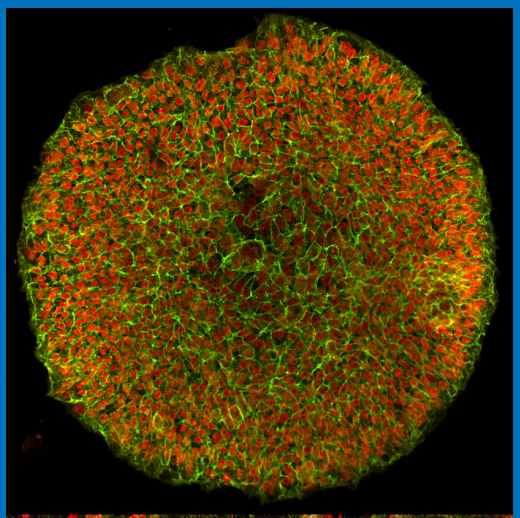
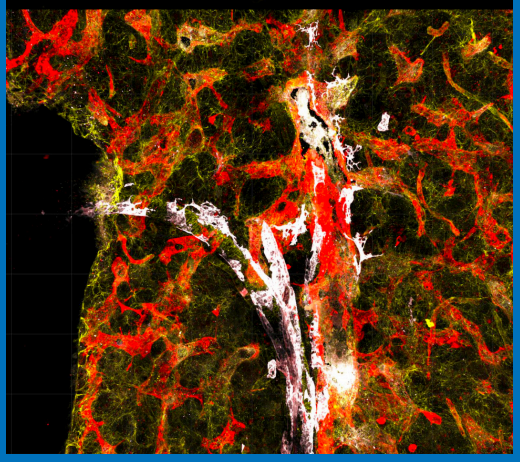
Cell Biology

Gene Function in Cell Growth, Differentiation & Development





Director

Univ.-Prof. Dr. rer. nat. Martin Zenke
Univ.-Prof. Dr. med. Dr. rer. nat. Rebekka Schneider

Institute for Biomedical Engineering – Cell Biology
RWTH Aachen University Hospital
Pauwelsstrasse 30, 52074 Aachen

Helmholtz Institute for Biomedical Engineering
Pauwelsstrasse 20, 52074 Aachen

Phone: +49-241-80 80760 (Office)
+49-241-80 80759 (Secretary)
Fax: +49-241-80 82008
Email: martin.zenke@rwth-aachen.de
Web: http://www.molcell.de
http://www.stemcellfactory.de

Staff

Mierau, Eveline, Administrative Assistant

Atakhanov, Salim, MSc Student
Böhnke, Janik, MSc, PhD Student
Cadoni, Maria Piera, MSc, Visiting Scientist
Cichoń, Anna, MSc, Visiting Scientist
Dibenedetto, Stella, MSc, Visiting Scientist
Flosdorf, Niclas, MSc, PhD Student
Gaebler, Armin, MD, Clinician Scientist
Götz, Katrin, MSc, Technician
Hamouda, Ahmed, MSc, PhD Student
Hieronymus, Thomas, PhD, Group Leader
Ma, Zhiyao, MSc Student
Piassi, Marcela, PhD, Visiting Scientist
Pritchard, Jess, MSc, PhD student
Reimer, Katharina, MD, Clinician Scientist
Satoh, Taiki, MSc Student
Schalla, Carmen, Technician
Schmitz, Susanne, Technician
Sechi, Antonio, PhD, Group Leader
Seré, Kristin, PhD, Group Leader
Wagner, Silke, Technician
Wanek, Paul, BSc, Technician
Wanner, Pia, MSc Student
Xu, Huaming, MSc, PhD Student

Stem Cell Biology and Cellular Engineering

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

Helmholtz Institute for Biomedical Engineering
Pauwelsstrasse 20, 52074 Aachen

Phone: +49-241-80 88611 (Office)
Fax: +49-241-80 82008
Email: wwagner@ukaachen.de
Web: http://www.stemcellbiology.ukaachen.de

Bocova, Ledio, MSc, PhD Student
Cypris, Olivia, MSc, PhD Student
Franzen, Julia, PhD, Postdoc
Glück, Philipp, MSc Student
Gobs, Michael, MSc Student
Goetzke, Roman, PhD, Postdoc
Han, Yang, MSc, PhD Student
Hennecke, Ann-Christine, MSc Student
Hollmann, Jonathan, MD Student
Kuo, Chao-Chung, PhD, Postdoc
Lubberich, Richard, MD Student
Nikolić, Miloš, MSc, PhD Student
Nüchtern, Selina, BSc, Technician
Maaßen, Catharina, Technician
Mulabdic, Melita Sara, MSc, PhD Student
Mabrouk, Mohamed, MSc, PhD Student
Mohr, Rebecca, MSc Student
Ramírez, Diana, PhD, Postdoc
Salz, Lucia, MSc, PhD Student
Sociale, Mariangela, PhD, Postdoc
Schnitker, Matthis, Technician
Schmidt, Marco, MSc, PhD Student
Sontag, Stephanie, PhD, Postdoc
Tharmapalan, Vithurithra, PhD Student
Zeevaert, Kira, MSc, PhD Student

Introduction

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

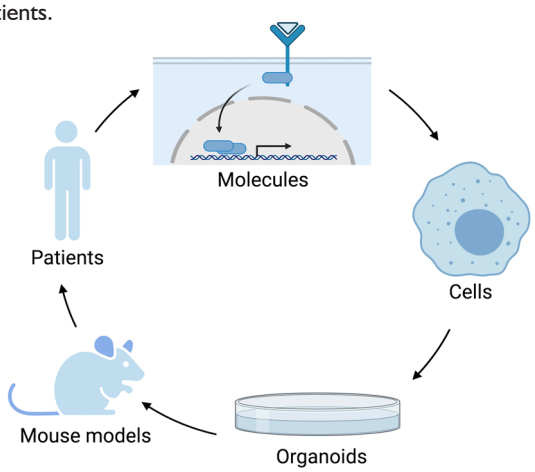


Fig. 1: Research topics of the year 2020 covered pre-clinical biomedical research at various levels (created with BioRender.com).

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

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

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

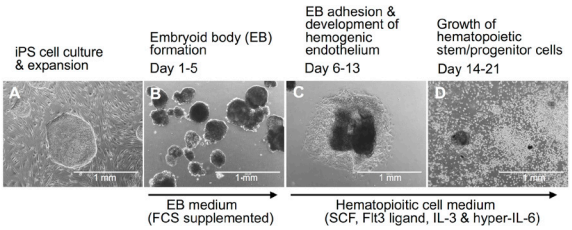


Fig. 2: Human iPS cells (A) are differentiated in an embryoid body (EB) protocol (B and C) toward hematopoietic cells (D). Scale bars: 500 µm.

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

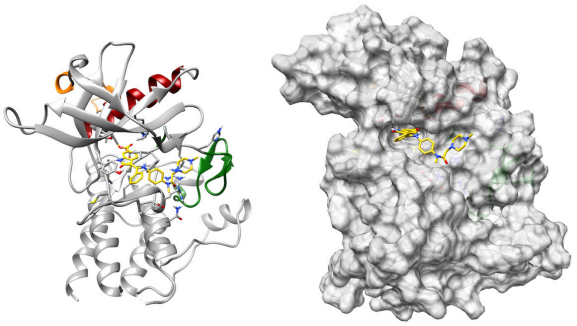


Fig. 3: Molecular docking shows KIT D816V ribbon structure with nintedanib in cartoon (left) and surface representation (right). Nintedanib is represented in yellow licorice.

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

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

HGF Receptor/Met-signaling regulates Dendritic Cell Migration

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

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

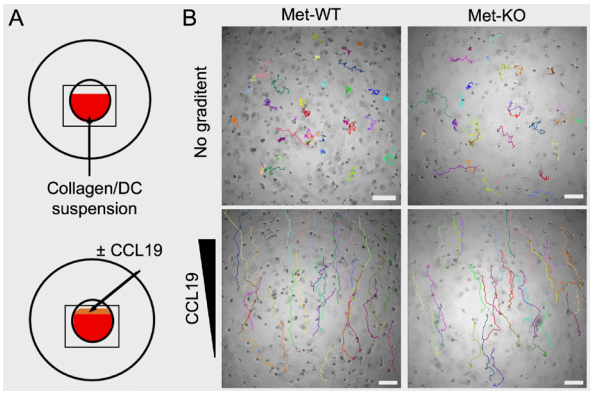


Fig. 5: Chemotaxis assay in 3D collagen gels. (A) Scheme of the experimental setup. (B) Met-signaling competent (Met-WT) and deficient (Met-KO) DC were applied on 3D collagen gels with or without a CCL-19 chemokine gradient. Migration of DC through the gel was recorded by time-lapse microscopy. Individual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

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

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

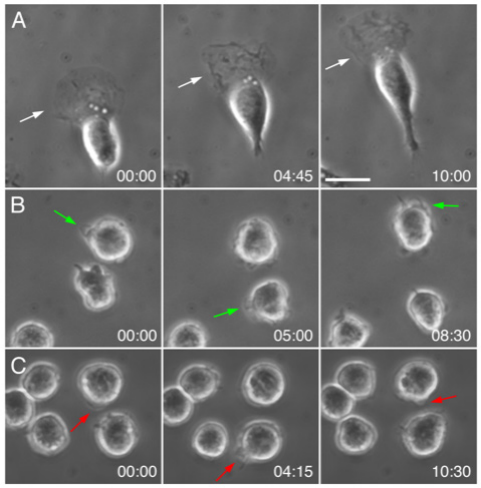


Fig. 6: LSP1 and myosin1e are essential for lamellipodia dynamics. (A-C) Time-lapse images showing lamellipodia morphology and dynamics in control (A), LSP1-deficient (B) and J774 cells expressing the LSP1 deletion mutant LSP1-ΔSBS (C). Note the large and very dynamic lamellipodium formed by control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

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

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

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

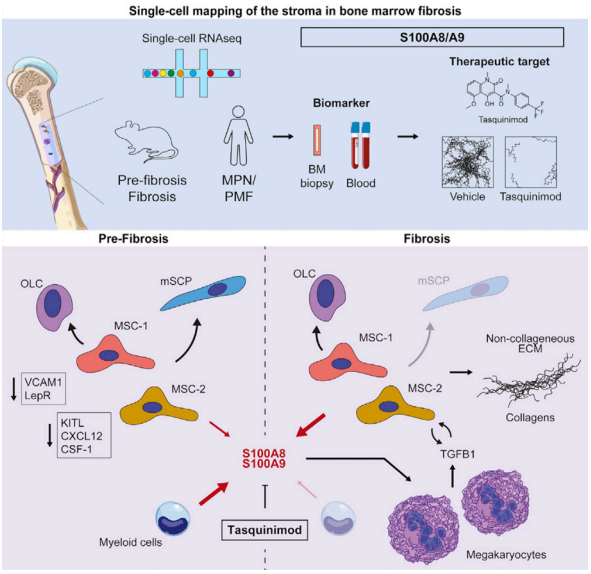


Fig. 7: Scheme showing the transition from a pre-fibrotic to a fibrotic stage in MPN, marked by expression of the alarmin complex S100A8/S100A9 (Leimkühler et al., 2020). Inhibition of S100A8/S100A9 by tasquinimod ameliorates the MPN phenotype.

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

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

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

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

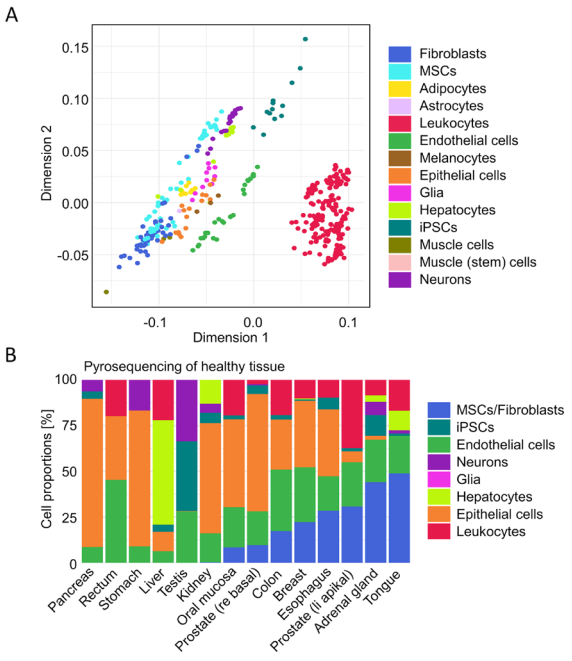


Fig. 8: Deconvolution of cellular subsets in human tissue. (A) DNA methylation profiles of various cell types of different studies are presented in a multidimensional scaling (MDS) plot. (B) Deconvolution of healthy tissues based on pyrosequencing of DNAm at the eight relevant CpGs.

Disease Modelling of Premature Aging Syndromes in iPS Cells

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

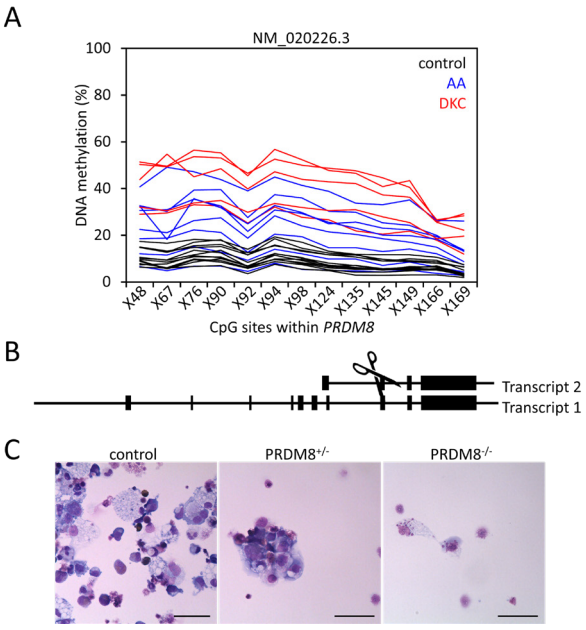


Fig. 9: PRDM8 is relevant for hematopoietic differentiation of iPS cells. (A) Aberrant hypermethylation in the gene PRDM8 was observed in patients with dyskeratosis congenita (DKC) and aplastic anemia (AA). (B) PRDM8 was knocked out in iPS cells with CRISPR/Cas9 technology. (C) PRDM8 knockout lines cannot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

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

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Team