**POSTER 26: Lymphomagenesis of ALK+ ALCL: a molecular and functional view of transformation**

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Anaplastic large cell lymphoma (ALCL) is an aggressive form of T-cell non-Hodgkin lymphoma. 60% of ALCL cases harbor a chromosomal translocation involving the anaplastic lymphoma kinase (*ALK*) gene. The most frequent translocation is the t(2;5)(p23;q35) fusing *ALK* to *NPM1*, leading to the expression of the NPM1-ALK fusion protein which acts to constitutively activate the ALK kinase. ALK uncontrolled activation leads to several cascades of signaling pathways. These pathways include the activation of several transcription factors and regulate the activity of DNA methylation regulators important for the maintenance of the malignant phenotype. Besides the t(2;5)(p23;q35) translocation, some somatic mutations have recently been identified in patients, their role in ALCL oncogenesis remain to be fully elucidated.

Using the CRISPR/Cas9 technology, we are able to induce the t(2;5)(p23;q35) translocation and reproduce ALK+ ALCL oncogenesis from healthy primary T lymphocytes to the tumors. Importantly the edited tumors faithfully recapitulate the immune and histological phenotype diversity of patients[[i]](https://cho2023.sciencesconf.org/review/controlboard?docid=489931#_edn1).

This original and robust model has the particularity to offer a large time window to analyze each key step of transformation from the primary lymphocytes of origin to *in vivo* tumors, including pre-transformed cells. Looking at replication timing and transcriptome over cell transformation, we have already identified transcription factors specific of ALK+ ALCL that need to be functionally validated.

In parallel, to decipher the role of patient somatic mutations in lymphomagenesis, I am also using the CRISPR to invalidate genes found mutated in patient and Ihave already identified other key pathways such as the Hippo pathway that may be important for cell transformation.

Overall, the identification of new ALK+ ALCL lymphomagenesis regulators through omics data integration will lead to a better definition of the molecular identity of ALK+ cancer cells and thus the identification of new therapeutic targets. Importantly, ALK constitutive activation is also found in numerous other solid tumors.

[[i]](https://cho2023.sciencesconf.org/review/controlboard?docid=489931#_ednref1) Babin et al., « De Novo Generation of the NPM-ALK Fusion Recapitulates the Pleiotropic Phenotypes of ALK+ ALCL Pathogenesis and Reveals the ROR2 Receptor as Target for Tumor Cells ».