Section: Contact Information

First Name : **Christopher**
Last Name : **Recklitis**
Institution : **Dana-Farber Cancer Institute**
Address 1 : **450 Brookline Avenue**
Address 2 :
City : **Boston**
State/Province/Region : **MA**
Country : **US**
Zip/Postal Code : **02215**
Phone Number : **(617) 632-3839**
Alternate Phone Number :
Email Address : **Christopher_Recklitis@dfci.harvard.edu**

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 Determinants of Posttraumatic Stress Disorder in Pediatric Cancer Survivors**
Planned research population (eligibility criteria) :
Survivor participants in CCSS, who answered the Posttraumatic Stress Diagnostic Scale (PDS) and were genotyped.
Proposed specific aims :
Diagnosis and living with cancer is highly stressful. Patients with cancer are known to have an increased risk of psychiatric symptoms (Mitchell, Lancet Oncol, 2011) and suicide (Fang, NEJM, 2012). Posttraumatic stress disorder (PTSD) is a stress-related mental disorder characterized by re-experiencing, avoidance, negative cognitions and mood, and arousal following a traumatic life event, such as a cancer diagnosis. Our recent work illustrated that receiving a cancer diagnosis is associated with drastically increased risk of a group of stress-related mental disorders, including PTSD, among adults in Sweden (Lu, JAMA Oncol, 2016). Such findings were later confirmed among adult cancer patients in US (Hawkins, JCO, 2017) and Canada (Cawthorpe, BJPsych Open, 2018).

Exposure to such adversity from early life is even more traumatic. A four-time higher risk of PTSD symptoms was previously reported in Childhood Cancer Survivor Study (CCSS), as compared to their cancer-free siblings (Stuber, Pediatrics, 2010). Significant PTSD symptoms were associated with cranial radiation in those treated before age 4 (OR=2.05) and those who overall received more intensive treatment (OR=1.36). No relationship of PTSD symptom elevation with recurrence or second malignant neoplasm was identified, although older survivors, unmarried survivors, and those with poor education, employment, income, were at significantly greater risk. Although all survivors

experienced the particular trauma, only 9% of them developed to significant PTSD. It is, therefore, of paramount importance to advance our current understanding of the varying trajectories of mental wellbeing after receiving a cancer diagnosis.

In addition to a handful of environmental factors (primarily trauma exposure), genetic predisposition to PTSD has gradually been picking up during the past decade, supported by the substantial heritability up to 46% (Duncan, Curr Psychiatry Rep, 2018). So far, the largest genome-wide association (GWA) study has identified six genetic markers of PTSD (Nievergelt, Bioxiv 458562). However, the majority of participants are limited to veteran populations. Large study samples homogenous with respect to trauma exposure, namely diagnosis and living with cancer since childhood, might add significantly to relatively weak evidence base for the genetic signature of PTSD, and offer first-hand evidence of prevention and early detection for PTSD in childhood cancer population.

By leveraging the genetic data of adult survivors in CCSS (total N=5739) who answered the Posttraumatic Stress Diagnostic Scale (PDS), the overarching aim of this proposal is to further our understanding of the genetic contribution to the varying risk of PTSD after receiving a cancer diagnosis in childhood. Specifically, we aim to:

1. Identify genetic determinants of PTSD among adult survivors of childhood cancer.
a. GWA approach: We will perform GWA analysis of PTSD symptoms in continuous score as well as in dichotomous cases vs. controls. We will replicate our findings in the deCODE Genetics in Iceland (total N=ca. 160,000), where both childhood and adulthood cancers are identifiable.
b. Candidate approach: We will specifically examine the association between PTSD symptoms and a collection of candidate alleles from novel genetic markers of PTSD (Nievergelt, Bioxiv 458562) and functional markers related to stress (Arloth, Neuron, 2015).

2. Develop an advanced prediction model for PTSD risk in CCSS, using polygenic risk scores for PTSD, functional markers related to stress, and/or common psychiatric disorders (e.g. depression and anxiety). The scores will be based on a collection of associated alleles from verified functional markers related to stress/PTSD (as mentioned in Aim 1b) and from Psychiatric Genetic Consortium (for other common psychiatric disorders).

3. Examine whether these genetic markers of PTSD are specific to childhood cancer survivors, by comparing with meta-analyzed GWAS summary statistics in adulthood cancer survivors based on the deCODE Genetics (adulthood cancers only) and Nurses' Health Study 2 (total N=8273). Dr. Donghao Lu has previously used these data sources to conduct research on genetic determinants of psychological distress.

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? :

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 :
Chronic Disease :
Psychology / Neuropsychology : **Primary**
Genetics : **Primary**
Cancer Control :
Epidemiology / Biostatistics : **Secondary**

Section: Outcomes or Correlative Factors

Late mortality :
Second Malignancy :

Group: Health Behaviors

Tobacco : **Correlative Factors**
Alcohol : **Correlative Factors**
Physical activity : **Correlative Factors**
Medical screening :
Other :
If other, please specify :

Group: Psychosocial

Insurance : **Correlative Factors**
Marriage : **Correlative Factors**
Education : **Correlative Factors**
Employment : **Correlative Factors**
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 : **Correlative Factors**
SF-36 :
CCSS-NCQ :
PTS : **Primary**

PTG :
Other :
If other, please specify :

Group: Other

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

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