WES Leukemia Research Foundation Research Summary

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Project Title: **Targeting CARM1-MYC axis as a promising therapeutical strategy in resistant and relapsed Acute Myeloid Leukemias.**

The Nimer Lab, located in Sylvester Comprehensive Cancer Center, the only NCI-designated cancer center in South Florida, is a dedicated team of scientists focused on unraveling the molecular mechanisms driving Acute Myeloid Leukemia (AML) and its resistance to current therapies. Despite advancements in treatment, patients who experience AML relapse still face a poor prognosis. As a research group committed to combating AML, we are deeply grateful to the When Everyone Survives (WES) Foundation for their invaluable support.

In our previous studies, we highlighted the crucial role of the methyltransferase CARM1 in the development and progression of myeloid leukemia, including AML. We also found that patients with higher CARM1 expression levels had shorter overall survival. With the support from WES Foundation, we leveraged cutting-edge technology in AML modeling to investigate the relationship between CARM1 and c-MYC, a potent and currently undruggable oncogene. We discovered that CARM1 and c-MYC regulate each other in a reciprocal oncogenic loop, which plays a key role in sustaining AML (the CARM1-MYC axis).

Our findings revealed that c-MYC promotes CARM1 overexpression by binding to specific regulatory regions within the CARM1 gene. In turn, CARM1 enhances c-MYC's oncogenic transcriptional activity and its pro-leukemic functions. For example, silencing CARM1 in various AML models led to a significant reduction in the expression of c-MYC-dependent genes. Similarly, targeting c-MYC reduced the expression of CARM1. In vivo experiments further confirmed this interaction: when attempting to generate c-MYC-driven AMLs, deleting CARM1 severely impaired the engraftment of leukemic precursors in the bone marrow and the circulation of leukemic cells in the bloodstream. This resulted in a significant increase in the survival of the animals.

These findings support the hypothesis that c-MYC relies on CARM1 to execute its oncogenic program in AML, positioning CARM1 as a promising therapeutic target to overcome resistance to therapies that address c-MYC activity in AML.