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Determining the impact of regulatory mutations and dysregulated transcription factors in neuroblastoma

Graham McVicker, PhD (Salk)
Peter Zage, MD, PhD (MCC)

Scientific Abstract:

Analysis of protein-coding mutations in high-risk neuroblastoma tumors has failed to discover many clinically actionable driver mutations. Several observations suggest that mutations that affect gene regulation have an important role in neuroblastoma tumors. First, the neuroblastoma genome is dominated by large somatic copy number alterations which span hundreds of kilobases and impact the expression of many genes. Second, the McVicker and Zage laboratories recently used allele specific expression (ASE) to identify genes with recurrent cis-acting regulatory changes in neuroblastoma tumors. While most genes with recurrent ASE in neuroblastoma are associated with somatic copy number alterations, many genes have ASE in samples that are copy neutral, suggesting that they are affected by as-of-yet unidentified regulatory mutations. Finally, genes with recurrent ASE often encode transcription factors and chromatin regulators suggesting that cis-acting mutations often impact genes involved in transcriptional regulation. The main objectives of this proposal are to discover important non-coding regulatory mutations in neuroblastomas, to determine the impact of these mutations on enhancer function, and to identify key transcription factors that affect molecular pathways that are important for neuroblastoma tumorigenesis. By discovering genes which are affected by regulatory mutations and aberrant transcription factor expression, this project dependencies and inform targets for personalized therapeutic interventions.

Lay Abstract:

Neuroblastoma is a tumor of developmental origin with high incidence of metastatic disease at initial diagnosis. Comprehensive DNA sequencing of high-risk neuroblastoma has identified few clinically actionable gene mutations and precision medicine has not benefited most neuroblastoma patients. Thus, there is an urgent need to develop innovative approaches to discover novel cancer dependencies and gene targets in neuroblastoma. Recently, we used DNA and RNA sequencing data to discover recurrently dysregulated genes in neuroblastoma. This proposal will use new molecular experiments to determine how genetic mutations affect gene expression, and downstream molecular pathways in neuroblastoma tumors. Discovering causes of aberrant gene expression in neuroblastomas is important because cancer cell identity is determined by gene expression, and gene expression influences important oncogenic processes like tumor growth and metastasis. The main objective of this proposal is to discover novel genetic mutations and cancer genes and determine their impact on neuroblastoma tumorigenesis. The long-term objective of this project is to discover prognostic biomarkers and therapeutic targets for early detection and treatment of neuroblastoma.