

### **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 : **Genetic modification of chemotherapy-associated subsequent malignant neoplasms**

Planned research population (eligibility criteria) :

**Participants of the Childhood Cancer Survivors Study who received chemotherapy for their first primary cancer, with or without radiation therapy.**

Proposed specific aims :

**Risk of subsequent malignant neoplasms (SMNs) after treatment for childhood cancer is known to be associated with receipt of chemotherapy as well as germline genetic variation. Limited genome-wide and candidate association studies of chemotherapy-associated SMNs suggest that variants in genes with important immune function affect risk. However, there is limited research evaluating the interaction between chemotherapy dose, genetic variation, and SMNs among survivors of childhood cancers. In a preliminary analysis of adult breast cancer survivors, we observed that a polygenic risk score (PRS) comprising variants associated with autoimmune disease was associated with the risk of subsequent contralateral breast cancer, particularly for women who received chemotherapy. Treatment for childhood cancers frequently involves chemotherapy, with both alkylating agents and anthracyclines known to increase the risk of second primary malignancies. In this application of intent, we propose to evaluate the interaction of an “autoimmune polygenic risk score (PRS)”, chemotherapy dose, and risk of subsequent SMNs in the Childhood Cancer Survivors Study (CCSS).**

**Aim 1. Evaluate genetic effect modification of the association between chemotherapy and subsequent hematological malignancies.**

**Genetic effect modification will be assessed by using a PRS comprising single**

nucleotide polymorphisms reported to be associated with autoimmune disease at genome-wide significance in prior studies. We will test for genetic effect modification of the overall association between cumulative dose of any alkylating agents or epipodophyllotoxins and hematological malignancies after a latency of at least 5 years, adjusting for receipt of radiation therapy and other confounders.

**Aim 2. Evaluate genetic effect modification of the association between chemotherapy and subsequent solid cancers.**

First, using the autoimmune PRS, we will evaluate modification of the association between cumulative dose of any alkylating agents and risk of subsequent solid cancers, specifically sarcomas and thyroid, breast, lung, genitourinary, and gastrointestinal tumors, after a latency of at least 10 years. We also propose to examine these interactions separately for dose of procarbazine and cyclophosphamide. Second, we will examine modification by the autoimmune PRS of the association between anthracyclines and risk of these solid cancers. All analyses will account for receipt of radiation therapy, type of childhood cancer, and age at diagnosis.

The expected outcome of this study is an understanding of whether genome-wide variation in immune function modifies the risk of chemotherapy-associated SMNs for survivors of childhood cancers.

Will the project require non-CCSS funding to complete? : **No**

If yes, what would be the anticipated source(s) and timeline(s) for securing funding? :

**N/A**

**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 :

**Section: Outcomes or Correlative Factors**

Late mortality :

Second Malignancy : **Primary**

**Group: Health Behaviors**

Tobacco : **Correlative Factors**

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 : **Correlative Factors**

Heart and vascular :

Respiratory :

Digestive : **Correlative Factors**

Surgical procedures : **Correlative Factors**

Brain and nervous system : **Correlative Factors**

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 : **Correlative Factors**

Family history : **Correlative Factors**

Chronic conditions (CTCAE v3) :

Health status :

***Group: Demographic***

Age : **Correlative Factors**

Race : **Correlative Factors**

Sex : **Correlative Factors**

Other :

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. :

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

If yes, which of the following? :

If other, please explain :

**Section: Other General Comments**

Other General Comments :

**This Application of Interest is being submitted as a revision to a previous submission, per recommendations by Drs. Bhatia and Armstrong.**

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