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POSTER 1: Application of high-dimensional spectral cytometry to the evaluation of drug responses in AML patient samples

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Acute myeloid leukemia (AML) is a phenotypically and genetically *heterogenous disease,* characterized by a clonal expansion of undifferentiated myeloid progenitor cells in the bone marrow, and associated with a very poor prognosis. Appropriate preclinical models are needed to improve the understanding of AML biology, to assess the efficacy of targeted therapies and to identify biomarkers associated with drug response or resistance. To address this need, we have developed a 35-colour full spectrum flow cytometry panel, that allows immunophenotyping of the major cell subsets of human bone marrow and peripheral blood and monitoring of specific cell populations throughout drug testing experiments. Intracellular markers have also been included to monitor the expression of key lineage-specific transcription factors (PU.1, GATA1) and oncogene (MYC).

SWItch/Sucrose Non-Fermentable (SWI/SNF) complexes are chromatin remodellers, that reposition nucleosomes along the chromatin in an ATP-dependent manner, thereby modulating chromatin accessibility, and affecting gene expression and lineage commitment. As SWI/SNF are essential for many aspects of normal hematopoiesis, their alterations contribute to the onset or progression of

leukemia. Today, there are evidences of the potential for SWI/SNF inhibition as a treatment for AML. In our project, we evaluated the utility of our 35-colour panel to characterize in detail the *ex vivo* biological consequences of inhibiting SWI/SNF in human AML samples, by analyzing the behavior of 6 primary human samples exposed to a small molecule inhibitor (FHD-286, provided by Foghorn Therapeutics, Inc) and directed against the mutually exclusive ATPAse subunits BRG1/SMARCA4 and BRM/SMARCA2.

Despite their genetic heterogeneity, all primary AML samples exposed to FHD-286 showed a dose-dependent reduction in immature or blasts cells and limited cell proliferation. While the percentage of CD15-positive cells decreased, an increase in the number of CD11B+ HLA-DR- cells was observed. We also noted a commitment to macrophage (2 cases) or granulocytic maturation (3 cases), highlighting the diversity of responses to the drug. In-depth analysis of myeloid maturation will complete this observational study. Overall, our cytometry assay demonstrated a rapid and optimal capture of the heterogeneity of AML samples at diagnosis and upon treatment, and allows efficient measurement of specific biological outcomes.