



July 26, 2010

Dr. Gavin Baumgardner
Chairman, Medical Advisory Council
The Cure Starts Now Foundation
10280 Chester Road
Cincinnati, Ohio 45215

Dear Dr. Baumgardner:

It is with great pleasure that we submit a grant proposal to the Cure Starts Now Foundation on behalf of Suzanne J. Baker, PhD, a member of the Department of Developmental Neurobiology at St. Jude Children's Research Hospital.

We have enclosed for your consideration a grant proposal for \$100,000, titled *P13K Signaling Effectors in Diffuse Intrinsic Potine Glioma* (DIPG). Funding of this proposal will help add to the existing body of knowledge already at St. Jude on DIPG. It is our hope that through continued research we will begin to see real improvements in the lives of children with brain stem glioma.

We are very grateful to the Cure Starts Now Foundation for your leadership in this area and for your continued investment in research that will ultimately lead to a cure.

Sincerely,

Ingrid V. McGraw, Senior Director
Foundation Relations

PI3K SIGNALING EFFECTORS IN DIFFUSE INTRINSIC PONTINE GLIOMA

Principal Investigator

Suzanne J. Baker, PhD

Member

Department of Developmental Neurobiology

St. Jude Children's Research Hospital

262 Danny Thomas Place


Memphis, TN 38105

Phone: 901-595-2254

Fax: 901-595-2270

Email: suzanne.baker@stude.org

Signature:


Suzanne J. Baker, PhD

Collaborator

Alberto Broniscer, MD

Associate Member

Department of Oncology

St. Jude Children's Research Hospital

262 Danny Thomas Place

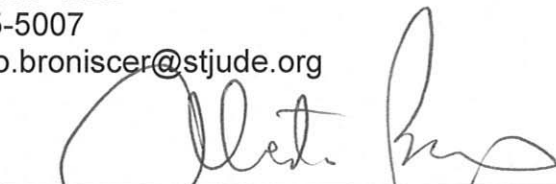
Memphis, TN 38105

Phone: 901-595-4925

Fax: 901-595-5007

Email: alberto.broniscer@stjude.org

Signature:


Alberto Broniscer, MD

Authorized Institutional Officer

James Downing, M.D.

Scientific Director

St. Jude Children's Research Hospital

262 Danny Thomas Place


Memphis, TN 38105

Phone: 901-595-3510

Fax: 901-595-8600

Email: james.downing@stjude.org

Signature:


James Downing, M.D.

EXECUTIVE SUMMARY

We propose two aims that will further understanding of the role of the phosphatidyl inositol-3 kinase (PI3K) pathway in diffuse intrinsic pontine gliomas (DIPG), and will impact therapy by providing insights needed for logical therapeutic use of PI3K inhibitors for DIPG. The proposal builds on several strengths, including a substantial collection of DIPG samples, and established expertise in the molecular analysis of tumors and the development of mouse models.

There is a dire need to identify therapeutic targets and predictors of tumor response to therapy in DIPG. Due to their vital location, DIPG are not treated surgically, and the lack of tumor material for research has greatly limited studies to define the molecular defects that cause this disease. Our collaborator, Dr. Alberto Broniscer, established a clinical protocol to prospectively collect DIPG samples for basic research at autopsy. We demonstrated that this material yields nucleic acid suitable for most basic research purposes (1), and conducted a large-scale unbiased analysis of genomic copy number imbalances in 43 DIPG samples. This approach identified *PDGFRA* as the most frequent target of focal amplification in the DIPG genome, in agreement with a published study of 11 DIPG from Dr. Hawkins, and our own results from a study of 78 pediatric high-grade gliomas, including 7 DIPG (2, 3). We also identified a number of additional recurrent focal amplifications in the collection of 43 DIPG that were not previously identified, demonstrating the importance of a large sample collection.

Defining genomic imbalances and gene expression patterns in DIPG provides a wealth of unbiased information about the molecular signatures of DIPG. However, many recurrent genetic changes in cancer occur as subtle mutations that will not be detected by these methods. For example, three major signaling pathways, the receptor tyrosine kinase (RTK)/PI3K, p53 and Rb signaling pathways are disrupted by mutation in virtually every adult glioblastoma. Many of these mutations were only detected by sequence analysis (4, 5). There is an industry-wide emphasis among pharmaceutical companies to develop new selective inhibitors that counteract activity of the RTK/PI3K pathway. An equally intense field of research is the identification of which mutations within these pathways create ideal therapeutic targets, and how mutation may influence response to pathway inhibitors (6, 7). It is essential to have a full understanding of the mutation spectrum within the PI3K pathway in DIPG to provide the foundation for logical use of PI3K inhibitors for DIPG.

In Aim 1, we will conduct an in-depth analysis to identify mutations in multiple effectors in the PI3K signaling pathway that may be important therapeutic targets, or may influence tumor response to different PI3K pathway inhibitors. This aim builds upon the valuable resource of DIPG samples and our long-standing background in the molecular biology of cancer, and in PI3K signaling.

In Aim 2, we will characterize novel transgenic mice that we developed to study the role of *PDGFRA* overexpression in DIPG. This is an essential step to develop an animal model in which the most commonly amplified gene in human DIPG drives tumor formation. The model will be an important resource for preclinical testing of selective therapeutic agents, and also to further understanding of the mechanisms through which *PDGFRA* contributes to DIPG formation.