**POSTER 22: TAK-981, a first-in-class inhibitor of SUMOylation, induces an anti-tumor immune response in Acute Myeloid Leukemias.**

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Acute Myeloid Leukemias (AML) represent a group of severe hematological malignancies with a dismal prognosis and limited treatment options. Our recent research focused on the role of SUMOylation, a posttranslational modification of proteins, in regulating AML response to therapies, in particular through the control of specific transcriptional programs (1). We demonstrate that TAK-981, a first-in-class inhibitor, has promising anti-leukemic activity in preclinical AML models. Notably, TAK-981 exhibits strong synergy with Azacitidine (AZA), a hypomethylating agent used in AML treatment. The combined targeting of SUMOylation and DNA methylation activates genes associated with differentiation, apoptosis and cell cycle control but also genes linked to the activation of immune responses, particularly by Natural Killer (NK) cells. TAK-981, in combination with AZA, increases NK activating ligands on the surface of AML cells, enhancing the cytotoxic potential of NK cells towards AML cells (2).

We then investigated if TAK-981 could directly affect immune cells and regulate their anti-tumor activity in AML. We demonstrate that TAK-981 enhances the activation and cytotoxicity of primary NK cells against AML cells. RNAseq analysis revealed a strong enrichment of a type I Interferon signature in NK cells treated with TAK-981, suggesting a potential pathway for enhancing their anti-leukemic activity. In addition, targeting SUMOylation induces a strong IFN-I secretion in monocytes, which activates NK *in trans*.

Altogether, we provide a preclinical demonstration of the therapeutical potential of SUMOylation inhibition through a direct effect on AML cells and by inducing an anti-AML immune response.

1- Boulanger M, Aqrouq M, Tempé D, et al. DeSUMOylation of chromatin-bound proteins limits the rapid transcriptional reprogramming induced by daunorubicin in acute myeloid leukemias. Nucleic Acids Research 2023;gkad581

2- Gabellier L, De Toledo M, Chakraborty M et al. The SUMOylation inhibitor TAK-981 (Subasumstat) synergizes with 5-azacitidine in preclinical models of Acute Myeloid Leukemia. Haematologica, 2023, in press