THE HARTWELL FOUNDATION

2018 Individual Biomedical Research Award

Lisa G. Roth, MD

Assistant Professor
Department of Pediatrics

Cornell University

Genotyping the Rare Cancer-Initiating Cell in Hodgkin Lymphoma

Classical Hodgkin lymphoma (cHL) is a cancer that starts in the circulating white blood cells (lymphocytes) of the immune system and presents clinically as swollen lymph nodes. About 3% of all childhood cancers are cHL, with non-cHL accounting for about another 5%; the difference being the malignancy develops from different cell types. The cancer-initiating cells in cHL are thought to be Reed-Sternberg cells, giant cells found with light microscopy in tissue biopsies from individuals with the cancer. Although the 5-year survival rate for cHL is about 86%, patients often die from sequelae related to therapy. cHL is rare in children younger than 5 years old but remains the most common cancer diagnosed in teenagers ages 15 to 19 years. Unfortunately, very little is known about the genetic mutations in the cells that are responsible for cHL and despite great investment in genomic profiling of tumors, personalized medical therapy based on such observed genetic alterations has failed in the majority of cases. I hypothesize that the failure in genomic profiling is due to the standard sequencing platforms used to genotype all cells in a tumor biopsy without focusing on the rare cancer-initiating cells. Shifting the focus to characterize and develop therapies tailored to the unique vulnerabilities of specific cells would be more effective and improve clinical outcomes. Standardized methods to genotype the cHL cancer-causing cells has failed in principle, because Reed-Sternberg cells make up less than 1% of a Hodgkin lymphoma tumor and bulk analysis is limited by *cell averaging*. As a result, therapies tailored to the so-called unique vulnerabilities of these cells do not narrowly target and kill the cells most responsible for the tumor. To address this unmet need, I have recently developed an effective method using flow cytometry to purify and isolate Reed-Sternberg cells in cHL. I will use this technology to enable a comprehensive genomic analysis of childhood Hodgkin lymphoma. Whole exome sequencing of 100 patient samples with diagnosed cHL, will enable me to describe the spectrum of genetic alterations in pediatric Hodgkin lymphoma Reed-Sternberg cells. From 50 clinical cases I will perform RNA sequencing of the purified Reed-Sternberg cells, providing a comprehensive description of Hodgkin lymphoma genomics. Based upon the observed genomic alterations in these cHL cancer-causing cells I will then use the information to develop the first known mouse model of the disease. If I am successful in genotyping cHL and creating an animal model of the cancer, it will be possible to significantly accelerate development of new and more effective therapies for cHL. A more effective targeted drug therapy will not only prolong the survival of children affected by cHL, but reduce the long-term sequelae of therapy and thus improve their quality of life.