

## **Section: Contact Information**

First Name : **Maria Monica**  
Last Name : **Gramatges**  
Institution : **Baylor College of Medicine**  
Address 1 : **413 Woodland St**  
Address 2 :  
City : **Houston**  
State/Province/Region : **TX**  
Country : **US**  
Zip/Postal Code : **77009**  
Phone Number : **5032674484**  
Alternate Phone Number :  
Email Address : [mmgramat@txch.org](mailto:mmgramat@txch.org)

## **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 : **Biological Mechanisms of Accelerated Aging Evidenced as Frailty in Survivors of Childhood Leukemia**

Planned research population (eligibility criteria) :

**This proposal leverages access to the original and expanded CCSS cohort. Our targeted enrollment will be 250 pre-frail or frail ALL survivors, and 250 non-frail ALL survivors. Eligible participants must have genotyping data or be scheduled for genotyping during the study period. Based on Dr. Ness's study demonstrating pre-frailty or frailty in 30% of ALL survivors in the SJ Lifetime Cohort, we anticipate at least 30% of leukemia survivors enrolled in the CCSS to be pre-frail or frail (~1844 out of 6148). This assumption is based on the fact that the CCSS ALL survivors are older than those in SJ Lifetime Cohort, with a mean age of 43.9 +/- 6.4 years vs. 33.6 +/- 8.1 years (Jan 2017). Therefore, we do not anticipate challenges in recruiting 250 pre-frail or frail ALL survivors.**

Proposed specific aims :

**Specific Aim 1: To determine the association between telomere length and pre-frailty/frailty through objective assessment of frailty among CCSS ALL survivors by:**

- a) Comparing LTL percentile in survivors, as determined by telomere flow FISH, to age-based norms**
- b) Determining the impact of specific therapeutic exposures including cranial**

radiation (CRT) on LTL

c) Determining SNP profiles in telomere biology genes that correspond with TL < 10th percentile

d) Investigating the relationship between LTL, relevant SNP profiles, and frailty score.

**Specific Aim 2: To determine the association between systemic inflammation and pre-frailty/frailty through objective assessment of frailty among CCSS ALL survivors by:**

a) Comparing pro-inflammatory cytokine profiles, as determined in plasma by multiplex immunoassay, to patterns observed in non-cancer controls

b) Determining the impact of specific therapeutic exposures including CRT on systemic inflammation

c) Determining SNP profiles in inflammatory pathway genes that correspond with systemic inflammation

d) Investigating the relationship between inflammation, relevant SNP profiles, and frailty score.

**Specific Aim 3: To determine the association between DNA methylation age relative to chronologic age and pre-frailty/frailty through objective assessment of frailty among CCSS ALL survivors by:**

a) Calculating DNA methylation age in survivors using established methods of assessing CpG island methylation patterns by methylation array, and the degree of deviation from biological age

b) Determining the impact of specific therapeutic exposures including CRT on DNA methylation age

c) Investigating the relationship between methylation age relative to chronologic age, and frailty score.

**Specific Aim 4: To determine the impact of therapeutic exposures on pre-frailty/frailty, as well as the individual and combined impact of host and genetic factors on frailty among CCSS ALL survivors.**

**Hypothesis: Accelerated aging, as evidenced by frailty, will increase with therapeutic intensity among survivors of childhood ALL, and will be associated with biologic host factors and related genetic determinants.**

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? : **NIH multi-PI R01, submitted June 23, 2017. Anticipated funding to start by March 2018.**

***Group: Does this project require contact of CCSS study subjects for:***

Additional self-reported information : **Yes**

Biological samples : **Yes**

Medical record data : **Yes**

If yes to any of the above, please briefly describe. :

**Using self-reported survey data from the CCSS Follow Up 5 (FU5) questionnaire, we will categorize ALL survivors as predicted to be frail or not frail, and use this data as a basis for our recruitment strategy. Simultaneous to this effort, we will distribute a brief survey interrogating well-established frailty metrics to ALL**

survivors who did not complete FU5 to ensure recruitment of the goal sample size. Consenting participants will have home visits for objective frailty assessment and blood collection. Investigators at St. Jude Children's Research Hospital (SJCRH) will recruit participants, establish the study cohort, and communicate subject contact information to Examination Management Services, Inc (EMSI). The BCM EpiCenter (Co-Director, Dr. Lupo) will supervise cohort follow up, including home visit completion and shipment of biospecimens to BCM. Weekly communications between the EpiCenter and EMSI will ensure timely completion of subject evaluations, as well as fidelity and accuracy of frailty assessments and adequate quality control of blood draws.

***Group: What CCSS Working Group(s) would likely be involved? (Check all that apply)***

Second Malignancy :

Chronic Disease : **Secondary**

Psychology / Neuropsychology :

Genetics : **Primary**

Cancer Control :

Epidemiology / Biostatistics :

### **Section: Outcomes or Correlative Factors**

Late mortality :

Second Malignancy :

#### ***Group: Health Behaviors***

Tobacco : **Correlative Factors**

Alcohol :

Physical activity : **Correlative Factors**

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 :

Heart and vascular :

Respiratory :

Digestive :

Surgical procedures :

Brain and nervous system :

Other : **Primary**

If other, please specify : **frailty**

***Group: Medications***

Describe medications :

***Group: Psychologic/Quality of Life***

BSI-18 :

SF-36 :

CCSS-NCQ :

PTS :

PTG :

Other :

If other, please specify : **Survey responses from FU5 questionnaire will be used to calculate frailty scores based on self-reported data. This information will be used to determine eligibility for recruitment to the case or control group.**

***Group: Other***

Pregnancy and offspring :

Family history :

Chronic conditions (CTCAE v3) : **Correlative Factors**

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 :

**Section: Anticipated Sources of Statistical Support**

CCSS Statistical Center :

Local institutional statistician : **Yes**

If local, please provide the name(s) and contact information of the statistician(s) to be involved. :

**Philip Lupo, BCM EpiCenter**  
[philip.lupo@bcm.edu](mailto:philip.lupo@bcm.edu)

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 :

**Biologic samples will be obtained prospectively for this study through home visits.**