MN FUTURES RESEARCH GRANT 2022-2024

Project Title: Investigating epigenetic mechanisms in the development of craniospinal sarcoma

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Chordomas are rare sarcomas that occur along the cranial-spinal axis, characterized by significant neurologic morbidity and lack of response to chemoradiation. Chordomas are thought to arise from cells of the notochord, a transient but essential tissue in developing embryos. A major advance in understanding the pathogenesis of chordoma is the discovery that expression of the TBXT gene is essential and is duplicated in familial chordoma. In the developing embryo, Brachyury is tightly regulated and is expressed in the notochord and is essential for maintaining notochord cell fate and function. TBXT expression is pathognomonic for diagnosis of chordomas. However, a lack of proper in vitro models and in vivo animal models limits the study of chordoma pathogenesis. We propose to develop an in vitro model of human iPSC-derived notochord cells with inducible manipulation of TBXT expression. We will also develop mouse models by genetically overexpressing Tbxt in the notochord cell lineage with and without Cdkn2a deletion, a hallmark seen in human chordoma. We will compare transcriptome and epigenetic signatures in these models and human chordoma samples. Through comparative analysis of these in vitro, in vivo and human patient samples, we will determine molecular players and epigenetic requirements involved in chordoma pathogenesis.