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POSTER 12: Modeling B-cell acute lymphoblastic leukemia induced by the PAX5P80R mutation

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B-cell acute lymphoblastic leukemia (B-ALL) is the most common form of pediatric cancer. The transcription factor PAX5 has been described as the guardian of B-cell identity but is also the main target of somatic alterations in B-ALL. Heterozygous deletions of *PAX5* are found in one-third of patients and are considered as secondary oncogenic events in the leukemia development. Moreover, somatic *PAX5* point mutations are found in about 7% in B-ALL patients and are predicted to result in lost or altered DNA-binding or transcriptional regulatory functions. Among them, the somatic mutation *P80R* of *PAX5* (*PAX5P80R*) was identified within its DNA-binding domain, and is the most frequent *PAX5* point mutation in B-ALL. In contrast to other somatic *PAX5* mutations, *PAX5P80R* induces a unique transcriptional program in patients and defines an independent B-ALL subtype, supporting the notion that *PAX5P80R* mutation acts as an initiating lesion in B-ALL. Therefore, *PAX5P80R* mutation represents a genetic alteration of interest to model the early steps of the B-ALL development and to identify its oncogenic collaborators involved in malignant progression.

To model *PAX5P80R* mutation, we transduced fetal liver lymphoid cells from *Pax5*-/- mice with CTL, PAX5 Wt or PAX5-P80R retroviral vectors. *In vitro* experiments demonstrate that PAX5-P80R fails to rescue the proliferation and the definitive B-cell commitment. Using

transplantation assay, we show that PAX5-P80R-expressing cells exhibit an aberrant engraftment potential and induce an efficient B-ALL development *in vivo*. At the molecular level, our analyses reveal that B-ALL transformation is associated with the selection of leukemic clones that have acquired secondary mutations affecting the JAK/STAT pathway. Moreover, transcriptomic data reveals the transcription factor Hif2a as a strong candidate in driving B-ALL. Finally, chemical screening of Hifa inhibitors identify the Acriflavine as a relevant compound that exhibit a synergistic activity with the Tofacitinib (JAK inhibitor) to target leukemic cells. Hence, our study provides a new strategy to model the multi-step process of B-ALL and sheds lights on the biological mechanisms by which *PAX5P80R* mutation leads to leukemia.