THE HARTWELL FOUNDATION

2019 Individual Biomedical Research Award

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Epigenetic Signatures as Novel Biomarkers for Targeted Brain Cancer Treatment

Cancer of the brain and spinal cord are the most common solid tumors of childhood. With approximately 4,000 new cases diagnosed each year in the United States, they are the leading cause of cancer mortality in children less than age 14. About 33 percent of all brain tumors are gliomas that arise from the abnormal growth of glial cells, a specialized type of cell that surrounds and supports nerves. Despite medical management, nearly all children with high-grade glioma (a rapidly spreading form of cancer of the brain) succumb to their disease within two years of diagnosis. Brainstem gliomas have the highest mortality and poorest clinical outcome because these tumors grow and infiltrate into an area rich in nerves responsible for communication between the brain and the rest of the body, which precludes surgical removal of the tumor and limits other interventions (radiation and adult glioma chemotherapies). The prevailing assumption is that because pediatric glioma tissue resembles adult glioma tissue under the microscope, the two gliomas must be biologically similar. However, therapies that improve outcomes in adult glioma have had little impact on survival for pediatric glioma. As a result, despite over forty years of clinical trials testing hundreds of treatment regimens, there has been no improvement in survival for children with high-grade glioma. To address this unmet need, Amanda proposes to integrate proteomic, genomic, and epigenetic analyses to characterize specific proteins coded by mutant DNA in clinically accessible pediatric specimens, including brain tumor tissue, blood, and cerebrospinal fluid (CSF). Based upon her discovery that a characteristic mutant histone protein called H3 circulates in the CSF of children with diffuse midline and high-grade glioma, she will seek to identify the epigenetic signatures of this mutation as a novel tumor biomarker. Histones are a family of proteins that associate with DNA in the nucleus, where transcription of genetic information encoded in DNA is in part regulated by secondary (chemical) modifications to the histone proteins. This is important because both mutant histones and their variable states of chemical modification following synthesis play a role in the regulation of genes (epigenetics) that contribute to tumorigenesis. Amanda proposes that the collective pattern of pediatric glioma histone codes (epigenetic signatures) result in gene expression patterns that contribute to tumorigenesis. These codes reflect a potential for response to therapy and can be used to identify targetable signaling pathways that tumors require for growth. If she is successful, the availability of these signatures as clinical diagnostic biomarkers will make it possible to assign children diagnosed with glioma to precision medicine therapy and effective clinical monitoring for longitudinal measurement of treatment response, which has the potential to improve their survival and quality of life.