Research profile for applicants

Name of DKFZ research division/group:	***Cancer Epigenomics (B370)***
Contact person:	***Christoph Plass*** *c.plass@dkfz.de* *0049 – 6221 42 3300*
Group homepage: *Visit this website for further information on current research and recent publications.*	***https://www.dkfz.de/en/cancer-epigenomics/cancer-epigenomics***

RESEARCH PROFILE AND PROJECT TOPICS

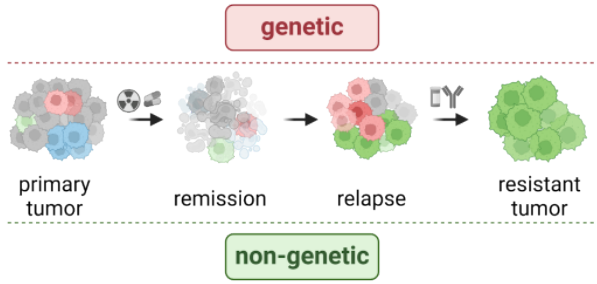

Figure 1: Non-genetic therapy resistance is driven by unique epigenetic configurations rendering a specific cell state resistant to cancer therapy.

Acute Myeloid Leukemia (AML) is an aggressive blood cancer with overall low survival and high relapse rates. Epigenetic dysregulation plays a major role in disease progression, since epigenetic regulators are frequently lost due to deletions and enter into haploinsufficiency. Furthermore, epigenetic drugs are now used as standard treatment [1]. A recent study showed that around 40 % of relapses can be attributed to epigenetic heterogeneity in the pool of leukemic cells at diagnosis (Figure 1). While epigenomic heterogeneity can be quantified using bulk approaches, understanding the relationship between a specific epigenetic configuration and relapse requires single-cell approaches. Understanding how epigenomic heterogeneity, together with the activation of oncogenes such as MNX1 [2, 3, 4], results in accelerated tumorigenesis or therapy resistance is crucial for improving AML treatment.

We hypothesise that haploinsufficiency of epigenetic regulators causes elevated levels of epigenomic heterogeneity, leading to accelerated tumour formation and resistance to therapy. To understand the specific epigenetic configuration driving relapse, we will profile samples from AML patients at diagnosis and relapse. Using various readouts of the epigenetic configuration — including single-cell ATAC-seq for profiling

chromatin accessibility and scTAM-seq [5] for profiling DNA methylation — we will analyse the molecular mechanisms driving heterogeneity. The project will entail running single-cell assays and computational analysis of the generated data in relation to the bulk data. Ultimately, we will explore the role of epigenetic regulation in therapy resistance in cancers beyond AML, such as lung and prostate cancer, paving the way for precision medicine.

References:

1. Brocks D, et al: **DNMT and HDAC inhibitors induce cryptic transcription start sites encoded in long terminal repeats.** *Nat Genet* 2017.
2. Weichenhan D, et al: **Altered enhancer-promoter interaction leads to MNX1 expression in pediatric acute myeloid leukemia with t(7;12)(q36;p13).** *Blood Adv* 2023.
3. Weichenhan D, et al: **Translocation t(6;7) in AML-M4 cell line GDM-1 results in MNX1 activation through enhancer-hijacking.** *Leukemia* 2023.
4. Sollier E, Riedel A, Toprak UH: **Enhancer hijacking discovery in acute myeloid leukemia by pyjacker identifies MNX1 activation via deletion 7q**. *Blood Cancer Discovery 2025*
5. Scherer M, et al: **Somatic epimutations enable single - cell lineage tracing in native hematopoiesis across the murine and human lifespan.** *Nature 2025.*