**Title:** Combined inhibition of MEK and HDACs improves the cytotoxicity of CD4 and CD8 T cells in NRAS;ASXL1-driven acute myeloid leukemia mice

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**Link:** https://www.abstractsonline.com/pp8/#!/20273/presentation/10990

**Citation:** AACR 2025 Annual Meeting

**Scientific Abstract:**

Acute myeloid leukemia (AML) is a heterogeneous malignant blood cancer that occurs mainly in the elderly. Its treatment outcome is greatly influenced by leukemia-driving mutations. Oncogenic NRAS mutations are associated with both AML progression and multi-drug resistance and treatment failure in AML. We have previously developed a NRAS; ASXL1-driven secondary AML (NA-AML) mouse model, which is characterized by a suppressive immune microenvironment resulting in reduced leukemia killing activities of T cells. Targeting hyperactive RAS/MEK signaling via trametinib (T, a MEK inhibitor) attenuates the exhaustion of CD8 T cells and prolongs the survival of NA-AML mice. To further boost the efficacy of T, we performed a re-purpose screen of ~2,500 drugs, either approved by FDA for treating various human diseases or currently under clinical evaluation, in the absence or presence of T. We identified that quisinostat (Q), a 2nd generation of HDAC inhibitor, potently inhibited the growth of both mouse and human NA leukemia cells and significantly synergized with T in vitro. In addition, combined T and Q (TQ) downregulated AP-1 transcription factors and expression of immune checkpoint ligands (PD-L1/L2, CD80, and CD86) while upregulated expression of MHC I/II in mouse NA-AML cells. We further validated our results in NA-AML mice. Vehicle (Veh) -treated mice rapidly succumbed to AML and died within 4-5 weeks post-treatment. T alone and Q alone slowed down AML progression and prolonged the survival of leukemia mice, while all TQ-treated mice remained alive ~22 weeks post-treatment. Surprisingly, TQ only provided moderate survival benefits in immunodeficient NSG mice engrafted with NA-AML cells, suggesting an important role of cytotoxic T cells in TQ-mediated AML alleviation. We then analyzed CD4 and CD8 T cells from moribund vehicle-treated mice and age-matched drug-treated mice. TQ decreased the exhaustion of CD4 and CD8 T cells and expanded the activated effector/memory T (Tem) cells. Single-cell RNA-Seq analysis showed increased expression of gene signatures associated with cytotoxicity of Tem cells, including CXCR3 and CXCR5. Consistent with these findings, leukemia: T cell co-culture experiments demonstrated significantly enhanced cytotoxicity of TQ-treated CD4 and CD8 T cells, which appeared to be mediated by increased expression of MHC I and II in AML cells. We are currently pursuing the underlying molecular mechanisms. Our data provide a strong rationale to develop immunotherapies via epigenetic modulation of both leukemia and leukemia-associated T cells.

**Written Lay Abstract:**

Acute myeloid leukemia (AML) is a type of blood cancer. Treatment option and outcome for AML depend on the DNA mutations (changes) that a person has. When someone has a mutation called NRAS, they have faster AML progression (cancer growth and spread), and treatment often does not work. Researchers want to understand why the NRAS mutation makes cancer treatment fail and find better ways to treat people with this type of AML.

For this study, the researchers tested about 2,500 drugs in AML cancer cells and in mice. They found that a drug called quisinostat (Q) may slow the growth of tumor cells. When using Q and another drug called trametinib (T) together, tumor cells did not grow or spread as quickly. In mice with AML, Q and T together worked better than just Q or T alone. Mice with AML not given T or Q only survived for about 4 weeks. Mice given just Q or T lived longer than 4 weeks, but mice given both Q and T lived for about 22 weeks. However, the Q and T treatment did not work as well in mice with lowered immune systems. This means these drugs may work by activating (boosting) our immune cells.

These findings tell us that the drugs quisinostat and trametinib together could be tested as treatments for AML. Future studies need to look at how these drugs work, and how to treat AML in people with these DNA mutations by activating their immune systems.

**Visual Lay Abstract:**

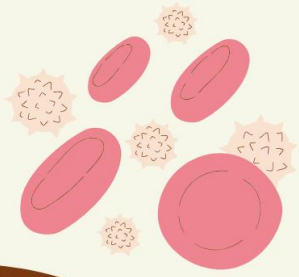
# New Drug Combo to Treat Acute Myeloid Leukemia

## WHY IS ACUTE MYELOID LEUKEMIA (AML) HARD TO TREAT?

This type of blood cancer is caused by different DNA mutations (changes). One mutation called NRAS causes fast growth and spread of cancer, and current treatment does not work well against it.

## WHAT DID WE FIND?

Researchers found that two drugs called quisinostat and trametinib used together helped mice with AML live much longer by activating (boosting) their immune systems. More studies are needed to see how to treat humans using these drugs.



## WHAT DID WE STUDY?

Researchers tested 2,500 drugs in AML cancer cells and mice to see what treatment could work for humans.

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