Florian Grebien - Identification of critical effectors of oncoproteins in acute leukemia

Leukemia is an aggressive cancer of the white blood cell lineage that is often associated with poor prognosis. Development of this disease is caused by malfunction of factors that are required to regulate normal blood development. While it is known that at the cellular level, leukemia is caused by excessive self-renewal at the expense of terminal differentiation, the molecular mechanisms and players that are critical for leukemogenesis are not well understood. Genomic studies have shown that leukemia oncoproteins often arise from mutations in genes that encode transcription factors and epigenetic modulators.

In the Grebien group, we hypothesize that oncogenic mechanisms of leukemia oncoproteins are hard-wired in specific networks of physical, genetic and epigenetic interactions of with key effector proteins. Functional exploration of these networks by systematic comparative approaches will provide new insights into cellular processes that depend on critical effector proteins among these networks. Thus, the goal of our research is a comprehensive systems-level investigation of oncogenic mechanisms employed by AML oncoproteins.

In the project that will be funded through the ARCH-ITN, we will combine genome-scale CRISPR/Cas9 loss-of function screens with global genomic and epigenomic approaches to identify potential effectors of oncoproteins that lead to the development of Acute Myeloid Leukemia (AML) that is driven by mutations in transcription factors. Clinical datasets will be interrogated to test the potential of identified candidates for diagnostic and/or therapeutic exploitation. The project builds on a large set of unique models, reagents and datasets the group has assembled and is expected to contribute to a better understanding of molecular mechanisms that underlie leukemia development.