pores with a smaller amount of synthetic material while maintaining the stability of the scaffold. Biofunctionalization of the microgels with cell adhesive peptides enables 3D cell culture with enhanced cell-cell interactions, which is critical for specific differentiation towards functional tissues. Cells attach to the surface of the assembled microgels, spread and proliferate in the macropores, while nutrients can diffuse to the cells via the interconnected microgel network, preventing necrosis.

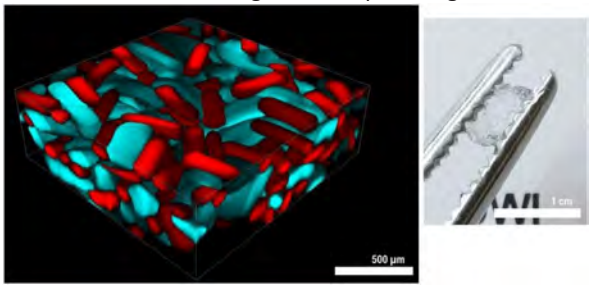


Fig. 3: Functionalized microgel rods chemically interlinked into soft macroporous structures for 3D cell culture.

Biophysical and Education Engineering (BEE)

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

Magnetically Actuated Controlled Drug Release from Biodegradable Scaffolds

Ioana Slabu received one of the most prestigious grants in Europe, the Starting Grant awarded by the European Research Council (ERC). She and her team are working on biodegradable implants for controlled drug delivery in vivo in the right place, at the right time and with the right dose. In her project "MAD Control", she is developing the still missing technology for implants with magnetic nanoparticles that allows imaging of the implants' aging process and the active release of drugs through magnetic excitation. MAD Control thus promises new opportunities for the research and development of biodegradable implants as well as of nanomedicines as drug release systems and finds applications for example in tissue engineering and

in cancer therapy, thus significantly contributing to the emerging area of personalized medicine.

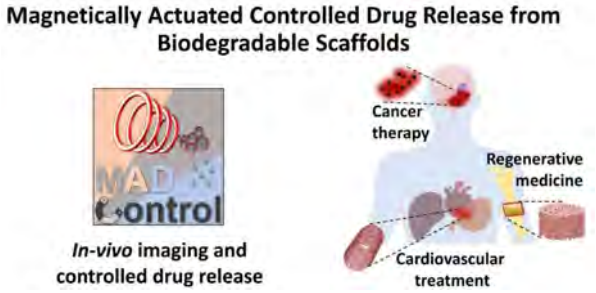


Fig. 4: Starting Grant awarded by the European Research Council to Ioana Slabu.

3D-Printing in Medical Education

Comparing 3D-prints of anatomical structures, e.g., heart or vertebral bodies, with the corresponding radiological 2D-images leads to a better understanding of the cause of the respective pathologies. Within this project grant of the Exploratory Teaching Space (ETS 479, Fig. 5), it could be shown that this boosts student motivation and trains students on the interpretation of anatomical projections. This was conducted in cooperation with the Clinic for Diagnostic and Interventional Radiology of the Uniklinik RWTH Aachen. Thanks to the positive evaluation by the students, the project has been integrated into the teaching curriculum.

Fig. 5: Lena Giebeler (student coworker), Dr. Lea Hitpaß, Dr. Andreas Ritter and Prof. Baumann present the teaching project at the RWTHtransparent event. (Photo by M. Rawanschad).

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 remodeling, regeneration, and self-repair. BioTex wants to make a significant contribution to progress in (regenerative) medicine. We follow the mission to develop bioengineering solutions for clinical needs by combining functional materials and biological components towards biohybrid systems. Therefore, we have set up the institute along the value chain from material development and processing to biohybrid implant development and biofunctionalization further to (pre)clinical testing. The BioTex institute is in a strong collaboration with the Aachen-Maastricht Institute for Biobased Materials and the DWI Leibniz Institute for Interactive Materials.

Fig. 6: The BioTex team during summer BBQ event.

Research Highlights of 2022:
PhD Defences: Caroline Kniebs, Matin Rostamitabar and Anja Lüngen
Caroline Kniebs successfully completed her doctorate on 15 June 2022. The topic of her doctoral thesis was "Development of fibrin-based, prevascularised 3D tumour models in respiratory tissue engineering". Matin Rostamitabar successfully his thesis on "Cellulose Based Aerogel Microfibers for Biomedical Applications" in the framework of the Marie Curie ITN FibreNet. Anja Lüngen completed her doctorate on 17 November 2022 with a successful defence of her thesis "Respiratory Tissue Engineering - Development of a Respiratory Mucosa Equivalent".

Article in the business magazine "Starkes Land Nordrhein-Westfalen" (Strong State of North Rhine-Westphalia)
The magazine "Starkes Land Nordrhein-Westfalen", the regional business magazine in DER SPIEGEL, recently published an article on the topic of "Biology meets Medicine".
Prof. Stefan Jockenhövel reports on the benefits and future of bio-based materials. You can also find out why the cross-border merger of RWTH Aachen University and Maastricht University to form AMIBM (Aachen-Maastricht Institute for Biobased Materials) is so promising.

New Projects

Research Alliance reACT
As part of the BMBF funding program "RUBIN - Regional Entrepreneurial Alliances for Innovation", the reACT project was successfully acquired together with our project partners. In this joint project, implant concepts are being researched to meet the urgent clinical need for temporally adaptive partially resorbable endoluminal support structures (stents).

DFG project "Lost in Granulation"
The project "Lost in Granulation - Respiratory mucosa model for in vitro analysis of tissue granulation by mechanical stimuli" was funded by the DGF. The work is being carried out in collaboration with the Ruhrland Clinic in the laboratories of Prof. Dr. Christian Taube in the "Experimental Pneumology" working group. In the proposed project, we are developing an in vitro model of the respiratory mucosa to decipher the mechanisms of granulation tissue formation in response to stent or valve implantation with respect to mechanical stimuli.
"Support of Women in Science" for Maria Cheremkhina
Maria Cheremkhina received the grant "Support of Women in Science" via the DFG SPP2014 program. The project investigates the influence of SARS-CoV-2, as well as through pre-activation of immune blood cells, on the endothelium in a biohybrid oxygenator model.

Publications:

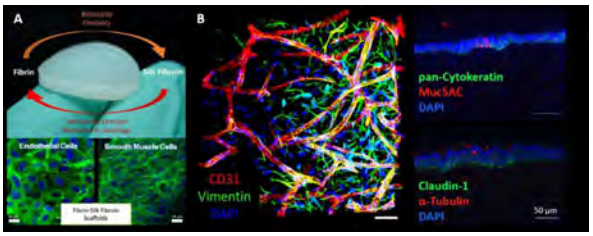


Fig. 7: A: El Maachi et al. successfully developed a scaffold made of two natural polymers (fibrin and silk fibroin), that offered the high mechanical properties of the silk fibroin and at the same time featured the extraordinary bioactivity of the fibrin.
B: Luengen et al. showed that epithelial morphology of tri-cultures with BM-MSCs most closely resembled native respiratory epithelium with respect to ciliation, mucus production as well as expression and localization of epithelial cell markers pan-cytokeratin, claudin 1, α-tubulin and mucin5AC.

Cardiovascular Engineering (CVE)

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

The year 2022 was characterized by a continuous return to normality after 2 years of pandemic with all its restrictions. Particularly consortia projects with multiple partners and projects with a high proportion of experimental (laboratory) activities in our focus areas Therapies & Applications and Research & Validation benefited there from.

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. Recently, platelet activation functionality was compared and good correlations between human and porcine abattoir blood was shown. Furthermore, the Ghost Cells (DFG) and the Ghost Blood (START) projects investigate the use of hemoglobin-deprived red blood cells (ghost cells) and blood analogues consisting of plasma and ghost cells for hemolysis and thrombogenicity investigations, respectively. Fig. 8 shows the test setup for PIV investigation of clotting in the left atrium appendix using the clottable ghost blood.

Fig. 8: Test setup with ghost blood and left atrium appendix model.

The new project ThromboSurf, a DFG-ANR cooperation, deals with the impact of surface structures on blood flow and platelet behaviour. The combined numerical and experimental approach tries to unravel the underlying mechanisms of improving material hemocompatibility by means of surface structures. In Fig. 9, the newly designed flow chamber for surface structure evaluation, with blood that allows for real-time platelet oberservation with a microscope, is shown schematically.

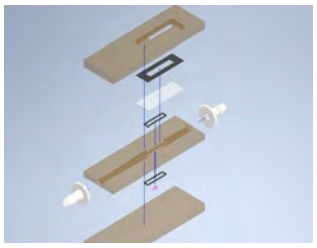


Fig. 9: Scheme of a flow chamber for real-time platelet observation.

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. 10 shows a two-photon microscope image of a pericardium patch after calcification testing. Intact collagen structures as well as calcification clots are visible.

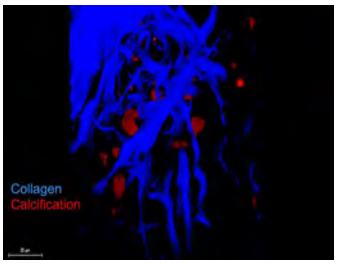


Fig. 10: Pericardium patch after calcification testing.

In cooperation with an industry partner, the TIBET project aims at the development and validation of an in-vitro thrombogenicity assessment of oxygenators. After test setup and protocol were established, the focus concentrated on the analysis of blood parameters and the oxygenator fiber mats. Fig. 11 shows a fluorescence image of mepacrine-labelled platelets on the fiber mats after blood contact.

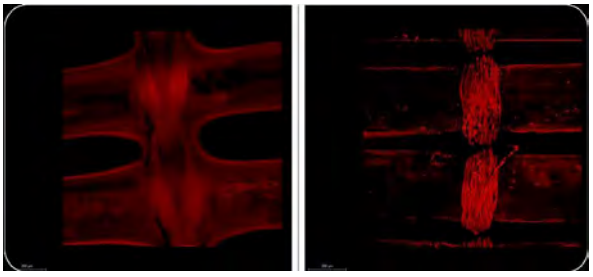


Fig. 11: Mepacrine-labelled platelets on oxygenator fiber mats.

Within the field Modeling & Simulation, a benchmark setup to assess mitral valve modeling approaches regarding their influence on ventricular hemodynamics has been introduced and five modeling strategies have been compared with each other. Crucial fluid dynamical features, such as the vortex ring formation and the asymmetrical propagation of the mitral jet were investigated and compared with each other, Fig. 12. A porous medium valve model has been identified as a viable alternative to more expensive fluid-structure interaction simulations.

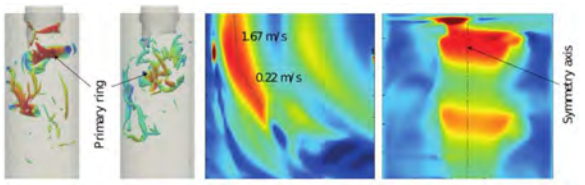


Fig. 12: Vortex ring formation and diastolic jet propagation of benchmark setup.

In a second project, the local hemodynamics of a cardiopulmonary assist system inflow jet during return within the pulmonary artery (PA) has been investigated. Several connection scenarios (lateral and central cannulation) using transient computational fluid dynamics simulations were analyzed, see Fig. 13. A central location is beneficial regarding flow distribution, but the resulting high wall shear stresses (WSS) might promote detachment of local thromboembolisms or influence the autonomic nervous innervation. Lateral locations, depending on jet path length, result in lower WSS at the cost of an unfavorable flow distribution that could promote pulmonary vasculature changes.

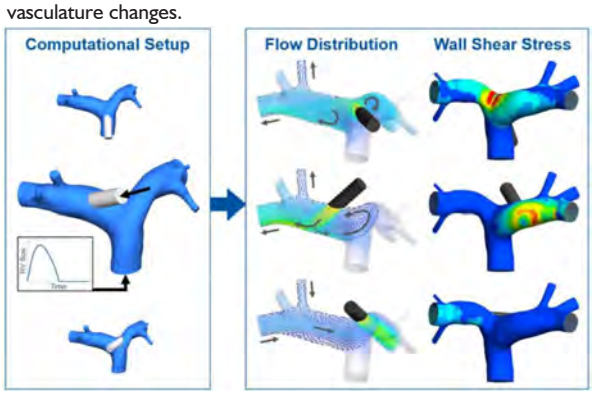


Fig. 13: Flow distribution and wall shear stresses for central and lateral cannulation.

Within the 3D lung project (SPP2014 – Towards an implantable lung) in Therapies & Application, a numerical model to efficiently predict gas-transfer and flow distribution in 3D structured TPMS membranes could be successfully implemented and validated (Fig. 14). Further progress is made in terms of the manufacturing of prototypes compatible to in-vitro blood testing and further work is planned on an optimization algorithm to automatically improve flow-distribution and gas-transfer by local variation of the permeability within the 3D TPMS membrane structure.

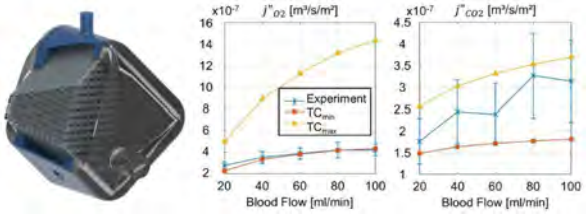


Fig. 14: CAD rendering of an oxygenator module consisting of 3D TPMS membrane (left); comparison of numerical gas-transfer prediction with experimental data (right).

As part of the Perinatal Life Support project within a European consortium, an artificial uterus prototype was developed. In addition to a fluid-filled housing to mimic the uterus and a filtering concept for the amniotic fluid, a completely new oxygenator concept was developed. The new oxygenator allows adding volume without interrupting blood flow to meet the growing needs of the infant. In an initial series of proof-of-principle tests (Fig. 15), the new oxygenator showed good results. More extensive tests are being conducted. Furthermore, umbilical cord cannulation as an interface between the infant and the oxygenator is being tested in vitro on a specially developed test rig using human umbilical cords.

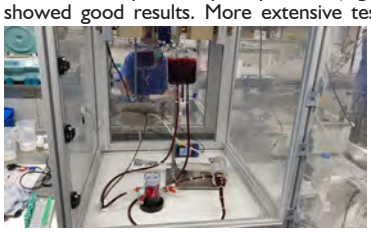


Fig. 15: In-vitro gas-transfer test of the new oxygenator concept.

Rehabilitation and Prevention Engineering (RPE)

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

The biomechanical analysis of physiological and pathological human movement and interrelated processing of signals from various sensors forms the core expertise of the Department of Rehabilitation & Prevention Engineering (RPE). Recent research additionally focuses on the design, development, and assessment of robot-assistive systems for use in caregiving and rehabilitation environments.
Muscular activation is influenced not only by movement velocity, joint position, and contraction type but also by aging. In cooperation with the Geriatric Center, Franziskus Hospital age-related changes in the muscular coordination patterns of upper extremity muscles as a function of angular velocity, joint angle and contraction type were investigated. Age-related activation pattern change in bachioradialis particularly corresponds to a loss of fine motor skills in the elderly.
People with low back pain (LBP) show altered trunk muscle function and impaired performance of their activities of daily living (ADL). Changes in muscular activation while performing 3 essential ADLs were investigated using a parcour (Fig. 16) designed to simulate "static waist flexion", "stand to sit" and "climbing stairs". While the subject performs these ADLs, the muscular activation of various back and oblique muscles is recorded. The validation of this instrument is currently underway in subjects with sub-acute and chronic low back pain.

Fig. 16: Parcour to simulate activities of daily living.

Manual pushing and pulling of heavy loads or equipment can pose a biomechanical risk. To investigate the effect of various loads pushed and movement velocity on spinal curvature a DIERS formetric scanning stereography device has been combined with a treadmill (Fig. 17). A push rod simulates the load to be pushed. Postural quantities e.g. kyphotic angle, lordotic angle and pelvic inclination are being studied. Results show that load and movement velocity affect trunk inclination while spinal curvature is only affected by movement velocity.

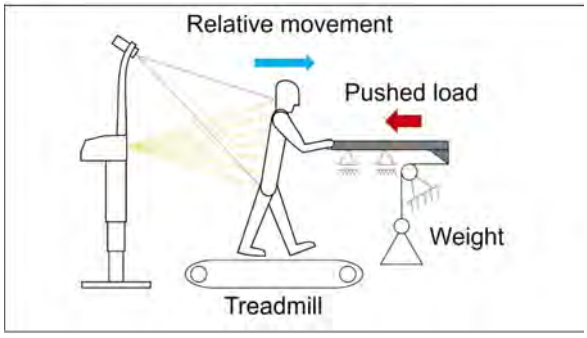


Fig. 17: Experimental set-up.

The assistive robotic system PfleKoRo aims to reduce the physical load on caregivers during nursing tasks. Particularly physically demanding tasks are "lifting and holding a patient's limb" and "turning a patient onto her/his side". In a user-centered design process, involving caregivers and nurses, two grippers were developed, and robot trajectories were determined to ensure safe and comfortable patient handling. For the first time the robotic system can execute holding and turning tasks autonomously.

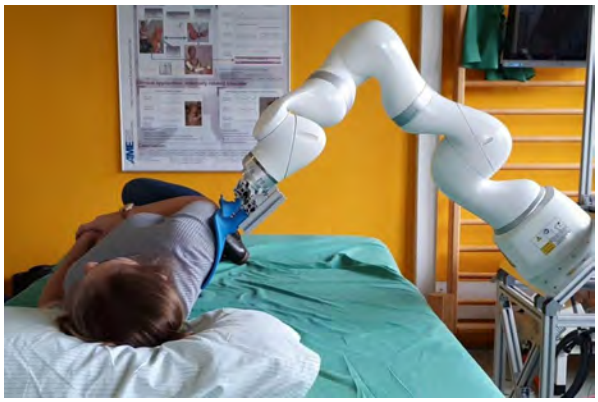


Fig. 18. Autonomous patient handling by assistive robotic system.

Little is known about the impact of robotic assistance on patient comfort. Increased muscular co-activation has been associated with the use of robotic assistance in rehabilitation. This addresses both patient comfort and the robotic system's compliance. A recent study investigated the influence of the robotic system's compliance on muscular activation during assisted nursing tasks. In contrast to rehabilitation, muscular co-contraction decreases with decreasing compliance of the robotic system, indicating that during nursing tasks patients prefer a stiffer robotic support.

Science Management (SCM)

Dr. Robert Farkas (Head)

Artificial intelligence (AI) is arguably one of the most promising innovations for future medicine and technology. Moreover, AI will even advance the innovation process itself, 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. This so-called 'Digital Compass' is able to start only from a product description. We adapted different search approaches, e.g., using Bidirectional Encoder Representations from Transformers (BERT), to different data sources (publications, clinical trials) to finally obtain a visualized knowledge graph as an integrated result of this seed document-based TAR (Technology Assisted Review). This project is funded by the State of North-Rhine Westfalia (see Fig. 19).

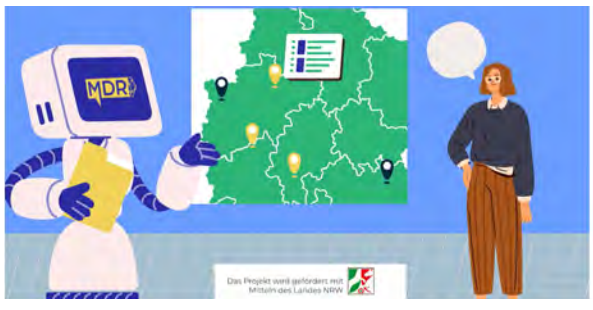
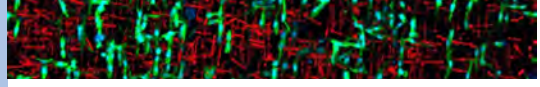


Fig. 19: Screenshot of the educational film explaining the goals and function of the Digital Compass, which provides guidance on the state of clinical knowledge to help companies implement the novel Medical Devices Regulation.



In addition, we continued the collaboration with the local Clinical Department of Internal Medicine I (MK1) focused on heart failure with preserved ejection fraction (HFpEF), developing 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 patient's risk suffering from HFpEF. The project named DARIO is funded by the German Federal Ministry of Education and Research – BMBF.

Acknowledgements

- The German Federal Ministry of Education and Research (BMBF).
- The German Research Foundation (DFG).
- The START Grant Program of University Hospital Aachen.
- All our Industrial Partners.
- The State North-Rhine Westfalia.

Awards

Kai Barbian, M. Sc., 2nd Place SPP Spring School Poster Award.
Martin Baumann, apl.-Prof. Dr. rer. nat. Dipl.-Ing, M.Sc., ETS-Project Grant, November 2022.

Julian Gonzalez-Rubio is part of the TERMIS SYIS-EU committee; Julian Gonzalez Rubio was elected as a new member of the Strategic Alliance Committee of the TERMIS SYIS-EU, part of the Tissue Engineering and Regenerative Medicine International Society, Inc. (TERMIS).

Fig. 20: Julian Gonzalez-Rubio is part of the TERMIS SYIS-EU committee.

Oliver Reisen, M. Sc., Heinrich Böll Stiftung, April 2022.
Elisa Romero Avila, Scholarship holder of the National Council for Science and Technology (CONACYT) and the German Academic Exchange Service (DAAD) for doctoral studies. 2022-2026.
Ioana Slabu, Priv.-Doz. Dr. rer. nat, ERC-Starting Grant, November 2022.

Selected Publications 2022

[1] S. Babu, I. Chen, S. Vedaraman, J. Gerardo-Nava, Ch. Licht, Y. Kittel, T. Haraszti, J. Di Russo, L. De Laporte. How do the Local Physical, Biochemical, and Mechanical Properties of an Injectable Synthetic Anisotropic Hydrogel Affect Oriented Nerve Growth? Advanced Functional Materials. 2022. DOI: 10.1002/adfm.202202468.

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Team

Third-party Funding

	Number of Projects	Total Expense of Projects (€)
German Research Foundation (DFG)	61	4.702.949,92 €
German Federal Ministry of Education and Research (BMBF)	34	3.075.448,17 €
EU	7	871.906,76 €
Industry	32	1.225.054,01 €
Other	50	3.567.859,67 €
Sum	184	13.443.218,53 €

Theses

	Number
Bachelor	73
Master	83
Doctoral	29
Habilitation	2
Sum	187

Staff

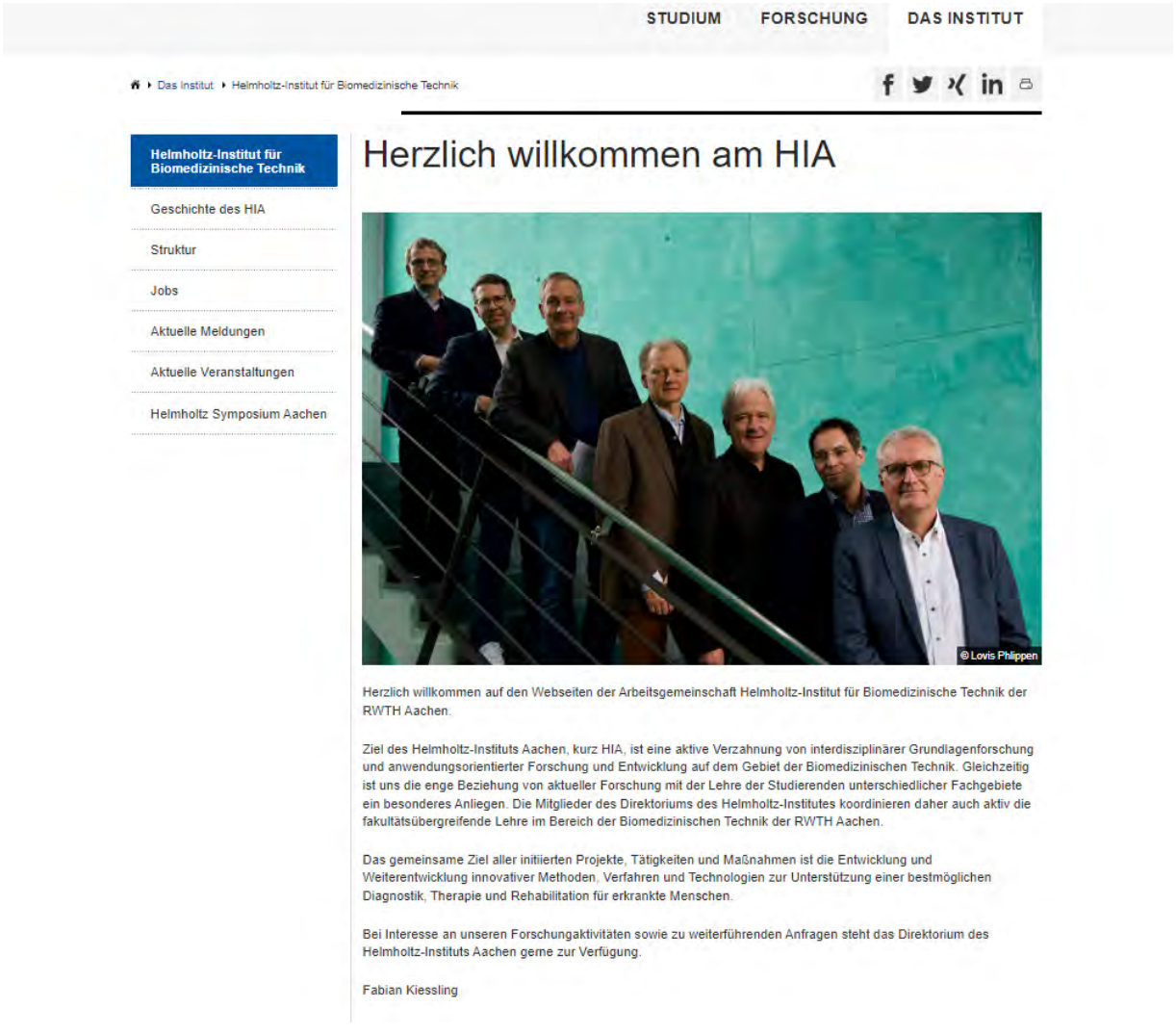
	Scientific	Non-Scientific
Total	213	36,1
Third party funded	196,9	9,5

in full-time equivalent (FTE)

Publications

	Number
Conference proceedings	72
Peer-reviewed journals	176
Books and book chapters	9
Sum	257

Patents and patent applications	12



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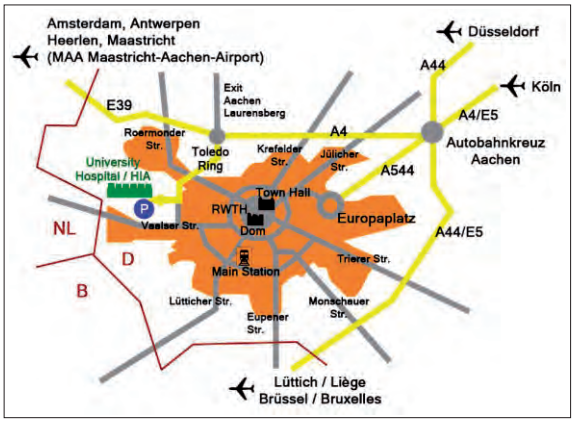

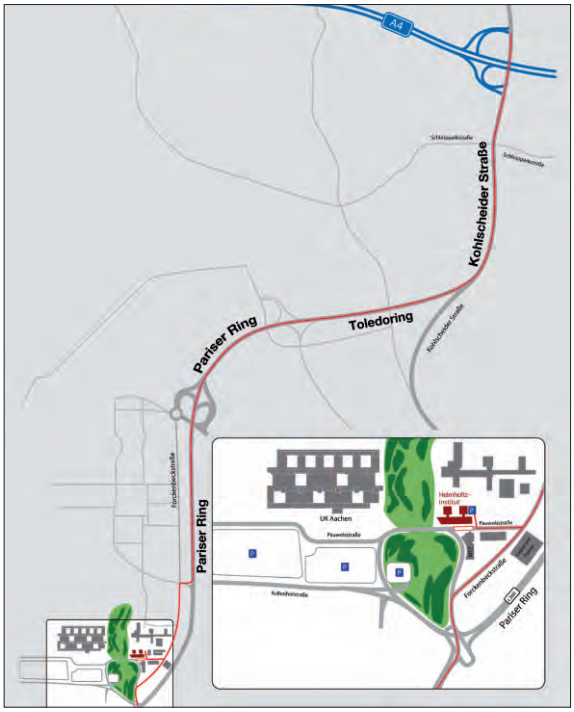

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By car

- Follow the motorway from Cologne or Netherlands to Aachen (A4) and take the exit towards Laurensberg.
- Turn right into Kohlscheider Strasse and follow the signs Uniklinik.
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- 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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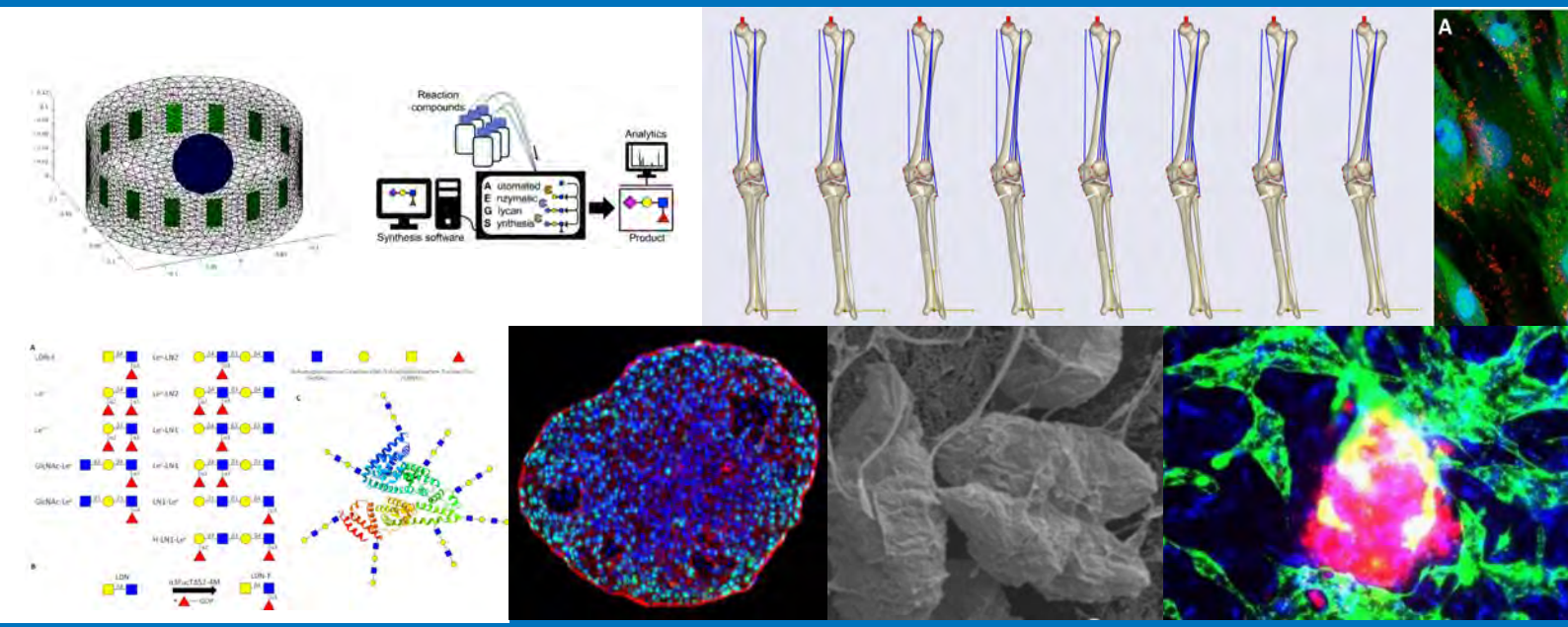

Imprint

Published by
Helmholtz-Institute for Biomedical Engineering

Pictures
Helmholtz-Institute for Biomedical Engineering

Coordination
Kathrin Kohl
Sabrina Herren

Printed by
frank druck+medien GmbH & Co. KG, Aachen