**POSTER 32: Impact of the germline mutation *GATA2*R396Q in leukemic initiation and study of its cooperation with *ASXL1* somatic mutations in leukemic transformation**

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Hematological malignancies result from genetic alterations in hematopoietic stem and progenitor cells (HSPC). While most cases occur *de novo*, inherited mutations in GATA2, a gene crucial for blood cell production, have been identified through genome sequencing. We identified the GATA2R396Q germline mutation in a family with a high incidence of Acute Myeloid Leukemia/Myelodysplastic Syndrome (AML/MDS). To study this mutation, we developed a mouse model carrying the Gata2R396Q mutation. These mice demonstrated altered distribution of HSPC subpopulations, which exhibited functional abnormalities. The GATA2R396Q mutation affects the second zinc finger of GATA2, implicated in DNA and protein interactions. To investigate DNA binding and proteic complex formation, we used the Cut&Run and Bio-ID techniques. Preliminary results reveal distinct DNA binding patterns between GATA2WT and GATA2R396Q.

Gata2R396Q/+ mice do not develop AML or MDS, indicating the need for additional genetic changes to induce leukemic transformation, as in GATA2-mutated patients. *Asxl1* alteration is one of the most frequent event. To explore the cooperative events during malignant transformation, we employed shRNAs targeting Asxl1 in transplant experiments. Our findings demonstrate that the collaboration between Gata2R396Q and Asxl1 alterations enhances the clonogenic activity of HSPC in *ex vivo* assays, intensifying the bias towards granular differentiation observed in cells with Gata2R396Q mutation alone.