# THE HARTWELL FOUNDATION

## 2019 Individual Biomedical Research Award

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### Regulating Tumor Growth in the Brainstem Microenvironment of Diffuse Intrinsic Pontine Glioma

Each year in the United States, approximately 5,000 brain and spinal cord tumors are diagnosed in children younger than 20. Almost 15% of pediatric brain cancer patients will be diagnosed with diffuse intrinsic pontine glioma (DIPG), an aggressive tumor with a 5-year survival rate of less than 1%. Derived from glial cells that surround and insulate nerves, DIPG grows in the brainstem, an area of the brain that regulates many essential body processes such as breathing, movement, and heart rate. Tumors forming within this brain area limit patients' ability to move, communicate, eat, and drink, and quickly become fatal. The tumors cannot safely be removed surgically, chemotherapy has not been proven effective and radiation unfortunately, provides only temporary remission. Clearly, there is an urgent need for an innovative strategy to selectively and noninvasively restrict DIPG growth and proliferation in the developing brain. To address this need, Lindsay proposes to focus on the microenvironment that surrounds the tumor. Her approach is based upon a seemingly disparate set of observations published recently regarding breast, colon, prostate, and pancreatic cancer, where tumor growth and progression were linked to the presence of a chemical messenger called norepinephrine (NE) that normally enables neurotransmission. The compelling role of NE signaling in brain cancer has not been examined but is consistent with the facts that NE neurons are concentrated in the brain area susceptible to DIPG (the brainstem) and that they release high levels of NE into this region (the tumor microenvironment) during postnatal brain development, when DIPG typically forms. That DIPG cells have surface receptors for NE reinforces a possible role for this messenger in tumor growth and is also consistent with the fact that NE stimulates growth of oligodendrocytes, the putative glial cell of origin for DIPG. Despite this encouraging data, the relationship between NE and glioma growth in vivo has not been recognized, in large part due to limited options for accurately modeling brain cancer in rodents and the challenge of targeting NE signaling in the brainstem without disrupting vital functions. To evaluate whether manipulating NE signaling in the tumor microenvironment alters DIPG growth, Lindsay will utilize a unique transgenic mouse model and deploy tissue clearing and light sheet imaging to evaluate the anatomical arrangement of DIPG and nearby NE neurons during postnatal development. Retrograde viral tracing will then be used to identify neurons that directly innervate the DIPG tumor. To quantify the effect of NE on tumor development and animal lifespan, she will modulate the activity of NE neurons. If successful, a novel treatment for children with DIPG will emerge that has the potential to prolong and improve the quality of their life.