Section: Contact Information

First Name: John
Last Name: Lucas
Institution: St Jude Children’s Research Hospital
Address 1: 262 Danny Thomas Place, MS210
Address 2: Department of Radiation Oncology St. Jude Children’s Research Hospital
City: Memphis, Tennessee
State/Province/Region: TN
Country: US
Zip/Postal Code: 38105-3678
Phone Number: 8436331158
Alternate Phone Number: 8436331158
Email Address: John.Lucas@StJude.org

Section: Project Requirements and Description

Group: Requirements to submit AOI

A comprehensive review of previously published data has been completed. Yes
The specific aims are clear and focused. Yes
The investigator has appropriate experience and expertise to develop the concept proposal; if not, has identified a mentor or senior co-investigator. Yes
The investigator agrees to develop an initial draft of the concept proposal within 6 weeks of approval of the AOI and to finalize the concept proposal within 6 months. Yes

Project Title: A Comprehensive Molecular Characterization of Therapy-Related Pediatric High Grade Gliomas

Planned research population (eligibility criteria):
Patients with any prior radiotherapy to the cranial vault for either prophylactic therapy or adjuvant/definitive intent who develop an intracranial glioma unrelated to their prior diagnosis.

Proposed specific aims:
Therapy related high-grade gliomas are an uncommon poorly characterized deadly brain tumor with no identifiable therapeutic approaches specific to their molecular features. Characteristic molecular subtypes have been described to have characteristic ages at presentation, prognoses, and tumor locations however the features nascent to therapy related gliomas are altogether uncharacterized. Extensive characterization of genetic alterations common to therapy related high grade gliomas and their relationship to existing methylation and mutation defined subsets are needed. To address this lack of knowledge, we propose to complete whole genome sequencing, methylation and copy number analysis of consecutive cases of therapy related high-grade gliomas.
Hypothesis 1: Therapy Related Pediatric High-grade Gliomas have a Common Characteristic Mutational and Copy Number Alteration Profile.
Measures: Identified synonymous and non-synonymous mutations will be characterized for significance and filtered for depth, known human variations, and functional impact to produce a list of mutations. The list of variations will be qualitatively compared according to frequency relative to other known somatic mutations which are identified in treatment naive high grade gliomas. Similarly, copy number gains and loss at the chromosomal and gene level will be characterized and reference relative to treatment naive high grade gliomas.

Anticipated Outcome: The data will prove to be invaluable in the molecular characterization of therapy related high grade gliomas and may inform potential novel therapeutic targets for definitive therapy.

Alternative Outcome: The absence of a differential mutational spectrum or common classes of mutations may mean that therapy related high grade gliomas lead to random genetic aberrations which have a heterogeneous molecular phenotype.

Hypothesis 2: Therapy related pHGG represent a distinctive subset of previously defined methylation and mutation defined biological subtypes of pHGG.

Measures: The methylation subtype will be derived by clustering the enriched population of therapy related high grade gliomas against published datasets. Subgroup assignment score will be compared across therapy related high grade gliomas and non-treatment related pHGG. The differential assignment of therapy related tumors to each methylation subtype will be tested for equivalence.

Anticipated Outcome: Methylation subtype assignment will differentially distribute therapy related high grade gliomas to the RTK1 methylation subgroup. Therapy related tumors will have closer relationships in a hierarchical clustering dendrogram than treatment naive high grade gliomas.

Alternative Outcome: Therapy related gliomas will be distributed in a random fashion to all methylation defined subgroups not suggestive of a common molecular origin.

Will the project require non-CCSS funding to complete? : Yes
If yes, what would be the anticipated source(s) and timeline(s) for securing funding? : Investigator discretionary funds, additional outside foundation funding; applying for Childhood Brain Tumor Foundation and Pediatric Cancer Research Foundation grants.

Group: Does this project require contact of CCSS study subjects for:
Additional self-reported information : No
Biological samples : No
Medical record data : Yes
If yes to any of the above, please briefly describe. :
Unstained sections, blocks and scrolls from formalin fixed paraffin embedded tissues will be used for sequencing and methylation analyses.

Group: What CCSS Working Group(s) would likely be involved? (Check all that apply)
Second Malignancy : Secondary
Chronic Disease:
Psychology / Neuropsychology:
Genetics: **Primary**
Cancer Control:
Epidemiology / Biostatistics:

**Section: Outcomes or Correlative Factors**

Late mortality: **Secondary**
Second Malignancy: **Primary**

**Group: Health Behaviors**
Tobacco:
Alcohol:
Physical activity:
Medical screening:
Other:
If other, please specify:

**Group: Psychosocial**
Insurance:
Marriage:
Education:
Employment:
Other:
If other, please specify:

**Group: Medical Conditions**
Hearing/Vision/Speech:
Hormonal systems:
Heart and vascular:
Respiratory:
Digestive:
Surgical procedures: **Correlative Factors**
Brain and nervous system: **Primary**
Other:
If other, please specify:

**Group: Medications**
Describe medications:

**Group: Psychologic/Quality of Life**
BSI-18:
SF-36:
CCSS-NCQ:
Group: Other

Pregnancy and offspring: Correlative Factors
Family history: Correlative Factors
Chronic conditions (CTCAE v3): Correlative Factors
Health status: Correlative Factors

Group: Demographic

Age: Correlative Factors
Race: Correlative Factors
Sex: Correlative Factors
Other: Correlative Factors

If other, please specify:

Group: Cancer treatment

Chemotherapy: Correlative Factors
Radiation therapy: Correlative Factors
Surgery: Correlative Factors

Section: Anticipated Sources of Statistical Support

CCSS Statistical Center: Yes
Local institutional statistician: Yes
If local, please provide the name(s) and contact information of the statistician(s) to be involved.
Tong Lin, Tong.Lin@StJude.org
Arzu Onar, arzu.onar@stjude.org

Will this project utilize CCSS biologic samples? Yes
If yes, which of the following? Buccal cell DNA, Peripheral blood, Second malignancy pathology samples
If other, please explain:

Section: Other General Comments

Other General Comments:
Brent Orr is designated as a key collaborating coinvestigator.

The analyses indicated above are intended as part of a larger investigation into both SJCRH and CCSS samples. We have already identified 11 treatment related high grade gliomas with tissue in our tumor bank. Methylation and sequencing
analyses have been completed on a subset of these 11 cases. We propose to complete these analyses on the SJCRH cohort as well as expand our cohort to the CCSS cohort.