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PB1825 IDENTIFYING GENE TARGETS FOR DRUG REPURPOSING TO COUNTER MYELOID LEUKEMIA IN CHILDREN WITH DOWN-SYNDROME (ML-DS)

Topic: 3. Acute myeloid leukemia - Biology & Translational Research

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Background:

Transient abnormal myelopoiesis (TAM) is a preleukemic disorder that affects 30% of newborns with Down syndrome, which can progress to myeloid leukemia (ML-DS). The current lack of effective treatments for TAM is due to limited clinical trials and the high sensitivity of trisomy 21 patients to chemotherapeutic toxicity. Preventing the progression from TAM to ML-DS remains a significant challenge.

Aims:

Our goal is to identity treatment options to prevent the progression from TAM to ML-DS by repurposing FDA-approved therapeutics.

Methods:

We created an aggressive TAM-like state in murine hematopoietic cells by overexpressing oncogenes located on chromosome 21 to model the genetic origin of ML-DS. We then conducted CRISPR-Cas9 knockout screens, targeting only genes connected to FDA-approved therapeutics, and integrated these findings with ML-DS cell line data. We used single knockout proliferation assays for validation and compared our results to the currently used treatment.

Results:

Our approach revealed over 30 candidates, with seven genes found to be directly connected in the same pathway. Patient-derived gene expression data and validation in the murine model and leukemic cell lines led to several promising therapeutics. In vitro drug testing of two drugs yielded particularly promising results, individually and when compared to the current treatment.

Summary/Conclusion:

Our approach of repurposing existing drug targets has led to the discovery of alternative treatments for TAM patients, advancing our long-term goal of preventing cancer in children with a premalignant state. By focusing on the underlying genetic mechanisms, we have increased treatment options, potentially reducing the toxicity burden for TAM patients.