

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 : **Investigation of Germline Predisposition to Pediatric Treatment-Induced High-Grade Glioma (TIHGG)**

Planned research population (eligibility criteria) :

The research population will be patients who received cranial radiation as treatment for a primary malignancy. The experimental group will be patients who went on to develop a high-grade glioma at least 5 years after undergoing radiation treatment. Of note, there are 38 patients in the CCSS who developed CNS second malignant neoplasms and have available host tissue; per Dr. Greg Armstrong, approximately half of these are HGGs. We have an additional 15 germline samples from TIHGG patients at Children's Hospital Colorado (most of which have already undergone WGS or WES). The control group will be patients who did not develop a high-grade glioma and are at least 12 years from the end of radiation treatment.

Proposed specific aims :

We hypothesize that germline variants in DNA repair that are not sufficient to be oncogenic themselves predispose affected patients to develop TIHGG after exposure to radiation therapy. This hypothesis arises from study of TIHGG tumor samples, which commonly showed high somatic mutation rates and impaired DNA repair. We will determine frequency and extent of homozygosity of mutations in known DNA repair genes (determined from established GSEA genesets) in TIHGG patients and the control cohort. We will perform a combined analysis of the experimental samples from CCSS and Children's Hospital Colorado, which total approximately 34. We have worked with our bioinformatics colleagues here in Colorado, and with our collaborators at St. Jude, to perform combined analyses of sequencing data from multiple sources/institutions for this project already so do not anticipate problems combining these cohorts. Genome-wide association studies and frequency of individual mutations will be used to determine mutations that are significantly more frequent in TIHGG compared to the control cohort. These mutations will then be analyzed for pathogenicity using established tools, e.g. genetics.bwh.harvard.edu/pph2/ and snpalyzer.uthsc.edu/.

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? :
**We are applying for an R01 that will include this aim, to be submitted in February 2021.
We have pilot local foundation funding to start the analysis in the meantime.**

Group: Does this project require contact of CCSS study subjects for:

Additional self-reported information : **No**

Biological samples : **No**

Medical record data : **No**

If yes to any of the above, please briefly describe. :

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 : **Secondary**

Section: Outcomes or Correlative Factors

Late mortality :

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 :

Brain and nervous system :

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 :

Chronic conditions (CTCAE v3) :

Health status :

Group: Demographic

Age : **Correlative Factors**

Race :

Sex : **Correlative Factors**

Other :

If other, please specify :

Group: Cancer treatment

Chemotherapy : **Correlative Factors**

Radiation therapy : **Correlative Factors**

Surgery :

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. :

Will this project utilize CCSS biologic samples? : **No**

If yes, which of the following? :

If other, please explain : **We would only use the germline samples themselves if they have not yet had DNA sequencing.**

Section: Other General Comments

Other General Comments :

I agree to share this information with St. Jude : **Yes**