# NAMPT inhibition as a novel therapy in T-acute lymphoblastic leukemia

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## Abstract

Acute lymphoblastic leukemia (ALL) is the most common form of leukemia found in children. ALL is classified into B-ALL and T-ALL based on cellular origin and immunophenotype. In pediatric cases, approximately 15% of cases represent T-ALL which is associated with a 10–15% lower survival rate compared to B-ALL. Tyrosine kinase inhibitors (TKI) like dasatinib have recently shown promise in T-ALL with ABL-fusions, and preclinical data has suggested that it could be applied for a significant portion of other T-ALL subtypes as well. However, monotherapy treatment is often overcome by activation of other pathways, thus negating the therapeutic efficacy. In our previous work, combination of dasatinib together mTOR1 inhibitor temsirolimus was able to kill T-ALL cells efficiently in cell lines and in a patient samples. However, only 40% of the tested cells lines or patient samples were sensitive to this approach.

Therefore, we seek to widen our earlier study to a wider collection of drugs that are specifically targeting metabolic pathways to test the efficacy of co-inhibition with dasatinib. A drug screen of 186 metabolism-targeting compounds revealed that daporinad, a NAMPT enzyme inhibitor, significantly reduced cell viability and induced cell death. The results were replicated using a second NAMPT inhibitor KPT-9274. The effect was further enhanced by simultaneous knockout of the *LCK* gene, a target of dasatinib, which resulted four-fold increase in sensitivity to treatment. In patient samples, daporinad demonstrated statistically significant efficacy in T-ALL cells compared to healthy cells.

Overall, these findings indicate a potential therapeutic avenue combining the use of dasatinib and NAMPT inhibiton in T-ALL treatment. Ongoing studies are focused on exploring additional NAMPT inhibitors, optimizing the scheduling of therapy, and further validating these results in patient samples.