



## The 65th ASH Annual Meeting Abstracts

## POSTER ABSTRACTS

**618.ACUTE LYMPHOBLASTIC LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS****A Novel Transgenic Mouse Model of Down Syndrome Acute Lymphoblastic Leukemia Identifies Targetable Vulnerabilities**

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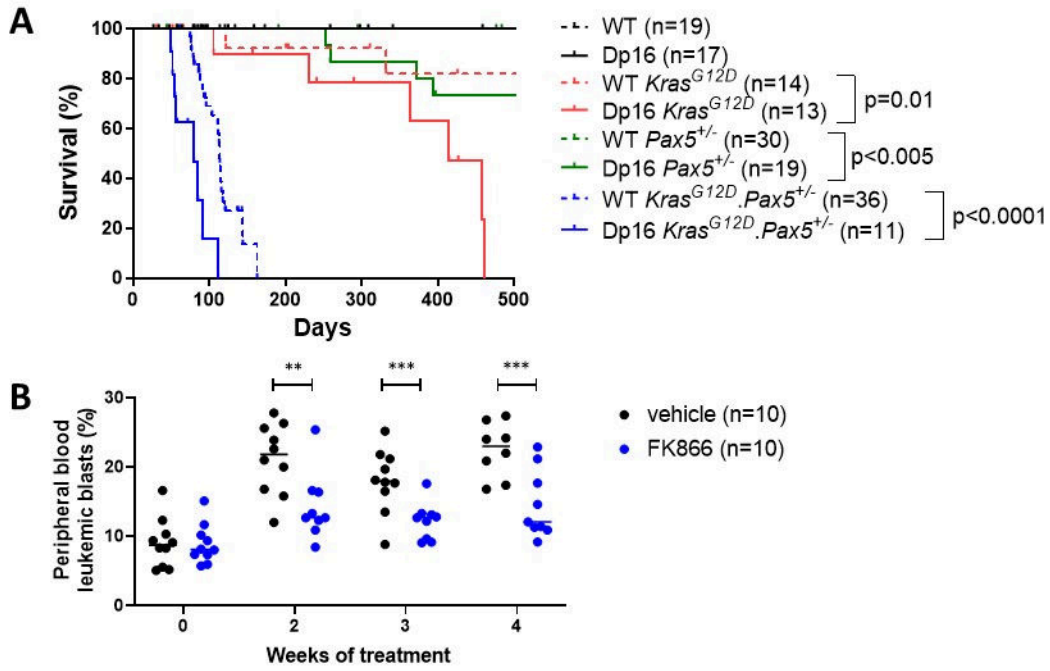
**Background:** Children with Down syndrome (DS) have a 10-fold increased risk of developing B-cell acute lymphoblastic leukemia (B-ALL), and they have poorer survival due to increased relapses and treatment-related mortality (TRM). Targeted therapies for DS-ALL are needed to improve anti-leukemic efficacy and reduce the risk of TRM. Mouse models and cell lines recapitulating DS-ALL are lacking, and may aid in identifying new targets for DS-ALL.

**Methods:** We used the Dp(16)1Yey (Dp16) mouse model of DS, which has a triplication of ~115 human chromosome 21 (Hsa21) orthologues. We introduced *Kras*<sup>G12D</sup> and *Pax5* heterozygosity, both driven in B cells by *CD19-Cre*, in Dp16 and non-DS wild-type (WT) mice. We performed RNA-Sequencing (RNA-Seq) and gene set enrichment analysis (GSEA) to identify differentially regulated signaling pathways in Dp16 and WT B-ALL blasts. We cultured B-ALL blasts from mice to generate immortal cell lines. We tested the chemosensitivity of Dp16 and WT B-ALL cell lines with 35 agents with known efficacy in hematologic malignancies, and with 481 anti-cancer compounds used in the Cancer Therapeutics Response Portal project, to screen for drugs effective in DS-ALL. We screened top candidate drugs in DS-ALL and non-DS ALL patient samples *in vitro*, and tested FK866 and cucurbitacin I *in vivo* in mice xenografted with a DS-ALL patient sample.

**Results:** *Kras*<sup>G12D</sup>.*Pax5*<sup>+/-</sup> mice developed B-ALL with complete penetrance, with significantly shorter median survival in the Dp16 versus WT background (Figure 1A; 80 versus 114 days,  $p < 0.0001$ ). GSEA demonstrated upregulation of DNA repair signaling pathways in Dp16 B-ALL, recapitulating a signature observed in human DS-ALL. Growth of Dp16 and WT B-ALL cell lines, and DS-ALL and non-DS ALL patient samples, was inhibited at low nanomolar concentrations by novel therapies targeting NAMPT, DNA damage responses, autophagy, and JAK and PI3K/mTOR signaling. In mice xenografted with a DS-ALL patient sample, the NAMPT inhibitor FK866 significantly reduced the leukemic burden compared to vehicle (Figure 1B; 14.6% vs 22.4% after 4 weeks of treatment,  $p < 0.005$ ). The effect of FK866 was also significant after weeks 2 and 3 of treatment.

**Conclusions:** We have generated the first *de novo* mouse model and cell lines recapitulating DS-ALL, which we have employed in drug screens to identify novel therapeutic approaches. These studies suggest promising candidates for further study in DS-ALL and other high-risk ALL subtypes to reduce toxicity and improve outcomes.

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**Figure 1: Development of a novel mouse model of DS-ALL to identify effective drug candidates. (A)** Dp16 *Kras*<sup>G12D</sup>.*Pax5*<sup>+/-</sup> and WT *Kras*<sup>G12D</sup>.*Pax5*<sup>+/-</sup> mice developed B-ALL with high penetrance, with a significantly shorter median latency in Dp16 *Kras*<sup>G12D</sup>.*Pax5*<sup>+/-</sup> compared to WT *Kras*<sup>G12D</sup>.*Pax5*<sup>+/-</sup> mice (80 vs 114 days, p<0.0001). Latency to disease was also shorter in Dp16 *Kras*<sup>G12D</sup> compared to WT *Kras*<sup>G12D</sup> mice (p=0.01), and Dp16 *Pax5*<sup>+/-</sup> compared to WT *Pax5*<sup>+/-</sup> mice (p<0.005). **(B)** FK866 significantly delayed the leukemic progression of mice xenografted with a DS-ALL patient sample (14.6% vs 22.4% in vehicle after 4 weeks of treatment, p<0.005). The effect of FK866 was also significant after weeks 2 and 3 of treatment. Treatment was initiated when groups had an equivalent disease burden in peripheral blood. Mice were treated with 20 mg/kg FK866 or vehicle via intraperitoneal injection for 5 days/week for 4 weeks.

Figure 1

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