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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 Metformin for Obesity Prevention in Adult Survivors of Childhood Cancer.

Planned research population (eligibility criteria)

Adult survivors of childhood cancer with a BMI>25

Proposed specific aims

SPECIFIC AIMS
Adult survivors of childhood cancer (ASCC) are at increased risk for central adiposity, metabolic disease, diabetes, and cardiovascular disease, and for obesity: 36.2% of survivors in their 30's compared to 31.6% in the general population, matched on age, sex, and race.1,2 The incidence of obesity grows through young and mid-adulthood, making it imperative to understand childhood risk factors for obesity.3 In the specific population of ASCC, the increased risk of overweight and obesity appears driven by several factors. The significant amount of time spent undergoing treatment for cancer reduces time available for activity in childhood and thus disrupts the formation of habits around physical activity, which tracks strongly into adulthood.4-6 Additionally, cancer treatments can affect the gut microbiome in ways that affect metabolic health and energy regulation.7

Disruptions in the gut microbiome lead to decreased integrity of the gut epithelium, and leakage of inflammatory proteins into systemic circulation.8,9 Systemic inflammation contributes to obesity by increasing insulin resistance and therefore the secretion of insulin, which is a weight-gain promoting hormone; and by

disrupting receptors in the brain for leptin, a satiety-promoting hormone.10,11 Therefore, treating dysbiosis of the gut microbiome may be critical for reducing the risk of obesity in survivors of childhood cancer. One medication that might have specific benefit for preventing obesity and metabolic disease in this population is metformin. Metformin is associated with reduced cancer mortality12 and is known to improve intestinal permeability and systemic inflammation.13-15 Pre-clinical and clinical assays of metformin demonstrate that it leads to lower levels of inflammatory molecules IL-6, TNF-α and IL-1β.16-18 Metformin also decreases inflammatory molecules crossing into the central nervous system (CNS), which may be specifically relevant for receptors in the CNS that regulate energy intake.19-25 Metformin has also been shown to improve weight maintenance over 10 years of follow-up.26

Given the increased risk for obesity-related disease in adult survivors of childhood cancer and the ways in which metformin addresses metabolic sequalae of obesity, our over-arching objective is to understand whether metformin reduces central adiposity and prevents weight gain and has favorable effects on mammalian target of rapamycin (mTOR), gut permeability, and systemic inflammation in this population. The current proposal will focus on central adiposity and prevention of weight gain to inform a future phase III randomized clinical trial that is fully powered to follow individuals long enough to understand obesity prevention as an outcome. We will accomplish the current aims with a decentralized, randomized trial of metformin versus placebo in young adult survivors of childhood cancer with overweight and obesity. The Childhood Cancer Survivors Study (CCSS) Cohort to will facilitate efficient recruitment of participants. Blood samples and anthropometric measurements will be obtained from Quest diagnostic centers near participants' homes, limiting barriers to participation.

Aim 1: To measure the effect of metformin versus placebo in reducing central adiposity and weight gain in adult survivors of childhood cancer with overweight and increased waist circumference.
Approach: We will conduct a randomized, double-blinded, placebo-controlled trial of metformin or placebo for 6 months in adult survivors of childhood cancer with a body mass index (BMI) between 25 to < 30 kg/m2 and waist circumference in the increased risk category (31 inches for women and 35.5 inches in men). There will be brief teaching on weight management behaviors; physical activity and dietary intake will be assessed.
Outcome: The primary outcome will be waist circumference and BMI as continuous outcomes.
Hypothesis: We hypothesize that those in the metformin arm will have approximately 3% lower BMI and waist circumference than the placebo arm at 6. months. The 12-week change in BMI from baseline will inform a future trial that is fully powered to assess metformin for preventing a BMI >= 30kg/m2.

Aim 2a: Quantify metformin's effect on mTOR, gut permeability, systemic inflammation, and global symptoms in adult survivors of childhood cancer. 2b: Assess heterogeneity by baseline biomarkers; 2c: Correlate biomarkers with BMI and waist circumference. We hypothesize that metformin will improve markers of gut permeability, systemic inflammation, and global symptoms more than placebo; that these changes will correlate with BMI; and that those with the higher inflammation at baseline will have greater response to metformin.

While the number of obesity treatments has grown, their long-term safety and acceptability in this population with previous cancer is unknown, so preventing obesity is important. These aims will provide information for understanding whether a safe, available medication prevents weight gain in this high-risk population.

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?

I will submit an NIH grant.

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			
Surgical Procedures			
Brain and Nervous System			
Other	✓		

If other, please specify

Weight (body mass index)

Medications

Describe medications

metformin

Psychologic/Quality of Life

	Primary	Secondary	Correlative Factors
BSI-18			

	Primary	Secondary	Correlative Factors
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

I am working with Stephanie Dixon and Alicia Kunin-Batson on a grant application.

Agree I agree to share this information with St. Jude

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