Fiscal Year:	FY 2018	**Task Last Updated:**	FY 05/07/2018
PI Name:	Suzuki, Carolyn Ph.D.		
Project Title:	Tissue Sharing Project- Effects of Space Radiation on the Cardiac Mitochondrial Stress Response		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Radiation health		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **SR**:Space Radiation		
Human Research Program Risks:	(1) **Cardiovascular**:Risk of Cardiovascular Adaptations Contributing to Adverse Mission Performance and Health Outcomes		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	07103-3535	**Congressional District:**	10
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2016-2017 HERO NNJ16ZSA001N-Crew Health (FLAGSHIP, OMNIBUS). Appendix A-Omnibus, Appendix B-Flagship
Start Date:	07/01/2017	**End Date:**	06/30/2019
No. of Post Docs:	1	**No. of PhD Degrees:**	1
No. of PhD Candidates:		**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
Contact Monitor:	Simonsen, Lisa	**Contact Phone:**	
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Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:	May 2018 report: There are no personnel changes.		
COI Name (Institution):	Azzam, Edouard Ph.D. (RUTGERS Biomedical and Health Sciences - New Jersey Medical School)		
Grant/Contract No.:	80NSSC17K0113		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Mitochondria are the powerhouses of the cell, which make up ~30% of the volume of cardiac myocytes. They provide the crucial energy supply needed for the heart to beat and to provide blood and oxygen throughout the body. The goal of this ground-based Tissue Sharing project is to determine the effects of low dose/low fluence space ionizing radiation on the mitochondrial stress response in the heart. We will examine heart tissue collected by our collaborator Dr. Edouard Azzam, whose current NASA-funded project is investigating “Oxidative Stress and the Cancer Risk of Space Radiation." His study employs 10 month-old male mice, which is an age that is equivalent to active astronauts who are between 35-55 years old. These mice are exposed to low mean absorbed doses of isovelocity (1 GeV/n) protons or high atomic number, high energy (HZE) particles, which are a component of galactic cosmic rays. Another group of mice are exposed to 137Cs gamma rays as reference radiation. Using these heart samples, we will employ histological techniques, as well as biochemical and molecular biological approaches to measure biomarkers of the mitochondrial stress response in heart in response to HZE particles and reference radiation. Cardiac inflammation and fibrosis will be examined histologically. Radiation-induced changes in mitochondrial DNA copy number and damage and mitochondrial RNA and protein expression will be measured. Space radiation has been shown to induce reactive oxygen species, which oxidatively damage nucleic acids, proteins, and lipids. We will also determine the relative protein levels and activity of crucial mitochondrial stress response proteins, which are expected to mitigate cardiac injury that may be caused by radiation-induced oxidative damage. The results of these experiments will fill knowledge gaps about radiation-induced degeneration or injury to cardiac mitochondria, and the adaptive stress response mechanisms, which potentially promote or mitigate potential risks to the heart.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	The mechanisms underlying radiation-associated cardiovascular and degenerative diseases are currently unknown. However, studies suggest that radiation-induced oxidative stressors promote cardiac dysfunction and injury. The identification and validation of biomarkers of cardiac oxidative stress and dysfunction are needed as they may provide surrogate markers of disease outcomes. Identifying the stressors as well as the stress response mediators will contribute to developing countermeasures to mitigate cardiac damage as a result of space radiation exposure.
Task Progress:	Histological analysis. We have begun to analyze cardiac morphology and cardiac oxidative stress of mice exposed to space radiation. Heart samples obtained from Dr. Azzam’s lab have been prepared for histochemical analysis, which have been obtained from mice exposed to 40Ca20+ or 16O ions, at 20 or 40 cGy, either in a single bolus or in fractionated irradiation. Currently, immunohistochemistry is being optimized for using antibodies that recognize protein carbonylation, which is a marker of oxidatively damaged proteins, and 4-hydroxynonenal (4HNE), which is produced by lipid peroxidation that can form adducts with proteins. As mitochondria are a primary source for producing reactive oxygen species (ROS), we are particularly interested in examining mitochondrial stress response proteins, which we predict will be upregulated during space radiation-induced oxidative stress. We will also look for evidence of major markers of radiation-induced cardiovascular disease such as fibrosis, inflammation, atherosclerosis, and other vascular changes. Analysis of proteins mediating the mitochondrial stress response. We have examined mediators of the mitochondrial stress response. Our preliminary results show that 2 keys mediators are upregulated -- the mitochondrial ATP-dependent Lon protease, which is a mitochondrial protein quality control protease and mitochondrial transcription factor A (TFAM), which is the master regulator of mitochondrial DNA (mtDNA) maintenance, expression, and transmission. Using immunoblot analysis, upregulation was observed in cardiac tissue from mice that have been exposed to 40Ca20+ at 20 cGy of 1.35 GeV/n ions (LET ~85 keV/µm), delivered either acutely as a single bolus, or, in 3 fractions (1 fraction/day over three consecutive days to simulate low dose-rate IR. Under these conditions, we have also shown by Oxyblot analysis that there is an increase in oxidatively damaged protein in response to 40Ca20+ at 20 cGy fractionated, and H+ 20 cGy administered acutely. In addition to mediating the mitochondrial stress response, the upregulation of Lon and TFAM may also reveal the possibility that space radiation induced stress stimulates a Lon- and TFAM- dependent reprogramming of the bioenergetic and metabolic flux within cardiac myocytes.
Bibliography Type:	Description: (Last Updated:)