Section: Contact Information

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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 synonomous and non-synonomous 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 :

PTS :
PTG :
Other :
If other, please specify :

Group: Other

Pregnancy and offspring :
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 :
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.