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WES Leukemia Research Foundation Research Grant Final Report

I am deeply grateful to the When Everyone Survives (WES) Leukemia Research Foundation for its generous support of my laboratory's project, *"Leveraging NF-κB and RAS pathway incompatibility as a novel therapeutic strategy for B-cell leukemia."*

B-cell acute lymphoblastic leukemia (B-ALL) is one of the most common childhood cancers. This disease develops when immature immune cells become arrested at an early stage of development. Instead of maturing into healthy B cells that help fight infections, these cells continue to grow uncontrollably. While current treatments are effective for many children, a significant number of patients experience relapse, and those cases are often difficult to treat. Our research aims to understand why these leukemia cells survive and grow—and how we might stop them.

With your support, we identified a previously unrecognized vulnerability in leukemia cells driven by a common cancer-causing mutation called RAS, which is present in about one-third of B-ALL cases and is associated with drug resistance and relapse. Using laboratory models of B-ALL, we discovered that RAS-driven leukemia cells are unexpectedly sensitive to activation of another cellular pathway known as NF-κB. Rather than working together to promote cancer growth, these two pathways interfere with each other—a phenomenon we refer to as "pathway incompatibility."

Importantly, we found that activating NF-κB pushes leukemia cells to resume normal immune cell development. This forces the cancer cells out of their abnormal, immature state and into a more mature form that can no longer tolerate RAS-driven growth. In essence, NF-κB acts as a developmental "reset button," removing the conditions that leukemia cells depend on to survive.

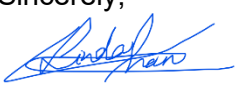
Although early drug combination studies in animal models did not immediately improve survival, your support allowed us to pivot quickly and pursue deeper analyses using advanced genomic and cellular tools. These studies are now revealing how NF-κB reshapes cancer cell signaling and gene expression, helping us refine therapeutic strategies that may ultimately be more effective for patients.

The findings supported by your funding have already had meaningful impact. They were presented at an international scientific meeting and formed the foundation for a recent NIH R01 grant application, which will allow us to continue and expand this work. Looking ahead, we aim to test whether activating this developmental pathway can make leukemia cells more responsive to standard chemotherapy and whether similar strategies may apply to other cancers that arise from developmental arrest.

Your support has enabled a new way of thinking about leukemia treatment. We are deeply grateful for your investment in this work and for your commitment to advancing research that may improve outcomes for children with leukemia.

Thank you for making this progress possible.

Sincerely,



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