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# Multi-omics profiling of JMML HSPCs reveals onco-fetal reprogramming and identifies novel prognostic biomarkers and therapeutic targets in high-risk JMML [Abstract]

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# Multi-Omics Profiling of JMML HSPCs Reveals Onco-Fetal Reprogramming and Identifies Novel Prognostic Biomarkers and Therapeutic Targets in High-Risk JMML

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## Abstract

Juvenile myelomonocytic leukemia (JMML) is a myeloproliferative neoplasm of early childhood, which is characterized by highly heterogenous clinical outcomes ranging from spontaneous resolution to early relapse after hematopoietic stem cell transplantation (HSCT). Established clinical risk factors as well as characteristic mutational patterns do not fully explain this heterogeneity. Recently, we and others identified DNA methylation subgroups in JMML, which were shown to be the only significant factor for predicting overall survival (Schönung et al., Clinical Cancer Research 2021). Together, these findings suggest a functional role for DNA methylation in the molecular pathogenesis of JMML.

To elucidate the impact of aberrant DNA methylation on pathogenesis and disease progression, we leveraged a multi-modal molecular analysis approach. We integrated flow cytometry data with single-cell RNA-seq and ultra-low input whole-genome bisulfite sequencing (WGBS) data in order to dissect the hematopoietic system across patients from all epigenetic subgroups (n=8). With this approach, we aimed to identify novel candidate prognostic biomarkers and therapeutic targets for high-risk JMML patients.

We observed conservation of epigenetic subgroups already in the hematopoietic stem and progenitor cell (HSPC) compartment, suggesting that differential methylation might be key to understand pathogenesis and course of the disease in JMML. In addition, single-cell transcriptomics revealed disease-specific aberrations to be most pronounced in the HSPC compartment relative to all other hematopoietic cell types. Consequently, we focused our work on JMML HSPCs, which revealed a high degree of immunophenotypic, transcriptomic and methylomic heterogeneity across JMML risk groups. This included the expression of proto-oncogenes belonging to the AP-1 family, *CTNNB1* and *MECOM* (*EVI1*). Furthermore, we observed divergent lineage priming across JMML subgroups which affected lymphoid, myeloid and erythroid differentiation programs.

Remarkably, subgroup-specific aberrations comprised upregulation of fetal developmental programs in HSPCs from high-risk JMML patients. This is of particular interest regarding the cell-of-origin in JMML, since mutations activating the RAS signaling pathway have been identified in newborn blood samples from children who later developed JMML (Behnert et al., Leukemia 2022). Comparing the methylome data of HSPCs from JMML patients with HSPCs from healthy individuals at different developmental stages (fetal, perinatal, juvenile and adult) suggested progressive epigenomic reprogramming of leukemic HSPCs towards high-risk JMML. As a consequence, we observed signatures of both accelerated aging and aberrant activation of onco-fetal programs. This included the downregulation of postnatal HSPC markers such as *AVP* and vice versa the upregulation of prenatal markers such as *HMGA2* in high-risk HSPCs, which was associated with differential methylation of these genes. Moreover, binding motifs of central hematopoietic and developmental transcription factors such as *RUNX1*, *FLI1*, *CDX4*, and several *HOX* genes were not only enriched in differentially methylated regions but were also found to be differentially methylated themselves.

Systematic comparison of JMML HSPCs with their healthy nearest normal counterparts revealed disease-specific expression of several cell surface markers. The expression patterns appeared to be regulated in a subgroup-specific manner, which nominates these factors as novel prognostic biomarkers in JMML. Moreover, we identified surface markers that were not only differentially methylated but also known drug targets in other entities, which is why we selected these genes as high confidence candidates for further functional validation. In a preclinical patient-derived xenograft (PDX) mouse model, targeted treatment with a therapeutic antibody against one of these candidates efficiently depleted high-risk JMML HSPCs and improved survival of JMML-PDX mice.

In conclusion, the personalized molecular analysis of JMML HSPCs disentangled disease-specific

dysregulation included onco-fetal reprogramming of JMML HSPCs and revealed novel prognostic biomarkers and promising novel drug targets specifically for high-risk JMML.

## Disclosures

**Staeble:***Affimed:* Current Employment. **Langstein:***AstraZeneca:* Current Employment. **Bernt:***Merck:* Other: Husband is an employee of Merck and has stock; *Epizyme:* Patents & Royalties; *Syndax:* Research Funding. **Buske:***Roche/Genentech, Janssen, BeiGene, Novartis, Pfizer, Incyte, AbbVie, Gilead Sciences, Celltrion, Morphosys, and Regeneron:* Honoraria; *Gilead Sciences, Janssen, Roche, Pfizer, BeiGene, Celltrion, AbbVie, Incyte, Regeneron, Morphosys, and Novartis:* Consultancy; *Roche, Janssen, BeiGene, Celltrion, AbbVie, Pfizer, and Gilead Sciences:* Speakers Bureau; *Roche/Genentech, Janssen, Celltrion, MSD, Pfizer, and Amgen:* Research Funding. **Niemeyer:***BMS:* Honoraria; *Novartis:* Honoraria; *Apriligen LLC:* Honoraria. **Erlacher:***Gilead Sciences:* Research Funding. **Lipka:***Infectopharm:* Other: current employment of my spouse.

## Author notes

* Asterisk with author names denotes non-ASH members.

Author notes

Marion Strullu et al., Blood

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