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Requirements to submit AOI

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

Genetic Mechanisms Underlying Cancer Treatment-related Cardiomyopathy in Childhood Cancer Survivors of Diverse Ancestry

Planned research population (eligibility criteria)

Childhood cancer survivors with existing genome-wide genetic (SNP, WGS, or WES) data.

Proposed specific aims

Aim 1: To comprehensively examine associations of both common and rare SNVs in cardiac structure, function, and mechanics, and CM/HF risk among 5,000 survivors of diverse ancestries from SJLIFE.
Aim 1a: We will perform ancestry-specific GWASs, trans-ancestry meta-analysis, and joint analyses of CM/HF and echocardiographic parameters, in addition to admixture mapping to identify novel loci. Rare variants will be examined separately. Significant findings will be replicated in ~9,000 independent survivors from the Childhood Cancer Survivor Study and Children’s Oncology Group cohorts and assessed for potential interactions with cancer treatments. Existing DNA methylation, RNA-seq and ATAC-seq data from survivors, alongside colocalization and fine-mapping, will be used to identify/prioritize the likely causal variants at each locus.

Aim 1b: Our group has substantial experience in validating genetic variants associated with doxorubicin-induced cardiotoxicity. We will use this expertise to functionally validate the top 10 genome-wide significant hits with evidence of replication, using CRISPR/Cas9-based variant introduction/correction in survivor-specific hiPSC-CMs and six well characterized biochemical and electrophysiological assays including RNA-seq.
Aim 2: To functionally characterize allele-specific gene regulatory effects of the top 1,000 ranked noncoding variants associated with CM/HF risk.
Aim 2a: We will perform an MPRA on the top 1,000 noncoding GWAS variants associated with diverse cardiac outcomes from Aim 1 (irrespective of genome-wide significance) in hiPSC-CMs from eight survivors of diverse ancestries to identify variants with significant allele-specific effects on gene regulatory activity.
Aim 2b: Significant gene regulatory variants identified via MPRA will be ranked for functional experimentation using CRISPR/Cas9-based variant introduction/correction in survivor-specific hiPSC-CMs. We will implement a polygenomic method for variant ranking that will combine MPRA results with RNA-seq and ATAC-seq data from survivors. This integrative strategy will prioritize for functionally active gene regulatory variants with strong allele-specific effects at transcription factor footprints that impact local chromatin accessibility and/or gene expression in cardiomyocytes. We will investigate the top 10 ranked variants.

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?

An R01 is being submitted in February 2025.

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		
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			
Hormonal Systems			
Heart and Vascular	✓		
Respiratory			
Digestive			

	Primary	Secondary	Correlative Factors
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	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

Other General Comments

Agree

I agree to share this information with St. Jude

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