A multi-layered genome-wide analysis to investigate the clinical relevance of subclonal mutations and gene expression signature in a large cohort of infant B-cell precursor acute lymphoblastic leukemia (iBCP-ALL)

Interfant99 treatment study

124 Infants (<12 months old) diagnosed with either pro-B or pre-B acute lymphoblastic leukemia (ALL)

- n=42 *de novo* samples
  - n=27 with the t(4;11) encoding for MLL-AF4
  - n=5 with the t(9;11) encoding for KMT2A-MLLT3 (MLL-AF9)
  - n=10 without *MLL* rearrangements *(MLLr)*

Bone marrow (BM) or peripheral blood (PB) ⋯▶ Infant B-cell precursors (iBCPs)

Multi-layered genome-wide analysis

WES and WGS analyses

- A silent mutation landscape in 3 iBCP-ALL subtypes: MLL-AF4+, MLL-AF9+ and non-MLL (n=42)
- 1 genomic rearrangement and 2.5 non-silent SNVs, 2-fold higher than previously reported
- 34% of the iBCP-ALL cases carry mutations in either *K-RAS* or *N-RAS*
- 1/3 mutations showed a mutant allele frequency (MAF) <20%

➡ **iBCP-ALL contains genetically different intratumoral subclones despite its genomic stability**

Deep sequencing analysis of B-Cell Receptor (BCR) repertoires

- Performed on t(4;11)/MLL-AF4+ iBCP-ALL PB samples using a PCR-based method
- BCR repertoires did not exhibit significantly exapanded VDJ rearranged B-cell clones either in diagnosis and relapse
- t(4;11)/MLL-AF4+ iBCP-ALL malignant cells are developmentally stalled at pro-B stage, and the cellular origin of such genomic drivers has to be a pre-VDJ stem/progenitor cell

Agraz-Doblas *et al.*, Haematologica, 2019