THE HARTWELL FOUNDATION

2019 Individual Biomedical Research Award

Peter "Pete" E. Zage, MD, Ph.D.

Associate Professor-in-Residence
Department of Pediatrics

University of California, San Diego

Targeting Expression of an Enzyme Essential for Prevention of Neuroblastoma Growth and Metastasis

Neuroblastoma is a cancer of the nervous system that develops from immature nerve cells found in several areas of the body. It occurs most often in infants and children less than 5 years of age, with about 800 cases diagnosed each year in the United States. Less than 2% are genetically inherited, with the rest thought to be the result of a random gene mutation. It usually begins from mutated nerve cells in the adrenal gland on top of the kidney, with metastases appearing in the abdomen, neck, chest, or pelvis, or anywhere along the spine. The initial signs and symptoms of neuroblastoma can resemble many common childhood illnesses and thus, early diagnosis may be slow to confirm. Although in some cases the tumors grow so slow that they may disappear on their own, they most commonly undergo rapid metastasis to the lymph nodes, bones, bone marrow, liver, and skin. Affected children suffer from widespread tumors and a host of painful and life-threatening symptoms, including the side effects from treatment options that include chemotherapy, surgery, stem cell transplantation, radiation therapy, and immunotherapy, alone or in combination. For children with the most common and aggressive form of the disease (high risk neuroblastoma), the estimated 5-yr survival rate is less than 50%. Improvement in the early detection of children at risk for neuroblastoma, coupled together with the means to monitor the effectiveness of interventions and the development of a new class of drugs that will extend survival, is essential to improving the quality of life for all children with this cancer. To address these unmet needs, Pete proposes a strategy to target what he recently discovered as the association between expression of the NME1 gene and neuroblastoma patient outcomes. The NME1 gene product is a histidine kinase, a protein that catalyzes the addition of phosphate groups to the amino acid histidine in other target proteins and for which its role in neuroblastoma is poorly understood. While phosphorylation is widely used for signal transduction to regulate certain cell functions, the gain or loss of function in NME1 may represent a previously undiscovered way to control the role of certain proteins required for neuroblastoma growth, survival, and metastatic spread. Not unexpectedly, mutations in NME1 have been identified in aggressive neuroblastomas but such mutations are very rare. Therefore, Pete will leverage existing neuroblastoma cell lines to evaluate the functional role of NME1 histidine target phosphorylation in cell migration, metastasis, and differentiation; identify the targets of NME1 histidine kinase activity and the signaling pathways impacted by NME1 expression and histidine kinase activity; and identify novel inhibitors of NME1 histidine kinase activity. If he is successful, it will be possible to identify new drug targets to treat neuroblastoma, which should lead to improvements in treatment options that will enhance the quality of life and chances of survival for all children diagnosed with this cancer.