Executive Summary
Experience shapes the developing brain, as neural circuit activity sculpts synaptic connections and promotes growth of the brain's white matter infrastructure during childhood. In recent work, we have shown that DIPG cells highjack these mechanisms of neuronal activity-dependent plasticity to promote cancer growth. This insight, together with the identification of key molecular mechanisms mediating neuronal activity-regulated DIPG growth identify a novel set of therapeutic targets. In the present proposal we seek to explore the hypothesis, supported by our preliminary studies, that secreted factors from active neurons similarly promote tumor cell infiltration/invasion. To accomplish this, we will use optogenetic techniques to elevate neuronal activity in a physiomimetic fashion and will test the effects of elevated neuronal activity on DIPG cell invasion *in vitro* and *in vivo*. We will then use our established optogenetically-controllable brain slice model to identify activity-regulated secreted factors that promote DIPG cell infiltrative/invasive behavior. Finally, we will perform RNA sequencing of DIPG cells exposed to neuronal activity-regulated factors to begin to identify the intracellular signaling mechanisms responsible for the the observed increase in infiltration/invasion.

DIPG is characteristically infiltrative (i.e. diffuse and intrinsic), and this infiltrative/invasive behavior is destructive both in the brainstem and in other areas of the central nervous system to which DIPG spreads during the course of the disease. If successful, the proposed experiments may identify innovative strategies to control infiltration of DIPG cells throughout the brainstem and prevent spread more diffusely to the cerebrum and spinal cord