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“A Novel Role for Histidine Kinase Activity in Neuroblastoma Pathogenesis”

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SCIENTIFIC ABSTRACT
There is a critical need for new treatment options for children with high-risk and relapsed neuroblastoma, and therapies directed against biologically relevant pathways are likely to be more effective with less toxicity. NME1 expression has been linked to neuroblastoma patient outcomes, but the functional role of NME1 in neuroblastoma pathogenesis has not been defined. NME1 was recently demonstrated to have activity as a histidine kinase, a novel post-translational modification with potential relevance for a broad range of cancers. We have demonstrated strong associations between NME1 gene expression and neuroblastoma patient outcomes and prognostic features and we have demonstrated NME1 histidine kinase activity in neuroblastoma cell lines. However, the regulation of histidine phosphorylation and the functional roles of histidine kinase signaling in the pathogenesis of neuroblastoma are unknown. We hypothesize that NME1 expression is associated with neuroblastoma prognostic factors and patient outcomes and that NME1 histidine kinase activity is associated with neuroblastoma pathogenesis and metastasis. We propose to determine the associations of NME1 expression with patient outcomes and prognostic features in neuroblastoma patient tumor samples, and we will investigate the functional roles of NME1 expression and histidine kinase activity in neuroblastoma tumor growth and response to therapy. The potential novel roles of NME1 and histidine phosphorylation in neuroblastoma pathogenesis represents an opportunity to identify novel therapeutic targets for the development of innovative, biologically-based therapies, potentially leading to improved success of neuroblastoma therapy and improved survival rates for children with neuroblastoma.

LAY ABSTRACT
Children with aggressive neuroblastoma have poor cure rates despite intensive treatment, and new treatments are needed. Treatments that inhibit important proteins and pathways in neuroblastoma are likely to be more effective with fewer side effects. In our initial experiments, we have identified an association between expression of the NME1 gene and the survival rates of children with neuroblastoma. NME1 can act as a histidine kinase, by adding phosphate to the amino acid histidine in other proteins in neuroblastoma cells, representing a previously undiscovered way for cells to control the function of proteins required for neuroblastoma growth and survival. We propose to evaluate the associations of NME1 expression in tumor samples from children with neuroblastoma with their survival rates and other tumor features, and we will explore how NME1 functions to affect neuroblastoma growth, survival, and

spread.
The results of these studies will likely identify new proteins that could serve as targets for new types of
treatment, leading to improved success of neuroblastoma therapy and improved chances of survival for
children with neuroblastoma.