# A NOVEL TRANSGENIC MOUSE MODEL OF DS-ALL IDENTIFIES UPREGULATION OF DNA REPAIR SIGNALING AND KINASE SIGNALING AS 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) compared to non-DS children with ALL. We need to identify targeted therapies for DS-ALL to improve anti-leukemic efficacy and reduce the risk of TRM. Mouse models and cell lines recapitulating DS-ALL are lacking, and would help us identify new targets to improve treatment for DS-ALL.

**Materials/Methods:** We used the Dp16 mouse model of DS, which has a triplication of ~115 Human chromosome 21 (Hsa21) orthologues on mouse chromosome 16. We introduced KrasG12D and Pax5 heterozygosity, both driven in B cells by CD19-Cre, in Dp16 and non-DS wild-type (WT) mice. We isolated RNA from resulting Dp16 or WT mouse B-ALL blasts and from B cells of Dp16 or WT control mice, and performed RNA-Sequencing (RNA-Seq) and gene set enrichment analysis (GSEA) to identify differentially regulated signaling pathways. 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 used in leukemia studies and with the Broad Informer Set, to screen for drugs effective in DS-ALL.

**Results:** Mice inheriting both KrasG12D and Pax5 heterozygosity developed B-ALL with complete penetrance, with median survival of 72 and 111 days in the Dp16 and WT backgrounds respectively ($p<0.0001$). RNA-Seq and GSEA revealed DNA repair genes and Flt3 are upregulated in Dp16 B-ALL, similar to human DS-ALL. The growth of Dp16 and WT B-ALL cell lines was inhibited at low nanomolar concentrations by novel therapies targeting DNA damage responses (dinaciclib and GSK461364) and kinase signaling (tirbanibulin, gilteritinib, and gedatolisib).

**Conclusions:** We have generated the first de novo mouse model and cell lines recapitulating DS-ALL, which we are using to identify novel therapies. This model displays upregulation of DNA repair genes, similar to human DS-ALL, and resulting cell lines were sensitive to agents impacting DNA repair processes and kinase signaling. Our next steps are to test these compounds ex vivo in DS-ALL and non-DS ALL patient samples, and in vivo in the Dp16 and WT B-ALL models and xenografted mice. These studies may identify new ways to improve survival of children with DS-ALL and may also be applicable to other leukemias.

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