Executive Summary

Background: Hundreds of clinical trials of chemotherapy given by systemic routes (oral or IV) have been conducted in DIPG, and every one has failed to improve outcomes. They have also caused significant damage to patients. Now, convection-enhanced delivery or CED, a method of delivering chemotherapy directly to DIPG tissue by catheter, is starting to show promising results in terms of prolonging survival, but these patients often die of metastatic disease. The standard treatment of DIPG, radiation to the tumor itself, is effective but not curative. Radiation therapy (RT) to the entire brain and spinal cord (CSI) carries more risk of side effects than RT to the tumor alone. Even though DIPG is known to move to the rest of the brain and spinal cord, CSI has been considered worthwhile, because patients generally die of local disease first. Now that CED will likely improve control of the local tumor, we believe that DIPG could potentially be cured by local RT and CED to control the primary tumor, and CSI to treat metastases.

Hypothesis: We hypothesize that a multimodality approach that includes chemotherapy via CED, along with craniospinal RT (CSI) with a focal boost, will produce long-term DIPG cures.

Goals and Clinical Significance: Our proposal aims to answer key questions that would allow us to design a trial like this with curative intent in the near future. First, does oral or IV chemotherapy have a role in this approach, or has systemic chemotherapy always failed because it simply cannot penetrate DIPG adequately? We will answer for the first time in clinical trials whether oral and IV chemotherapy can penetrate DIPG tissue. Either answer will be useful: If no, we will be able to focus these resources on trials in CED. If yes, we will continue searching for better drugs to target DIPG's unique biology. Along the way, we will also determine whether mouse models of DIPG, which are being used more and more, adequately model this drug delivery issue. Secondly, we will study whether the addition of CSI can help control metastatic disease. If it can, this will provide adequate evidence to justify the extra toxicity of CSI in a DIPG clinical trial. If no, we will see if metastases can instead be controlled by another approach like systemic chemotherapy. Accomplishing our aims will answer crucial questions on the way to a combined treatment approach to final provide hope for long-term survival in DIPG.

Design and Methods: In Aim 1, we use two oral/IV chemotherapy medicines that we have already shown cross the blood-brain barrier and are effective against models of DIPG, gemcitabine and selinexor. We will use two clinical trials that involve treatment of newly-diagnosed DIPG patients with one of these drugs immediately before biopsy, in order to assess how well each drug penetrates the tumor. These will be the first two clinical trials of this kind; the PI on this proposal, Dr. Green, is Chair of both of these studies, and the preclinical data for both has been produced by his lab. We will use parallel trials with these drugs in mouse patient-derived xenograft (PDX) models with which we have developed significant expertise. In mice, the drugs will be given both systemically and by CED. This will allow us to compare the systemic results between humans and mice, and to compare CED versus systemic delivery. In Aim 2, we will use our DIPG PDX model to measure whether the addition of CSI to tumor-directed RT improves the control of metastatic disease, and potentially even survival. We will use a mouse preclinical irradiator to precisely deliver focal RT to one group of mice, and focal RT plus CSI to another group. We will then compare metastatic disease over time in the two groups by high-resolution MRI, and by histology at necropsy. We will also compare survival.

Amount Requested: $199,957