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Project Requirements and Description

Requirements to submit AOI (all answers must be "yes" to proceed)

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

Investigating the Role of Genetically Regulated Expression in Childhood Cancer Survivorship

Planned research population (eligibility criteria)

Five-year survivors of childhood cancer in the St. Jude Lifetime Cohort (SJLIFE) and Childhood Cancer Survivor Study (CCSS) with whole genome/exome sequencing or SNP array data for common variant analysis.

Proposed specific aims

Aim 1a: To impute genetically regulated expression (GReX) of both canonical genes and enhancer RNAs (eRNAs) across 49 human cell and tissue types for childhood cancer survivors in the SJIFE and CCSS cohorts. The resulting individual-level, imputed expression values will be used to perform transcriptome-wide association studies (TWAS) of both late effects (i.e. cardiovascular disease, subsequent neoplasms, neurocognitive outcomes, and endocrine disorders) and continuous traits (i.e. body mass index, lipid measurements, and global longitudinal strain) among these individuals.

Aim 1b: To utilize Mendelian randomization (MR) to infer causality for any significant TWAS associations. Under this approach. We will test whether each transcript's genetic instrument (i.e. SNP eQTLs) causally influence outcome (i.e. the associated phenotype) via its mediation of the exposure (i.e. GReX). Multiple MR approaches will be tested, including the MR-JTI, MR-Egger, median-based, maximum likelihood, and inverse-variance weighted methods.

Aim 1c: To explore the functional pathways in which TWAS transcript associations are involved. Gene set enrichment analysis and gene over-representation analyses will be performed. Additionally, any transcripts are associated with neurocognitive outcomes, the NeuroimaGene framework may be utilized to link the associated GReX to neuroimaging derived brain features.

Aim 2: To explore the use of TWAS associations in constructing transcriptome risk scores (TRSs) of chronic disease in childhood cancer survivors.

Aim 3: To impute individual-level, tissue-specific chromatin contact frequency utilizing the GReX of eRNAs and canonical genes imputed in Aim 1. The resulting imputed values will be used to perform contactome-wide association studies (CWAS) of the same phenotypes of interest from Aim 1.

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?

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.

What CCSS Working Group(s) would likely be involved? (Select all that apply)

	Primary	Secondary
Second Malignancy		
Chronic Disease		
Psychology/Neuropsychology		
Genetics	✓	
Cancer Control		
	Primary	**Secondary**
Epidemiology/Biostatistics		

Outcomes or Correlative Factors

	Primary	Secondary	Correlative Factors
Late Mortality			
Second Malignancy	✓		

Health Behaviors

	Primary	Secondary	Correlative Factors
Tobacco	✓		
Alcohol	✓		
Physical Activity	✓		
Medical Screening			
Other			

If other, please specify

Psychosocial

	Primary	Secondary	Correlative Factors
Insurance	✓		
Marriage	✓		
Education	✓		
Employment	✓		
Other			

If other, please specify

Medical Conditions

	Primary	Secondary	Correlative Factors
Hearing/Vision/Speech	✓		

	Primary	Secondary	Correlative Factors
Hormonal Systems	✓		
Heart and Vascular	✓		
Respiratory	✓		
Digestive	✓		
Surgical Procedures			
Brain and Nervous System	✓		
Other			

If other, please specify

Medications

Describe medications

Psychologic/Quality of Life

	Primary	Secondary	Correlative Factors
BSI-18			
SF-36			
CCSS-NCQ			
PTS			
PTG			
Other			

If other, please specify

Other

	Primary	Secondary	Correlative Factors
Pregnancy and Offspring			
Family History			
Chronic Conditions (CTCAE v3)	✓		
Health Status			

Demographic

	Primary	Secondary	Correlative Factors
Age	✓		
Race	✓		
Sex	✓		
Other			

If other, please specify

Cancer Treatment

	Correlative Factors
Chemotherapy	✓
Radiation Therapy	✓
Surgery	✓

Anticipated Sources of Statistical Support

CCSS Statistical Center	No
Local Institutional Statistician	No

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

Other General Comments

Agree

I agree to share this information with St. Jude

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