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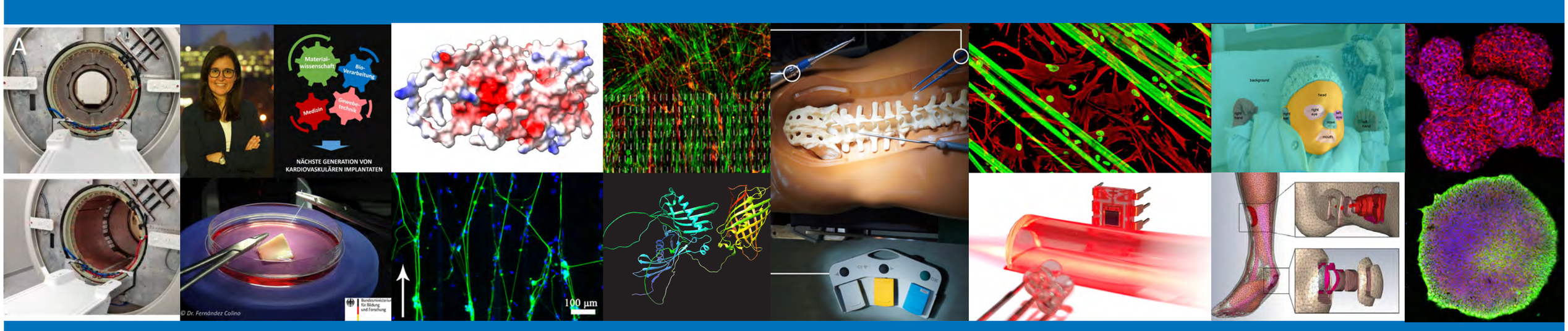
Helmholtz-Institute for Biomedical Engineering

Annual Report 2021



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Preface

The Helmholtz Institute for Biomedical Engineering HIA is a hotspot for interdisciplinary basic and application-oriented research and development in biomedical engineering at RWTH Aachen University and beyond. In 2021, the Corona pandemic continued to affect our research and teaching activities. Video conferencing and digital teaching became routine for interaction with colleagues and students.
The members of the Helmholtz Institute participate in the bachelor's, master's degree and doctoral studies' programs of the medical, engineering, and natural science faculties of RWTH Aachen University and coordinate master's degree 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 Bio-interface 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. Members of the Helmholtz Institute for Biomedical Engineering have been instrumental in raising funds for research and coordinating teaching. In 2021, third-party funding alone reached well over 205,75.

This 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 our annual report 2021. We are happy to provide you with further information on the topics reported here and to discuss with you future opportunities for collaboration in the fascinating field of biomedical engineering.

Aachen, March 2022

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Cell Biology

Gene Function in Cell Growth, Differentiation & Development

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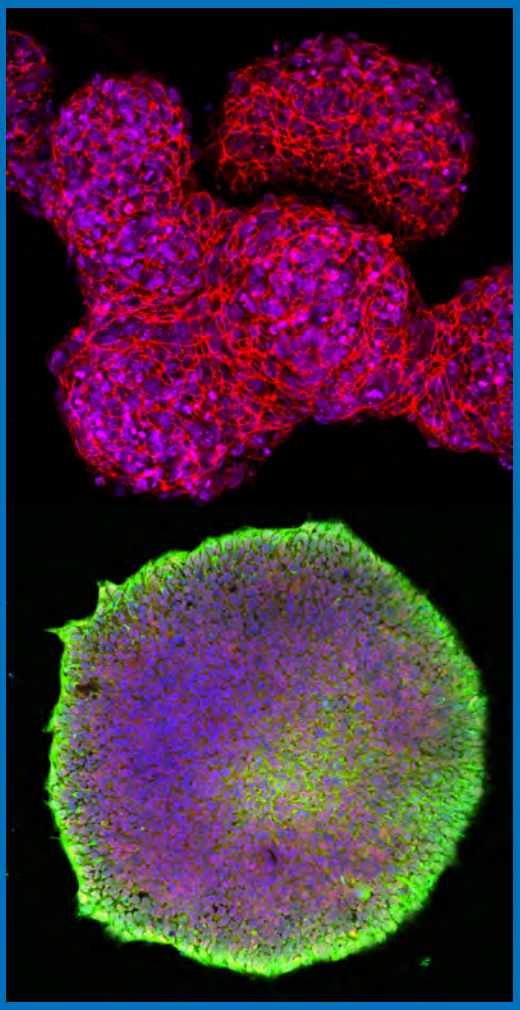

Stem Cell Biology and Cellular Engineering

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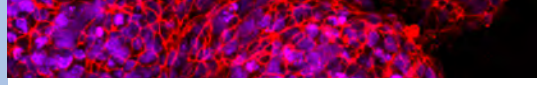


Introduction

The main goal of modern medicine is to tailor specific treatment to each individual. This is challenging because each patient has a unique disease state and genetic background. Induced pluripotent stem cells (iPS cells) can be derived from the patients and can be differentiated into almost all different cell types of the body. Thus, they provide powerful model systems to understand molecular mechanisms of diseases and to test therapeutic options.

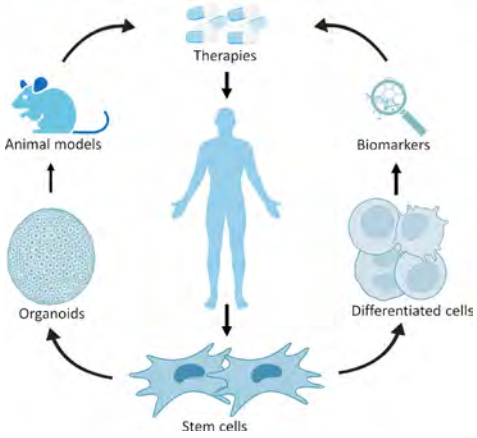


Fig.1: Focused on personalized biomedical technology, we culture stem cells, create organoids and diseae models in animals in order to screen for new therapeutics. In parallel, we aim to unravel the cellular mechanisms that regulate stem cells and their differentiation, identifying biomarkers to better monitor and control this process.(partly created with BioRender.com)

At our institute we have several research lines (Fig. 1). One research line aims to unravel the cellular mechanisms that determine cellular fate of iPS cells by employing a variety of genome wide approaches (microarrays, RNA-Seq, ChIP-Seq, ATAC-Seq and HiChIP-Seq) and by genetically altering cells using precise genome editing tools such as CRISPR/Cas9. Another research line focusses on hematopoietic stem cells (HSC). Abnormalities in self renewal and differentiation of HSC can result in myeloid malignancies. We aim to dissect the mechanisms that dysregulate hematopoietic self-renewal and differentiation to develop novel therapies that will specifically target disease initiating cells. To pinpoint these disease initiating cells, techniques with single cell resolution are utilized such as single-cell RNA sequencing.

A challenge of stem cell research is that the cells are grown and maintained in an external cell culture environment. We investigate how these culture conditions affect the differentiation potential and attempt to improve culture conditions to better mimic the in vivo situation. The impact of different biomaterials of different elasticities and different adhesives are tested. Aside from culture conditions, the age of stem cells is relevant for their regenerative potential. We have shown that the DNA methylation (DNAm) profile changes during aging but also during differentiation into specific cell types. We aim to identify and better understand these age-associated DNAm changes and establish epigenetic biomarkers to monitor chronological and biological aging. In parellel, we aim to establish DNAm profiles that are cell type specific, which in turn can be used to unravel the cellular composition of unknown samples.

CRISPR/Cas9 editing for genome engineering and studying stem cells

CRISPR/Cas9 editing is a particular versatile technology for introducing mutations or deletions in complex genomes and for repairing disease-causing mutations. Stem cells are particularly well suited for genome editing, since the mutation(s) introduced (or repaired) is/are propagated to the daughter generation, including differentiated cells. In such protocols stem cells are subjected to CRISPR/Cas9 editing, amplified and then differentiated into the desired cell type.

We use CRISPR/Cas9 editing to study disease specific iPS cells of patients with hematological malignancies and pain (Toledo et al., 2021; Olschok et al., 2021; in collaboration with the Department of Hematology, Oncology, Hemostaseology and Stem Cell Transplantation, RWTH Aachen University Hospital and Institute of Physiology, RWTH Aachen University Medical School). For example, using CRISPR/Cas9 we introduced the KIT D816V mutation in human embryonic stem cells (ES cells). These KIT D816V ES cells recapitulated the KIT activity observed in iPS cells of patients with the KIT D816V mutation and are employed for compound screening (Toledo et al., 2021). We also used CRISPR/Cas9 editing in conditionally immortalized HoxB8 hematopoietic stem cells, which were then differentiated into antigen presenting dendritic cells to study gene regulation (Xu et al., 2021). This study also included mutated Cas9 variants deficient in nuclease activity, referred to as dead cas9 (dCas9). dCas9 is fused to effector domains, such as a transcriptional activator or repressor to achieve gRNA targeted gene activation and silencing, respectively.

For compound screening, we collaborated with the Fraunhofer Institute for Production Technology (IPT) and the RWTH laboratory for Machine Tools and Production Engineering, to expand the protocols for our automatic cell production facility to include automated iPS cell culture of clonal lines and their differentiation into blood cells (Fig. 2)

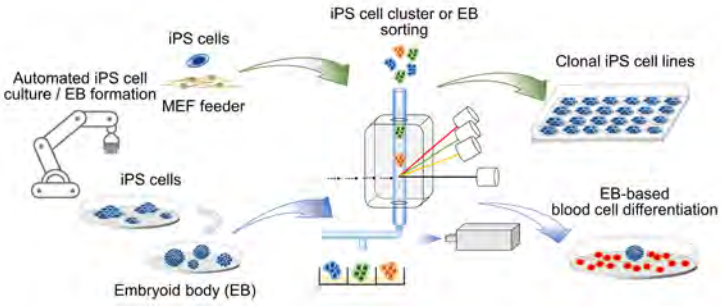


Fig. 2: Robotics and cell cluster sorting are employed in our automatic cell production facility to obtain clonal iPS cell lines (top panel) and embryoid bodies (EB) of defined size for blood cell differentiation (bottom panel).

Role of DNMT3A mutations for hematopoietic differentiation of human iPS cells

DNA methyltransferase 3A (DNMT3A) is frequently mutated in many hematological malignancies, indicating that it may be essential for hematopoietic differentiation. Therefore, we aimed to investigate the impact of DNMT3A mutations on the differentiation of human iPS cells and on changes in the DNA methylome. Using CRISPR/Cas9 editing, we deleted exons of the DNMT3A gene in iPS cells. Deletion of exon 19 or exon 23 lead to loss of almost the entire de novo DNA methylation during mesenchymal and hematopoietic differentiation, while the differentiation capability was hardly affected. We compared DNA methylation patterns of our iPSC-derived hematopoietic progenitors with primary acute myeloid leukemia (AML) patient data and found that our models recapitulate patterns of AML. As development of leukemia is dependent on clonal selection processes, we further investigated whether knockouts reveal subclonal dominance compared to wild type cells. Indeed, multicolor genetic barcoding showed competitive growth advantage of exon 23 knockout iPSC-derived hematopoietic progenitor cells (Fig. 3). Thus, our model system can help to gain a better understanding on the relevance of DNMT3A during hematopoietic development and malignant transformation (Cypris et al., 2021).

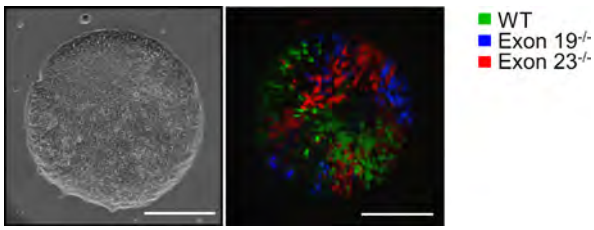


Fig. 3: Impact of DNMT3A mutations on human iPSCs and derived hematopoietic progenitors. iPSCs with wild type (WT) DNMT3A and with deletion of exon 19 or exon 23 were mixed for competitive growth assays and subsequent long-term culture. After hematopoietic differentiation, outgrowth of the exon 23 knockout cell lines was observed.

SARS-CoV-2 induces fibrosis in an iPSC-derived kidney organoid model

The coronavirus SARS-CoV-2 not only causes lung disease in COVID-19, but also affects other organs of the human body, such as the kidneys. After uncovering a striking association between kidney fibrosis and COVID-19 in a cohort of 62 patients that died of the disease, we aimed at uncovering the mechanism by which the virus harms the kidneys. To achieve this, we harnessed the advantages of an iPS cell-derived kidney organoid system, uncovering the direct actions of the virus in an immune-deprived environment. After exposing the kidney organoids to SARS-CoV-2, we mapped the virus to individual cells by single cell RNA sequencing combined with targeted perturbed sequencing of the virus genome. In addition, the virus particles were visualized in a quantifiable fashion intracellularly by focused ion beam scanning electron microscopy. In Masson's trichrome and Collagen I immunofluorescence stainings, fibrotic extracellular matrix was significantly increased in SARS-CoV-2-exposed vs. mock-infected organoids (Fig. 4). A compound by the COVID Moonshot consortium and an established TGFb inhibitor were able to ameliorate infection and generation of fibrotic matrix in SARS-CoV-2-infected kidney organoids.

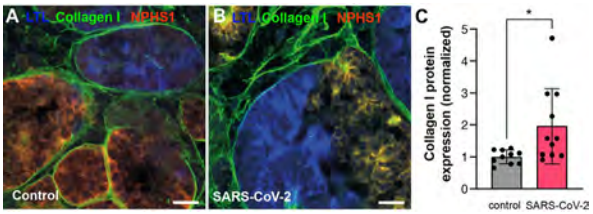


Fig. 4: Higher Collagen I expression in SARS-CoV-2-infected iPSC-derived kidney organoids (A,C) compared to mock-infected control organoids (B). Figures derived from Jansen, Reimer, Nagai et al., Cell Stem Cell, 2022.

Role of CCNY/CDK16 in the regulation of osteoclast differentiation and alveolar bone remodeling

Periodontal disease and orthodontic tooth movement are both characterized by the intense remodeling of the alveolar bone. Among the cells participating in these processes, osteoclasts, the bone resorbing cells, play a major role under physiological and pathological conditions. Specifically, osteoclasts remodel the bone surface upon creating an isolated microenvironment, which requires actin cytoskeleton reorganization and the assemble of a sealing zone composed of several juxtaposed podosomes (Fig. 5).

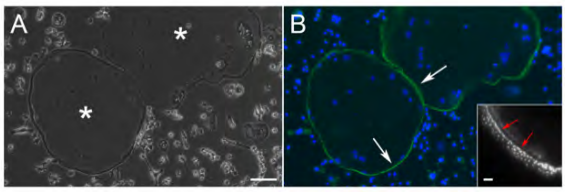
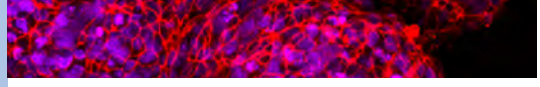


Fig. 5: Generation of osteoclasts from Raw 264.7 murine macrophages. (A-B) Phase contrast (A) and actin labelling (B) showing two large osteoclasts (asterisks in A) surrounded by several small undifferentiated Raw 264.7 macrophages. Osteoclasts are characterized by a robust actin labelling at their periphery (arrows in B) corresponding to the juxtaposition of several adjacent podosomes (red arrows in the inset). Scale bars: 100 µm (A, B), 5 µm (inset).

The regulation of these activities is still poorly understood. In this project, we focus on CCNY/CDK16 kinase that is thought to influence actin cytoskeleton-dependent processes. Following a mass spectrometry screen, we found 41 new potential CCNY/CDK16 targets, many of which have been implicated in the regulation of actin cytoskeleton remodeling. We are currently validating these targets and investigating the impact and regulation of their CCNY/CDK16-dependent phosphorylation in the context of osteoblast differentiation and bone resorption. The outcome of these investigations is expected to provide a deeper understanding of the molecular mechanisms by which osteoclasts resorb bone under physiological and pathological conditions.



Met-signaling regulates podosome formation and function in dendritic cell migration

Dendritic cells (DC) are highly specialized immune cells with a key role in antigen presentation and hence regulation of adaptive immune responses. DC act as sentinels in almost all peripheral tissues of our body. Following antigen uptake, DC are activated, leave the peripheral tissue and migrate to lymphoid organs for antigen-specific T cell stimulation. We previously identified HGF receptor/Met-signaling in skin DC as essential in this process.

To overcome tissue boundaries some cells, including DC, can form podosomes (also known as invadopodia in invasive tumor cells), which are highly dynamic actin-rich structures that mediate adhesion to extracellular matrix (ECM) factors and their subsequent degradation. Podosome formation regulates the activity of proteolytic enzymes involved in ECM degradation, including matrix metalloproteases and ADAMs (a disintegrin and metalloprotease) for which we have shown before to play a role in DC migration (Baek et al., 2012; Diener et al., 2021). We have now found that DC with knockout of Met (Met-KO) are more impaired at forming podosomes and are thus less efficient at degrading ECM factors (Fig. 6). In addition, Met-KO DC exhibited further impaired motile properties (Hamouda et al. 2021).

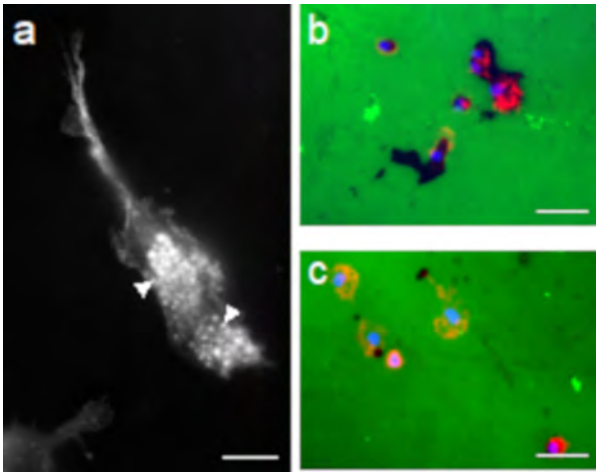


Fig. 6: Podosome formation and gelatin degradation by DC. Representative micrographs of DC with wild type Met (Met-WT) and Met-KO, cultured on fluorescently labelled gelatine (green). (a) DC with clusters of actin-cores that together form podosomes. Arrowheads indicate single actin-cores. Scale bar: 40 µm. (b, c) Gelatine degradation (black areas) by (b) Met-WT DC and (c) Met-KO DC. Actin staining in red; blue: Dapi. Scale bar: 20 µm.

Toward clinical application of leukocyte counts based on targeted DNA methylation analysis

White blood cells (leukocytes) are components of our immune system and their composition can be indicative for various diseases. Conventional methods that quantify leukocyte subsets in fresh blood are based on cell size, granularity, or characteristic surface proteins for specific leukocyte subsets. We developed Epi-Blood-Count, an epigenetic-based approach to quantify leukocytes in low volumes of fresh as well as frozen blood samples using DNA methylation. DNA methylation is the addition of a methyl group to cytosine residues in CG dinucleotides (CpG sites) and plays a role in gene expression and cell development. For each leukocyte subsets we have identified single cell specific CpG sites, whose methylation level is used for cell deconvolution. We have performed relative (%) and absolute (cells/µl) leukocyte counts and shown the similarity of our result with conventional methods for granulocytes, lymphocytes (CD4+ T cells, CD8+ T cells, B cells, NK cells) and monocytes, in a large cohort of healthy and patient donors (Sontag, Bocova et al., 2022). The performance of Epi-Blood-Count was evaluated further by participating in a ring trial with more than 400 other laboratories, to measure granulocytes, lymphocytes, and monocytes in 36 blood samples. Epi-Blood-Count results were within the measuring range of the other laboratories and correlated with the average of the ring trial measurements, indicating a reliable performance.

An additional benefit of Epi-Blood-Count is the application in small volumes of blood (up to 10 microliter) which can be collected by a single finger prick from a clinician or at home using Neoteryx Mitra micro-sampling device (Fig. 7A). Our analysis on more than 100 finger capillary blood samples revealed similar results with conventional counters for granulocytes, lymphocytes, and monocytes (Fig. 7B). Currently, we are trying to quantify more cell types, including hematopoietic stem cells and implement next generation sequencing for leukocyte deconvolution analysis

A

B

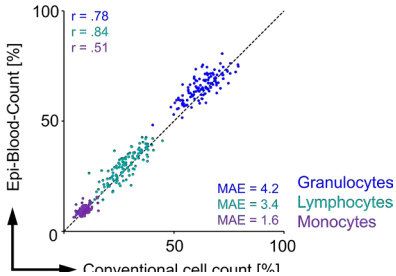
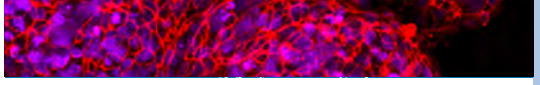


Fig. 7: Epi-Blood-Count deconvolution on capillary blood samples. A) Neoteryx® Mitra® micro-sampling device for collection of up to 10 microliter blood which can be dried and analyzed in a later time. B) Relative Epi-Blood-Counts from capillary blood in comparison to conventional cell counts from venous blood for granulocytes, lymphocytes, and monocytes. Pearson correlation r and mean absolute error (MAE) are given for each cell type.



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Selected References in 2021

[1] Achenbach P., Hambeukers I., Pierlinga A., Gerardo-Nava J.L., Hillerbrand L., Sechi A.S., Glücks K., Dalton P.D., Pich A., Die vernich A., Weis J., Altinova H. and Brook G.A. (2021). A simp le, cost-effective and standardized cell exclusion zone assay preserving cell culture substrate and nanofibre-derived topographical cues. J. Neurosci. Methods, 361, 109289.

[2] Becker J., Böhme P., Reckert A., Eickhoff S.B., Koop B.E., Blum J., Gündüz T., Takayama M., Wagner W., and Ritz-Timme S. (2021). Evidence for differences in DNA methylation between Germans and Japanese: Impact on epigenetic age estimation. Int. J. Legal Med., 136(2):405-413.

[3] Blanco G. E. O., de Souza C.W.O., Bernardo M.P., Zenke M., Mattoso L.H.C., and Moreira, F.K.V. (2021). Antimicrobially , active gelatin/[Mg-Al-CO3]-LDH nanocomposites based on clove essential oil for skin wound healing. Materials Today Communications 27, 102169.

[4] Boehnke J., Atakhanov S., Toledo M.A.S., Schüler H.M., Sontag S., Chatain N., Koschmieder S., Brümmendorf T.H., Kramann R., and Zenke M. (2021). CRISPR/Cas9 mediated CXCL4 knockout in human iPS cells of polycythemia vera patient with JAK2 V617F mutation. Stem Cell Res. 55, 102490.

[5] Božić T., Kuo C., Hapala J., Franzen J., Eipel M., Platzbecker U., Kirschner M., Beier F., Jost E., Thiede C., and Wagner W. (2022). Investigation of Measurable Residual Disease in Acute Myeloid Leukemia by DNA Methylation Patterns. Leukemia 36: 80–89

[6] Bernardo M.P., da Silva B.C.R., Hamouda A.E.I., de Toledo M.A.S., Schalla C., Rütten S., Goetzke R., Mattoso L.H.C., Zenke M. and Sechi A. (2022). Hydroxyapatite/PLA scaffolds exhibit in vitro immunological inertness and promote robust osteogenic differentiation of human mesenchymal stem cells without osteogenic stimuli. Sci. Rep., 11;12(1):2333

[7] Cichoń M.A., Klas K., Buchberger M., Hammer M., Seré K., Zenke M., Tschachler E., and Elbe-Bürger A. (2021). Distinct distribution of RTN1A in immune cells in mouse skin and lym phoid organs. Front. Cell Dev. Biol 8, 608876.

[8] Cypris O., Franzen F., Frobel J., Glück P., Kuo C., Schmitz S., Nüchtern S., Zenke M. and Wagner W. (2021). DNMT3A knockouts in human iPSCs prevent de novo DNA methylation and reveal growth advantage during hematopoietic differentiation. bioRxiv. 10.1101/2021.12.15.472782

[9] Diener N., Fontaine J.F., Klein M., Hieronymus T., Wanke F., Kurschus F.C., Ludwig A., Ware C., Saftig P., Bopp T., Clausen B.E., and Backer R.A. (2021). Posttranslational modifications by ADAM10 shape myeloid antigen-presenting cell homeostasis in the splenic marginal zone. Proc. Natl. Acad. Sci. USA, 118: e2111234118.

[10] Elsafi Mabrouk, M.H., Goetzke R., Abagnale G., Yesilyurt B., Salz L., Cypris O., Glück P., Liesenfelder S., Zeevaert K., Ma Z., Toledo M.A.S., Li R., Costa I.G., Lampert A., Pachauri V., Schnakenberg U., Zenke M., and Wagner, W. (2022). The spacial self-organisation within pluripotent stem cell colonies is continued in detaching aggregates. Biomaterials 282, 121389. Online ahead of print.

[11] Franzen J., Nüchtern S., Tharmapalan V., Vieri M., Nikolić M., Han Y., Balfanz P., Marx N., Dreher M., Brümmendorf TH., Dahl E., Beier F. and Wagner W. (2021). Epigenetic Clocks Are Not Accelerated in COVID-19 Patients. Int. J. Mol. Sci., 22(17):9306

[12] Franzen J., Georgomanolis T., Selich A., Kuo CC., Stöger R., Brant L., Mulabdić MS., Fernandez-Rebollo E., Grezella C., Ostrowska A., Begemann M., Nikolić M., Rath B., Ho A.D., Rothe M., Schambach A., Papantonis A., and Wagner W. (2021). DNA methylation changes during long-term in vitro cell culture are caused by epigenetic drift. Commun. Biol., 4(1):598

[13] Hamouda A.E.I., Schalla C., Sechi A., Zenke M. and Hieronymus T. (2021). Met-signaling controls Dendritic Cell migration by regulating podosome formation and function. bioRxiv., 10.1101/2021.04.28.441791.

[14] Jansen J., Reimer K.C., Nagai J.S., Varghese F.S., Overheul G.J., de Beer M., Roverts R., Daviran D., Fermin L.A.S., Willemsen B., Beukenboom M., Djudjaj S., von Stillfried S., van Eijk L.E., Mastik M., Bulthuis M., den Dunnen W., van Goor H., Hillebrands J., Triana S.H., Alexandrov T., Timm M.,. van den Berge B.T., van den Broek M., Nlandu Q., Heijnert J., Bindels E.M.J., Hoogenboezem R.M., Mooren F., Kuppe C., Miesen P., Gruenberg K., Ijzermans T., Steenbergen E.J., Czogalla J., Schreuder M.F., Sommerdijk N., Akiva A., Boor P., Puelles V.G., Floege J., Huber T.B., The COVID Moonshot consortium, van Rij R.P., Costa I.G., Schneider R.K., Smeets B., and Kramann R.. (2022). SARS-CoV-2 infects the human kidney and drives fibrosis in kidney organoids. Cell Stem Cell., 29(2):217-231.e8

[15] Li Z., Kuppe C., Ziegler S., Cheng M., Kabgani N., Menzel S., Zenke M., Kramann R., and Costa I.G. (2021). Chromatin-accessibility estimation of single-cell ATAC data with scOpen. Nat. Commun., 12, 6386.

[16] Neuberger E., Sontag S., Brahmer A., Philippi K.F.A., Radsak M.P., Wagner W., and Simon P. (2022). Physical activity specifically evokes release of cell-free DNA from granulocytes thereby affecting liquid biopsy. Clin. Epigenetics, in press.

[17] Naue J., Pfeifer M., Augustin C., Becker J., Fleckhaus J., Grabmüller M., Han Y., Heidorn F., Hollaender O., Klein-Unseld R., Kulstein G., Lichtenwald J., Neubauer J., Suarez P., Haas C., Schneider P.M., Vennemann M., Böhme P., and Arbeitsgemeinschaft Molekulare Altersschätzung der Deutschen Gesellschaft für Rechtsmedizin (DGRM). (2021). Forensische DNA-Methylierungsanalyse: Zweiter, technischer Ringversuch der Arbeitsgruppe „Molekulare Altersschätzung“ der Deutschen Gesellschaft für Rechtsmedizin. Rechtsmedizin 31: 202–216.

[18] Olschok K., Han L., Toledo M.A.S., Boehnke J., Theocharides A., Maurer A., Schüler H.M., Buhl E.M., Kalmer M., Pannen K., Gupta S., Boor P., Gezer D., Brümmendorf T.H., Zenke M., Chatain N., and Koschmieder S. (2021). CALR frameshift mutations in MPN patient-derived iPSCs accelerate maturation of megakaryocytes. Stem Cell Reports 16, 2768-2783.

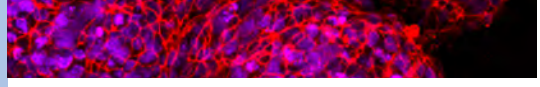
[19] Park Y.S., Lee Y., Choi N.Y. Hwang H.S., Rose-John S., Zenke M. and Ko K. (2022). Enhancement of proliferation of human umbilical cord blood-derived CD34+ hematopoietic stem cells by a combination of hyper-interleukin-6 and small molecules. Biochem Biophys Rep. 29, 101214.

[20] Riegert J., Töpel A., Schieren J., Coryn R., Dibenedetto S., Braunmiller D.L., Zajt K., Schalla C., Rütten S., Zenke M., Pich A. and Sechi A. (2021) Guiding cell adhesion and motility by modulating mechanical and topographic properties of microgel arrays. PLoS ONE 16(9): e0257495.

[21] Satoh T., Toledo M.A.S., Boehnke J., Olschok K., Küstermann C., Sontag S., Seré K., Koschmieder S., Brümmendorf T.H., Chatain N., Tagawa Y.I., and Zenke M. (2021). Human DC3 antigen presenting dendritic cells from induced pluripotent stem cells. Front. Cell Dev. Biol. 9, 667304.

[22] Schäringer K., Maxeiner S., Schalla C., Rütten S., Zenke M. and Sechi A. (2021). LSP1-myosin1e bi-molecular complex regulates focal adhesion dynamics and cell migration. FASEB J., 35(2): e21268.

[23] Schmidt M., Maixner F., Hotz G., Pap I., Szikossy I., Pálfi G., Zink A. and Wagner W. (2021). DNA methylation profiling in mummified human remains from the eighteenth century. Sci. Rep., 11(1):15493



[24] Sebastian R., Buhl E.M., Drescher S., Schalla C., Zenke M., Mattoso L.H.C. and Sechi A. (2021b). Curauá-derived carbon dots: fluorescent probes for effective Fe(III) ion detection, cellular labeling and bioimaging. Mater. Sci. Eng. C, 129, 112409.

[25] Sebastian R., Hamouda A.E.I., Toledo M.A.S., Hu C., Bernardo M.P., Schalla C., Leite L.S.F., Buhl E.M., Dreschers S., Pich A., Zenke M., Mattoso L.H.C. and Sechi A. (2021a). Functionalized cellulose nanocrystals (CNCs) for cellular labelling and bioima ging Biomacromolecules, 22, 454-466.

[26] Siahaan T., Reckert A., Becker J., Eickhoff S.B., Koop B., Gündüz T., Böhme P., Mayer F., Küppers L., Wagner W., and Ritz-Timme S. (2021). Molecular and morphological findings in a sample of oral surgery patients: What can we learn for multi variate concepts for age estimation? J. Forensic Sci., 66: 1524-1532

[27] Sibert N.T., Ferreira M.S.V., Wagner W., Eipel M., Brümmendorf T.H., Orlikowsky T., and Beier F. (2021). Cord blood telomere shortening associates with increased gestational age and birth weight in preterm neonates. Exp. Ther. Med., 21: 344.

[28] Sontag S., Bocova L., Hubens W.H.G., Nüchtern S., Schnitker M., Look T., Schröder K.M., Plümäkers B., Tharmapalan V., Wessiepe M., Kraus T., Kramer J., Rink L., Koschmieder S., and Wagner W. (2022). Toward clinical application of leukocyte Chemistry.

[29] Toledo M.A.S., Gatz M., Sontag S., Gleixner K.V., Eisenwort G., Feldberg K., Hamouda A.E.I., Kluge F., Guareschi R., Rossetti G., Sechi A.S., Dufva O.M.J., Mustjoki S.M., Maurer A., Schüler H.M., Goetzke R., Braunschweig T., Kaiser A., Panse J., Jawhar M., Reiter A., Hilberg F., Ettmayer P., Wagner W., Koschmieder S., Brümmendorf T.H., Valent P., Chatain N., and Zenke M. (2021). Nintedanib targets KIT D816V neoplastic cells derived from induced pluripotent stem cells of systemic mastocytosis. Blood 137, 2070-2084.

[30] Tripathi P., Guo H., Dreser A., Yamoah A., Sechi A., Jesse C.M., Katona I., Doukas P., Ernst S., Nikolin S., Ernst S., Aronica E., Troost D., Glass H., Hermann A., Steinbusch H., Feller A.C., Bergmann M., Jaarsma D., Weis J. and Goswami A. (2021). Pathomechanisms of ALS8: Altered autophagy and defective RNA binding protein (RBP) homeostasis due to the VAPB P56S mutation. Cell Death Dis., 12, 466.

[31] Wagner A.D., Wittkop U., Thalmann J., Willmen T., Gödecke V., Hodam J., Ronicke S., and Zenke M. (2021). Glucocorticoid effects on tissue residing immune cells in giant cell arteritis: Importance of GM-CSF. Front. Med. 8, 709404.

[32] Wagner W. How to translate DNA methylation biomarkers into clinical practice. Front. Cell. Dev. Biol., in press.

[33] Xu H., Look T., Prithiviraj S., Lennartz D., Cáceres, M.D., Götz K., Wanek P., Häcker H., Kramann R., Seré K., and Zenke M. (2021). CRISPR/Cas9 editing in conditionally immortalized HoxB8 cells for studying gene regulation in dendrtic cells. Eur. J. Immunol. Online ahead of print

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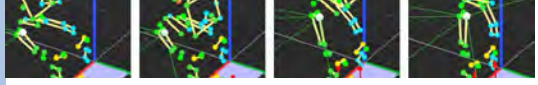


Introduction

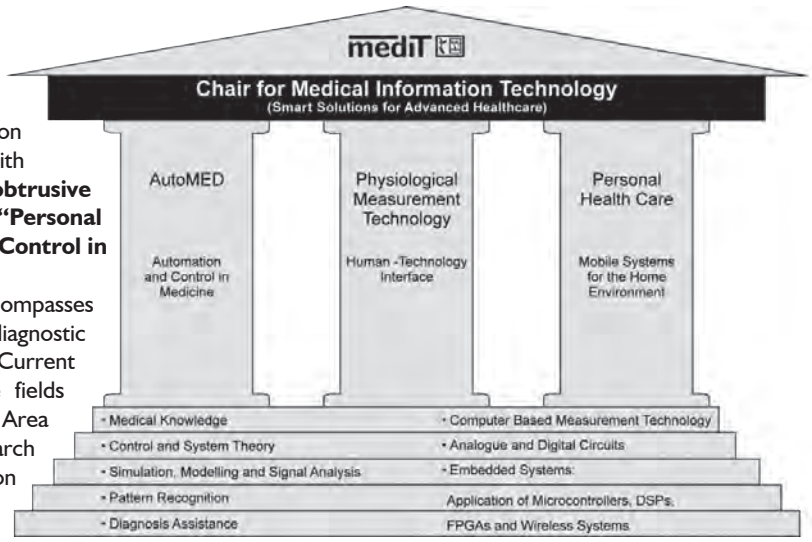


Fig. 1: Research profile of MedIT.

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

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

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

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

Ongoing Research - Selected Projects

Rehabilitation Robotics for Patients with limited Walking Ability

Wearable lower-limb exoskeletons can assist patients with limited walking abilities, e.g., due to post-stroke hemiplegia, by providing additional torques to the subject's joints. We investigate novel drive concepts and different control approaches to make such systems more secure and user-friendly. On the hardware side, we focus on lower limb exoskeletons with variable stiffness actuators (VSAs), see Fig. 2.

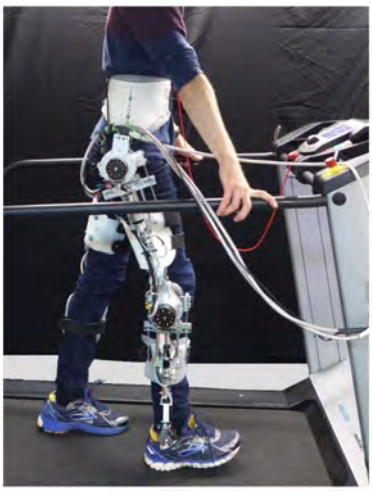


Fig. 2: Gait experiment on a treadmill with lower-limb exoskeleton and serial elastic actuators in hip and knee joint.

These actuators are characterized by an elastic, adjustable coupling between the exoskeleton and the patient, thus ensuring a higher safety. Additionally, the elastic element functions as a torque sensor for the human-machine interaction torque by measuring the spring deflection using high precision encoders.

One crucial part in cooperatively assisting the patient's rest motor function with these VSAs is to detect the pa-tient's intention to move. Our approach to addressing this challenge is based on the system theoretical know-ledge. Using detailed mathematical models of the exoskeleton's and patient's dynamical behavior and the interaction torque measurement via the elastic actuator, we can estimate the patient's movement in real-time. This approach is advantageous because the patient does not need to be equipped with additional sensors such as electrodes to measure muscle activity. Having detailed knowledge about the patient's movement intention is essential for implementing further control strategies. For example, it can be used to realize a behavior of the exoskeleton similar to an e-bike, where a certain assisting factor amplifies the subject's torque. On the other hand, the information about the patient's joint torque can also be used to quantify the strength and fatigue of the patient during rehabilitation training. Our goal is to combine the concepts of variable stiffness actuators, patient-cooperative control, fatigue estimation and gait stabilization to obtain an overall concept that safely and user-friendly assists patients and physiotherapists in rehabilitation training.

Funded by: German Research Foundation (DFG) and Stiftung Universitätsmedizin Aachen.

Hybrid FES-Exoskeleton on Human Body Rehabilitation

Clinical rehabilitation and postoperative rehabilitation are critical for patients' health, especially for the elders. The most common impairment is a lower limb and upper limb paresis. Functional electrical stimulation (FES) and exoskeleton are regarded as necessary methods to rehabilitate body motion. However, implementing these two methods alone cannot achieve the desired goal of gait motion control. One promising way to assist body rehabilitation is a hybrid electromechanical system. Therefore, the objective of the project is to develop and evaluate a hybrid robotic system, which combines FES technology, body motion track system, and sensors, see Fig. 3.

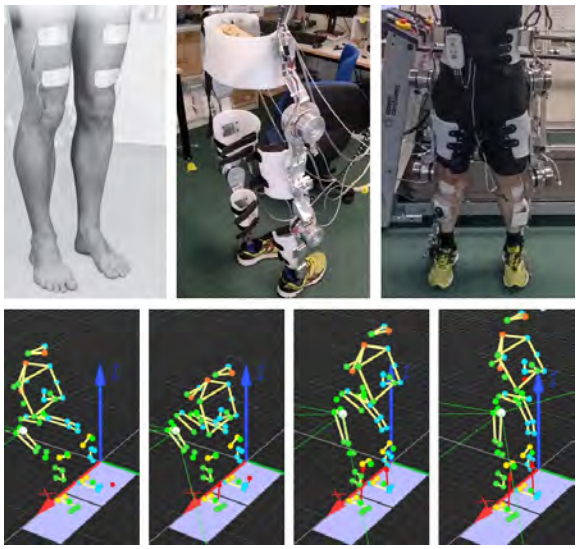


Fig. 3: Concept of hybrid exoskeleton in body motion rehabilitation during sit to stand test.

To archive this goal, the motion capture system is first used to get the precise trajectory of basic body motions as walking, sit-to-stand and so on. Exoskeletons with four motors are designed and attached to hips and knees. They mainly keep the body stable and provide torque assistance when moving. The FES system, which has four channels, is applied on the tibialis muscle, soleus muscle, gracilis muscle, and rectus femoris muscle. Instead of stimulating the muscle itself, stimulating the muscle's nerve will fully contract the muscles. Furthermore, muscle fatigue and EMG signal are also considered in the rehabilitation process. Combining the exoskeleton with neurological methods and sensors could enhance the performance of the closed-loop system. This hybrid system can be applied in rehabilitation centres. Further studies and applications are underway to evaluate the efficacy and control strategy in a clinical trial.

Multi-modal Camera-based Wound Diagnosis by Means of Neuromorphic Computing

The term chronic wound refers to a breach of our protective barrier, the three layers of skin. Here the orderly wound healing process somehow stagnates, often at the inflammatory stage. In order to timely treat or even to prevent such wounds, an early detection and a close supervision of conclusive wound parameters is desired, for instance dimensions and temperature distribution. This could not only improve the treatment, but also reduce the costs and the stress for the patients. This project envisions to relief healthcare professionals in hospitals or outpatient care from paper forms, disposable rulers and subjective, educated guesses during (chronic) wound evaluation by developing a small, mobile, AI-based and contact-less 1-Click-Solution. The resulting diagnostic tool will only require one push of a button to perform visual and thermal inspection, infer the wound parameters, store them on clinical servers, conduct an analysis of the long-term development and report all of this back to the attending physician, see Fig. 4.

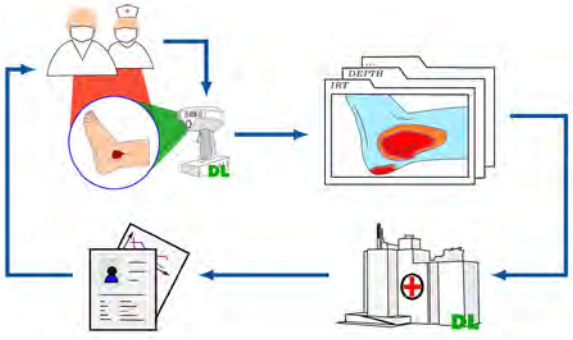
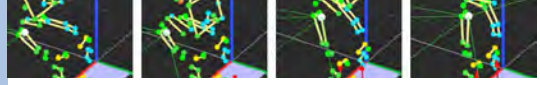


Fig. 4: Illustration of smart wound scanner.

Designing such a mobile wound scanner involves a multi-modal, camera-based approach for visual and thermal image acquisition. It is also equipped with a brain-like processing unit for image processing and computationally intensive deep learning (DL) algorithms. Currently, available GPUs for AI-applications are not yet optimized for energy efficiency though, hence limiting the abilities of mobile devices. Therefore, this project is embedded into the future cluster NeuroSys, consisting of 30 academic and industrial project partners. The cluster aims to establish a leading local industry for development of so-called neuromorphic hardware for such autonomous systems, dedicated to artificial intelligence. This kind of hardware will be solely designed for a fast and energy efficient implementation of neural networks, allowing complex yet mobile applications such as the wound scanner.

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



Modelling and Validation of a decentralized Breathing Gas Source Estimation

The global Covid-19 pandemic came with a severe shortage of mechanical ventilators due to a mismatch of high demand and insufficient availability. Aiming for an affordable and fast producible but yet life-saving ventilator the MedIT institute designed and built its very own one: the people's ventilator "PV1000". However, this ventilator still relies on a high pressure supply with respect to both air and oxygen and the distribution of the latter can be challenging depending on the infrastructure of the country. For further steps it is therefore desired to add a decentralized source of breathing gas. The first approach includes the use of a medical blower to compress the surrounding air and a common oxygen concentrator for an increased fraction of Oxygen (FiO2). Designing the functional architecture in general with its hardware components alone while searching for an optimum can be time-consuming and the testing procedure of mechanical ventilators under realistic circumstances comes with high cost and effort. Therefore, a precise simulation instrument not only with respect to pressure and flow but also with respect to oxygen concentration is of high interest. For this purpose Mathworks provided an enhanced Simscape model such that H2O (humidity), O2, CO2 and N2 can be tracked. Fig. 5 shows the structure of the Simscape model.

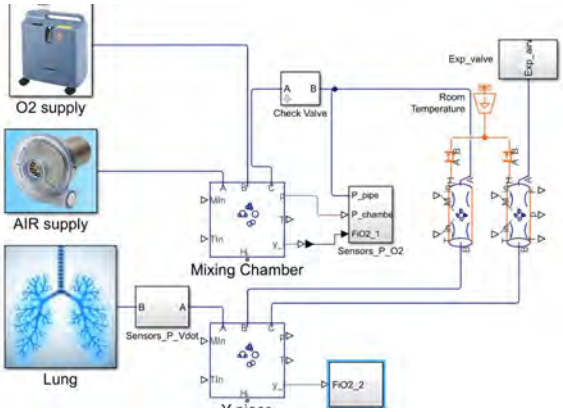


Fig. 5: Model of the decentralized breathing gas source.

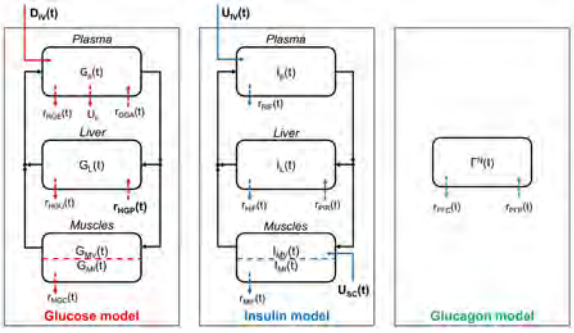
Low compressed air and oxygen is delivered by constant flow sources and both outputs are fed into a mixing chamber. A check valve ensures uni-directional flow towards the lung. Pressure, flow and oxygen concentration can be obtained at multiple locations and the model is aimed to be validated using a hardware test bench of equal architecture with several modes of ventilation.

The overall purpose is to create a simplified digital twin for simulating mechanical ventilation but also with respect to the effect on a potential patient. Further stages of oxygen diffusion, transport and consumption are going to be included in the future.

Blood Glucose Control in the Intensive Care Unit

Patients in the intensive care unit often face stress hyperglycemia and high glycemic variability. Stress hyperglycemia can occur after an acute illness, surgery, or disease and is described by high blood glucose levels exceeding 140 mg/dl. Glycemic variability describes the strength of oscillations in BG throughout the day. As recent studies show, both stress hyperglycemia and high glycemic variability are associated with higher morbidity and mortality. Stress hyperglycemia is induced by a series of stress hormones, which increase insulin resistance. The detailed mechanisms are still unknown. Intensive insulin therapy of critically ill patients can reduce the risk of hyperglycemia. Nonetheless, a successful treatment needs to prevent hypoglycemia where blood glucose drops below 70mg/dL. There is no global consensus for a protocol and a glycemic target for insulin therapy in the critically ill. Furthermore, current treatments are limited due to the non-continuous monitoring of the blood glucose level.

Mathematical models describing the blood glucose metabolism enhance understanding of the pathophysiology of stress hyperglycemia. Typically, these models describe the interaction of glucose, insulin, and glucagon in different body compartments, see Fig. 6. The impact of nutrition or exogenously administered insulin on blood glucose can be studied. Especially changes in insulin sensitivity and resistance and their influence on the blood glucose dynamic



are of interest.

Fig. 6: Compartment model to describe the blood glucose metabolism. The model consists of subsystems for glucose, insulin and glucagon.

Models of the glucose metabolism can assist in improving insulin therapy and developing closed-loop systems for automatized insulin therapy. Especially robust control methods are of interest as they guarantee a stable and robust performance for a large patient group.

Blood Glucose Control during Physical Activity in type 1 Diabetes Mellitus

Patients with Diabetes mellitus type 1 cannot produce the blood glucose lowering hormone insulin. Instead, the blood glucose level is controlled by an exogenous injection of insulin. An adequate insulin dose is essential to prevent low blood glucose levels (hypoglycemia), which pose an acute danger. Additionally, it can prevent high blood glucose levels (hyperglycemia), which cause secondary diseases in the long-term. Due to the delayed effect of subcutaneously injected insulin, the insulin dose must be determined foresightedly. Multiple disturbances like meals or physical activity impede a precise prediction of the insulin demand. This project focuses on the particularly challenging impact of physical activity, which depends on multiple factors like exercise type, intensity, duration, nutritional status, and inter-individual differences.

Mathematical models of the glucose-insulin metabolism are a valuable tool in the development of strategies for blood glucose control. They enable simulations and forecasts of the blood glucose level and can thus be used to develop and validate control strategies. The literature describes several models of the glucose-insulin metabolism considering the impact of physical activity. However, none of these models was thoroughly evaluated. Even though the model accuracy is essential for the significance of simulation results and derived control strategies, there is only little information about it.

In the course of this project, pre-existing models describing the impact of physical activity on the glucose-insulin metabolism are analyzed, and a new model is developed. Both models from literature and the newly developed model are implemented and evaluated with clinical data to identify the best model. There are two long-term objectives. The first goal is the implementation of a simulator, which can be used to develop and validate blood glucose control strategies during exercise. Different exercises and patients shall be covered. The second goal is a model-based assistance system, which provides individually optimized suggestions for therapy adaptations for announced physical activity, see Fig. 7.

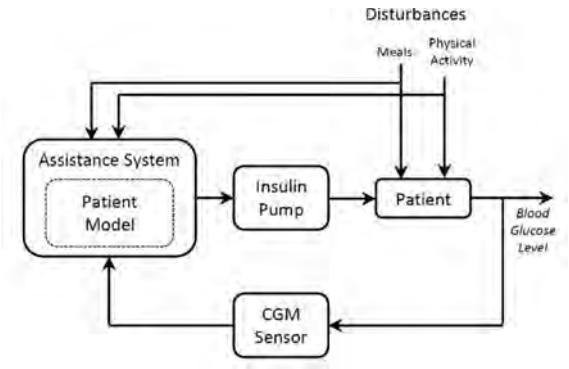


Fig. 7: Scheme of the assistance system: The assistance system receives manually inserted information on meal intake and physical activity and is furthermore informed by a sensor for continuous glucose monitoring (CGM). The insulin delivery is then adapted based on the received information and on an individualized model of the glucose insulin metabolism.

Funded by: Studienstiftung des deutschen Volkes

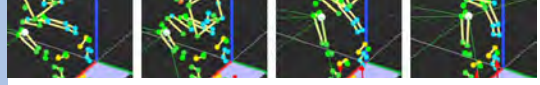
Electrical Impedance Tomography for Mammography

Breast cancer is the most common life-threatening cancer affecting women around the world. Its survival rate can be significantly improved with early diagnosis and early treatment. There are different imaging modalities for breast cancer detection such as magnetic resonance imaging (MRI) screening, mammography with two x-ray beams at different angles, and sonography based on ultrasound-screening. The quality and performance of these techniques are still limited, for example, when dealing with dense breast tissue, facing the variability of personal experience and struggling with the issue of time consumption. To overcome these disadvantages, a novel approach for the detection of breast cancer is developed in this project.

The main goals are to develop an imaging modality that allows for early detection of breast cancer and its therapy. Together with our project partners (Goethe University Frankfurt, Lisa Laser Products OHG, Dr. Sennewald Medizintechnik GmbH and Infineon Technologies AG), we develop a system that combines imaging of breast cancer and minimally invasive therapy. For the therapy a laser system will be developed by Lisa Laser Products OHG for the early treatment of breast cancer. The imaging will be realized with the help of electrical impedance tomography (EIT) and millimeter-wave-radar (mmW). In the past, both EIT and mmW were implemented individually with mediocre success. Since EIT and mmW cover different parts of the electromagnetic spectrum, a combination of both techniques should be able to compensate for the drawbacks of each individual technology.

Although EIT has been well established in the two-dimensional domain, technology transfer to the three-dimensional domain is limited and will be a challenging task. Hence, further research on optimal patterns of current injection and voltage measurement is required in order to reconstruct breast images effectively. Due to the lack of short-term impedance dynamics inside the breast, new reconstruction algorithms will be developed, because time-difference EIT cannot be applied in a meaningful way. Thus, we will focus our research on image reconstruction using AI methods. Artificial neural networks are a promising way to enable reference free reconstructions of EIT images. However, the main challenge is to find appropriate ways to generate sufficient training data. These challenges can be overcome by strong cooperation with all project partners.

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



Selected References in 2021

[1] Lyra, S.; Mayer, L.; Ou, L.; Chen, D.; Timms, P.; Tay, A.; Chan, P.Y.; Ganse, B.; Leonhardt, S.; Hoog Antink, C. (2021),"A Deep Learning-Based Camera Approach for Vital Sign Monitoring Using Thermography Images for ICU Patients", Sensors, doi: 10.3390/s21041495, 2021

[2] B. Penzlin, L. Bergmann, Y. Li, L. Ji, S. Leonhardt, C.Ngo, "Design and First Operation of an Active Lower Limb Exoskeleton with Parallel Elastic Actuation", Actuators, doi: 10.3390/act10040075, 2021

[1] B. Hentze, T. Muders, C. Hoog Antink, C. Putensen, A. Larsson, G. Hedenstierna, M. Walter, S. Leon-hardt, „A model-based source separation algorithm for lung perfusion imaging using electrical impedance tomography", Physiol. Meas., doi: 10.1088/1361-6579/ac0e84, 2021

[3] L. Bergmann, S. Leonhardt, D. Greven, B. J. E. Misgeld, "Optimal Assistive Control of a Pedal-electric Drive Unit", Control Engineering Practice (CEP), doi: 10.1016/j.conengprac.2021.104765, 2021

[4] R. D. Pollock, C. J. Jolley, N. Abid, J. H. Couper, L. Estrada-Petrocelli, P. D. Hodkinson, S. Leonhardt, S. Magor-Elliott, T. Menden, G. Rafferty, G. Richmond, P. A. Robbins, G. A. D. Ritchie, M. J. Segal, A. T. Stevenson, H. D. Tank, T. G. Smith, "Pulmonary effects of sustained periods of high-G acceleration relevant to suborbital spaceflight", Aerospace Medicine and Human Performance, doi: 10.3357/AMHP.5790.2021, 2021

[5] T. Menden, G. B. Alcaín, A. T. Stevenson, R. D. Pollock, H. Tank, P.Hodkinson, C. Jolley, T. G. Smith, S. Leonhardt, M. Walter, "Dynamic Lung Behavior under high G-Acceleration Monitored with Electrical Impedance Tomography", Physiol. Meas., doi: 10.1088/1361-6579/ac1c63, 2021

[6] X. Yu, C. Hoog Antink, S. Leonhardt, L. C. Bollheimer, T. Laurentius, „Non-Contact Measurement of Heart Rate Variability in Frail Geriatric Patients: Response to Early Geriatric Rehabilitation and Comparison with Healthy Old Community-Dwelling Individuals - A Pilot Study", Gerontology. doi: 10.1159/000518628, 2021

[7] M. Lueken, J. Loeser, N. Weber, C. Bollheimer, S. Leonhardt, C. Ngo, "Model-Based Step Length Esti-mation Using a Pendant-Integrated Mobility Sensor", IEEE Transactions on Neural Systems and Rehabilitation Engineering, doi: 10.1109/TNSRE.2021.3133535, 2021

[8] L. Korn, S. Dual, J. Rixen, M. Meboldt, S. Leonhart, M. Schmid Daners, M. Walter, „Dual-modality Volu-me Measurement integrated on a Ventricular Assist Device", IEEE Transactions on Biomedical Engineering, doi: 10.1109/TBME.2021.3115019, 2021

[9] S. Dahlmanns, S. Reich-Schupke, F. Schollemann, M. Stücker, S. Leonhart, D. Teichmann, „Classification of chronic venous diseases based on skin temperature patterns", Physiol. Meas., doi: 10.1088/1361-6579/abf020, 2021

Prizes and Awards

• C. Hoog Antink has been appointed as professor in the Department of Medical Engineering at the Department of Electrical Engineering and Information Technology at TU Darmstadt.

• S. Leonhardt has been awarded with VDE Badge of Honour in Silver.

• S. Leonhardt has been accepted into IEEE's Technical Committee of Cardiopulmonary Systems and Physiology-Based Engineering (CSPE).

• K. Schröder has been awarded the title of Germany's best apprentice in the state-recognized training occupation of mathematical-technical software developer.

• M. Walter has finished his habilitation and was awared the venia legendi, the permission for independent university teaching.

People at MedIT

Lehr- und Forschungsgebiet Biomaterialien

RWTH AACHEN UNIVERSITY

Laboratory for Biomaterials

Faculty of Mathematics, Computer Science and Natural Sciences

Synthesis and Application of Glycoconjugates

Director

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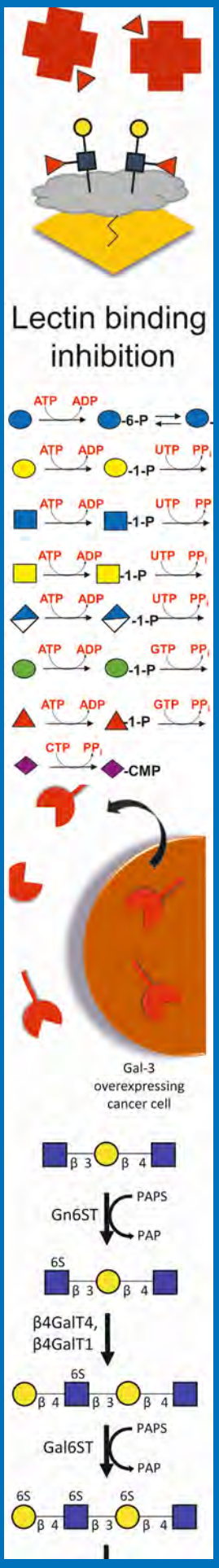

Introduction

Sugar chains (glycans) of glycoproteins, glycolipids, and proteoglycans encode biological information on the cell surface and in the extracellular matrix (ECM). The complexity of glycans is the key for many cell-cell and cell-ECM interactions. Glycan-binding proteins, known as lectins, specifically decode the glycan information. In a disease state, altered glycan structures of cell surface receptors trigger the binding of specific lectins with subsequent cell responses. Cell-surface glycans are adhesion points for specialized pathogens (bacteria, viruses) and bacterial toxins. Human milk glycans are essential for infant nutrition and intestinal protection against pathogens. Polysaccharides are essential components of therapeutic and cosmetic products. With this background, sugar-based biomaterials are of special interest as diagnostic and therapeutic tools in biomedical research.
Also in 2021, the progress of our research projects was markedly hampered by the corona crisis. In this annual report, we provide an overview of our research efforts on the synthesis and applications of glycoconjugates. We summarize our general synthetic strategy using Leloir-glycosyltransferases. Optimized enzyme-cascades accelerated the multi-gram-scale synthesis of nucleotide sugars as substrates for Leloir glycosyltransferases. Cascading of immobilized enzymes facilitated the synthesis of the biopolymer hyaluronic acid. With our collaboration partners, we developed a novel biosensor for encoding and decoding glycan information as well as potent glycopolymers for effective inhibition of the tumor-related galectin-3. This chapter summarizes the most recent results from our peer-reviewed publications in 2021.

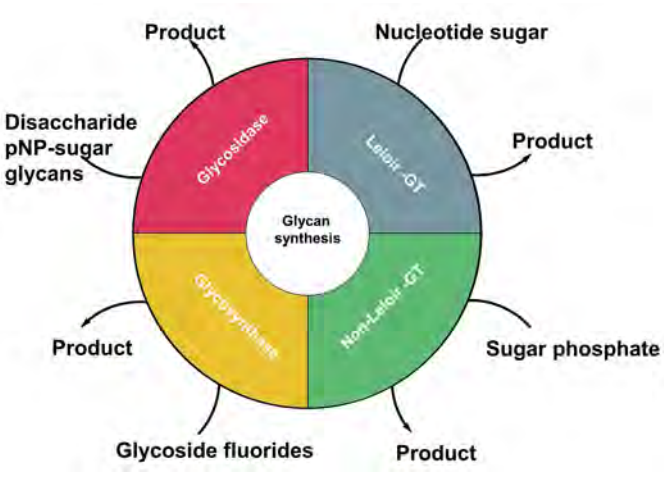

Fig. 1: Main enzyme families for glycan synthesis.[1]

Combinatorial Biocatalysis

The Golgi Glycan Factory (GGF)

The Golgi Glycan Factory (GGF) provides synthetic strategies for the enzymatic synthesis of glycans. Leloir glycosyltransferases (GTs) are one of the four main enzyme classes for carbohydrate synthesis (Fig. 1).[1] They use activated nucleotide sugars as donor substrates exclusively and retain or convert the anomeric configuration of the transferred sugar in the newly formed glycosidic bond. GTs which are dependent on a sufficient supply of divalent metal ions for the binding of the nucleotide donor substrate are classified as the GT-A family. GT-B assigned glycosyltransferases are independent of metal ions, and substrate binding relies on basic amino acids.

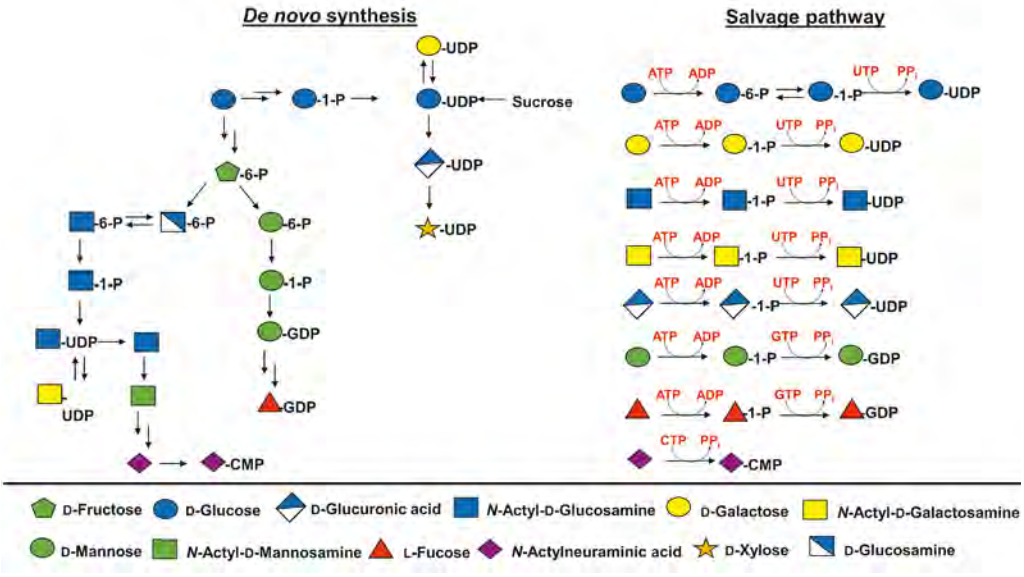

Fig. 2: De novo and salvage pathway synthesis of the nine main nucleotide sugars.[1]

The in vitro production of complex glycans with GTs needs a coordinated supply of activated monosaccharides. Therefore, nucleotide sugars are synthesized in gram quantities applying two main synthesis pathways (Fig. 2).[1] For the in vitro synthesis of natural glycan structures, Leloir GTs are the first choice since they feature a high regio- and stereoselectivity. Cascading different Leloir GTs allow a defined assembly of very complex linear, branched or repetitive glycan structures (Fig. 3).[1] However, some GTs tend to catalyze the hydrolysis of their donor substrates, even in presence of the acceptor substrate, leading to reduced product titers. Furthermore, the production of GTs is limited with bacterial production systems, since cell lysis and protein

purification are challenging on a high scale. However, promising new technologies are available for the high-scale synthesis of Leloir GTs, leading to an interesting future perspective and an enhanced toolbox of more versatile GT availability.

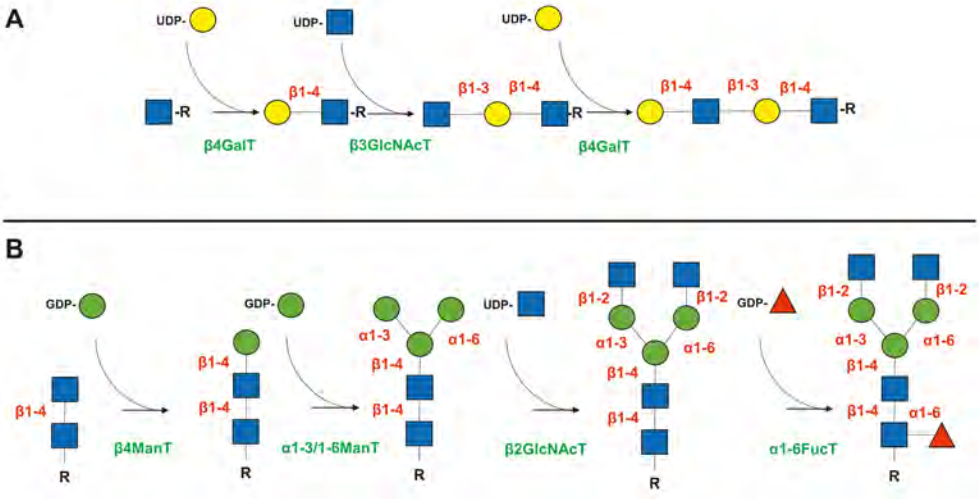

Fig. 3: Cascades of Leloir glycosyltransferases for the synthesis of linear and complex glycans. A: Synthesis of LacNAc tetrasaccharides. B: Cascade synthesis of a fucosylated bi-antennary N-glycan structure.[1]

Working Group

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M. Sc. Raphael Heinzler, Prof. Dr. Matthias Franzreb, Karlsruhe Institute for Technology KIT.

Selected Reference

[1] Rexer, T., Laaf, D., Gottschalk, J., Frohnmeyer, H., Rapp, E., and Elling, L. (2020) Enzymatic Synthesis of Glycans and Glycoconjugates, in Advances in Glycobiotechnology, Rapp, E., Reichl, U. (Eds.), Advances in Glycobiotechnology. Springer International Publishing, Cham, pp. 231-280. DOI: 10.1007/10_2020_148.

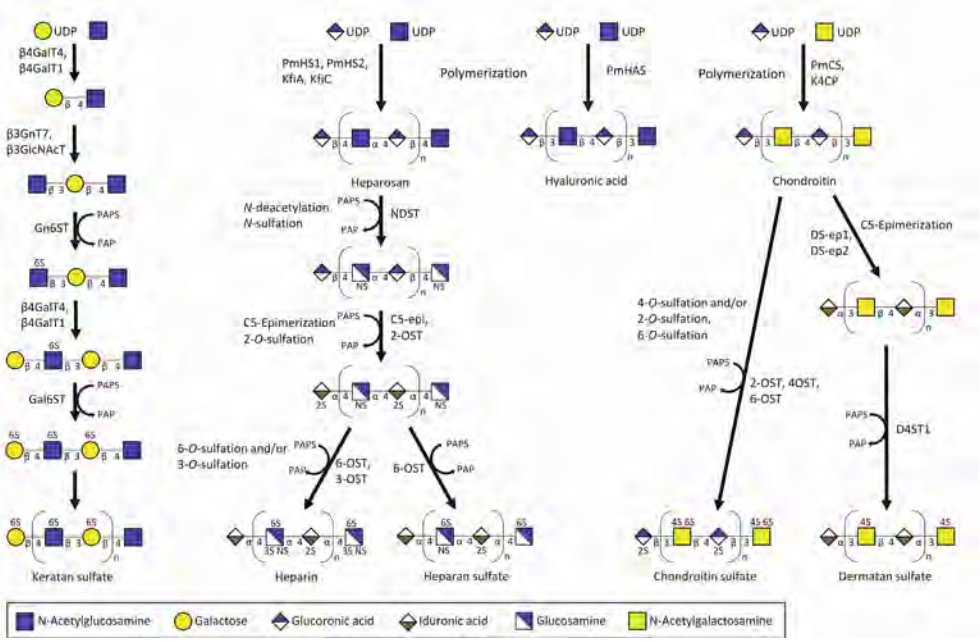

Fig. 4: Enzyme cascades for the synthesis of glycosaminoglycans.

Financial Support

Financial support by the BMBF, funding the projects "The Golgi Glycan Factory" and "The Golgi Glycan Factory 2.0" (AZ: -31P7317 and AZ: 031A557A) in the BMBF program Biotechnology 2020+ - Basic Technologies, is gratefully acknowledged.

Enzymatic Synthesis of Hyaluronic Acid and Glycosaminoglycans

Glycosaminoglycans (GAGs) are linear anionic polysaccharides assembled by Leloir glycosyltransferases, of which most sugars are specifically sulfated. In studies on GAGs that have been going on for decades, a broad set of biological functions was discovered. They are involved in pathogen/viral defense, coagulation, inflammation, and cell adhesion. Therefore, they are interesting candidates for medical and therapeutic applications, and many

drugs based on GAGs were developed. Today, the common industrial production of GAGs is based on extraction from animal tissue. Obstacles of these processes are contamination with animal proteins, high dispersity, and non-uniformed sulfation patterns. The increasing demand for pure and well-defined GAGs calls for synthetic approaches like highly controllable (chemo-) enzymatic processes (Fig. 4).[2]

While nearly all GAGs show different N- and O-sulfate patterns and are often conjugated with proteins, Hyaluronic acid (HA) is the only GAG that is not further modified during biosynthesis. It is composed of repeating disaccharide units ([-3)GlcNAc(β1-4) GlcA(β1-]$_n$) with a molecular size up to 10^7 Da. Due to its polyanionic character, HA is a viscoelastic gel that binds large amounts of water. In the human body, the naturally occurring HA is involved in biological tasks like tissue repair, cell proliferation, inflammation, and skin moisturization. It is applied in treatments of arthritis or during ophthalmic surgery and is also used for different cosmetic applications. Current industrial production of high molecular weight (HMW) HA is based on harsh solvent-based extraction from rooster combs or bacterial fermentation with *Streptococcus* strains resulting in a highly dispersed and possibly contaminated HA product, which affects the biological properties of HA. We established an enzymatic in *vitro* synthesis with the bifunctional hyaluronan synthase from *Pasteurella* multocida (PmHAS) starting from the substrate's glucuronic acid (GlcA, building block of pectin) and *N-acetylglucosamine* (GlcNAc, building block of chitin).

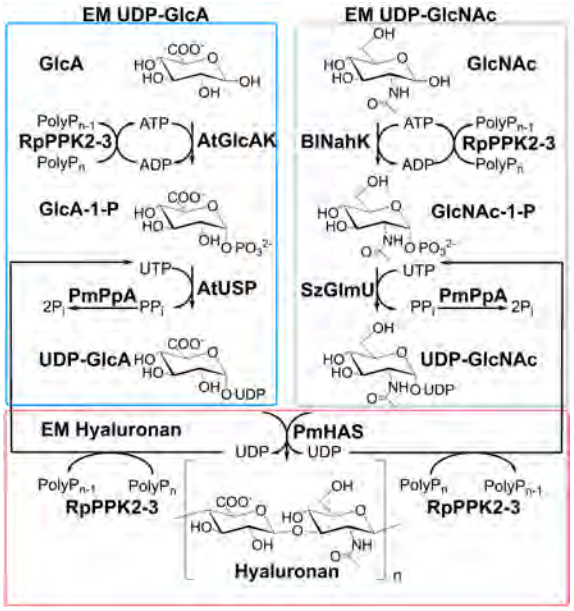

Fig. 5: Enzyme cascade for the synthesis of hyaluronic acid with cofactor regeneration.

By optimizing the enzyme cascade for in situ generations of both nucleotide sugars (UDP-GlcA and UDP-GlcNAc) and combination with PmHAS in a one-pot synthesis, the production of HA with defined MW and the low dispersity was achieved. However, a stoichiometric amount of ATP, which is costly and inefficient for large-scale production, is needed. Therefore, an ATP regeneration system employing polyphosphate (PolyP) and polyphosphate kinase family 2 class 3 from *Ruegeria pomeroyi* (RpPPK2-3) was integrated, extending the enzyme cascade (Fig. 5).

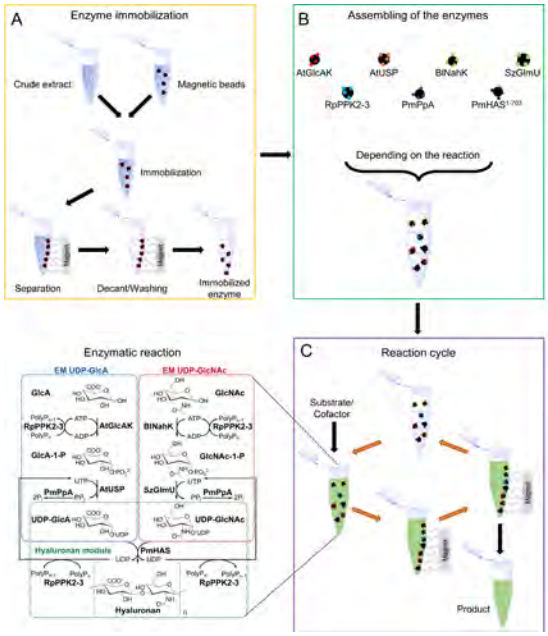

Fig. 6: Immobilized enzyme cascade for the synthesis of hyaluronic acid.

In a one-pot synthesis with all seven enzymes and optimal starting concentrations of $MgCl_2$ (25 mM) and ATP (0.1 mM) in the presence of 20 mM PolyP we reached a HA concentration of 0.81 g/L with an average MW of 1.17 MDa a dispersity of 1.08, and an ATP regeneration cycle of 75.[3]

In an approach to further develop the enzymatic, HA synthesis and address obstacles like high production costs and improvement of activity, stability, and purity of enzymes, an immobilization system was applied. Here, we selectively immobilized enzymes via the non-covalent poly-histidine method on magnetic Sepharose™ beads (MBs) (Fig. 6). By conducting the well-established immobilization protocol using an end-to-end mixer and mild reaction conditions, we were able to immobilize a maximum of nearly 20 mg enzyme per g MBs. To establish the seven-enzyme-one-pot synthesis for immobilized enzymes, each reaction module was individually characterized and the reaction parameters were evaluated and adapted. In summary, all enzymes remained active and PmHAS even showed higher activity. To evaluate the reusability of the immobilized enzymes, repeating reaction cycles were carried out. For all reaction modules, the yields significantly decreased with each additional cycle. Nevertheless, we reached a HA concentration of 0.37 g/L with an average MW of 2.7-3.6 MDa and a low dispersity of 1.02-1.03 in a one-pot synthesis over three days.[4] Since mechanical stress and the continuous exposition to reaction temperature, pH value, and inhibitory reaction compounds could lead to accelerated enzyme degradation, the implementation of a different reactor system should be reflected. Having the enzymatic tools and key parameters in hand, qualitative and quantitative upscaling of enzymatically synthesized HA should now be an achievable goal.

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M. Sc. Johannes Gottschalk, M. Sc. Philip Palm, B. Sc. Lea Blaschke, M. Sc. Simon Rüben

Collaborations

Dr. Miriam Aßmann, Dr. J. Kuballa, GALAB Laboratories GmbH Hamburg.

Selected References

[2] Gottschalk, J., and Elling, L. (2021) Current state on the enzymatic synthesis of glycosaminoglycans, Curr. Opin. Chem. Biol. 61, 71-80, DOI: 10.1016/j.cbpa.2020.09.008.

[3] Gottschalk, J., Blaschke, L., Aßmann, M., Kuballa, J., and Elling, L. (2021) Integration of a Nucleoside triphosphate regeneration system in the one-pot synthesis of UDP-sugars and hyaluronic acid, ChemCatChem 13, 3074-3083. DOI: 10.1002/cctc.202100462.

[4] Gottschalk, J., Aßmann, M., Kuballa, J., and Elling, L. (2021) Repetitive Synthesis of High-Molecular-Weight Hyaluronic Acid with Immobilized Enzyme Cascades, ChemSusChem 14, DOI: 10.1002/cssc.202101071.

Financial Support

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

The Glyco-BioInterface

Biosensor for encoding and decoding glycan information

The analysis of glycan-encoding information and decoding by the binding behavior of lectins is of high interest in the biomedical field. In cooperation with Prof. Uwe Schnakenberg (IWE-1, RWTH Aachen University), we developed an electrochemical impedance spectroscopy (EIS) biosensor, which displays natural-like multivalent neo-glycoproteins by direct covalent attachment on a gold chip (Fig. 7).[5] Modification of the neo-glycoprotein by a bacterial fucosyltransferase was detected with a fucose-specific lectin (*Aleuria aurantia* lectin = AAL). EIS enabled the label-free and real-time monitoring of binding processes to further determine the binding kinetics of the fucosyltransferase. With this, we established a new platform for the monitoring of glycosylation reactions on a sensor chip. Potential application as a diagnostic biosensing tool for the detection of pathogens in disease diagnosis is envisaged.

Working Group

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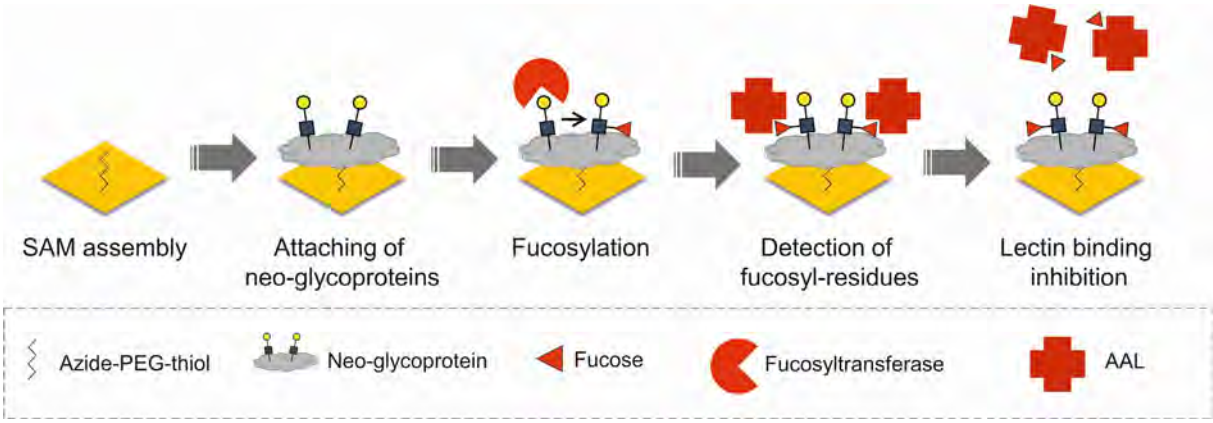

Fig. 7: Biosensor assembly for encoding and decoding glycan information.

Collaborations

Prof. Dr.-Ing. Uwe Schnakenberg, Dr. Tom Kremers, Chair of Micro- and Nanosystems and Institute of Materials in Electrical Engineering 1, RWTH Aachen University,

Selected Reference

[5] Heine, V., Kremers, T., Menzel, N., Schnakenberg, U., and Elling, L. (2021) Electrochemical Impedance Spectroscopy Biosensor Enabling Kinetic Monitoring of Fucosyltransferase Activity, ACS Sensors 6, 1003-1011. DOI: 10.1021/acssensors.0c02206.

Financial Support

Deutsche Forschungsgemeinschaft (DFG) in the framework of the Collaborative Research Center (SFB 985) – Functional Microgels and Microgel Systems.

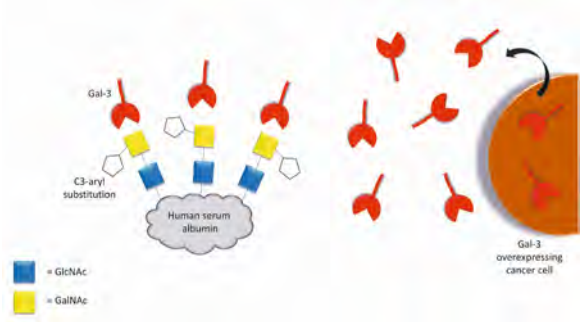

Fig. 8: Immunoprotective neo-glycoprotein for targeting Gal-3.

Multivalent glycoconjugates for the Tumor-related Lectin Galectin-3

The galactose binding protein galectin-3 (Gal-3) plays a crucial role in cancerogenesis and therefore targeting Gal-3 is of high interest in the glycoscience and medical community. Huge progress has been achieved regarding the design of artificial glycomimetics. Recently, in cooperation with our cooperation partners in Prague, the synthesis of a glycomimetic-decorated neo-glycoprotein was

accomplished (Fig. 8)[6]. Here, a C3-aryl-substituted disaccharide was coupled to human serum albumin. The multivalent presentation of the glycomimetic revealed affinity of Gal-3 in the nanomolar range. The ability to scavenge exogenous Gal-3 of cancer cells as well as the inhibition of cell apoptosis demonstrated the high potential of these glycomimetic-carrying proteins as non-toxic and immunoprotective agents in cancer therapy.

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Dr. rer. nat. Helena Pelantová, NMR Faculty, Czech Academy of Sciences, Prague, Czech Republic.

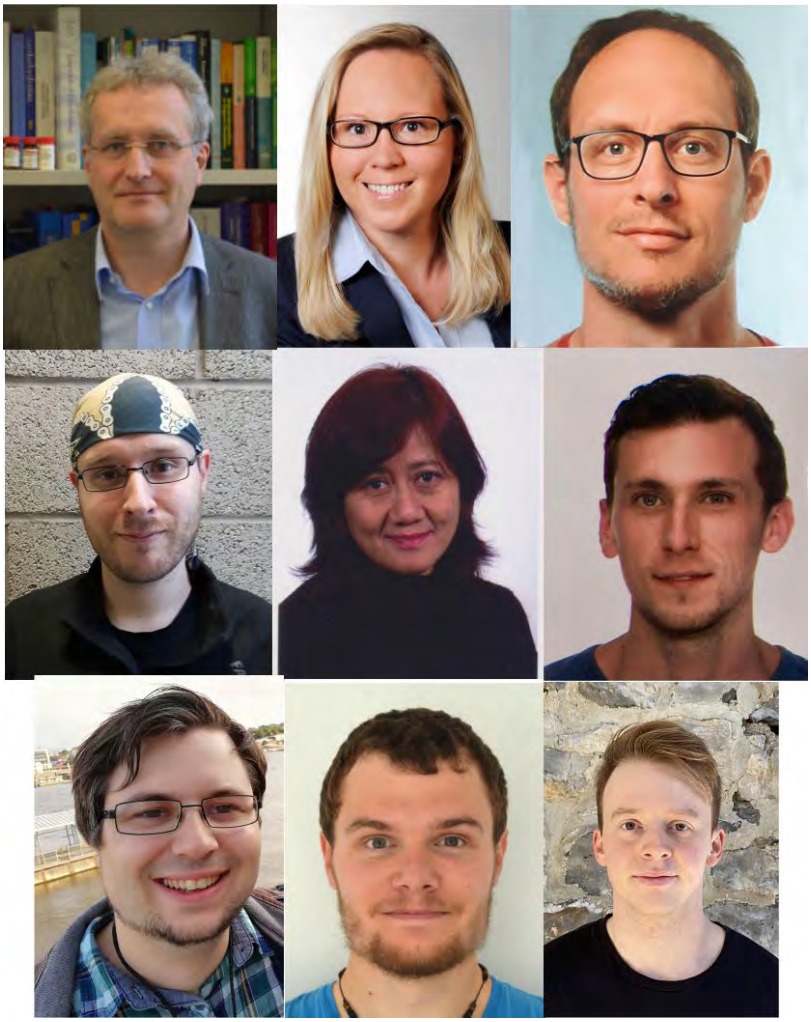
Selected References

[6] Heine, V., Hovorková, M., Vlachová, M., Filipová, M., Bumba, L., Janoušková, O., Hubálek, M., Cvačka, J., Petrásková, L., Pelantová, H., Křen, V., Elling, L., and Bojarová, P. (2021) Immunoprotective neo-glycoproteins: Chemoenzymatic synthesis of multivalent glycomimetics for inhibition of cancer-related galectin-3, Eur. J. Med. Chem. 220, 113500. DOI: 10.1016/.ejmech.2021.113500.

Financial Support

Networking support from the EU-COST action CA18103 and the bilateral mobility project DAAD-20-04 between DAAD and the Czech Academy of Sciences.

OUR TEAM



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Introduction

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

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

Apart from international publications and a practical transfer and implementation of scientific findings, the education of our students from different disciplines and specialties is a major objective. In addition to basic research grants, industrial cooperations, corresponding to about 50% of our annual turn-over, represent an important complementary application-oriented pillar of our work for the transfer of our research and developments into clinical applications.
In 2021 the pandemic situation continued to challenge our team regarding teaching as well as research activities. Especially our novice students and younger colleagues, even not knowing "normal" live and cooperative work, suffer from the ongoing demanding boundary conditions. However, based on established networks and our long lasting cooperation with partners from research, industry and clinics, we have been able to succeed in creating fertile ground for diverse ongoing as well as new activities in research and teaching.
This annual report summarizes some examples of our project work.

Selected Projects

Impact of spinal stenosis on CSF hydrodynamics

The impact of spinal stenosis on cerebrospinal fluid (CSF) dynamics is still unclear. In particular, the correlation with the disease normal pressure hydrocephalus (NPH), respectively with its pathogenesis is vague. Therefore, we experimentally investigated the influence of varying degrees of stenosis in the cervical region on CSF hydrodynamics with respect to NPH. An in vitro model of the craniospinal CSF dynamics, developed in our lab, was used. The stenoses were located in the C6 region. The hydrodynamic cross-sectional area varied in seven measurements from no stenosis to total blockage to simulate different degrees of stenosis. Intracranial pressure (ICP), spinal flow and cranial and spinal compliances were measured. The results show an increase of the ICP amplitude and an accompanying decrease in overall compliance. Increased ICP amplitudes and a decreased craniospinal compliance are typical characteristics of NPH patients. Nevertheless, it is not clear whether a spinal stenosis favors the development of NPH. Therefore, clinical studies will be conducted to determine the prevalence and severity of spinal canal stenoses in NPH patients.

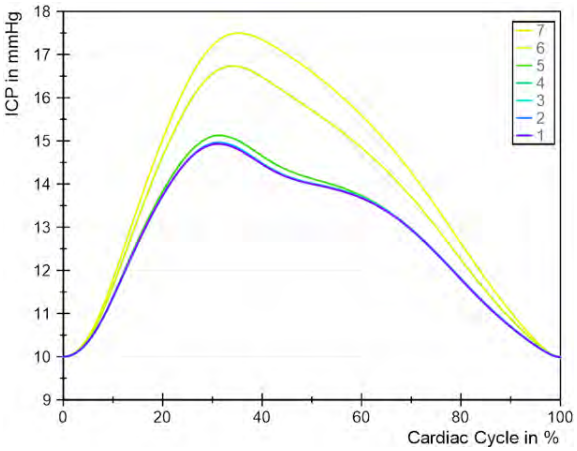

Fig. 1: ICP measurements with increasing cervical stenosis from 1 (no stenosis) to 7 (full blockage).

Patient-specific biomechanics of the knee

In vivo native knee kinematics are of relevance for different clinical applications. The measurement however is time consuming and not part of the clinical routine. Further drawbacks are exposure to radiation or inaccuracies of non-invasive measurement methods. An attractive alternative for the prediction of individual knee kinematics are patient-specific simulation models. Previously, a multi-body simulation model of TKA was developed and validated. The existing model was used as a basis for the derivation of a native knee simulation model. Validation and sensitivity studies were performed in order to assess the prediction accuracy of the model for specific settings.

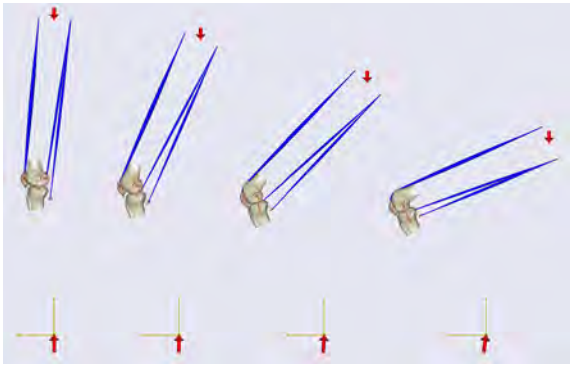

Fig. 2: Patient-specific simulation model for different degrees of knee flexion.

Robotic Bin Picking of Surgical Instruments

Usage of robots for the reprocessing of surgical instruments can reduce risk by avoiding manual interaction of humans with contaminated instruments, as well as avoiding nosocomial infections through standardised and reproducible process control. An important prerequisite for enabling the robot to reach into a tray with contaminated instruments and identify gripping positions is automated instrument detection by means of computer vision. To

solve this problem a basic set of instruments, which make up more than 60% of the reprocessed instruments, have been analysed.

With the help of a camera designed for bin-picking metallic objects, point clouds can be captured, which are evaluated by an algorithm based on RANSAC. Because the robot first removes the instruments on top, the tray is divided into levels based on the depth information in order to reduce the computational effort and to improve the detection accuracy by filtering out occluded instruments.

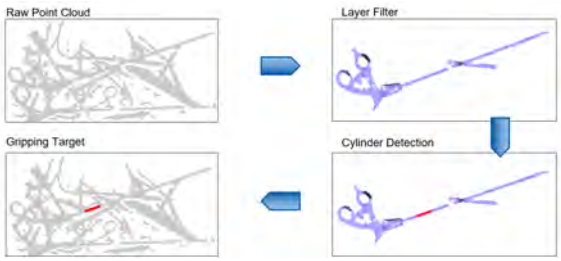

Fig. 3: Identification of gripping targets in unordered instrument tray by applying Layer Filter to reduce clutter

Reference architecture for surgical robot design

Surgical robots have different modular layouts. Modules are often difficult or impossible to identify. In order to make different systems comparable with each other, reference functions can be defined by which each robotic system can be functionally described. These reference functions can be specified for an application scenario. For instance, the reference function "move tool in volume" can be specified to "move burr in a volume of 30x50x10 mm³" to specify the size of a required implant bed in unicondylar knee arthroplasty. Consequently, we have developed a reference system architecture in which not only reference functions but also potential technical and human-based solution principles are collected and linked. Using property-based modularization methods, robots can be systematically modularized by matching properties of solution principles with module drivers and requirements.

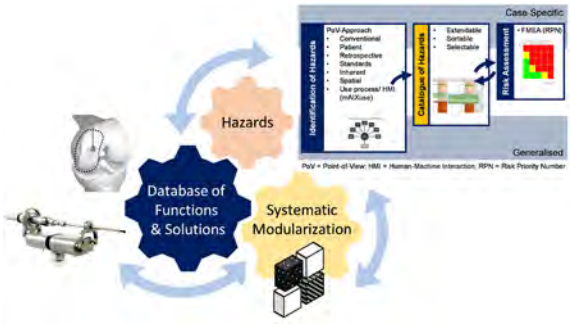

Fig. 4: Reference system architecture: a fundamental part of systematic modularization of surgical robots.

3D robotic ultrasound

For diagnosis and treatment planning in orthopedics, e.g. total knee arthroplasty, 3D imaging is often required. Today's standard for 3D image acquisition is CT or MRI. Both techniques cause high costs and CT emits harming radiation in addition. In contrast, ultrasound is commonly available at chairside, comes at low costs and does not expose the patient to radiation. Interpretation of ultrasound images however is a difficult task, in particular for volumetric images. Sonographer require years of experience to reliably detect the bone surface. Fast and precise diagnostics, e.g. of cruciate ligament rupture or periimplantitis, thus depends on automatic processing. We investigate the potential of robotic ultrasound scanning.
For image acquisition the robot moves along the region of interest while a contact force between the skin and the probe must be maintained. Challenges include robot control strategies as well as image processing for an accurate bone segmentation.
Latest research involves customized machine learning architectures for leveraging the spatial information: The transformer architecture, originally developed for natural language processing tasks, proofs to be a promising alternative to the convolutional neural network.

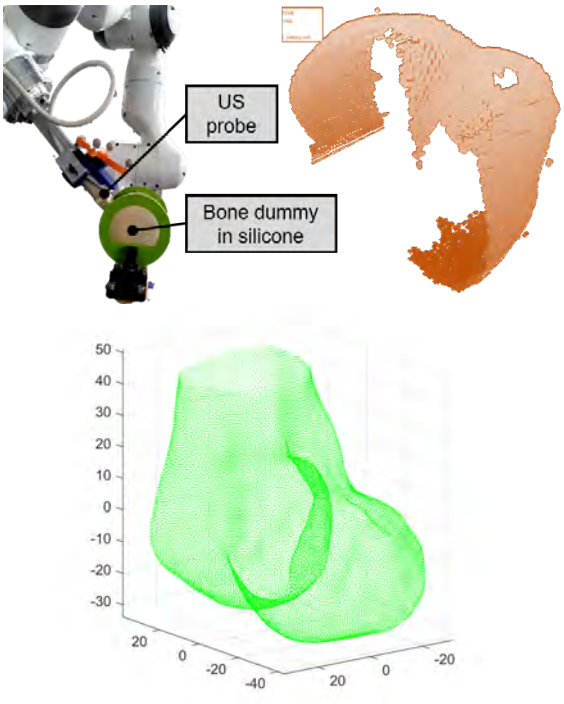

Fig. 5: Scanning of bone dummy (top/left), initial 3D reconstruction of scanned bone dummy regions (top/right), fully automatic reconstruction of a distal femur bone from ultrasound (bottom): Image slices were segmented by a vision transformer architecture, the segmented partial 3D bone surface was completed using a statistical shape model (SSM).

US based navigation on the wrist

For minimally invasive fixation of scaphoid fractures, a navigated approach based on ultrasound images represents a cost-efficient and non-invasive alternative as compared to fluoroscopy, while at the same time addressing the problem of 3-dimensional screw placement based on projective 2-dimensional imaging. We propose a machine learning based two-stage approach that tackles the tasks of image segmentation and point cloud registration individually, achieving a full automation and a significant reduction of processing time. For this purpose, state-of-the-art architectures are employed and trained on in-vitro and in-vivo datasets created at our institute.

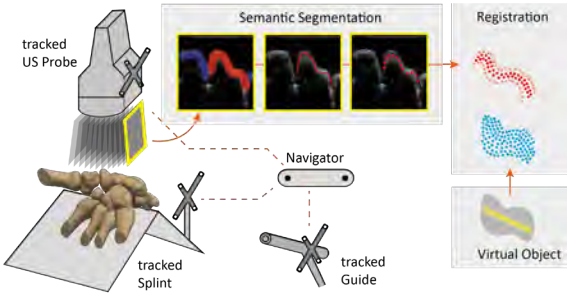

Fig. 6: Procedure for the ultrasound-based intra-operative registration of pre-operative planning data for percutaneous scaphoid fixation

Modelling cooperative surgical robotics

Surgery consists of complex sensorimotor tasks with multiple degrees of freedom. Complete automation like in industrial applications is generally impractical due to the unstructured and highly variable nature of surgical tasks. However, cooperative robotics can support surgeons by providing planning dependent (e.g. virtual fixtures) and planning independent (e.g. tremor filter) assistance functions. Thereby, different types of cooperative robotic systems (handheld, hands-on, telemanipulated) provide different scopes of assistance functions. Based on prior user centered studies, model based analysis of cooperative robotic assistances in the surgical context have been conducted on a process, a task, and a control level (Figure 7). Model architectures and relevant parameters were identified and evaluated in known applications. Modelling human robot cooperation and characteristic scenarios enables an systematic approach towards optimized surgical robotics regarding usability and risk management.

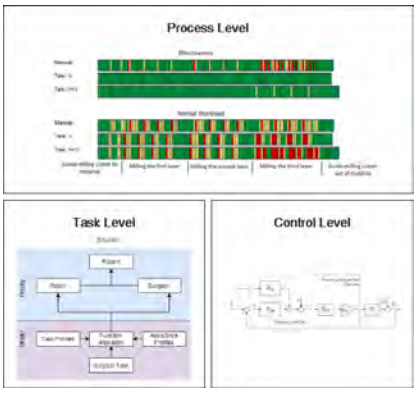

Fig. 7: Modelling Cooperative Assistance Functions on Process, Task and Control Level

A handheld robot for bone milling tasks

Current surgical robotic systems consist either of a large serial arm, resulting in higher risks due to their high inertia and no inherent limitations of the working space, or they are bone-mounted, adding substantial additional task steps to the surgical workflow.

To overcome these disadvantages, a robot was developed that has a handy and lightweight design and can be easily held by the surgeon. No rigid fixation to the bone or a cart is necessary. For the comfort of the surgeon, a support unit can be optionally added. A high-speed tracking camera together with a realtime control system ensures the accurate positioning of the milling tool, while automatically compensating for movements of the surgeon or the patient's bone.

After the manipulator has been pre-positioned and activated by the surgeon, the milling tool is automatically moved by the robotic system along a previously planned trajectory. In case of any unforeseen event, the manipulator can be stopped at any time or, since it is a handheld device, just being withdrawn from the surgical site by the operator. Milling out cavities e.g. for unicompartmental knee arthroplasty, the position and orientation of the cavity according to plan and a smooth surface are essential. First results in cortical bone phantom material show high accuracy with a mean error of 0.13 mm. Only at the edges of the cavity, where milling direction is changed, higher deviations of up to 0.7 mm occur.

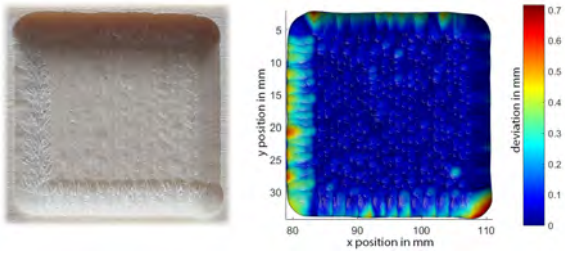

Fig. 8: Milled standard test cavity and accuracy evaluation

Control of critical devices in open OR networks

Medical devices in the operating room (OR) must be able to provide their functions reliably and on their own at all times. However, sharing information and control capabilities across the OR network with other devices enables added benefits regarding patient safety and ergonomics. For example, a wireless multi-purpose footswitch can drastically reduce the amount of switches and cables placed at the feet of the surgeon. The switch triggers different devices based on the current state of the operation. However, critical equipment such as burrs, saws or electrocautery tools (Fig. 9) impose strong safety requirements on the data exchange paths in the OR network with real time control. However, isolating critical real-time traffic from low-priority traffic accordingly is not a trivial task, especially since the device ensemble and architecture may change when devices are added or removed even during an ongoing operation. The automatic network configuration must succeed without any intervention by clinical staff.

In this context, we develop new models for the self-description of medical devices and automatic provisioning of network resources based on device profiles. These developments lay the groundwork to integrate critical medical devices more securely and seamlessly into an ever-growing operating room ensemble, including novel technologies such as 5G private networks and surgical robotics.

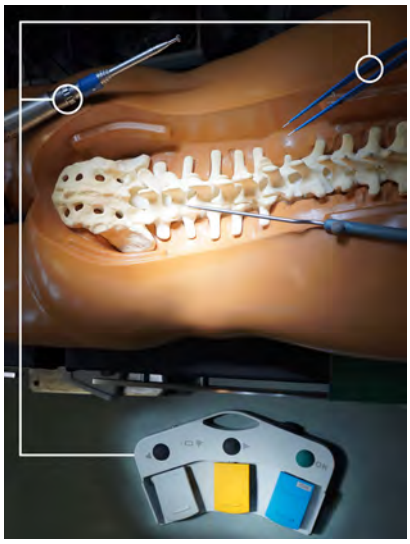

Fig. 9: Critical devices such as a medical burr or electrocautery tweezers may be controlled by the same foot pedal depending on the current workflow step

Process Optimization and Context Management in the open networked operating room (PriMed)

There are more than 17 million surgeries per year in German hospitals, and an operating room (OR) is very expensive to maintain. Therefore, a high utilization of the OR is highly desirable. Today, optimization often takes place on device-level, but not enough on process or management level. Existing medical devices are able to detect if and how they are currently being used or not. In the EFRE funded PriMed project, process optimization is achieved by integration open networking based on service oriented device connectivity (SDC), according to the international standard ISO IEEE 11073 SDC, into medical devices, as well as Standard Operating Procedures (SOPs).

Fig. 10: PriMed SDC Workstation on the DMEA booth

A combination of those can determine the actual phase of a surgical intervention. Phone calls, just to ask how far a surgical procedure is, will become unnecessary, if the context information is automatically transmitted to the OR-Management. Furthermore, context and device data such as patient status, current medications, allergies, and supplemented medications can be used for automated documentation during the intervention. Those features are integrated into central surgical, anesthetic and OR management workstations (Fig. 10).

Hybrid test bench for radial shock waves

Radial shock wave therapy is used for different therapeutic indications. In order to assess the effect on the treated tissue, it is important to know the parameters of the sound field. However, it is difficult to measure the pressure curves, especially at high pulse repetition rates. The whole sound field can be characterised using a wet test bench, but the process is cumbersome and cavitation is likely to occur at high pulse repetition rates. This effect is avoided using a dry test bench where the measurement position is limited to a single spot. Therefore, a hybrid test bench was developed combining the dry bench's device mounting and coupling with a small water basin. The ballistic device was coupled to the basin filled with degassed ultrapure water using a latex membrane covered with ultrasound gel. The contact pressure was applied with a spring. A fibre optic pressure hydrophone was used for the sound field measurements. The pressure curves of every 10th shot were measured on the beam axis 1mm from the membrane. The device was analysed at different driving pressures and pulse repetition rates.
The test setup enables an easy handling and reproducible results at all pulse repetition rates. The ballistic device provides constant peak pressures over different frequencies. The small water basin has the advantage that the water quality is easy to control and the measuring process is fast and uncomplicated. Cavitation suppression requires a clean water basin filled with degassed ultrapure water kept at a constant, low temperature. The hybrid test bench can be used to easily study shock wave parameters of ballistic devices at high repetition rates

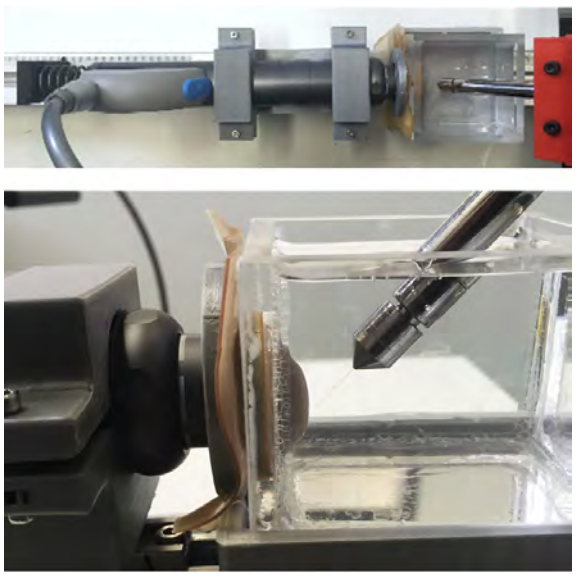

Fig. 11: In-vitro test setup for sound filed measurements of ballistic pressure wave devices.

Acknowledgements

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- the German Ministry of Health (BMG)
- 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, please visit our website www.meditec.rwth-aachen.de or contact us directly.

Selected Publications

[1] M. Asseln, S.A.G.A. Grothues & K. Radermacher: Relationship between the form and function of implant design in total knee replacement. Journal of Biomechanics, 2021, 119, pp. 110296

[2] A. Benninghaus, L. Stellmann, U. Kehler & K. Radermacher: In vitro investigation of the influence of cervical spinal canal stenosis on CSF hydrodynamics. Abstracts from Hydrocephalus 2021: The Thirteenth Meeting of the International Society for Hydrocephalus and Cerebrospinal Fluid Disorders, Fluids and barriers of the CNS, 18(60), 2021

[3] P. Broessner, B. Hohlmann & K. Radermacher: Ultrasound-based Navigation of Scaphoid Fracture Surgery. In: C. Palm, T.M. Deserno, H. Handels, A. Maier, K. Maier-Hein & T. Tolxdorff (ed.): Bildverarbeitung für die Medizin 2021, Springer, 2021, pp. 28-33

[4] P. Brößner, B. Hohlmann, K. Welle & K. Radermacher: Validation of Automated Ultrasound-based Registration for Navigated Scaphoid Fixation: Evaluation of registration performance regarding simulated screw placement. Current Directions in Biomedical Engineering, 7(1), 2021, pp. 116-120

[5] S. Drobinsky, T. Lindemann, P. Schleer & K. Radermacher: Usability of Haptic Volumetric Assistance for Surgical Navigation Tasks. Current Directions in Biomedical Engineering, 7(1), 2021, pp. 11-16

[6] 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, 2021, Onlinefirst, pp. 110526

[7] M. Gatz, S. Schweda, M. Betsch, T. Dirrichs, M. de la Fuente, N. Reinhardt & V. Quack: Line- and Point-Focused Extracorporeal Shock Wave Therapy for Achilles Tendinopathy: A Placebo-Controlled RCT Study. Sports Health: A Multidisciplinary Approach, 2021, 13(5), pp. 511-518

[8] S.A.G.A. Grothues & K. Radermacher: Variation of the Three-Dimensional Femoral J-Curve in the Native Knee. Journal of Personalized Medicine, 2021, 11(7), pp. 592

[9] J. Habor, M.C.M. Fischer, K. Tokunaga, M. Okamoto & K. Radermacher: The Patient-Specific Combined Target Zone for Morpho-Functional Planning of Total Hip Arthroplasty. Journal of Personalized Medicine, 2021, 11(8), pp. 817

[10] J. Heibeyn, P. Gödde, P. Görtz, A. Janß & K. Radermacher: Ermittlung von Leistungsfaktoren im Rahmen der Instrumentenaufbereitung zur gezielten Workflowunterstützung. Zentralsterilisation Abstractheft 25 Jahre DGSV e.V. - 24. Fachkongress der Aufbereitung von Medizinprodukten, 29, 2021, pp. 7-9

[11] J. Heibeyn, N. König, N. Domnik, M. Schweizer, M. Kinzius, A. Janß & K. Radermacher: Design and Evaluation of a Novel Instrument Gripper for Handling of Surgical Instruments. Current Directions in Biomedical Engineering, 2021, 7(1), pp. 1-5

[12] B. Hohlmann, P. Brößner, K. Welle & K. Radermacher: Segmentation of the Scaphoid Bone in Ultrasound Images: A comparison of two machine learning architectures for in-vivo segmentation. Current Directions in Biomedical Engineering, 7(1), 2021, pp. 76-80

[13] L. Phlippen, M. Vossel, M. de la Fuente & K. Radermacher: Development and evaluation of a straightforward method to identify the elastic structure of a lightweight robot. 2021 European Control Conference (ECC), 2021, pp. 1925-1930

[14] N. Reinhardt, T. Dick, L. Lang, K. Radermacher & M. de la Fuente: Hybrid test bench for high repetition rate radial shock wave measurement. Current Directions in Biomedical Engineering, 2021, 7(2), pp. 395-398

[15] P. Schleer, M. Vossel, L. Heckmann, S. Drobinsky, L. Theisgen, M. de la Fuente & K. Radermacher: Usability of cooperative surgical telemanipulation for bone milling tasks. International Journal of Computer Assisted Radiology and Surgery (IJCARS), 2021, 16(2), pp. 311-322

[16] R.M. Sellei, U. Warkotsch, P. Kobbe, C.D. Weber, N. Reinhardt, M. de la Fuente, K. Radermacher & F. Hildebrand: Non-invasive and reliable assessment of compartment elasticity by pressure related ultrasound: An in-vitro study. Injury, 2021, 52(4), pp. 724-730

[17] M. Verjans, L. Phlippen, Z. Li, P. Schleer & K. Radermacher: Semi-automated stair climbing of a wheel hub-based patient transportation aid for emergency medical services. at - Automatisierungstechnik, 2021, 69(6), pp. 550-561

[18] M. Verjans, L. Phlippen, K. Radermacher, M. Kinzius, M. Eichenbrenner & D. Struck: SEBARES: Ein neuartiges Konzept für den Patiententransport. Rettungsdienst, 2021, 44(2), pp. 18-22

[19] M. Verjans, P. Schleer, M. Kinzius, P. Krumholz, L. Phlippen, S. Drobinsky & K. Radermacher: Evaluation of a novel stair-climbing transportation aid for emergency medical services. Biomedical Engineering / Biomedizinische Technik, 2021, 66(3), pp. 323-333

[20] M. Vossel, M. Müller, A. Niesche, L. Theisgen, K. Radermacher & M. de la Fuente: MINARO HD: control and evaluation of a handheld, highly dynamic surgical robot. International Journal of Computer Assisted Radiology and Surgery, 2021, 16, pp. 467–474

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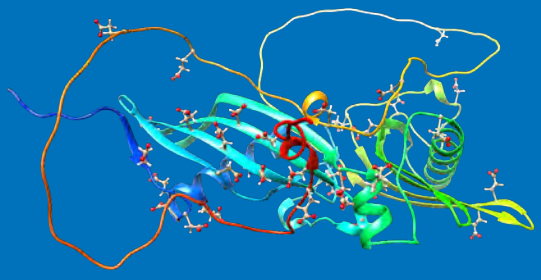
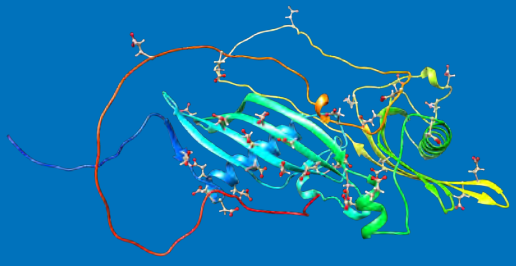
Biointerface Laboratory at Helmholtz-Institute for Biomedical Engineering

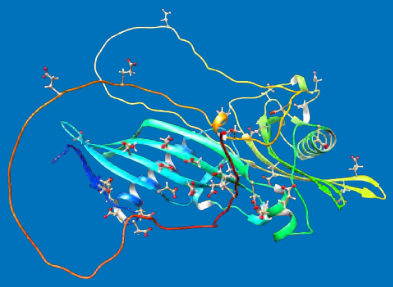
RWTH AACHEN UNIVERSITY

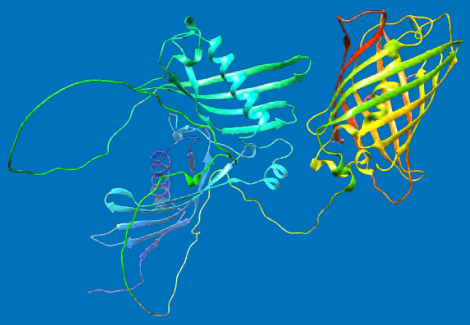
Faculty of Medicine

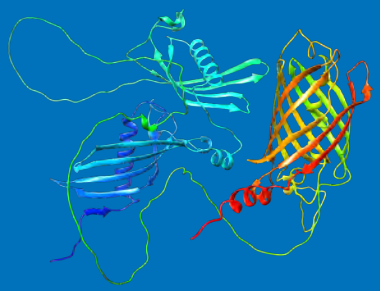
Cell-Material Interactions: Translating Basic Science Into Clinical Applications











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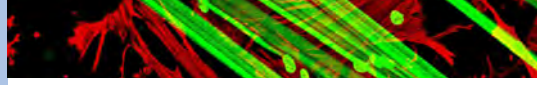


Cover Figures: Recombinant Fetuin-A Fusion Proteins modelled with Alphafold

Introduction

Willi Jahnen-Dechent, Professor

Like the year 2020, 2021 was tainted by COVID. Just when we thought the pandemic was over after two long years, and the outlook was bright, we found ourselves in a political nightmare with war striking in the midst of Europe. Against dramatic worldwide challenges our little world of science may seem insignificant, but it isn't. Brilliant research has ended the COVID threat by providing vaccines in "lightspeed", and research in other areas may help alleviate the environmental and societal ills that drive conflicts around the world. Can fetuin or biomaterial research make a difference? I don't know, but I do know that our research like any other is about reasoning and embracing the unknown – something that frightens all demanding "simple answers". There are none! So once again let us share progress made in the past year, however little it may be.

We secured continued external funding to study the structure and function of the mineral chaperone fetuin-A, the development of a miniaturized device for calcification testing, the role of periodontal ligament cells in alveolar bone healing, bio-functionalized microgels and their influence on mesenchymal stromal cell differentiation, ceramic-based implants for cardiovascular tissue engineering, all of which is presented below.

After many successful years of research on the role of fetuin-B in reproductive biology, Julia Floehr, Carlo Schmitz and Seynab Sadr all expertly finished their projects. They have already left for new jobs or will soon take employment elsewhere. Fetuin-A researchers Sina Koeppert left after completing her PhD defense "with distinction". Andrea Gorgels completed all PhD exams just in time before taking maternal leave. We thank all these great colleagues for their contributions in and outside the lab. It is always a bit sad to see established young scientists leave the group. But isn't that what University training is all about? All the more rewarding to see alumni thrive in their new professional and personal careers. We are proud and most importantly, we stay in touch!

Stem Cells and Tissue Engineering

Sabine Neuß-Stein, Professor

Our work continues to focus on three main research topics: (i) mesenchymal stem cells (MSC) and periodontal ligament stem cells (PDL cells) in wound healing and tissue regeneration, (ii) bone tissue engineering and (iii) cardiovascular tissue engineering.

Together with the group of Michael Wolf (Clinic for Orthodontics) we identified striking differences in kinase-dependent signaling of periodontal ligament (PDL) cells from the upper and lower jaw to support healing of the alveolar bones. We started a project on understanding the PDL cell-cementum interphase to provide a basis for periodontal-cementum research. Chloé Radermacher presents the results of her Master thesis below. She continues her work as a PhD candidate.

The second phase of our externally funded project with Andrij Pich (Institute of Textile and Macromolecular Chemistry) studies fibrin-based hydrogels containing dextran or extracellular matrix molecules to form functional microgels (figure 1). These microgels are further decorated with growth factors and cytokines to regulate (stem) cell recruitment and differentiation. In addition, lipid-membrane coated microgels housing sensors and DNA are compared against established cell lines to replace lipid-membrane based "artificial cells" for live cells in cell-based assays.

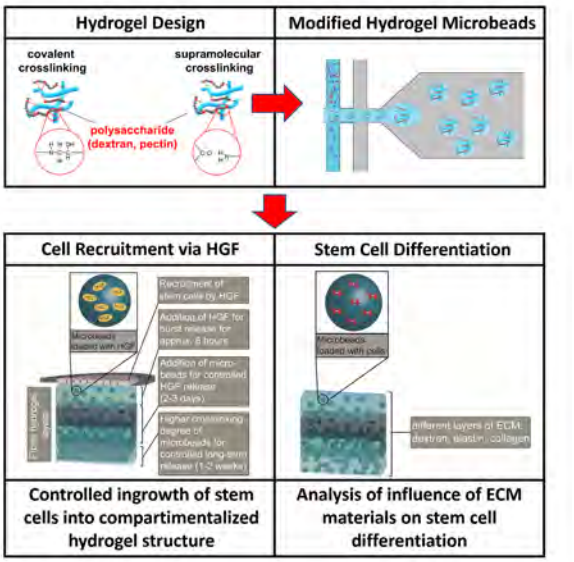


Fig. 1: Development of hierarchical and compartmentalized hydrogels for stem cell recruitment, targeted cell growth and differentiation using microgels.

We also continue our work with our long-lasting cooperation partner Karolina Schickle (Institute of Mineral Engineering) to develop ceramic-based implants for cardiovascular tissue engineering. Here we found that monocrystalline ceramics of different anatomical layers are hemocompatible and have different impact on cell behaviour, in particular on thrombocyte adhesion and activation.

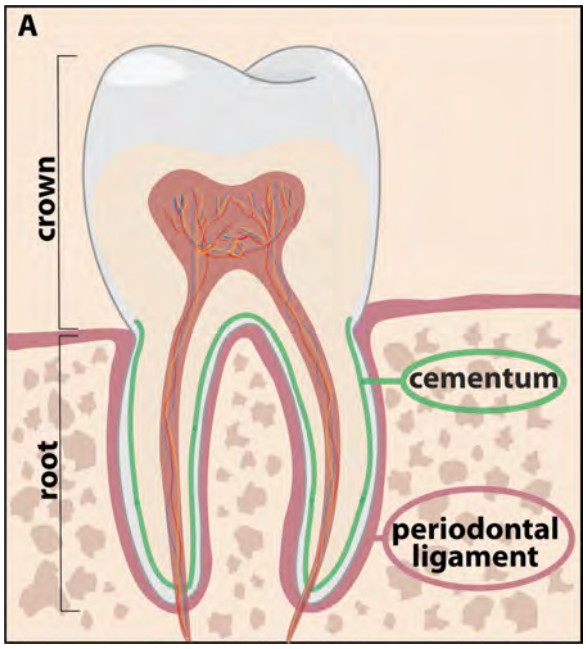
Besides, we develop GMP protocols for translational research within the newly founded FiT-center ("first in translation") jointly operated by the Leibniz Institute for Interactive Materials and the Center for Biohybrid Medical Systems (CBMS), which are located in close proximity on the RWTH Aachen Research Campus "Melaten". FiT addresses the gap between research projects and clinical translation. Specifically, our satellite project studies ceramic surfaces loaded with bioactive molecules to better integrate into bone tissue.

What started out as a fun project fuelled by a lot of enthusiasm and some crowd funding has quickly turned into an exciting biomaterial project for bone tissue engineering. Learn more about Anna Bartz's work with spider silk below and watch her on YouTube (https://www.youtube.com/watch?v=1YLWi2hcqkU).

Understanding the PDL cell/ cementum interphase, their interplay under mechanical stress and periodontal remodelling to provide a basis for periodontal-cementum research.

Chloé Radermacher, PhD candidate

Orthodontic treatments together with their resulting side effects play an important role in the 21st century because of psychosocial, functional, and dental issues. These treatments cause a pathological process for up to 46% of patients depending on the brace type. In this case, the patient is affected by inflammatory root resorption, which can lead to permanent loss of dental root structure. Today, there is no mechanistic explanation for orthodontically inflammatory root resorption, but the following factors are implicated: mechanical forces, the morphology of tooth roots, alveolar bone, periodontal ligament, cementum, and several biological messengers. The cementum is a key tissue in the initial periodontal development process as well as in regeneration after periodontal diseases. Indeed, this mineralized tissue is covered by root lining cells called cementoblasts. These cells can be stimulated by mechanical or biological signals to build up new cementum and repair tooth roots. The project aims at investigating the role of cementoblasts and their interaction with the periodontal ligament. My master thesis´ goal is to establish an isolation method of cementoblasts and periodontal ligament cells from the same patient and the characterization of these cell types.



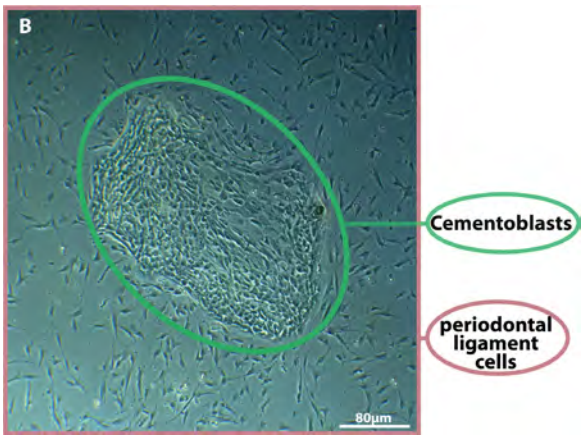


Fig. 2: (A) Anatomical scheme of the tooth with particular focus on the tissues of interest: cementum and periodontal ligament. (B) Cementoblast colony surrounded by periodontal ligament cells three days after isolation. Scale bar: 80 μm

New concepts in regenerative medicine - spider silk-based scaffolds for bone replacement strategies

Anna Bartz, PhD candidate

Spider silk has special biomedical properties (very high tensile strength, high elasticity, antibacterial effect, cyto- and biocompatibility, degradability, heat stability) that make it particularly interesting as a matrix for supporting cell functions in bone replacement material. The aim of our research project is to produce a functional biohybrid, three-dimensional construct, consisting of a carrier material (silk from spider and/or caterpillar) surrounded by a hydrogel (fibrin- or collagen-based) with integrated bone cells, which are differentiated in vitro from mesenchymal stem cells (MSC) or periodontal ligament cells (PDL cells), as well as capillaries from co-cultured endothelial cells for subsequent connection to the vascular system.

As there are no pre-fabricated devices available on the market which could be used for "milking" the spiders and for winding the silk threads onto miniature frames, the project had to start from scratch by developing and testing several appliances which are currently optimised with support from the company Status pro Maschinentechnik GmbH. This will allow us to wind the spider silk in an exact and reproducible way onto the weaving frames.

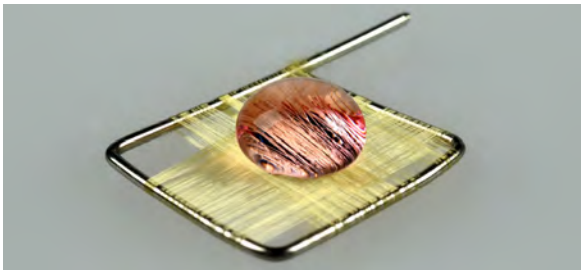


Fig. 3: Miniature weaving frame with the machine-wound spider silk used in this study (Photo: University Hospital RWTH Aachen)

First results demonstrate that spider silk is cytocompatible and that the MSC remain long-term viable when adhering to the spider silk fibres. Promising results were also achieved with MSC embedded in a fibrin-based hydrogel surrounding the silk fibres.

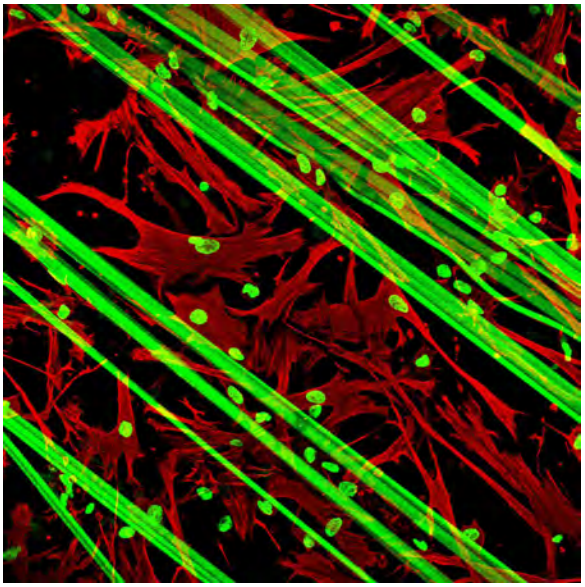
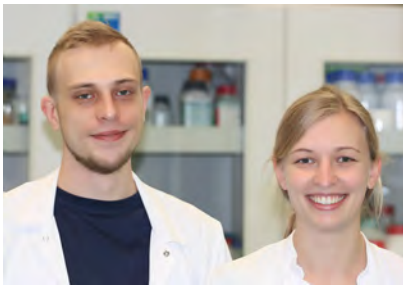


Fig. 4: Two-Photon-Microscopy (2PM) of spider silk in combination with MSC embedded in a fibrin-based hydrogel

Another novel scaffold material for culturing bone replacement biohybrid scaffolds,is tested in parallel: we currently use fish skin xenografts from Atlantic cod to verify its suitability for osteogenic differentiation of MSC. First results indicate that the fish skin has very good cytocompatibility and that the MSC preferentially colonize the fish scale side and migrate into the fish skin. Also in this case, the combination with a fibrin-based hydrogel supported a more effective cell growth and proliferation. First results indicate that spider silk and fish skin are promising biomaterials for bone replacing strategies.
In this research project, we collaborate with different cooperation partners: Aquazoo Löbbecke Museum Düsseldorf, Tierpark + Fossilium Bochum, Clinic for Orthodontics at RWTH Aachen University, Institute for Textile Machinery and Textile High Performance Materials Technology (ITM) at the University of Dresden, Status Pro Maschinenmesstechnik GmbH and the Icelandic Startup Kerecis.

Structure-function analysis of recombinant Fetuin-A



Christian Hasberg, Camilla Winkler, PhD candidates

The word protein was derived from the Greek word “proteios” for basic, primary. The all-important structure of a protein is determined by the sequence of its building blocks, the amino acids. After synthesis in the cells, proteins fold from a thread of amino acids into helices and loops, and ultimately bend into defined three-dimensional structures, which determine the function of a protein.
Two proteins of the cystatin superfamily, fetuin-A and fetuin-B are the focus of our structure-function research. Both fetuins are similar in structure and consist of three domains. The first two domains are cystatin-like CYS domains, which consist of an alpha helix surrounded by 5 anti-parallel beta sheets. The third domain is called the C-terminal region CTR. Fetuins are predominantly made in the liver and secreted into the blood stream. Despite their structural similarity, the functions of fetuin-A and fetuin-B strongly differ. Fetuin-A is a binding protein regulating mineralization and scavenging excess calcium phosphate from the circulation and thus protecting against ectopic calcification. Fetuin-B is a potent inhibitor of the oocytes-specific proteinase ovastacin, which regulates oocyte fertility.

For structure-function studies our group produced with the help of recombinant protein technology fetuins and related proteins in E. coli bacteria, in chinese hamster ovary (CHO), and in human embryonic kidney (HEK) cells. The proteins possess binding tags to facilitate protein purification and fluorescent tags to aid their detection.

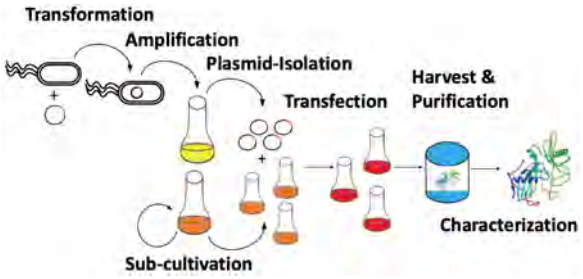
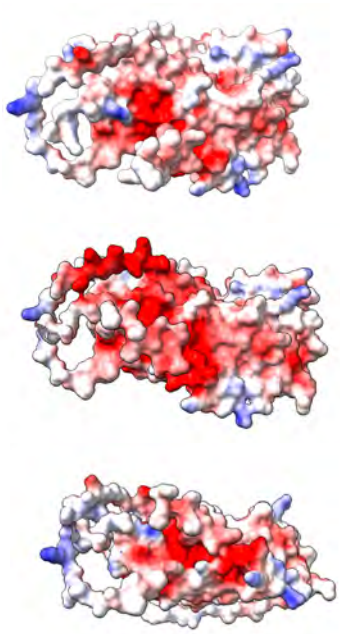


Fig. 5: Scheme of recombinant protein expression and purification.

Using established molecular biology routines, we substitute amino acids deemed important for protein function. For instance, we replaced cysteine residues linking fetuin CYS1 to CTR to study the influence of this domain-bridging disulfide bond on overall protein stability. Other protein mutants study the role of phosphorylation and glycosylation in fetuin function. Up to now, we produced more than 50 fetuin variants, which allow us to pinpoint features regulating the function and activity of these proteins.

Although the amino acid sequence for the fetuins has been known for a long time, no complete 3D-structure of fetuin-A was known. Recently,we published the structure of fetuin-B in collaboration with Proffs Gomis-Rüth and Stoecker from Barcelona and Mainz, respectively. Based on the fetuin-B structure we could also model a complete 3D structure of fetuin-A. In mid-2021 the AlphaFold structural modeling suite revolutionized the visualization of almost any protein purely based on the amino acid sequence. For the first time we can now any visualize fetuin variants to make informed decisions about optimized versions of functional fetuins.
Fig. 6: Computer models of recombinant fetuin-A variants. Small amino acid sequence changes in these proteins dramatically change their surface charge and mineral binding capacity.



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

Aaron Morgan, PhD candidate

Biohybrid implants (those made from both biological and non-biological components) are a promising development in medical technology but often suffer from issues like thrombogenesis (the formation of blood clots) and calcification (calcium build-up, causing tissue hardening). Testing for these types of materials can be difficult and expensive, due to the nature of the materials, fabrication methods, or special reagents. To facilitate the testing and validation of these materials, we have developed a miniaturized calcification chamber that recreates the flow conditions found in arterial blood vessels.

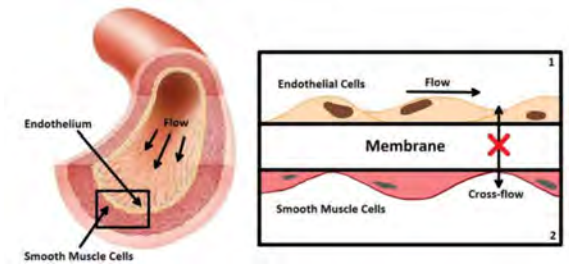


Fig. 7: (Left) Blood vessel cross-section with the cells of interest indicated. (Right) Simplified schematic view of the cell environment recreated in the chip.

This chamber holds a material sample between two fluid channels. Each fluid channel may contain a different medium and be pumped independently, though the device is designed to be driven by a single pump. The "high flow" side uses flowing medium to exert physiological shear stress onto the material surface (1-12 dyne/cm2), while the "low flow" side circulates the medium without exposing the material to significant shear stress. This more closely reproduces the physiological conditions of both the blood-facing layer, the endothelium, and the smooth muscle cells underneath.

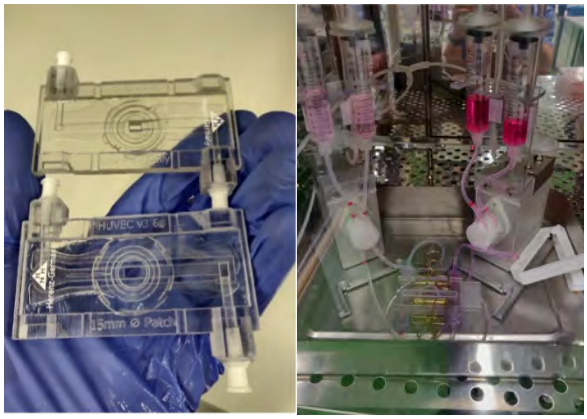


Fig.8: (Left) One complete chip, ready for use. (Right) The medium in the chips is driven using two syringe pumps, each with unique cell medium.

Using this device, we conducted calcification experiments to compare the device with a larger, more expensive testing device that is routinely used. The results showed comparable positive calcification in samples of bovine pericardium, while showing no signs of calcification in samples on PCU (negative control). Additionally, the bovine pericardium was then sectioned to determine the location of the calcification. Using von Kossa staining, we can see that the calcified lesions are located just below the outermost layer and can clearly be seen in the deeper layers of the material.
Going forward, we plan to work alongside other groups to test a wide range of biohybrid materials and hydrogels. We intend to investigate the mechanisms that allow calcification to begin using live-imaging and fluorescent markers, specifically through insights into the physiological and pathophysiological endothelium and the role this barrier plays in the process.

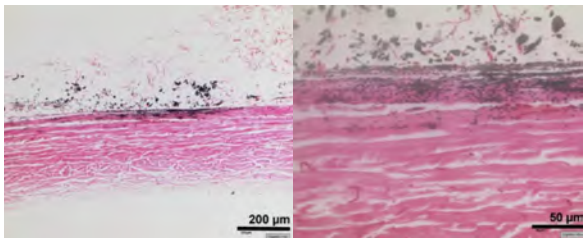


Fig. 9: Bovine pericardium (heart tissue) sections after seven days in the chip, under flow. Calcified lesions can be seen on the side exposed to calcification medium, while the other side remains uncalcified.

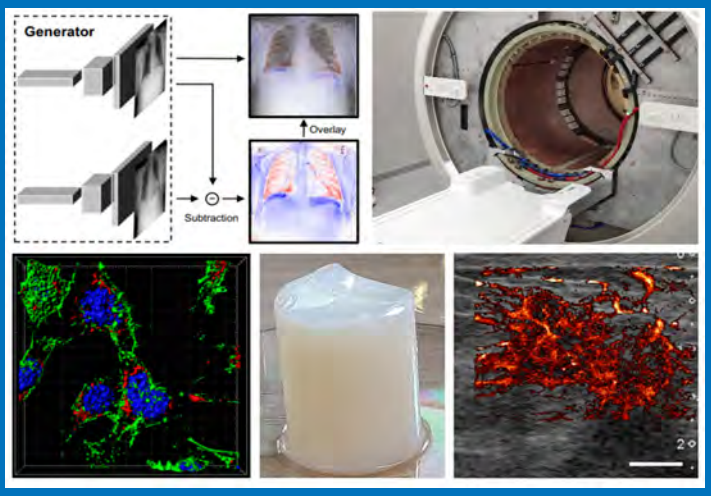
Selected References

[1] Knaup I, Symmank J, Bastian A, Neuss S, Pufe T, Jacobs C, Wolf M. Impact of FGF1 on human periodontal ligament fibroblast growth, osteogenic differentiation and inflammatory reaction in vitro. J Orofac Orthop 2021.
[2] Jaminon AMG, Akbulut AC, Rapp N, Kramann R, Biessen EAL, Temmerman L, Mees B, Brandenburg V, Dzhanaev R, Jahnen-Dechent W, Floege J, Uitto J, Reutelingsperger CP, Schurgers

LJ. Development of the BioHybrid Assay: Combining Primary Human Vascular Smooth Muscle Cells and Blood to Measure Vascular Calcification Propensity. Cells 2021.
[3] Schmitz C, Sadr SZ, Körschgen H, Kuske M, Schoen J, Stöcker W, Jahnen-Dechent W, Floehr J. The E-modulus of the oocyte is a non-destructive measure of zona pellucida hardening. Reproduction 2021.
[4] Schunk SJ, Triem S, Schmit D, Zewinger S, Sarakpi T, Becker E, Hütter G, Wrublewsky S, Küting F, Hohl M, Alansary D, Prates Roma L, Lipp P, Möllmann J, Lehrke M, Laschke MW, Menger MD, Kramann R, Boor P, Jahnen-Dechent W, März W, Böhm M, Laufs U, Niemeyer BA, Fliser D, Ampofo E, Speer T. Interleukin-1α Is a Central Regulator of Leukocyte-Endothelial Adhesion in Myocardial Infarction and in Chronic Kidney Disease. Circulation 2021.
[5] Koeppert S, Ghallab A, Peglow S, Winkler CF, Graeber S, Büscher A, Hengstler JG, Jahnen-Dechent W. Live Imaging of Calciprotein Particle Clearance and Receptor Mediated Uptake: Role of Calciprotein Monomers. Front Cell Dev Biol 2021.
[6] Kuske M, Floehr J, Yiallouros I, Michna T, Jahnen-Dechent W, Tenzer S, Stöcker W, Körschgen H. Limited proteolysis by acrosin affects sperm-binding and mechanical resilience of the mouse zona pellucida. Mol Hum Reprod 2021.
[7] Rudloff S, Janot M, Rodriguez S, Dessalle K, Jahnen-Dechent W, Huynh-Do U. Fetuin-A is a HIF target that safeguards tissue integrity during hypoxic stress. Nat Commun 2021.
[8] Azraq I, Craveiro RB, Niederau C, Brockhaus J, Bastian A, Knaup I, Neuss S, Wolf M. Gene expression and phosphorylation of ERK and AKT are regulated depending on mechanical force and cell confluence in murine cementoblasts. Ann Anat 2021.
[9] Desante G, Labude N, Ruetten S, Roemer S, Kaufmann R, Zybala R, Jagiello J, Lipinska L, Chlanda A, Telle R, Neuss S, Schickle K. Graphene oxide nanofilm to functionalize bioinert high strength ceramics. Appl Surf Sci 2021.
[10] Tsanaktsidou E, Kammona O, Labude N, Neuss S, Krüger M, Kock L, Kiparissides C. Biomimetic Cell-laden MeHA Hydrogels for the Regeneration of Cartilage Tissue. Polymers 2020.

Team in December 2021 at the "Three-Country-Corner" (D-B-NL) in Aachen Town Forrest

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, such as nanoparticles, polymeric carriers, liposomes, micelles and microbubbles as well as physical and pharmacological treatments of the vasculature and the adjacent tumor stroma in order to improve drug accumulation and tumor penetration. Research of ExMI has gained increasing international visibility. As major achievements in 2021, Prof. Dr. F. Kiessling and Prof. Dr. T. Lammers were, for the third time, recognized as Highly Cited Researchers by Clarivate Analytics. Furthermore, Dr. Yang Shi received his ERC Starting Grant and two external professorship offers at prestigious universities, and was invited to be an Associate Editor for Journal of Nanobiotechnology. Dr. Roger Molto Pallares started as new group leader being funded by the prestigious JPI Fellow program of RWTH Aachen. Finally, Prof. Dr. F. Kiessling was appointed to the board of Directors of the German Society for Biomedical Engineering (DGBMT, VDE).

Diagnostic and Therapeutic Ultrasound

Univ.-Prof. Dr. med. Fabian Kiessling

Over the last years, together with Prof. Georg Schmitz from Ruhr University Bochum, ExMI has developed and refined the super-resolution ultrasound technology "motion-model Ultrasound Localisation Microscopy" (mULM) that allows the morphological and functional characterisation of tissue vasculature at highest detail. Using this technology, we performed a mixed preclinical and clinical trial (clinicaltrials.gov: NCT03385200) to elucidate whether chemotherapy effects on breast cancer can be improved by contrast-enhanced sonopermeation [1]. This first prospective clinical evaluation on this topic showed that results on tumor-bearing rodents cannot easily be transferred to the situation in humans, where hardly any effects on tumor perfusion and treatment outcome were found. Despite the negative outcome of the clinical study, our work elucidated important tissue responses to ultrasound that must be explored in future studies. Therefore, Rix et al. started to perform a meta-analysis on the effects of (contrast-enhanced) ultrasound on the immune system, of which the protocol was published recently [2].
Furthermore, we continued to explore multifunctional ultrasound materials and systematically evaluated the drug loading capacities of our polymeric microbubble (MB, ultrasound contrast agent) platform [3]. In this context, for the first time, we could demonstrate that molecular MRI can be performed with microbubbles (additionally to ultrasound) when loading the MB with iron oxide nanoparticles (SPION) and targeting them against integrins at the tumor neovasculature [4]. Finally, we intensified our collaboration with Prof. Andreas Herrmann from DWI Leibniz Institute and together published a new strategy for ultrasound-guided thrombin formation based on sonoresponsive materials [5].

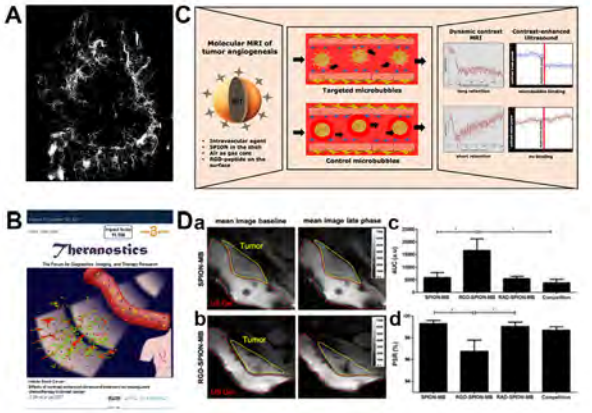

Fig. 1. A: Super-resolution ultrasound image of a human breast cancer. B: Cover image of the study on sonopermeation in breast cancer. C: Concept of molecular MRI and ultrasound with targeted SPION-containing MB and representative intensity-time curves from both modalities. D: T2w MR images of tumors in mice after injection of non-targeted (SPION-MB) and targeted RGD-SPION-MB (left) and the according quantification (right) based on the Area Under the Curve (AUC; upper plot) and the degree of wash out (bottom plot); images in C and D were taken from Pathak et al., Biomaterials 2021 [4].

Nanomedicine and Theranostics

Univ.-Prof. Dr. Dr. Twan Lammers

Nanomedicines are designed to improve the biodistribution of systemically administered (chemo-) therapeutic drugs. By delivering drugs more specifically to pathological sites, and by preventing them from accumulating in healthy tissues, nanomedicines help to improve the balance between drug efficacy and toxicity.
We are developing different types of nanomedicine formulations, including polymeric micelles and liposomes, and we use them to improve the treatment of cancer, inflammatory and fibrotic disorders [6,7,8]. In recent efforts, we studied the whole-body to cellular biodistribution of chemically core-crosslinked polymeric micelles, illustrating that nanomedicine formulations prominently engage with

immune cells in tumors and in several healthy tissues [*1]. Using physically stabilized micelles loaded both with a drug and with an imaging agent, we demonstrated that the extent of nanomedicine tumor accumulation correlates with therapeutic outcome, and that the heterogeneity in EPR-based tumor accumulation increases during the course of therapy (Fig. 2A-B; [*2]).

To promote product development and clinical translation, we are furthermore developing lyophilization (i.e., freeze-drying) protocols. Building upon previous experience with freeze-drying of polymeric microbubbles [*3], we recently demonstrated that chemically core-crosslinked polymeric micelles can be lyophilized using trehalose or sucrose as cryoprotectants (Fig. 2C; [9]). Via such means, cold-chain supply issues can be overcome.

Last but not least, we provided convincing proof-of-concept for the clinical use and added value of formulating corticosteroids in nanomedicine. Specifically, in this randomized controlled clinical trial, the therapeutic efficacy of intravenously administered liposomal prednisolone (Nanocort) was compared to that of gold-standard treatment with intramuscular methylprednisolone (Depo-Medrol). As shown in Fig. 2D, in patients with rheumatoid arthritis flares, Nanocort was found to be significantly more efficient than Depo-Medrol in reducing patient pain scores [*4].

[*1] Biancacci, Sun, Moeckel et al, J Control Release 2020
[*2] Biancacci, De Lorenzi, Theek et al, Adv Sci 2022
[*3] Ojha, Pathak et al, Pharmaceutics 2020
[*4] Metselaar et al, J Control Release 2022

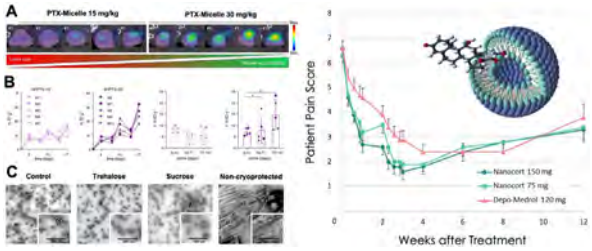

*Fig. 2. A-B: Tumor accumulation of Cy7-labeled and paclitaxel-loaded polymeric micelles in mice bearing 4T1 tumors after 3 weeks of theranostic treatment. C: Lyophilization of core-crosslinked polymeric micelles using different cryoprotectants. Control depicts non-lyophilized micelles. D: Efficacy of liposomal vs. standard corticosteroid treatment in patients with rheumatoid arthritis flares. Drugs were administered on day 0 and 15. Images reproduced from [*2,9, *4].*

Physics of Molecular Imaging Systems

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

The PMI group researches, develops, and evaluates medical imaging systems ranging from established techniques like Magnetic Resonance (MR) and Positron Emission Tomography (PET) to the emerging method Magnetic Particle Imaging (MPI).

In cooperation with UMC Utrecht, the group has successfully installed the first ring of PET detectors in a dedicated clinical PET/MR system in November 2021 (Fig. 3A). The system is engineered to enable the localization of small mobile metastasis with great precision, allowing to better treat metastatic tumors. In combination with MR-guided radiotherapy, which is already available at UMC Utrecht, this will provide a next step in tumor detection, therapy and surveillance. First patients are expected to be scanned in summer 2022.

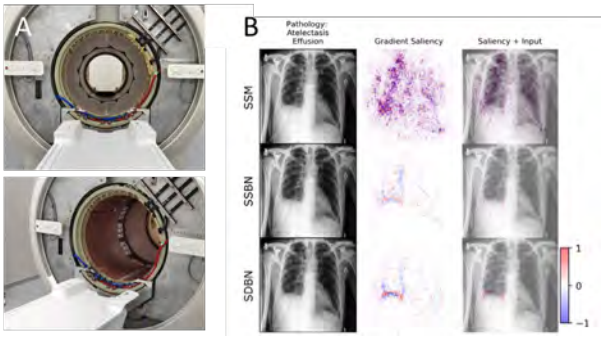

Fig. 3. A: PET/MR system installed at UMC Utrecht. Top: Frontal view of the open bore. Bottom: Tilted view into the bore where the PET detector ring is installed. B: Saliency maps can help in guiding specialists to the correct diagnosis. Loss gradients were plotted with respect to their input pixels for the X-ray dataset. Rows top to bottom: Standard model (SSM), adversarially trained model with a single batch norm (SSBN) and dual batch norm (SDBN), [14].

In the area of PET data processing, advances have been made in form of a high throughput positioning algorithm based on gradient tree boosting, enabling near real-time processing for full PET systems [10].

The group is investigating analog detector concepts using the PETsys TOFPET2 ASIC and analog silicon photomultipliers. In continuation of the successful investigations of 2019 and 2020, the PETsys TOFPET2 ASIC has been evaluated in multi-channel coincidence experiments [11].

Analog components are further used in the development of a PET/MRI insert for a preclinical 7T MRI. In the scope of this project, a new shielding concept was evaluated by means of optically transparent RF-shielding materials that are directly incorporated into the PET modules [12].

Magnetic Particle Imaging (MPI) applies magnetic fields to visualize the distribution of superparamagnetic iron-oxide nanoparticles (SPIONs), that act as tracers. A novel technique to measure flow velocities based on MPI and the principle of the well-known Doppler effect was developed (Doppler-MPS) [13]. The method was successfully validated by simulations and flow velocity quantification of a moving SPION sample. Besides that, the passive Dual Coil Resonator (pDCR), a purely passive coil insert for a preclinical MPI system, was developed. Phantom measurements prove frequency-selective signal boost and image resolution enhancement when using the pDCR compared to the integrated receiver system.

Lastly, the PMI group has been working on unmasking the decision-making process of machine learning models, which is essential for implementing diagnostic support systems in clinical practice. In a recent work [14], it was demonstrated that adversarially trained models can significantly enhance the usability of pathology detection as compared to their standard counterparts. The models are further improved by the application of dual-batch normalization. In this project, the PMI group collaborated with six experienced radiologists to rate the interpretability of saliency maps in datasets of X-ray, Computed Tomography, and Magnetic Resonance Imaging scans (Fig. 3B).

Polymer Therapeutics

Dr. Yang Shi

Polymers play important roles in a high variety of therapeutic systems for human diseases and are also the cornerstone of many novel disease treatment strategies under development. The group Polymer Therapeutics is mainly focusing on developing translatable cancer treatment strategies based on self-designed synthetic polymers. These strategies include: 1) clinical translation of polymeric nanomedicines for combination chemo-immunotherapy based on patented ∏-∏-stacking-stabilized micelles; 2) engineering of self-assembled polymer-prodrug vesicles for immunoactivation via intracellular pattern recognition receptors in antigen presenting cells. The vesicles are produced from amphiphilic conjugates of hydrophilic polymers and hydrophobic prodrugs of low molecular weight immunostimulants, such as Toll-like receptor and stimulator of interferon genes (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 molecule and/or macromolecular drugs and cells via systemic or local administration.
The group recently proposed a new direction in biomaterials-assisted cancer immunotherapy – using polymer systems to engineer B cells to provoke strong anti-cancer immunity. The group has designed nanosystems, such as the polymer-prodrug vesicles, and macroscale materials, such as hydrogels, to modulate B cells and control their immunological functions for cancer therapy. The project has been funded by ERC Starting Grant 2021 (1.5M EUR for 5 years) which will officially start in the second half of 2022.

Biohybrid Nanomedical Materials

Dr. Roger Molto Pallares

The Biohybrid Nanomedical Materials group was established in September 2021 at ExMI, and it focuses on developing different hybrid materials, including functionalized gold nanoparticles and polymeric microbubbles, for biosensing [*5] and smart drug targeting [*6].
To this end, gold nanoparticles offer unique opportunities as they produce strong electromagnetic fields that boost the spectroscopic signatures of molecules located near their surface. Hence, surface-enhanced Raman spectroscopy based on gold nanoparticles can provide high sensitivity, even down to single molecule detection [*7]. Moreover, gold nanoparticles can also be functionalized with a wide range of targeting moieties and (chemo-) therapeutics, acting as delivery vehicles. Upon pulsed laser irradiation, the cargo of gold nanoparticles is released, increasing the therapeutic effect locally [*8].
In parallel, the group is also working on the synthesis and tuning of polymeric microbubbles to maximize their physicochemical properties for image-guided, targeted, and triggered drug delivery [*9].
Lastly, the group is also carrying out a collaboration project with colleagues from the Uniklinik RWTH Aachen to apply -omics approaches [*10, *11] to characterize the toxicity of clinically relevant materials and contrast agents.

[*5] Pallares et al. Nanoscale 2019
[*6] Wilczewska et al. Pharmacological reports 2012
[*7] Langer et al. ACS Nano 2019
[*8] Goodman, ACS Nano 2017
[*9] Kiessling, Journal of Nuclear Medicine 2012
[*10] Pallares et al. PNAS 2021
[*11] Pallares et al. J. Biol. Inorg. Chem 2021

Basic research for precision medicine

PD Dr. Wiltrud Lederle

ExMI investigates the pathophysiological mechanisms of carcinogenesis, organ fibrosis and inflammation to identify diagnostic biomarkers and develop novel therapeutic strategies. We have a strong focus on exploring the influence of the tumor microenvironment, including metabolic changes on tumor progression [15], as well as on identifying and overcoming barriers that impair drug delivery. ExMI also collaborates with pharmaceutical companies to explore the mechanisms of action of anti-cancer therapies. In a research collaboration with Bayer AG, we investigated the effects of combination therapy using the multi-kinase inhibitor regorafenib and the immune checkpoint inhibitor anti-PD-1 in colorectal carcinomas. Combination therapy significantly improved anti-tumor activity compared with single agents by exerting synergistic immune-modulatory effects and completely prevented tumor regrowth and liver metastasis of orthotopic colon carcinomas after drug discontinuation [16].
With respect to the assessment of therapy effects by noninvasive imaging, we compared Annexin V-based optical apoptosis imaging to changes in the glucose metabolism using 18F-FDG-PET/CT for monitoring the response to cytotoxic and anti-angiogenic therapy. Both molecular imaging approaches enabled to visualize the therapy effects. Nevertheless, the early and strong tumor apoptosis induced by the anti-angiogenic agent sunitinib was more sensitively and reliably captured by monitoring the glucose metabolism as compared to Annexin V-based apoptosis imaging [17].

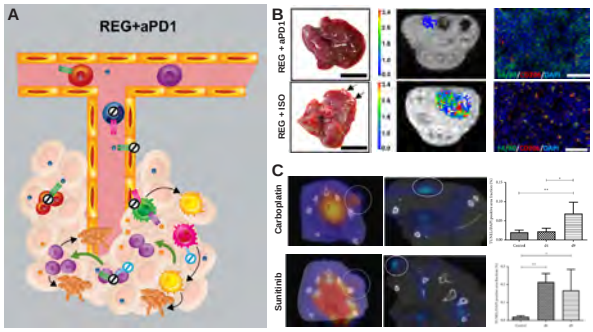

Fig. 4. A: Mechanism of sustained tumor inhibition by regorafenib and "aPD1". B: Regorafenib and aPD1 in combination blocks liver metastasis (left) and reduces tumor vascularization (DCE-MRI, middle) and M2 tumor macrophages (right) even after treatment stop. C: Uptake of 18F-FDG (PET/CT, left) and accumulation of Annexin V (FMT-CT, middle) in tumors in response to carboplatin and suninitib treatment. TUNEL stainings show an increase in tumor apoptosis in response to carboplatin (upper graph) and sunitinib (lower graph); images A and B are taken from [16], images in C from [17].

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- Funding Agencies: European Commission (Horizon 2020, EFRE), ERC, DFG, BMBF, ERS, IZKF, START, BMWI (AIF).

Awards

- B. Theek: "Friedrich Wilhelm Award 2021"
- F. Kiessling, T. Lammers were recognized as "Highly Cited Researchers 2021" by Clarivate in the Pharmacology and Toxicology category.
- F. Baskaya: Poster Award: World Molecular Imaging Conference 2021 (WMIC), Miami USA (hybrid). Detection and differentiation of pathophysiological changes in non-alcoholic steatohepatitis and inflammatory liver fibrosis in mice by multiparametric MRI.
- E. Rama: Poster Award: WMIC 2021, Miami USA (hybrid). Monitoring the remodeling of biohybrid tissue-engineered vascular grafts by multimodal molecular imaging.
- F. Baskaya received the Student Travel Stipend Award by the WMIC 2021.
- Dasgupta, Student Travel Stipend Award by the WMIC 202Z.
- Dasgupta: top 100 abstract WMIC 2021, Miami USA (hybrid). Microbubble Shape: a new design parameter in ultrasound-mediated drug delivery.
- K. Benderski, price for the „Best Pitch Presentation" at Nano TME.
- K. Roemhild, price for the „Best Pitch Presentation" at Nano TME.
- C. Hark 2nd place for the „Best Poster Presentation Award" by the Doktorandenkonferenz hosted by the medical faculty of the RWTH Aachen University.

Publications

[1] Rix A, et al. Effects of contrast-enhanced ultrasound treatment on neoadjuvant chemotherapy in breast cancer. Theranostics. 2021 Sep21;11(19):9557- 9570. 10.7150/thno.64767. eCollection 2021.

[2] Rix A, et al. Development of a Systematic Review Protocol and a Scoping Review of Ultrasound-Induced Immune Effects in Peripheral Tumors. Mol Imaging Biol. 2021 Nov 29.

[3] Liu M, et al. Strategies to Maximize Anthracycline Drug Loading in Albumin Microbubbles. ACS Biomater Sci Eng. 2021 Dec 21.

[4] Pathak V, et al. Molecular magnetic resonance imaging of Alpha-v-Beta-3 integrin expression in tumors with ultrasound microbubbles. Biomaterials 2021

[5] Zhao P, et al. Activation of the Catalytic Activity of Thrombin for Fibrin Formation by Ultrasound. Chem Int Ed Engl.2021 Jun 21; 60(26):14707-14714.

[6] Llop J, et al. Nanoparticles for Cancer Diagnosis, Radionuclide Therapy and Theranostics. ACS Nano. 2021 Nov 8.

[7] Sofias AM, et al. Therapeutic and diagnostic targeting of fibrosis in metabolic, proliferative and viral disorders. Adv Drug Deliv Rev. 2021 Aug; 175:113831.

[8] Sofias AM, et al. A paradigm shift in cancer nanomedicine: from traditional tumor targeting to leveraging the immune system. Drug Discov Today. 2021 Jun;26(6):1482- 1489.

[9] Ojha T, et al. Lyophilization stabilizes clinical-stage core-crosslinked polymeric micelles to overcome cold chain supply challenges. Biotechnol J. 2021 Jun;16(6): e2000212.

[10] Wassermann C, et al. High throughput software-based gradient tree boosting positioning for PET systems. Biomed Phys Eng Express. 2021 Aug 19;7(5).

[11] Nadig V, et al. Hybrid total-body pet scanners - current status and future perspectives. Eur J Nucl Med Mol Imaging. 2021 Oct 14.

[12] Yin L, et al. RF shielding materials for highly-integrated PET/MRI systems. Phys Med Biol. 2021 Apr 28;66(9).

[13] Pantke D, et al. Flow velocity quantification by exploiting the principles of the Doppler effect and magnetic particle imaging. Sci Rep 2021 Feb 25;11(1):4529.

[14] Han T, et al. Advancing diagnostic performance and clinical usability of neural networks via adversarial training and dual batch normalization. Nat Commun 2021 Jul 14;12(1):4315.

[15] Roemhild K, et al. Iron metabolism: pathophysiology and pharmacology. Trends Pharmacol Sci. 2021 Aug;42(8):640-656. Epub 2021 Jun 2.

[16] Doleschel D, et al. Regorafenib enhances anti-PD1 immunotherapy efficacy in murine colorectal cancers and their combination prevents tumor regrowth. J Exp Clin Cancer Res. 2021 Sep 13;40(1):288.

[17] Gross J, et al. Change of Apoptosis and Glucose Metabolism in Lung Cancer Xenografts during Cytotoxic and Anti-Angiogenic Therapy Assessed by Annexin V Based Optical Imaging and 18F-FDG-PET/CT. Contrast Media Mol Imaging. 2021 Apr 10;2021: 6676337.eCollection 2021.

[18] Kiessling F. US Microbubbles as Smart Sensors of Portal Venous Pressure. Radiology. 2021Jan;298(1):112-113.

[19] Klinkhammer BM, et al. Nat Rev Nephrol. Non-invasive molecular imaging of kidney diseases. 2021 Oct;17(10):688-703.

[20] Theek B, et al. Automation of data analysis in molecular cancer imaging and its potential impact on future clinical practice. Methods. 2021 Apr; 188:30-36. Epub 2020 Jun 29.

[21] Liang C, et al. B ∏ electron-stabilized polymeric micelles potentiate docetaxel therapy in advanced-stage gastrointestinal cancer. Biomaterials. 2021 Jan; 266:120432.

[22] Kiessling F, et al. Editorial for Investigation of Effects of Gadolinium-Based Contrast Agents on Uterine Contractility Using Isolated Rat Myometrium. Reson Imaging. 2021 Oct 31.

[23] Merkes JM, et al. Sensing Reactive Oxygen Species with Photoacoustic Imaging Using Conjugation-Extended BODIPYs. ACS Sens. 2021 Dec 24;6(12):4379-4388.

[24] Klinkhammer BM, et al. Non- invasive molecular imaging of kidney diseases. Nat Rev Nephrol. 2021 Oct;17(10):704.

[25] Rezvantalab S, et al. Experimental and Computational Study on the Microfluidic Control of Micellar Nanocarrier Properties. CS Omega. 2021 Aug 30;6(36):23117-23128.eCollection 2021 Sep 14.

[26] Zuo S, et al. Mixing Matrix-corrected Whole-body Pharmacokinetic Modeling Using Longitudinal Microcomputed Tomography and Fluorescence-mediated Tomography. Mol Imaging Biol. 2021 Dec;23(6):963-974.

[27] Schollemann F, et al. An Anatomical Thermal 3D Model in Preclinical Research: Combining CT and Thermal Images. Sensors 2021, 21(4), 1200.

[28] Wolf F, et al. Corrigendum to MR and PET-CT monitoring of tissue-engineered vascular grafts in the ovine carotid artery [Biomaterials 216 (2019) 119228]. Biomaterials. 2021 Apr;271: 120723.

[29] Merkes JM, et al. Temperature-Controlled Conversion of Boc-Protected Methylene Blue: Advancing Solid-State Time-Temperature Indicators. Chemistry Open. 2021 Nov;10(11):1129-1132.

[30] Nolte T, et al. Confounding factors in breast magnetic resonance fingerprinting: B+1B1 +, slice profile, and diffusion effect. Magn Reson Med. 2021 Apr;85(4):1865-1880.

[31] Schrammen PL, et al. Weakly supervised annotation-free cancer detection and prediction of genotype in routine histopathology. J Pathol. 2022 Jan;256(1):50-60. .

[32] Nadig V, et al. Evaluation of the PETsys TOFPET2 ASIC in multi-channel coincidence experiments. EJNMMI Phys. 2021 Mar 24;8(1):30.

[33] Nolte T, et al. Study of flow effects on temperature-controlled radiofrequency ablation using phantom experiments and forward simulations. Med Phys. 2021 Sep;48(9):4754-4768.

[34] Siepmann R, et al. Image-derived mean velocity measurement for prediction of coronary flow reserve in a canonical stenosis phantom using magnetic particle imaging. PLoS One. 2021 Apr

22;16(4): e0249697.eCollection 2021.
[35] Branderhorst W, et al. Evaluation of the radiofrequency performance of a wide-bore 1.5 T positron emission tomography/magnetic resonance imaging body coil for radiotherapy planning. Phys Imaging Radiat Oncol. 2020 Dec 23; 17:13-19. eCollection 2021 Jan.
[36] Hou Y, et al. Stimuli-Responsive Nanotheranostics. Adv Healthc Mater. 2021 Mar;10(5): e2100243.
[37] Baumeister J, et al. Progression of Myeloproliferative Neoplasms (MPN): Diagnostic and Therapeutic Perspectives. Cells. 2021 Dec 16;10(12):3551.
[38] Ettlinger R, et al. Toxicity of metal-organic framework nanoparticles: from essential analyses to potential applications. Chem Soc Rev. 2022 Jan 5.
[39] Saeed M, et al. From Design to Clinic: Engineered Nanobiomaterials for Immune Normalization Therapy of Cancer. Adv Mater. 2021 Jul;33(30): e2008094.
[40] Metselaar JM, et al. Intravenous pegylated liposomal prednisolone outperforms intramuscular methylprednisolone in treating rheumatoid arthritis flares: A randomized controlled clinical trial. MJ Control Release. 2021 Dec 10;341: 548-554.
[41] Merkes JM, et al. Tuning the optical properties of BODIPY dyes by N-rich heterocycle conjugation using a combined synthesis and computational approach. New Journal of Chemistry, Published NOV 1 2021.
[42] Y Shi. PLAN B for immunotherapy: Promoting and leveraging anti-tumor B cell immunity. Journal of Controlled Release 339, 156-163, 2021.
[43] Bagivalu Lakshminarasimha A, et al. Leptin system loss of function in the absence of obesity in zebrafish. Endocrinol. 2021 Aug 16;251(1):41-52.
[44] Möhlhenrich SC, et al. Evaluation of different grafting materials for alveolar cleft repair in the context of orthodontic tooth movement in rats. Sci Rep. 2021 Jun 30;11(1):13586.
[45] Möhlhenrich SC, et al. Establishing a new alveolar cleft model in rats to investigate the influence of jaw reconstructions on orthodontic tooth movement. Ann Anat. 2021 Jul;236 151713.
[46] Escudé Martinez de Castilla P, et al. Extracellular vesicles as a drug delivery system: A systematic review of preclinical studies. Adv Drug Deliv Rev. 2021 Aug; 175:113801.
[47] Kratochwil N, et al. A roadmap for sole Cherenkov radiators with SiPMs in TOF-PET, Physics in medicine and biology, 66 (19), 195001, 2021.
[48] Bohner, L. et al. Assessment of Trabecular Bone During Dental Implant Planning using Cone-beam Computed Tomography with High-resolution Parameters, The open dentistry journal, 15 (1), 57-63, 2021.
[49] Gundacker, S. et al. Vacuum ultraviolet silicon photomultipliers applied to BaF22 cross-luminescence detection for high-rate ultrafast timing applications, Physics in medicine and biology, 66 (11), 114002, 2021.
[50] Sofias, AM, et al. Cyclic Arginine-Glycine-Aspartate-Decorated Lipid Nanoparticle Targeting toward Inflammatory Lesions Involves Hitchhiking with Phagocytes, Advanced science, 8 (13), 2100370, 2021.
[51] Martinazzoli L, et al. Scintillation properties and timing performance of state-of-the-art Gd33Al22Ga33O1212 single crystals, nuclear instruments & methods in physics research / A, 1000, 165231, 2021.
[52] Lecoq P, et al. SiPM applications in positron emission tomography : toward ultimate PET time-of-flight resolution EPJ, 136 (3), 292, 2021.
[53 Felgendreff P, et al. Identification of tissue sections from decellularized liver scaffolds for repopulation experiments, Heliyon, 7 (2), e06129, 2021.
[54 Nadig V, et al. On the Combination of a Dedicated HF Readout Circuit and the TOFPET2 ASIC to Push the Timing Performance of PET Systems, Eur J Nucl Med Mol Imaging 48, 1– 648 (2021).
[55] Nadig V, et al. Methods to Improve the Timing Resolution of Positron Emission Tomography Systems, Nuklearmedizin 2021; 60(02): 151- 152. 10.1055/s-0041-1726743.

Gruppenbild

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Building Bridges, Creating Innovation

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Introduction

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

The guiding principle of our Institute of Applied Medical Engineering (AME) is the convergence of disciplines („convergence research“) to address urgent medical needs and specific healthcare challenges. Our intellectually diverse team consists of scientists and students from the fields of engineering, medicine, biology, life sciences, physics, materials science and computer science who work closely together on many research and development projects.
The 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.
Our collaborations with national and international academic and industrial partners result in innovative diagnostic and therapeutic approaches, new impulses for teaching and an extensive catalog of jointly supervised engineering, natural science and medical dissertations.
The institute consists of 6 departments, whose 2021 research activities are described below. CVE and RPE are located in the Helmholtz Institute building (HIA), BEE and SCM in the Medical Technology Center (MTZ), and AMB, BioTex, and again CVE on two floors of the new Center for Biohybrid Medical Systems (CBMS). All locations are in close proximity to each other and to the University Hospital (UKA).

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

Advanced Materials for Biomedicine (AMB)

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

The Department for Advanced Materials for Biomedicine (AMB) focuses on the synthesis and (self)-assembly of synthetic molecules and micron-scale building blocks to create 3D constructs for tissue growth and regeneration. The research group forms a bridge between the University Hospital, the Chemistry Department of the RWTH, and the DWI-Leibniz Institute for Interactive Materials. Polymer synthesis is combined with in-mold polymerization techniques, microfluidics, and fiber spinning to 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 2021:

- Biomimetic scaffolds often fail to mimic hierarchical tissues in the body. With 2-photon lithography, we designed and produced an in vitro high-throughput platform with discrete anisometric guidance cues to study how much guidance nerve cells need to grow in a linear manner. This platform is vital to engineer injectable scaffolds (like Anisogels) for enhanced nerve repair. (doi: 10.1002/adhm.202100874 Fig. 2).

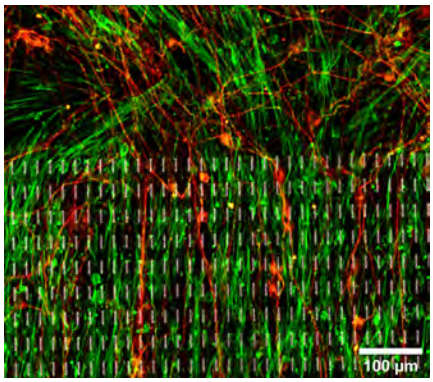


Fig. 2: Nerve cells (red) and fibroblasts (green) orienting linearly on the anisometric microelement array (white).

- Synthetic Anisogels modified with novel bicyclic RGD peptides act as superior scaffolds for oriented nerve growth compared to conventional linear or monocyclic RGD peptides. The bicyclic peptides, engineered by Pepscan (NL), impart high affinity and selectivity towards integrin proteins, paving the way for a new class of biomolecules for nerve regeneration and many other tissues. (doi: 10.1039/d0bm02051f Fig. 3).

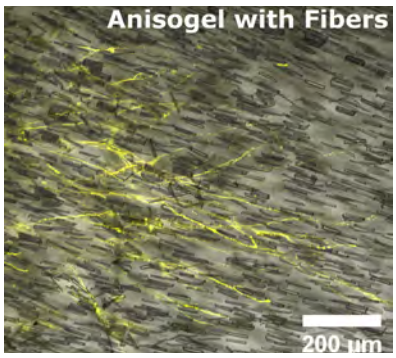


Fig. 3: Nerve cells (yellow) grow aligned inside PEG Anisogels with short magnetically oriented fibers and bicyclic RGD modification.

- Microgels are crosslinked, water-swollen networks with a 10 nm to 100 μm diameter and can be modified chemically or biologically to render them biocompatible for advanced clinical applications. We show the fundamental aspects of microgel research and development and discuss their specific applications for theranostics and therapy in the clinic while focussing on microgels for drug delivery, scavenging, imaging, and tissue engineering and regeneration (doi: 10.1002/adhm.20210198 Fig. 4).

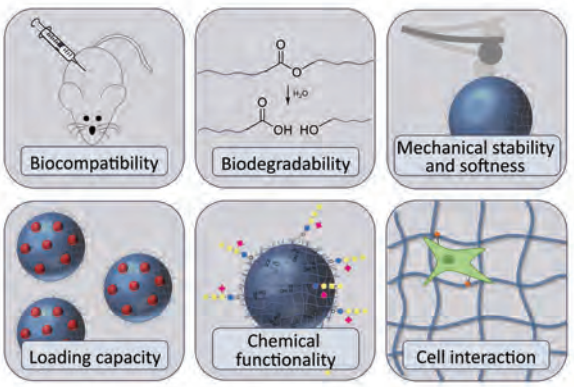


Fig. 4: Overview of microgel requirements for clinical applications.

Biophysical & Education Engineering (BEE) Nanomagnetic Engineering/NME

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

In the NME group, superparamagnetic iron oxides nanoparticles, so-called SPIONs, were investigated and further developed. For this automated and highly scalable production processes to enable the fabrication of SPIONs with tailored sizes, magnetization, and stabilizing shell were employed (Fig. 5). In order to control the

parameter of the synthesis (such as pressure and temperature), powerful inline measurement techniques were used. Such standardized and automated processes pave the way towards clinical translation of SPIONs for specific applications.

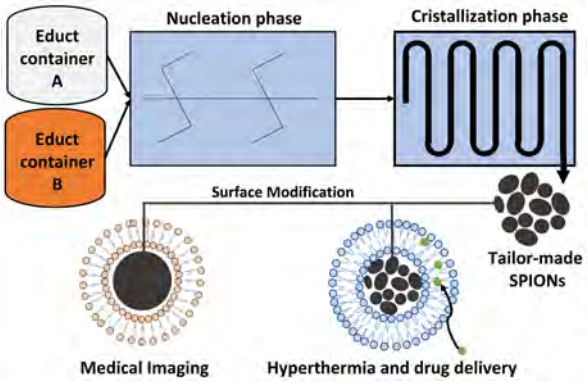


Fig. 5: Sketch of continuous automated synthesis process enabling the large-scale production of SPIONs with well-defined properties for various biomedical applications in diagnostics and therapy.

Due to their superparamagnetic property, SPIONs show unique responses to static and alternating magnetic fields. SPIONs are used both as actuators for therapy, e.g., to release drugs and/or thermal energy into tissue, and as sensors for diagnostics, e.g., as contrast agents in medical imaging. Exploiting their actuator ability, SPIONs were used for the development of hybrid stents to treat hollow organ tumours by hyperthermia (Fig. 6). The structure and position of the stents inside the human body can be delineated with magnetic resonance imaging (MRI).

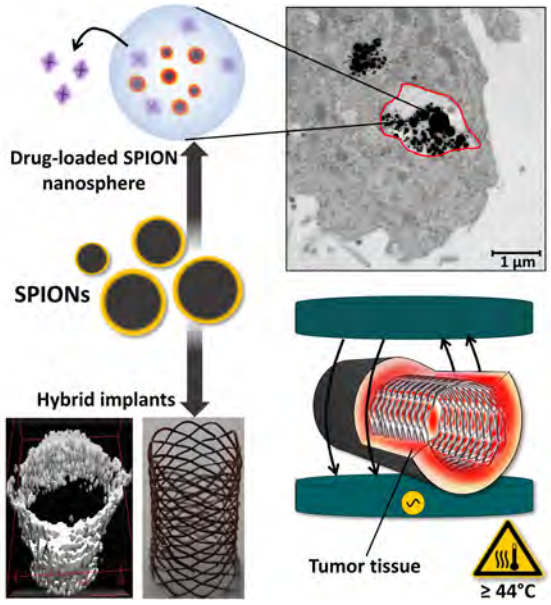


Fig. 6: Sketch of SPIONs consisting of a metallic core with a stabilizing organic shell. They can interact with the cell directly delivering drugs to the cell. Further, SPIONs inside hybrid implants can be activated in an alternating magnetic field to generate local heat and destroy neighbouring cancer tissue (DOI: https://doi.org/10.3390/nano11030618).

NRW Schwerpunktprofessur Biohybrid & Medical Textiles (BioTex)

Univ. Prof. Dr. med. Stefan Jockenhövel

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

Fig. 7: Construction of the Leibniz Joint - Lab first-in-translation (fiT) at the DWI Leibniz Institute is in progress.

Research Highlights of 2021:

BioTex represents RWTH Aachen University in the 150 year anniversary exhibition at the Centre Charlemagne

The joint anniversary exhibition of RWTH Aachen University and the City of Aachen in the Centre Charlemagne provides insights into the history and development of RWTH, which was founded as the „Royal Rhenish-Westphalian Polytechnic School". It provides an opportunity to learn about research highlights and focal points of the university's various departments. The exhibition was running from October 30, 2021 until February 13, 2022.

Fig. 8: Cell meets Textile - Made by BioTex: Living implants with textile reinforced structure.

Prof. Stefan Jockenhoevel is the coordinator of the consortium Biobased Value Circle, a Marie Skłodowska-Curie European Industrial Doctorate (EID).

The Biobased Value Circle consortium consists of four European universities, one research institute and nine European companies, and involves the training of 12 Ph.D students. The mission of the program is to contribute to the development of a circular biobased economy by exploiting the potential of biobased materials.

The BioTex department plays a significant role within the consortium, and it is involved in 2 out of the 12 projects that conforms the program. Both projects are focused on the development of aortic heart valve replacements by combining the principles of materials science and tissue engineering.
Both projects are co-supervised by excellent industrial partners: Technical proteins nanobiotechnology SL (TPNBT) and Spintex Engineering Limited (United Kindom).

Fig. 9: Consortium Biobased Valve Circle

BMBF Young Scientists Competition

Alicia Fernández Colino has been selected winner of the BMBF Young Scientists Competition NanoMatFutur. The competition is part of the „From Material to Innovation" framework program of the German government's high-tech strategy. With this funding grant of 1.85 million euros, Dr. Fernández Colino will set up her own independent Junior Research Group at BioTex (AME, Uniklinik RWTH Aachen University), and will focus on the development of biomimetic cardiovascular implants based on Elastin-like Recombinamers (ELR).

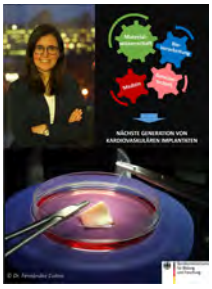


Fig. 10: Alicia Fernández Colino: next generation of cardiovascular implants.

Heinrich Hertz Foundation

Caroline Kniebs received a grant from the Heinrich Hertz Foundation for a research stay at the Chinese University of Hong Kong in the group of Prof. Blocki with the topic „Establishment of a 3D in vitro model to study tumor cell intravasation in microfluidic systems". In this project, a dynamic tumor microen-vironment will be created on a laboratory scale to observe and understand the intravasation of tumor cells into the surrounding vascularized network.

Fig. 11: Caroline Kniebs.

Project fundings:

Within the DFG-funded Priority Program "Towards an Implantable Lung" two projects were funded at BioTex in the Respiratory Tissue Engineering Group: (i) EndoSpray – Efficient cell coating of biohybrid lungs by atomization of shear-stress resistant endothelial cells derived from induced pluripotent stem cells (PIs: Dr. Anja Lena Thiebes, Dr. Christian Cornelissen und Dr. Ruth Olmer (MHH)) and (ii) EndOxy in Flame – Influence of a Biohybrid Lung on In-flammatory Pathways and Immune System-Endothelial Cell-Interaction (PIs: Univ.-Prof. Dr. med. Stefan Jockenhövel und Prof. Dr. med. Klaus Tenbrock (UKA)).
Disease X-Chip - funded by the Volkswagen Stiftung, for the generation of novel 3D bioprinted tissue chips mimicking the human trachea to be applied in the research of COVID and other respiratory diseases. PIs: Dr. Daniela F. Duarte-Campos, Dr. Anja Lena Thiebes, Prof. Dr. Mirko Trilling (Essen).
PleuraPlug - funded by the BMBF through the Bio4MatPro project, for the development of surface-functionalized biobased and injectable patches for tissue regeneration in traumatic pleural injuries. PIs: Prof. Dr. Ulrich Schwaneberg (DWI), Dr. Felix Jakob (DWI), Dr. Alexander Boes (DWI), Prof. Dr. Andrij Pich (DWI), Dr. Anja Lena Thiebes. Partners: Fibrothelium, Pfeifer & Langen.
"ENDOcoatings – Endothelium-mimicking coatings for preventing stent thrombosis and restenosis" - funded within the framework of the "9th Call for Proposals for RWTH Start-Up – for New Independent Research (ERS Project Support, RWTH Aachen University)"
BMBF NanoMatFuture (see above)

Cardiovascular Engineering (CVE)

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

In 2021, we started 8 new research projects with funding from public and private organizations, and published our work in 24 peer-reviewed articles. Most importantly, we could continue our ongoing projects in our focus areas Therapies & Applications, Research & Validation and Modeling & Simulation almost as planned even in pandemic peaks, thanks to stringent hygiene protocols and a responsible team effort.
Research & Validation concentrates on the in-vitro evaluation of interactions between biological and technical systems for cardiopulmonary applications.
After successfully finishing the DFG-funded project Ghost Cells, a follow-up project was granted. The aim is to modify the produced ghost cells in a way that allows for real-time hemolysis detection in combination with PIV (particle image velocimetry) in medical devices such as rotary blood pumps.
Within the project DurImplant, which is part of the DFG PAK 961 - Towards Model-based Control of Biohybrid Implant Maturation, a test setup for new biomaterials used for artificial heart valves was developed. This includes a micro flow chamber and a calcification fluid that allows for accelerated in-vitro calcification testing of materials and heart valve prostheses prior to animal trials.

Fig. 12: Flow chamber

Another test setup was developed in the project TIBET and its follow-up project ELIOT. Since in-vitro thrombogenicity testing of oxygenators is hardly possible so far, a comparative setup with two test objects in parallel was developed. Using low-anticoagulated porcine blood, blood parameter analyses and different imaging techniques, timely resolved thrombus formation in oxygenators is investigated.

Fig. 13: Microscopic view on in vitro cultivated thrombus in ECMO oxygenator.

In-vitro tests run with blood are only feasible for several hours; therefore, the project OxyBench (START) develops an alternative to whole blood that allows for oxygenator testing over days and weeks. The focus of analyses lies on markers that are a hint for thrombus formation, such as fibrin or thrombin generation.

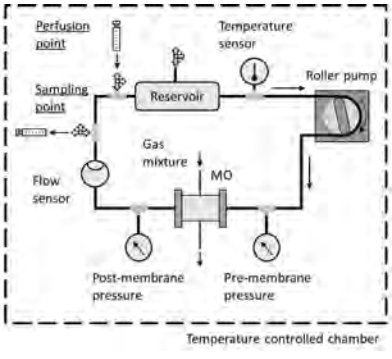


Fig. 14: Schematic of the test set-up with sampling and water perfusion locations as well as temperature, pressure, and flow measuring points

Since the majority of in-vitro tests require a large amount of blood, which exceeds the volume of standard human blood donation, porcine blood is used as alternative. To validate the comparability of human and porcine blood, several smaller projects focus on particular blood parameters (e.g. platelet aggregation or complement system) and the comparability between the two species.

Within the field Modeling & Simulation, a numerical computational fluid dynamics model for thrombus prediction in rotary blood pumps has been developed. The model allows the determination of thrombosis potential by looking at the platelet activation due to mechanical stresses and chemical cues, Fig. 15. The model has been tested on the HeartMate II Ventricular Assist Device and showed very good correlation with clinical data on thrombus deposition with only minimal additional computational ressources. It can further be translated to other blood-contacting medical devices.

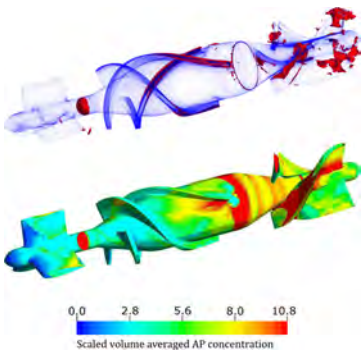


Fig. 15: Scaled activated platelet (AP) concentration in HeartMate II geometry with 9000 rpm and 2 L/min.

In a second project RenOx , a mathematical model for the investigation of the patient-device interaction during extracorporeal membrane oxygenation (ECMO) has been developed. The model provides a numerical representation of the cardiovascular circulation, lung mechanics, gas exchange, and the dynamics of the ECMO system. The mod-el parameters can be fitted with a Bayesian optimization approach, to allow the calculation of detailed hemodynamical and respiratory parameters for various patient conditions, e.g. during venoarterial ECMO, see Fig. 16.

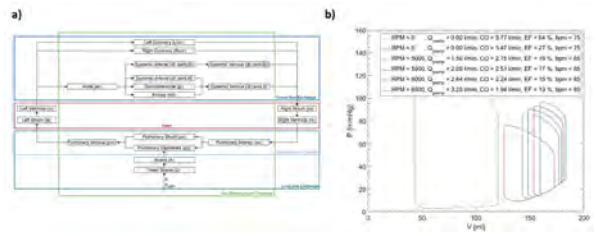


Fig. 16: a) Mathematical model of ECMO. b) Left ventricular pressure-volume loops at different conditions of venoarte-rial ECMO support.

Within Therapies & Applications progress in the research of TPMS shaped membranes for the use in artificial lungs have been made. Seamless distortion of the TPMS elements (Fig. 17) now allow for a local variation of flow resistance through the artificial lung and a corresponding design contributes to a homogenous flow distribution maximizing efficiency and minimizing thrombotic risks. New simulation models have been developed in order to predict the flow behavior through the distorted TPMS membranes. Numerical predictions of the respective gas-exchange are under further development.

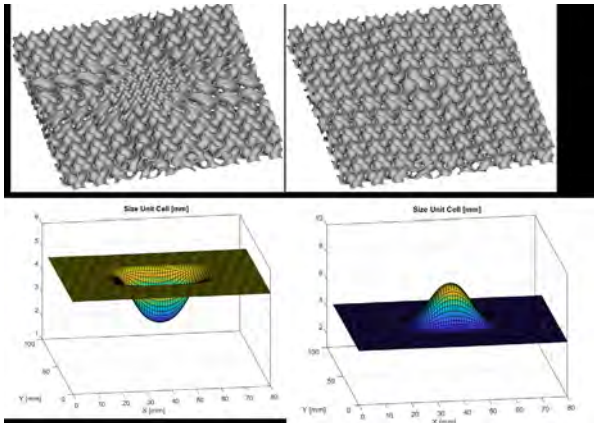


Fig. 17: TPMS membrane distortion for local variation of flow resistance.

As a part of a European consortium in the project Perinatal Life Support, the artificial placenta of the life support system was defined. The artificial placenta consists of a dialyzer concept for the amniotic fluid and an oxygenator for gas exchange of the perinate. The new oxygenator concept is now filed as a patent. Both artificial placenta parts are manufactured as prototypes and will be tested for hemocompatibility (oxygenator part) and biocompatibility (dialyzer). Further, the cannulation requirements for the umbilical cord has been defined and a test stand was developed in order to test human umbilical cords in vitro.

Rehabilitation and Prevention Engineering (RPE)

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

Research expertise in the Department of Rehabilitation & Prevention Engineering (RPE) extends from the biomechanical analysis of human movement and the processing of signals from various sensors to the assessment of the technical and neuromuscular factors influencing the interplay between assistive robotics and humans in medical environments.
Analysis of human movement and coordination
Understanding CNS-modulated muscular coordination strategies is essential for refining personalized rehabilitation. Research into the coordination of muscular activation among agonistic and antagonistic muscles at the elbow, focused on control strategies during unfamiliar tasks. Arm movements and surface electromyography (sEMG) signals were recorded during elbow flexion/extension performed in the horizontal plane at constant torque but at various angular velocities and external loads (Fig. 18). Analysis (biomechanical, sEMG) showed that less well-entrenched neuromuscular coordination patterns were observed, notably higher muscle coactivation, in order to maintain joint stability and perform the unfamiliar task.

Fig. 18: Experimental setup. The subject's arm is connected via a sling to a pulley machine. The horizontal armrest provides stability and standardizes the movements performed.

Intelligent rehabilitation aids

Low back pain (LBP) sufferers increasingly seek medical advice. Yet as individualised physiotherapeutic rehabilitation grows more relevant, patients' compensatory movements, due to pain, limit rehabilitative success. In
the autoPräz project 30 healthy subjects performed 3 LBP rehabilitation exercises in 2 categories involving typical compensatory movement (TCM). Back movement was recorded using 3 inertial measurement units (IMU). The IMU data, was used to train a classifier, that successfully detects compensatory movement and supports LBP patients' rehabilitation.

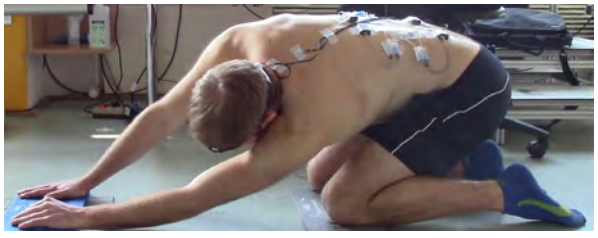


Fig. 19: IMU placement and an example of compensatory movement during the exercise Prone-Rocking.

PfleKoRo – cooperative robotics making caregiving easier
PfleKoRo aims to develop a robotic assistance system, that supports nurses during physically demanding aspects of patient care. Ensuring safe physical grasping and patient-robot contact was a particular challenge. Different geometries, surfaces, and movement patterns of an end-effector were tested and evaluated leading to a concept based on a vacuum pad.

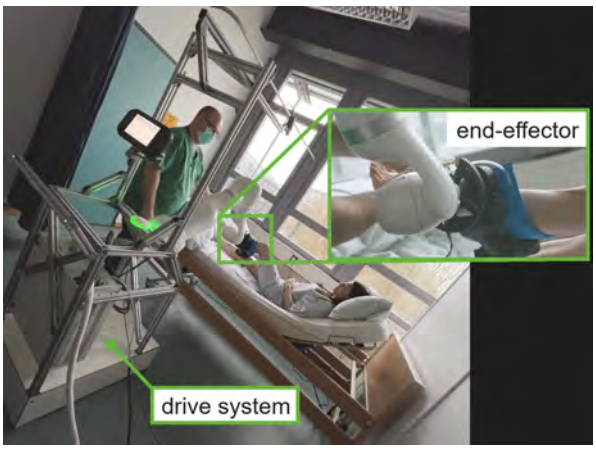


Fig. 20: PfleKoRo-System.

To offset the robotic system's high weight, a mecanum drive system was designed allowing ergonomic system transport, maximal manoeuvrability in caregiving environments and ease of use by caregivers. First prototypes were manufactured and tested in the RPE's Linving Lab, which simulates a real-world care environment. (Fig. 20).

Science Management (SCM)

Dr. Robert Farkas (Head)

Artificial intelligence (AI) is arguably one of the most promising innovation for the future of diagnosis and therapy. However, translating such technologies into the clinical workflow of hospitals is a challenging task in terms of integrating not only data, but moreover resources, safety and protection of patient rights, interdisciplinary research, and more. Our analysis under the roof of the Comprehensive Diagnostic Center Aachen CDCA of University Hospital Aachen revealed both existing local gaps in using AI and the overall state of the German healthcare system for implementing novel data technologies from an international perspective.
Consequently, we continued the collaboration with the local Clinical Department of Internal Medicine I (MK1) focussed on heart failure with preserved ejection fraction (HFpEF), a severe and due to various phenotypes difficult to identify disease with a 5-year mortality of 76%. Since early and comprehensive diagnosis is essential for treatment, SCM together with its partners MK1 and Biomax Informatics AG will collaborate on the development of a digital decision support system for early diagnosing HFpEF. Using artificial intelligence and the future-oriented terminology standard SNOMED CT, structured as well as unstructured data (text) will serve as fundament to train cutting-edge machine learning algorithms for the explainable prediction of the patients risk suffering from HFpEF. The project named DARIO (see Fig.21) is funded by the German Federal Ministry of Education and Research – BMBF.

Fig. 21: Outline of our BMBF funded research project DARIO aiming at improving the diagnosis of heart failure with preserved ejection fraction (HFpEF).

Acknowledgements

the German Federal Ministry of Education and Research (BMBF)

Awards

Anja Lüngen won the first science award 2020 of the West German Respiratory Society (WDGP) that was granted at the 10th WDGP Congress 2022 in Münster. The award was assigned for the publication „Choosing the right differentiation medium to develop mucociliary phenotype of primary nasal epithelial cells in vitro" published in Scientific Reports.

Fig. 22: Anja Lüngen at the 10th WDGP Congress 2022 in Münster.

Ben Schürmann: yESAO exchange Award, ESAO, Sept. 2021
Catherine Disselhorst-Klug: Fellow der „International Society of Biomechanics". Juli 2021.
Kristin Hugenroth: Young Investigator Award, EuroElso, Mai 2021
Lennart Göpfert M. Sc.: Graduiertenförderung, RWTH Aachen, Mai 2021
Peter Schlanstein/ Matthias Menne/ Niklas Steuer (HBOX): RWTH Innovation Award 2020, Febr. 2021
Peter Schlanstein/ Matthias Menne/ Niklas Steuer (HBOX): BioRiver Boost 2021, Okt. 2021

Peter Schlanstein/ Matthias Menne/ Niklas Steuer (HBOX): UIC 2021, Okt. 2021
Sergio Acosta has been awarded the "Julia Polak European Doctorate Award 2021" by the European Society for Biomaterials (ESB).

Fig. 23: Sergio Acosta, winner of the "Julia Polak European Doctorate Award 2021.

Selected Publications

[1] Babu S, Albertine F, Omidinia-Anarkoli A, De Laporte L. Controlling structure with injectable biomaterials to better mimic tissue heterogeneity and anisotropy. Advanced Healthcare Materials 2021, 10: e2002221
[2] Bogunovic N., Meekel JP., Majolée J., Hekhuis M., Pyszkowski J., Jockenhövel S., Kruse M., Riesebos E., Micha D., Blankensteijn JD., Hordijk PL., Ghazanfari S., Yeung KK.: Patient-Specific 3-Dimensional Model of Smooth Muscle Cell and Extracellular Matrix Dysfunction for the Study of Aortic Aneurysms. J Endovasc Ther. 2021 Aug;28(4):604-613.
[3] De Keer L, Cavalli F, Estupiñán D, Krüger AJD, Rocha S, Van Steenberge PHM, Reyniers M-F, De Laporte L, Hofkens J, Barner L, D'hooge DR. Synergy of advanced experimental and modeling tools to underpin the synthesis of static step-growth-based networks involving polymeric precursor building blocks. Macromolecules 2021, 54: 9280-98
[4] Engelmann U. M., Shasha C., Slabu I.: "Magnetic Nanoparticle Relaxation in Biomedical Application. Focus on Simulating Nanoparticle Heating." In Magnetic Nanoparticles in Human Health and Medicine, 327-354, 2021
[5] Fernández-Colino A., Jockenhoevel S.: Advances in Engineering Venous Valves: The Pursuit of a Definite Solution for Chronic Venous Disease. Tissue Eng Part B Rev. 2021 Jun;27(3):253-265.
[6] Frerich K., Mark B., Geisler S., Farkas R.: On the Potential of Taxonomic Graphs to Improve Applicability and Performance for the Classification of Biomedical Patents. In: Applied Sciences 11 (2), S. 690. (2021) DOI: 10.3390/app11020690.
[7] Göpfert L., Mustafa A., Mues B., Slabu I.:"High Magnetic Field Gradient Particle Separation For Biomedical Applications".In 26. Symposium Electromagnetic Phenomena in Nonlinear Circuits online 2021-04-07 - 2021-04-09, 2021
[8] Grünwald A., Korte J., Wilmanns N., Winkler C., Linden K., Herberg U., Groß-Hardt S., Steinseifer U. & Neidlin M.. Intraventricular Flow Simulations in Singular Right Ventricles Reveal Deteriorated Washout and Low Vortex Formation. Cardiovascular Engineering and Technology (Nov 2021).

[9] Heitzer M., Möhlhenrich SC., Kniha K., Tolba R., Jockenhoevel S., Hölzle F., Modabber A.: Microvascular anastomo-sis techniques using the medical adhesive VIVO and expandable micro-stents in a rat carotid artery model. Ann Anat. 2021 Nov;238:151782.
[10] Helmedag M., Heise D., Eickhoff R., Kossel KM., Gries T., Jockenhoevel S., Neumann UP., Klink CD., Lambertz A.: Cross-section modified and highly elastic sutures reduce tissue incision and show comparable biocompatibility: in-vitro and in-vivo evaluation of novel thermoplastic urethane surgical threads. J Biomed Mater Res B Appl Biomater. 2021 May;109(5):693-702.
[11] Hesselmann F., Scherenberg N., Bongartz P., Djeljadini S., Wessling M., Cornelissen Ch., Schmitz-Rode T., Steinseifer U., Jansen SV., Arens J.: Structure-depend gas transfer performance of 3D-Membranes for artificial membrane lungs. Journal of Membrane Science 634(2005):119371. May 2021 DOI: 10.1016/j.memsci.2021.119371
[12] Hildebrand S., Diedrich M., Brockhaus M., Finocchiaro T., Cuenca E., De Ben H., Steinseifer U., Schmitz-Rode T., Jansen SV.: Controlling the flow balance: In vitro characterization of a pulsatile total artificial heart in preload and afterload sensitivity. ARTIFICIAL ORGANS, Early Access Jul 2021.
[13] Kaesler A., Rudawski FL., Zander MO., Hesselmann F., Pinar I., Schmitz-Rode T., Arens J., Steinseifer U., Clauser JC.: In-Vitro Visualization of Thrombus Growth in Artificial Lungs Using Real-Time X-Ray Imaging: A Feasibility Study. CARDIOVASCULAR ENGINEERING AND TECHNOLOGY, Early Access Sept 2021. DOI: 10.1007/s13239-021-00579-y
[14] Kittel Y., Kuehne AJC., De Laporte L.: Translating therapeutic microgels into clinical applications. Advanced Healthcare Materials 2021, Online
[15] Kniebs C., Luengen AE., Guenther D., Cornelissen CG., Schmitz-Rode T., Jockenhoevel S., Thiebes AL.: Establishment of a Pre-vascularized 3D Lung Cancer Model in Fibrin Gel-Influence of Hypoxia and Cancer-Specific Therapeutics. Front Bioeng Biotechnol. 2021 Oct 14;9:761846.
[16] Kreimendahl F., Kniebs C., Tavares Sobreiro AM., Schmitz-Rode T., Jockenhoevel S., Thiebes AL.: FRESH bi-oprinting technology for tissue engineering - the influence of printing process and bioink composition on cell behavior and vascularization. J Appl Biomater Funct Mater. 2021 Jan-Dec;19:228080002110288O8.
[17] Lindemann M. C., Luttke T., Bauer B., Nottrodt N., Schmitz-Rode T., and Slabu I.: "FEM based Simulation of Magnetic Drug Targeting in a Multibranched Vessel Model", Computer Methods and Programs in Biomedicine, 210: 106354, 2021.
[18] McManus L., Lowery M., Merletti R., Sogaard K., Besomi M., Clancy EA., Van Dieen JH., Hug F., Wrigley T., Besier T., Carson RG., Disselhorst-Klug C., Enoka RM., Falla D., Farina D., Gandevia S., Holobar A., Kiernan MC., McGill K., Perreault E., Rothwell JC., Tucker K., Hodges PW.: Consensus for experimental design in electromyography (CEDE) project: Terminology matrix. Journal of Electromyography and Kinesiology: 2021,59:102565. DOI10.1016/j.jelekin.2021.102565.
[19] Merletti R., Campanini I., Rymer WZ., Disselhorst-Klug C.: Editorial: Surface Electromyography: Barriers Limiting Widespread Use of sEMG in Clinical Assessment and Neurorehabilitation. Frontiers in Neurology: 2021, 12, 642257. DOI10.3389/fneur.2021.642257.
[20] Mues B., B. Bauer, Ortega J., Buhl E. M., Teller H., Gries T., Schmitz-Rode T., Slabu I.: "Assessing hyperthermia performance of hybrid textile filaments: The impact of different heating agents", Journal of Magnetism and Magnetic Materials, 519: 167486, 2021.
[21] Mues B., Bauer B., Roeth A., Ortega J., Buhl E. M., Radon P., Wiekhorst F., Schmitz-Rode T., Slabu I.: "Nanomagnetic Actuation of Hybrid Stents for Hyperthermia Treatment of Hollow Organ Tumors", Nanomaterials, 11: 618, 2021.
[22] Mues, Bauer , J. K. Ortega, T. Gries, T. Schmitz-Rode, I. Slabu:"Nonlinear Magnetization Effects of Magnetic Nanoparticles for Implant Based Hyperthermia Tumor Therapy ". In 26. Symposium Electromagnetic Phenomena in Nonlinear Circuits online 2021-04-07 - 2021-04-09, 2021
[23] Nothdurft K., Muller DH., Murtz S., Meyer AA., Brands T., Guerzoni LPB., Jahns A., Kuehne AJC., De Laporte L., Bardow A., Vedaraman S., Richtering W.: Dynamics of the cononsolvency-induced collapse of pNIPAM microgels: A two-step process? The Journal of Physical Chemistry B 2021, 125:1503-12
[24] Palzer J., Eckstein L., Slabu I., Reisen O., Neumann U. P., Roeth A. A.: "Iron Oxide Nanoparticle-Based Hyperthermia as a Treatment Option in Various Gastrointestinal Malignancies", Nanomaterials, 11:3013, 2021.
[25] Palzer J., Mues B., Goerg R., Aberle M., Rensen S. S., Olde Damink S. W. M., Vaes R., Cramer T., Schmitz-Rode T., Neumann U. P., Slabu I., Roeth A. A.: "Magnetic fluid hyperthermia as treatment option for pancreatic cancer cells and pancreatic cancer organoids", International Journal of Nanomedicine, 21:2965, 2021.
[26] Pedersoli F., Wilkmann, C., Penzkofer T., Disselhorst-Klug C., Schmitz-Rode T., Kuhl C., Bruners P., Isfort P.: An accelerometer-based guidance device for CT-guided procedures: an improved wireless prototype. Minimally Invasive Therapy & Allied Technologies: 2021. DOI10.1080/13645706.2021.2002363.
[27] Pérez Sanpablo A. I., Romero Avila E., & González Mendoza A.: Three-dimensional printing in healthcare. Mexican Journal of Biomedical Engineering, 42(2), 32-48. (2021). DOI https://doi.org/10.17488/rmib.42.2.3.
[28] Roeth A., Garretson I., Beltz M., Herbold T., Schulze-Hagen M., Quaisser S., Georgens A., Slabu I., Klink C. D., Neumann U. P., Linke B. S.: "3D-Printed Replica and Porcine Explants for Pre-Clinical Optimization of Endoscopic Tumor Treatment by Magnetic Targeting", Cancers, 13: 5496, 2021.
[29] Rostamitabar M., Abdelgawad AM., Jockenhoevel S., Ghazanfari S.: Drug-Eluting Medical Textiles: From Fiber Production and Textile Fabrication to Drug Loading and Delivery. Macromol Biosci. 2021 Jul;21(7):e2100021.
[30] Rostamitabar M., Subrahmanyam R., Gurikov P., Seide G., Jockenhoevel S., Ghazanfari S.: Cellulose aerogel micro fibers for drug delivery applications. Mater Sci Eng C Mater Biol Appl. 2021 Aug;127:112196.
]31] Schöps M., Groß-Hardt SH., Schmitz-Rode T., Steinseifer U., Brodie D., Clauser JC., Karagiannidis C.: Hemolysis at low blood flow rates: in-vitro and in-silico evaluation of a centrifugal blood pump. J Transl Med. 2021 Jan 5;19(1):2. DOI: 10.1186/s12967-020-02599-z
[32] Thiebes AL., Uhl FE., Hauser M., Cornelissen CG., Jockenhoevel S., Weiss DJ.: Endoscopic atomization of mesen-chymal stromal cells: in vitro study for local cell therapy of the lungs. Cytotherapy. 2021 Apr;23(4):293-300.
[33] Tuladhar SR., Mulderrig S., Della Barbera M., Vedovelli L., Bottigliengo D., Tessari C., Jockenhoevel S., Gregori D., Thiene G., Korossis S., Mela P., Iop L., Gerosa G.: Bioengineered percutaneous heart valves for transcatheter aortic valve replacement: a comparative evaluation of decellularised bovine and porcine pericardia. Mater Sci Eng C Ma-ter Biol Appl. 2021 Apr;123:111936.
[34] Vedaraman S., Licht JC., Bernhagen D., Timmerman P., De Laporte L.: Bicyclic RGD peptides enhance nerve growth in synthetic PEG-based Anisogels. Biomaterials Science 2021, 9: 4329-42
[35] Vedaraman S., Perez-Tirado A., Gerardo-Nava J., Haraszti T., Nishiguchi A., De Laporte L.: Anisometric microstructures to determine minimal critical physical cues required for neurite alignment. Adv. Healthcare Materials 2021, e2100874
[36] Wang H., Klosterhalfen B., Müllen A., Otto T., Dievernich A., Jockenhövel S.: Degradation resistance of PVDF mesh in vivo in comparison to PP mesh. J Mech Behav Biomed Mater. 2021 Jul;119:104490.
[37] Wolf F., Paefgen V., Winz O., Mertens M., Koch S., Gross-Weege N., Morgenroth A., Rix A., Schnoering H., Chalabi K., Jockenhoevel S., Lammers T., Mottaghy F., Kiessling F., Mela P.: Corrigendum to „MR and PET-CT monitoring of tissue-engineered vascular grafts in the ovine carotid artery". Biomaterials. 2021 Apr;271:120723.
[38] Xu Y., Zheng H., Schumacher D., Liehn E. A., Slabu I., Rusu M. : "Recent Advancements of Specific Functionalized Surfaces of Magnetic Nano- and Microparticles as Theranostics Source in Nanomedicine", ACS Biomaterials Science & Engineering, 7: 1914, 2021. (* shared last authors)

Team

Fig. 24: The AME team.

Third-party Funding

	Number of Projects	Total Expense of Projects (€)
German Research Foundation (DFG)	65	3.792.446,96 €
German Federal Ministry of Education and Research (BMBF)	36	2.679.942,09 €
EU	**7**	729.137,03 €
Industry	34	1.325.157,21 €
Other	55	2.732.354,05 €
Sum	182	11.259.037,34 €

Theses

	Number
Student Mini-Thesis (SA + PA)	8
Bachelor	105
Diploma/Master	142
Doctoral	26
Habilitation	2
Sum	283

Staff

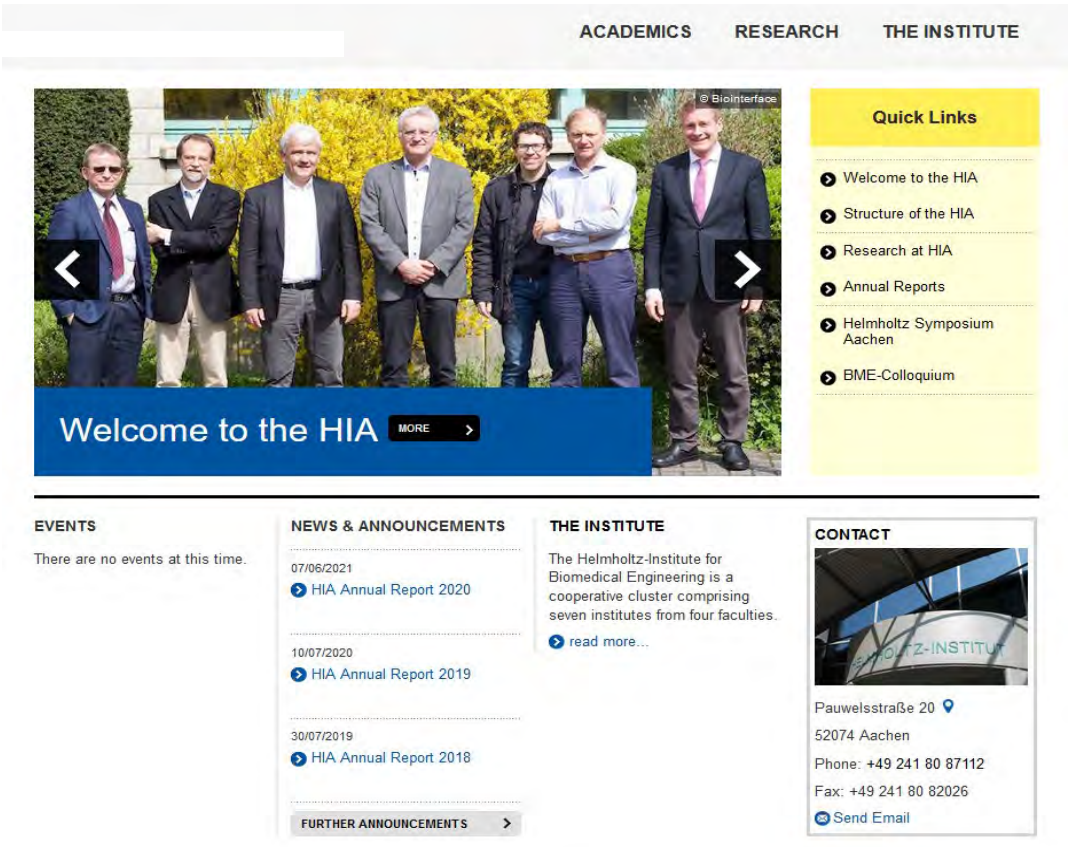
	Scientific	Admin. & Techn.
Total	302,5	65,5
Third party funded	205,75	15,5
in full-time equivale	91	2

Publications

	Number
Conference proceedings	50
Peer-reviewed journals	196
Books and book chapters	28
Sum	274

Patents and patent applications: 3

Webpage: www.hia.rwth-aachen.de



Content

Annual Report
2021
Helmholtz-Institute for Biomedical Engineering
RWTH Aachen University

How to reach us

Address

Helmholtz-Institute for Biomedical Engineering
Pauwelsstrasse 20
52074 Aachen
Germany

By car

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

By train/bus

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

By plane

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

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