

## CD73 and MEK Inhibition improve T Cell function in NRAS-Mutant AML: A Strategy for Post-Transplant Immune Surveillance

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Relapse after allogeneic hematopoietic stem cell transplantation (allo-HCT) remains a major obstacle in the treatment of acute myeloid leukemia (AML), often driven by immune escape mechanisms. NRAS mutations, found in ~12% of AML cases, activate RAS-MAPK signaling and are frequently acquired late in disease progression, suggesting a role in immune evasion and post-transplant relapse.

Using a syngeneic transplantation mouse model with NRAS<sup>G12D</sup>-transduced hematopoietic stem cells (HSCs), we show that NRAS activation upregulates CD73 on myeloid cells and suppresses T cell function—marked by reduced TNF- $\alpha$ , impaired CD4<sup>+</sup>/CD8<sup>+</sup> proliferation, and increased Tregs. These immunosuppressive effects were largely reversed upon transplantation of CD73-deficient, NRAS-transduced cells, which also exhibited increased MHC class II expression

In an allogeneic model, NRAS-driven leukemia induced similar T cell dysfunction, including reduced effector proliferation and cytokine production. CD73 inhibition restored T cell effector function, increased granzyme B, enhanced memory differentiation, and further upregulated MHC-II.

MEK inhibition (Trametinib) reduced CD73 expression, enhanced T cell proliferation, and improved leukemia control in a recall immunity experiment, suggesting durable anti-leukemic memory.

Our findings identify CD73 as a central immune checkpoint in NRAS-mutant AML. Targeting CD73 and MEK represents a promising strategy to enhance post-transplant immune surveillance and prevent relapse

### Preferred type of presentation

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