THE HARTWELL FOUNDATION

2017 Individual Biomedical Research Award

Panagiotis "Panos" Ntziachristos, Ph.D.

Assistant Professor
Department of Biochemistry and Molecular Genetics

Northwestern University

Splicing Errors and Drug Resistance in Acute Lymphoblastic Leukemia

Each year, over 3,000 US children are diagnosed with acute lymphoblastic leukemia (ALL). As the most prevalent childhood malignancy among children younger than 15, it is a cancer that starts with an increase in the proliferation of immature white blood cells (lymphocytes) in the bone marrow, where new blood cells are made. The abnormal cells are unable to function properly and they crowd out healthy cells; causing anemia, bruising and bleeding, fever, and an inability to fight infection. Although ALL is due principally to acquired genetic alterations in bone marrow cellular DNA, it does not appear to be an inherited disease. The exact cause is unknown and therapy is limited; radiation causes lasting cognitive problems in children and chemotherapy (often ineffective) may lead to secondary cancer. The cure rate is only about 40% and morbidity is high among survivors. Current research on the development of ALL focuses mainly on mutated genes and the first step in their level of expression (transcription), where a strand of DNA nucleic acids is copied into a new molecule of messenger RNA (mRNA). Each mRNA transcript specifies the amino acid sequence of a protein product and serves as a template for protein production (translation). For 95% of transcripts, portions of intervening DNA (introns) must be removed after transcription, with the final remaining mRNA consisting of spliced sequences of DNA (exons) connected to one another. Splicing of pre-mRNA is catalyzed by a complex assembled from five small RNA molecules and numerous protein factors (spliceosome). It is thought about a third or more of all disease-causing mutations affect the splicing process, where aberrant patterns of “stitching” exons together alters cell growth and the development of cancer. Remarkably, aggressive forms of ALL can occur without genetic mutations in the spliceosome, while exhibiting abnormal stitching patterns and resistance to chemotherapy. Based upon his discovery that the amount of splicing factor protein increases in aggressive ALL compared to the time of diagnosis, Panos proposes that splicing errors are responsible for drug resistance. Such errors may not only contribute to cancer initiation and progression, but have the potential to affect tumor suppressor genes and enzymes that can make ALL refractory to chemotherapy. Using cell culture and preclinical mouse models of standard and high-risk leukemia (refractory or relapsed following chemotherapy), he will determine the effect of small molecule inhibitors of splicing on spliceosome activity in ALL; whether the protein and transcript levels related to aberrant splicing are different; and whether therapy can be improved using the inhibitors in combination with chemotherapy. If Panos is successful in developing a new targeted therapy for children diagnosed with ALL, it will improve clinical outcomes by reducing relapse and extend the quality of their life.