EXECUTIVE SUMMARY

Brainstem gliomas constitute 10 to 15% of all brain tumors in children. Diffuse intrinsic pontine gliomas (DIPG) account for 80% of all brainstem tumors. The treatment of children with DIPG represents a formidable challenge because of the critical location of these tumors, and their refractoriness to therapy. Surgery to confirm the diagnosis is only recommended for patients with atypical tumors by magnetic resonance imaging (MRI). Radiation therapy (RT) is the mainstay of therapy. Although 60% to 80% of affected patients benefit from RT, the clinical improvement is generally temporary. Less than 10% of children with DIPG survive more than 3 years from diagnosis. Standard chemotherapy has not been beneficial in the treatment of children with this cancer.

Since surgery to obtain a sample of DIPGs is rarely required, very little is known about the biology of these tumors. Recently, new treatment approaches combining biologic agents (synthetic antibodies or medications called small-molecule inhibitors) during and/or after RT have been used in the treatment of children with DIPG. These new drugs target specific molecules or signaling pathways within tumors; however, since little is known about the molecular and genetic abnormalities associated with DIPG, it has been impossible to elaborate on important therapeutic issues such as the selection of the most appropriate drug(s) to be used, or which patients would most benefit from a specific drug.

In this multi-institutional study, we are prospectively collecting tumor and constitutional tissue samples from patients with DIPG and other types of brainstem gliomas either during therapy or at autopsy to perform an extensive analysis of the genetic make-up of these tumors. Our hypothesis is that the better understanding of the genetic abnormalities underlying DIPGs will provide the tools to design better and specific treatments for affected children. Such broad and extensive analysis has never been done before because of lack of appropriate tissue samples.

We have been conducting this prospective study at our institution since June 2006. To date, tumor tissue samples with or without control normal tissue (blood and/or normal brain) have been obtained from 23 research participants. Tissue samples were obtained at autopsy in 21 patients (one case at diagnosis and the remainder after tumor progression). Tissue was obtained at diagnosis in 4 research participants. One research participant had tumor samples collected at diagnosis and after tumor progression. Only 3 autopsies took place at our institution. The remaining procedures have occurred at different hospitals in 11 different states (Alabama, Arkansas, Florida, Georgia, Massachussetts, Missouri, New York, North Carolina, Ohio, Rhode Island, and Tennessee).

All available tumor tissue samples have been reviewed by Dr. David W. Ellison, who is a co-investigator in this study and an international expert in the field. The tissue samples will be analyzed at the laboratory of Dr. Suzanne Baker, Ph.D., who has extensive expertise in genetic and molecular analysis of tumor samples. Dr. Baker's laboratory has already analyzed the quality of DNA obtained from all available tissue samples. The extracted DNA has been of excellent quality and suitable for the proposed genetic studies. We have not yet completed the analysis of quality of RNA.

Our proposed budget will finance the initial SNP and gene expression microarray studies of the tissue samples collected so far.