Multi-Dimensional Genomic Profiling of Acute Leukemias Characterized by MLL Gene Rearrangements

Jacquie Hirsch For A.L.L. Foundation Research Grant 2009

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Research Summary

The overarching goal of this project is to identify and characterize the key genes and pathways underlying MLL-associated ALL for future validation and translation into overall clinical therapies.

Acute lymphocytic leukemia (ALL) is a blood cancer characterized by unchecked rapid growth of undifferentiated abnormal white blood cells. ALL represents the most common pediatric cancer and comprises 20% of acute leukemias in adults. A particularly challenging group of ALL patients are those that present at diagnosis with abnormalities in the MLL (mixed lineage leukemia) gene. MLL expressing ALL is associated with unique clinical and biological features and is typically refractory to standard chemotherapy.

It is known that the MLL gene is linked with a number of different "partner" genes in many types of acute leukemia. A key feature of these "marriages" between MLL with its partner genes is the ability of these fusions to transform normal blood cells into leukemia cells in the laboratory.

In order to better understand the biology of MLL associated ALL on a molecular level and identify genes and/or pathways that may serve as superior drug targets, we will perform an in-depth multi-dimensional genomic profiling of human MLL leukemia patient samples using cutting edge technologies available at the Genomics and Microarray Core Resource at Roswell Park Cancer Institute.

We will scan the entire genome for:

1. Changes in expression of all known human genes (gene expression analysis)
2. Submicroscopic changes observed as gains and losses of DNA (array Comparative Hybridization Analysis)
3. Alterations in expression of non-coding single stranded RNA regulating gene expression (microRNAs)
4. Attachment of DNA methyl groups altering gene transcription and suppression (global methylation analysis)

If possible, comparisons between leukemia patient samples with different MLL-gene partnerships and diverse clinical presentations will be made. **Results of these analyses will be subjected to statistical analysis using specialized software in order to determine which corresponding target genes and pathways represent potential therapeutic targets.** For example, gene products specific to MLL-associated ALL that are present in greater amounts than normal and whose function is relevant to cancer (such as cellular proliferation) may represent potentially good drug targets.